EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/CHMP/516229/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rydapt

International non-proprietary name: midostaurin

Procedure No. EMEA/H/C/004095/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE = adverse event

AHD = associated haematologic disorder

AHN = associated haematological neoplasm

AHNMD = associated clonal haematological non-mast cell lineage disease

ALT = alanine transaminase

AML = acute myeloid leukaemia

ANC = absolute neutrophil count

ASCT = allogeneic haematopoietic stem cell transplantation

ASM = aggressive systemic mastocytosis

AST = Aspartate transaminase

ATP = adenosine triphosphate

AUC0-t and AUCtau = Area under the plasma concentration-time curve from time zero to time t, using the log-linear trapezoidal rule. Where t is shown as τ (tau) this denotes the AUC under a dosing interval

AUCinf = Area under the plasma concentration-time curve from time zero to infinity. For extrapolation to infinity Clast / λz is used, where Clast is the estimated concentration at the last sample time point above LOQ from linear regression of the terminal elimination phase

$AUC_{Ctrough}$ = Area under the plasma concentration-time curve from time predose Cmin time 0 to predose Cmin day 7, using predose Cmin at each day from day 1 to day 7 [mass x day x volume-1]

AV = atrioventricular

B/R = benefit-risk

BCRP = Breast Cancer Resistance Protein (ABCG2)

BCS = Biopharmaceutics Classification System

BE = Bioequivalence

bid = Bis-in-diem; twice daily

BM = bone marrow

BOR = best overall response

BSA = Body surface area

CEBPA = CCAAT/enhancer-binding protein alpha

Cmax = Maximum plasma concentration after a single dose

CHMP = Committee for Medicinal Products for Human Use

CI = confidence interval

CID = cumulative incidences of death

CIR = cumulative incidences of relapse

CL/F = Apparent plasma clearance

CLp = Plasma clearance, calculated as Dose / AUCinf after an intravenous dose

CMML = chronic myelomonocytic leukaemia

CNS = central nervous system

CrCl = Creatinine clearance

CR = complete response

CRF = case record form

CSF = cerebrospinal fluid

CSF1 = Clinical Service Formulation 1

CSR = clinical study report

CTA = clinical trial assay

CTC = common toxicity criteria

CYP450 = Cytochrome P450

DCR = disease control rate

DDI = Drug-Drug interaction

DFS = disease-free survival

DNA = desoxy-ribonucleic acid

DOR = duration of response

EC = European Commission

ECG = Electrocardiogram

ECOG PS = Eastern Cooperative Oncology Group performance status

EFS = event-free survival

EMA = European Medicines Agency

EOT = end of treatment

EU = European union

F = Fraction of the dose systemically available (absolute bioavailability)

FAB = French–American–British classification

FAS = full analysis set

FDA = Food and Drug Administration

FFM = Fat Free Mass

FGFR = fibroblast growth factor receptor

FLT3 = Fms-like tyrosine kinase 3

FLT3 = Fms-like tyrosine kinase 3 gene

FLU = Fluconazole

FMI = Final market image

GC = Gas chromatography

GCP = good clinical practice

GI = Gastro-intestinal

GLP = good laboratory practice

GMR = Geometric mean ratio

GMP = good manufacturing practice

GPR = good partial response

hERG = human ether-a-go-go-related gene

HES/CEL= hypereosinophilic syndrome/ chronic eosinophilic leukaemia

HLA= human leucocyte antigen

HPLC = High performance liquid chromatography

HPLC-MS/MS = high performance liquid chromatography coupled with tandem mass spectrometry

HR = hazard ratio

IC_{50} = half maximal inhibitory concentration

ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-OES = Inductively coupled plasma optical emission spectrometry

IFN-α = Interferon-α

ILD = interstitial lung disease

IPC = In-process control

IR = Infrared

IR = incomplete remission

ISM = indolent systemic mastocytosis

ITDs = internal tandem duplications

ITT = intention to treat

IWG = International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) - referred to as IWG criteria

KF = Karl Fischer titration

KIT = CD117

KIT = gene encoding CD117

LLOQ = lower limit of quantitation

LVEF = left ventricular ejection fraction

MATE = Multi-anion and toxin extrusion protein

MC = mast cell

MCL = mast cell leukaemia

MD PAS = Multiple Dose Pharmacokinetic Analysis Set

MDS = myelodysplastic syndrome

MinR = minor response

MPN = myeloproliferative neoplasm

MR = major response

MSAS = Memorial Symptom Assessment Scale

MTD = Maximum tolerated dose

MUGA = multiple gated acquisition

NA = North America

NF = National Formulary

NNA = non-North America

NPM1 = nucleophosmin-1

OAT = Organic anion transporter

OATP = Organic anion transporting polypeptide

OCT = Organic cation transporter

ORR = overall response rate

OS = overall survival

PA = polyamide

PB = peripheral blood

PBT = persistent, bioaccumulative and toxic

PCR = pure clinical response

PD = pharmacodynamics

PD = progressive disease

PDE = Permitted Daily Exposure

PDGFR = platelet-derived growth factor receptor

PE = Polyethylene

Peak Cmin = Highest concentration that is identified as actual pre-dose

PEC = predicted environmental concentration

PEP = primary efficacy population

PET = polyethylene terephthalate

PFS = Progression-free survival

P-gp = P-glycoprotein (ABCB1)

Ph. Eur. = European Pharmacopoeia

PK = pharmacokinetics

PKC = protein kinase C

PNEC = predicted no effect concentration

PopPK = Population pharmacokinetics

ppm = parts per million

PPS = per-protocol set

PR = partial response

PRAC = Pharmacovigilance Risk Assessment Committee

PROs = patient reported outcomes

PVC = Polyvinyl chloride

q.d. = quaque die; once daily

QTc interval = measure between Q wave and T wave in the heart's electrical cycle corrected for heart rate

Racc = Accumulation index, calculated as AUCtau steady-state / AUCtau single dose

RBC = red blood cell

RFS = relapse free survival

RIF = Rifampicin

RH = Relative humidity

RT = radiotherapy

SAE = serious adverse event

SAWP = scientific advice working party

SCF = stem cell factor

SCT = stem cell transplantation

SD = stable disease

SD PAS = Single Dose Pharmacokinetic Analysis Set

SF-12 = Short Form health survey

SM = systemic mastocytosis

SM-AHNMD = systemic mastocytosis with an AHNMD

SM-AHN = systemic mastocytosis with an AHN

SMEDDS = self-micro-emulsifying drug delivery system

SmPC = Summary of product characteristics

SOC = system organ class

SSC = study steering committee

SSM = smouldering systemic mastocytosis

STP = sewage treatment plant

SWOG/AMLSG = South-Western oncology group/German AML study group

T1/2 = Apparent terminal elimination half-life

TAD = time after dosing

TD = transfusion dependent

TDI = Time-dependent inhibition

t.i.d = ter in die; three times daily

TKD = tyrosine kinase domain

Tmax = Time to the maximum observed serum concentration

TSE = Transmissible spongiform encephalopathy

TTC = Threshold of toxicological concern

TTR = Time to response

U = unspecified

UGT = Uridine 5'-diphospho- glucuronosyltransferase

ULN = upper limit of normal

USP = United States pharmacopoeia

UV = Ultraviolet

VEGFR2 = vascular endothelial growth factor receptor 2

Vss/F = Apparent volume of distribution at steady-state

V/F = Apparent volume of distribution during the terminal elimination phase

WBC = White blood cell (count)

WHO = World Health Organisation

XRPD = X-ray powder diffraction

%CV = Coefficient of variation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 22 July 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Rydapt, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

Rydapt was designated as an orphan medicinal product EU/3/04/214 on 29 July 2004 and EU/3/10/765 on 4 August 2010 in the following conditions: Treatment of acute myeloid leukaemia and Treatment of mastocytosis, respectively.

The applicant applied for the following indications:

- in combination with standard induction and consolidation chemotherapy followed by Rydapt single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms-like tyrosine kinase receptor-3 (FLT3) mutation-positive;

- as monotherapy for the treatment of adult patients with advanced systemic mastocytosis (SM).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Rydapt as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000072.jsp&mid=WC0b01ac058001d12b

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2010/08/human_orphan_000788.jsp&mid=WC0b01ac058001d12b

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0039/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0039/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised

orphan medicinal products.

Applicant's requests for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance midostaurin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 18/10/2018, 26/06/2014, 22/01/2015 and 22/01/2015. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula B. van Hennik   Co-Rapporteur: Bjørg Bolstad

- The application was received by the EMA on 22 July 2016.

- Accelerated Assessment procedure was agreed-upon by CHMP on 26 May 2016. The timetable was reverted to standard timetable at the time of the List of Questions.

- The procedure started on 18 August 2016.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 18 November 2016.

- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 February 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 March 2017.

- During the PRAC meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.

- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 June 2017.

- During the CHMP meeting on 22 June 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 June 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 July 2017

- During the CHMP meeting on 19 July 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting on 17-20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rydapt on 20 July 2017.

- The CHMP adopted a report on similarity of Ceplene, Vidaza, and Dacogen on 20 July 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Acute myeloid leukaemia (AML)

Treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms like tyrosine kinase receptor 3 (FLT3) mutation positive in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy.

Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN) or mast cell leukaemia (MCL)

Treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Acute myeloid leukaemia

The annual crude incidence of AML is 3.7 per 100,000 and the number of new cases per year in Europe is estimated at 18,400. AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemias in adults in the Western world. The incidence of AML increases sharply with age, ranging from 1.8 cases per 100,000 people aged less than 65 years of age to 17.6 cases per 100,000 people over 65 years of age. More than half of the subjects with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67, and AML is more common in men than in women.

ASM, SM-AHN, MCL

The incidence of ASM ranges between 0.01 and 0.03 cases per 100,000 person-years and its prevalence is between 0.1 and 0.3 cases per 100,000. The incidence rate of MCL is 0.01 per 100,000 per year (Cohen et al., 2014).

2.1.3. Biologic features

Acute myeloid leukaemia

Acute myeloid leukaemia is a form of leukaemia – i.e. cancer of the white blood cells – characterised by infiltration of proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated haematopoietic cells of myeloid lineage in the bone marrow, blood, and other tissues. The prognosis of patients with AML varies dramatically as a result of a number of factors, including age, performance status, and cytogenetic and/or molecular genetic alterations including *FLT3*, *NPM1*, and *CEBPA*.

Genetic alterations in FLT3 in AML

Among the prognostic molecular alterations, one of the most important factors is the presence of FMS-like tyrosine kinase 3 (*FLT3*) gene mutations, which occur in ~30% of adult patients with AML and have a substantial negative impact on prognosis (Pemmaraju, Kantarjian, Ravandi, & Cortes, 2011). *FLT3* encodes a class III receptor tyrosine kinase that consists of 5 immunoglobulin-like domains, a transmembrane domain, a cytoplasmic juxtamembrane domain, and 2 tyrosine kinase domains. FLT3 plays a critical role in normal haematopoiesis and cellular growth in primitive haematopoietic stem and progenitor cells. Under normal conditions, FLT3 is expressed on bone marrow haematopoietic stem cells, but this expression is gradually lost as cells differentiate.

Mutant FLT3 is constitutively activated, which results in the proliferation and survival of leukaemic blasts. Two forms of *FLT3*-activating mutations are identified commonly in the blasts from patients with AML — internal tandem duplications (ITDs) and point mutations, both of which can occur in the juxtamembrane domain or the tyrosine kinase domain.

FLT3-ITD mutations are observed in 20%-25% of *de novo* AML patients and in 30%-35% of the cytogenetically normal newly diagnosed AML patients (~30% of all patients with AML). The ITDs lead to an additional 3 to ≥100 amino acids inserted into the receptor, resulting in the ligand-independent, constitutive activation of FLT3. Point mutations of the FLT3 protein tyrosine kinase domain (*FLT3*-TKD mutations) are observed in 5%-10% of all AML patients and in 11%-14% of cytogenetically normal AML patients (Ferrara & Schiffer, 2013). Point mutations in the juxtamembrane domain appear to result in less activation compared with tyrosine kinase domain (TKD) point mutations or ITDs of the juxtamembrane domain.

In addition to ITDs and TKD mutations, overexpression of FLT3 has been detected in both adult and paediatric patients with AML without *FLT3* mutations and this overexpression may have an unfavourable prognostic impact on OS.

Other relevant genetic alterations in AML

Like alterations in *FLT3*, alterations in *NPM1* and *CEBPA* have been shown to affect outcome of patients with AML, and in the 2016 revision to the WHO classification of myeloid neoplasms and acute leukaemia, *"AML with mutated NPM1"* and *"AML with biallelic mutations of CEBPA"* have become separate clinical entities. Furthermore, it is expected that additional markers (e.g., *RUNX1*, *ASXL1*, and *TP53*) that have consistently been associated with an inferior outcome will soon be included in these recommendations.

ASM, SM-AHN, MCL

Mastocytosis is a heterogeneous myeloproliferative disorder characterised by the abnormal growth and accumulation of morphologically and immunophenotypically abnormal mast cells (MCs) in one or more organs. The disease can be limited to the skin (cutaneous mastocytosis) or involve extracutaneous tissues (systemic mastocytosis). Mastocytosis is frequently associated with a gain-of-function mutation in the *KIT* gene, and an Asp816 to Val (D816V)-encoding point mutation is present in 70-90% of patients with adult onset SM (Kristensen, Vestergaard, & Moller, 2011; Orfao, Garcia-Montero, Sanchez, Escribano, & Rema, 2007; Sotlar et al., 2010; Valent et al., 1994).

Genetic alterations in KIT in ASM and MCL

KIT is located at chromosome 4q12 and encodes KIT, a class III receptor tyrosine kinase. The type III class also includes platelet-derived growth factor receptor (PDGFR), colony-stimulating factor 1 and FLT3 and is characterised by an extracellular component of 5 immunoglobulin-like domains, a transmembrane segment, a juxtamembrane domain and a cytoplasmic kinase domain with a 70–100 amino acid kinase insert near its centre. Normally, KIT is activated when bound to its ligand, the stem cell factor (SCF), which is encoded by *SCF* on chromosome 12q22. KIT (CD117) is notably expressed by MCs, haematopoietic stem cells, germ cells, melanocytes and Cajal cells of the gastrointestinal tract and is therefore functionally relevant for MC development, haematopoiesis, gametogenesis and melanogenesis (Lim, Pardanani, & Tefferi, 2008).

A large number of somatic heterozygous *KIT* alterations (point mutations and deletions/insertions) have been identified in patients with SM. In any given patient, one *KIT* alteration, or a combination of two or more *KIT* alterations, can occur. For several of these genetic alterations of *KIT*, changes in downstream KIT signalling pathways in MC have been identified (for review, see (Haenisch, Nothen, & Molderings, 2012)). As a result of these changes, KIT is converted into a constitutively active, dysregulated tyrosine kinase that signals independent of its endogenous ligand SCF (Molderings, 2015).

In the majority of patients with SM (70-90%), MCs display mutations in the activation loop of KIT, most frequently *KIT* D816V in exon 17. However, mutations outside of exon 17 occur in up to 44% of patients. In addition, genetic alterations in other genes are also found in a large proportion of the patients (e.g. alterations in *TET2* in 20-30% of the patients, alterations in *IL4* in up to 70% of the patients, alterations in *IL13* in 80% of the patients, and alterations in *KRAS* in 10% of the patients; reviewed in (Molderings, 2015).

The *KIT* D816V mutation was not found to be associated with survival in patients with mastocytosis (Lim, Tefferi, et al., 2009; Pardanani et al., 2016). Also, *KIT* D816V mutation burden does not correlate with the clinical manifestation of SM in a given individual, indicating that the combination of mutated genes could be the most relevant factor in terms of symptomatology (Molderings, 2015).

In conclusion, 70-90% of patients with ASM harbour a *KIT* mutation. In MCL, the frequency of *KIT* mutations appears slightly lower, approximately 50% (Georgin-Lavialle et al., 2013). *KIT* mutations are therefore a key characteristic of SM and are considered a key driver in the aetiology and progression of the disease.

2.1.4. Clinical presentation, diagnosis and prognosis

Acute myeloid leukaemia

In AML, leukaemic blasts replace normal blood cells in bone marrow and peripheral blood, which leads to anaemia, neutropenia, and thrombocytopenia. This is associated with symptoms of fatigue,

shortness of breath, disturbed wound healing, infections and bleedings. If left untreated, AML results in death within a few weeks to months.

The procedures used to diagnose and classify AML are: morphologic assessment of bone marrow specimens and blood smears (with ≥20% blasts in the bone marrow or peripheral blood being diagnostic of AML), analysis of the expression of cell-surface and cytoplasmic markers (by flow cytometry), identification of chromosomal findings (through cytogenetic testing), and screening for selected molecular genetic alterations. Currently, three molecular markers are used as part of standard clinical practice for risk stratification (European LeukemiaNet recommendations; (Dohner et al., 2010)): Alterations in nucleophosmin-1 (*NPM1*); alternations in CCAAT/enhancer-binding protein alpha (*CEBPA*); and alterations in Fms-like tyrosine kinase 3 (*FLT3*).

Prognostic factors in AML can be subdivided into those that are related to the patient and those that are related to the disease. Patient-associated factors (e.g., increasing age, coexisting conditions, and poor performance status) commonly predict treatment-related early death, whereas disease-related factors (e.g., white-cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukaemic-cell genetic changes including alterations in *FLT3*) predict resistance to current standard therapy.

In this application the requested indication concerns patients with newly diagnosed AML who have *FLT3* mutated disease, defined as ≥5% mutated *FLT3* alleles (internal tandem duplication or tyrosine kinase domain mutation) in AML blast cells, as determined by polymerase chain reaction. Patients positive for *FLT3* alterations have a poorer prognosis compared to patients negative for *FLT3* (Pemmaraju et al., 2011). This concerns around 30% of patients with newly diagnosed AML.

Overall, the 5-year survival rate for AML is 19%. The mortality rate strongly correlates with age: 5-year survival rates are 3% to 8% in patients aged 60 years and older compared with 5-year survival rates of up to 50% for younger patients (Visser et al., 2012). In FLT3 mutated AML patients, the complete remission (CR) rate with standard first line induction chemotherapy regimens is generally equivalent to that of patients without FLT3 mutations (78% vs. 82%). However the median time to relapse, disease free survival, event free survival and overall survival at 5 years is significantly worse (Gilliland & Griffin, 2002; Kottaridis et al., 2001; Schnittger et al., 2002; Thiede et al., 2002).On average, the median time to relapse for FLT3 mutated AML patients <60 years of age in first remission is estimated at approximately 9 months, compared to ~27 months for FLT3 WT AML patients <60 years (Ciolli et al., 2004; Frohling et al., 2002; Kottaridis et al., 2001).

*ASM, SM-AHN, MCL*Prognostic factors of overall survival (OS) in mastocytosis are WHO subtype, advanced age, history of weight loss, anaemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow (BM) blasts (>5%) (Lim, Tefferi, et al., 2009).

Table 1. WHO classification of mastocytosis

WHO mastocytosis classification
1. Cutaneous mastocytosis (CM)
2. Systemic mastocytosis
a. Indolent systemic mastocytosis (ISM)*
b. Smoldering systemic mastocytosis (SSM)*
c. Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)†
d. Aggressive systemic mastocytosis (ASM)*
e. Mast cell leukemia (MCL)
3. Mast cell sarcoma (MCS)

*These subtypes require information regarding B and C findings for complete diagnosis,[20] all of which may not be available at the time of initial tissue diagnosis.

†This category is equivalent to the previously described "systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)." AHNMD and AHN can be used synonymously.

Systemic mastocytosis

Systemic mastocytosis (SM) is mostly seen in adults and defined by multifocal histological lesions in the bone marrow (which is affected almost invariably) or other extracutaneous organs, together with cytological and biochemical signs of systemic disease. The diagnosis of SM is established if at least 1 major and 1 minor or 3 minor of the following criteria are fulfilled (Valent et al., 2001):

Major criteria

- Multifocal dense infiltrates of MC (>15 MC aggregating) detected in sections of BM and/or of other extracutaneous organ(s) by tryptase-immunohistochemistry or other stains

Minor criteria

- In MC infiltrates detected in sections of BM or other extracutaneous organs, >25% of MC are spindle-shaped, or: in BM smears, atypical MC (type I plus type II) comprise >25% of all MC

- *KIT*+ MCs in BM or blood or other extracutaneous organ(s) co-express CD2 or/and CD25

- Serum tryptase level >20 ng/ml (does not count in cases with an AHNMD)

- Detection of a *KIT* point mutation at codon 816 in BM or blood or other extracutaneous organ(s)

SM is further divided into the following categories:

- Indolent systemic mastocytosis (ISM)

- Smouldering systemic mastocytosis (SSM)

- SM with an associated clonal haematologic non-MC lineage disease (abbreviated SM-AHNMD or AHN, associated haematological neoplasm)

- Aggressive systemic mastocytosis

- MCL

Aggressive systemic mastocytosis

To determine the subtype of SM, a bone marrow biopsy, serum tryptase levels, complete blood counts with differential and liver function tests are typically performed. In addition to these assessments, the presence of "B" and "C findings" needs to be determined. The algorithm to define ASM and MCL is depicted in Figure 1. Because the application is focussed on ASM and MCL, the diagnosis of other

subtypes of SM will not be discussed here. As shown in Figure 1, ASM must be associated with the presence of one or more C findings, i.e., findings related to organ function impairment due to excessive MC infiltration.

Clinical findings are present in aggressive systemic mastocytosis and may be observed in MCL. These include cytopenias, palpable hepatomegaly with ascites and elevated liver function tests, palpable splenomegaly with hypersplenism, malabsorption due to MC infiltration of the intestinal tract with hypoalbuminemia and weight loss, and bone lesions with large osteolyses and/or severe osteoporosis with spontaneous and/or pathologic fractures.

Mast cell leukaemia

MCL is characterised by the presence of ≥20% MCs in a BM smear (Figure 1). Depending on whether there are ≥10% MCs in a peripheral blood smear or less than 10%, leukaemic MCL or aleukaemic MCL is diagnosed. Aleukaemic MCL is slightly more frequent than leukaemic MCL (~60% of cases; (Georgin-Lavialle et al., 2013).

Figure 1. Stepwise approach in defining subvariants of systemic mastocytosis: proposed algorithm using WHO criteria
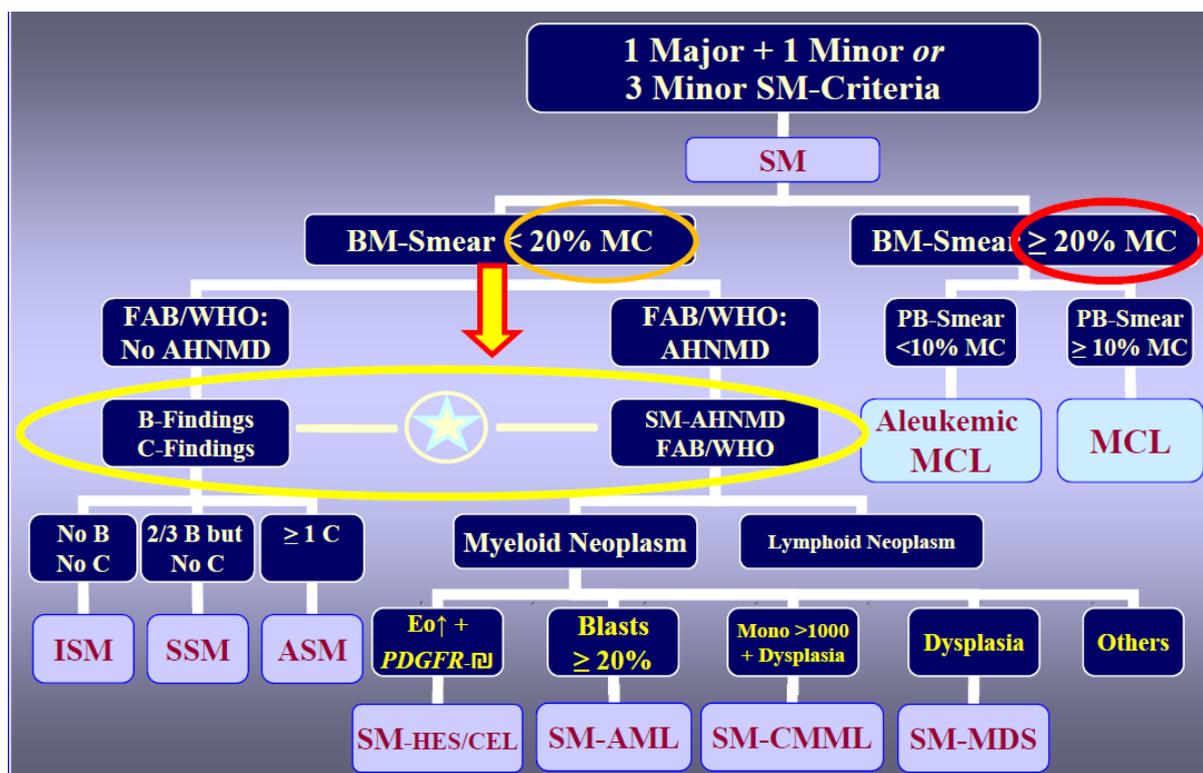
Source: European Competence Network on Mastocytosis, www.ecnm.net.

Abbreviations: BM = bone marrow; PB = peripheral blood; FAB = French–American–British classification; MC = mast cell; WHO = World Health Organisation; AHNMD = associated clonal haematological non-mast cell lineage disease; SM = systemic mastocytosis; ISM = indolent systemic mastocytosis; SSM = smouldering systemic mastocytosis; ASM = aggressive systemic mastocytosis; HES/CEL= hypereosinophilic syndrome/ chronic eosinophilic leukaemia; MDS = myelodysplastic syndrome; CMML = chronic myelomonocytic leukaemia, AML = acute myeloid leukaemia

ASM is associated with a poor prognosis, with a median OS of 3.5 years in patients with ASM, 2 years in those with an AHN (SM-AHN), and less than 6 months in those with MCL (Figure 2). Within the

subgroup of patients with SM-AHN, prognosis differs depending on the type of associated haematological neoplasm present (Figure 3).

Figure 2. Overall survival of patients with systemic mastocytosis according to subtype
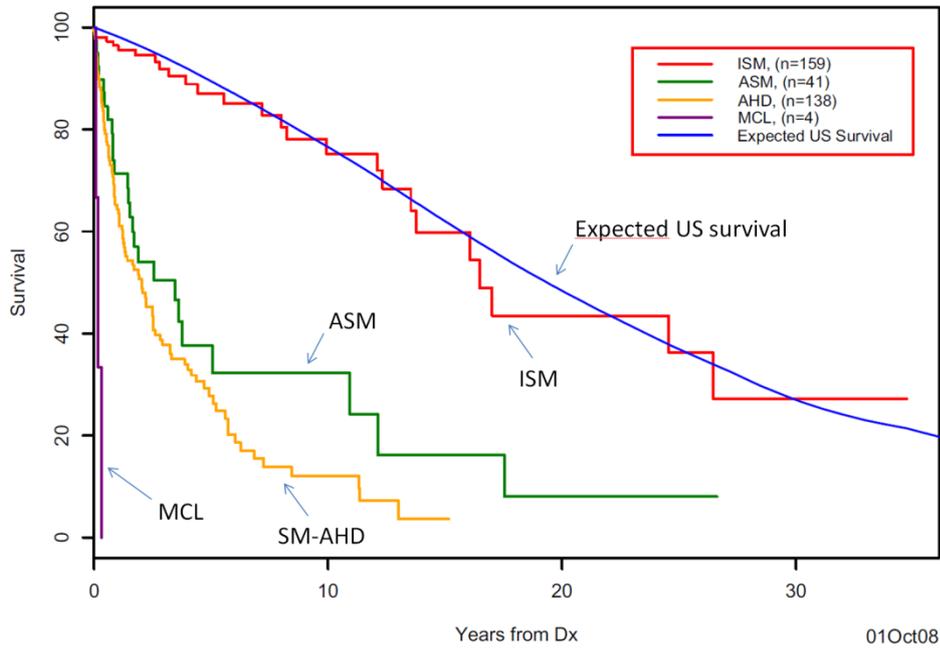
Abbreviations: SM = systemic mastocytosis; ISM = indolent systemic mastocytosis; ASM = aggressive systemic mastocytosis; AHD = associated haematologic disorder; MCL = mast cell leukaemia. Figure adapted from (Lim, Tefferi, et al., 2009).

Figure 3. Overall survival of patients with systemic mastocytosis with associated myeloid neoplasm
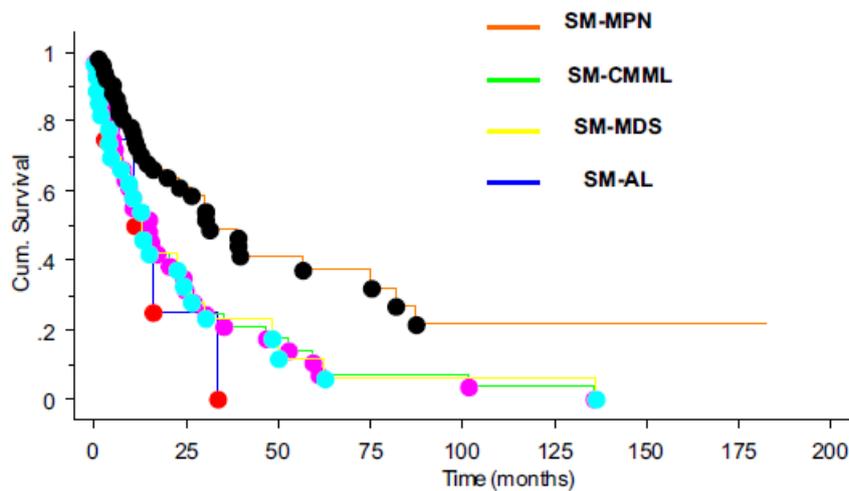
Abbreviations: SM = systemic mastocytosis; MPN = myeloproliferative neoplasm; MDS = myelodysplastic syndrome; CMML = chronic myelomonocytic leukaemia, AL = acute leukaemia. Figure adapted from adapted from (Pardanani et al., 2009).

2.1.5. Management

Acute myeloid leukaemia

Although AML was incurable 50 years ago, it is now cured in 35 to 40% of adult patients who are 60 years of age or younger and in 5 to 15% of patients who are older than 60 years of age (Dohner et al., 2010). Treatment of AML is with curative intent whenever possible. The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. In patients eligible for intensive induction chemotherapy, treatment consists of a combination of an anthracycline and continuous-infusion cytarabine in the classic '3+7' regimen, i.e., 3 days of intravenous administration of an anthracycline, combined with 7 days of continuous intravenous cytarabine.

If complete remission is achieved after intensive therapy, appropriate post-remission therapy is essential. There is no consensus on a single 'best' post-remission treatment, but it preferably includes intermediate or high-dose cytarabine-based chemotherapy, or consists of stem cell transplantation, depending on the risk group. Patients with good-risk AML should receive at least one cycle of intensive cytarabine-based consolidation chemotherapy. Patients with AML in intermediate and poor risk groups with an HLA-identical sibling may be candidates for allo-SCT, provided their age and performance status allow for such treatment.

In the EU, recently approved agents include decitabine (Dacogen) is authorised for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy. Azacitidine (Vidaza) is also authorised for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with: intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS); chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder, acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification and AML with >30% marrow blasts according to the WHO classification. Finally, histamine dihydrochloride (Ceplene) is authorised for adult patients with AML in first remission concomitantly treated with interleukin-2 (IL-2).

*ASM, SM-AHN, MCL*Patients with ASM, SM-AHN, or MCL have limited treatment options, and generally have a poor prognosis with a shortened life expectancy (Lim, Pardanani, Butterfield, Li, & Tefferi, 2009). To date there are no approved standard therapies in the EU for ASM or MCL, but there are different therapies available which are commonly used in clinical practice (Ferrara & Schiffer, 2013; Ustun et al., 2016; Valent, Sperr, & Akin, 2010)

About the product

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits FLT3 receptor signalling and induces cell cycle arrest and apoptosis in leukaemic cells expressing FLT3 ITD or TKD mutant receptors or over expressing FLT3 wild type receptors. *In vitro* data indicate that midostaurin inhibits D816V mutant KIT receptors at exposure levels achieved in patients (average achieved exposure higher than IC50). *In vitro* data indicate that KIT wild type receptors are inhibited to a much lesser extent at these concentrations (average achieved exposure lower than IC50) (SmPC, section 5.1).

The applicant requested the approval for the following indications:

Rydapt is indicated

- in combination with standard induction and consolidation chemotherapy followed by single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive;

- for the treatment of adult patients with advanced systemic mastocytosis (advanced SM).

The final indications following CHMP review of this application is:

Rydapt is indicated:

•   in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive;

•   as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL) (SmPC, section 4.1).

For AML the recommended dose of Rydapt is 50 mg twice daily. Rydapt is dosed on days 8 21 of induction and consolidation chemotherapy cycles, and then for patients in complete response every day as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each (SmPC, section 4.2).

For the advanced SM indication, the recommended starting dose of Rydapt is 100 mg twice daily. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs (SmPC, section 4.2).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that the provided data indicated that more patients obtained a CR in the midostaurin-treated arm when compared to placebo, and it was shown that patients treated with midostaurin up to receiving SCT in CR1 had an OS benefit relative to patients who were transplanted in CR1 and were treated with placebo up to SCT. Thus, this indicated a lost chance for patients diagnosed with AML who do not receive midostaurin in first-line, which would justify the claim of major public health interest.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, since major objections had been identified, which precluded an accelerated assessment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a soft capsule containing 25 mg of midostaurin as active substance.

Other ingredients are:

Capsule content: macrogolglycerol hydroxystearate, macrogol, anhydrous ethanol, maize oil mono-di-triglycerides and all-rac-alpha-tocopherol.

Capsule shell: gelatin, glycerol, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172) and purified water.

Printing ink: carmine (E120), hypromellose and propylene glycol.

The product is available in PA/Al/PVC/Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of midostaurin is *N*-[(2*S*,3*R*,4*R*,6*R*)-3-methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triaza-octacyclo [12.12.2.1^{2,6}.0^{7,28}.0^{8,13}.0^{15,19}.0^{20,27}.0^{21,26}] nonacosa-8,10,12,14,19,21,23,25,27-nonaen-4-yl]-*N*-methylbenzamide corresponding to the molecular formula $C_{35}H_{30}N_4O_4$. It has a relative molecular mass of 570.65 g/mol and the following structure:
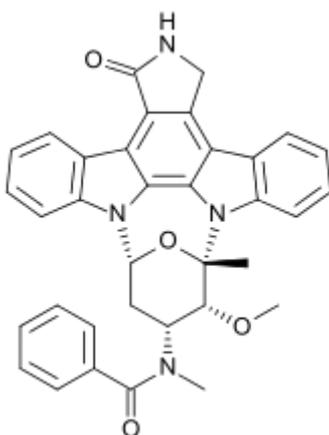
Figure 4. Structure of midostaurin

The chemical structure of midostaurin was inferred from the route of synthesis and confirmed by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, elemental analysis, infrared spectroscopy, ultraviolet spectroscopy and x-ray crystallography. The solid state properties of the active substance were measured by differential scanning calorimetry, thermogravimetric analysis and x-ray powder diffraction.

The active substance is a white to light yellow or light green slightly hygroscopic crystalline powder. Due to its lipophilic properties, lack of ionisable moieties and planar structure, it is highly insoluble in aqueous media irrespective of pH but shows increased solubility in less polar alcohols and polar aprotic solvents. As a result of these properties, the active substance is dissolved in a combination of liquid excipients, inside a capsule, which self-emulsify on dissolution in aqueous media.

Midostaurin exhibits stereoisomerism due to the presence of four chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation of the active substance.

Polymorphism has been observed for midostaurin and the correct physical form is ensured by the crystallisation process. Since the active substance is dissolved during formulation, physicochemical properties are mostly relevant to the isolation and stability of the active substance.

Midostaurin is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives and salts have ever been active substances in products authorised in Europe.

Manufacture, characterisation and process controls

Midostaurin is synthesized in two main steps followed by crystallisation and milling. The first step is a fermentation process carried out by one manufacturer, with the working cell bank considered to be the source material and starting point of manufacture. Suitable specifications and detailed characterisation data have been provided. A master cell bank has been established in order to preserve the production

strain and product working cell banks as needed. The microorganism is not genetically modified and is non-toxic and non-pathogenic.

A second manufacturer carries out the subsequent purification of staurosporine, benzoylation and recrystallization processes with the milling step carried out by a third manufacturer.

The fermentation step is described in detail with input materials and reaction parameters for both propagation and production steps defined. The process for harvest and subsequent purification is also defined as per the Ph. Eur. monograph on products of fermentation. Methods for inactivation and removal of biomass are defined, along with in process controls to ensure removal. Adequate in-process controls are applied during the chemical synthesis process. The specifications and control methods for intermediate products and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The main change was from the amorphous active substance used in early development to the crystalline active substance used in later clinical studies. Otherwise, only minor changes to the process have been made resulting in improvements to the quality of the active substance.

The active substance is packaged in polyethylene (PE) bags which comply with the Regulation No 10/2011 as amended, as well as the Ph. Eur. monograph on polyolefins. The bags are placed in additional PE bags which are stored in drums.

Specification

The active substance specification includes tests for appearance, identity (IR, XRPD), specific optical rotation, colour and clarity of solution (Ph. Eur.), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-OES), residue on ignition (Ph. Eur.), particle size distribution (laser diffraction) and microbial enumeration (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Mutagenic impurities have been shown to be purged to well below the TTC levels in the active substance by way of spiking studies and so no limits are included in the specification. Control of elemental impurities is in line with ICH Q3D – no elemental impurity has been observed above 30% of the PDE in the tested batches.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 26 pilot to production scale batches of the active substance manufactured via the intended commercial process (or earlier minor variations thereof) and used in clinical, toxicological and stability studies were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from six pilot scale batches of active substance from the proposed manufacturers using minor variations of the process stored in the intended commercial package stored for up to 60 months

under long term (25 °C / 60% RH) and intermediate (30 °C / 75% RH) conditions and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. In addition, stability studies using 3 production scale batches have been instigated and data after 12 months under intermediate conditions and 6 months under accelerated conditions is available. Studies on these batches will be continued up to the end of the proposed retest period. Batches were tested for appearance, identity, specific optical rotation, colour and clarity of solution, assay, impurities and water content. The analytical methods used were the same as for release and are stability indicating. No significant trends to any of the measured parameters were observed and batches complied with the specification at every time point.

Photostability testing following the ICH guideline Q1B was performed on one batch. Significant degradation occurred so midostaurin is to be protected from exposure to light.

Stress testing in the solid state shows that midostaurin is not sensitive to moisture, oxygen and heat up to 100 °C although it does show reversible uptake of a small amount of water. Forced degradation studies in aqueous solution show that midostaurin is inert to acid and base. Minor degradation was observed on exposure to hydrogen peroxide and light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months stored not above 30 °C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Rydapt is presented as orange soft gelatin capsules containing 25 mg midostaurin dissolved in the liquid contents. The capsules are packaged in PA/Al/PVC-Al blisters.

Midostaurin is poorly soluble in aqueous media but highly permeable (BCS class II). Initial studies showed midostaurin to be poorly bioavailable when dosed orally. The aim of development therefore was to find a stable dosage form which would allow midostaurin to be delivered orally and in solution so as to be bioavailable without a rate-limiting dissolution step. The active substance is dissolved in a mixture of lipophilic and hydrophilic solvents with a surfactant such that a micro-emulsion is formed spontaneously on addition to aqueous media without it precipitating. The fill solution is encapsulated within a soft gelatin capsule for ease of administration.

The selection of excipients for the fill solution was based on the solubility and stability of midostaurin in the individual and combined excipients and its ability to spontaneously form a micro-emulsion on addition to water. The fill solution is a mixture of corn oil mono-di-triglycerides, macrogolglycerol hydroxystearate, macrogol 400, ethanol and all-rac-α-tocopherol and was shown to form a homogeneous solution with the active substance. The inclusion of an anti-oxidant is justified and the amount added has been optimised to adequately control oxidative degradation. Equilibrium solubility studies were carried out to show that midostaurin remains in solution and no phase separation occurs under the manufacturing and storage conditions and that no precipitation occurs on addition to aqueous media. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards where applicable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Drug substance release rate was expected to depend on disintegration time of the capsule since midostaurin is already in solution and thus doesn't need to dissolve. Media pH and apparatus were

investigated for development of a discriminatory dissolution method. The method is considered to be discriminatory since it detects batches which fail to disintegrate adequately.

The proposed commercial formulation was used during phase 1-3 clinical studies. However, earlier clinical studies used a different soft capsule formulation, hard capsules and an oral solution. Relative bioavailability or bioequivalence was demonstrated on each shift between formulations as appropriate.

The primary packaging is PA/Al/PVC-Al blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: preparation of the fill solution; preparation of the gelatin mass; encapsulation followed by washing and drying; imprinting. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on three consecutive production scale batches of finished product. The process parameters to control the preparation of the fill solution have been shown to be robust. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs used to test the fill solution, gel mass, and filled capsules are adequate. Holding times and storage conditions for intermediates have been defined and justified.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (contents and shell), appearance by light microscopy, identity (HPLC and UV), identity and assay of antioxidant (HPLC), identity and assay of ethanol (GC), appearance in water, droplet size (laser light scattering), disintegration time (Ph. Eur.), dissolution (UV), water content (KF), degradation products (HPLC), microbial enumeration (Ph. Eur.), uniformity of dosage units (Ph. Eur.), and assay (HPLC).

Since the performance of the finished product depends on midostaurin being dissolved in the fill solution, the capsules rupturing on oral administration, and the contents emulsifying on contact with gastrointestinal fluid, controls are included in the specification which test these attributes. Disintegration time is measured to ensure rapid release of the drug. The capsule contents are examined by light microscopy to detect midostaurin precipitation or phase separation. Visual appearance on dilution and emulsion droplet size are also checked to ensure midostaurin remains in solution and a sufficiently fine micro-emulsion is formed. Specified impurities are either metabolites or degradation products and have been toxicologically qualified at the levels indicated.

The colourants are tested for identity before use and the colour of the final gelatin mass is checked as an IPC. Therefore, no test for colourants is included in the specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 9 representative production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies were carried out on 8 production scale batches stored in various blister packs made from the same PA/Al/PVC forming component but with 3 separate backing component materials under 6 sets of conditions: -20 ^{o}C / ambient humidity; 5 ^{o}C / ambient humidity; 25 ^{o}C / 60% RH (long term conditions); 30 ^{o}C / 75% RH (intermediate conditions); 40 ^{o}C / 75% RH and 50 ^{o}C / ambient humidity. Three batches were stored in blisters backed with PET/Al/vinyl based heat-sealed lacquer (blister 1), two in blisters backed with Al/vinyl based heat-sealed lacquer (blister 2), and three in blisters backed with the proposed commercial material Al/acryl-vinyl based heat-sealed lacquer (blister 3). Batches were tested for appearance (shell and contents), appearance by light microscopy, appearance in water, disintegration time, assay of antioxidant, assay of ethanol, droplet size, dissolution, water content, degradation products, microbial enumeration, and assay of midostaurin.

Data from 3 batches stored in blister 1 for up to 60 months under long term and intermediate conditions showed no significant changes to any of the measured parameters were observed, other than a minor increase in one impurity. After storage for up to 6 months under accelerated conditions, an increase in impurities and decrease in antioxidant content was observed. However, all measured parameters remained within their specification limits. Similar trends were observed for 2 batches stored in blister 2 for up to 36 months under long term and intermediate conditions and for up to 6 months under accelerated conditions, and for 3 batches stored in proposed commercial blister 3 for up to 18 months under long term and intermediate conditions and for up to 6 months under accelerated conditions. The three packaging configurations are therefore considered equivalent.

Batches stored at 50 °C for 1 month showed slight deformation of the capsule but no changes to any other measured parameters. No changes were observed for batches stored under the colder conditions and subjected to freeze/thaw cycles, showing that refrigeration and freezing have no detrimental impact on quality.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All tested parameters remained within their specification limits indicating that Rydapt is not photosensitive.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from human origin have been used and none are subject to TSE risk. Gelatin is of porcine origin whilst the carmine in the printing ink is derived from insects.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

All the pivotal preclinical safety studies were conducted in compliance with GLP. Dose range finding studies do not all claim GLP compliance, but were conducted in a GLP-compliant facility. Except for the hERG channel tests for both major metabolites of midostaurin, safety pharmacology studies were not performed according to GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Activity of midostaurin against purified kinase isoforms (RD-2008-01357)

Midostaurin was tested at a concentration of 1 μM in replicate against 220 purified kinases. Values of ≥80% inhibition were observed for 12 kinases with 1 μM midostaurin. For these 12 kinases and a selected group of enzymes (based on their drug-sensitivity and their sequence similarity) IC_{50} determinations were performed. The IC_{50} against wild-type FLT3 and the mutated FLT3 D835Y kinase was determined as 19.8 and 3.64 nM, respectively.

Activity of midostaurin against wild-type KIT and other purified kinase isoforms (Fabbro et al, 2000, and PKF-98-02545)

Inhibition of wild-type KIT, various protein kinase C isoforms and other kinases were investigated using several different methods including incorporation of ^{32}P from $[\gamma\text{-}^{32}P]ATP$. Anti-kinase activity with IC_{50} values below 1 μM for midostaurin was reported against wild-type KIT, the conventional PKC isoforms, PPK, the src-family kinase SYK and the proangiogenic kinase KDR (VEGFR2).

Binding affinity of midostaurin for purified kinases and kinase domains (Karaman et al, 2008)

Dissociation constants for more than 180 purified kinases or kinase domains were determined by competition binding assays using immobilized midostaurin. The affinity constant of midostaurin was below 100 nM for 36 of the kinases. Oncogenic FLT3 mutants and KIT mutants ranked among the kinases for which midostaurin had the highest affinity.

Inhibition of FLT3 mutated AML cell proliferation (RD-2004-01878; Grundler, 2003)

The murine pro-B cell line BaF3 expresses FLT3 mutations implicated in AML (Grundler et al 2003). Midostaurin inhibited the cell growth of both FLT3-ITD and FLT3-TKD mutants at nanomolar concentrations.

In a follow-up study, midostaurin was tested in proliferation assays using human AML cell lines expressing mutant or wild-type FLT3 (RD-2004-01878). Some of these cell lines harboured additional mutations in oncogenes or were growth factor dependent. Midostaurin inhibited the two FLT3-ITD dependent AML cell lines MV4-11 and MOLM13. In addition, midostaurin inhibited the proliferation of FIP1L-PDGFR expressing eosinophilic cell line EOL1. Midostaurin did not show significant inhibition of proliferation in the FLT3-ITD expressing human pro-myelocytic leukaemia cell line PL21. The mean IC_{50} values obtained for midostaurin in various leukaemia cell lines are shown in Table 4 together with the respective growth factor information.

Table 2: Inhibition of cell proliferation by midostaurin in various leukaemia cell lines

Cell line	Mutation	Growth Factor	Proliferation
	Mean IC50 [nM] ± SEM (number of determinations)		
MV4-11	FLT3-ITD homozygous K-ras-G12D/A18D	none	26.3 ± 7.1 (6)
MOLM13	FLT3-ITD heterozygous	none	48.4 ± 6.9 (3)
PL-21	FLT3-ITD heterozygous	none	>1000 (3)
OCI-AML5	wtFLT3 wt-ras	none GM-CSF	821 (1) 639 ± 70 (3)
MUTZ-2	wtFLT3 wt-ras	SCF	902 (1)
SEM	wtFLT3 wt-ras	none	91 ± 1 (2)
SEM-K2	wtFLT3 wt-ras	none	157 ± 76 (3)
EOL-1	FIP1L-PDGFR	none	8.1 ± 1.4 (3)
M07e *	wtFLT3 wt-ras	GM-CSF SCF IL-3	183 ± 16 (3) 186 ± 24 (3) 158 (1)
HL-60	wtFLT3 N-ras-Q61L	none	1334 ± 536 (3)

The effect of midostaurin on cell proliferation was determined with AlamarBlue (* or ATPLite, respectively) and calculated as percent inhibition and dose-response curves were used to calculate IC50 values, expressed as mean ± SEM, ( ) = number of experiments.

The anti-proliferative activity of midostaurin in MV4-11 cells has also been investigated by other groups, resulting in IC_{50} values ranging from 12 to 35 nM (Furukawa et al 2007; Ogderel et al 2008; Zarrinkar et al 2009).

<u>Cytotoxic response of midostaurin and CGP52421 on primary AML mononuclear cells (MNCs) expressing wild-type or mutated FLT3 (Knapper, 2006; Levis, 2006)</u>

Cytotoxicity assays were conducted using cryopreserved primary AML MNCs obtained from the bone marrow and blood of 96 newly diagnosed AML patients (Knapper et al 2006). In this study, the IC_{50} values were significantly higher than observed in studies using leukaemia cell lines, and ranged from 1 to 10 μM. Cytotoxic responses were highly heterogeneous, and FLT3 mutation status was found to have no significant effect on the cytotoxicity response. Further, it was found that variations in FLT3 expression level had little impact on the *in vitro* sensitivity to midostaurin. The cytotoxic response of midostaurin in combination with cytarabine was also investigated. The results showed that there was

no statistical evidence to support synergy in any of the FLT3 mutational subpopulations treated with the midostaurin/cytarabine combination.

In another similar study, the cytotoxicity of midostaurin was also investigated using primary AML samples isolated from patients (Levis, 2006). Midostaurin (100 nM) induced virtually no cytotoxicity in the FLT3 wild-type AML samples and only a modest effect in the FLT/ITD mutant samples (Table 5). Following up these results, five samples were selected and investigated for cytotoxicity in response to both midostaurin and CGP52421, one of the main metabolites of midostaurin. Over the dose range 100 to 500 nM CGP52421 was more cytotoxic than midostaurin. When midostaurin and CGP52421 were combined in the cytotoxic assay, there was no difference in effect with CGP52421 alone as compared with the combination. Thus, in this assay CGP52421 was more cytotoxic to AML blasts than its parent compound, midostaurin.

Table 3: Summary of MTT assay results for primary AML samples treated with midostaurin

Dose	Wild-type FLT3	FLT3/ITD
50 nM	96.4 ± 2.2	82.2 ± 4.8
100 nM	96.0 ± 2.7	79.2 ± 5.3

<u>Inhibition of proliferation of mast cell lines and primary mast cells expressing mutant KIT (Growney, 2005; Gleixner, 2006)</u>

Midostaurin was tested against 14 different KIT mutations associated with human malignancies (AML, systemic mast cell disease and gastrointestinal stromal tumours) in the murine hematopoietic cell line BaF3 (Growney et al 2005). KIT D816Y and D816V expressing cells were sensitive to midostaurin despite resistance to imatinib mesylate. In these cells, midostaurin, but not imatinib mesylate, inhibited auto-phosphorylation of c-KIT and activation of downstream effectors signal transducer and transcriptional activator (Stat) 3 and 5.

In another study, the human mast cell lines HMC-1.1 and HMC-1.2 were used to analyse the inhibitory effects of midostaurin on KIT receptor phosphorylation and cell proliferation (Gleixner et al 2006). HMC-1.1 express the V560G mutation, while HMC-1.2 express both D816V and V560 mutations. Total inhibition of receptor phosphorylation was observed with 1 µM midostaurin in both cell lines, while IC_{50} values for anti-proliferative effects by midostaurin ranged from 50 to 250 nM.

The anti-proliferative activity of midostaurin was also tested in primary mast cells from a single patient harbouring smouldering systemic mastocytosis (SSM). This culture contained mostly imatinib resistant D816V positive cells. In this culture, the IC_{50} value for midostaurin was close to 50 nM (Gleixner et al 2006).

<u>Induction of apoptosis in AML and ASM cell lines (Armstrong, 2003; Odgerel, 2008; Nordigarden, 2009; Gleixner, 2006)</u>

Treatment with 500 nM midostaurin resulted in marked induction of apoptosis measured by Annexin V staining in FLT3-ITD expressing (MV4-11) or wild-type FLT3 overexpressing (SEMK2-M1) AML cell lines (Armstrong et al 2003).

In another study, treatment with 100 nM midostaurin resulted in marked induction of apoptosis measured by detecting DNA fragmentation using a TUNEL assay in FLT3-ITD expressing MV4-11 AML cell line (Odgerel et al 2008).

To analyse the mechanism of midostaurin to induce apoptosis at the level of Bim and Puma genes, both of which are regulators of apoptosis, mononuclear cells from several AML patients with FLT3-ITD mutations were exposed to midostaurin (100 and 300 nM) (Nordigarden et al 2009). AML cells from four patients were responsive to midostaurin and showed a decrease in numbers of viable cells after 72

hours. Real-time PCR analysis demonstrated a significant up-regulation of Bim and Puma after 24 hours of midostaurin treatment, ranging from a 1.3- to 4.7-fold increase compared with no treatment.

The pro-apoptotic effects of midostaurin were also analysed in cell models of ASM (Gleixner et al 2006). Treatment with midostaurin resulted in marked induction of apoptosis determined by PI/Annexin V staining in KIT D816V expressing human mast cell line HMC-1.2. Using electron microscopy, HMC-1.2 cells cultured with midostaurin frequently displayed signs of apoptosis including cell shrinkage, membrane ruffling, vacuolization, and condensation of the nuclear chromatin.

Mechanism of synergistic activity of midostaurin (Seedhouse, 2006)

DNA repair was investigated in FLT3-ITD and FLT3 wild-type cells (Seedhouse et al, 2006). Using the comet assay, it was observed that midostaurin significantly inhibited repair of DNA damage in the FLT3-ITD expressing MV4-11 cell line and FLT3-ITD patient samples, but not the FLT3 wild-type cells. The reduction in DNA repair in midostaurin-treated FLT3-ITD cells was shown to be associated with downregulation of RAD51 mRNA and protein expression, and correlated with the maintenance of phosphorylated H2AX levels, implying that midostaurin inhibits the homologous recombination double-strand break repair pathway in FLT3-ITD cells. This suggested that midostaurin may reverse the drug-resistant phenotype of FLT3-ITD-AML cells by inhibiting repair of chemotherapy-induced genotoxic damage.

Effect of midostaurin in combination with other drugs in ASM cell lines (Gleixner, 2006)

In order to determine if addition of midostaurin to other drugs result in enhanced efficacy, midostaurin plus several TKI or standard of care agents were assessed in the human mast cell line HMC-1 by a 3H-thymidine uptake (Gleixner et al 2006). Midostaurin was found to cooperate with AMN107 (a novel TK targeting drug), imatinib, and cladribine in producing growth inhibition of HMC-1. However, clear synergistic drug interaction were only observed with the V560G mutant expressing HMC-1.1 cell variant, while the synergetic drug interaction was weak in the D816V / V560G mutant expressing HMC-1.2 cells.

Biological activity in presence of plasma (PKF-98-02553)

In an initial study, a reduction in the midostaurin-mediated inhibition of PKC-α activity by approximately one order of magnitude was found in the presence of 10% human plasma. This effect was specific to human plasma, since neither mouse, rat nor porcine plasma had any effect on the potency of midostaurin to inhibit PKC- α. Additional studies revealed that the human plasma proteins responsible for this effect is most likely the α-1 acidic glycoprotein (AAG), followed by α-1-anti-trypsin and albumin. In fact, in the presence of 1.0 mg/ml of human AAG corresponding to 20 µM (the normal circulating levels of AAG in human plasma) the IC_{50} for inhibition of PKC-α *in vitro* was shifted by two orders of magnitude. A similar shift in IC_{50} for the anti-proliferative effects of midostaurin against human bladder carcinoma T24, epidermoid carcinoma A431 and colon carcinoma HCT-116 cells was observed in the presence of human AAG. No effect was observed when performed in the presence of 1.0 mg/ml of rat AAG.

Analysis of free drug activity ex vivo by plasma inhibitory assay (Levis, 2006)

The pharmacodynamic activity of plasma samples from midostaurin-treated AML patients were analysed in an *ex vivo* reporter assay. In this study, midostaurin had >100 fold less biological activity in plasma compared to medium. This effect is likely related to binding of midostaurin to plasma proteins leading to a reduction of the pharmacologically active free fraction. However, inhibition of target phosphorylation was demonstrated using plasma form midostaurin treated patients.

Pharmacological profile of the major metabolites of midostaurin (RD-2008-01357; RDS-2015-00401; Zarrinkar, 2009; Karaman, 2008; Levis, 2006; Peter, 2015)

In humans, midostaurin is rapidly transformed to mainly two major metabolites - the 7-hydroxy-derivate CGP52421, which consists of two epimers, and O-demethylation product CGP62221. The biological activity of both metabolites was analysed to explore if they can contribute to the pharmacological activity of the parent compound. In general, the metabolite CGP62221 showed on target potencies in the biological assays similar to that of midostaurin. CGP52421, showed potencies that were up to one log weaker compared to those of midostaurin. The 7-hydroxy-derivate CGP52421 exists in two epimeric forms which were found to display similar biological activities in cell based assays (RDS-2015-00401).

<u>Inhibition of receptor auto-phosphorylation and substrate phosphorylation in FLT3 dependent cell systems (Barry, 2007; Weisberg, 2008)</u>

The effect of midostaurin on FLT3 auto-phosphorylation, STAT5 and ERK phosphorylation was tested in murine BaF3 cells (Barry et al 2007, Weisberg et al 2008). The cells expressed several constitutively active oncogenic FLT3 mutants which had been identified in AML patients. These encompassed FLT3-ITD (internal tandem duplication) as well as FLT3-TKD (tyrosine kinase domain) mutants. The activation loop mutations were all identified in AML patients but with different frequencies and different transforming potential. The most prevalent being the D835V mutation. Midostaurin inhibited phosphorylation of the FLT3 receptor, and its downstream targets STAT5 and ERK in a dose-dependent manner. Reduction of the phospho-signal was observed at midostaurin concentrations of 30 nM for the FLT3-ITD mutant and 100 nM for the FLT3-TKD mutants.

<u>Inhibition of receptor auto-phosphorylation and substrate phosphorylation in AML cell systems (Odgerel, 2008; Armstrong, 2003; George, 2004; Knapper, 2006)</u>

Midostaurin inhibited FLT3, STAT5, ERK and AKT phosphorylation in a concentration-dependent manner. These results indicated that midostaurin inhibits the activity of the FLT3 signalling pathway in AML cells (Odgerel et al 2008, Armstrong et al 2003, George et al 2004). The pharmacodynamic activity of midostaurin was also determined in primary mononuclear cells from AML patients with FLT3 mutants or FLT3 wild-type status (Knapper et al 2006). Midostaurin inhibited the phosphorylation of the FLT3 receptor at concentrations similar to those observed in non-patient-derived cell lines. Similar results were reported for bone marrow derived mononuclear cells from AML patients with wild-type or mutated FLT3 receptor status (Odgerel et al 2008).

<u>Inhibition of receptor auto-phosphorylation and substrate phosphorylation in KIT dependent cell systems (Growney, 2005; Gleixner, 2006; Lee, 2011)</u>

In SM the KIT receptor is frequently mutated and constitutively activated in a ligand-independent fashion. Murine BaF3 cells, which express several constitutively active oncogenic KIT mutants seen in SM patients, were used to assess the pharmacodynamic effect of midostaurin and to determine its effects on KIT auto-phosphorylation and STAT5 phosphorylation (Growney et al 2005). The results from this study showed that the phospho-signal was reduced at midostaurin concentrations of 10-50 nM.

In another study, the human mast cell lines HMC-1.1 and HMC1.2 were used to analyse the inhibitory effects of midostaurin on KIT receptor phosphorylation and proliferation (Gleixner et al 2006). Total inhibition of receptor phosphorylation was observed with 1 µM midostaurin in both cell lines.

One assay was performed using antibodies recognizing either phosphorylated forms of KIT-D816V or KIT-D816Y (Gleixner et al 2006). Midostaurin fully inhibited KIT-D816V phosphorylation at 1 µM, while imatinib was ineffective and nilotinib (AMN107) was only partially effective. Similar results were reported for KIT-D816V receptor phosphorylation and MITF expression by (Lee et al 2011).

In vivo studies

Anti-tumour activity of midostaurin against FLT3-ITD expressing MV4-11 cells in the s.c. xenograft model (RD-2014-00163)

The anti-proliferative activity of midostaurin against s.c. implanted human acute myeloid leukaemia FLT3-ITD expressing MV4-11 cells ($5x10^6$ cells/200µl) was investigated in female athymic nude mice. Ten days after inoculation, treatment was started with midostaurin at a daily p.o. dose of 5, 20, 50 and 150 mg/kg/10 ml. Treatment with 5 and 20 mg/kg of midostaurin resulted in reduced tumour growth throughout the experiment with a final % T/C of 53 and 42 respectively. This difference was not statistically significant. Whereas oral doses of 50 and 150 mg/kg resulted in a significant dose-dependent tumour regression throughout the experiment with final regressions of 58% and 100%, respectively. The anti-tumour activity was observed with doses which did not yield significant changes of body weight. However, one animal died in the group treated at 150 mg/kg. The cause of death is not stated in the study report.

Anti-leukemic activity of midostaurin in the bone marrow transplantation (BMT) model (Weisberg, 2002)

The *in vivo* anti-leukemic activity of midostaurin was investigated in Balb/c mice transplanted with murine bone marrow cells expressing FLT3-ITD (Weisberg et al 2002). This model is established at approximately 30 days post transplantation. Midostaurin or placebo (n=22/group) were dosed orally from day 30 to day 88 in trial 1 and from day 25 to day 68 in trial 2. Data collected included total and differential white blood cell counts, gross morphological features, and spleen weight. Organs from all animals were fixated and analysed for histological features of disease. The immune-phenotype of spleen cells of four animals from each group was also analysed. Midostaurin resulted in significant survival benefit versus placebo treated controls in two separate experiments ($p < 0.005$ and 0.009; log rank test). Mean spleen weight (401 mg) was significantly higher for placebo animals compared to midostaurin-treated mice (80 mg). Similarly, the mean white blood cell count for placebo animals was 25.8×10^6 /ml compared to 3.6×10^6 /ml for drug-treated animals. Histopathologic examination of the spleen showed that splenic architecture was effaced in the placebo mice by a marked expansion of red pulp comprised of maturing myeloid cells and scattered admixed megakaryocytes. The spleen displayed marked hyper-cellularity and myeloid hyperplasia consisting predominantly of mature granulocytic elements. In contrast, the drug-treated animals showed a partial recovery of splenic architecture, a reduction in myeloid hyperplasia, and a corresponding increase in the proportion of other hematopoietic lineages.

Drug levels in midostaurin-treated animals were analysed in selected animals at trial end. Blood samples were obtained from six mice sacrificed 8–12 hr after dosing, and showed mean concentrations of 0.954 µM, well above the *in vitro* anti-proliferative concentration range.

Anti-leukemic activity of midostaurin in a FLT3-ITD transgenic mouse model (Weisberg, 2008)

To investigate further the *in vivo* antitumor efficacy of midostaurin, a mouse model of acute leukaemia in which tumour burden was quantified by non-invasive imaging of luminescent leukemic cells was applied. Taconic Line NCr nude mice were inoculated with FLT3-ITD-BaF3 cells engineered to stably express firefly luciferase. Non-invasive imaging was used to assess leukemic burden, and mice with established leukaemia were divided into cohorts with similar disease burden. Midostaurin administered orally at a dose of 100 mg/kg, once daily was able to suppressed leukaemia burden in mice compared with vehicle-treated controls.

Therapeutic activity of midostaurin in a FLT3-ITD transgenic mouse model yielding B- or T-lymphoid disease (Lee, 2005)

Midostaurin was also studied in a transgenic mouse model in which FLT3-ITD was expressed under the control of the vav hematopoietic promoter. Most vav-FLT3-ITD transgenic mice developed a myeloproliferative disease (MPD) with high penetrance. A clonal immature B- or T-lymphoid disease was observed in two additional founder mice, respectively, that could be secondarily transplanted to recipient mice that rapidly developed lymphoid disease. Treatment of these mice with midostaurin resulted in suppression of disease and a statistically significant prolongation of survival.

Secondary pharmacodynamic studies

No secondary pharmacodynamic were submitted. Possible additional modes of action by midostaurin which were described in literature, including inhibition of anti-IgE-induced release of histamine in basophils and mast cells reversion of Pgp mediated multi drug resistance were presented. Midostaurin inhibits anti-IgE-induced release of histamine in basophils and mast cells at pharmacological concentrations, which can be of clinical importance in ASM/SM-AHN/MCL patients who are candidates for targeted drug therapy (Krauth, 2009). Reversion of Pgp mediated multi-drug resistance (MDR) by midostaurin can be caused by overexpression of Pgp (p-glycoprotein). Midostaurin has been found to revert the Pgp-mediated MDR phenotype by inhibiting the function of Pgp. A pro-apoptotic activity of midostaurin against both mutated and non-FLT3-mutated AML blast cells with Pgp expression was observed (Utz, 1998; Hunter, 2004).

Safety pharmacology programme

In vitro neurotransmitter effects in rat brain slices and brain homogenate (PKF 90-02620, non-GLP):

The effect of 10 µmol/L midostaurin on neurotransmitter release, 10 and 100 µmol/L midostaurin on neurotransmitter uptake and 1 mM midostaurin on phosphatidylinositol turnover was investigated in rat pre-labeled brain slices or brain homogenate. At 10 µmol/L [3H]noradrenaline (NA), [3H]serotonin (5-HT) and [3H]-dopamine (DA) were marginally decreased, whereas [3H]GABA and [3H]acetylcholine (ACh) were not affected. Midostaurin moderately inhibited (19%) the basal release of [3H]GABA at 10 µM and caused weak inhibition of uptake of [3H]NA, [3H]5-HT and [3H]GABA at 100 µM in rat mid brain synaptosomes. In addition, at 1mM midostaurin had no effect on the activity of 1,4,5-triphosphate 5-phosphatase and inositol monophosphate phosphatase.

In vivo CNS observation test, rotarod test, potentiation of ethanol-induced narcosis and motility in mice (PKF 90-02621, non-GLP):

Male Tif:MAGf (SPF) mice were exposed to 10, 30, 100, 300 or 1000 mg/kg midostaurin orally (n=4). Mice were observed up to 24 hours and behavioural alterations were scored. A marginal increase in ataxia was observed at 10-1000 mg/kg orally at 0.5-4 hours after exposure. In the rotarod assay, no significant differences were observed compared to control. At two hours after exposure, body temperature was significantly increased at 10 mg/kg and higher, which may be indicative of a potential CNS effect. Midostaurin did not have an effect on potentiation of ethanol induced narcosis. Finally, midostaurin did not have an effect on motility. Overall, midostaurin did not induce prominent behavioural alterations.

In vitro electrophysiology studies (Studies 0250111 (non-GLP), 0770504 (GLP), 0770505, (GLP)):

The effect of 12 µM midostaurin on hERG channel current expressed in HEK293 cells was tested using patch-clamp. Exposure to midostaurin resulted in an hERG tail current inhibition of 1.2%. Due to solubility of midostaurin, 12 µM was the highest feasible dose.

The effect of 0.34, 1.5 and 4.74 µM CGP52421 on hERG channel current expressed in HEK293 cells was tested using patch-clamp. Statistically significant inhibition of the hERG current was 16.5%, 38.5% and 26.4% at 0.34, 1.5 and 4.74 µM, respectively. The effect of 1.21 µM CGP62221 on hERG channel current expressed in HEK293 cells was tested using patch-clamp. Exposure to CGP62221 resulted in an hERG tail current inhibition of 11.3%. Due to solubility of CGP62221, 1.21 µM was the highest feasible dose.

The highest predicted total concentration of midostaurin, CGP52421 and CGP62221 in patients receiving 100 mg b.i.d of midostaurin was 8.7 µM (fu=0.087 µM), 4.8 µM (fu=0.048 µM) and 5.9 µM (fu=0.059 µM) respectively. The highest concentrations tested in-vitro in the hERG assay were approximately 138, 31 and 21-fold higher than highest concentrations (fu) of midostaurin, CGP52421 and CGP62221 in patients, respectively.

Additional *in vitro* cardiovascular studies in isolated organs (PKF-90-02622, non-GLP):

In isolated guinea-pig atria, midostaurin applied in single concentrations of 0.18, 1.8 and 18 µM had no consistent effects on either the force or the rate of contraction. In isolated perfused mesenteric vascular beds of the rat, midostaurin at 0.18 -18 µM produced concentration dependent inhibition of both noradrenaline and potassium chloride induced vasoconstriction (IC50's: 0.67 and 0.41 µM) suggesting relaxant effects which may partly explain the decreased blood pressure effects in rats at high intravenous doses. Midostaurin (1-30 µM) had no relaxant effects in isolated rabbit thoracic aorta rings pre-constricted with noradrenaline and angiotensin II.

In vivo cardiovascular and renal study in rats (PKF 90-02622, non-GLP):

Male rats (Tif:RAIf, SPF) were exposed for thirty minutes to 3, 8 or 25 mg/kg (0.10, 0.27, and 0.83 mg/kg/min) midostaurin intravenously or 300 mg/kg orally. Thirty minute infusions of 8 and 25 mg/kg decreased mean arterial pressure (31-47%) and heart rate (18-21%). Infusion of 2.5 mg/kg/min in rats induced severe hypotension and respiratory arrest and was lethal after 14 to 21 minutes of infusion (after total doses of 35-53 mg/kg). The oral dose of 300 mg/kg midostaurin had no effects on mean arterial pressure and heart rate during the 6-hour observation period. Oral administration of midostaurin (30 to 300 mg/kg) increased sodium and chloride excretion by about 100% and 50% respectively at doses of 100 and 300 mg/kg with no effects on urine volume or potassium excretion suggesting weak diuretic effects.

Pharmacodynamic drug interactions

Anti-proliferative activity of midostaurin was tested in combination with standard of care agents in the MOLM13 cell line by a resazurin based assay. Midostaurin was tested in fixed-ratio combinations with daunorubicin or cytarabine (Ara-C). These combinations were repeatedly yielding combination indices <1 over the most accurately defined dose/effect range.

2.3.3. Pharmacokinetics

The nonclinical absorption, distribution, metabolism and excretion (ADME) studies have been conducted in the same species and generally in the same strains as used in the toxicology studies. The pharmacokinetics (PK) of midostaurin (PKC412 or CGP41251) has been investigated upon single dose intravenous (IV) or oral (PO) administration. Multiple dose TK was examined upon daily intravenous and oral administration, which is the intended clinical route. The ADME information was obtained using rats, Beagle dogs, rabbits and cynomolgus monkeys (TK, IV only).

Specific and sensitive bioanalytical assays have been developed and validated for the quantitative determination of midostaurin in rat, monkey and dog plasma. The methods for quantitation of midostaurin utilized a common liquid/liquid extraction with tert-butylmethylether, followed by reversed phase liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) or an HPLC with fluorescence detection. Metabolites were characterized and quantified by HPLC with radioactivity detection and their chemical structures were elucidated by LC-MS/MS and, when possible, co-elution with non-radiolabelled standards.

Midostaurin PK parameters in plasma after a single oral dose in animal species and human and after a single IV dose in animals are displayed in Table 6 and Table 7 respectively.

Table 4: Midostaurin pharmacokinetic parameters in plasma (LC MS/MS) after a single oral dose in animal species and human

PK parameters	Rat	Rabbit	Dog	Human
p.o. dose (mg/kg) [a]	10	10	3	0.69 (50mg)
Tmax (h)	4-8	6.7	4.0	1.7 (median 1)
Cmax (ng/mL) [nM]	46.6 [81.8]	30.5 [53.5]	144 [252]	1210 [2120]
AUClast (ng·h/mL) [nM·h]	NR	731 [1280]	1640 [2870]	15200 [26700]
AUCinf (ng·h/mL) [nM·h]	946 [1660]	742 [1300]	1660 [2910]	15700 [27500]
Apparent terminal T1/2 (h)	10	15	9.6	20
Absorption (%)[b]	High (>90%)	Moderate (64%)	Moderate (40-47%)	High (>90%)
Bioavailability (%)	9.3	1.8	48.5	NR

[a] Doses were microemulsions.

[b] Absorption was estimated based on % metabolites of the dose detected in excreta together with the stability data of Midostaurin in faeces after an oral dose or based on the AUC ratio of radioactivity in blood or plasma.

Table 5: Midostaurin pharmacokinetic parameters after a single IV dose in animals

PK parameters	Rat (n=3)	Rabbit (n=1)	Dog (n=2)
i.v. dose (mg/kg)	1	2	0.5
Cmax (ng/mL) [nM]	1850 [3250]	144 [252]	1210 [2120]
AUClast (ng·h/mL) [nM·h]	NR	8280 [14500]	562 [985]
AUCinf (ng·h/mL) [nM·h]	1020 [1790]	8280 [14500]	570 [999]
Clearance, CL (L/h/kg)	0.98	0.24	0.90
Vss (L/kg)	1.20	1.36	3.77
Apparent T1/2 (h)	λ_1 0.5, λ_2 3.2	λ_1 0.2, λ_2 7.3	λ_1 0.9, λ_2 4.0

Repeated-dose TK of midostaurin was characterized in the toxicity studies conducted in the rat and beagle dog using daily oral dosing (Table 8).

Table 6. Toxicokinetic parameters of midostaurin in rats and dogs at steady state

Dose (mg/kg/day)	Species, Sex	Cmax (nM)	Tmax (h)	AUC [c] (nM·h)
3	Rat [a], M/F	73 / 116	1 / 1	385 / 423
10	Rat [a], M/F	147 / 246	2 / 2	1250 / 2350
30	Rat [a], M/F	385 / 778	1 / 8	4010 / 9280
1	Dog [b], M/F	55 /45	3 / 3	748 / 524
10	Dog [b], M/F	665 / 746	3 / 3	8400 / 7760

[a] Data represent overall mean of values at weeks 5, 26, and 52 (median for Tmax) and were rounded to 2 or 3 significant figures.

[b] Data represent overall mean of values at weeks 26 and 52 (median for Tmax) and were rounded to 2 or 3 significant figures.

[c] Predicted steady state AUC of midostaurin in AML and ASM patients was 75600 nM·h (50 mg b.i.d.) and 88200

Dose (mg/kg/day)	Species, Sex	Cmax (nM)	Tmax (h)	AUC [c] (nM·h)
nM·h (100 mg b.i.d.), respectively.				

Midostaurin showed a very high plasma protein binding in the rat, dog and human (>99%). The fraction unbound (Fu) was dependent on the measurement method, i.e. ~1.2% for rat, dog and human measured by ultrafiltration method and 0.10%, 0.08% and 0.01%-0.07% for rat, dog and human, respectively, as measured by equilibration gel filtration method. The binding was independent of concentration in animals. In human, a concentration dependent increase in Fu was observed, but the Fu of midostaurin did not appear to be concentration dependent at a clinically relevant steady state concentration range. At the clinically relevant midostaurin concentrations, Fu was 8-10-fold higher in rat and dog than in humans (0.01%). The two major metabolites of midostaurin, CGP52421 and CGP62221, showed a comparable, concentration dependent, protein binding similar as midostaurin in human plasma, but not in rat or dog plasma. At the (pre)clinically relevant concentrations, Fu of the metabolites (CGP52421 & CGP62221) was 0.02% & 0.04% in humans, 0.24% & 0.23% in rat and 0.20% & 0.19% in dog, which means a 2-4 fold higher free fraction than of midostaurin. Blood to plasma (B/P) ratio of midostaurin was not reported. [14C]-related radioactivity B/P distribution was 0.8 shortly after [14C]midostaurin dosing in the rat, suggesting low partitioning into red blood cells.

The *in vivo* tissue distribution of [14C]midostaurin was investigated in the rat (male, albino and pigmented) at 0.083h up to 168h post dosing, and assessed quantitatively by measuring radioactivity in homogenized tissues. Upon both oral and intravenous administration, radioactivity was quickly distributed to all tissues studied and tissue to blood ratio (T/B) was found to be higher than 1 for most tissues at 5 min post dose. The highest 14C-related radioactivity was found in organs or tissues involved in the absorption, metabolism and excretion such as the organs of the gastrointestinal tract, liver (T/B 40x) and kidneys (T/B 12-15x), but also in the brown fat (T/B 10-30x) and in glandular tissues such as the pancreas (T/B 9-11x) and the adrenal glands (T/B 12-30x). Exposure in these latter two tissues appeared also to be related to toxicological findings, which can be found in the toxicology section. At 168h post single dose administration of [14C]midostaurin, radioactivity was low but still measurable in blood and several tissues, especially in liver and kidney. Radioactivity from [14C]midostaurin crossed the blood brain barrier and the highest [14C]concentrations were seen in the frontal cortex. No melanin binding was observed but melanin containing tissues, like skin, were not measured in the pigmented rats. After repeated oral dosing of [14C]midostaurin to rats (18 days), the radioactivity levels in investigated organs and tissues increased, in line with blood levels, and approached steady-state levels, which were 2- to 10-fold higher than those after a single dose.

Based on the radioactivity tissue distribution in the pregnant rats studied by on gestation days 12 and 17, the drug related radioactivity was distinct and moderately distributed to the foetus with a 'whole foetus'-to-maternal blood ratio of 2 - 5 on GD 12 and 0.6 – 1.2 on GD 17. Radioactivity crossed the blood brain barrier and the foetal brain-to-maternal blood ratios ranged from 0.27 - 0.47 on GD 17. Upon oral dosing of 20 mg/kg [14C]midostaurin to pregnant rabbits (GD 17), the transfer of radioactivity was similarly distributed as in the rat. At 24h after dosing, the radioactivity was equal to maternal blood in foetal liver and 2-fold lower than that in the maternal blood in the whole foetus and foetal brain showing prolonged systemic exposure of the foetus to midostaurin. Following a single oral 30 mg/kg dose of [14C]midostaurin to lactating dams, [14C]midostaurin-related radioactivity was excreted into the milk with peak concentrations at 4 hours post dose.

Midostaurin was mainly eliminated by extensive oxidative metabolism in the rat, rabbit, dog and human. The primary biotransformation pathways observed in the ADME studies included mono-hydroxylation, O-demethylation, N-demethylation (human only) and amide hydrolysis (human only). O-demethylation and/or N-demethylation coupled with an extra hydroxylation led to the formation of

several additional metabolites. Other secondary biotransformation pathways involving the primary biotransformation products included di-hydroxylation, glucuronidation and glycine conjugation. In plasma, unchanged midostaurin was one of most abundant drug-related components found in all four species (22% in humans, 25% in rat, 41% in rabbit and in dog 57% of the total drug-related AUC), following a single oral dose of [14C]midostaurin. Circulating metabolites that were common to all species were P37.7 (epimer 1 of CGP52421, mono-hydroxylation metabolite on the pyrrolidinone moiety) and P39.8 (epimer 2 of CGP52421), accounting respectively for 5% & 33% in human, 20% & 37% in rat, 22% & 19% in rabbit and 22% & 4% in dog. The steady state plasma exposures of midostaurin and its two major metabolites, CGP52421 (epimer 1 plus epimer 2) and CGP62221 were higher in AML and ASM patients than those in rats, dogs, monkeys and rabbits. In AML patients, CGP52421 exposure increased to 3 – 8-fold the midostaurin exposure upon prolonged treatment. This is in line with the long apparent half-life of CGP52421 and CGP62221 in human (495 and 33 h, respectively). The total human/animal AUC ratios in the rat and dog, the general toxicology species, were higher for midostaurin (13 - 20 fold), CGP52421 (17 - 33 fold), and CGP62221 (71 fold), while the exposure of CGP62221 was not detectable in rat. Taking protein binding species differences into account, the free human/animal AUC ratios were 3.4 – 4.0 fold for midostaurin and 1.6 - 3.4 fold for CGP52421 in rat and dog and 13.8 fold for CGP62221 in dog. In excreta, following an IV or oral dose of [14C]midostaurin to the intact rat, rabbit, dog or human, midostaurin was extensively metabolized and excretion of radioactivity was primarily through the faecal route leaving 6.3%, 11.2% and 18.7% as unchanged midostaurin in rat, rabbit and dog respectively. In human, after oral administration, only 3.4% of the dose was detected as unchanged midostaurin in the faeces, with the remainder (74%) excreted as oxidative metabolites. Of the metabolites found in human faeces all were <6% of the administered dose, except for P29.6B (26.7%), which has both the O-demethylation and the pyrrolidinone hydroxylation modification.

The *in vitro* biotransformation of [14C]midostaurin by human liver slices, human hepatocytes or microsomes occurred mainly via oxidative pathways. This involved primary hydroxylation and O-demethylation pathways. The metabolic profiles of rat, dog, monkey, human liver slices and human hepatocytes incubations showed qualitative and quantitative differences. The biotransformation reactions observed *in vitro* were the same as those observed *in vivo* but the N-demethylation metabolites, which were found *in vivo* in humans, were not observed. The formation of hydroxylated and O-demethylated metabolites of midostaurin was predominantly catalysed by CYP3A4, with a very minor contribution of CYP1A1. No metabolism of midostaurin was noted *in vitro* with CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A5.

In all species the excretion of [14C]midostaurin-associated radioactivity was predominantly through the faecal (biliary) pathway, and, for the intact rat, rabbit and dog, it accounted for ~67% to 98% of the radioactivity dose while the urinary route contributed 0.7 - 2.1%. In bile duct-cannulated rats, excretion into the urine, faeces and bile was <1.6%, 9.8%, and 83.7% of the radioactivity dose, respectively, following intravenous administration indicating a predominant biliary clearance. Similarly, in humans, 77.6% of the administered radioactivity was found in the faeces while ~4.0% was excreted in the urine. After 7 and 20 days 71.2% and 77.6% of the administered single dose was recovered in human. This slow recovery may be related to the long half-life of the metabolites, such as CGP52421, which has a terminal half-life of 495h.

2.3.4. Toxicology

Single dose toxicity

The single dose toxicity studies with midostaurin were conducted in mice, rats and dogs as summarized in Table 9.

Table 7 Single dose toxicity studies with midostaurin

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
			Mouse	
936215 May 1994 GLP CIBA-GEIGY Ltd Basel Switzerland	Mouse, Tif MAGf Group 1: 1M Group 2: 5M. 5F	Oral, gavage Group 1:1280, Group 2: 2000	Observed maximum non-lethal dose: N.D. LD50: ±2000	**=1280:** **Mortality**:none **Overt symptoms :** No relevant findings Gross pathology: No relevant findings **=2000::** **Mortality:**3 M, 1F **Overt symptoms** ↓(transient) BW, ataxia, stiff and staggered gait, hunched posture, piloerection, ventral recumbency, dyspnea, ptosis, body cool to touch **Gross pathology:** No relevant findings
94016 Oct 1995 GLP CIBA-GEIGY Ltd Basel Switzerland	Mouse, Tif MAGf Group 1: 1M Group 2: 1F Group 3: 5M, 5F	Oral, gavage Group 1:1400 Group 2: 2000 Group 3: 2000	Observed maximum non-lethal dose: >2000 LD50: >2000	**=1400:** **Mortality**:none **Overt symptoms :** No relevant findings **Gross pathology :** No relevant findings **=2000** **Mortality:**1 M, 1F **Overt symptoms** ↓activity, abnormal gait and cool body (1 M) and poor general condition, ventral recumbency, dyspnea, and muscular hypotonia (1 F) **Gross pathology:** No relevant findings
946081 Nov 1995 GLP CIBA-GEIGY Ltd Basel Switzerland	Mouse, Tif MAGf Group 1: 1F Group 2: 5M, 5F	Intravenous injection Group 1:60 Group 2: 60	Observed maximum non-lethal dose: N.D. LD50: >60	**Mortality**: none **Overt symptoms** ↓activity, dyspnea, piloerection, cool body and hypersensitivity to touch **Gross pathology** No relevant findings
Rat				
926033 Sept 1993 GLP CIBA-GEIGY Ltd Basel Switzerland	Rat, Tif RAIF 5M, 5F	Oral gavage 1280	Observed maximum non-lethal dose: N.D. LD50: <1280 (F) LD50: >1280 (M)	**Mortality:** 4F **Overt symptoms** ↓BW, emaciation and depression (slight in M and moderate to severe in F) **Gross pathology** pulmonary edema and gastric haemorrhage in animals that died
936216 May 1994 GLP CIBA-GEIGY Ltd Basel Switzerland	Rat, Tif RAIF 5M, 5F	Oral gavage 1280	Observed maximum non-lethal dose: N.D. LD50: >1280	**Mortality:** none **Overt symptoms** No relevant findings **Gross pathology** No relevant findings

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
946040 Feb 1995 GLP CIBA-GEIGY Ltd Basel Switzerland	Rat, Tif RAIF Group 1: 1F Group 2: 1F Group 3: 5M, 5F Group 4: 5M, 5F	Intravenous injection Group 1: 10 Group 2: 0 Group 3: 10 Group 4: 0	Observed maximum non-lethal dose: ≥10 LD50: >10	**Mortality:** none **Overt symptoms** No relevant findings **Gross pathology** No relevant findings
			Dog	
92-6034 Sept 1993 GLP CIBA-GEIGY Ltd Basel Switzerland	Dog/Beagle 1F	Oral, capsules 120	Observed max non-lethal dose: >120 LD50: N.D.	**Mortality:** none **Overt symptoms** diarrhea, vomiting, and salivation (between 1 to 6h post-dose) Feces and vomit contained traces of the test compound. Transient reduction in food intake was observed (most pronounced 24h postadministration). **Gross pathology** No relevant findings
94-6041 March 1995 GLP CIBA-GEIGY Ltd Basel Switzerland	Dog/Beagle Group 1: 1F Group 2: 1F	Oral, capsules Group 1: 1 Group 2: 0	Observed max non-lethal dose: >1 LD50: >1	**Mortality:** none **Overt symptoms** **=1:** Transient clinical signs: head shaking, hyperemia, salivation, ventral recumbency, panting. **Gross pathology** No relevant findings

Repeat dose toxicity

An Overview of the repeat-dose toxicity studies with midostaurin is summarized in Table 10.

Table 8 Overview of the repeat-dose toxicity studies with midostaurin

Study ID	Species/Sex/ Number/Group	Route/ Dose (mg/kg/ day)	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
Mouse					
98-1021 June 1999 Dose-range finding Study Non-GLP Novartis, Basel, CH	Mouse/CD1 4/sex/dose	Oral gavage, 0, 10, 30, 100, 300 Batch: 840296 Vehicle: Gelucire 44/14	4 weeks	NA	**Mortality :** =100: 3 (misdosing) ; =300: 3 (poor condition), remainder euthanized **Overt Symptoms :** =300: ↓activity, ptosis, rough coat, deep respiration **Hematology: ≥10:** ↓WBC (F), PMN (F), ↓eosinophils (F), basophils (F) **≥30:** ↓WBC (M). ↓RBC (M). ↓PMN (M), ↓eosinophils (M), ↓basophils (M); **≥100:** slight anemia (M); **=300:** ↓lymphocyte, ↓eosinophils, ↓reticulocytes, ↑PMN **Serum chemistry: ≥30:** ↓cholesterol, ↑AST (M), ↑ALT, ↓triglyceride, ↓albumin **=300:** ↑creatine kinase (M), ↑K+(M) **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* =100: enlarged spleen + skin nodule (1M); =300: small thymus, small spleen, discolored cardiofundic junction of the stomach *Organ weights:* =300: ↑spleen (M) *Histopathology:* =300: Thymus+spleen: lymphoid atrophy, Bone marrow: depletion, Stomach: nonglandular ulcerations, Liver: centrilobular apoptotic changes
Rat					
90-6263 April 1991 Dose-range finding Study Non-GLP CIBA-GEIGY Ltd, Stamfort Lodge, UK	Rat/SD M/F: 5	Oral gavage, 0, 30, 100, 300 Batch 7 Vehicle: 0.5%aqeous Klucel HF	10 days	<30	**Mortality** =300: 2M, 2F (due to moribund condition) **Overt Symptoms** =300: ↓activity, ↓BW, ↓FC, liquid feces, extended abdomen, hunched posture, unkept fur, muscular hypotonus, diarrhea, chromorhinorrhea **Hematology** **≥100:** ↓WBC, ↓lymphocytes, ↑thrombocytes **=300:** ↓reticulocytes, ↓fibrinogen (M), ↓(slight) MCV (M), ↑PMN, ↓(slight) thrombocytes (M), ↓(slight) electrolytes **Serum chemistry : ≥30:** ↑AST, ↑ALT **=300:** ↓protein, ↓albumin, ↓α-1 globulin, ↓calcium, ↓ALP, ↓cholinesterase, ↓glucose, ↓cholesterine, ↓triglycerides, ↓sodium, ↓potassium **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* =300: Caecum: thickened walll *Organ weights:* ≥100: ↓thymus, =300: ↓spleen, ↓lungs (M), ↓kidneys, ↓heart, ↓liver (M), ↑adrenals *Histopathology* **≥100:** Caecum: epithelial atrophy/degeneration (1F) **=300:** Caecum: thickened wall, Bone marrow: hypocellularity, Spleen/liver: ↓hematopoiesis, Small/large intestine: mucosal degeneration, Liver: multifocal necrosis/inflammation (F)

Study ID	Species/Sex/Number/Group	Route/Dose (mg/kg/day)	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
94-6052 Dec 1994 Dose-exploratory Study Non-GLP Ciba-GEIGY Ltd, Basel, CH	Rat/SD Main Study M/F: 5 Tox-kinetics M/F: 6	Intravenous 0, 1, 3, 10 Vehicle: polysorbat 80, Myogliol 812, sojalecithin, lipoid S100, lactose	2 weeks	3	**Mortality:** none **Overt Symptoms :** **≥1:** ↓(transient) FC **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology: ≥10:** ↓lymphocytes, ↓reticulocytes **Serum chemistry: ≥10:** ↑(slight) albumin, ↓α-1 globulin **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* **≥10:** ↓(slight) thymus (M) *Histopathology:* **≥10:** Thymus: slight atrophy
95-6015 Sept 1996 Dose-exploratory Study GLP Ciba-GEIGY Ltd, Basel, CH	Rat/SD Main Study M/F: 10 or 15	Intravenous 0, 1, 3, 10 Vehicle: Aqueous polysorbat 80, Myogliol 812, sojalecithin, lipoid S100, lactose	3 months 1 month recovery	3	**Mortality:** none **Overt Symptoms :** **≥3:** irritation injection site **=10:** salivation **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology: ≥3:** ↓reticulocytes, ↑thrombytes (F) **=10:** ↓(slight) RBC, ↓Hb, ↓Hct, ↑(slight) MCV, ↓WBC, ↓lymphocytes, ↑fibrinogen, ↑thrombytes (M), ↑PTT(M), ↑TT **Serum chemistry: ≥3:** ↑cholesterol (F); **=10:** ↓protein, ↓albumin, ↑bilirubin (M), ↑cholinesterase (M) **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* **=10:** ↓thymus, ↑spleen (F), ↑liver (F) *Histopathology:* **≥1:** Mammary gland(M): ↓secretion, ↓proliferation ; **≥3:** Thymus: atrophy, Mesenteric lymph nodes: lymphoid depletion, Spleen: hemosiderosis
92-6036 Febr 1993 GLP CIBA-GEIGY Pharmaceuticals, Stamfort Lodge, UK	Rat/SD M/F: 5	Oral gavage 0, 10, 30, 100 Vehicle: aqueous Gelucire 44/14.	14 days	10	**Mortality:** 1F (dosing accident)) **Overt Symptoms : ≥30:** abdominal distension; **=100:** salivation, ↓BW gain (M), ↓FC **Hematology : ≥30:** ↓RBC, ↓WBC, ↓lymphocytes, ↓PMN **Serum chemistry: ≥30:** ↑AST, ↑ALT, ↑urea, ↓triglycerides; **=100:** ↑ bilirubin, ↓ALP, ↓cholesterol, ↓glucose, ↓phosphate (M), ↓protein, ↓albumin, ↓globulins, ↓triglycerides, ↓potassium, **Urinalysis: =100:** ↓ potassium **Pathology** *Gross pathology:* **=100:** GI tract: stomach and cecal distension, raised white areas in stomach, Heart: ↓size *Organ weights :* **=100:** ↓spleen, ↓thymus, ↓salivary glands, ↓heart, ↓kidneys, ↓liver (M), ↓prostate, ↓seminal vesicles, ↓uterus *Histopathology* **≥30:** spleen, mesenteric/axillary lymph nodes: lymphocyte depletion **=100:** GI tract: mucosal atrophy gastritis, erosion, ulceration and focal hyperkeratosis of the stomach and mucosal alterations of the small/large intestine, Lymphoid and hematopoietic systems: lymphocyte depletion absence of splenic extramedullary hematopoiesis Bone marrow: hypocellularity, ↑myeloid:erythroid ratio, Reproductive tract: uterine atrophy and ↓corpora lutea, degenerate spermatogonia, Pancreas: degranulation and atrophic acini, Salivary gland: atrophic and vacuolated acini. Adrenal glands: cortical hypertrophy, dilated zona reticularis sinusoids

Study ID	Species/Sex/Number/Group	Route/Dose (mg/kg/day)	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
92-6037 May 1993 GLP CIBA-GEIGY Pharmaceuticals, Stamfort Lodge, UK	Rat/SD <u>Main Study</u> M/F: 15 <u>Tox-kinetics</u> M/F: 6	Oral gavage 0, 10, 20, 30 <u>Vehicle:</u> aqueous Gelucire 44/14	3 months + 1 month recovery	10	**Mortality:** none **Overt Symptoms :** **≥20**: salivation **;** **=30**: ↓ BW **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology:** **=30**:↓Hb, ↓RBC, ↓PCV **Serum chemistry:** **≥20**: ↑(slight) AST, ↑(slight)ALT, ↑(slight)ALP (M) **Urinalysis:** **=30**: ↑urine volume (F). **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* **≥20**: ↑(slight) liver; **=30**: ↓thymus *Histopathology:* No remarkable findings
95-6016 June 1997 GLP Novartis, Summit US	Rat/SD <u>Main Study</u> M/F: 15 or 25 <u>Tox-kinetics</u> M/F: 5	Oral gavage 0, 30, 60, 100 (100 only for 3 weeks) <u>Vehicle</u>: aqueous Gelucire 44/14	26 weeks + 4 weeks recovery	<30	**Mortality :** **=0**: 1F, **=30**: 2M, **=60**: 1M, **=100**: 3M, 1F, all males euthanized at week 3 **Overt Symptoms** **≥30**: salivation, perineal staining (F) **≥60**: ↓BW (M), abdominal distention **=100**: perineal staining, ↓skin elasticity(dehydration), ↓FC **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology :** **≥30**:↓(slight) Hb, ↓(slight) Hct, ↓slight RBC, ↓(slight) eosinophils, ↓lymphocytes, ↑platelets **≥60**: ↓WBC, ↓PMN **Serum chemistry :** **≥30**: ↑AST, ↑ALT, ↓protein, ↓albumin ; **=100**: ↑globulin (F), ↑(slight)cholesterol (F) **Urinalysis:** **≥30**: ↓(slight)specific gravity. **Pathology** *Gross pathology:* **≥60**: uterine distension *Organ weights:* **≥30**: ↓thymus (M), ↓spleen (F) **≥60**: ↓thymus (F), ↓spleen (M), ↓liver (F) *Histopathology* **≥30**: <u>Thymus</u>: atrophy, <u>Mesenteric lymph nodes</u>: hemosiderosis, <u>Ovaries</u>: follicular distension, ↓corpora lutea; **≥60**: <u>Uterus</u>: luminal dilation **=100**: <u>GI tract</u>: mucosal alterations. <u>Bone marrow</u>: hypocellularity + haemorrhage (M), <u>Spleen + mesenteric lymph nodes</u>: lymphoid depletion (M), <u>Testes</u>: degeneration seminiferous tubules, <u>Epididymis</u>: sperma necrosis, <u>Seminal vesicle</u>: atrophy <u>Salivary gland</u>: acinar necrosis (M), <u>Adrenals</u>: cortical hypertrophy (M) <u>Pancreas</u>: atrophy, <u>Liver</u>: hepatocellular necrosis (F)
93-6281 Jan 1996 GLP CIBA-GEIGY Pharmaceuticals, Stamfort Lodge, UK	Rat/SD <u>Main Study</u> M/F: 35 <u>Tox-kinetics</u> M/F: 4	Oral gavage 0, 3, 10, 30 <u>Vehicle</u>: aqueous Gelucire 44/14	12 months + 4 weeks recovery (interim sacrifice at 6 months)	3	**Mortality** **=0**: 2M, 1F, **=3**: 2M, 3F, **=3**: 1M, 1F, **=30**: 3M, 4F **Overt Symptoms :** **≥10**: salivation **=30**: ↓BW (M) **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology :** **≥10**: ↓WBC, ↓RBC, ↓Hb, ↓Hct, ↓lymphocytes, ↑thrombocytes, ↓(slight) PTT, ↑fibrinogen (F) **Serum chemistry** **≥10**: ↑AST, ↑ALT, ↑ALP (M), ↑(slight) cholesterol (F), **=30**: : ↑AST, ↑ALT, ↑ALP, ↓(slight) triglyceride (M) **Urinalysis:** **=30**: ↑urine volume, ↓(slight) specific gravity **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* **=30**: ↑liver *Histopathology:* **=30**: <u>Bone marrow</u>: ↓cellularity, <u>Epididymides</u>: (slight) spermic debris
Rabbit					

Study ID	Species/Sex/ Number/G roup	Route/ Dose (mg/kg/ day)	Duration	NOEL/ NOAEL (mg/kg /day)	Major findings
96-6090 Nov 1996 Explorat ory Study Non-GLP CIBA-GEIGY Ltd Basel, CH	Rabbit/ Chinchilla Main Study/ Tox-kinetics M/F: 2	Oral gavage 0, 3, 10, 30 Vehicle: aqueous Gelucire 44/14	2 weeks	3	**Mortality:** none **Overt Symptoms :** No relevant findings **Hematology:** No relevant findings **Serum chemistry:** ≥10: ↓cholinesterase =30: ↑cholesterol, ↑triglycerides **Pathology** *Gross pathology:* =30: Liver: discoloration *Organ weights:* =30: ↑liver (1M) *Histopathology:* 30: Liver: fatty change, vacuolation, single cell degeneration
Dog					
94-6053 April 1995 Dose-range finding Study Non-GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main Study/ Tox-kinetics M/F:2	Intraveno us 0.6, 2, 6 Vehicle: Aqueous polysorbat 80, Myogliol 812, sojalecithi n, lipoid S100, lactose	2 weeks	N.D.	**Mortality:** none **Overt Symptoms** =0 and ≥0.6: hyperemia, salivation, deep respiration, diarrhea, emesis, decreased activity, somnolence ≥2: staggered gait or ventral recumbency **Hematology:** =0 and ≥0.6: normochromic-normocytic, anemia and leukopenia =6: reticulopenia **Serum chemistry:** =0 and ≥0.6: ↑ALT, ↑ALP, ↓(slight)protein, ↓(slight) albumin **Urinalysis:** No remarkable findings **Pathology** *Gross pathology* =6: inflammation at injection site *Organ weights:* ≥2: ↓prostate; =6: ↓testes *Histopathology:* ≥2: Epididymis: cellular debris =6: Testes: spermatic giant cells, Epididymides:moderate oligospermia
91-6023 Feb 1992 Explorat ory Study Non-GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main Study/ Tox-kinetics M/F: 1	Oral, capsules 60	10 days	N.A.	**Mortality:** none **Overt Symptoms :** emesis (F), diarrhea (F), ↓FC (F) **Hematology** ↓HCT, ↓RBC, ↓Hb, ↓lymphocytes **Serum chemistry:** ↑AST, ↓(lsight) protein, ↓albumin, ↑fibrinogen (M) **Urinalysis:** No remarkable findings **Pathology** *Organ weights:* =60: ↓thymus, ↓spleen (F) *Histopathology:* =60: Blood: abnormal RBC morphology (M)
92-6039 Febr 1993 Dose-range finding Study Non-GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main Study/ Tox-kinetics M/F: 1	Oral, capsules 60 Vehicle: Geluicire 44/14	2 weeks	N.A.	**Mortality**: none **Overt Symptoms** ↓(slight) BW (M) **Hematology:** ↓WBC, ↓(slight) Hb (M), ↓(slight) RBC (M), ↓(slight) Hct (M), ↓(slight) Hb (M)↓reticulocytes (M); ↓myelogram cell counts (M) **Serum chemistry:** ↑(slight) AST, ↓(slight) cholesterol, ↓(slight) protein **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* GI tract: red foci (M) *Organ weights:* No remarkable findings *Histopathology:* GI tract, bladder, heart: focal haemorrhage (M), Bone marrow: hypocellularity (M), Mesenteric lymph nodes: slight focal haemorrhage, Spleen: ↑hemosiderin, Thymus: atrophy (M)

Study ID	Species/Sex/Number/Group	Route/Dose (mg/kg/day)	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
92-6041 Aug 1993 GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main Study/ Tox-kinetics 3/sex/dose	Oral, capsules 0, 3, 10, 30 Vehicle: Geluicire 44/14	3 months + 1 months recovery	<3	**Mortality**: none **Overt Symptoms :** =30: emesis **Ophthalmology :** No remarkable findings **Electrocardiography :** ≥10: ↓heart rate, ↑PQ interval ; =10: AV block **Hematology:** ≥10: ↓(slight)RBC, ↓(slight) Hb, ↓(slight)Hct, ↓(slight)RBC,↓(slight) WBC (M), ↓(slight) PMN (M),; =30: ↓(slight) WBC, ↓(slight) PMN, **Serum chemistry:** ≥10: ↓(slight) protein, ↓(slight) albumin **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* ≥3: ↓(slight) testes, ↓(slight) epididymides, ↓(slight) prostate *Histopathology:* ≥3: : Testes: ↓spermatogenesis, Epididymides: oligospermia ≥10:, Epididymides: spermatic debris. Prostate: atrophy, Stomach: follicular lymphoid hyperplasia, Kidney: pyelitis
93-6198 Nov 1994 GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main Study/ Tox-kinetics 3M/dose	Oral, capsules 0, 0.3, 1, 3 Vehicle: Geluicire 44/14	3 months 2months recovery	3	**Mortality**: none **Overt Symptoms :** No remarkable findings **Ophthalmology :** No remarkable findings **Electrocardiography :** No remarkable findings **Hematology:** No remarkable findings **Serum chemistry** **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* No remarkable findings *Histopathology:* No remarkable findings
94-6003 Jan 1997 GLP CIBA-GEIGY Ltd Basel, CH	Dog/Beagle Main sudy/, Tox-kinetics M/F: 3	Oral, capsules 0, 1, 3, 10 Vehicle: Geluicire 44/14	12 months (interim at 6 months)	1	**Mortality:** =0: 1M **Overt Symptoms :** No relvant findings **Ophthalmology :** No relvant findings **Electrocardiography :** No relvant findings **Hematology :** =10: ↓Hb, ↓RBC, ↓Hct, ↓reticulocytes, ↓WBC, ↓PMN, ↓lymphocytes **Serum chemistry:** ≥3: ↑(slight) AST, ↑(slight) ALT, =10: ↓(slight) protein (M), ↓albumin, ↓(slight) urea **Urinalysis:** No remarkable findings **Pathology:** *Gross pathology* =10: ↓size (slight) testes *Organ weights:* =10: ↓(slight) spleen *Histopathology:* =10: Testes ↓spermatogenesis, epithelial vacuolation, Epididymides: oligospermia, cellular debris
Monkey					
95-6013 Aug 1995 Dose-range finding Study GLP Ciba Pharmaceuticals, Stamford Lodge, UK	Monkey/ Cynomolgus Main sudy/, Tox-kinetics M/F: 1	Intravenous Group 2: 4 → 8 → 12 Group 3: 8 Group4: 0 → 6	Group 2: 4 days/dose Group 3: 14 days Group 4: 14 days → 7 days	ND	**Mortality:** none **Overt Symptoms** **Group 2:** vomiting, salivation, struggling, vocalization, inappetence **Group 3:** salivation, vomiting, struggling **Group 4:** salivation and vomiting **Hematology: Groups 2 and 3:** ↓(slight) erythrocyte parameters, ↓(slight) leukocytes **Serum chemistry: Group 2 (8 and/or 12 mg/kg only):** ↓(slight) GGT, ↑(slight) ALT (M and F), ↑(slight) AST, ↓α-1 globulin **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* No remarkable findings *Histopathology:* No remarkable findings

Study ID	Species/Sex/Number/Group	Route/Dose (mg/kg/day)	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
95-6014 May 1996 GLP Pharmaceuticals, Stamford Lodge, UK	Monkey/Cynomolgus Main sudy, M/F: 3 Tox-kinetics M/F: 2 or 3	Intravenous 0, 0.6, 2, 6	3 months, 1 month recovery	2	**Mortality:** none **Overt Symptoms :** =6: injection site swelling + staining:, salivation, vomiting **Ophthalmology :** No remarkable findings **Hearing test :** No remarkable findings **Hematology:** =6: ↓Hb, ↓RBC, ↓Hct **Serum chemistry:** No remarkable findings **Urinalysis:** No remarkable findings **Pathology** *Gross pathology:* No remarkable findings *Organ weights:* =6: ↓testes *Histopathology:* No remarkable findings

Abbreviations: F=female; M=male; ↓=decreased; ↑=increased; Hct=hematocrit; Hb=hemoglobin; RBC= red blood cell count WBC=white blood cell count; PMN=neutrophils; BW=body weight; FC=food consumption; ALT=alanine aminotransferase; AST= aspartate aminotransferase; GGT=gamma-glumamyl transferase, GI=gastrointestinal, PCV=packed cell volumes; PTT= partial thromboplastin time; TT= thrombin time.

Genotoxicity

An overview of genotoxicity studies with midostaurin is presented in Table 11.

Table 9: Genotoxicity studies with midostaurin

Type of test (study ID)	Test system (strain)	S9	Concentration/Dose	Results	GLP
In vitro					
Ames test (AFP 59)	*S.typhimurium* (TA98, TA100, TA1537) *E.coli* (WP2 *uvr*A)	±	0-5000 µg/plate	Negative	No
Ames test(926113)	*S.typhimurium* (TA98, TA100, TA1537) *E.coli* (WP2 *uvr*A)	±	0-5000 µg/plate	Negative	Yes
Forward gene mutation (926298)	Chinese hamster V79 cells	±	0-200 µg/mL	Negative	Yes
Chromosomal aberration (926300)	CHO cells	±	0-25 µg/mL	Negative	Yes
In vivo					
Micronucleus test (926299)	Rat bone marrow	n.a	0, 50, 100, 200 mg/kg	Negative	Yes

Carcinogenicity

No carcinogenicity studies have been conducted (see non-clinical discussion).

Reproduction Toxicity

Table 10. Overview of the major findings of the reproductive and developmental toxicity studies

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
964123 Male and female fertility GLP	SD rat 24/sex/dose	Oral gavage 0, 10, 30, 60 mg/kg/day	M: 70 days prior mating F: 14 days	M: =60: General toxicity F Fertility: =60: ↓ pregnancy rate, implantation sites, live embryos, ↑ resorptions, pre- and postimplant	M and F Fertility: 30 mg/kg/day M

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
			prior mating – GD6	loss M fertility: ≥10: atrophy and degeneration of seminiferous tubules =60: ↓ sperm motility	reproductive organs: N.D.
936240 Embryo-fœtal development DRF - GLP	SD rat 10F/dose	Oral gavage 0, 3, 10, 30 mg/kg/dag	GD6 -17	=30: ↓ fetal weight	F0: 30 mg/kg/day F1: 10 mg/kg/day
936241 Embryo-fœtal development GLP	SD rat 24F/dose	Oral gavage 0, 3, 10, 30 mg/kg/dag	GD6 -17	≥3: ↑ resorptions, ↓ fetal weight =30: ureter kinked and dilated, severe renal pelvic cavitation, incomplete ossification, extra rib	F0: 30 mg/kg/day F1: N.D.
936242 Embryo-fœtal development DRF - GLP	NZW rabbit 8F/dose	Oral gavage 0, 10, 30, 75 mg/kg/day	GD7 -20	F0: ≥10: ↓ BW ≥30: Mortality F1: ≥30: Foetal weight	F0: N.D. F1: 10 mg/kg/day
936243 Embryo-fœtal development GLP	NZW rabbit 20F/dose	Oral gavage 0, 2, 10, 20 mg/kg/day	GD7 -20	F0: ≥10: ↓ water consumption, hypoactivity, ↓ BW =20: Mortality, pale placenta F1: ≥10: unossified metacarpels and astragalus =20: ↓ Fetal weight	F0 and F1: 2 mg/kg/day
0770270 Peri & postnatal GLP	SD rat 24F/dose	Oral gavage 0 5, 15, 30 mg/kg/day	GD6 – LD23	F0: ≥5: salivation =30: dystocia, ↓ live pups F1: =30: ↓ BW, accelerated complete eye opening and delayed auricular startle	F0 and F1: 15 mg/kg/day

Toxicokinetic data

At the maximum tolerated doses tested in animals, the systemic exposure (AUC) of midostaurin was 7- and 20- times lower (exposure multiple 0.15 and 0.05) than that in patients administered midostaurin at 50 mg bid or 100 mg bid respectively. Exposure of the two major human metabolites CGP52421 and CGP62221 was similarly much lower in animals than in patients. Protein binding was high across species (>99 %,) but higher in humans than in rats and dogs. When corrected for protein binding, the free drug concentrations of midostaurin and the metabolites in animals while slightly higher were still below those in patients (4 – 1.4 times lower for midostaurin). There are therefore no margins of safety for midostaurin when comparing animal exposures at the MTDs and human exposure at the clinical doses.

Local Tolerance

A number of iv tolerability studies were conducted in rabbits (studies 956134, 946042, 0970338). No local irritation was observed after 5 consecutive doses of 0.1% midostaurin. When administered as a single, 2-hour infusion at 0.179 mg/kg (suspended in PEG300, Polysorbate 80, ethanol and 5% glucose), phlebitis/ periphlebitis, thrombosis, haemorrhages, inflammatory cell infiltration in interstitium and oedema were recorded in both groups (midostaurin-treated and control) after dosing and were considered related to the application procedures in combination with the vehicle. The incidence of the thrombosis and haemorrhage was slightly higher in midostaurin-treated animals. On day 5 after administration, phlebitis/periphlebitis and inflammatory cell infiltration in interstitium

remained in both vehicle and midostaurin-treated groups whereas thrombosis and haemorrhage only remained in one animal each treated with midostaurin. There was a tendency for increased incidence and/or severity of these lesions in midostaurin-treated animals.

Other toxicity studies

The antigenicity of the midostaurin formulation was investigated in guinea pigs using active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA) tests *(study 93041)*. No signs of antigenicity due to antigen-antibody reaction were observed with midostaurin (ASA test), nor were antibodies specific to midostaurin detected in the PCA test. The results indicated that PKC412 did not cause either active systemic or passive cutaneous anaphylaxis reaction.

The phototoxic potential after po and iv administration midostaurin was evaluated in albino, hairless mice (2/sex/group) (study 936267). Mild skin reactions (very slight erythema and oedema) were seen only in the 300 mg/kg treated group after oral administration and UV-A irradiation or combined UV-A and UV-B irradiation. No skin reactions were seen after iv administration of PKC412 at doses up to and including 30 mg/kg, and UV-A irradiation of mice.

Repeated administration of 0.5% and 1% midostaurin ointment by instillation into the conjunctival sac of both eyes did not lead to ocular irritation in rabbits (study 15888-02), but led to ocular irritation and morphological changes in dogs (study 16025/02). The changes tended to be more pronounced with increasing concentrations of midostaurin. Single subconjunctival and retrobulbar injection of microspheres with up to 50% midostaurin in rabbits led to treatment-related irritation and morphological changes (study 15889/1/02). The changes tended to be more pronounced with increasing concentrations of midostaurin.

In vivo results of ocular irritation studies in beagle dogs (Study 15889/1/02) indicated that a midostaurin ointment was irritating in concentrations as low as 50 µg/eye. Similar concentrations were not irritating to rabbit eyes (Study 15888-02). The bovine corneal opacity (BCOP) assay used to in order to determine the risk of ocular irritation from low residue levels of midostaurin on the blistered capsules. The BCOP assay categorized midostaurin as a non-irritant at concentrations of 20 µg/ml to 2 mg/ml. Based on these results, the low levels of midostaurin residues (<80 µg/capsule) on capsules would not be expected to pose a risk of ocular irritation to handlers of midostaurin during clinical use (study 1570160).

Midostaurin appeared as a weak lymph node activator and weak skin irritant in the murine LLNA (tier I-study 0317010), leading to lymph node hyperplasia and skin irritation exceeding the applied thresholds. The finding was without statistical significance, and is therefore considered as an equivocal result. In LLNA tier II (study 0317017) no allergy-relevant changes were found on ear weight and draining lymph node hyperplasia and no changes in body weight were noted in the study. In conclusion, midostaurin was not a skin sensitizer in the murine LLNA (tier II).

Computational analysis showed the metabolites CGP52421 and CGP62221 are structurally similar to, midostaurin. Both metabolites were not mutagenic in an Ames test, with or without metabolic activation (studies 001647 and 001648).

The identified impurities 545-06 (desmethyl-PKC412, CGP62221), 513-03 (7-oxo-PKC412, CGP47772), 511-03 (staurosporine, CGP39360) and palmitoyl staurosporine are specified at a limit $\leq$ 0.10% in the drug substance.

2.3.5. Ecotoxicity/environmental risk assessment

Table 11. Summary of main study results

Substance (INN/Invented Name): midostaurin			
CAS-number: 120685-11-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117: unknown study type:	log K_{ow} 4.26 log K_{ow} 5.5	Potentially PBT: (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	2993 L/kg and 2095 L/kg	based on total radioactivity. Potentially B
Persistence	DegT50 soil	52, 48, 99 d	at 12°C
	DegT50 water:sediment	$DT_{50, system}$ = 463 d (r) $DT_{50, system}$ = >1000 d (p)	r=river; p =pond; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	TBD* 5 µg/L 14 µg/L	T
	CMR	not investigated	
PBT-statement :	Midostaurin is considered to be potentially PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC$_{surface water}$, refined	0.014	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated		(Y/N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	soil K_{oc} =162913 L/kg K_{oc} =248323 L/kg K_{oc} =190059 L/kg sludge K_{oc} = 75558 L/kg K_{oc} = 84194 L/kg K_{oc} = 15776 L/kg	Geomean used in risk assessment: $K_{oc,soil}$ 197373 L/kg, and $K_{oc,sludge}$ of 46472 L/kg.
Ready Biodegradability Test	OECD 301		waived
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ 845 d (r) $DT_{50\ system}$ 218 d (r) $DT_{50\ water}$ 166 d (p) $DT_{50\ system}$ >1000 d (p) Sediment shifting	r=river; p =pond DT_{50} values at 20°C. Significant shifting to

		30.8% to 91.4% (r) 30.9% to 95.3% (p)			sediment observed.

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	0.27	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	5.0	µg/L	Reproduction and growth
Fish, Early Life Stage Toxicity Test/ *Danio rerio*	OECD 210	NOEC	14.0	µg/L	Hatching, survival, body length and weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	respiration

Phase IIb Studies

Bioaccumulation/ *Oncorhynchus mykiss*	OECD 305	BCF	2993 2095	L/kg L/kg	%lipids:5 total radioactivity
Aerobic and anaerobic transformation in soil	OECD 307	DT50	24.4, 22.8, 46.6	d d d	20°C; <0.5%CO_2
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	EC10 EC10	>100 >100	mg/kg	
Terrestrial Plants, Growth Test/*Glycine max, Lycopersicon esculentum, Avena sativa*	OECD 208	NOEC	≥1000	mg/kg	mortality and dry weigh
Earthworm, Acute Toxicity Tests/*Eisenia fetida*	OECD 207	NOEC	≥1000	mg/kg	mortality
Collembola, Reproduction Test/*Folsomia candida*	ISO 11267	NOEC	≥1000	mg/kg	survival, reproduction
Sediment dwelling organism/ *Chironomus riparius*		NOEC	>416	mg/kg	normalised to 10% o.c.

2.3.6. Discussion on non-clinical aspects

Although midostaurin has a high binding affinity with a strong enzyme inhibition for FLT3 and KIT mutated receptors, it is not a very selective kinase inhibitor. This may explain unexplained effects in the repeated dose toxicology and human safety studies.

The CGP52421 and CGP62221 metabolites are present in human plasma at similar or higher concentrations compared to midostaurin and may contribute to safety issues. In addition, P33 (the O-demethylated and hydroxylated metabolite of midostaurin) is the most abundant (7.1%) of the four minor human metabolites which were not observed in animals. Kinase inhibition data showed that metabolite CGP62221 is comparable to or up to a factor 2 higher than the parent compound midostaurin. Midostaurin and CGP62221 can therefore be considered multi-kinase inhibitors with a similar potency for a range of kinases and metabolite CGP62221 is expected to contribute to the pharmacological and toxicological endpoints of this product. Kinase inhibition of CGP52421 is in general

less potent than midostaurin. Therefore, metabolite CGP52421 is expected to contribute less to pharmacology and toxicology of the product.

Due to dose limiting toxicity, clinical therapeutic exposure levels could not be reached in animals. All animal findings described below were observed at midostaurin exposure significantly lower than therapeutic levels (SmPC, section 5.3).

In vitro, midostaurin did not inhibit hERG channel activity up to the limit of solubility of 12 μM. The two major human metabolites GGP52421 and CGP62221 (also tested at the limit of solubility) inhibited hERG current with moderate safety margins (SmPC, section 5.3). Due to technical limitations in the hERG channel tests, higher concentrations could not be tested, but it can be assumed that stronger inhibition would occur at higher concentrations.

Safety pharmacology studies indicated that midostaurin is unlikely to interfere with vital functions of the central nervous system (SmPC, section 5.3).

The midostaurin hERG test and the *in vivo* rat cardiovascular safety pharmacology study are not considered to be conducted under GLP. Furthermore, individual data for the *in vivo* study is lacking, and this level of detail would have been preferred. However, due to the information on cardiovascular toxicity gained from repeated dose toxicity studies in dogs (prolongation of PQ interval with sporadic AV block) a possible risk for human cannot be ruled out. To further investigate cardiovascular effects of midostaurin, a clinical thorough QT study was performed (see clinical safety section). Despite the shortcomings in the non-clinical package, no further non-clinical studies are considered necessary.

No respiratory safety pharmacology studies were provided by the applicant. However pulmonary toxicity was observed in the juvenile rat toxicity studies following repeated doses of midostaurin at 15 mg/kg and was characterized by minimal to slight haemorrhage and minimal to moderate mixed cell infiltration in the lungs. The lung changes observed by histopathology correlated with pulmonary dark area(s) noted macroscopically. There were no treatment-related clinical signs. Pulmonary events in the clinic included pneumonitis and interstitial lung disease and were reported infrequently in both advanced SM and AML patients. The proportion of patients with pulmonary toxicity was low among patients with advanced SM and similar to placebo in AML patients in the clinical trials (see clinical safety section and RMP).

In the repeat dose studies in dogs, a decrease in heart rate, prolongation of the P-Q interval, and sporadically occurring atrioventricular blocks were seen in individual animals.

In the repeat dose studies, target organs for toxicity were the gastrointestinal tract (emesis in dogs and monkeys, diarrhoea and mucosal alteration), testes (decreased spermatogenesis), bone marrow (hypocellularity) and lymphoid organs (depletion/atrophy). The effect on the bone marrow and lymphoid organs was accompanied by haematological changes of decreased white blood cells, lymphocytes and erythrocytic parameters. An increase in liver enzymes (ALT and AST) was seen consistently in rats and in dogs and monkeys in long term studies of ≥ 3 months duration, without histopathological correlates (SmPC, section 5.3).

All these toxicological findings in rats and dogs are in line with observations from animal studies with other multi-kinase inhibitors like sunitinib, sorafenib, ponatinib and regorafenib. For midostaurin, leukopenia, pulmonary toxicity and cardiac dysfunction have been included in the RMP. Regarding pancreatitis, the data collected thus far in patients treated with midostaurin does not support a causal relation of midostaurin and pancreas toxicity (see clinical safety section). Effects including hyperglycemia, and adverse effects on the blood, lymphatic system, blood coagulation, gastrointestinal tract and the respiratory are adequately reflected in section 4.8 the SmPC. Additional measures are not needed from the nonclinical point of view.

In a fertility study in rats, midostaurin was associated with reduced fertility, testicular degeneration and atrophy, reduced sperm motility, oligo- and aspermia, increased resorptions, decreased pregnancy rate, number of implants and live embryos (SmPC, section 5.3).

In embryo-foetal development studies in rats and rabbits, increased numbers of late resorptions, reduced foetal weight and reduced skeletal ossification were observed (SmPC, section 5.3).

In a pre- and post- natal developmental study, maternal dystocia and reduced litter size, lower pup body weights, accelerated complete eye opening and delayed auricular startle ontogeny were noted .

In a toxicity study in juvenile rats, midostaurin was administered from days 7 to 70 postpartum. A reduction in body weight, haemorrhage and mixed cell infiltration in the lungs, and erythrocytosis/erythrophagocytosis in the mesenteric lymph nodes were seen. There were no effects on physical development, sensory function or behavioural function. Mating index, fertility index and conception rates were reduced at 0, 5 and 15 mg/kg/day, but not at 2 mg/kg/day (SmPC, section 5.3).

In vitro and *in vivo* genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of mutagenic or clastogenic activity (SmPC, section 5.3).

No carcinogenicity studies have been performed (SmPC, section 5.3). This approach is in line with the ICH S1A that no long-term carcinogenicity studies are required if the life-expectancy in the indicated patient populations is short. Patients with the ASM/SM-AHN/MCL indication have an overall median survival of 26 months. Patients with the AML indication have an overall median survival about 5 years but these patients receive also chemotherapy and may therefore have an increased risk for cancer.

Women of childbearing potential should be informed that animal studies show midostaurin to be harmful to the developing foetus. Sexually active women of child bearing potential are advised to have a pregnancy test prior to starting treatment with Rydapt and that they should use effective contraception (methods that result in less than 1% pregnancy rates) when using Rydapt and for at least 4 months after stopping treatment with Rydapt. It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception (SmPC, section 4.6). The impact of midostaurin on oral contraceptives after 28 days of treatment will be investigated by the applicant (see Risk Management Plan).

Midostaurin can cause foetal harm when administered to a pregnant woman. There are no adequate and well controlled studies in pregnant women. Reproductive studies in rats and rabbits demonstrated that midostaurin induced foetotoxicity. Rydapt is not recommended during pregnancy or in women of childbearing potential not using contraception. Pregnant women should be advised of the potential risk to the foetus (SmPC, section 4.6). Reproductive toxicity and developmental toxicity have been categorized as potential risks (see Risk Management Plan).

It is unknown whether midostaurin or its active metabolites are excreted in human milk. Available animal data have shown that midostaurin and its active metabolites pass into the milk of lactating rats. Breast feeding should be discontinued during treatment with Rydapt and for at least 4 months after stopping treatment (SmPC, section 4.6). The use of midostaurin during lactation has been categorized as potential risk (see Risk Management Plan).

There are no data on the effect of Rydapt on human fertility. Animal studies with midostaurin have shown impaired fertility (SmPC, section 4.6).

No melanin binding was observed but melanin containing tissues, like skin, were not measured in the pigmented rats. In phototoxicology study, however, no toxicological findings were reported, suggesting that if melanin binding occurred, this apparently has no toxicological consequences.

Environmental risk assessment studies have shown that midostaurin has the potential to be persistent, bioaccumulative and toxic to the environment (SmPC section 5.3). A risk to the groundwater, surface water, soil and sediment compartment and the STP following the use of midostaurin as prescribed, is not anticipated.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.3) and in the RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 12. Clinical studies in Advanced Systemic Mastocytosis (Advanced SM)

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
D2201	29/ Australia, Austria, Belgium, Canada, France , Germany, Netherlands, Norway, Poland, Turkey, United Kingdom, United States	Phase II, single arm, open-label, registration study	Midostaurin 100mg bid continuously for 6 cycles (of 4 weeks each)	Efficacy and safety in patients with ASM or MCL with or without AHNMD	116 (FAS; 111w,2b,1o, 2 missing)/ 89 (PEP; 86w,1b,1o, 1 missing)	Continuously until SM or AHNMD disease progression, intolerable toxicity, or non-compliance	76/40;		Overall response (ORR)
A2213	3/ United States	Phase II, proof-of-concept single arm, open-label study	Midostaurin 100mg bid up to 12 cycles (each cycle was 28 days in duration)	Efficacy and safety in patients with ASM/MCL ± AHNMD	26 (21w, 4o, 1 missing)	Continuously up to 12 cycles (each cycle was 28 days in duration). Any patient with a continued response after one year of therapy and without a requirement for any	15/11; Median 60.5 years Range: 24-79 years		Overall response (ORR)

Table 13. Tabular listing of clinical studies in acute myeloid leukemia (AML)

Study ID	Design	Study Posology	Study Objective	Subjs by arm entered	Duration	Gender M/F Age	Diagnosis Incl. criteria	Primary Eff. Endpoint
A2104	Phase II, proof-of-concept, single-arm	Midostaurin 75 mg x 3	Preliminary efficacy in patients, PD activity *in vitro*	Total: 20	Until disease progression/AE	14 / 6 Median age: 61.5y (29-78)	Relapsed / refractory AML or high-risk MDS, FLT3 mutated	Best clinical response
A2104E1	Phase II, proof-of-concept study of two midostaurin doses	Midostaurin 50 mg x 2 or 100 mg x 2	Preliminary efficacy in patients, PD activity *in vitro*	Total: 95 50 mg: 51 100 mg: 44	Until disease progression/AE	49 / 46 Mean age: 60.5 (20-94)	Relapsed / refractory AML or high-risk MDS, FLT3 mutated or WT	
A2104E2	Phase I/II, proof-of-concept, two arms (dose escalation and concomitant itraconazole)	Dose escalation: 100 mg to 600 mg/day Itraconazole arm: 100 mg x 2	Safety, tolerability, preliminary efficacy in patients, PD activity *in vitro*	Total: 29[a] Dose escalation arm: 16 Itraconazole arm: 13	28D cycles until disease progression/AE	Arm 1: 10 / 6 Arm 2: 5 / 8 Age: 12 < 65y 17 ≥ 65y	Relapsed / refractory AML or high-risk MDS, FLT3 mutated or WT	Best clinical response
A2106	Phase Ib, open-label study of midostaurin given sequentially or concomitantly with standard chemotherapy	Midostaurin 50 mg x 2 or 100 mg x 2	Safety, tolerability, efficacy	Total: 69 Sequential therapy: 34 Concomitant therapy: 35	28-42D cycles Induction: 1 cycle Consolidation: ≤3 cycles Continuation: ≤3 years	Arm 1: 17 / 17 Mean age: 46.0 (20-60) Arm 2: 17 / 18 Mean age: 45.1 (23-65)	De novo AML, FLT3 mutated or WT	Investigator CR
A2301	Phase III, randomised 1:1, double-blind, midostaurin vs. placebo in combination with standard CT followed by single-agent maintenance therapy	Midostaurin 50 mg x 2	Efficacy, safety, PK	Total: 717 Midostaurin arm: 360 Placebo arm: 357	28D cycles Induction: up to 2 cycles Consolidation: 4 cycles Continuation: 12 cycles	Arm 1: 174 / 186 Arm 2: 145 / 212 Mean age: 45.2 (18-60)	Newly diagnosed FLT3 mutated AML	OS, not censored for SCT
ADE02T	Phase II, single-arm, before and after alloHSCT or high-dose cytarabine	Midostaurin 50 mg x 2	Efficacy, safety	-	Induction: 1-2 cycles á 28 days Continuation: 1 year	18-70 years	Newly diagnosed FLT3-ITD AML	EFS Ongoing study
A2114	Phase I/II, open-label, dose-escalation study	Midostaurin 30 or 60 mg/m^2 bid	Safety, tolerability, PK	Total: 22	Until disease progression/AE	Arm 1: 2 / 5 Arm 2: 5 /10 Mean age: 7.1 (0.5-17.1)		

a. Two patients were recruited from the study A2104E1.
b. Abbreviations: CT = chemotherapy; CR = complete response; EFS = event free survival; OS = overall survival.

2.4.2. Pharmacokinetics

An overview of all clinical pharmacology studies and studies with a PK component is provided in Table 16.

In addition, population pharmacokinetic analyses were performed separately for ASM/SM-AHN/MCL and AML and separately for midostaurin and its two active metabolites, with the aim to characterize the concentration-time relationships. A physiologically based pharmacokinetic modelling (PBPK) was performed to predict the outcome of drug-drug interaction with midostaurin and metabolites' clinical exposure following single and multiple dosing scenarios.

Table 14. Clinical pharmacology studies with midostaurin

Study No.	Phase	Study Objective	Population /FPFV	No. of Subjects/patients	Treatment Duration	Medication (midostaurin) dose and day (n)	Type of control
Studies in healthy subjects							
Biopharmaceutics (BA/BE/food effect studies)							
CPKC412A2108	1	(r)BA study of midostaurin following a single oral dose of 50 mg given as CSF, FMI or oral solution formulations.	Healthy subjects /12-Dec-2007	CSF:18 FMI:18 Oral solution: 18	Single dose	50 mg	N/A
CPKC412A2111	1	Effect of food on the PK of the FMI capsule, BA of midostaurin FMI and oral solution formulations in fed state	Healthy subjects / 15-Oct-2010	FMI fasted:13 FMI standard meal:12 FMI high- fat meal:13 Oral solution standard meal:12	Single dose	50 mg	N/A
Pharmacokinetic studies							
CPKC412A001	1	Single-dose PK, dose proportionality safety and tolerability	Healthy subjects / 19-Sep-1994	18	Single dose	1, 4, 12.5, 25 mg	Placebo
CPKC412A2107	1	Absorption, distribution, metabolism and excretion (Mass Balance)	Healthy subjects / 25-Feb-2004	6	Single dose	50 mg ^{14}C-midostaurin	NA
Special Safety Studies							
CPKC412A2113	1	Dedicated QT study, placebo and active control	Healthy subjects / 31-Mar-2008	Midostaurin: 80 Moxifloxacin: 44 Placebo: 68	3 days	Midostaurin or Placebo: 75 mgtwo times daily on Days 1 and 2 Midostaurin or Placebo:75 mg once daily on Day 3 Moxifloxacin or Placebo: 400 mg (Avelox®)	Placebo Moxiflox acin (Avelox®)
Drug-Drug interaction studies							
CPKC412A2109	1	Drug-drug interaction study between ketoconazole and single-dose midostaurin	Healthy subjects / 24-Sep-2008	47	10 days	50 mg-single dose midostaurin (Day 6) 400 mg once daily ketoconazole or placebo for 10 days	Placebo
CPKC412A2110	1	Drug-drug interaction study between rifampicin and single-dose midostaurin	Healthy subjects / 06-Oct-2009	47	14 days	50 mg-single dose midostaurin (Day 9) 600 mg once daily rifampicin or placebo for 14 days	Placebo
CPKC412A2112	1	Drug-drug interaction study between midostaurin and single-dose midazolam	Healthy subjects / 07-Jan-2010	20	4 days	100 mg once daily then 50 mg twice daily for 3 days of midostaurin (Day 3 to 6) 4 mg of midazolam (Day 1, Day 3 and Day 8)	N/A
Studies in special populations							
CPKC412A2116	1	PK, Safety and tolerability of midostaurin in subjects with hepatic impairment, compared to healthy control subjects	Healthy subjects and patients with mild, moderate and severe hepatic impairment / 07-Mar-2011	Severe: 0, ongoing Mild: 10 Moderate: 7 HV: 13	7 days	50 mg bid from day 1 to Day 6, 50 mg single dose on Day 7	Age and weight matched healthy subjects
CPKC412A1101	1	Single-dose pharmacokinetics, safety and tolerability of midostaurin in Japanese Subjects	Healthy Japanese subjects / 28-Aug-2012	40; 8 subjects at each dose level	Single dose	25 mg, 50 mg, 75 mg, 100 mg, Placebo	Placebo
CPKC412A2114	1/2	Pediatric PK, safety, tolerability of midostaurin monotherapy	Pediatric AML patients / 21-Sep-2009	22	Until unacceptable toxicity or progressive disease	30 mg/m² bid (7 patients) 60 mg/m² bid (15 patients)	N/A
Studies in patients							

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Study No.	Phase	Study Objective	Population /FPFV	No. of Subjects/patients	Treatment Duration	Medication (midostaurin) dose and day (n)	Type of control
CPKC412A002	1b	PK, safety and tolerability of midostaurin	Patients with advanced tumors / 31-Jul-1995	32	Until unacceptable toxicity or progressive disease	12.5 mg once daily (3 patients), 12.5 mg twice daily (3 patients) 25 mg bid (3 patients) 50 mg bid (3 patients) 75 mg bid (4 patients) 75 mg tid (9 patients) 100 mg tid (7 patients)	N/A
C-99-PKC412-001	1	PK, safety and tolerability of midostaurin	Patients with diabetes mellitus / 28-Aug-1999	86	28 days	25 mg bid (13 patients) 50 mg bid (13 patients) 75 mg bid (14 patients) 75 mg tid (15 patients) 100 mg tid (9 patients) Placebo (19 patients)	Placebo
CPKC412A006	2	PK, safety and tolerability of midostaurin	Patients with stage III-IV chronic lymphocytic leukemia or non-Hodgkin's lymphoma / 14-May-1997	21	14 days	25 mg qd (7 patients) 75 mg bid (7 patients) 75 mg tid (7 patients)	N/A
Studies in advancedAdSM patients							
CPKC412A2213	2	PK, safety and tolerability of midostaurin monotherapy	Patients with advanced systemic mastocytosis and MCL / 27-Jun-2005	26	Until unacceptable toxicity or progressive disease	100 mg bid	N/A
CPKC412D2201	2	PK, safety and tolerability of midostaurin monotherapy	Patients with advanced systemic mastocytosis / 06-Jan-2009	Stage 1: 63 Extension: 53	Until unacceptable toxicity or progressive disease	100 mg bid	N/A
Studies in AML patients							
CPKC412A2104	2	PK, safety and tolerability of midostaurin monotherapy	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3 / 29-Jan-2002	Core: 20	Until unacceptable toxicity or progressive disease	75 mg tid	N/A
CPKC412A2104E1	2	PK, safety and tolerability of midostaurin monotherapy	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3 / 27-Mar-2003	E1: 95	Until unacceptable toxicity or progressive disease	50 mg bid (51 patients) and 100 mg bid (44 patients)	N/A
CPKC412A2104E2	2	PK, safety and tolerability of midostaurin monotherapy or combination with itraconazole	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3 / 21-Aug-2003	E2: 29	Until unacceptable toxicity or progressive disease	Arm 1: intra-dose escalation up to 300 mg bid (16 patients) Arm 2: midostaurin (100 mg for 2 days followed by 50 mg bid) combination with itraconazole: (13 patients)	N/A
CPKC412A2106	1b	PK, safety and tolerability of twice daily oral dosing of midostaurin administered in combination sequentially and concomitantly with daunorubicin and cytarabine for consolidation.	Patients with newly-diagnosed FLT3+ AML / 01-April-2003	69	Until relapse, or for up to 3 years from the time of diagnosis, in the absence of safety concerns	100 mg bid (29 patients) 50 mg bid (40 patients)	N/A
CPKC412A2301 (CALGB 10603)	3	Study of induction (daunorubicin /cytarabine) and consolidation (high-dose cytarabine) chemotherapy of + midostaurin or placebo	Newly diagnosed patients <60 years of age with FLT3 mutated AML / 03-Jul-2008	714	18 months	50 mg bid	Placebo

Source: Individual CSRs, FPFV: first patient first visit

Absorption

The absolute bioavailability of midostaurin from oral formulation could not be estimated because the study A2120 was terminated due to severe adverse event occurred in the first subject with the treatment of midostaurin intravenous infusion (grade 4 anaphylactic reaction).

In the mass-balance study A2107 (with oral solution, single dose of 50 mg under fasting conditions) oral absorption of midostaurin was rapid with peak plasma concentrations being observed at 1-3 h post dose. The oral absorption was estimated to be high following administration of a single dose of 50 mg midostaurin since only 3.4% of the parent was found in the faeces and the compound was stable in the gut. Since the total radioactivity recovered in the urine was only 4.0% of the dose, it was not possible to estimate the absorption based on the urinary data.

Study A2111 was conducted to investigate the effect of food on pharmacokinetics of midostaurin and the active metabolites for FMI formulation, and to also compare the absorption of midostaurin in FMI and oral solution under fed conditions. The study was designed as a single dose (50 mg) open-label, randomised, four parallel groups study in healthy subjects under three conditions i.e. fasting (for FMI), fed with a standard meal (for FMI and oral solution) and with a high fat meal (for FMI). A standard meal was defined as a 450 calorie breakfast consisting of 25% fat, whereas high fat meal was about 9000-1000 calorie breakfast. In total 50 subjects were enrolled in the study: 12 each in FMI [fed-standard] and oral solution [fed-standard] treatment groups and 13 each in FMI [fed-high] and [fasted] treatment groups respectively. The rate of absorption of midostaurin and its metabolites was decreased (Cmax ratio: 0.73, (90% CI: 0.59 - 0.90)) while the extent of absorption was increased (AUCinf ratio: 1.59 (90% CI: 1.22 - 2.08)) when administered with high-fat meal as compared to fasted conditions (Table 17). The absorption was delayed by 1.5 hours. The effect of a standard meal on the PK of 50 mg midostaurin was of a lower magnitude from that of a high-fat meal. After a standard meal, the Cmax of midostaurin decreased by 20% and the AUCinf increased by 22%, while the median Tmax was delayed by 1 hour as compared to fasting conditions.

Table 15. Food effect: summary of statistical analysis of primary PK parameters for capsule – Study A2111

	AUCinf			AUC0-t			Cmax			Tmax		
	Ratios (90% CI)			Ratios (90% CI)			Ratios (90% CI)			Difference (Range)		
Comparison	Mido staur in	C622 21	C524 21	Mido staur in	C622 21	C524 21	Mido staur in	C622 21	C524 21	Mido staur in	C622 21	C524 21
[high fat]: [fasted]	1.59 (1.22 ; 2.08)	1.37 (1.09 ; 1.73)	1.24 (0.74 ; 2.09)	1.60 (1.23 ; 2.08)	1.30 (1.07 ; 1.58)	1.10 (0.88; 1.37)	0.73 (0.59 ; 0.90)	0.85 (0.76 ; 0.95)	0.77 (0.67; 0.90)	1.50 (0.50 ; 2.00)	2.03 (1.00 ; 4.00)	3.00 1.02; 5.02)
[fed-standard]: [fasted]	1.22 (0.94 ; 1.60)	1.17 (0.93 ; 1.48)	1.50 (0.90 ; 2.49)	1.22 (0.94 ; 1.59)	1.13 (0.93 ; 1.37)	1.11 (0.89; 1.39)	0.80 (0.64 ; 0.98)	0.91 (0.81 ; 1.02)	0.92 (0.79; 1.06)	1.00 (0.50 ; 2.00)	1.51 (0.02 ; 2.02)	2.03 (1.00; 3.00)

In clinical studies, the efficacy and safety of Rydapt were investigated following administration with a light meal. After oral administration of a single 100 mg dose of midostaurin under fed conditions in ASM, SM AHN and MCL patients, AUC_{inf}, Cmax and T_{max} were 49600 ng*h/ml, 2940 ng/ml and 3 h, respectively, for midostaurin. For CGP52421, AUC0-12h and Cmax were 2770 ng*h/ml and 299 ng/ml, respectively. AUC_{0-12h} and C_{max} for CGP62221 were 8700 ng*h/ml and 931 ng/ml, respectively. After 100 mg bid multiple oral doses

of midostaurin the Cmin,ss plasma midostaurin in AML and ASM, SM-HN, MCL patients were 919 and 1060 ng/ml, respectively. The CGP62421 $C_{min, ss}$ in the AML and the ASM, SM-AHN, MCL population were 1610 ng/ml and 2020 ng/ml, respectively. The CGP52421, $C_{min,ss}$ in the AML and the ASM, SM-AHN, MCL population were 8630 ng/ml and 2860 ng/ml, respectively (SmPC section 5.2).

Distribution

Midostaurin has a tissue distribution of geometric mean of 95.2 l (Vz/F). Midostaurin and its metabolites are distributed mainly in plasma rather than red blood cells. *In vitro* data showed midostaurin is more than 98% bound to plasma proteins, such as albumin, α1 acid glycoprotein (AGP) and lipoprotein (SmPC, section 5.2).

Elimination

Midostaurin is metabolised by CYP3A4 mainly via oxidative pathways. The major plasma components included midostaurin and two major active metabolites, CGP62221 (via O demethylation) and CGP52421 (via hydroxylation), accounting for 27.7±2.7% and 38.0±6.6%, respectively, of the total plasma exposure at 96 hours after a single 50 mg dose of midostaurin (SmPC, section 5.2).

The median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.5, 32.3 and 482 hours. The mean apparent plasma clearance (CL/F) was 2.4-3.1 l/h in healthy subjects. In AML and ASM, SM-AHN and MCL patients, population pharmacokinetic estimates for clearance of midostaurin at steady state were 5.9 l/h and 4.4 l/h, respectively. The Human Mass Balance study results indicated that faecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose), while unchanged midostaurin accounts for 3% of the dose. Only 4% of the dose is recovered in urine (SmPC, section 5.2).

Dose proportionality and time dependencies

Dose proportionality

Table 16. Dose proportionality analysis for midostaurin after a single dose

Parameter (unit)	Total daily dose range (mg)	Equivalence bound	Estimate of beta	90% CI Lower	90% CI Upper
AUC0_inf (ng*hr/mL)	25 - 100	(0.84 - 1.16)	0.964	0.711	1.217
AUC0_12h (ng*hr/mL)	25 - 100	(0.84 - 1.16)	1.045	0.921	1.168
Cmax (ng/mL)	25 - 100	(0.84 - 1.16)	0.87	0.756	0.985

Results are based on the power model with fixed effect for race: ln(parameter) = alpha + beta ln(dose)+ error.

Table 17. Dose proportionality analysis for CGP62221 and CGP52421 after a single dose in dose range of 25 to 100 mg

Analyte	Parameter (unit) Equivalence bound	AUC0_12h (ng*hr/mL) Estimate of beta (90% CI)	Cmax (ng/mL) Estimate of beta (90% CI)
CGP62221	(0.84 - 1.16)	0.944 (0.860; 1.027)	0.861 (0.781; 0.941)
CGP52421	(0.84 - 1.16)	1.101 (1.018; 1.184)	1.036 (0.950; 1.123)

Results are based on the power model with fixed effect for race: ln(parameter) = alpha + beta ln(dose) + error.

Time dependencies

In Study A2213, 23 ASM/MCL patients were included, and each patient received 100 mg b.i.d. midostaurin for up to 12 cycles (one cycle = 28 days). For the multiple dose PK, the geometric mean plasma concentrations of midostaurin accumulated notably during at least the first 3 days of the dosing cycle, reaching a peak concentration (peak C_{trough}) of 2649.03 ng/mL (CV%=72.59%). On Cycle 1 Day 8, the geometric-mean pre-dose concentrations decreased to 1828.21 ng/mL, (CV%=97.5%). The levels continued to decline up to 760.46 ng/mL (CV% = 21.61%) towards the end of the cycle (Day 28 pre-dose). The concentrations of the metabolite CGP62221 showed the same type of PK pattern as the parent over the first cycle with an initial concentration accumulation. The geometric mean peak Ctrough 3256.75 ng/mL (CV% =51.44%) was observed at Day 8 followed by a decrease up to 1812.02 ng/mL (CV%=17.67%) at Day 28 pre-dose. In contrast, the geometric plasma concentrations of CGP52421 increased steadily over the dosing cycle till the last day of sampling. The geometric mean peak plasma concentrations were reached on Day 28 pre-dose (3379.41 ng/mL ± 13.64).

In study D2201, midostaurin, CGP62221 and CGP52421 showed time-dependent kinetics. Following daily dosing (100 mg b.i.d.), midostaurin and CGP62221 metabolite plasma concentrations accumulated notably in the first 3-6 days in ASM/MCL patients. Thereafter their levels declined substantially, until reaching a plateau after 22 days of treatment. The geometric mean plasma concentrations of midostaurin accumulated notably during the first 3 days of the dosing cycle, reaching a pre-dose peak concentration (peak C_{trough}) of 2762.16 ng/mL (CV% =59.52%) which thereafter declined towards a steady state ($C_{trough\ SS}$) value of 1122.77 ng/mL (CV% =66.66%) at Day 28.

The concentration-time profile of the metabolite CGP62221 showed the same pattern as the parent compound with an initial accumulation reaching a geometric mean peak concentration (peak Ctrough) of 3194.15 ng/mL (CV% =45.11%) at Day 8 followed by a decrease to 2113.47 ng/mL (CV%=43.87%) at Day 28.

The geometric mean plasma concentrations of CGP52421 increased steadily over the dosing cycle until reaching a plateau on Day 28, with a geometric Cmin of 2518.50 ng/mL (CV%=39.06) (study A2213).

In study A2104E1 in AML patients, the doses of 100 mg b.i.d. and 50 mg b.i.d. were used in two groups of the patients respectively. The PK profile of midostaurin and both active metabolites were shown in the figures below (100 mg b.i.d. up to 6 cycles and 50 mg b.i.d. up to 4 cycles).

Determination of steady state and accumulation ratio

Based on the statistical analysis presented in Table 20 and Table 21 (ASM/MCL Studies: D2201 (100mg b.i.d.), A2213 (100mg b.i.d.); and AML study A2104 E1 (50mg b.i.d. and 100mg b.i.d.)), steady state is reached after one month of treatment (by C2D1 = Day 29) for midostaurin and CGP62221. The CGP52421 steady-state was reached after one month of treatment in the ASM/MCL population, whereas for AML patients, the concentrations were observed to continue to increase until C3D1. However, CGP52421 concentrations are not available beyond this time point from pooled data.

Analyses were performed for the individual concentrations of moieties, for patients from single agent studies who received no CYP3A4 medication.

Table 18. summary of statistical analysis for midostaurin and CGP62221 plasma Cmin over time for patients in single agent studies receiving no CYP3A4 perpetrators.

Visit	Comparison(s)	n*	Adjusted geo-mean	Geo-mean ratio	Treatment comparison 90% CI Lower	Upper
Midostaurin						
C2D1		78	978			
C2D15	C2 D15 / C2 D1	44	915	0.935	0.833	1.050
C3D1	C3 D1 / C2 D1	58	896	0.916	0.825	1.017
CGP62221						
C2D1		79	1480			
C2D15	C2 D15 / C2 D1	44	1400	0.942	0.865	1.025
C3D1	C3 D1 / C2 D1	58	1410	0.954	0.883	1.030

Table 19 summary of statistical analysis for midostaurin and CGP52421 plasma Cmin over time for patients in single agent studies receiving no CYP3A4 perpetrators.

Indication	Visit	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Treatment comparison 90% CI Lower	Upper
AML	C2 D1	32	6030				
	C3 D1	16	7890	C3 D1 / C2 D1	1.309	1.016	1.686
AdSM	C2 D1	44	2850				
	C2 D15	40	2910	C2 D15 / C2 D1	1.020	0.960	1.084
	C3 D1	39	2890	C3 D1 / C2 D1	1.012	0.950	1.078

Special populations

Based on population pharmacokinetic analyses no significant impact of age on the pharmacokinetics of midostaurin and its two active metabolites was identified for patients aged between 65 and 85 years. In adult patients with ASM, SM-AHN and MCL or AML, no midostaurin dose adjustment is required based on age (SmPC section 5.2).

Table 20. PK studies in elderly population

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
AML patients (non-RATIFY)	43/180	27/180	2/180
ASM patients	49/141	16/141	0/141
Total	92/321	43/321	2/321

The pharmacokinetics of midostaurin in paediatric patients were explored in a phase I dose escalation monotherapy study with 22 patients (12 aged 0-2 years and 10 aged 10-17 years) with AML or MLL-rearranged ALL using a population pharmacokinetic approach. The pharmacokinetics of midostaurin were less than dose proportional with the doses of 30 mg/m^2 and 60 mg/m^2 after single and multiple doses. Due to the limited pharmacokinetic data in paediatric patients, no comparison with midostaurin pharmacokinetics in adults can be made (SmPC section 5.2).

Based on population pharmacokinetic model analyses of the effect of gender on clearance of midostaurin and its active metabolites, there was no statistically significant finding and the anticipated changes in exposure (<20%) were not deemed to be clinically relevant. No midostaurin dose adjustment is required based on gender (SmPC section 5.2).

There are no differences in the pharmacokinetic profile between Caucasian and Black subjects. Based on a phase I study in healthy Japanese volunteers, pharmacokinetic profiles of midostaurin and its metabolites (CGP62221 and CGP52421) are similar compared to those observed in other pharmacokinetic studies conducted in Caucasians and Blacks. No midostaurin dose adjustment is required based on ethnicity (SmPC section 5.2).

A dedicated hepatic impairment study assessed the systemic exposure of midostaurin after oral administration of 50 mg twice daily for 6 days in subjects with baseline mild or moderate hepatic impairment (Child Pugh Class A or B, respectively) and control subjects with normal hepatic function. The maximum concentration was reached between 2 and 3 hours after administration after single or repeated doses for all groups. On day 1, the AUC0 12 and Cmax were 8130 ng*h/ml and 1206 ng/ml, respectively, for healthy subjects. AUC0 12 was decreased by 39% and 36% in subjects with mild and moderate hepatic impairment, respectively. On day 7, AUCCtrough (exposure under the curve of Ctrough from day 1 to day 7) was 5410 ng*h/ml in healthy subjects and was decreased by 35% and 20% in subjects with mild and moderate hepatic impairment, respectively. AUCtau was decreased by 28% and 20% on day 7, respectively. Finally, the long term data from patients were analysed using a population pharmacokinetic approach. No impact of hepatic impairment could be identified in patients with mild or moderate hepatic impairment in the ASM, SM AHN, MCL and AML populations (SmPC section 5.2).

Overall, there was no clinically relevant increase in exposure (AUC) to plasma midostaurin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. The pharmacokinetics of midostaurin have not been assessed in patients with baseline severe hepatic impairment (Child-Pugh Class C) (SmPC section 5.2).

Renal elimination is a minor route of elimination for midostaurin. No dedicated renal impairment study was conducted for midostaurin. Population pharmacokinetic analyses were conducted using data from clinical studies in patients with AML (n=180) and ASM, SM-AHN and MCL (n=141). Out of the 321 patients included, 177 patients showed pre-existing mild (n=113), moderate (n=60) or severe (n=4) renal impairment (15 ml/min ≤ creatinine clearance [CrCL] <90 ml/min). 144 patients showed normal renal function (CrCL >90 ml/min) at baseline. Based on the population pharmacokinetic analyses, midostaurin clearance was not significantly impacted by renal impairment and therefore no dosage adjustment is necessary for patients with mild or moderate renal impairment (SmPC section 5.2).

Pharmacokinetic interaction studies

In vitro

The potential of midostaurin, CGP62221 and CGP52421 to inhibit human CYP enzyme activity was assessed (reports R0300937, R0300937b, R0300937c, R0900508 and R1500784). Time-dependent inhibition of CYP3A4/5 by midostaurin, CGP52421, and CGP62221 was observed (Table 23).

Table 21. Summary of CYP inhibition by midostaurin, CGP52421 and CGP62221

CYP Enzyme	Probe reaction	IC_{50} value[a] (µM)		
		Midostaurin	CGP52421	CGP62221
CYP1A2	phenacetin *O*-deethylation	~ 3	~45	~1.5
CYP2A6	coumarin 7-hydroxylation	> 100	> 100	> 100
CYP2B6	bupropion hydroxylation	~ 100	> 100	> 100
CYP2C8	paclitaxel 6α-hydroxylation	~ 5	~15	~5
CYP2C9	diclofenac 4'-hydroxylation	~ 0.5	~30	<1
CYP2C19	*S*-mephenytoin 4'-hydroxylation	> 100	>100	~100
CYP2D6	bufuralol 1'-hydroxylation	~ 1	~5	>100
CYP2E1	chlorzoxazone 6-hydroxylation	~ 0.5	>100	>100
CYP3A4/5	midazolam 1´-hydroxylation	~1.5 [b]	~1.5	<1
CYP3A4/5	testosterone 6β-hydroxylation	>100 [b]	~2	~1

[a] Concentration producing 50% inhibition of probe substrate metabolism; values not corrected for microsomal protein binding.
[b] Performed at high (~5%) organic solvent concentration due to poor solubility

Pregnane X receptor transcriptional activation by midostaurin, CGP62221 and CGP52421, in comparison to the positive control, rifampicin, was assessed in a CYP3A4 reporter gene assay (report R0400365). Midostaurin, CGP62221 and CGP52421 were found to activate reporter gene suggesting that all compounds can act as *in vivo* inducers of CYP3A. The induction potential of midostaurin, CGP52421 and CGP62221 to induce the mRNA and activity levels of CYP enzymes, UGT1A1, and the mRNA levels of P-gp and MRP2 *in vitro* was evaluated in human hepatocytes prepared from three separate donor livers. Midostaurin, CGP52421 and CGP62221 induced mRNA levels of several CYP enzymes and transporters (CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2J2, CYP3A4, CYP3A5, UGT1A1 and MRP2) that may result in decreased exposure to co-administered compounds (report R0700598).

Midostaurin uptake into human hepatocytes was shown to be mainly via passive diffusion and not facilitated by the major hepatic uptake transporters (report R1200335).

The potential for midostaurin to inhibit P-glycoprotein (P-gp, MDR1, ABCB1), the human breast cancer resistance protein (BCRP, ABCG2) and multidrug resistance associated protein 2 (MRP2) was examined (reports R0300018 and R0900746). Partial inhibition of P-gp and BCRP activities was observed by midostaurin suggesting a potential for midostaurin to affect the pharmacokinetics of P-gp and BCRP substrates *in vivo*. Midostaurin was shown not to inhibit MRP2 activity.

The potential interaction of midostaurin with efflux proteins was also examined following transport studies across confluent Caco-2 (report R0900809) and LLC-PK1/MDR1 (report R1300627) cell monolayers. No evidence for P-gp- or MRP2-mediated transport was apparent in these studies.

The potential of midostaurin, CGP62221 and CGP52421 to inhibit the transport activities of the organic anion transporting polypeptide 1B1 (OATP1B1) or organic anion transporting polypeptide 1B3 (OATP1B3) were examined (reports R1200326 and R1500741). Midostaurin, CGP62221 and CGP52421 more potently inhibited OATP1B1 transport activity compared to OATP1B3 suggesting a potential effect on the pharmacokinetics of co-medications whose clearance is significantly mediated by OATP1B1.

The potential inhibitory effect of midostaurin, CGP52421, and CGP62221 on the activity of human renal organic anion transporters 1 (OAT1) and 3 (OAT3) was examined (reports R1200327 and R1500678). Midostaurin, CGP62221 and CGP52421 had little effect on the activity of either transporter suggesting that clinical concentrations due to OAT1 and OAT3 inhibition are unlikely.

The potential inhibitory effect of midostaurin, CGP52421 and CGP62221 on the activity of organic cation transporter (OCT) 1 and OCT2, multidrug and toxin extrusion transporter (MATE) 1, or MATE2-K was examined (reports R1200410, R1200637 and R1500735). Midostaurin, CGP52421 or CGP62221 had little effect on the transport activity of OCT1, OCT2 and weakly inhibited transport mediated by MATE1 or MATE2-K.

In vivo

Study CPKC412A2109 was an open-label, randomized, parallel group study to evaluate the impact of the strong CYP3A4 inhibitor ketoconazole, administered to steady-state, once daily at 400 mg for 10 days, on the pharmacokinetics of a single oral 50 mg dose of midostaurin in healthy subjects. Summary of statistical analysis of primary PK parameters are shown in Table 24.

Table 22. Summary of statistical analysis of primary PK parameters: DDI with ketoconazole - study CPKC412A2109

Comparison: Ketoconazole/placebo[1]	AUCinf Ratios (90% CI)	AUC0-t Ratios (90% CI)	Cmax Ratios (90% CI)	Tmax Difference (Range)
Midostaurin	10.42 (7.46; 14.56)	6.10 (4.96; 7.51)	1.83 (1.63; 2.05)	0.5 (0.0; 0.5)
CGP62221	3.51 (2.48; 4.98)[3]	0.994 (0.815; 1.21)	0.562 (0.482; 0.656)	114.0 (92.8; 116.0)
CGP52421[2]	Not available	1.21 (0.954; 1.54)	0.490 (0.415; 0.579)	116.7 (93.9; 117.9)
Exposure to the sum of active moeties	2.25 (1.32; 3.84)	3.57 (3.01; 4.23)	1.56 (1.39; 1.75)	-

[1] Ketoconazole 400 mg Day 1 to Day 10 + midostaurin 50 mg Day 6
[2] CGP52421 data was generated using a different method compared to the other studies.
[3] CGP52421 shows a long elimination half-life in human subjects, therefore estimation of its AUC0-inf was excluded from statistical analysis.
AUCt= AUC0-120

In study CPKC412A2104E1 a total of 29 patients with AML/MDS were enrolled to explore the safety, tolerability, PK, and preliminary clinical efficacy of the two regimens consisting of an itraconazole combination arm, and the intra-patient dose escalation arm described below. In order to increase the plasma exposure of midostaurin, two strategies were explored. One study arm investigated the impact of intradose escalation, while another arm, investigated the impact of co-administration of the strong CYP3A4 inhibitor itraconazole on the exposure of midostaurin. The ratio of PK parameters for midostaurin and the metabolites CGP62221 and CGP52421 on day 21 and day 28 of administration are summarized in **Table 25**.

Table 23. Ratio of PK parameters on day 21 and day 28 in itraconazole combination arm — study CPKC412A2104E2

Analyte	Ratio AUCtau,D28/AUCtau,D21 (n)	Ratio Cmin,D28/Cmin,D21 (n)	Ratio Cmax,D28/Cmax,D21 (n)
Midostaurin	1.63 (7)	2.09 (7)	1.49 (7)
CGP62221	0.865 (5)	1.16 (7)	0.941 (7)
CGP52421	1.20 (6)	1.33 (7)	1.22 (7)
Exposure to the sum of active moeities	1.13 (7)	1.18 (7)	1.16 (7)

In a pooled analysis across ASM and AML patients receiving midostaurin as single-agent therapy, a 2.7-fold increase of midostaurin exposure (Cmin) at steady-state upon co-administration with strong CYP3A4 inhibitors was observed. When exposure to the sum of active moieties was investigated, the geometric mean Cmin increased by 76% upon co-administration with CYP3A4 inhibitors.

Study CPKC412A2110 was an open-label, randomized, parallel group study to evaluate the impact of the strong CYP3A4 inducer rifampicin administered to steady-state, once daily at 600 mg for 14 days, on the pharmacokinetics of midostaurin administered as a single oral 50 mg dose in healthy subjects. Summary of statistical analysis of primary PK parameters are presented in Table 26.

Table 24. Summary of statistical analysis of primary PK parameters: DDI with rifampicin — study CPKC412A2110

Comparison: Midostaurin + Rifampicin/Midostaurin	AUCinf Ratios (90% CI)	AUClast Ratios (90% CI)	Cmax Ratios (90% CI)	Tmax Difference (Range)
Midostaurin	0.06 (0.05; 0.07)	0.06 (0.05; 0.07)	0.27 (0.23; 0.31)	-0.48 (-0.50; -0.02)
CGP62221	0.08 (0.06; 0.09)	0.08 (0.06; 0.09)	0.63 (0.56; 0.70)	-1.50 (-2.00; -1.50)
CGP52421	NA	0.41 (0.36; 0.46)	0.65 (0.59; 0.72)	-0.98 (-1.47; 0.00)
Exposure to the sum of active moieties	0.097 (0.080; 0.117)	0.091 (0.076; 0.109)	0.351 (0.307; 0.402)	-

Midostaurin +Rifampicin= rifampicin 600 mg once daily plus midostaurin 50 mg once daily; Midostaurin = placebo plus midostaurin 50 mg once daily
AUClast= 144 h

When midostaurin was co-administered with rifampicin, the geometric mean Cmax and AUClast values decreased by 73% and 94% reduction, respectively, compared to the placebo arm. The geometric mean apparent elimination half-life of midostaurin decreased from 23 hours to 5.1 hours in the presence of rifampicin. The geometric mean of apparent clearance (CL/F) increased by approximately 16.9-fold, from 2.2 mL/min to 37.1 mL/min. Similarly, exposure to both active metabolites decreased. The Cmax of CGP62221 and CGP52421 decreased by 37% and 35%, respectively. The AUClast of CGP52421 and CGP62221 decreased by 92% and 59%, respectively. The apparent elimination half-life also decreased. The extent of decrease for the sum of active moieties was similar to that reported for individual moieties.

In this study (CPKC412A2110) CYP3A4 induction was assessed by endogenous biomarkers 6β-hydroxycortisol to cortisol ratio and/or 4β-hydroxycholesterol. The circulating plasma level of the metabolite 4β-hydroxycholesterol increases when CYP3A4 is induced by a strong inducer and in urine, the ratio of cortisol and its metabolite 6β-hydroxycortisol has been established as a method of evaluating CYP3A4 induction. Pre-treatment of subjects for 9 days with clinically relevant doses of rifampicin was associated with a notable

increase in the plasma concentration of 4β-hydroxycholesterol and in the ratio of 6β-hydroxycortisol/cortisol excreted in urine. These increases are evidence of CYP3A4 enzyme induction.

The effect of CYP3A4 inhibitors and inducers on midostaurin and metabolites has been evaluated using the Simcyp model (report R1500784-01), using *in vitro* data and PK data from six clinical trials: CPKC412A2108, control arms from CPKC412A2109 and CPKC412A2110, CPKC412A2111, CPKC412A2113 and CPKC412A2116. The simulation results suggested that DDI effects at steady-state levels would be lesser in magnitude compared to those following the administration of a single midostaurin dose.

In the Phase 3 AML pivotal trial CPKC412A2301, most patients received concomitant antifungal therapy, including strong, moderate and mild CYP3A4 inhibitors. An analysis was performed to determine the impact co-administration of strong CYP3A4 inhibitors on drug exposure and total circulating activity, compared to all other patients, *i.e.* those who received other concomitant medications, including mild and moderate CYP3A4 inhibitors. In patients who received concomitant strong CYP3A4 inhibitors, midostaurin concentrations were 1.44-fold higher compared to all remaining patients in the study, and the overall change in exposure to the sum of active moieties was estimated to be 1.22-fold (Table 27).

Table 25 Summary of statistical analysis of plasma Cmin versus CYP3A4 medication for midostaurin and the active metabolites and total exposure in study CPKC412A2301 (50 mg bid in combination)

Analyte	n*	m	CYP3A4 medication	Adjusted Geo-Mean	Comparison	Treatment Comparison 90% CI		
						Geo-Mean Ratio	Lower	Upper
Midostaurin	252	112	No strong CYP3A4 inhibitor	1330	Strong CYP inhibitor vs. no Strong CYP3A4 inh			
	113	55	Strong CYP Inhibitor	1910		1.44	1.17	1.77
TOTEXPO AML	253	109	No strong CYP3A4 inhibitor	3490	Strong CYP inhibitor vs. no Strong CYP3A4 inh			
	114	56	Strong CYP Inhibitor	4250		1.22	0.988	1.5
CGP62221	252	112	No strong CYP3A4 inhibitor	1660	Strong CYP inhibitor vs. no Strong CYP3A4 inh			
	114	56	Strong CYP Inhibitor	1580		0.951	0.826	1.1
CGP52421	253	109	No strong CYP3A4 inhibitor	1960	Strong CYP inhibitor vs. no Strong CYP3A4 inh			
	114	56	Strong CYP Inhibitor	2170		1.11	1	1.23

n*- number of evaluable samples

m – number of subjects with non-missing values.

TOTEXPO AML: potency adjusted exposure to the sum of active moieties with AML potencies

A significant effect of concomitant use of strong CYP3A4 inhibitors on midostaurin clearance was identified in the AML population PK analysis (Population pharmacokinetics of midostaurin and its metabolites in Acute Myeloid Leukemia Modeling Report). The analysis showed that patients with strong CYP3A4 inhibitors had approximately the double of the exposures compared to those who were not on concurrent inhibitors.

Study CPKC412A2112 was an open label, single-arm study to evaluate midostaurin as a perpetrator of CYP3A4-mediated drug interactions. Single doses (4 mg each) of the sensitive substrate of CYP3A4, midazolam, were administered on day 1 (reference day), day 3 (assessment of acute inhibition), and day 8 (assessment of induction) with washout at day 2 and a resting day at day 7.

When co-administered with midostaurin, the geometric mean Cmax for midazolam and 1'-hydroxymidazolam decreased by 9% and 25%, respectively, on day 8 when compared to day 1. The average decrease in AUCinf was 5% for midazolam and 24% for 1'-hydroxymidazolam. The PK of midazolam or its metabolite 1'-hydroxymidazolam was not affected in a clinically meaningful manner following four dosing days of midostaurin in healthy subjects. The dose of midazolam was administered only after four dosing days of midostaurin and not at steady-state. Therefore the possibility of midostaurin being a CYP3A4 inducer cannot be excluded from this study.

In the the Simcyp model (report R1500887-01) also the effect of midostaurin, CGP52421 and CGP62221 on the pharmacokinetics of midazolam (sensitive CYP3A4 substrate) was predicted. It predicted an overall weak induction effect at steady-state.

Study CPKC412A2106 was a Phase 1b combination study of midostaurin administered sequentially and concomitantly with daunorubicin and cytarabine in AML patients. The effect of midostaurin on the PK of daunorubicin and cytarabine was assessed by comparing plasma levels of daunorubicin and cytarabine in sequential versus concomitant dosing schedules. Summary of daunorubicin PK parameter comparison, alone versus combined with midostaurin, is presented in Table 28.

Table 26. Summary of daunorubicin PK parameter comparison (alone versus combined with midostaurin) from study CPKC412A2106

Daunorubicin PK parameters (adj.geomean)	Midostaurin 100 mg bid			Midostaurin 50 mg bid		
	Concomitant arm (n=11)	Sequential arm (n=7)	conc:seq Geometric mean ratio [90%CI]	Concomitant arm (n=16)	Sequential arm (n=14)	conc:seq Geometric mean ratio [90%CI]
AUC0-24 (ng.h/mL)	140	328	0.43 [0.16-1.12]	206	210	0.98 [0.56-1.69]
Cmax (ng/mL)	80.9	180	0.45 [0.23-0.86]	97.1	89.3	1.09 [0.63-1.86]

Exposure to daunorubicin (AUC and Cmax) seemed to decrease approximately 2-fold in the presence of midostaurin 100 mg bid, while no variation of daunorubicin concentrations was seen in the presence of midostaurin 50 mg bid.

In some studies, CYP3A4 induction by midostaurin was assessed by endogenous biomarkers 6β-hydroxycortisol to cortisol ratio. In study CPKC412A2112 pre-treatment of subjects with midostaurin at clinically relevant doses (100 mg once daily followed by 50 mg twice daily for 3 days) for 4 days was not accompanied by any notable changes in the plasma concentration of 4β-hydroxycholesterol or in the ratio of 6β-hydroxycortisol/cortisol excreted in urine. In study CPKC412A2116, in the normal hepatic function group, the median 6β-hydroxycortisol/cortisol ratio was 4.41 at baseline and 6.02 on day 7. This increase following multiple dosing could be related to CYP3A4 induction by midostaurin. In study CPKC412D2201 analysis of the urinary 6β-hydroxycortisol to cortisol ratios on days 1, 3, 8, 15, 22 and 28 of cycle 1, and day 15 of cycle 2 did not show any induction of CYP3A4 by midostaurin and its metabolites with no significant changes in the geo-mean ratio across time points.

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies were submitted.

Primary and Secondary pharmacology

In a phase II study of midostaurin monotherapy in AML or high-risk MDS with FLT3 mutated disease (PKC412A2104), FLT3 inhibition was measured in patients' bone marrow and peripheral blood cells. No formal analysis could be conducted in this study as PD data were available for only 7 patients. Evidence of FLT3 inhibition (defined as greater than 30% decrease in activity from baseline) within 4 hours of midostaurin treatment was observed in 3 patients. Specifically, the percent decreases were 45%, 5%, 68%, 18%, 19%, 39%, and 4%. These findings could not be related to treatment response, as no responses (complete or partial) were observed in this trial.

No clinical pharmacodynamic data are provided in relation to the ASM indication.

A dedicated QT/QTc study (PKC412A2113) a phase I, randomised, double-blinded, placebo and active controlled three-way parallel study to investigate the effect of midostaurin on cardiac intervals in 192 healthy subjects. Twelve-lead digital ECGs were obtained in triplicate at 9 time points over 24 hours at the same relative time during baseline (Day -1) and on study Day 3, and at 2 time points on Day 1. Midostaurin or matching placebo was administered orally at 75 mg b.i.d. on days 1 and 2 and q.d. on day 3. Moxifloxacin 400 mg tablets or placebo was administered orally o.d. on day 3.The maximum mean change in QTcF from baseline for midostaurin, compared to placebo, occurred at 24 hours post-dose on day 3 and was 0.715 ms and the upper bound of the 90% CI was 4.707 ms, which excluded 10ms. At day 3, mean (SD) Cmax values of midostaurin, CGP62221 and CGP52421 were 2273.3 (710.28), 1882.0 (432.47) and 1248.6 (208.36) ng/mL, respectively. Due to its short duration, this study was not meant to address directly the longacting metabolite CGP52421, which accumulates over 3 to 4 weeks. Therefore, the change from baseline in QTcF with the concentration of midostaurin and both metabolites was further explored in the Phase 2 study D2201 in AdSM.

Analyses were conducted between the exposure of midostaurin, CGP62221 and CGP52421, and QTcF interval using a time-matched concentration-QTcF change model. These analyses suggested no increase in QTcF change with increasing exposure of midostaurin, CGP62221 or CGP52421 (corresponding to QTcF slope estimates of -2.2817, -3.2888 and 0.1693 ms per ng/mL respectively).

The effect of pharmacokinetic exposure of midostaurin, CGP62221 or CGP52421 was studied in relation to various clinical endpoints, including CR, DFS, EFS and OS. No significant associations were found for midostaurin and CGP52421 C1D21 PK on CR. There was a slight positive effect of CGP62221 exposure on response, suggesting a higher probability of response with higher CGP62221 exposure. A 50% decrease in CGP62221 (corresponding to a reduction from 50 mg b.i.d. to 25mg b.i.d.) exposure corresponded to a ~29% reduction in the odds of response (OR: 0.71; 90%CI: 0.525-0.951). No relationship was observed for the sum of active moieties and response. No significant association was observed between midostaurin, CGP62221, and CGP52421 concentrations at C1D21 of induction therapy and EFS. Also no significant

associations were observed between midostaurin, CGP62221 or CGP52421 concentrations on Day 1 of Cycle 8 of the continuation phase and OS or DFS. No significant association was observed between midostaurin or CGP52421 concentrations at C1D21 of induction therapy and OS in Study A2301. However, higher concentrations of CGP62221 were associated with a better OS (HR=1.37; 95% CI: 1.08-1.74, for a 2-fold decrease of CGP62221; p=0.009). Also, a trend towards increased OS was seen for higher midostaurin concentrations (HR for 2-fold decrease in midostaurin concentration 1.18 (95%CI: 0.98-1.43; p=0.083).

The impact of midostaurin exposure (ASM/SM-AHN/MCL indication), was evaluated on BOR, DOR, serum tryptase level, and MCs. No significant exposure-efficacy relationship was found between the Cmin C1D28 of midostaurin or its metabolites and the occurrence of response. However, a trend was found for higher peak Cmin values of midostaurin correlated with higher probability of response (OR for 2.67-fold decrease in midostaurin exposure: 0.37; 90%CI: 0.17-0.79). Analyses of DOR by Cmin exposure quartiles showed no obvious exposure-response relationship between last Cmin and the DOR.

No significant association between the Cmin C1D28 of the three active moieties and the maximum % change from baseline of MCs was established within the exposure range of a daily midostaurin dose of 100 mg b.i.d.. However, a decrease in the maximum change from baseline in serum tryptase was highly correlated with the peak Cmin of midostaurin and the exposure to the sum of active moieties when analysed with a linear regression model (midostaurin: estimate -81, 90%CI: -139 to -22.8, p=0.0230; sum of active moieties: estimate -86.6, 90%CI: -153 to -20.2, p=0.0328).

2.4.4. Discussion on clinical pharmacology

There were 4 formulations of midostaurin used in PK studies, in which bioequivalence has been investigated among three mainly used formulations with and without food. The commercial formulation (FMI) gave slightly higher exposure than CSF2 and oral solution under fasting conditions. This small difference is not expected to have impact on PK investigation. Bioequivalence with food has been demonstrated between FMI and oral solution.

Overall, PK of midostaurin is complex; it is dose and time dependent. Midostaurin is a compound with good absorption and poor solubility (BCS class II). Two of its metabolites demonstrated pharmacological activities (CGP52421 and CGP62221). Following multiple doses, the pharmacokinetics of midostaurin and CGP62221 were time dependent, with an initial increase observed in the first week followed by a decline of concentrations until reaching steady state on day 28. CGP52421 concentrations do not appear to decline as significantly as for midostaurin and CGP62221 (SmPC, section 5.2). In humans, the absorption of midostaurin was rapid after oral administration, with Tmax of total radioactivity observed at 1 3 hours post dose (SmPC, section 5.2).The population pharmacokinetic analysis did not identify any change in the absorption characteristics in patients after multiple dose administration (SmPC, section 5.2). The absolute bioavailability of midostaurin following oral administration is not known (SmPC, section 5.2). The 81.6% total recovery of radioactivity in the mass balance study with only 3.4% being parent compound seems high absorption.

In healthy subjects, after administration of a single dose of 50 mg midostaurin with food, AUC of midostaurin was increased to 20800 ng*h/ml and Cmax was decreased to 963 ng/ml. Similarly, for CGP52421 and CGP62221 AUC increased to 19000 and 29200 ng*h/ml and Cmax decreased to 172 and 455 ng/ml, respectively. Time to peak concentration was also delayed in the presence of a high fat meal. Tmax was delayed for all entities, midostaurin median Tmax was 3 h, and for CGP52421 and CGP62221 Tmax was delayed to 6 and 7 hours respectively (SmPC, section 5.2).

As Cmax level is considered relevant to the safety profile of midostaurin and food is mainly important to achieve optimal AUC, midostaurin is recommended to be taken with food, which was applied also in all clinical efficacy studies.

The volume of distribution of midostaurin was high indicating tissue distribution. Midostaurin and the active metabolites were highly bound to plasma proteins (>99%). Midostaurin was mainly metabolised by CYP3A4 and metabolites were excreted via fecel route mainly (77.6% in feces and 4 % via urine).

The average of terminal elimination half-life of midostaurin was estimated to be 19-25 hours, 29-39 hours, and 16-31 days for midostaurin, CGP62221 and CGP52421, respectively, following a single oral dose of 50 mg. Following single dose administration under fasting conditions, midostaurin and its metabolites showed no major deviation from dose-proportionality in the range of 25 mg to 100 mg although the rate of absortion seemed somewhat less than dose proportional. This might be due to poor solubility of midostaurin. It should be noted that in simulated intestinal fluid the solubility of midostaurin was increased by food intake from 0.07 mg/ml (fasted) to 0.12 mg/ml (fed). A pooled analysis of single dose data from healthy subjects under fasting conditions showed less than dose proportional increase of AUC and Cmax between 50 mg and 100 mg dose. However, the PK data of the 100 mg single dose was only from 7 subjects. Thus, the single dose proportionality of midostaurin is still inconclusive. After multiple doses with food, there was a less than dose-proportional increase in exposure within the dose range of 50 mg to 225 mg daily. In AML patients the exposure following 50 mg b.i.d. and 100 mg b.i.d. was comparable. The less than dose-proportional pharmacokinetics of midostaurin in AML patients could be due to a combination of reduced absorption and increased auto-induction at the higher dose.

In general, midostaurin and its metabolites showed no major deviation from dose proportionality after a single dose in the range of 25 mg to 100 mg. However, there was a less than dose proportional increase in exposure after multiple doses within the dose range of 50 mg to 225 mg daily (SmPC, section 5.2).

Following multiple oral doses, midostaurin displayed time dependent pharmacokinetics with an initial increase in plasma concentrations during the first week (peak Cmin) followed by a decline with time to a steady state after approximately 28 days (2.5 fold decrease). While the exact mechanism for the declining concentration of midostaurin is unclear, it is likely due to the auto induction properties of midostaurin and its two active metabolite CGP52421 and CGP62221 on CYP3A4. The pharmacokinetics of the CGP62221 metabolite showed a similar trend. However, CGP52421 concentrations increased up to 2.5 fold for ASM, SM AHN and MCL and up to 9 fold for AML, compared to midostaurin after one month of treatment (SmPC, section 5.2).

At steady state midostaurin and CGP62221 exposures were not different in AML and AdSM patients, whereas CGP52421 concentrations were 4-fold higher in patients with AML with dose of 100 mg b.i.d., compared to patients with AdSM. In AML patients, the dose of 100 mg b.i.d. was reduced to 50 mg b.i.d. due to gastrointestinal side effects. Exposure to midostaurin and CGP62221 were comparable for 50 mg b.i.d and 100 mg b.i.d while CGP52421 concentrations were 1.6-fold higher at 100 mg bid than 50 mg bid. Overall the safety profile with 50 mg b.i.d. was not better than 100 mg b.i.d. The dose of 50 mg b.i.d. is recommended to the patients with AML, and 100 mg b.i.d. is recommended to the patients with AdSM (SmPC section 4.2).

According to popPK analyses, except CYP3A4 inhibitor no covariates were identified to have effect on clearance of midostaurin. There was a slight decrease in exposure of midostaurin and metabolites (7 to 22%) in females compared to males. This difference in exposure is too small to explain the differential treatment effect observed for females vs. males (see discussion on clinical efficacy). For hepatic impairment, the bioavailability of midostaurin in moderate hepatic impairment was decreased but the elimination half-life was longer at day 7, compared with subjects with normal hepatic function. At Day 7, exposure of midostaurin was

not different in subject with moderate hepatic impairment compared to healthy subjects. In the study, there was approximately 40% reduction in drug exposure in patients with mild hepatic impairment, which is likely due to the reduction in absorption. After multiple dosing, the decrease in exposure was 28% in subjects with mild hepatic impairment. Thus dose adjustment is not needed for mild and moderate hepatic impairment. No data in patients with severe hepatic impairment are available and this has been adequately mentioned in the SmPC. The applicant committed to submit the results of study A2116, an open label, multiple dose study designed to evaluate the PK of midostaurin in subjects with mild, moderate and severe hepatic impairment compared to matched healthy subjects, which is ongoing (see Risk Management Plan).

Based on the popPK analyses, creatinine clearance (as surrogate for renal function) showed no impact on the PK of midostaurin and its active metabolites. Justification for lack of pharmacokinetic study for severe renal impairment is accepted, as only 4% of the drug excreted in urine, no study is needed for renal impairment.

Drug-drug interactions have been evaluated *in vitro* and *in vivo* for midostaurin. Midostaurin and metabolites are mainly substrate for CYP3A4. Co-administration of both strong CYP3A4 inhibitor and inducer had a significant effect on exposure of midostaurin and also the active metabolites.

Strong CYP3A4 inhibitors may increase midostaurin blood concentrations. In a study with 36 healthy subjects, co administration of the strong CYP3A4 inhibitor ketoconazole to steady state with a single dose of 50 mg midostaurin led to a significant increase in midostaurin exposure (1.8 fold Cmax increase and 10 fold AUCinf increase) and 3.5 fold increase in AUCinf of CGP62221, while the Cmax of the active metabolites (CGP62221 and CGP52421) decreased by half. At steady state of midostaurin (50 mg twice daily for 21 days), with the strong CYP3A4 inhibitor itraconazole at steady state in a subset of patients (N=7), midostaurin steady state exposure (Cmin) was increased by 2.09 fold. Cmin of CGP52421 was increased by 1.3 fold, whereas no significant effect in exposure of CGP62221 was observed (SmPC section 4.5).

Due to the high interindividual variability in the effect of the CYP 3A4 inhibitor on midostaurin exposure (no increase up to 4-fold increase) a general dose reduction cannot be recommended.

Caution is required when concomitantly prescribing with midostaurin medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g. ketoconazole), certain antivirals (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin) and nefazodone because they can increase the plasma concentrations of midostaurin especially when (re)starting with midostaurin treatment. Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin related toxicity (SmPC, section 4.4).

Strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites (CGP52421 and CGP62221). In a study in healthy subjects, co administration of the strong CYP3A4 inducer rifampicin (600 mg daily) to steady state with a 50 mg single dose of midostaurin decreased midostaurin Cmax by 73% and AUCinf by 96% on average, respectively. CGP62221 exhibited a similar pattern. The mean AUClast of CGP52421 decreased by 60% (SmPC section 4.5) Concomitant administration of potent CYP3A4 inducers, e.g. rifampicin, St. John's Wort (Hypericum perforatum), carbamazepine, enzalutamide, phenytoin is contraindicated (SmPC, section 4.3).

Based on *in vitro* data, midostaurin and/or its metabolites have the potential to inhibit CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2E1 and CYP3A4/5 enzymes (SmPC section 4.5).

Inhibition of CYP3A5 *in vitro* by midostaurin and its metabolites is lacking and the CHMP recommended the applicant to investigate it *in-vitro.*

Based on in vitro data, midostaurin and/or its metabolites have the potential to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 enzymes. Midostaurin inhibited OATP1B1, BCRP and P glycoprotein (P gp) *in vitro*. The combination of data on in vivo midostaurin auto induction upon repeated dosing and increase in plasma 4β OH cholesterol levels suggest that midostaurin may be at least a moderate CYP3A4 inducer in vivo (SmPC section 4.5).

Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and oral contraceptives have been categorized as potential risk (see Risk Management Plan).

Potential interactions with transporters and CYP2D6 were already demonstrated *in vitro*. The applicant committed to conduct *in vivo* studies at single dose level in order to investigate the impact of a single dose of midostaurin on the PK of substrates of the transporters P-gp and BCRP. Addition of a sensitive substrate of CYP2D6 to evaluate the inhibitory effect of midostaurin in a single dose study was also required (see Risk Management Plan). The drug-drug interactions with OATP1B1, P-gp, BCRP and BSEP transporter substrates have been categorized as potential risk (see Risk Management Plan).

A study to examine the inhibitory effect of midostaurin and CGP62221 and CGP52421 on BSEP efflux is planned and will be submitted by the applicant (see Risk Management Plan).

In vivo studies have not been conducted for the investigation of induction and inhibition of enzymes and transporters by midostaurin and the active metabolites. Medicinal products with a narrow therapeutic range that are substrates of CYP1A2 (e.g. tizanidine), CYP2D6 (e.g. codeine), CYP2C8 (e.g. paclitaxel), CYP2C9 (e.g. warfarin), CYP2C19 (e.g. omeprazole), CYP2E1 (e.g. chlorzoxazone), CYP3A4/5 (e.g. tacrolimus), CYP2B6 (e.g. efavirenz), P gp (e.g. paclitaxel), BCRP (e.g. atorvastatin) or OATP1B1 (e.g. digoxin) should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure. (SmPC section 4.5).

The impact of midostaurin on the PK of a substrate of OATP1B1 transporters based on dynamic modeling of the steadystate concentrations of midostaurin, CGP52421 and CGP62221 will be assessed in a planned study (see Risk Management Plan).

It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception (SmPC section 4.5).

No interaction studies except for an interaction study with midazolam have been conducted to investigate the interaction potential of midostaurin as a perpetrator *in vivo*. The interaction study with midazolam indicated that midostaurin was not a moderate or strong CYP3A4 inhibitor *in vivo*, whereas the inducing effect of CYP3A4 was uncertain because of the short, 3 days, treatment with midostaurin (SmPC section 4.5).

The available data on PK interactions indicated that there is a high risk of midostaurin affecting the PK of other drugs through induction of CYP enzymes, including CYP3A4/5. As a result, midostaurin is likely to negatively affect the efficacy of many co-medications that are administered to patients with AML. Drugs that are prone to reduced efficacy (e.g. CYP3A4 substrates) were administered at a very high frequency in the pivotal study of Rydapt (>60% when CYP3A4/5 is considered alone, and even higher when other enzymes are also considered), and these drugs include those which are critical for the safety and well-being of AML, including anti-infective drugs for treatment of infections, and anti-emetics for treatment of nausea/vomiting. To assure that midostaurin treatment does not negatively affect the well-being of AML patients by affecting PK of many co-administered drugs which are critical for optimal treatment of these patients, the applicant commited to investigate the impact of midostaurin on the PK of a cocktail of the following CYP substrates: CYP2B6, CYP2C8 and CYP3A4. The impact on these CYP will be investigated after 28 days of treatment.

These three CYP are considered as the most sensitive to midostaurin. The results will then be extrapolated on the other CYPs and will be submitted by December 2020 (see Risk Management Plan). The CHMP also recommended the applicant to submit PK data for the supportive trial ADE02T.

Limited clinical pharmacodynamic data were provided to support target engagement of FLT3 by midostaurin and its metabolites in patients with AML. It is unclear to which degree FLT3 is inhibited at the concentrations achieved at the recommended dose of 50 mg b.i.d. (apart from extrapolation using an IC_{50} values in vitro). In the pivotal phase III trial in AML patients (PKC412A2301), no formal pharmacodynamic analyses were conducted. The geometric mean Cycle 1 day 21 predose concentrations in this study was 3760.80 ng/mL. This would lead to unboud concentrations of >65 nM (assuming protein binding of 99%). These are above the IC_{50} values needed to inhibit mutant and wild type FLT3. However, variability in exposure was large, ranging from 0 to 33700 ng/mL, possibly leading to subtherapeutic concentrations in a subset of patients.

The relevance of *FLT3* mutational status (TKD versus ITD) and allelic ratios of ITD is unclear. Overall, the limited clinical pharmacodynamic data provided suggest FLT3 engagement but the degree of target engagement in patients is unclear. The limited available data, combined with the low specificity of midostaurin for FLT3 make that there is limited clinical evidence supporting that the effect of midostaurin in AML is specifically due to inhibition of FLT3, and the contribution of inhibition of other kinases is unclear.

No pharmacodynamic studies were submitted to support the primary pharmacology in ASM. In study PKC412D2201 (pivotal study in ASM), the 100 mg b.i.d. dose resulted in a mean (SD) midostaurin C_{max} of 3044.71 (964.249) ng/mL on cycle 1 day 1. This would lead to unbound concentrations of >50 nM (assuming protein binding of 99%), well above the IC_{50} values needed to inhibit mutant KIT 7.7 nM, but below the IC_{50} of wild type KIT (600 nM).

In the pivotal trial in ASM/SM-AHN/MCL (PKC412D2201), *KIT* D816V mutation was positively associated with OS. The mechanism of this association (prognostic in ASM or predictive of response to midostaurin) is unclear. However, the latter hypothesis (predictive association) is supported by the markedly lower affinity of midostaurin for wild type KIT receptor and the fact that in literature *KIT* mutational status was found to have no prognostic role in ASM (Lim, Tefferi, et al., 2009).

Overall, the *in vitro* and non-clinical rationale for FLT3 inhibition in AML and KIT inhibition in ASM/SM-AHN/MCL are reasonably justified. However, limited clinical pharmacodynamic data confirmed the effect of midostaurin on FLT3 and KIT in patients.

In study PKC412D2201 (pivotal study in ASM), the 100 mg b.i.d. dose resulted in a mean (SD) midostaurin C_{max} of 3044.71 (964.249) ng/mL on cycle 1 day 1 (with individual patients reaching concentrations of up to 5150.0 ng/mL). The geometric mean (CV%) C_{min} of CGP52421 was 2518.50 (39.06) ng/mL at day 28 and the geometric mean (CV%) C_{min} of CGP62221 was 3194.15 ng/mL on day 8. Given that pharmacokinetic exposure in trial PKC412A2113 was lower than at the Applicant's highest proposed dose of 100 mg b.i.d. at steady state, the dedicated QT trial insufficiently predicts the cardiac safety profile and exposure-safety relationship of midostaurin at steady state.

In the ASM/SM-AHN/MCL pivotal study (D2201), 8.6% of patients had a dose reduction or interruption due to a prolonged QT interval. Moreover, 41 patients (39.0%) had a QTcF increase from baseline of at least 30 ms and 8 patients (7.6%) an increase of at least 60 ms. In the pivotal study in AML (A2301), the overall frequency of QT prolongation events was 19.2% for midostaurin and 16.8% in the placebo arm (for further discussion see safety section).

A dedicated QT study in 192 healthy subjects with a dose of 75 mg twice daily did not reveal clinically significant prolongation of QT by midostaurin and CGP62221 but the study duration was not long enough to estimate the QTc prolongation effects of the long acting metabolite CGP52421. Therefore, the change from baseline in QTcF with the concentration of midostaurin and both metabolites was further explored in a phase II study in 116 patients with ASM, SM AHN or MCL. At the median peak Cmin concentrations attained at a dose of 100 mg twice daily, neither midostaurin, CGP62221 nor CGP52421 showed a potential to cause clinically significant QTcF prolongation, since the upper bounds of predicted change at these concentration levels were less than 10 msecs (6.3, 2.4, and 4.7 msecs, respectively). In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one ECG measurement with a QTcF greater than 450 ms and 4.7% greater than 480 ms (SmPC, section 5.1).

Different exposure-response analyses in AML were performed with dose intensity as a predictor and clinical endpoints including EFS and OS as investigated outcomes. These analyses are considered methodologically unsound as dose intensity has a reciprocal relationship with the clinical endpoints (i.e. EFS affects dose intensity and vice versa). The fact that treatment failure (or toxicity) lead to lower dose intensity may create an artificial correlation between dose intensity and e.g. EFS; hence biasing the association. Analyses between PK and clinical endpoints are considered more robust.

No specific pharmacodynamic interaction studies have been discussed. Midostaurin is likely to interact pharmacodynamically with cytostatic and cytotoxic agents, and thereby increase the risk of adverse events related to immunosuppression including infections. The results in terms of safety profile of pharmacodynamic interactions between midostaurin and the cytotoxic agents used in AML, specifically anthracyclines and cytarabine, are discussed in the safety section.

NPM1 status does not affect the treatment effect of midostaurin, and midostaurin is effective both in NPM1 mutated and NPM1 wildtype FLT3-mutated disease. Midostaurin is metabolised to a large extent via CYP3A4. CYP3A4 and CYP3A5 polymorphisms are likely to have a large impact on PK of midostaurin (and metabolites). Therefore, these polymorphisms might also have an impact on the B/R of midostaurin in genetic subpopulations. Pharmacogenetics data are required to determine whether dose adjustments are required in patients carrying CYP3A4/CYP3A5 variants that lead to reduced enzyme activity. Effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity and effect on efficacy is classified as missing information in the risk management plan. The applicant will conduct a pharmacogenetics association study (PKC412E2301) in newly diagnosed AML patients with wild-type FLT3 to determine the impact of CYP3A4 and CYP3A5 polymorphisms on the exposure of midostaurin, CGP52421 and CGP62221, and on treatment-related toxicity (see Risk Management Plan). The effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity has been categorized as potential risk (see Risk Management Plan).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of midostaurin and the active metabolites has been investigated to a reasonable extent. PK data indicated that the risk of midostaurin affecting other drugs due to induction of CYP enzymes is high (including induction of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2B6), and midostaurin is thus likely to affect the efficacy of many co-medications, including e.g. anti-emetics and anti-infective drugs. This will be followed through post-marketing studies (see Risk Management Plan).

2.5. Clinical efficacy

2.5.1. Dose response studies

The dose response studies that were performed to support the dose selection for midostaurin are displayed in

Table 29.

Table 27.Summary of dose-finding studies

Study No.	Study type, population	Purpose of study	No. of patients	Midostaurin dosage
Midostaurin as a single agent				
Study 0002	Phase 1b dose-escalation study in patients with advanced, non-hematologic malignancies	Determine MTD; assess safety and tolerability	32	12.5 mg 12.5 mg bid 25 mg bid 50 mg bid 75 mg bid 75 mg tid 100 mg tid
Study 0006	Phase 2 exploratory study in patients with advanced CLL and NHL	Monitor tolerability, safety, and biological activity	21	25 mg 75 mg bid 75 mg tid
Study A2104	Phase 2, Proof-of-concept, single-arm study in patients with relapsed/refractory AML or high-risk MDS and mutated FLT3	Preliminary anti-tumor activity in patients, PD activity in vitro	20	75 mg tid
Study A2104E1	Phase 2, Proof-of-concept study of 2 midostaurin doses in patients with relapsed/refractory AML or high-risk MDS and WT or mutated FLT3	Preliminary anti-tumor activity in patients, PD activity in vitro	95 (51 at 50 mg bid and 44 at 100 mg bid)	50 mg bid 100 mg bid
Study A2104E2	Phase 1/2, Proof-of-concept study of 2 midostaurin regimens (intra-patient dose escalation, and itraconazole combination) in patients with relapsed/refractory AML or high-risk MDS and WT or mutated FLT3	Safety, tolerability, and preliminary anti-tumor activity, and PD activity in vitro	29* Dose escalation arm: 16 Itraconazole arm: 13	Dose escalation arm: 100 mg bid to 300 mg bid Itraconazole arm: 100 mg bid
Midostaurin in combination with standard chemotherapy				
Study A2106	Phase 1b, open-label study of midostaurin administered in combination sequentially and concomitantly with standard chemotherapy in patients with de novo AML	Safety, tolerability and efficacy	69 (Sequential therapy: 34 Concomitant therapy: 35)	50 mg bid 100 mg bid

MTD = maximum tolerated dose, PD = pharmacodynamics, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome, WT = wild type, NHL= non-Hodgkin lymphoma, CLL = chronic lymphoid leukemia, FLT3 = Fms like tyrosine kinase 3
* two patients were recruited from the A2104E1 study into the dose escalation arm

Acute myeloid leukaemia indication

A dose-escalation study of midostaurin as monotherapy (study 0002) was conducted in patients with non-haematological malignancies, where patients received midostaurin for 28 days (in a 4 week on, 1 week off schedule) at one of 7 dose levels, ranging from 12.5 to 300 mg daily (as 100 mg t.i.d.). The maximum tolerated dose (MTD) was not determined. Grade 3 treatment-related adverse events included nausea, fatigue, anaemia, anorexia, vomiting, headache, increased sweating, coughing and arthralgia. No clear relationship between dose and these toxicities could be shown. No dose-response relations were identified in this study, as only one patient (3%) had a partial response (a cholangiosarcoma patient who was treated at the 12.5 mg dose level). The dose of 225 mg/day was considered to be the maximum feasible dose due to a slightly increased number of grade 3 gastrointestinal events (nausea and vomiting) causing discontinuation in patients receiving 225-300 mg/day, and the fact that ingestion of 12 or more capsules (as only 25 mg capsules are produced) per day (at the 300 mg dose) was deemed unpractical from a patient perspective.

A phase II study in patients with advanced CLL or NHL (study 0006) evaluated doses of 25, 150, and 225 mg/day in a continuous schedule, which confirmed the tolerability of midostaurin as single agent at doses up to 225 mg/day. The median overall duration of exposure was 41 days (range: 14-93).

A phase II monotherapy study (study 2104) evaluated continuous daily dosing of 225 mg (75 mg t.i.d.) midostaurin in patients with *FLT3* mutant (*FLT3*-ITD mutation or D835Y TKD mutation) AML or high-risk MDS. At this dose, 30% of the patients discontinued treatment due to adverse events. The median duration of treatment was 35.5 days. None of the patients had a CR or PR, but 15 patients (out of a total of 20) had a blast reduction (greater than 50% reduction in peripheral blasts).

Study 2104E1 evaluated 50 mg b.i.d. and 100 mg b.i.d. continuous regimens of midostaurin (as single agent) in patients with AML or high-risk MDS, either *FLT3*-mutated or wild type. The results showed that there was little difference between the exposures to midostaurin (measured as pre-dose concentrations) at the two dose levels, and indicated a less-than-proportional increase in exposure with increasing dose within this dose range. Clinical activity and a similar response rate were observed in the 50 mg b.i.d. and 100 b.i.d. dose groups in patients with *FLT3* mutations. A clinical response was observed in most patients with *FLT3*-mutated AML (71.4%) but also in more than half of the patients with *FLT3*-wild-type AML (56.1%).

Study 2104E2 evaluated two dosing regimens: intra-patient dose-escalation of midostaurin up to a maximum of 600 mg/day in a continuous regimen, and the effect of concomitant administration of itraconazole (100 mg b.i.d.) with midostaurin 50 mg b.i.d. In patients with *FLT3*-mutated AML, a clinical response in the midostaurin dose escalation arm was achieved in five (55.6%) patients (95%CI: 21.2%-86.3%), and for each patient this comprised blast reduction alone or in combination with MR. No patients with *FLT3*-mutated AML in the midostaurin + itraconazole arm achieved a clinical response. In patients with *FLT3*-wild-type AML, a clinical response in the midostaurin dose escalation arm was achieved in two (28.6%) patients (95% CI: 3.7%, 71.0%) and in the midostaurin + itraconazole arm a clinical response was obtained in four (66.7%) patients (95% CI: 22.3%-95.7%). One patient (16.7%) in the *FLT3*-wild-type group obtained a CR in the midostaurin + itraconazole treatment arm. The data from this study did not indicate obvious improvements in clinical response in patients with AML receiving midostaurin doses higher than 50 mg b.i.d..

Study 2106 was a phase IB, open-label study to determine the safety and pharmacokinetics of twice daily oral dosing of midostaurin combination sequentially or concomitantly with standard induction chemotherapy in AML. In this study (which enrolled 69 patients), dosages of 100 mg b.i.d. and 50 mg b.i.d. where explored in combination with induction therapy (daunorubicin 60 mg/m^2/day IV over 30 min for 3 days on days 1-3

and cytarabine 200 mg/m^2/day IV over 24 hours for 7 days on days 1-7). Sequential (arm 1) and concomitant (arm 2) dosing of midostaurin in relation to chemotherapy was explored. The initial dosing regimen of midostaurin 100 mg b.i.d. was poorly tolerated both in sequential and concomitant regimens and was associated with a high rate of treatment discontinuation (71.4% in arm 1 and 85.7-87.5% in arm 2 of which 14.3% in both arms due to adverse events). The most common reasons for discontinuation were unsatisfactory therapeutic effect and withdrawal of consent. Protocol amendments were implemented that reduced the midostaurin dosage from the initial 100 mg b.i.d. to 50 mg b.i.d. Administration of midostaurin 50 mg b.i.d. was associated with an acceptable safety and tolerability profile (corresponding to discontinuation rates, due to any reason, of 35% in arm 1 and 55% in arm 2). Discontinuation due to adverse events at the 50 mg b.i.d. dosage occurred in 5 and 10% in arm 1 and 2, respectively. There was no clear difference in the incidence of most SAEs between the cohorts within each treatment arm. However, the SAEs of nausea, vomiting and diarrhoea were only reported in the 100 mg b.i.d. cohorts, as were SAEs associated with increases in liver function test results (ALT, AST, total bilirubin). No effect of midostaurin was observed on cytarabine plasma concentrations whereas exposure to daunorubicin appeared to decrease 2-fold at the 100 mg b.i.d. midostaurin dose. However, due to the large variability in the PK parameters for daunorubicin it was not possible to conclude that this decrease was caused by a drug-drug interaction. The CR rate was 52.9% and 60.0% in Arm 1 and Arm 2, respectively. The CR rate was higher in the 50 mg b.i.d. cohorts in each arm (60.0% and 75.0% in the respective arms). Overall, the CR rate was higher for patients with *FLT3* mutation positive AML (78.9%) than patients with wild type *FLT3* AML (48.0%). The median OS was also longer in patients with *FLT3* mutation positive AML (~2.9 years), compared to those with wild type *FLT3* AML (~1.7 years).

Aggressive systemic mastocytosis indication

No dose selection studies were conducted in ASM (see discussion on clinical efficacy).

2.5.2. Main studies

- **RATIFY study (A2301)**

Methods

This was a randomised, phase III, double-blind study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in newly diagnosed patients <60 years of age with FLT3 mutated acute myeloid leukaemia.

Study Participants

The study included patients younger than 60 years of age with newly diagnosed FLT3-mutation positive AML (ITD or TKD mutation) according to WHO criteria. FLT3 positivity was defined as a 5% or higher percentage of measured mutant FLT3 alleles in a wild type background.

Key inclusion criteria

1)   Unequivocal diagnosis of AML (>20% blasts in the bone marrow based on the WHO classification), excluding M3 (acute promyelocytic leukaemia). Patients with neurologic symptoms suggestive of CNS leukaemia are recommended to have a lumbar puncture. Patients whose CSF is positive for AML blasts were not eligible.

2)   Documented FLT3 mutation (ITD or point mutation), determined by analysis in a protocol-designated FLT3 screening laboratory

3)   Age $\geq$ 18 and <60 years

4)   No prior chemotherapy for leukaemia or myelodysplasia with the following exceptions: emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxyurea for $\leq$ 5 days, cranial RT for CNS leukostasis (one dose only), growth factor/cytokine support

Key exclusion criteria

1)   Patients who have developed therapy related AML after prior RT or chemotherapy for another cancer or disorder

2)   Patients with symptomatic congestive heart failure

3)   Total bilirubin $\geq$ 2.5x upper limit of normal.

4)   Cerebrospinal fluid evaluation positive for the presence of AML blasts

5)   Pregnant or nursing patients

Treatments

Patients were randomised in a 1:1 ratio to standard first-line induction and consolidation chemotherapy with daunorubicin/cytarabine and high-dose cytarabine, plus either placebo or midostaurin (50 mg twice daily). Patients were stratified based on FLT3 mutation status (ITD allelic ratio < 0.7, ITD allelic ratio $\geq$ 0.7, or TKD). Midostaurin or placebo were administered during induction and consolidation treatment, and as maintenance treatment up to 12 cycles of 28 days (336 days) after finishing consolidation therapy in patients who remained in CR.

The study comprised 3 treatment phases, as shown in **Error! Reference source not found.**.

•   Induction: In Cycle 1, patients received induction therapy with cytarabine (200 mg/m^2/day on Days 1-7) and daunorubicin (60 mg/m^2/day on Days 1-3). Midostaurin or placebo was administered on Days 8-21. Patients who achieved a CR were to proceed to consolidation therapy while those who failed to achieve a CR (bone marrow aspirate with $\geq$ 5% leukaemic blasts in a cellular marrow) were to receive a second course of the same remission-induction therapy starting on or shortly after Day 24 (i.e., $\geq$ 3 days after completing midostaurin/placebo).

After the induction therapy, a bone-marrow aspiration was performed within one week after haematological recovery (absolute neutrophil count; ANC $\geq$ 1000/µL and platelets $\geq$ 100000/µL) to assess response. Patients with residual AML after cycle 2 were to be discontinued from study treatment.

- Consolidation: Patients who achieved CR during induction received up to four 28-day cycles of consolidation therapy with high-dose cytarabine (3 g/m^2 over 3 hours every 12 hours on Days 1, 3, and 5) and continued midostaurin or placebo on Days 8-21 of each cycle (Cycles 2-5 or 3-6).

- Continuation/maintenance: Patients who remained in CR after 4 cycles of consolidation therapy received midostaurin or placebo administered continuously for a maximum of 12 cycles of 28-days (i.e. up to 336 days).

Patients who received SCT were discontinued from study treatment; however they were continued to be followed for efficacy (response/survival). There was no crossover between treatment arms.

Design of study A2301/RATIFY (pivotal phase III study)
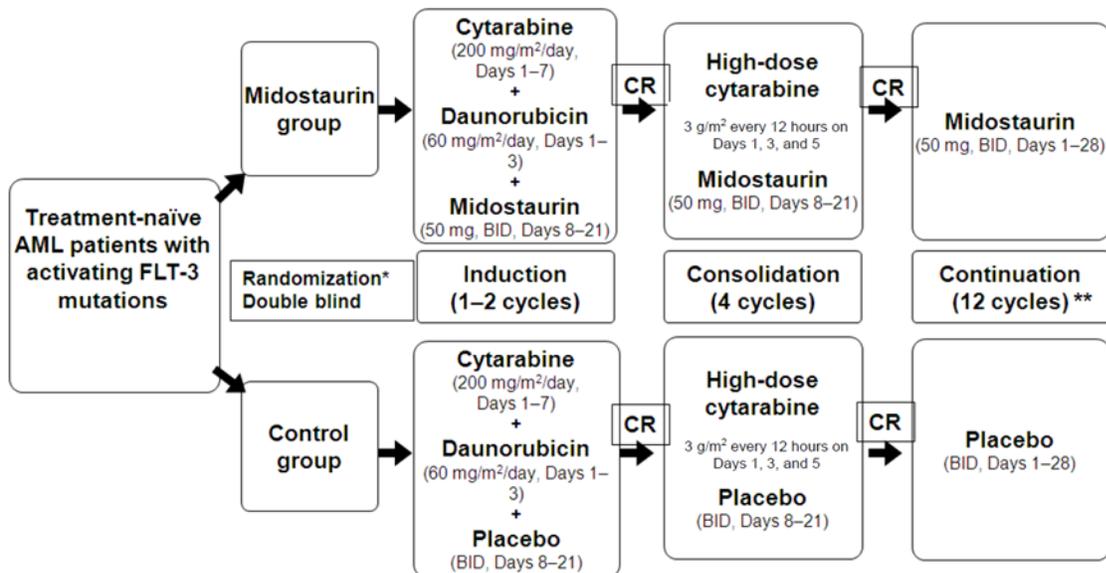
AML = acute myeloid leukemia; bid = twice a day; CR = complete remission
* Central randomization within 3 strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥ 0.7; FLT3-ITD with allelic ratio <0.7
** Up to 12 cycles

FLT3 screening

Patients were screened at diagnosis for the presence of a FLT3 mutation (ITD or TKD) in either bone marrow or peripheral blood blast cells using a polymerase chain reaction based method performed at one of nine designated central laboratories. The cut-off for FLT3 positivity was set at 0.05 (mutant:wild type ratio calculated using the signal output from the assay), i.e., patients were classified as FLT3 positive if ≥ 5% mutated FLT3 alleles were present in blasts. Test assay performance was regularly monitored (every 6 months) throughout the study at these participating central labs through the use of cross-validation panel testing. Laboratory failure resulted in suspension until CTA proficiency was demonstrated in the following round. Patient samples were diverted to other laboratories for testing during suspensions.

Objectives

Primary objective: To determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improves overall survival (OS) in both the mutant FLT3-ITD and FLT3-TKD AML patients.

Key secondary objective: To determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improves event-free survival (EFS) in both the mutant FLT3-ITD and FLT3-TKD AML patients.

Other secondary objectives:

- To compare the OS in the two groups using an analysis in which patients who receive a stem cell transplant (SCT) are censored at the time of transplant.

- To compare the complete remission (CR) rate between the two study treatments.

- To compare the disease-free survival (DFS) of the two study treatments.

- To compare the DFS rate one year after completion of the continuation phase of the two groups.

- To assess the toxicity of the experimental combination.

- To describe the interaction between treatment outcome and pretreatment characteristics such as age, performance status, white blood cell (WBC) count, morphology, cytogenetics, and molecular and pharmacodynamic features.

- To assess the population pharmacokinetics (PopPK) of midostaurin and its two major metabolites, CGP52421 and CGP62221. The potential associations between pharmacokinetics (PK) exposure and FLT3 status, OS, EFS and clinical response were explored.

- To compare the SCT rates between the two treatment groups.

Outcomes/endpoints

Table 28. Endpoints and definitions

Endpoints		Definitions
Primary endpoint	Overall survival (non-censored at Stem cell transplantation)	The OS time is the period from the date of registration/randomisation in the study until death by any cause.
Key secondary endpoint	Event free survival (non-censored at SCT)	EFS event defined as failure to achieve CR within 60 days of initiation of protocol therapy, or relapse, or death from any cause.
Secondary endpoint	Complete remission (CR)	CR rate within 60 days of start of treatment.

Secondary endpoint	Disease free survival (non-censored at SCT)	Patients who achieved a CR by Day 60 after study treatment initiation. DFS measured from the date of first CR to relapse or death from any cause, whichever occurred first.
Secondary endpoint	Remission duration/cumulative incidence of relapse (CIR)	Remission duration was the time from CR achieved within 60 days to relapse or death due to AML, whichever occurred first. Patients who died due to other causes without relapsing prior to death were censored. Remission duration was depicted as Cumulative incidence of relapse (CIR).
Secondary endpoint	SCT rate	SCT rates compared between the two treatment groups
Secondary endpoint	OS (censored at SCT)	The OS time is the period from the date of registration/randomisation in the study until death by any cause.
Secondary endpoint	EFS (censored at SCT)	EFS event defined as failure to achieve CR within 61 days of initiation of protocol therapy, or relapse, or death from any cause
Secondary endpoint	DFS (censored at the time of SCT)	DFS measured from the date of first CR to relapse or death from any cause, whichever occurred first.
Secondary endpoint	DFS after continuation	Patients who had a CR in the 60 day window, had completed continuation therapy and still were in remission at the end of continuation. DFS one year after completion of continuation therapy

Other relevant definitions

- CR was defined as all of the following, by 60 days after initial induction therapy started, unless otherwise specified in the analysis:

Peripheral blood counts: ANC ≥ 1000/MI; Platelet count ≥100000/µL; No leukemic blasts in the peripheral blood; Adequate erythroid recovery so that red blood cell (RBC) transfusions are not necessary

Bone marrow: Adequate cellularity; No Auer rods; <5% blast cells

No extramedullary leukemia (such as CNS or soft tissue involvement): Patients achieving a CR after Day 60 were still eligible to receive consolidation therapy.

- A treatment failure was defined as a failure to achieve a CR by 60 days after initial induction therapy started.

- A relapse was defined as any of the following occurring after a CR:

  o The reappearance of circulating blast cells not attributable to "overshoot" following recovery from myelosuppressive therapy.

- o >5% blasts in the marrow, not attributable to another cause (*e.g.* CSF, bone marrow regeneration).

- o Development of extramedullary leukemia.

Sample size

In December 2010, the sample size calculation was revised (protocol amendment 4) based on a blinded review of the data. The proportion of FLT3-TKD patients was expected to increase from 14% to 26% and the proportion of patients receiving SCT to increase from 15% to 25%. Taking into account these new proportions and that no additional benefit of midostaurin would be observed for patients receiving SCT, the expected median OS times for placebo and midostaurin were considered to be 16.3 months and 20.9 months, respectively (HR=0.78). The study was determined to be underpowered (68%) and the sample size was increased to accrue a total of 714 patients, with a 2.9 years accrual period and 1.6 years of follow-up period. Within this timeframe, it was expected to observe 509 OS events by May 2013, to attain a power of 84% to detect a HR of 0.78, with a one-sided test at an overall one-sided alpha level of 0.025.

In March 2015 it was decided to perform the primary analysis based on 350 OS events. The death rate was lower than expected, and the protocol was amended (protocol amendment 10) to perform the final confirmatory analysis with a data cut-off of 1 April 2015 without waiting for the originally targeted 509 OS events to occur.

After amendment 4, type I error control was extended to include EFS as key secondary endpoint. Based on external trial data (SWOG/AMLSG), median EFS of 8.5 months was estimated for placebo patients. If it was assumed a median EFS of 14 months for midostaurin patients (3 additional months in remission for patients who were not long-term survivors, 8% increase in the rate of long term survivors and no treatment difference for the patients who had an SCT in CR1), 507 EFS events could have been observed with a minimum follow up of 3.5 years for all patients after randomization. Under these assumptions, the trial would have a power of approximately 89% using a one-sided alpha of 2.5% for the key secondary endpoint to detect a hazard ratio of 1.34 with a Cox regression model.

Randomisation

All AML *FLT3* mutated patients were randomly assigned to the two treatments based on FLT3 mutation status: FLT3 TKD (No ITD), ITD Allelic ratio<0.7 (with or without FLT3 TKD) and ITD Allelic ratio≥ 0.7 (with or without FLT3 TKD).

Blinding (masking)

The pivotal study was double-blinded.

Statistical methods

The primary efficacy endpoint was OS and all deaths up to and including the cut-off date of 1 April 2015 was taken into account as OS events. All patients irrespective of when they stopped study treatment or received SCT were followed up for this endpoint. Patients alive at study termination were censored either at their date of last contact before 1 April 2015 (cut-off data) or at cut-off date.

The primary efficacy evaluation tested the superiority of midostaurin compared to placebo on OS in the ITT population. The ITT population included all randomized patients with a signed protocol informed consent. Patients were analysed according to the treatment arm and stratum they were assigned to at randomization. The following statistical methodology was applied:

- Log-rank test, adjusting for the FLT3 mutation strata used in the randomization, was used to test the null hypothesis and calculate the one-sided p-value

- Stratified Cox regression models adjusting according to the FLT3 mutation strata were used to provide estimates of the HRs and associated Wald 95% CIs

- Kaplan-Meier plots were used to depict OS over time in each treatment arm. Median survival was obtained along with 95% Cis calculated using the method of Brookmeyer and Crowley. Kaplan-Meier estimates with 95% Cis at specific time points were summarized every 6 months using Greenwood's formula for the standard error of the Kaplan-Meier estimate

The test OS was significant if the associated one-sided p-value was less than the remaining alpha available considering the alpha already spent at the interim analysis.

A pre-specified alpha level of 0.005 was to be spent at the interim analysis, meaning the one-sided test of OS was significant if the p-value was less than 0.005. The one-sided alpha level in the final analysis of the primary endpoint OS was determined to be 0.0239 to maintain the pre-specified overall alpha level of 0.025

A conditional probability of less than 0.10 was ground for stopping the study early for futility. Conditional power was calculated as the probability of having a significant p-value at the primary analysis assuming an underlying HR of 0.78 on OS, given the observed effect at the futility look.

Analysis sets

The full analysis set (FAS) included all randomized patients with a signed protocol informed consent to whom a treatment arm was assigned by Alliance at randomization. Patients were analysed according to the treatment arm and the stratum they were assigned to at randomization. The FAS was used for the analyses of the efficacy endpoints and also for all baseline characteristics.

The per protocol set (PPS) is a subset of the FAS, and included all randomized patients with a signed protocol treatment informed consent, who received at least one dose of study drug (midostaurin/placebo), and who had no major protocol deviation regarding inclusion/exclusion criteria or randomization issues that could affect response to treatment. Sensitivity analyses of the primary and the key secondary efficacy endpoints were produced on the PPS by region.

The safety set included all patients with a signed protocol informed consent who received at least one dose of study drug (midostaurin or placebo). The safety set was used for the analyses of the safety endpoints, concomitant medications and treatment exposure.

The Pharmacokinetic set (PK set) included all patients with a signed protocol and PK informed consent, who received at least one dose of midostaurin and who provided at least one evaluable PK concentration. The PK set was used for the analyses of the PK endpoints.

Results

Participant flow

Figure 5 Schematic of participant flow in study A2301

Randomization
N=717

Midostaurin
N=360

Placebo
N=357

Did not receive
any trt, n=5

Did not receive
any trt, n=3

Induction trt
N=355

Induction

Induction trt
N=354

Discontinued during
induction, n=124

Cycle 1
n=355

Cycle 1
n=354

Discontinued during
induction, n=144

Alternative therapy n=36
Progressive disease, n=7
Withdrew/refused trt, n=12
Adverse event, n=15
Death, n=16
Other disease, n=1
Other, n=37

Cycle 2
n=81

Cycle 2
n=101

Alternative therapy n=41
Progressive disease, n=4
Withdrew/refused trt, n=32
Adverse event, n=8
Death, n=11
Other disease, n=1
Other, n=47

Consolidation trt
N=231

Consolidation

Consolidation trt
N=210

Cycle 1
n=231

Cycle 1
n=210

Discontinued during
consolidation, n=111

Cycle 2
n=175

Cycle 2
n=158

Discontinued during
consolidation, n=125

Alternative therapy n=69
Progressive disease, n=19
Withdrew/refused trt, n=6
Adverse event, n=8
Death, n=2
Other disease, n=1
Other, n=6

Cycle 3
n=150

Cycle 3
n=128

Alternative therapy n=65
Progressive disease, n=27
Withdrew/refused trt, n=7
Adverse event, n=9
Death, n=7
Other disease, n=1
Other, n=9

Cycle 4
n=129

Cycle 4
n=103

Continuation trt
N=120

Continuation

Continuation trt
N=85

Discontinued during
continuation, n=51

Discontinued during
continuation, n=34

Alternative therapy n=4
Progressive disease, n=32
Withdrew/refused trt, n=4
Adverse event, n=9
Other disease, n=1
Other, n=1

Alternative therapy n=1
Progressive disease, n=27
Withdrew/refused trt, n=1
Adverse event, n=5

Finished 12 cycles
of continuation trt
N=69

Finished 12 cycles
of continuation trt
N=51

Recruitment

Patients were enrolled across 13 countries at 177 study centres as follows: Australia (1 centre), Austria (5 centres), Belgium (4 centres), Canada (5 centres), Czech republic (4 centres), France (1 centre), Germany (64 centres), Hungary (1 centre), Italy (24 centres), The Netherlands (1 centre), Slovakia (1 centre), Spain (8 centres), United States (58 centres).

Conduct of the study

A summary of the main protocol amendments to the pivotal study protocol is provided in Table 31.

Table 29 Summary of main amendments to the pivotal study protocol – study A2301

Amendment no/ Date / No of patients*	Key features of amendment	Rationale and justification
1 15-Feb-2009 71 patients	• Clarification of eligibility criterion for patients with neurologic symptoms • Changes in dose modification required in cases of QTc prolongation between 470 ms and 500 ms. • Added dose modification requirement for cases of ≥ grade-2 neurotoxicity due to high-dose cytarabine	Amendment was implemented for clarity on registration procedures among certain sites of Alliance cooperative study as well as the submission of results; slight changes in dose modification with regards to cardio- and neurotoxicity were also made for giving clearer guidance to physicians in case these events were to occur.

2 01-Apr-2009 101 patients	• Change in dosing regimen for midostaurin/placebo continuation therapy from 14 days of each 28 day cycle to continuous daily dosing, continuing for 12 cycles, along with clarifying rationale • Adding dose modification requirement for cases of QTc prolongation • Clarifying dose modification requirements for non-hematologic toxicities of grade 3/4 severity • Change in prohibited ancillary therapy (i.e. use of aprepitant was not permitted)	Changes to dosing regimen implemented to maintain midostaurin drug concentrations above IC50 ensuring continuous target suppression and potentially more effective treatment Other changes implemented to clarify certain procedures, roles and responsibilities
3 01-Dec-2009 279 patients	• Changes in reporting of AEs for NNA sites as well as for their expedited reporting requirements • Addition of collection of concomitant medications • Revised information regarding drug accountability, storage and stability, and unblinding of midostaurin • Revision on statistical analyses to be performed for secondary endpoints • Revision on requirement for bone marrow aspiration during remission induction stage and response assessments	Changes implemented for clarity on clinical practice for administration, storage, and accountability of study treatment as well as on statistical analysis requirements.
4 15-Dec-2010 549 patients	• At the time of protocol version 1, the transplantation option was estimated to be available for about 15% of the population eligible for the study. This rate of withdrawal from study treatment for patients in first CR was factored into the estimate of sample size. At Amendment 4, based on blinded data from the study to date, 25% of all randomized patients were expected to have received an SCT. The sample size and power justification were therefore revised and justification for amending statistical considerations was added to reflect revised sample size. • Addition of a new secondary objective to compare the OS in the two groups using an analysis in which patient who receive an SCT are censored at the time of transplantation	Revisions in the statistical analysis plan were implemented; of particular note was the adjustment to sample size and power, which was based on blinded data received up to that point. Novartis did not have access to any blinded efficacy data.
5 15-May-2011 615 patients	• Revision of response assessment to include time requirement for bone marrow aspiration after recovery of ANC and platelet count to document complete response	Changes implemented to clarify certain procedures, roles and responsibilities
6 15-Sep-2011 707 patients	• Changes in AE reporting for NA and NNA sites	Changes implemented to clarify certain procedures, roles and responsibilities
7 15-Nov-2011 719 patients	• Update in administrative procedure for the unblinding of patients	Changes implemented to clarify certain procedures, roles and responsibilities
8 05-May-2013 719 patients	• Editorial / Administrative changes	
9 15-Feb-2015 719 patients	• Editorial / Administrative changes	

Amendment no/ Date / No of patients*	Key features of amendment	Rationale and justification
10 15-Jun-2015 719 patients	• The protocol was amended to perform the final confirmatory analysis with a data cut-off of 01-Apr-2015 without waiting for the originally targeted 509 OS events to occur. • The secondary endpoint EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint is significant. In addition, the SCT rate was added as a secondary efficacy endpoint.	Given the slow accrual rate of OS eventsthe originally targeted 509 OS events were not expected to be reached within a reasonable time-frame. The patient FU time at the time of the data cut-off was considered sufficient to assess an improvement in OS since all patients had more than 3 years FU (time form randomization to data cut off). SCT rate was added as a secondary endpoint due to the increase in the number of patients who have an SCT.

ANC = absolute neutrophil count; AE = adverse event; FU = follow-up; NA = North America; NNA = Non-North America; OS = overall survival; SCT = stem cell transplantation
*Number of patients randomized at the time of the amendment

Protocol deviations

Major protocol deviations occurred in 106 patients (14.8%). The incidence of major protocol deviations was similar in the two treatment arms (14.7 and 14.8%).

Table 30 Summary of major protocol deviations (FAS) – study A2301

Protocol deviation	Midostaurin N = 360 n (%)	Placebo N = 357 n (%)	ALL N = 717 n (%)
Any protocol deviation	250 (69.4)	243 (68.1)	493 (68.8)
Any major protocol deviation (excludes from PPS)	53 (14.7)	53 (14.8)	106 (14.8)
Patient randomized but did not receive midostaurin or placebo	17 (4.7)	20 (5.6)	37 (5.2)
Prior treatment for leukemia or myelodysplasia received (including HU for >5 days)	19 (5.3)	15 (4.2)	34 (4.7)
Treatment switched ≥ 1 x during the study	9 (2.5)	7 (2.0)	16 (2.2)
Dosing (midostaurin or placebo) interrupted for >28 consecutive days but not discontinued	4 (1.1)	4 (1.1)	8 (1.1)
Study treatment continued following the completion of all protocol-specified treatments	4 (1.1)	4 (1.1)	8 (1.1)
CSF positive for AML blasts at BL	1 (0.3)	3 (0.8)	4 (0.6)
Patient received treatment from the other arm	0	2 (0.6)	2 (0.3)
FLT3 mutation allelic ratio < 0.05 at BL*	2 (0.6)	0	2 (0.3)
Developed therapy related AML after RT or chemotherapy for another cancer or disorder	0	2 (0.6)	2 (0.3)
Age ≥60 years at BL	0	1 (0.3)	1 (0.1)
Histological diagnosis other than AML	1 (0.3)	0	1 (0.1)
Positive for FAB sub-type M3 (acute promyelocytic leukemia) at BL	0	1 (0.3)	1 (0.1)

AML = acute myeloplastic leukemia; BL = baseline; CSF = cerebrospinal fluid; FAB = French-American-British; HU = hydroxyurea; ICF = informed consent form; PPS = per protocol set; RT = randomized treatment
A patient may have had multiple protocol deviations.
Manual protocol deviations are only reported for Non-NA sites while programmable PDs are reported for NA and NNA.
Note: the list of protocol deviations differs between NA and NNA.

Baseline data

Demographic and disease characteristics at baseline are shown in Table 33 and Table 34.

Table 31 Demographic characteristics (FAS) – Study A2301 (RATIFY)

Baseline characteristics	MIDOSTAURIN N=360	PLACEBO N=357	ALL N=717
Age (Years)			
n	359	356	715
Mean	44.9	45.5	45.2
SD	10.41	10.84	10.63
Min	19	18	18
Median	47.0	48.0	47.0
Max	59	60	60
Gender -n (%)			
Female	186 (51.7)	212 (59.4)	398 (55.5)
Male	174 (48.3)	145 (40.6)	319 (44.5)
ECOG/Zubrod performance status –n (%)			
0	164 (45.6)	142 (39.8)	306 (42.7)
1	159 (44.2)	168 (47.1)	327 (45.6)
2	29 (8.1)	36 (10.1)	65 (9.1)
3	6 (1.7)	9 (2.5)	15 (2.1)
4	2 (0.6)	2 (0.6)	4 (0.6)
Race -n (%)			
White	147 (40.8)	128 (35.9)	275 (38.4)
Black or African American	8 (2.2)	9 (2.5)	17 (2.4)
Asian	8 (2.2)	5 (1.4)	13 (1.8)
American Indian or Alaskan Native	0	1 (0.3)	1 (0.1)
Not Reported	1 (0.3)	2 (0.6)	3 (0.4)
More than one race (1)	2 (0.6)	1 (0.3)	3 (0.4)
Unknown	194 (53.9)	211 (59.1)	405 (56.5)
Region -n (%)			
North America	121 (33.6)	115 (32.2)	236 (32.9)
Non North America	239 (66.4)	242 (67.8)	481 (67.1)

(1) If more than one race is reported for a patient, he/she is described only in this category and is not described in the other race categories.
All percentages are calculated on the FAS using N as denominator.

Table 32 Disease characteristics (FAS) – Study A2301 (RATIFY)

Disease status	MIDOSTAURIN N=360 n (%)	PLACEBO N=357 n (%)	ALL N=717 n (%)
Clinical onset of AML -n (%)			
De novo	343 (95.3)	338 (94.7)	681 (95.0)
Treatment related	0	2 (0.6)	2 (0.3)
MDS-related	14 (3.9)	16 (4.5)	30 (4.2)
Missing	3 (0.8)	1 (0.3)	4 (0.6)
Time since initial pathologic diagnosis (days)			
N	359	356	715
Mean (SD)	9.4 (77.25)	14.6 (174.28)	12.0 (134.54)
Median (min, max)	5.0 (-58, 1465)	5.0 (1, 3293)	5.0 (-58, 3293)
WHO diagnosis -n (%)			
AML with t(8;21) (q22;q22)	14 (3.9)	7 (2.0)	21 (2.9)
AML with inv(16)(p13q22) or t(16;16)(p13;q22)	11 (3.1)	14 (3.9)	25 (3.5)
AML with 11q23 (MLL) abnormalities	5 (1.4)	6 (1.7)	11 (1.5)
AML with multilineage dysplasia with prior MDS	8 (2.2)	9 (2.5)	17 (2.4)
AML with multilineage dysplasia without prior MDS	49 (13.6)	49 (13.7)	98 (13.7)
Acute basophilic leukemia	0	0	0
Acute panmyelosis with myelofibrosis	1 (0.3)	0	1 (0.1)
Myeloid sarcoma	1 (0.3)	1 (0.3)	2 (0.3)
Other	253 (70.3)	256 (71.7)	509 (71.0)
Missing	18 (5.0)	15 (4.2)	33 (4.6)
Leukemia classification (FAB sub-type) -n (%)			
Undifferentiated acute myeloid leukemia (M0)	15 (4.2)	11 (3.1)	26 (3.6)
Acute myeloid leukemia without maturation (M1)	80 (22.2)	85 (23.8)	165 (23.0)
Acute myeloid leukemia with maturation (M2)	73 (20.3)	65 (18.2)	138 (19.2)
Acute myelomonocytic leukemia (M4)	101 (28.1)	86 (24.1)	187 (26.1)
Acute monocytic leukemia (M5)	67 (18.6)	79 (22.1)	146 (20.4)
Acute erythroid leukemia (M6)	1 (0.3)	3 (0.8)	4 (0.6)
Acute megakaryoblastic leukemia (M7)	1 (0.3)	0	1 (0.1)
Other	17 (4.7)	21 (5.9)	38 (5.3)
Missing	5 (1.4)	7 (2.0)	12 (1.7)
Extramedullary disease involvement – n (%)			
Any extramedullary disease involvement	57 (15.8)	84 (23.5)	141 (19.7)
Central nervous system	1 (0.3)	2 (0.6)	3 (0.4)
Peripheral nervous system	1 (0.3)	0	1 (0.1)
Gingival hypertrophy	38 (10.6)	49 (13.7)	87 (12.1)
Mediastinal mass	3 (0.8)	3 (0.8)	6 (0.8)
Skin	8 (2.2)	16 (4.5)	24 (3.3)
Other	12 (3.3)	25 (7.0)	37 (5.2)
Missing	1 (0.3)	1 (0.3)	2 (0.3)
Presence of Auer rods -n (%)			
Absent	220 (61.1)	228 (63.9)	448 (62.5)
Present	100 (27.8)	102 (28.6)	202 (28.2)
Not assessed	22 (6.1)	19 (5.3)	41 (5.7)
Missing	18 (5.0)	8 (2.2)	26 (3.6)

FAB = French-American-British (classification)
All data presented in this table are collected on the CRF on-study form C-1619.
All percentages are calculated on the FAS using N as denominator.

Numbers analysed

Table 33. Analysis sets (All randomized patients)-Study A2301

Analysis Sets	MIDOSTAURIN N=360 n (%)	PLACEBO N=357 n (%)	ALL N=717 n (%)
Full analysis set	360 (100)	357 (100)	717 (100)
ITD <0.7	171 (47.5)	170 (47.6)	341 (47.6)
ITD ≥ 0.7	108 (30.0)	106 (29.7)	214 (29.8)
TKD	81 (22.5)	81 (22.7)	162 (22.6)
Per protocol set	307 (85.3)	303 (84.9)	610 (85.1)
Safety set [1]	343 (95.3)	337 (94.4)	680 (94.8)
PK set	187 (51.9)	1 (0.3)	188 (26.2)

ITD = internal tandem duplication; TKD = tyrosine kinase domain
Note: ITD <0.7, ITD ≥ 0.7 and TKD are the randomization strata.
[1] Two patients randomized to the placebo arm received only midostaurin. These patients are captured as randomized in this table, but are analyzed in the midostaurin treatment arm for the safety analyses.

A total of 3279 patients were screened, and 719 patients were randomised in Study A2301. Two patients were excluded due to informed consent form issues at the site, resulting in 717 patients included in the analyses. Of the 717 patients in the full analysis set (FAS), 709 patients – 355 vs. 354 in the midostaurin and placebo arms, respectively – received at least one dose of study treatment (cytarabine, daunorubicin, or midostaurin/placebo) in the induction phase. 81 patients in the midostaurin arm and 101 patients in the placebo arm received a second cycle of induction therapy.

A total of 441 patients (231 vs. 210 in the midostaurin and placebo arms, respectively) received consolidation therapy, and 129 and 103 patients (midostaurin and placebo, respectively) received all four cycles of consolidation treatment. 205 patients received continuation therapy (120 vs. 85 in the midostaurin and placebo arms, respectively), and 120 patients completed all study treatments per protocol (69 vs. 51 in the respective arms).

All patients had completed study treatment (or discontinued) as of 2 August 2013, however patients continued to be followed for response and survival. The median time from date of randomisation to data cut-off date (1April 2015) was 60.2 months in both treatment arms.

Outcomes and estimation

Primary endpoint - Overall survival

The results of the primary endpoint, OS are presented in Figure 7 and Table 36.

Figure 6 Kaplan-Meier Plot of Overall Survival determined without censoring for SCT- Primary Analysis, data cut-off date of 1 April 2015– Study A2301

No. of patients still at risk
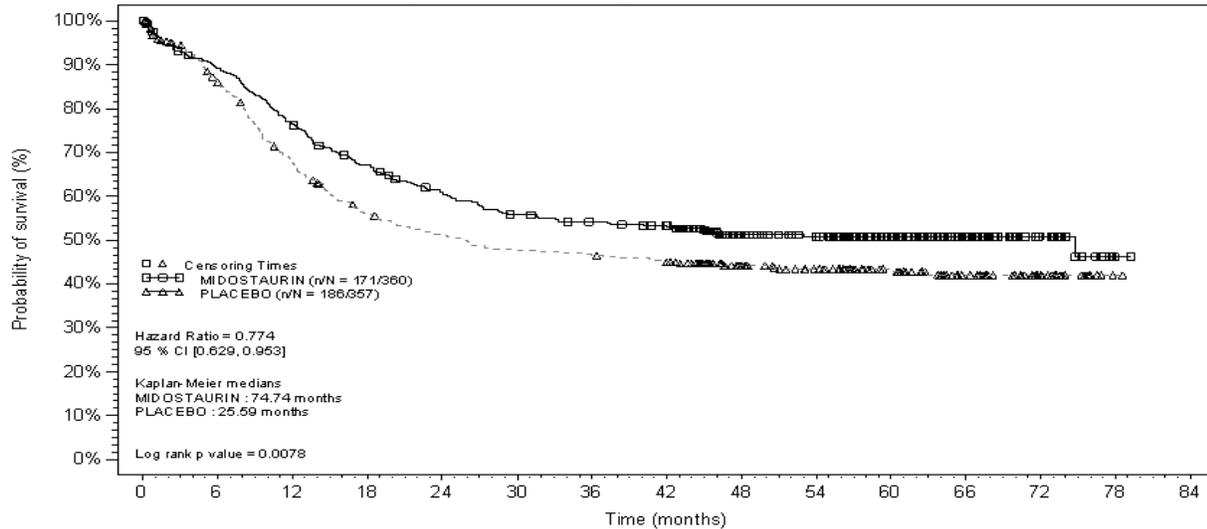
Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
MIDOSTAURIN	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
PLACEBO	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization.

Table 34. Overall survival – non-censored at the time of SCT (FAS)-Study A2301

Overall Survival	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN / PLACEBO [1]	p-value [2]
Number of deaths (%)	171 (47.5)	186 (52.1)	0.774 (0.629, 0.953)	0.0078
Number of censored (%)	189 (52.5)	171 (47.9)		
KM estimates (95% CI)				
at 12 months	0.76 (0.72, 0.81)	0.68 (0.62, 0.72)		
at 36 months	0.54 (0.49, 0.59)	0.47 (0.41, 0.52)		
at 60 months	0.51 (0.45, 0.56)	0.43 (0.38, 0.49)		
25th percentile (95% CI)	12.94 (10.51, 15.08)	9.33 (8.21, 10.84)		
Median (95% CI)	74.74 (31.54, NE)	25.59 (18.63, 42.87)		
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)		

CI = Wald confidence interval; KM = Kaplan-Meier; NE = not estimable

[1] Hazard ratio estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.

[2] p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Greenwood formula is used for CIs of KM estimates. P-values are one-sided.

A multivariable analysis performed to determine the hazard ratio for the treatment effect after adjusting for baseline prognostic factors yielded a similar result: HR 0.79, 95%CI 0.64-0.99, p=0.038.

In the updated analysis, updated mortality figures are provided with a cut-off date of 5 September 2016, which represents an additional 15 months of follow-up compared to the primary analysis (Table 37 and Figure 8).

Table 35. OS, non-censored at the time of SCT in Study A2301 (update) (FAS)

	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN/ PLACEBO	p-value
Number of deaths (%)	176 (48.9)	189 (52.9)	0.787 (0.641, 0.966)	0.0109
Number of censored (%)	184 (51.1)	168 (47.1)		
Alive at cutoff date	11 (3.1)	5 (1.4)		
Last contact date within 6 months before cutoff date	44 (12.2)	42 (11.8)		
Last contact date within 6 months - 1 year before cutoff date	57 (15.8)	53 (14.8)		
Last contact date more than 1 year before cutoff date	72 (20.0)	68 (19.0)		
KM estimates (95% CI)				
at 6 months	0.89 (0.86, 0.92)	0.86 (0.82, 0.89)		
at 12 months	0.76 (0.72, 0.81)	0.68 (0.62, 0.72)		
at 18 months	0.67 (0.62, 0.72)	0.56 (0.50, 0.61)		
at 24 months	0.61 (0.56, 0.66)	0.51 (0.46, 0.57)		
at 36 months	0.54 (0.49, 0.59)	0.47 (0.41, 0.52)		
at 48 months	0.51 (0.46, 0.57)	0.44 (0.39, 0.50)		
at 60 months	0.51 (0.46, 0.56)	0.43 (0.38, 0.49)		
25th percentile (95% CI)	12.94 (10.51, 15.08)	9.33 (8.21, 10.84)		
Median (95% CI)	74.74 (31.54, NE)	25.59 (18.63, 42.87)		
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)		

Hazard ratio (HR) estimated using Cox regression model stratified according to the randomization FLT3 mutation factor. CI: Wald Confidence Interval.

p-value (one-sided) calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

Cutoff: 05-Sept-2016

Figure 7 Kaplan-Meier Plot of Overall Survival – Updated Analysis- – Study A2301
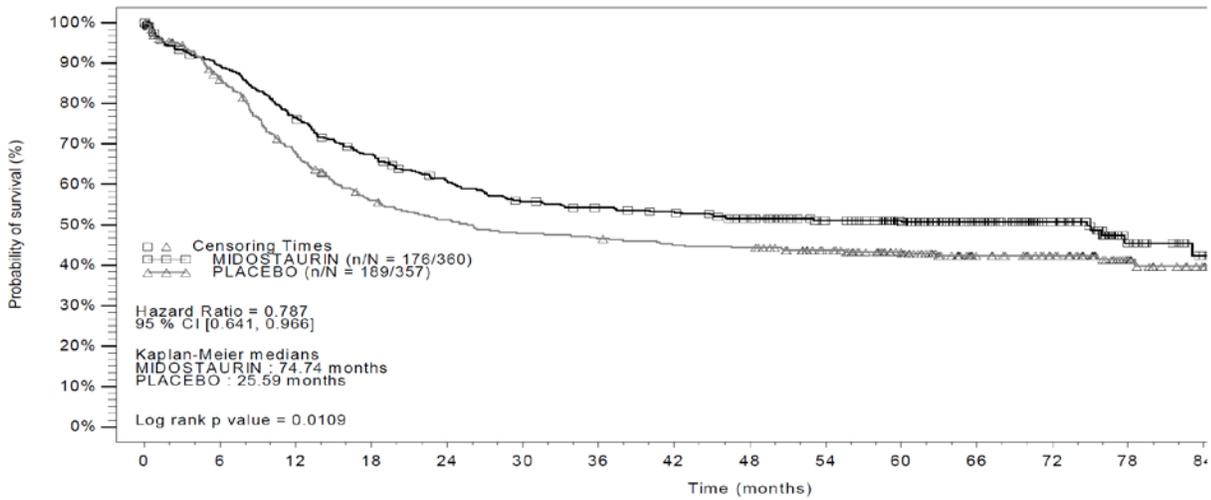
No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	8
MIDOSTAURIN	360	314	269	234	208	189	181	176	164	150	127	91	60	24	1
PLACEBO	357	284	221	179	163	152	148	142	140	124	102	69	56	28	1

Logrank test and Cox regression model stratified for FLT3 mutation strata used in the randomization
Cutoff: 05-Sept-2016.

Subgroup analyses

Subgroup analyses for OS (not censored for SCT) are presented in Figure 9.

Figure 8 Forest plot for subgroup analyses, OS, not censored for SCT (FAS) – Study A2301
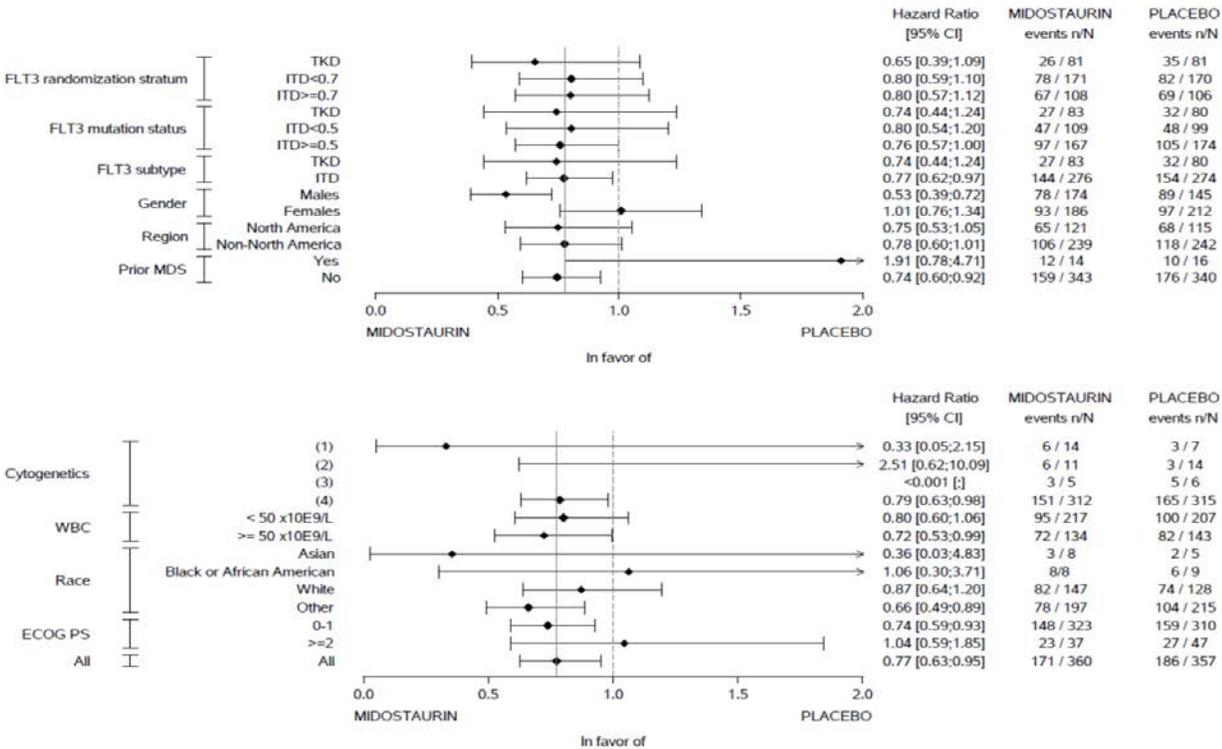
Dotted line shows no effect point. Bold line shows overall treatment effect point (for all patients).
CI = Confidence Interval. M = Midostaurin. P = Placebo.
FLT3 mutation status in categories from the CRF FLT3 results form C-1744.
NA = North America. NNA = Non-North America.
Cytogenetics: (1) AML with t(8;21) (q22; q22) / (2) AML with inv(16) (p13; q22) or t(16; 16) (p13; q22) / (3) AML with
11q23 (MLL) abnormalities / (4) Other. WBC = WBC counts at baseline. ECOG PS = ECOG Performance Status.

The individual overall survival curves for males and females are shown in Figure 10 and in Figure 11.

Figure 9 Kaplan-Meier Plot of Overall survival of males - Study A2301
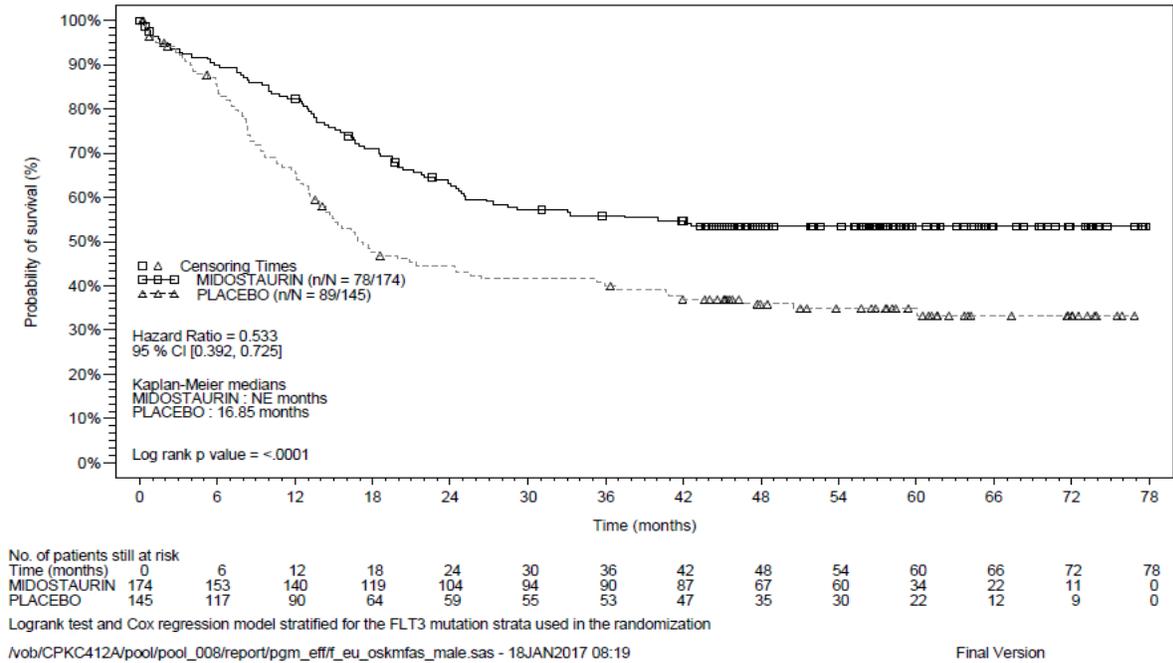
Figure 10 Kaplan-Meier Plot of Overall survival of females (FAS) - Study A2301
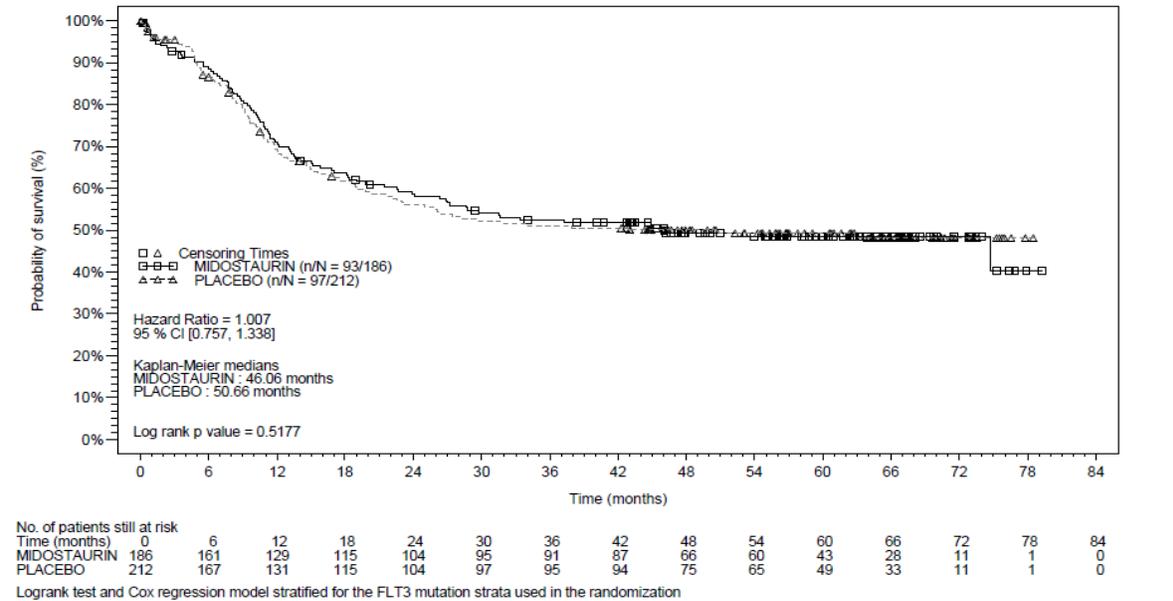
The analysis of the OS non censored at the time of SCT for male and female patients are displayed in Table 38 and Table 39.

Table 36. Overall Survival non censored at the time of SCT for male patients – study A2301 (Full analysis set)

```
                                                                          HR [95% CI]
                                         MIDOSTAURIN     PLACEBO    MIDOSTAURIN / PLACEBO  p-value
Overall Survival                           N=174          N=145             (1)             (2)
_____

Number of deaths (%)                     78 ( 44.8)     89 ( 61.4)    0.533 (0.392, 0.725)  <.0001
Number of censored (%)                   96 ( 55.2)     56 ( 38.6)
  Alive at cutoff date                   81 ( 46.6)     44 ( 30.3)
  Last contact date within 6 months before  4 (  2.3)      0
cutoff date
  Last contact date within 6 months - 1 year   1 (  0.6)    0
before cutoff date
  Last contact date more than 1 year before  10 (  5.7)    12 (  8.3)
cutoff date
```

Table 37. Overall Survival non censored at the time of SCT for female patients – study A2301 (Full analysis set)

```
                                                                          HR [95% CI]
                                         MIDOSTAURIN     PLACEBO    MIDOSTAURIN / PLACEBO  p-value
Overall Survival                           N=186          N=212             (1)             (2)
_____

Number of deaths (%)                     93 ( 50.0)     97 ( 45.8)    1.007 (0.757, 1.338)  0.5177
Number of censored (%)                   93 ( 50.0)    115 ( 54.2)
  Alive at cutoff date                   78 ( 41.9)     89 ( 42.0)
  Last contact date within 6 months before  5 (  2.7)      2 (  0.9)
cutoff date
  Last contact date more than 1 year before  10 (  5.4)    24 ( 11.3)
cutoff date
```

Key secondary endpoint – Event-free survival

The results for the EFS analysis (CR within 60 days of study treatment start), no censored for SCT are displayed in

Table 40 and

Figure 12.

Table 38. Event-free survival (CR within 60 days of study treatment start), no censored for SCT (FAS)

Event-free survival	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] PLACEBO / MIDOSTAURIN [1]	p-value [2]
Number of events (%)	256 (71.1)	280 (78.4)	0.784 (0.662, 0.930)	0.0024
Treatment failure	147 (40.8)	166 (46.5)		
Relapse	91 (25.3)	90 (25.2)		
Death	18 (5.0)	24 (6.7)		
Number of censored (%)	104 (28.9)	77 (21.6)		
KM estimates (95% CI)				
at 12 months	0.43 (0.38, 0.49)	0.31 (0.27, 0.36)		
at 36 months	0.29 (0.24, 0.33)	0.22 (0.18, 0.26)		
at 60 months	0.28 (0.23, 0.33)	0.19 (0.15, 0.24)		
25th percentile (95% CI)	1.15 (0.92, 1.41)	0.99 (0.89, 1.18)		
Median (95% CI)	8.18 (5.42, 10.68)	2.99 (1.91, 5.91)		
75th percentile (95% CI)	NE (27.70, NE)	19.98 (13.86, 47.38)		

CI = Wald confidence interval.
[1] Hazard ratio estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.
[2] p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Greenwood formula is used for CIs of KM estimates.

Figure 11 Kaplan-Meier Plot of Event-free survival (CRs within 60 days of study treatment start), non-censored for SCT (FAS) - Study A2301
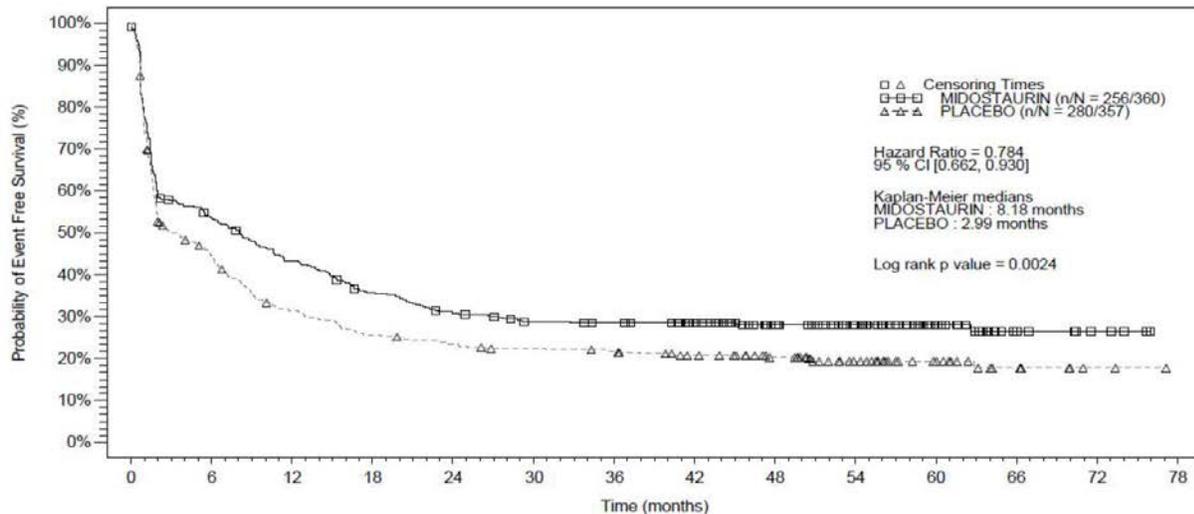
No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
MIDOSTAURIN	360	190	153	124	106	95	92	83	65	51	27	9	4	0
PLACEBO	357	153	106	86	78	73	70	60	49	32	18	8	2	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization

A summary of results of EFS sensitivity analyses is diosvcpayed in **Table 41**.

Table 39. Summary of results of EFS sensitivity analyses

	Median EFS (95% CI), months		HR (95% CI)
Sensitivity analysis	**Midostaurin** **N=307**	**Placebo** **N=303**	
Considering all CRs during induction without the 60-day window, FAS	10.15 (8.05, 13.90)	5.55 (2.89, 6.70)	0.728 (0.613, 0.866)
PPS	8.05 (5.26, 10.68)	4.57 (1.97, 6.21)	0.824 (0.685, 0.991)
Where relapse events are not considered if observed after ≥ 2 consecutive missing assessments, FAS	8.18 (5.42, 10.68)	2.99 (1.91, 5.91)	0.792 (0.668, 0.939)
For patients without a CR, the date of treatment failure = date of randomization + 1, FAS	8.18 (5.42, 10.68	3.58 (0.03, 5.91	0.783 (0.659, 0.929)
Considering all CRs up to 30 days after treatment discontinuation, FAS	11.37 (8.74, 15.31)	6.18 (4.83, 7.52)	0.735 (0.617, 0.875)

CR = complete remission; EFS = event-free survival; FAS = full analysis set; PPS = per protocol set

Results of subgroup analyses for EFS are displayed in
Figure 13.

Figure 12 Forest plot for subgroup analyses, EFS (CRs defined as within 60 days of study treatment start), non-censored for SCT (FAS) - Study A2301

		Hazard Ratio [95% CI]	MIDOSTAURIN events n/N	PLACEBO events n/N
FLT3 randomization stratum	TKD	0.65 [0.44;0.96]	43 / 81	57 / 81
	ITD<0.7	0.85 [0.67;1.09]	127 / 171	131 / 170
	ITD>=0.7	0.77 [0.58;1.04]	86 / 108	92 / 106
FLT3 mutation status	TKD	0.67 [0.45;0.99]	44 / 83	55 / 80
	ITD<0.5	0.86 [0.63;1.18]	81 / 109	77 / 99
	ITD>=0.5	0.77 [0.61;0.98]	130 / 167	146 / 174
FLT3 subtype	TKD	0.67 [0.45;0.99]	44 / 83	55 / 80
	ITD	0.81 [0.67;0.97]	211 / 276	224 / 274
Gender	Males	0.79 [0.61;1.03]	118 / 174	110 / 145
	Females	0.81 [0.65;1.02]	138 / 186	170 / 212
Region	North America	0.78 [0.57;1.06]	79 / 121	87 / 115
	Non-North America	0.79 [0.64;0.97]	177 / 239	193 / 242
Prior MDS	Yes	2.10 [0.91;4.85]	13 / 14	14 / 16
	No	0.76 [0.64;0.91]	241 / 343	265 / 340

0.0 0.5 1.0 1.5 2.0
MIDOSTAURIN — PLACEBO
In favor of

		Hazard Ratio [95% CI]	MIDOSTAURIN events n/N	PLACEBO events n/N
Cytogenetics	(1)	0.28 [0.08;0.91]	9 / 14	7/7
	(2)	0.91 [0.35;2.40]	8 / 11	10 / 14
	(3)	<0.001 [;]	4 / 5	6/6
	(4)	0.82 [0.68;0.98]	225 / 312	245 / 315
WBC	< 50 x10E9/L	0.81 [0.64;1.01]	147 / 217	155 / 207
	>= 50 x10E9/L	0.77 [0.59;1.00]	104 / 134	119 / 143
Race	Asian	0.75 [0.14;4.09]	5 / 8	3 / 5
	Black or African American	1.09 [0.36;3.35]	8/8	8 / 9
	White	0.91 [0.68;1.20]	99 / 147	93 / 128
	Other	0.72 [0.58;0.90]	144 / 197	176 / 215
ECOG PS	0-1	0.77 [0.64;0.93]	228 / 323	243 / 310
	>=2	0.87 [0.53;1.44]	28 / 37	37 / 47
All	All	0.78 [0.66;0.93]	256 / 360	280 / 357

0.0 0.5 1.0 1.5 2.0
MIDOSTAURIN — PLACEBO
In favor of

Dotted line shows no effect point. Bold line shows overall treatment effect point (for all patients).
CI = Confidence Interval. M = Midostaurin. P = Placebo.
FLT3 mutation status in categories from the CRF FLT3 results form C-1744.
NA = North America. NNA = Non-North America.
Cytogenetics: (1) AML with t(8;21) (q22; q22) / (2) AML with inv(16) (p13; q22) or t(16; 16) (p13; q22) / (3) AML with 11q23 (MLL) abnormalities / (4) Other. WBC = WBC counts at baseline. ECOG PS = ECOG Performance Status.

The EFS considering all complete remissions in induction non censored at the time of SCT for male and female patients are displayed in Table 42 and Table 43 respectively.

Table 40. Event Free Survival considering all complete remissions in induction non censored at the time of SCT for male patients – study A2301 (Full analysis set)

Event Free Survival (EFS)	MIDOSTAURIN N=174	PLACEBO N=145	HR [95% CI] PLACEBO / MIDOSTAURIN [1]	p-value [2]
Number of events (%)	110 (63.2)	111 (76.6)	0.660 (0.506, 0.861)	0.0010
Treatment failure	53 (30.5)	58 (40.0)		
Relapse	47 (27.0)	39 (26.9)		
Death	10 (5.7)	14 (9.7)		
Number of censored (%)	64 (36.8)	34 (23.4)		
No post-baseline data	1 (0.6)	0		
In remission at last planned assessment prior to cutoff date	63 (36.2)	34 (23.4)		
Last assessment within 6 months before cutoff date	46 (26.4)	23 (15.9)		
Last assessment within 6 months - 1 year before cutoff date	8 (4.6)	4 (2.8)		
Last assessment more than 1 year before cutoff date	9 (5.2)	7 (4.8)		

Table 41. Event Free Survival considering all complete remissions in induction non censored at the time of SCT for female patients – study A2301 (Full analysis set)

Event Free Survival (EFS)	MIDOSTAURIN N=186	PLACEBO N=212	HR [95% CI] PLACEBO / MIDOSTAURIN [1]	p-value [2]
Number of events (%)	134 (72.0)	166 (78.3)	0.825 (0.656, 1.037)	0.0479
Treatment failure	72 (38.7)	92 (43.4)		
Relapse	51 (27.4)	63 (29.7)		
Death	11 (5.9)	11 (5.2)		
Number of censored (%)	52 (28.0)	46 (21.7)		
In remission at last planned assessment prior to cutoff date	52 (28.0)	46 (21.7)		
Last assessment within 6 months before cutoff date	37 (19.9)	24 (11.3)		
Last assessment within 6 months - 1 year before cutoff date	3 (1.6)	9 (4.2)		
Last assessment more than 1 year before cutoff date	12 (6.5)	13 (6.1)		

Secondary endpoint – Overall survival censored for SCT

The results of the analysis of OS censored at the time of SCT are presented in Table 44.

Table 42 Overall survival – censored for SCT (FAS) - Study A2301

Overall Survival (OS)	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN / PLACEBO (1)	One-sided p-value (2)
Number of deaths (%)	71 (19.7)	81 (22.7)	0.749 (0.544, 1.031)	0.0373
Number of censored (%)	289 (80.3)	276 (77.3)		
KM estimates (95% CI)				
at 1 month	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)		
at 12 months	0.82 (0.76, 0.86)	0.70 (0.63, 0.76)		
at 36 months	0.65 (0.57, 0.72)	0.58 (0.49, 0.65)		
at 60 months	0.64 (0.56, 0.71)	0.56 (0.47, 0.63)		
25th percentile (95% CI)	17.08 (12.39, 26.94)	9.95 (7.85, 14.39)		
Median (95% CI)	NE (NE, NE)	NE (27.43, NE)		
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)		

(1) Hazard ratio (HR) estimated using Cox regression model stratified according to the randomization FLT3 mutation factor. CI: Wald Confidence Interval.
(2) p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Greenwood formula is used for CIs of KM estimates. P-values are one-sided.

Overall survival by SCT status

In addition to the censored analysis for OS, additional analyses were performed to determine if there was a treatment benefit following SCT.

The results of the analysis of OS (non-censored for SCT) by SCT status is displayed in Table 45.

Table 43. OS (non-censored for SCT) by SCT status in Study A2301 (FAS)

Overall Survival	SCT		No SCT	
	MIDOSTAURIN N=214	PLACEBO N=197	MIDOSTAURIN N=146	PLACEBO N=160
Number of deaths (%)	100 (46.7)	105 (53.3)	71 (48.6)	81 (50.6)
Number of censored (%)	114 (53.3)	92 (46.7)	75 (51.4)	79 (49.4)
KM estimates (95% CI)				
at 6 month	0.97 (0.94, 0.99)	0.94 (0.90, 0.96)	0.77 (0.69, 0.83)	0.75 (0.67, 0.81)
at 12 months	0.84 (0.78, 0.88)	0.77 (0.71, 0.83)	0.66 (0.57, 0.73)	0.54 (0.45, 0.62)
at 18 months	0.74 (0.67, 0.79)	0.62 (0.55, 0.69)	0.58 (0.49, 0.65)	0.47 (0.38, 0.55)
at 24 months	0.66 (0.59, 0.72)	0.56 (0.49, 0.63)	0.53 (0.45, 0.61)	0.45 (0.36, 0.53)
at 36 months	0.57 (0.50, 0.64)	0.50 (0.42, 0.56)	0.50 (0.41, 0.58)	0.42 (0.34, 0.50)
at 48 months	0.53 (0.46, 0.60)	0.47 (0.40, 0.54)	0.49 (0.40, 0.57)	0.41 (0.32, 0.49)
25th percentile (95% CI)	16.59 (13.11, 21.52)	12.39 (10.58, 14.88)	6.74 (3.29, 10.18)	5.91 (4.07, 7.62)
Median (95% CI)	74.74 (37.26, NE)	35.94 (22.57, NE)	31.70 (16.92, NE)	14.65 (9.95, 36.90)
75th percentile (95% CI)	NE (74.74, NE)	NE	NE	NE
HR [95% CI] MIDOSTAURIN / PLACEBO	0.780 (0.593, 1.026)		0.798 (0.580, 1.098)	
p-value	0.0376		0.0822	

The K-M curve for OS (non-censored for SCT) for patients with SCT and the K-M curve for OS for patients without SCT are discpayed in Figure 14 and in Figure 15.

Figure 13. OS (non-censored for SCT) for patients with SCT in Study A2301 (FAS)
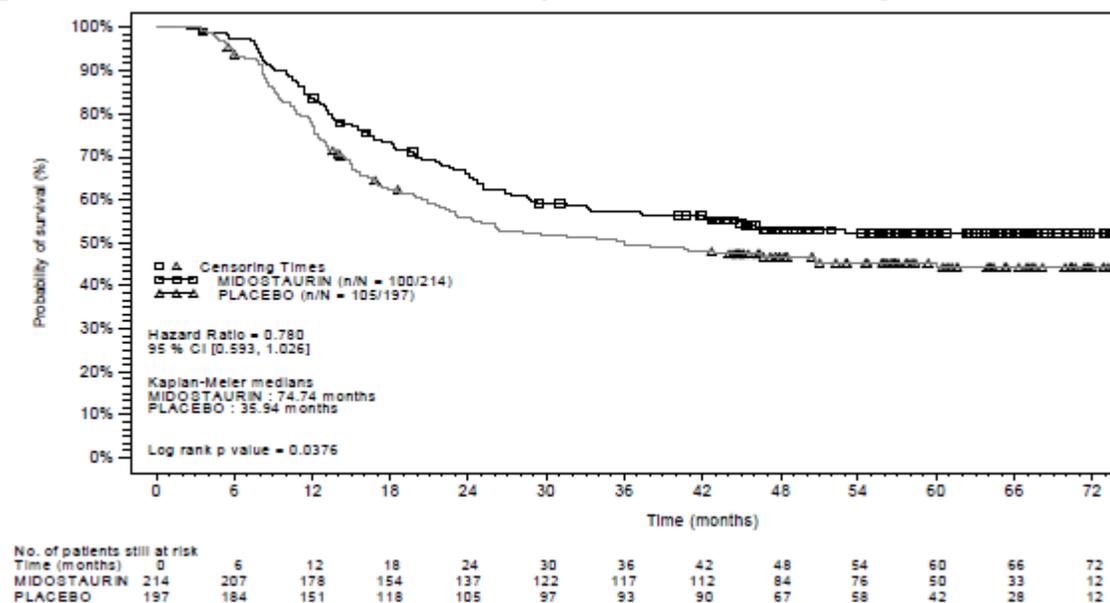
Figure 14 OS for patients without SCT in Study A2301 (FAS)
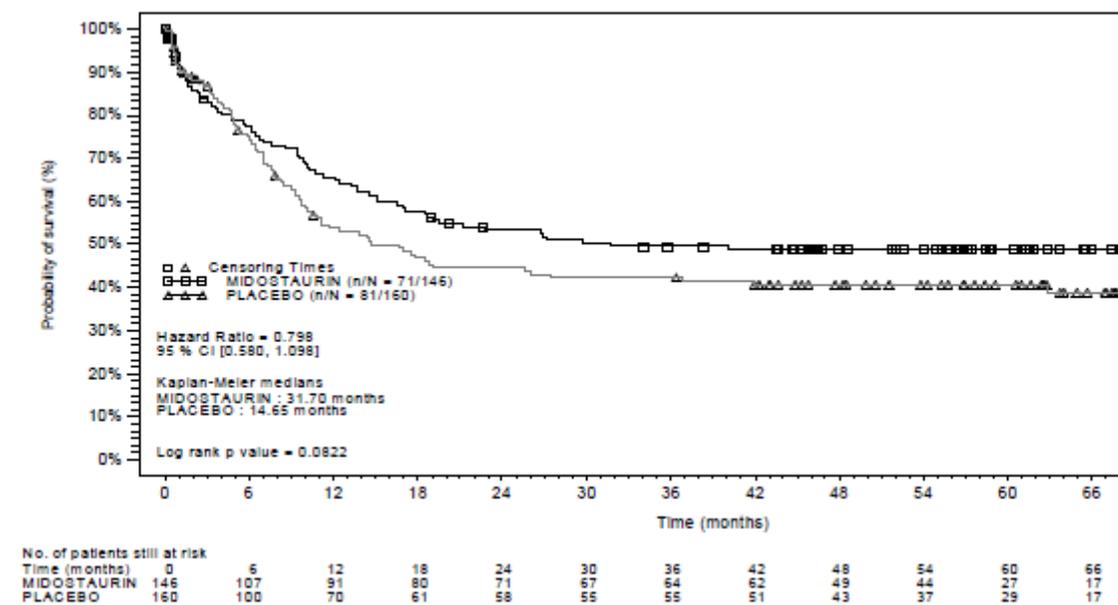
The K-M curve for OS from the time of SCT during CR1 (SCT in CR in Cycle 1) in induction is displayed in Figure 16.

Figure 15 Kaplan-Meier curve for OS, from the time of SCT during CR1 in induction (FAS) - Study A2301
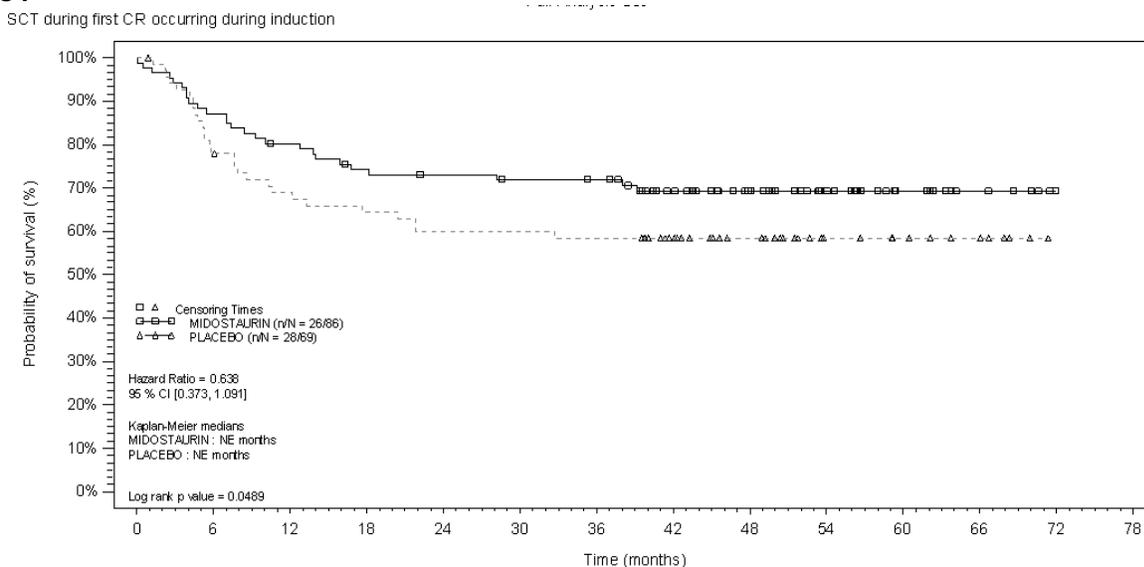
Secondary endpoint – Event-free survival censored for SCT

The results from the analysis of EFS (all CRs during induction), censored at the time of SCT is displayed in Table 46.

Table 44.Event-free survival, sensitivity analysis (all CRs during induction), censored at the time of SCT (FAS)

Event-free survival	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN / PLACEBO [1]	p-value [2]
Number of events (%)	224 (62.2)	242 (67.8)	0.813 (0.677, 0.975)	0.0124
Treatment failure	147 (40.8)	166 (46.5)		
Relapse	75 (20.8)	68 (19.0)		
Death	2 (0.6)	8 (2.2)		
Number of censored (%)	136 (37.8)	115 (32.2)		

KM estimates (95% CI)

at 12 months	0.43 (0.38, 0.49)	0.30 (0.25, 0.35)
at 36 months	0.25 (0.20, 0.31)	0.23 (0.18, 0.28)
at 60 months	0.25 (0.20, 0.31)	0.21 (0.16, 0.27)
25th percentile (95% CI)	1.15 (0.92, 1.41)	0.99 (0.89, 1.18)
Median (95% CI)	8.31 (5.78, 10.68)	2.83 (1.91, 5.91)
75th percentile (95% CI)	NE (21.22, NE)	19.98 (11.76, NE)

CI = Wald confidence interval; KM = Kaplan-Meier; NE = not estimable

[1] Hazard ratio estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.

[2] p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor. Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

Greenwood formula is used for CIs of KM estimates. P-values are one-sided.

An EFS event is defined as a failure to obtain a complete remission within the 60 days following initiation of protocol therapy, relapse from complete remission, or death due to any cause, whichever occurs first.

Secondary endpoint – Complete response rate

The results of the complete remission within 60 days of study treatment start and of the complete remission during induction are displayed in Table 47 and in Table 48 respectively.

Table 45. Complete remission within 60 days of study treatment start (FAS)

Complete remission	MIDOSTAURIN N=360 n (%)	PLACEBO N=357 n (%)	Difference in proportions and 95% CI [1]	p-value [2]
Complete remission	212 (58.9)	191 (53.5)	0.05 (-0.02,0.13)	0.073
Induction - end of cycle 1	186 (51.7)	154 (43.1)	0.09 (0.01 ,0.16)	
Induction – end of cycle 2	14 (3.9)	26 (7.3)	-0.03 (-0.07,-0.00)	
Consolidation	5 (1.4)	4 (1.1)	0.00 (-0.01,0.02)	
After treatment discontinuation	7 (1.9)	7 (2.0)	-0.00 (-0.02,0.02)	
No complete remission	148 (41.1)	166 (46.5)		

[1] Wald 95% Confidence Interval.

[2] One-sided p-value calculated using Cochran-Mantel-Haenszel test for two proportions adjusted for the FLT3 randomization stratum.

Complete Remission is only considered if it occurs by 60 days after initial induction therapy started.

For the Overall category, CRs which occurred outside of induction but within 60 days are considered.

Table 46 Complete remission during induction (FAS)

Complete remission	MIDOSTAURIN N=360 n (%)	PLACEBO N=357 n (%)	Difference in proportions and 95% CI [1]	p-value [2]
Complete remission	234 (65.0)	207 (58.0)	0.07 (-0.00,0.14)	0.027
Induction – end of cycle 1	186 (51.7)	154 (43.1)	0.09 (0.01 ,0.16)	
Induction – end of cycle 2	48 (13.3)	53 (14.8)	-0.02 (-0.07,0.04)	
No complete remission	126 (35.0)	150 (42.0)		

[1] Wald 95% Confidence Interval.
[2] One-sided p-value calculated using Cochran-Mantel-Haenszel test for two proportions adjusted for the FLT3 randomization stratum.
Complete Remission is considered if it occurs during induction.

CR rates per mutational stratum were: TKD: 69.1% midostaurin versus 59.3% placebo; ITD allelic ratio <0.7: 67.8% midostaurin versus 54.1% placebo; ITD allelic ratio ≥ 0.7: 57.4% midostaurin versus 63.2% placebo.

The results of the clinical response, considering all complete remissions during induction, by gender for males and females are diaplsyed in Table 49 and in Table 50 respectively.

Table 47 Clinical response, considering all Complete Remissions during induction, by gender – study A2301 (Full analysis set) - Male

				MIDOSTAURIN-PLACEBO	
Clinical response	MIDOSTAURIN N=174 n(%)	PLACEBO N=145 n(%)	Difference in proportions and 95% CI (1)	Odds Ratio 95% CI (2)	p-value
Induction – end of Cycle 1					
Complete Remission	95 (54.6)	63 (43.4)	0.11 (0.00 ,0.22)		
No complete Remission	79 (45.4)	82 (56.6)	-0.11 (-0.22,-0.00)		
Induction – end of Cycle 2					
Complete Remission	25 (14.4)	24 (16.6)	-0.02 (-0.10,0.06)		
No complete Remission	14 (8.0)	23 (15.9)	-0.08 (-0.15,-0.01)		
Overall	174	145			
Complete Remission	120 (69.0)	87 (60.0)	0.09 (-0.02,0.19)	0.675 (0.425,1.072)	0.048
Induction 1	95 (54.6)	63 (43.4)	0.11 (0.00 ,0.22)		
Induction 2	25 (14.4)	24 (16.6)	-0.02 (-0.10,0.06)		
No complete Remission	54 (31.0)	58 (40.0)			

Table 48 Clinical response, considering all Complete Remissions during induction, by gender – study A2301 (Full analysis set) - Female

				MIDOSTAURIN-PLACEBO	
Clinical response	MIDOSTAURIN N=186 n(%)	PLACEBO N=212 n(%)	Difference in proportions and 95% CI (1)	Odds Ratio 95% CI (2)	p-value
Induction – end of Cycle 1					
Complete Remission	91 (48.9)	91 (42.9)	0.06 (-0.04,0.16)		
No complete Remission	95 (51.1)	121 (57.1)	-0.06 (-0.16,0.04)		
Induction – end of Cycle 2					
Complete Remission	23 (12.4)	29 (13.7)	-0.01 (-0.08,0.05)		
No complete Remission	19 (10.2)	26 (12.3)	-0.02 (-0.08,0.04)		
Overall	186	212			
Complete Remission	114 (61.3)	120 (56.6)	0.05 (-0.05,0.14)	0.824 (0.552,1.230)	0.172
Induction 1	91 (48.9)	91 (42.9)	0.06 (-0.04,0.16)		
Induction 2	23 (12.4)	29 (13.7)	-0.01 (-0.08,0.05)		
No complete Remission	72 (38.7)	92 (43.4)			

Secondary endpoint – Disease-free survival

The results of the DFS (CR within 60 days of study treatment start), non-censored at the time of SCT are displayed Table 51.

Table 49 Disease-free survival (CR within 60 days of study treatment start), non-censored at the time of SCT (FAS)

Disease-free survival	MIDOSTAURIN N=360	PLACEBO N=357	HR [95% CI] MIDOSTAURIN / PLACEBO [1]	p-value [2]
Number of patients at risk [3]	212 (58.9)	191 (53.5)		
Number of events (%)	109 (51.4)	114 (59.7)	0.709 (0.545, 0.923)	0.0051
Relapse	91 (42.9)	90 (47.1)		
Death	18 (8.5)	24 (12.6)		
Number of censored (%)	103 (48.6)	77 (40.3)		
at 12 months	0.71 (0.64, 0.76)	0.57 (0.49, 0.64)		
at 36 months	0.48 (0.41, 0.55)	0.40 (0.33, 0.48)		
at 60 months	0.48 (0.41, 0.54)	0.37 (0.29, 0.44)		
25th percentile (95% CI)	9.82 (7.82, 13.40)	6.14 (4.93, 7.26)		
Median (95% CI)	26.74 (19.35, NE)	15.51 (11.33, 23.46)		
75th percentile (95% CI)	NE (NE, NE)	NE (61.44, NE)		

CI = Wald confidence interval; KM = Kaplan-Meier

[1] Hazard ratio estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.

[2] p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

[3] Patients who achieved complete remission by 60 days after initial induction therapy started.

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982). Greenwood formula is used for CIs of KM estimates.

Considering all CRs during induction (without 60 day restriction), the median DFS for patients in the midostaurin arm compared to the placebo arm was 28.1 months vs. 14.1 months, respectively. The risk of having a DFS event was reduced by 34% in favour of the midostaurin arm (HR=0.66; 95%CI: 0.52-0.85; p=0.0006, one-sided).

When in the analysis of DFS there was censored for SCT, and considering all CRs in induction, the median DFS was longer in the midostaurin arm compared to the placebo arm (20.7 months vs. 14.5 months, respectively) (HR=0.72; 95%CI: 0.54-0.97).

For patients who had an SCT in CR1, DFS was assessed after SCT. The risk of relapse or death was reduced by 48% for patients in the midostaurin arm (HR=0.52; 95%CI: 0.32-0.84).

Secondary endpoint – Cumulative incidence of relapse

The results of the Cumulative incidence of relapse, considering all complete remissions in induction and non-censored at the time of SCT are displayed in **Figure 17**.

Figure 16. Cumulative incidence of relapse, considering all complete remissions in induction and non-censored at the time of Stem Cell Transplantation - Study A2301 (FAS) Full Analysis Set
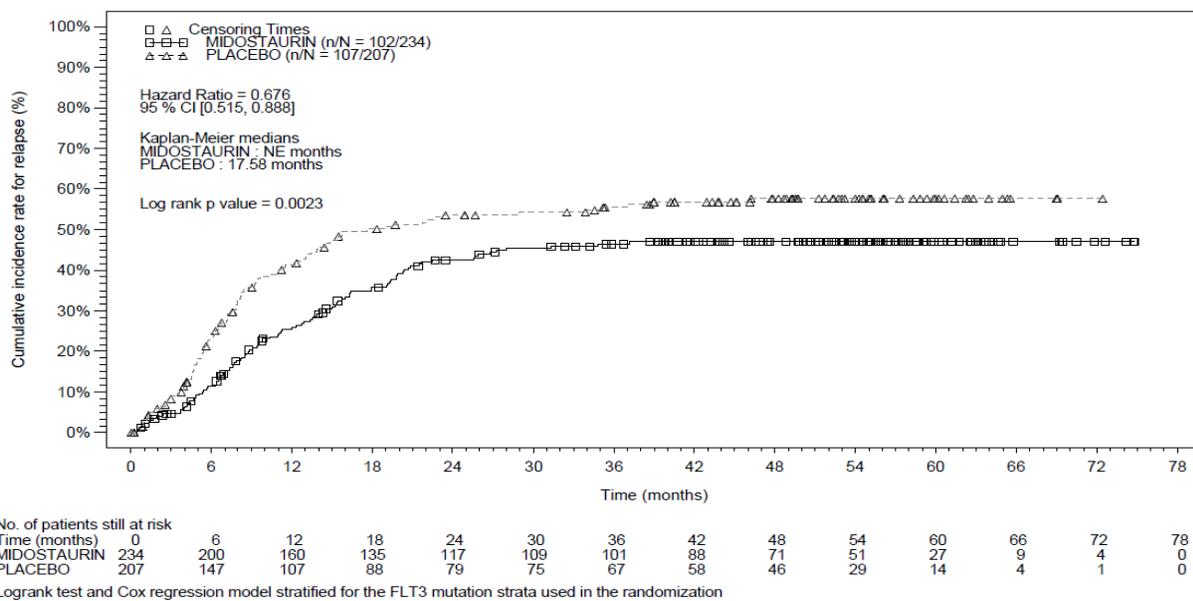
The results of the Cumulative incidence of relapse by gender and FLT3 randomization stratum are displayed in Table 52 and in

Table 53 for males and female respectiverly.

Table 50 Cumulative Incidence of Relapse (considering definition of CRs in induction) overall, by gender, and by gender and FLT3 randomization stratum – study A2301 (Full analysis set)-Male

Remission Duration	MIDOSTAURIN N=174	PLACEBO N=145	HR [95% CI] MIDOSTAURIN / PLACEBO (1)	p-value (2)
Number of patients at risk (3)	120 (69.0)	87 (60.0)		
Number of events (%)	49 (40.8)	41 (47.1)	0.662 (0.436, 1.006)	0.0259
Relapse	47 (39.2)	39 (44.8)		
Death due to AML	2 (1.7)	2 (2.3)		
Number of censored (%)	71 (59.2)	46 (52.9)		
In remission at last planned assessment prior to cutoff date	63 (52.5)	34 (39.1)		
Last assessment within 6 months before cutoff date	46 (38.3)	23 (26.4)		
Last assessment within 6 months - 1 year before cutoff date	8 (6.7)	4 (4.6)		
Last assessment more than 1 year before cutoff date	9 (7.5)	7 (8.0)		
Death not due to AML	8 (6.7)	12 (13.8)		

Table 51 Cumulative Incidence of Relapse (considering definition of CRs in induction) overall, by gender, and by gender and FLT3 randomization stratum – study A2301 (Full analysis set)-Female

```
                                                                      HR [95% CI]
                                      MIDOSTAURIN      PLACEBO    MIDOSTAURIN / PLACEBO  p-value
Remission Duration                      N=186          N=212            (1)              (2)
_____

Number of patients at risk (3)        114 ( 61.3)    120 ( 56.6)
Number of events (%)                    53 ( 46.5)     66 ( 55.0)   0.742 (0.516, 1.069)   0.0539
  Relapse                               51 ( 44.7)     63 ( 52.5)
  Death due to AML                       2 (  1.8)      3 (  2.5)
Number of censored (%)                  61 ( 53.5)     54 ( 45.0)
  In remission at last planned assessment 52 ( 45.6)   46 ( 38.3)
prior to cutoff date
    Last assessment within 6 months before 37 ( 32.5)  24 ( 20.0)
cutoff date
    Last assessment within 6 months - 1 year 3 ( 2.6)   9 (  7.5)
before cutoff date
    Last assessment more than 1 year before 12 ( 10.5)  13 ( 10.8)
cutoff date
  Death not due to AML                   9 (  7.9)      8 (  6.7)
```

Secondary endpoint – Stem cell transplantation rates

Overall, 57% of patients underwent SCT, exceeding the pre-study estimated SCT rate of 15%, and revised rate (per protocol amendment no. 4) of 25%. The SCT rates were similar in the two treatment arms: 59.4% in the midostaurin arm and 55.2% in the placebo arm. The higher than anticipated transplant rates reflect the increasing use of SCT in clinical practice for higher risk AML patients during the course of this study.

There were no major differences in SCT rate between treatment arms, or between the types of SCT used.

Secondary endpoint – DFS after completion of one year continuation therapy

DFS was assessed for all patients having a CR within 60 days of treatment initiation, and who had completed continuation therapy (i.e. had taken study drug for a minimum of 335 days) and were still in CR. The definition of DFS was modified to reflect time from end of continuation to relapse/death from any cause. This analysis included 59 patients in the midostaurin arm and 41 patients in the placebo arm. The estimated probability to be without an event at 1 year after completing continuation therapy for patients on midostaurin was 74% (95% CI: 0.61, 0.84) compared to 90% (95% CI: 0.76, 0.96) for patients on placebo (HR=1.42 [95% CI: 0.63, 3.22]).

Analyses to determine the effect of maintenance / continuation therapy

An analysis to assess the benefit of maintenance/continuation therapy after consolidation therapy, by performing exploratory analyses comparing the patients entering continuation phase in the two arms for OS and DFS as measured from the start of the continuation phase (no re-randomisation prior to continuation therapy was performed in the study) was conducted.

More patients in the midostaurin arm (n=120) than in the placebo arm (n=85) entered the continuation phase and were included in this analysis. Most patient and disease characteristics were balanced between the two treatment arms with the exception of fewer patients presenting with extramedullary disease in the midostaurin arm (19.2% to midostaurin arm vs. 28.2% to placebo arm).

Overall survival was assessed from the start of the continuation phase (120 patients on midostaurin and 85 patients on placebo). The HR was 0.80 (95%CI: 0.50-1.28). With 48 patients in the midostaurin arm and 24 patients in the placebo arm censored for SCT, the HR was 0.47 (95%CI: 0.23-0.97).

Ancillary analyses

Gender subgroups by FLT3 status (FLT3 TKD, FLT3 ITD allelic ratio <0.7, FLT3 ITD allelic ratio ≥ 0.7)

The results of the analysis of the gender subgroups by *FLT3* status (*FLT3* TKD, *FLT3* ITD allelic ratio <0.7, *FLT3* ITD allelic ratio ≥ 0.7) are presented in Table 54.

Table 52 Hazard ratios for the six subgroups defined by gender and *FLT3* randomisation stratum (FAS) - Study A2301

```
Multivariate analysis for OS, including treatment, FLT3 randomization stratum,
                gender and interaction terms - study A2301
                        Full Analysis Set

Factors in Cox regression model                        P-value*
----------------------------------------------------------------

Treatment: Midostaurin vs Placebo                      0.0768
Gender: Male vs Female                                 0.2959
FLT3 randomization stratum                             0.0086
Treatment * Gender                                     0.4059
Treatment * FLT3 randomization stratum                 0.0542
Gender*FLT3 randomization stratum                      0.0208
Treatment*Gender*FLT3 randomization stratum            0.0195

Gail-Simon test of qualitative interaction             0.38259 #
```

Overall Survival (OS)	Midostaurin Event n / N	Placebo Event n / N	HR (95% CI)
Male, ITD < 0.7	32/ 83	48/ 76	0.42 (0.27, 0.66)
Female, ITD < 0.7	46/ 88	34/ 94	1.43 (0.92, 2.23)
Male, ITD ≥ 0.7	32/ 48	28/ 36	0.59 (0.36, 0.99)
Female, ITD ≥ 0.7	35/ 60	41/ 70	0.91 (0.58, 1.43)
Male, TKD stratum	14/ 43	13/ 33	0.83 (0.39, 1.77)
Female, TKD stratum	12/ 38	22/ 48	0.55 (0.27, 1.11)

HR calculated using a Cox regression model.
CI=Wald Confidence Interval.

Genetic differences in PD response

Analyses on the association between NPM1 and CEBPA mutations and response to midostaurin in patients with FLT3-mutated AML were submitted. Information on CEPBA mutation status was available in 236 patients. Due to the low mutation rate (6/236 patients, 2.5%), analyses regarding CEBPA were not further pursued.

The NPM1 analysis set (NPM1AS) was defined as all randomized patients from Study A2301 with a signed consent for research studies and NPM1 mutation status results, and included 563 patients (294 in the midostaurin arm and 269 in the placebo arm). Baseline disease characteristics and FLT3 mutation status were generally balanced across treatment arms within NPM1AS, and similar to the FAS. Fewer females randomized to the midostaurin arm (52.0% females) than the placebo arm (61.7% females). NPM1 mutations were more frequent in females (201/319 patients, 63.0%) than males (123/244 patients, 50.4%), which is consistent with the higher incidence of NPM1 mutations in females reported in literature. Within the female population, there were 91/153 patients (59.5%) with NPM1 mutations in the midostaurin arm and 110/166 patients (66.3%) with NPM1 mutations in the placebo arm. Within the male population there were

71/141 (50.4%) patients with NPM1 mutations in the midostaurin arm and 52/103 (50.5%) patients with NPM1 mutations in the placebo arm.

Subgroup analyses in patients with known NPM1 status showed that OS and EFS benefit from midostaurin occurred in all subgroups of patients according to NPM1 status: NPM1 mutated, OS: HR 0.72 (95%CI: 0.52-1.01), EFS: HR=0.73 (95% CI: 0.56-0.96); NPM1 wildtype, OS: HR 0.74 (95%CI: 0.54-1.03), EFS: HR=0.72 (95% CI: 0.53-0.96) (data not shown).

OS, EFS, CR and DFS by age groups (A2301)

Several analyses were conducted to evaluate effect of age on efficacy outcomes in Study A2301. The results of analyses of CR, EFS, DFS and OS for 5 subgroups defined by age are summarized in (Figure 18).

Figure 17. **OS, EFS, CR and DFS by age groups (A2301)**
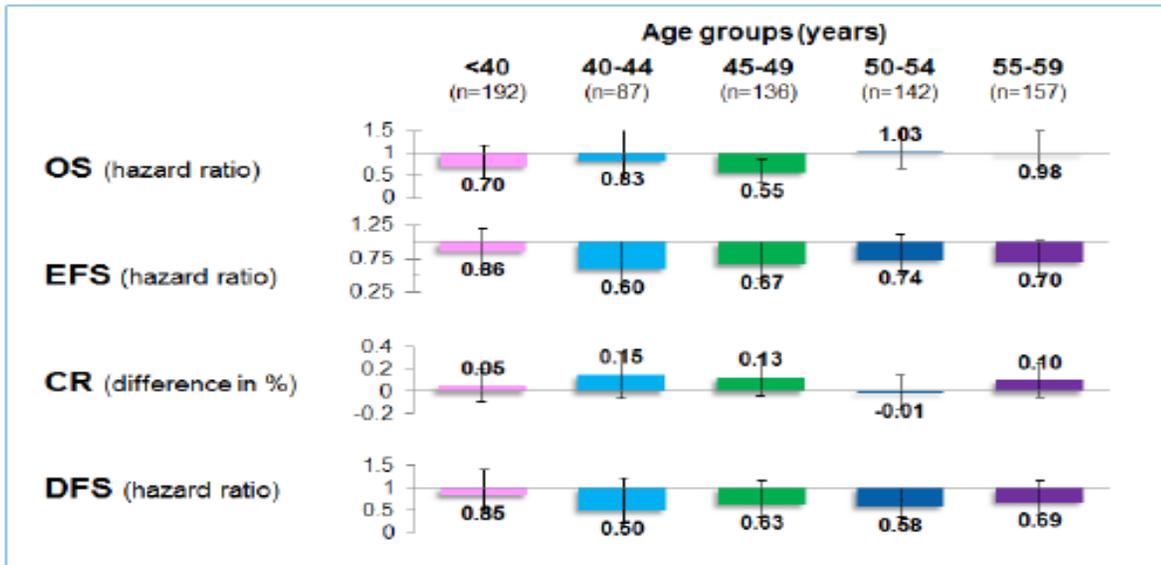
- **Study D2201**

Methods

Study D2201 was a single arm, phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukaemia with or without an AHNMD.

Patients were required to have a diagnosis of ASM or MCL with or without an AHNMD, and at least one measurable C-finding as per modified Valent/Cheson criteria.

Study Participants

Key inclusion criteria

- Male or female patients aged ≥ 18 years of age who provided written informed consent

- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 3 and life expectancy >12 weeks

- Electrocardiogram (ECG) with a QTcF ≤ 450 ms

- Patients must have the following laboratory values:

  - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5 x upper limit of normal (ULN) if the elevation was solely due to ASM/SM-AHN/MCL ; otherwise AST, ALT ≤ 2.5 x ULN

  - Serum bilirubin ≤ 3x ULN if the elevation was solely due to ASM/MCL; otherwise serum bilirubin ≤ 1.5 x ULN

  - Serum creatinine ≤ 2.0 mg/dL

The diagnosis of SM was based on WHO criteria (Valent et al. 2001); the sub-variants of SM were defined using the algorithm according to WHO criteria as presented in Figure 19

As shown in Figure 19, 1 major plus 1 minor, or 3 minor SM criteria were required for diagnosis of SM.

- Major criterion: Multifocal dense infiltrates of MCs (≥ 15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)

- Minor criteria: Greater than 25% of all MCs were atypical cells (type I or type II) on BM smears or were spindle-shaped in MC infiltrates detected on sections of visceral organs; *KIT* point mutation at codon 816 in the BM or another extracutaneous organ; MCs in BM or blood or another extracutaneous organ expressed CD2 or/and CD25; Baseline serum tryptase concentration >20 ng/mL (in the case of an associated myeloid neoplasm, not valid as an SM criterion)

To be eligible, patients with ASM and MCL needed to have one or more of the following measurable C-findings:

  - Absolute neutrophil count (ANC) <1.0 x 10^9/L or hemoglobin <10 g/dL or platelets <100 x 10^9/L

  - Hepatomegaly with impaired liver function – i.e., elevated transaminases and/or bilirubin levels and/or hypoalbuminemia (with or without ascites or portal hypertension)

  - Palpable splenomegaly with signs of hypersplenism (e.g., as documented by thrombocytopenia; platelets <100,000/μL)

  - Malabsorption with hypoalbuminemia and/or significant weight loss – defined as ≥ 10% documented weight loss over the last 6 months

Patients with non-measurable C-findings, such as skeletal lesions or hepatomegaly only with ascites or portal hypertension, were not permitted to be included in the study.

For patients with MCL, the following criterion was required (in addition to the SM and ASM criteria mentioned above): BM aspirate smears with ≥ 20% immature MCs (± elevated peripheral blood MC percentage).

Following protocol amendment, a C-finding was defined as a clinical finding which was considered attributable to the MC disease component and not to an AHNMD or any other cause. This was determined by the investigator and needed to be corroborated by the SSC chairperson or designee.

It was left to the discretion of the investigator to determine whether a biopsy was required to evaluate whether the C-findings resulted from local MC infiltrates, from the AHNMD component, or both. Patients presenting with the C-finding of anaemia or thrombocytopenia and who were receiving RBC or platelet

transfusions were required to have another measurable C-finding present at study entry. An exception to this requirement was patients presenting with transfusion-dependent-anaemia (≥ 4 units of RBCs within 56 days of study start), who were allowed to enroll into the study even if they did not have any measurable C-finding including haemoglobin <10 g/dL.

Patients with AHNMD were eligible to enter the study if the AHNMD was not life threatening or in an acute stage; otherwise, the patient was to be treated first for this disorder before being considered for entry into the study.

Figure 18 Algorithm using WHO criteria-stepwise approach in defining sub variants of SM
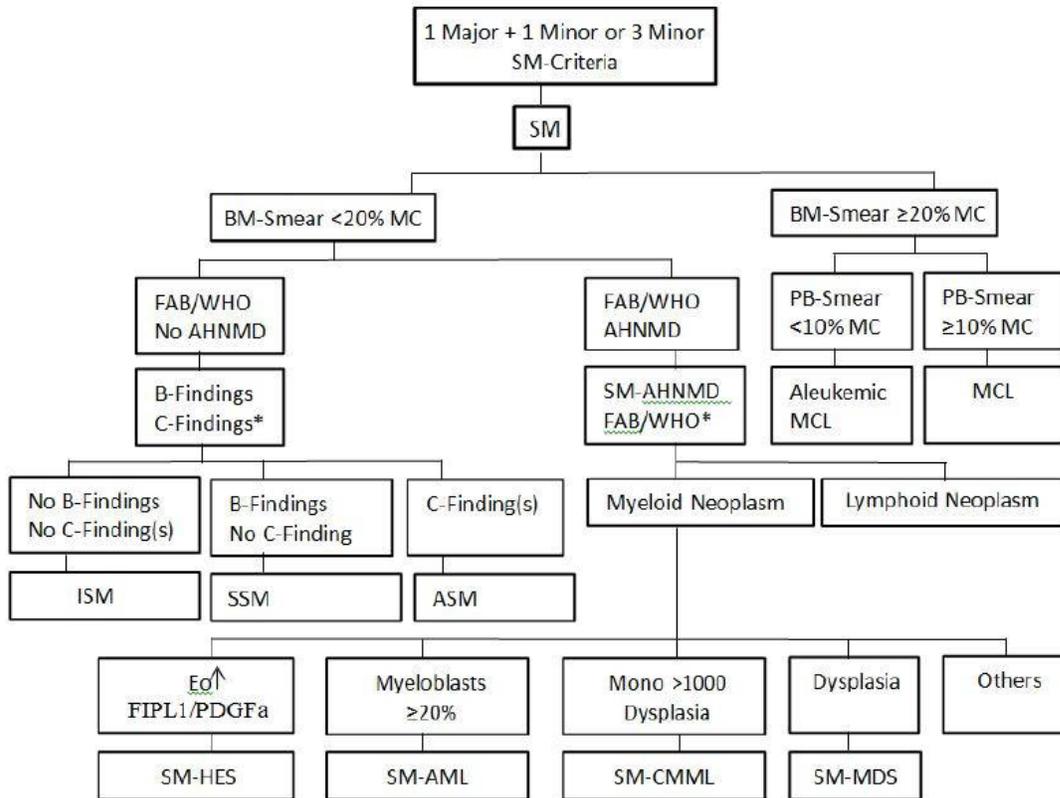
*At this stage, presence of B- or C-findings as well as criteria of an AHNMD was determined. In patients with SM-AHNMD, the nature of the SM component as well as the subtype of the AHNMD (according to WHO criteria) was defined (leading to the diagnosis of e.g., ASM-HES, ASM, AML, ASM-CMML, etc.).

SM= systemic mastocytosis, BM=bone marrow, FAB= French-American-British Cooperative Leukaemia group, WHO= World Health Organization, MC= mast cell, AHNMD= associated hematological clonal non-mast cell lineage disease, MCL=mast cell leukemia, ISM= indolent systemic mastocytosis, SSM= smouldering systemic mastocytosis, ASM= aggressive systemic mastocytosis, HES- hypereosinophilic syndrome, AML= acute myeloid leukemia, CMML= chronic myelomonocytic leukemia, MDS= myelodysplastic syndrome

Key exclusion criteria

- Patients with any other known concurrent severe and/or uncontrolled medical condition (except carcinoma in-situ), which could compromise the participation in the study

- Patients with cardiovascular disease including congestive heart failure grade III or IV according to the New York Heart Association classification, left ventricular ejection fraction (LVEF) of <50%, myocardial infarction within previous 6 months, and poorly controlled hypertension

- Patients with a heart block of any degree at screening (for Canada only)

- Patients with a known confirmed diagnosis of HIV infection or active viral hepatitis

- Patients with an AHNMD who required immediate cytoreductive therapy or targeted therapy (other than midostaurin)

- Patients who had demonstrated relapse to 3 or more prior regimens of SM treatment regardless of treatment regimen for supportive care (e.g., symptom-limiting therapies)

- Patients who received any investigational agent, targeted therapy, chemotherapy, IFN-α, or 2-chlorodeoxyadenosine within 30 days prior to start of midostaurin treatment

- Patients who had ASM with eosinophilia and known positivity for the FIP1L1- PDGFRα fusion unless they had demonstrated relapse or disease progression on prior imatinib therapy

- Patients who had received hematopoietic growth factor support within 14 days of Day 1 of midostaurin treatment

- Patients with any pulmonary infiltrate, including those suspected to be of infectious origin. In particular, patients with resolution of clinical symptoms of pulmonary infection but with residual pulmonary infiltrates on chest x-ray were not eligible until the pulmonary infiltrates had completely resolved. Exception: patients with ASM/MCL ±AHNMD related pleural effusion as judged by the Investigator and approved by the SSC Chairperson or designee were permitted to enter the study

Treatments

Midostaurin was administered by oral dosing (i.e., 4 capsules of midostaurin 25 mg at each administration) beginning on day 1 and was to be taken with water following breakfast or dinner. Patients continued study drug until confirmed disease progression or discontinuation for any other reason.

Patients were advised to swallow the capsules whole. An interval of approximately 12 hours between doses was recommended. If vomiting occurred, no re-dosing was allowed before the next scheduled dose. If a dose of midostaurin was missed by the patient, the missed dose was not to be taken, and the patient was to take the next scheduled dose. Other anticancer agents including chemotherapy, radiation therapy, or biologic response modifiers were not permitted during the study. Where possible, investigators were advised to refrain from administering CYP3A4/5 inducers or inhibitors to patients prior to initiation and during treatment with midostaurin.

Dose reductions

Dose interruptions and dose reductions were to be applied for pre-specified haematological and non-haematological toxicities. In case of haematological and non-haematological toxicity the dose of midostaurin was to be reduced to 50 mg b.i.d. after AEs had resolved. Dose reduction below 50 mg b.i.d. was not allowed, and treatment had to be discontinued in case patients could not tolerate 50 mg b.i.d.

Objectives

Primary objective:

The primary objective was to determine the efficacy of midostaurin when administered orally at a dose of 100 mg b.i.d. continuously for 6 cycles (of 4 weeks each) in patients with ASM or MCL with or without AHNMD as measured by overall response rate (ORR). The ORR was defined as the percentage of patients classified as

confirmed responders (major response [MR] or partial response [PR]) adjudicated by the SSC according to response assessment criteria specified in the protocol.

Secondary objectives:

- To determine duration of response (DOR)

- To determine time to response (TTR)

- To determine progression-free survival (PFS)

- To determine overall survival (OS)

- To determine safety and tolerability of midostaurin

- To determine histopathologic response based on mast cell (MC) infiltration in the bone marrow (BM) and changes in serum tryptase levels as surrogate marker for histopathologic response

Exploratory objectives:

- To explore the pharmacokinetic (PK) profile of midostaurin and its metabolites in the given dose regimen in patients with ASM or MCL (with or without AHMND) and the potential relationship between PK exposure of midostaurin and its metabolites versus clinical response and biomarker parameters

- To explore the CYP3A4 induction by midostaurin

- To explore the patient-reported outcomes (PRO) / quality of life (QoL) measurements

- To explore the effect of midostaurin on mediator-related symptoms

- To explore the clinical benefit or disease control rate (DCR)

- To explore the changes in all C-findings combined, including non-measurable ones

- To explore the histopathologic response in the AHNMD compartment of the disease

- To explore the effect of midostaurin changes in the peripheral blood

- To characterize the *KIT* mutational status in the SM compartment and if applicable also in the AHNMD compartment of the disease at baseline, after 6 cycles of therapy, and at end of treatment (EOT) and explore potential associations with efficacy outcomes

Biomarker analyses:

- Serum tryptase was measured during treatment in order to monitor the disease and potential treatment effects in SM

- Histopathology analyses, immunohistochemistry (IHC) and *KIT* mutational analyses were also performed

- The assessment of histamine levels either measured from whole blood or urine could be performed at the discretion of the investigator but were not part of the study assessments

Outcomes/endpoints

Primary endpoint

The primary endpoint was ORR, defined as the percentage of patients with a confirmed response (MR or PR) as adjudicated by the SSC based on response criteria specified in the protocol (modified Valent/Cheson criteria) and with an initial response occurring in the first 6 cycles (Table 55).

Table 53 Overview of response criteria

Response [a]	C-finding(s) (CF)	Subcategory [b]	MC infiltrate in organ	Tryptase level	Organomegaly
MR	≥ 1 CF resolved and no other CF progressed	CR	disappeared (and) ↓ <20 ng/mL (and) disappeared		
	≥ 1 CF resolved and no other CF progressed	IR	decrease (and/or) ↓ >50% (and/or) ↓ >50%		
	≥ 1 CF resolved and no other CF progressed	PCR	no significant change	↓≤ 50% - 0%	no significant change
PR	≥ 1 CF improved by >50% and no other CF progressed	GPR	NA	NA	no significant change
	≥ 1 CF improved by >20% - ≤ 50% no other CF progressed	MinR	NA	NA	no significant change

Response [a]	C-finding(s) (CF)	Subcategory [b]	MC infiltrate in organ	Tryptase level	Organomegaly
NR	CFs show constant range and do not meet criteria for response or progression	SD	NA	NA	NA
	≥ 1 CF worsened by >20%	PD	NA	NA	NA

[a] MR: Major Response; PR: Partial Response; NR: No Response

[b] CR: Complete Remission; IR: Incomplete Remission; PCR: Pure Clinical Response; GPR: Good Partial Response; MinR: Minor Response; SD: Stable Disease; PD: Progressive Disease

≥ 1 CF: one or more than one C-finding

NA: not applicable, i.e., the evolution of these parameters did not influence the categorization of response

Source: Derived from Valent et al 2003

Changes in C-findings reflecting the different response categories are shown in Table 56.

Table 54 Definition of responses in measurable C-Findings

Measurable C-finding [1]	Major Response (100%)	Good Partial Response (>50%)
BM/blood		
Absolute neutrophil count (ANC) <1000/µL	ANC >1000/µL	Decrease below 1000/µL reverted by >50% and minimum increase of 200 ANC/ µL required
Anemia, Hemoglobin <10 g/dL	Hemoglobin >10 g/dL	Decrease below 10 g/dL reverted by >50% and minimum increase of 1.5 g/dL hemoglobin required
TD anemia [2] and patients receiving RBC transfusions within 56 days prior to study entry	Refer to Table 9-4	Refer to Table 9-4
Thrombocytopenia (platelets <100,000/ µL)	Platelets >100,000/ µL	Decrease to <100,000/ µL reverted by >50% and a minimum increase of 20,000 platelets/µL blood required
TD thrombocytopenia [3] and patients receiving platelet transfusions within 56 days prior to study entry	Refer to Table 9-5	Refer to Table 9-5
Liver		
Elevated enzyme levels, total bilirubin	Decrease to normal	Increase reverted by >50%
Hypoalbuminemia	Increase to normal	Decrease reverted by >50%
Spleen		
Palpable splenomegaly with hypersplenism-thrombocytopenia	No signs of hypersplenism platelets >100,000/µL	Parameters indicating hypersplenism (platelet count) improved by >50%, and a minimum increase of 20,000 platelets/µL required
GI tract		
Malabsorption with hypoalbuminemia and/or weight loss	Normal albumin Pre-study weight (within 6 months + 3 weeks)	Decrease in albumin improved by >50% Weight loss reverted by >50%, or regaining >5% weight

[1]Reproducibly measurable criteria, selected from Valent et al 2003

[2]Transfusion dependent (TD) anemia was defined as ≥ 4 units of RBC transfusions within a period of 56 days administered in the absence of another explanation such as acute infection, gastrointestinal bleeding, surgery, hemolysis, etc.

[3]TD thrombocytopenia was defined as ≥ 4 units of platelet transfusions within a period of 56 days administered in the absence of another explanation than the relationship to the underlying disease.

Responses based on C-findings had to be confirmed at least 8 weeks (56 days) apart. Progression based on C-findings had to be confirmed at least 4 weeks (28 days) apart. Responses and progression based on transfusions alone (as assessed within a 56 day period) required confirmation in the subsequent period of 56 days.

Changes in C-findings or any other relevant parameters to assess response were compared to baseline. The responses were adjudicated by the SSC. Histopathologist comments pertaining to SM and AHNMD status from the review of BM biopsies/aspirations and associated markers (if performed) were captured in the CRF. In those patients presenting with an AHNMD, the evolution of the AHNMD-component of the disease was followed using the typical cytological and/or clonal markers for that disease. It was captured on the CRF by recording the observations in the comments section.

For patients presenting with the C-finding of anaemia and/or thrombocytopenia and who received RBC and/or platelet transfusions within a 56 day period prior to entry into the study (cycle 1, day 1), modified criteria applied for the assessment of response so as to account for interference by transfusions (as described in the CSR of study D2201).

Major Response : An MR was characterised by complete resolution of at least one or more C -finding(s) and no confirmed progression in other C-findings. In patients with multiple C-findings, the C-finding that showed the best response was the determinant.

Major response was further classified into:

- Complete remission (CR): disappearance of all mast cell infiltrates in affected organs, decrease of serum tryptase level to <20 ng/mL, and disappearance of SM-associated organomegaly.

- Incomplete remission (IR): decrease in mast cell infiltrates in affected organs and/or substantial decrease (>50%) of serum tryptase level from baseline and/or visible regression of organomegaly.

- Pure clinical response (PCR): no significant response in mast cell infiltrates, tryptase levels, or organomegaly that defines a CR or IR.

- Unspecified: No reliable information on bone marrow mast cell infiltration, serum tryptase level, or hepatomegaly/splenomegaly available to determine the sub-category of MR (this classification was not defined in the protocol).

Partial Response

A PR was a measurable improvement in one or more C-findings without confirmed progression in other C-findings. In patients with multiple C-findings, the C-finding that showed the best response was the determinant. For the assessment of ORR only the measurable C-findings defined in **Table 56** was considered.

A PR was further classified into: Good partial response (GPR): >50% regression of one or more C-findings and no progression in other C-findings; Minor response (MinR): >20% to ≤50% regression of one or more C-findings and no progression in other C-findings.

No Response

- Stable disease (SD): C-findings that showed a constant range, not meeting the criteria for a response or progressive disease

- Progressive disease (PD): one or more C-findings showing progression.

Secondary endpoints

Duration of response defined as the time from the start of the first confirmed response occurring before the end of Cycle 6 until the date of first confirmed PD or death due to ASM/SM-AHN/MCL.

Overall survival defined as the time from the start of treatment to the date of death due to any cause.

Time to response (TTR) defined as the time from the date of start of treatment to the date of onset of first confirmed response (MR or PR) and presented by summary statistics.

Progression-free survival (PFS) defined as the time from the start of treatment to the date of the first confirmed progression or death due to any cause. If a patient did not progress or die at the time of the analysis cut-off, PFS was censored at the date of the last adequate response assessment. If a patient

received any further anti-neoplastic therapy before the time of the analysis cut-off, PFS was censored at the date of the last adequate response assessment prior to the start of the anti-neoplastic therapy.

Histopathologic response was summarised to demonstrate the best change from baseline in percentage of MC infiltrations in the BM.

Organomegaly: A listing summarizing liver and spleen measurements by CT/Magnetic Resonance Imaging/Ultra sound scan with the corresponding percent change in unidimensional and volumetric measurement from baseline was produced.

Patient-reported outcomes: The Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) and the Short Form health survey (SF-12) questionnaires were used to assess patient reported outcomes (PROs).

Sample size

Based on the ASM literature from previous studies using treatments other than midostaurin, and based on preliminary results from the ongoing investigator-initiated study PKC412A2213 in which 11 out of 15 patients with ASM obtained an MR using Valent Criteria (Valent et al 2003), the proportion of responders under the null hypothesis was set to 0.30 and under the alternative, 0.50.The original protocol had the sample size was an adaption of the Fleming two-stage design with 40 patients in stage 1 and 20 in stage 2 to test H0: response rate ≤ 030 vs Ha: response rate ≥0.50. The testing procedure was : if 14 of fewer responses in stage 1 then reject H1; if 20 or more responses in stage 1 then reject H0; if between 15 up to and including 19 responses then proceed to stage 2; if 27 or more responses out of 60 after stage 2 then reject H0, otherwise reject Ha. With this testing procedure the type I error of stage 1 was 0.015 and the type I error for stage 2 (i.e. the probability under H0 to enter stage 2 and then reject H0) was 0.005, so total type I error 0.020. The power to reject H0 (given the response rate was ≥0.50) was 0.682 in stage 1 and 0.157 in stage 2 (i.e. the probability to enter stage 2 and then reject H0).

Randomisation

This was a non-randomised, open-label, study.

Blinding (masking)

This was an open-label study.

Statistical methods

Binary endpoints (e.g. ORR) had their 95%-CI estimated with the exact binomial method. The Kaplan-Meier method was used to analyse time to event endpoints, with 95%-CI at specific time points estimated using Greenwood's formula, and 95%-CI of the median with the Brookmeyer-Crowley method.
Sensitivity analyses to the primary analysis of ORR (on PEP, per SCC) included analysis on FAS (non-eligible patients as per SCC designated non-evaluable / subtype non-responders), idem on PPS, analysis based on response based on investigator and calculated by Novartis, analysis including late responders (after cycle 6), analysis excluding C-finding of anaemia/thrombocytopenia in presence of RBC/platelet-transfusions.
PFS and DOR were censored for >1 missed visits, start new anti-cancer therapy, and deaths due to reason

other than deterioration of 'study indication'. Sensitivity analyses included events after >1 missed visits.

The chosen Fleming two-stage design (testing procedure: see sample size) implied an interim analysis at which 0.015 was spent. The total type I error (so including the possibility to enter stage 2) was originally 0.020.

The ORR in PEP was summarized for stage 1 patients, extension phase patients and for stage 1 and extension phase patients together. The primary efficacy analysis of ORR controlling the type I error was the analysis performed on the 40 stage I patients.

A post-hoc analysis of Study D2201 data was conducted using the new (more stringent) response criteria published in 2013 by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM; referred to as IWG criteria. The IWG response criteria are more stringent, primarily because of inclusion of minimum duration of improvement of 12 weeks, and a minimum range of improvement for most C-findings. The analysis of response per IWG is purely algorithm based, whereas in the primary efficacy analysis performed by the Applicant both eligibility and responses based on the modified Valent criteria were adjudicated by the SSC. Patients whose only C-finding at baseline was ascites (n=2) were removed from the analysis according to IWG criteria because history of ascites symptoms could not be adequately assessed in this post-hoc analysis. For the same reason, for patients who had a C-finding of ascites in addition to other C-findings, ascites was not counted as a C-finding.

Full Analysis Set (FAS)

The FAS was defined according to the Intention to Treat (ITT) principle and comprises all patients to whom study treatment has been assigned. For this was single arm trial, study treatment was determined to be assigned if the patient received at least one dose of the study drug in the "Drug Administration Record" CRF. Demographics, medical history, and baseline disease characteristics were summarised using the FAS. Sensitivity analyses of efficacy endpoints were done using the FAS.

Primary Efficacy Population (PEP)

The PEP consisted of patients in the FAS meeting the diagnostic criteria for ASM or MCL, and presenting with at least one measurable C-Finding at study entry and/or patients with transfusion dependent (TD) anaemia due to their underlying disease at study entry as confirmed by the SSC in the "Eligibility adjudication" CRF form. All efficacy end-points were summarised using the PEP. Patients with haemoglobin or platelet as the only C-Finding required another C-Finding in the presence of transfusions.

Per-Protocol Set (PPS)

The per-protocol Set consisted of all patients from the PEP who did not have any major protocol deviations (related to inclusion, exclusion criteria and study conduct) which could affect the evaluation of the primary endpoint. The primary efficacy endpoint of ORR was summarised using the Per-protocol Set.

Pharmacokinetic Set (PK Set)

The PK set consisted of all patients who received at least one dose of midostaurin and had at least one evaluable post-baseline midostaurin concentration measurement.

Safety Set

The Safety Set included all patients who received at least one dose of study drug. The safety set was used for all safety analyses.

Results

Participant flow

Figure 19 Patient flow and analysis sets in study D2201
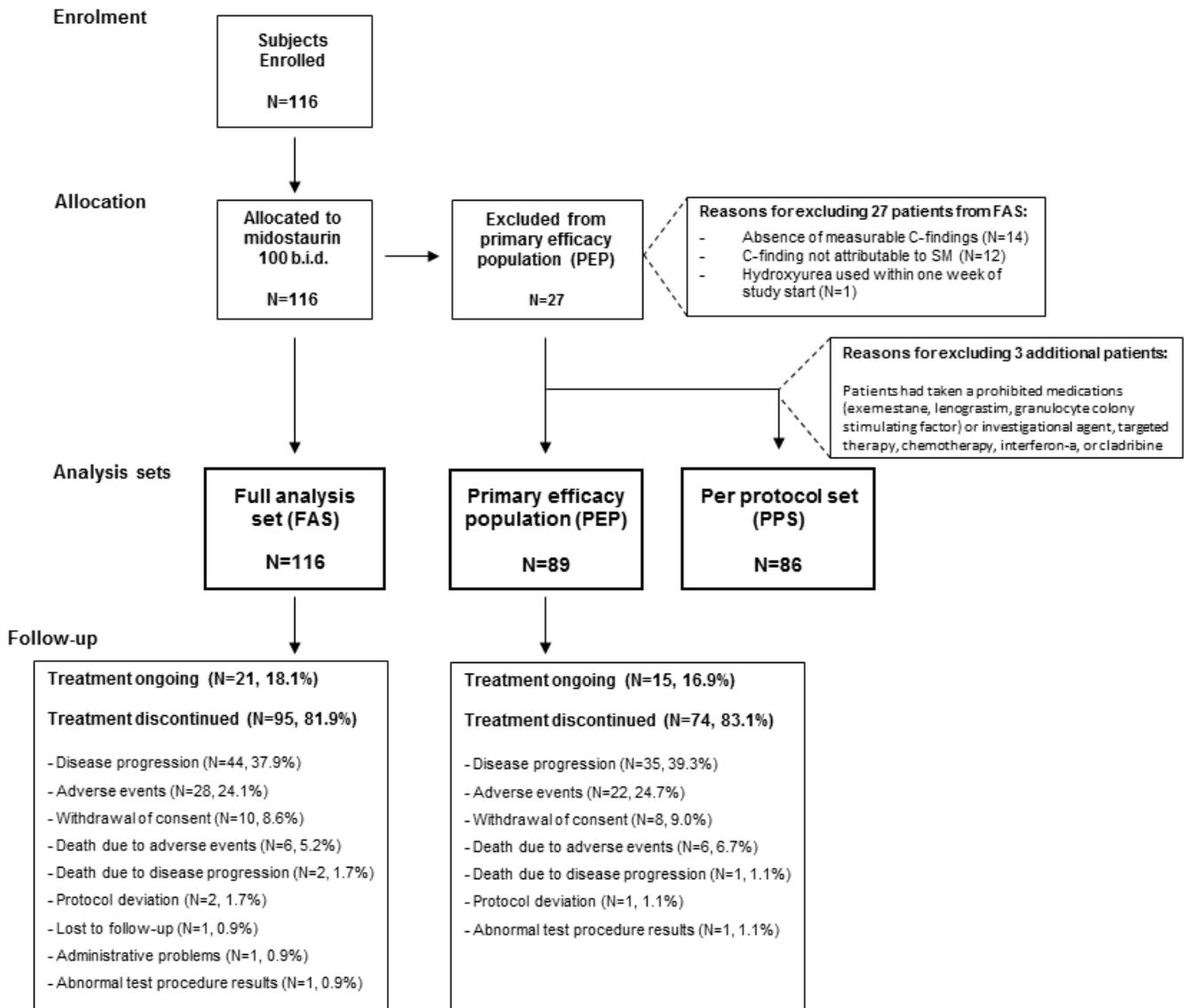
Recruitment

Study initiation date: 6 January 2009 (first patient first visit).

Study completion date: 14 June 2012 (last patient first visit).

Study D2201 enrolled 116 patients across 29 centres in 12 countries. Study centres: Australia (2), Austria (1), Belgium (1), Canada (2), France (2), Germany (5), Netherlands (1), Norway (1), Poland (1), Turkey (1), United Kingdom (3), United States (9).

Conduct of the study

There were a total of six protocol amendments:

Amendment 1 (25-Nov-2008) was issued to include changes to the inclusion and exclusion criteria and, to the schedule of examinations to optimize the capturing of disease evolution, and the sampling scheme to alleviate the burden on patients (BM, imaging, PK sampling etc.), and to the overall language for further refinement and better clarity.

Amendment 2 (23-Nov-2010) was issued to ensure that only patients with measurable C -findings due to mastocytosis were enrolled into the study. Among the Stage I patients enrolled in the study 36% were considered by the SSC to be ineligible for response assessment.

To address these issues, systematic collection of the following information was added: history of weight and blood product transfusions, ongoing transfusions, mediator-related symptoms, and antineoplastic therapies since discontinuation of study drug. Changes were made to the response criteria for patients receiving blood transfusions prior to or during study treatment. A patient enrolment approval process by the SSC chair was implemented. Histopathologic response was added as a secondary objective. The definition of the PEP and additional sub-analyses to observe the impact of these were added. In addition, an extension phase was implemented to provide more information on safety and efficacy of midostaurin.

Amendment 3 (6-Dec-2010) was issued to address the request from the Canadian Health Authorities to add an exclusion criterion of "Patients with heart block of any degree at screening". The protocol was amended for Canada only.

Amendment 4 (8-Feb-2012) was issued to clarify the follow-up for patients who discontinued study treatment in the absence of disease progression (e.g., due to AE). These patients were to be followed for disease status until the time of disease progression, initiation of another antineoplastic therapy, or end of study, whichever was first. Also, the definition of disease progression was updated to comprise a laboratory abnormality not existing at baseline that occurred during study treatment and was attributed to SM. If this new C–Finding demonstrated a worsening >20% from the value at baseline and was maintained for at least 28 days, this circumstance was defined as disease progression.

Amendment 5 (20-Aug-2012) was issued to include language that allowed patients to continue to receive midostaurin in accordance with local regulations.

Amendment 6 (27-May-2014) was issued to revise the definition of the end of study to allow for an extended collection period of efficacy and safety data. The end of study definition was revised to occur five years after last patient first treatment, or when all patients had discontinued study treatment, whichever occurred first. This extended period of data collection will be reviewed through supplemental annual central adjudication meetings by the SSC. Moreover, patients who continue to benefit from treatment with midostaurin will continue to have access to study treatment. In addition, retrospective collection of the date of diagnosis of

SM/ASM/MCL was added to allow comparative assessment of OS data from this study with that from historical data.

Protocol deviations

Table 55 Summary of protocol deviations - study D2201

```
                                                              All Patients
                                                              N=116
Protocol Deviation                                            n  (%)
_____

Any protocol deviation
   -Total                                                     97(83.6)

Any major protocol deviation (excluded from Per Protocol Set)
   -Total                                                     30(25.9)
   Disease diagnosis for ASM/MCL not met as per SSC adjudication   27(23.3)
   Patient has taken a prohibited concomitant medication, as defined in   3( 2.6)
   protocol, from start of treatment with midostaurin (study drug).
   Patients who have received any investigational agent, targeted therapy,   3( 2.6)
   chemotherapy, interferon-a, or 2-chlorodeoxyadenosine (2-CdA, clad

Any minor protocol deviation
   -Total                                                     94(81.0)
   At least one inclusion criteria evaluation not performed   2( 1.7)
   Bilirubin is > 3 x Upper Limit of Normal (ULN) if it is solely due to ASM/MCL   1( 0.9)
   Date of CT/MRI abdomen/pelvis is >14days or not performed prior to C1D1   42(36.2)
   Date of ECHO/MUGA is > 14 days or not performed prior to C1D1   56(48.3)
   Date of baseline chest x-ray is >28 days or not performed prior to C1D1   15(12.9)
   Date of laboratory evaluations are >7 days prior to study drug start   12(10.3)
   Date of skeletal bone survey (whole body x-ray/DXA) is > 3 months or not   19(16.4)
   performed prior to C1D1
   ECG shows QTcF > 450 ms (as per protocol QTc always refers to QTcF)   2( 1.7)
   Interruption or dose modification of midostaurin treatment (study drug) was   8( 6.9)
   not done as per protocol.
   Laboratory samples from Visit 2 onwards taken >48hours before or after   27(23.3)
   scheduled Visit date.
   Midostaurin (study drug) dose was below 50 mg b.i.d. (100 mg/day).   30(25.9)
   Midostaurin treatment was interrupted for > 21 days and patient was not   6( 5.2)
   discontinued.
```

Minor protocol deviations were reported in 94 patients (81.0%).

Baseline data

The demographic characteristics of the enrolled patients are summarised in Table 58. The status of systemic mastocytosis at baseline in enrolled patients is shown in Table 59.

Table 56 Demographic characteristics at baseline (FAS and PEP) - study D2201

| | Midostaurin | |
| | FAS | PEP |
Demographic variable	N=116	N=89
Age (years)		
Mean (standard deviation)	61.8 (11.76)	63.0 (11.59)
Median	63.0	64.0
Min – Max	25.0 – 82.0	25.0 – 82.0
Age category (years), n (%)		
<65	65 (56.0)	46 (51.7)
≥ 65	51 (44.0)	43 (48.3)
≥ 75	14 (12.1)	12 (13.5)
Sex, n (%)		
Male	76 (65.5)	57 (64.0)
Female	40 (34.5)	32 (36.0)

| | Midostaurin | |
| | FAS | PEP |
Demographic variable	N=116	N=89
Race, n (%)		
Caucasian	111 (95.7)	86 (96.6)
Black	2 (1.7)	1 (1.1)
Other	1 (0.9)	1 (1.1)
Missing	2 (1.7)	1 (1.1)
Ethnicity, n (%)		
Hispanic/Latino	3 (2.6)	3 (3.4)
Other	110 (94.8)	85 (95.5)
Missing	3 (2.6)	1 (1.1)
ECOG PS, n (%)		
0	22 (19.0)	18 (20.2)
1	55 (47.4)	39 (43.8)
2	31 (26.7)	25 (28.1)
3	8 (6.9)	7 (7.9)

FAS = full analysis set; PEP = primary efficacy population

As per central histopathology review, of the 89 patients with SM in the PEP, 73 patients (82.0%) had ASM and 16 patients (18.0%) had MCL. An associated AHNMD component was detected in 57/73 patients with ASM (78.1%), and 6/16 patients with MCL (37.5%). The most frequent AHNMD subtypes were CMML (28.1% of all patients) and MDS/MPN-U (24.7% of all patients).

Table 57 Diagnosis of systemic mastocytosis at baseline per central histopathology assessment (FAS and PEP) - study D2201

| | Midostaurin | |
| | FAS
N=116 | PEP
N=89 |
Characteristic	n (%)	n (%)
Diagnosis of SM		
Yes	116 (100)	89 (100)
Diagnosis of SM with AHNMD		
Yes (SM with AHNMD)	83 (71.6)	63 (70.8)
No (SM without AHNMD)	18 (15.5)	15 (16.9)
Not assessable (SM with AHNMD status unknown)	15 (12.9)	11 (12.4)
Diagnosis of MCL		
Yes	21 (18.1)	16* (18.0)
No	64 (55.2)	48 (53.9)
Not assessable[a]	31 (26.7)	25 (28.1)
Diagnosis of MCL with AHNMD		
Yes (MCL with AHNMD)	10 (8.6)	6 (6.7)
No (MCL without AHNMD)	5 (4.3)	5 (5.6)
Not assessable (MCL with AHNMD status unknown)	6 (5.2)	5 (5.6)
AHNMD subtype		
CMML	32 (27.6)	25 (28.1)
MDS/MPN-U	30 (25.9)	22 (24.7)
MDS	10 (8.6)	7 (7.9)
Other	5 (4.3)	4 (4.5)
HES/CEL	4 (3.4)	4 (4.5)
PMF	1 (0.9)	0
MPN-U	1 (0.9)	1 (1.1)
Immunocytochemistry		
CD117	116 (100)	89 (100)
Tryptase	116 (100)	89 (100)
CD25	112 (96.6)	85 (95.5)
CD2	2 (1.7)	2 (2.2)
Other	2 (1.7)	2 (2.2)

[a] Patients were not assessable for MCL diagnosis at baseline due to the poor quality of BM aspirate smears. Nevertheless, they were diagnosed with ASM based on the presence of at least one measurable C-finding and core biopsy findings consistent with ASM according to the SSC.

*Determination of ASM required adjudication of C findings by the SSC.

The baseline *KIT* mutation status of both the SM and AHNMD components is presented in Table 60.

Table 58 *KIT* mutation analysis at baseline (FAS and PEP) - study D2201

| | Midostaurin | |
| | FAS N=116 | PEP N=89 |
Characteristic	n (%)	n (%)
KIT mutation at codon 816 in the SM disease compartment		
Yes	98 (84.5)	77 (86.5)
No	13 (11.2)	10 (11.2)
Subtype		
D816V	94 (81.0)	73 (82.0)
D816Y	3 (2.6)	3 (3.4)
Other*	1 (0.9)	1 (1.1)
KIT mutation at codon 816 in the AHNMD disease compartment		
Yes	29 (25.0)	25 (28.1)
No	27 (23.3)	21 (23.6)
Subtype		
D816V	27 (23.3)	23 (25.8)
D816Y	2 (1.7)	2 (2.2)

The measurable disease-related C-findings at baseline according to SSC adjudication are presented for the PEP in Table 61.

Table 59 Measurable C-findings identified by Study Steering Committee (PEP) - study D2201

| | Midostaurin N=89 |
C-finding	n (%)
Number of C-findings at baseline	
≥ 3	38 (42.7)
2	20 (22.5)
1	31 (34.8)
Type of C-finding	
Thrombocytopenia	55 (61.8)
Hypoalbuminemia	48 (53.9)
Anemia	28 (31.5)
High total bilirubin	25 (28.1)
Transfusion-dependent anemia	20 (22.5)
Weight loss	12 (13.5)
Neutropenia	7 (7.9)
High ALT	6 (6.7)
High AST	2 (2.2)

Prior antineoplastic therapy

In the FAS, 47 patients (40.5%) had received prior anti-neoplastic medication for SM. Twenty patients (17.2%) had received ≥2 prior anti-neoplastic regimens, and in some cases therapy was directed toward the

AHNMD component. In the PEP, 32 patients (36.0%) had received prior anti-neoplastic medication for SM, and 13 patients (14.6%) had received ≥2 prior anti-neoplastic regimens.

Numbers analysed

The different analysis sets are listed in Table 62.

Table 60 Analysis sets - study D2201

Analysis set	Midostaurin N=116 n (%)
Full analysis set	116 (100)
Primary efficacy population	89 (76.7)
Per-protocol set	86 (74.1)
Safety set	116 (100)
PK set	87 (75.0)

The median duration of study follow-up (the difference between the study treatment start date and the data cut-off date of 01-Dec-2014) was 43 months (range: 29 – 70 months).

The PEP consisted of 89 patients in the FAS who presented with at least one measurable C-finding at study entry related to the SM component and/or with TD anaemia due to their underlying disease as confirmed by the SSC.

Table 61 Patient disposition: full analysis set (FAS) and primary efficacy population (PEP) - study D2201

Disposition	Midostaurin	
	FAS N=116 n (%)	PEP N=89 n (%)
Patients treated		
Treatment ongoing*	21 (18.1)	15 (16.9)
End of treatment	95 (81.9)	74 (83.1)
Primary reason for end of treatment		
Disease progression	44 (37.9)	35 (39.3)
Adverse event(s)	28 (24.1)	22 (24.7)
Patient withdrew consent	10 (8.6)	8 (9.0)
Death	8 (6.9)	7 (7.9)
Protocol deviation	2 (1.7)	1 (1.1)
Lost to follow-up	1 (0.9)	0
Administrative problems	1 (0.9)	0
Abnormal test procedure results	1 (0.9)	1 (1.1)

*Treatment was ongoing at the data cut-off date (01-Dec-2014)

Outcomes and estimation

Primary endpoint: Overall response rate

The results of the best overall response per SSC adjudication are diaplyed in Table 64.

Table 62 Best overall response per SSC adjudication (PEP)- study D2201

Best overall response	Midostaurin N=89 n (%)
Major Response (MR)	40 (44.9)
Complete Remission (CR)	0
Incomplete Remission (IR)	19 (21.3)
Pure Clinical Response (PCR)	15 (16.9)
Unspecified	6 (6.7)
Partial Response (PR)	13 (14.6)
Good Partial Response (GPR)	11 (12.4)
Minor Response (MinR)	2 (2.2)
Unspecified (U)	0
Stable Disease (SD)	11 (12.4)
Progressive Disease (PD)	10 (11.2)
Not Evaluable	15 (16.9)
Overall Response Rate (ORR=MR+PR)*	53 (59.6)
95% CI for ORR**	[48.6,69.8]
Two sided p-value***	<0.001
Disease control rate (DCR=MR+PR+SD)#	64 (71.9)
95% CI for DCR**	[61.4,80.9]

*Overall response rate (ORR) was defined as the proportion of patients in the PEP with a confirmed best response of MR or PR in the first 6 cycles of treatment (confirmed at least 56 days apart) as assessed by the SSC using modified Valent/Cheson criteria.

Disease control rate (DCR) was defined as the proportion of patients with a confirmed best overall response of MR or PR or SD in the first 6 cycles of treatment as assessed by the SSC using modified Valent/Cheson criteria.

**Exact (Clopper-Pearson) confidence interval

***Exact two sided p-value, null hypothesis, ORR ≤ 30%

The best overall response as per Study Steering Committee adjudication: ASM without AHNMD vs. SM-AHNMD vs. MCL patients for the ASM, SM-AHN and MCL subgroups are displayed in Table 65, Table 66 and

Table **67**.

Table 63 Best overall response as per Study Steering Committee adjudication: ASM without AHNMD vs. SM-AHNMD vs. MCL patients (PEP)- ASM subgroup- study D2201

```
                                                    All patients
                                                        N=16
                                                        n(%)
_____

Best overall response
    Major response (MR)                            10  (62.5)
        Complete remission (CR)                     0
        Incomplete remission (IR)                   6  (37.5)
        Pure clinical response (PCR)                4  (25.0)
        Unspecified (U)                             0
    Partial response (PR)                           2  (12.5)
        Good partial response (GPR)                 1  ( 6.3)
        Minor response (MinR)                       1  ( 6.3)
        Unspecified (U)                             0
    Stable disease (SD)                             1  ( 6.3)
    Progressive disease (PD)                        1  ( 6.3)
    Not evaluable                                   2  (12.5)

Overall response rate (ORR=MR+PR)*                 12  (75.0)
    95% C.I. for ORR**                         [47.6,92.7]
```


Table 64 Best overall response as per Study Steering Committee adjudication: ASM without AHNMD vs. SM-AHNMD vs. MCL patients (PEP)-SM-AHNMD subgroup - study D2201

```
Disease: SM-AHNMD

                                                    All patients
                                                        N=57
                                                        n(%)
_____

Best overall response
    Major response (MR)                            23  (40.4)
        Complete remission (CR)                     0
        Incomplete remission (IR)                   9  (15.8)
        Pure clinical response (PCR)                9  (15.8)
        Unspecified (U)                             5  ( 8.8)
    Partial response (PR)                          10  (17.5)
        Good partial response (GPR)                10  (17.5)
        Minor response (MinR)                       0
        Unspecified (U)                             0
    Stable disease (SD)                             7  (12.3)
    Progressive disease (PD)                        6  (10.5)
    Not evaluable                                  11  (19.3)

Overall response rate (ORR=MR+PR)*                 33  (57.9)
    95% C.I. for ORR**                         [44.1,70.9]
```

Table 65 Best overall response as per Study Steering Committee adjudication: ASM without AHNMD vs. SM-AHNMD vs. MCL patients- (PEP)- MCL subgroup-study D2201

```
Disease: MCL
                                        All patients
                                            N=16
                                            n(%)


Best overall response
    Major response (MR)                     7 (43.8)
        Complete remission (CR)             0
        Incomplete remission (IR)           4 (25.0)
        Pure clinical response (PCR)        2 (12.5)
        Unspecified (U)                     1 ( 6.3)
    Partial response (PR)                   1 ( 6.3)
        Good partial response (GPR)         0
        Minor response (MinR)               1 ( 6.3)
        Unspecified (U)                     0
    Stable disease (SD)                     3 (18.8)
    Progressive disease (PD)                3 (18.8)
    Not evaluable                           2 (12.5)

Overall response rate (ORR=MR+PR)*          8 (50.0)
    95% C.I. for ORR**                    [24.7,75.3]
```

Sensitivity analyses of Overall Response Rate

Different sensitivity analyses were conducted:

- Best overall response (BOR) for the FAS. For these analyses, all patients who were considered to be ineligible for the PEP were assessed as being "non-evaluable" and were classified as subtype "non-responders".

    o In the FAS, the ORR was 45.7% (95%CI: 36.4-55.2; p<0.001)

    o In the PPS (n=86), the ORR was 58.1% (95%CI: 47.0-68.7)

- By Valent/Cheson criteria, without ancillary information: based on isolated responses of C-findings without consideration of the clinical context, the ORR in the PEP was 46.1% (95%CI: 35.4-57.0), with 38 patients having an MR, and 3 patients a PR.

- By investigator assessment: The ORR in the PEP in the first 6 cycles of treatment according to the Investigator assessment was 52.8% (95%CI: 41.9, 63.5), with 33 patients having an MR and 14 patients having a PR.

Table 66 Sensitivity analyses of ORR (PEP) - study D2201

	All Patients ORR	
Sensitivity analysis	n (%)	95% CI
Based on SSC assessment		
Primary analysis (N=89)	53 (59.6)	48.6, 69.8
Per-protocol set (N=86)	50 (58.1)	47.0, 68.7
Full analysis set (N=116)*	53 (45.7)	36.4, 55.2
Including late responders (N=89)	58 (65.2)	54.3, 75.0
Excluding patients receiving transfusions (RBC or platelet) (N=89)	51 (57.3)	46.4, 67.7
Including patients who received high-dose steroids (N=89)	57 (64.0)	53.2, 73.9
Investigator assessment (N=89)	47 (52.8)	41.9, 63.5
Algorithm-based calculation of response (N=89)	41 (46.1)	35.4, 57.0

* In the analysis based on the FAS, patients who were considered to be ineligible for the PEP were assessed as "non-evaluable" and were classified as "non-responders".

The concordance between the investigator and SSC assessments of BOR in the PEP is presented in Table 69. The concordance rate was 40 out of 89 patients = 45%.

Table 67 Concordance of local investigator review and study steering committee adjudication in best overall response (PEP) - study D2201

Study steering committee	Investigator review					
	Major response n (%)	Partial response n (%)	Stable disease n (%)	Progressive disease n (%)	Non-evaluable n (%)	Total n (%)
Major response	25 (28.09)	7 (7.87)	8 (8.99)	0	0	40 (44.94)
Partial response	3 (3.37)	2 (2.25)	7 (7.87)	1 (1.12)	0	13 (14.61)
Stable disease	2 (2.25)	1 (1.12)	7 (7.87)	1 (1.12)	0	11 (12.36)
Progressive disease	0	0	5 (5.62)	5 (5.62)	0	10 (11.24)
Non-evaluable	3 (3.37)	4 (4.49)	4 (4.49)	3 (3.37)	1 (1.12)	15 (16.85)
Total	33 (37.08)	14 (15.73)	31 (34.83)	10 (11.24)	1 (1.12)	89 (100.0)

Response rate based on IWG-MRT-ECNM criteria in Study D2201

The best overall response as per IWG criteria by disease subtype is presented in Table 70.

Table 68 Best overall response as per IWG criteria by disease subtype in study D2201 (eligible patients)

	All Patients evaluated N=113 n (%)	ASM N=15 n (%)	SM-AHNMD N=72 n (%)	MCL N=21 n (%)	Subtype unknown N=5 n (%)
Best overall response					
Complete Remission (1)	1 (0.9)	0	0	1 (4.8)	0
Partial Remission (2)	17 (15.0)	5 (33.3)	8 (11.1)	3 (14.3)	1 (20.0)
Clinical improvement (3)	14 (12.4)	4 (26.7)	7 (9.7)	3 (14.3)	0
Overall Response Rate (4)	32 (28.3)	9 (60.0)	15 (20.8)	7 (33.3)	1 (20.0)
95% CI for ORR	[20.2, 37.6]	[32.3, 83.7]	[12.2, 32.0]	[14.6, 57.0]	[0.5, 71.6]

Confirmation period for responses: 12 weeks
Analysis excludes ascites as a C-fining.
1) Patients with all organ damages in complete remission
(2) Patients with at least one organ damage in partial remission AND no progression on any other organ damage
(3) Patients with at least one organ damage clinically improved AND patient not in complete remission AND patient not in partial remission. A clinical improvement cannot be considered if a progression started before confirmation of clinical improvement
(4) Sum of patients in complete remission, patients in partial remission and patients with clinical improvement

Subgroup analysis of ORR

The results of the ORR by AHNMD status are displayed in Table 71.

Table 69 Best overall response as per IWG response criteria, according to presence of AHNMD at baseline, removing the Ascites C-Findings (12 weeks confirmation) (Eligible patients)

	All Patients evaluated N=113 n (%)	AHNMD=Yes N=82 n (%)	AHNMD=No N=17 n (%)	AHNMD not assessed N=14 n (%)
Best overall response				
Complete Remission	1 (0.9)	0	0	1 (7.1)
Partial Remission	17 (15.0)	10 (12.2)	4 (23.5)	3 (21.4)
Clinical improvement	14 (12.4)	8 (9.8)	4 (23.5)	2 (14.3)
Overall Response Rate	32 (28.3)	18 (22.0)	8 (47.1)	6 (42.9)
95% CI for ORR	[20.2, 37.6]	[13.6, 32.5]	[23.0, 72.2]	[17.7, 71.1]
Confirmation period for responses: 12 weeks				

The results of the ORR as per IWG criteria by KIT-D816 mutation status are displayed in Table 72.

Table 70 ORR as per IWG response criteria (12 weeks confirmation) - by D816 all alleles c-KIT mutation in SM, removing the Ascites C-Findings (Eligible patients)

	All patients	D816 mutated	D816 WT	D816 unknown
	n=113	N=95	N=13	N=5
Best overall response, n (%)				
Complete Remission (1)	1 (0.9)	1 (1.1)	0	0
Partial Remission (2)	17 (15.0)	16 (16.8)	1 (7.7)	0
Clinical improvement (3)	14 (12.4)	12 (12.6)	2 (15.4)	0
Overall Response Rate (4)	**32 (28.3)**	**29 (30.5)**	**3 (23.1)**	**0**
[95% CI]	[20.2, 37.6]	[21.5, 40.8]	[5.0, 53.8]	[0.0, 52.2]
Duration of response (month)				
n/N (%)	3/32 (9.4)	3/29 (10.3)	0/3 (0.0)	0
median [95% CI]	NE	NE	NE	NE
Overall survival (month)				
n/N (%)	65/113 (57.5)	51/95 (53.7)	11/13 (84.6)	3/5 (60.0)
median [95% CI]	29.9 [20.3, 42.0]	34.3 [22.1, 44.4]	10.7 [6.0, 22.1]	28.0 [14.3, NE]
survival probability, % [95% CI]				
1-year survival	74.1 [64.7 ,81.3]	77.9 [67.8 ,85.1]	38.5 [14.1 ,62.8]	100
2-year survival	53.2 [43.3 ,62.2]	57.3 [46.3 ,66.8]	23.1 [5.6 ,47.5]	60.0 [12.6 ,88.2]

Confirmation period for responses: 12 weeks

D816 mutated includes 93 patients with D816V, 3 patients with D816Y, and 1 patient with D816L

1) Patients with all organ damages in complete remission

(2) Patients with at least one organ damage in partial remission AND no progression on any other organ damage

(3) Patients with at least one organ damage clinically improved AND patient not in complete remission AND patient not in partial remission. A clinical improvement cannot be considered if a progression started before confirmation of clinical improvement

(4) Sum of patients in complete remission, patients in partial remission and patients with clinical improvement

Secondary endpoint: Duration of response

The results of the time to response analysis and duration of response as per Modified Valent Criteria considering patients with new anti-cancer therapy as PD are displayed in Table 73 and Figure 21.

Table 71 Summary of time to response and Duration of response as per Modified Valent Criteria considering patients with new anti-cancer therapy as PD (Primary efficacy population) - study D2201

```
                              All Patients
                              evaluated        ASM              SM-AHN           MCL
                              N=53             N=12             N=33             N=8
-----------------------------------------------------------------------------------------------

Time to response (months)
  Median                      0.3              0.3              0.5              0.3
  [95% CI]                    [ 0.1,  0.5]     [ 0.1,  1.4]     [ 0.1,  0.5]     [ 0.1,  0.5]
  Range                       0.1- 3.7         0.1- 1.9         0.1- 3.7         0.1- 3.0
Duration of response (months)
  Median                      18.6             36.8             10.7             NE
  [95% CI]                    [ 9.9, 34.7]     [ 5.5, NE ]      [ 7.4, 22.8]     [ 3.6, NE ]
  Range                       1.9+- 66.9+      2.5 - 66.9+      1.9+- 52.1+      3.6 - 65.8+
```

Figure 20. Kaplan-Meier plot of sensitivity analysis of DOR as per IWG criteria considering patients with new anti-cancer therapy as PD in Study D2201 (Eligible patients)
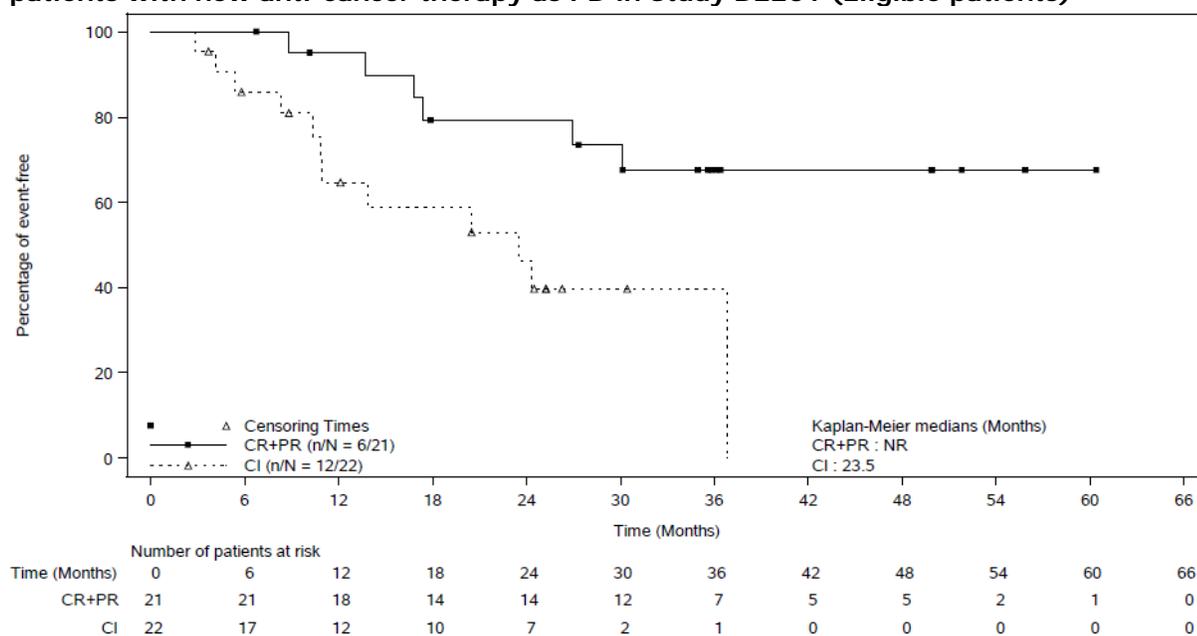
A summary of duration of response as per IWG response criteria (12 weeks confirmation) in an analysis with removing the Ascites C-Finding and considering patients with new anti-cancer therapy as PD is dispayed in Table 74.

Table 72. Study D2201: Summary of duration of response as per IWG response criteria (12 weeks confirmation) – removing the Ascites C-Finding and considering patients with new anti-cancer therapy as PD (Eligible patients)

|	All Patients evaluated N=32	ASM N=9	SM-AHN N=15	MCL N=7	Subtype unknown N=1
n/N (%)	11/32 (34.4)	4/9 (44.4)	4/15 (26.7)	3/7 (42.9)	0/1 (0.0)
Median time to censoring (months)	30	35	26	37	60
Percentiles (95% C.I) (months)					
25%	23.5 [8.7 , 36.8]	30.1 [10.3, 36.8]	27.0 [5.4 , .]	8.7 [4.1 , .]	. [., .]
Median	. [27.0, .]	36.8 [10.3, 36.8]	. [17.3, .]	. [4.1 , .]	. [., .]
75%	. [., .]	36.8 [., .]	. [27.0, .]	. [23.5, .]	. [., .]
% Event-free probability estimate [95% C.I]:					
6 months	93.8 [77.3 , 98.4]	100.0 [,]	93.3 [61.3 , 99.0]	85.7 [33.4 , 97.9]	100.0 [,]
12 months	83.4 [64.6 , 92.8]	88.9 [43.3 , 98.4]	84.8 [51.2 , 96.0]	71.4 [25.8 , 92.0]	100.0 [,]
18 months	76.2 [56.3 , 87.9]	77.8 [36.5 , 93.9]	75.4 [40.8 , 91.5]	71.4 [25.8 , 92.0]	100.0 [,]
24 months	72.2 [51.8 , 85.1]	77.8 [36.5 , 93.9]	75.4 [40.8 , 91.5]	53.6 [13.2 , 82.5]	100.0 [,]
36 months	61.9 [39.8 , 77.9]	64.8 [25.3 , 87.2]	60.3 [22.5 , 84.3]	53.6 [13.2 , 82.5]	100.0 [,]
48 months	51.6 [25.7 , 72.4]	0.0 [,]	60.3 [22.5 , 84.3]	53.6 [13.2 , 82.5]	100.0 [,]
60 months	51.6 [25.7 , 72.4]	0.0 [,]	. [., .]	. [., .]	100.0 [,]

- Patients who have started new anti-cancer therapy (ANP) are considered as having a PD at the date of ANP.
- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
- % Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point
- % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
- n : Total number of DOR events included in the analysis.
- N : Total number of subjects included in the analysis.

Secondary endpoint: Overall survival

In the PEP, at the time of data cut-off, 54 patients (60.7%) died. Overall survival is shown in Figure 22 for patients with ASM, SM-AHN, or MCL.

Figure 21 Kaplan-Meier plot of overall survival - ASM without AHNMD vs. SM-AHNMD vs. MCL patients (PEP) - study D2201

ASM without AHNMD are all patient who have MCL diagnosis = 'No or missing' and AHNMD = 'No or missing' at baseline as per Central histopathologist review.
SM-AHNMD are all patient who have MCL diagnosis = 'No or missing' and AHNMD = 'Yes' at baseline as per Central histopathologist review.
MCL are all patient who have MCL diagnosis = 'Yes' at baseline as per Central histopathologist review.

Overall survival is shown in Figure 23 for patients with and without a *KIT* D816 mutation present at baseline.

Figure 22 Kaplan-Meier plot of overall survival - Baseline *KIT* D816 mutation in SM (positive, negative) (PEP) - study D2201

A summary for OS by disease subtypefor the PEP and the FAS is presented in Table 75 and Table 76 respectively.

Table 73. Summary of overall survival (OS) — by disease subtype (PEP) — study-D2201

	All Patients evaluated N=89	ASM N=16	SM-AHN N=57	MCL N=16	Subtype unknown N=0
n/N (%)	54/89 (60.7)	5/16 (31.3)	39/57 (68.4)	10/16 (62.5)	0
Median time to censoring (months)	37	38	37	37	NA
Percentiles (95% C.I) (months)					
25%	9.8 [7.5 , 16.0]	34.7 [9.8 , .]	10.7 [6.0 , 16.3]	7.5 [3.4 , 8.7]	. [., .]
Median	26.8 [17.6, 34.7]	51.1 [28.7, .]	20.7 [16.3, 33.9]	9.4 [7.5 , .]	. [., .]
75%	. [42.0, .]	. [51.1, .]	42.0 [32.2, .]	. [9.4 , .]	. [., .]
% Event-free probability estimate [95% C.I]:					
6 months	89.6 [81.0 , 94.5]	100.0 [,]	87.3 [75.1 , 93.7]	87.5 [58.6 , 96.7]	. [., .]
12 months	70.2 [59.2 , 78.8]	93.3 [61.3 , 99.0]	70.2 [56.0 , 80.6]	47.1 [21.6 , 69.1]	. [., .]
18 months	59.1 [47.8 , 68.8]	93.3 [61.3 , 99.0]	55.0 [40.8 , 67.2]	40.4 [16.7 , 63.1]	. [., .]
24 months	50.5 [39.3 , 60.7]	86.2 [55.0 , 96.4]	45.5 [31.9 , 58.2]	33.7 [12.3 , 56.8]	. [., .]
36 months	38.2 [27.5 , 48.8]	69.6 [37.4 , 87.5]	31.0 [18.9 , 43.9]	33.7 [12.3 , 56.8]	. [., .]
48 months	29.8 [18.4 , 42.2]	69.6 [37.4 , 87.5]	19.9 [8.6 , 34.5]	33.7 [12.3 , 56.8]	. [., .]
60 months	26.1 [14.6 , 39.2]	34.8 [1.7 , 76.2]	19.9 [8.6 , 34.5]	33.7 [12.3 , 56.8]	. [., .]

- Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
- % Event-free probability estimates are the estimated probabilities that a patient will remain event-free up to the specified time point
- % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
- n : Total number of OS events included in the analysis.
- N : Total number of subjects included in the analysis.

Table 74. Summary of overall survival (OS) by disease subtype (FAS) — study-D2201

	All Patients evaluated N=113	ASM N=15	SM-AHN N=72	MCL N=21	Subtype unknown N=5
n/N (%)	65/113 (57.5)	4/15 (26.7)	49/72 (68.1)	12/21 (57.1)	0/5 (0.0)
Median time to censoring (months)	38	38	37	36	55
Percentiles (95% C.I) (months)					
25%	11.3 [7.7 , 16.8]	51.1 [9.8 , .]	10.9 [6.4 , 16.6]	8.3 [3.4 , 14.3]	. [., .]
Median	29.9 [20.3, 42.0]	51.1 [34.7, .]	22.1 [16.8, 32.2]	22.6 [8.3 , .]	. [., .]
75%	. [45.5, .]	. [51.1, .]	44.4 [34.3, .]	. [22.6, .]	. [., .]
% Event-free probability estimate [95% C.I]:					
6 months	90.1 [82.8 , 94.4]	100.0 [,]	87.2 [76.8 , 93.1]	90.5 [67.0 , 97.5]	100.0 [,]
12 months	74.1 [64.7 , 81.3]	92.9 [59.1 , 99.0]	72.4 [60.2 , 81.4]	60.3 [36.1 , 77.8]	100.0 [,]
18 months	61.8 [51.8 , 70.2]	92.9 [59.1 , 99.0]	56.1 [43.6 , 66.9]	50.3 [27.4 , 69.4]	100.0 [,]
24 months	53.2 [43.3 , 62.2]	92.9 [59.1 , 99.0]	44.3 [32.3 , 55.6]	45.2 [23.3 , 64.9]	100.0 [,]
36 months	42.4 [32.6 , 51.8]	75.0 [40.3 , 91.3]	33.0 [21.9 , 44.4]	37.7 [16.4 , 59.0]	100.0 [,]
48 months	34.5 [24.1 , 45.1]	75.0 [40.3 , 91.3]	21.2 [10.6 , 34.2]	37.7 [16.4 , 59.0]	100.0 [,]
60 months	31.8 [21.3 , 42.9]	37.5 [1.5 , 79.5]	21.2 [10.6 , 34.2]	37.7 [16.4 , 59.0]	100.0 [,]

Secondary endpoint- Mast cell improvement

Summaries of best improvement relative to baseline in the percentage of decrease in MC burden are given in Table 77.

Table 75 Mast cell improvement (PEP) - study D2201

Number of patients	All Patients N=89 n (%)
<10% decrease in mast cells compared to baseline	16 (18.0)
>=10-30% decrease in mast cells compared to baseline	25 (28.1)
>=30-50% decrease in mast cells compared to baseline	15 (16.9)
>=50-70% decrease in mast cells compared to baseline	9 (10.1)
>=70-90% decrease in mast cells compared to baseline	6 (6.7)
>=90% decrease in mast cells compared to baseline	1 (1.1)

Secondary endpoint-Serum tryptase reductions

Thirty-four patients (38.2%) in the PEP had a ≥50% decrease in serum tryptase level relative to baseline that was sustained for at least 56 days. In the FAS, the percentage was similar, 39.7%.

Secondary endpoint-Spleen volume

A decrease in spleen volume was seen on at least one occasion for the majority of patients who had volumetric spleen size data available at baseline and post-baseline (34/45 patients, 75.6%). Furthermore, 26.7% of these patients had a best decrease in spleen volume of at least 35% (previously been considered a threshold for clinical improvement in splenomegaly among patients with myeloproliferative disorders; Harrison *et al.* 2012, NEJM).

Changes in mast cell infiltration, spleen volume, and serum tryptase levels over the course of treatment

An overview of changes in mast cell infiltration, spleen volume, and serum tryptase levels over the first 12 28-day cycles of treatment in Study D2201 are provided in the tables below.

Table 76 Mast cell infiltration (%) over time (PEP) - study D2201

Time point	Statistics	n	Value	Change from baseline	% change from baseline
Baseline	Mean (SD)	89	48.7 (23.74)		
	Median		50		
	Q1;Q3		30; 65	NA	NA
	Min; Max		8; 98		
C3D28	Mean (SD)	59	37.6 (21.82)	-14.9 (21.77)	-23.28 (45.729)
	Median		30	-10	-25
	Q1;Q3		20; 50	−30; 0	−53; 0
	Min; Max		5; 80	-70; 40	-90.9; 160.0
C6D28	Mean (SD)	53	34.2 (23.54)	-18.4 (25.51)	-27.42 (54.186)
	Median		30	-20	-33
	Q1;Q3		15; 50	−35; 0	−67; 0
	Min; Max		2; 95	-85; 40	-90.9; 160.0
C12D28	Mean (SD)	41	30.5 (24.97)	-25.3 (31.50)	-37.31 (59.475)
	Median		20	-25	-53
	Q1;Q3		15; 40	−45; −5	−75; −7.7
	Min; Max		5; 90	-90; 55	-94.7; 220.0
NA=not applicable					

Table 77 Spleen volume (cm3) over (PEP) - study D2201

Time point	Statistics	n	Value	Change from baseline	% change from baseline
Baseline	Mean (SD)	51	1480 (1209.9)		
	Median		1200		
	Q1;Q3		794; 1843	NA	NA
	Min; Max		17; 7762		
C3D28	Mean (SD)	40	1421 (1687.4)	-127 (616.39)	-10.03 (21.203)
	Median		1033.3	-150	-13
	Q1;Q3		688; 1596	−265; 9	−24; 0.7
	Min; Max		12; 10648	-1253; 2886	-51.1; 37.2
C6D28	Mean (SD)	40	1214 (770.41)	-146 (417.06)	-9.09 (30.523)
	Median		982.4	-149	-16
	Q1;Q3		726; 1591	−364; 6.4	−29; 0.6
	Min; Max		211; 4123	-1110; 998	-59.0; 72.5
C12D28	Mean (SD)	31	1179 (809.23)	-105 (531.78)	-6.02 (40.760)
	Median		879.4	-132	-14
	Q1;Q3		652; 1412.5	−352; 94.5	−35.1; 15
	Min; Max		270; 3874	-1228; 1564	-65.3; 128.7
NA=not applicable					

Table 78 Serum tryptase levels (microgram/L) over time (PEP) - study D2201

Time point	Statistics	n	Value	Change from baseline	% change from baseline
Baseline	Mean (SD)	89	570.62 (1362.23)	-	-
	Median		236	-	-
	Q1;Q3		174; 436	NA	NA
	Min; Max		26.6; 12069.0		
C1D28	Mean (SD)	81	322.49 (463.450)	-267.3 (1246.33)	-12.94 (91.405)
	Median		197	-71	-36
	Q1;Q3		91; 298	−218; 0	−61; 0
	Min; Max		10.9; 2890.0	-10845.0; 1034	-98.7; 587.5
C2D28	Mean (SD)	75	289.93 (441.466)	-294.4 (1244.38)	-16.80 (91.504)
	Median		189	-69	-31
	Q1;Q3		105; 284	−251; 0	−63; −0.2
	Min; Max		12.2; 3530.0	-10671.0; 328.0	-92.1; 636.8
C3D28	Mean (SD)	72	303.63 (398.260)	-287.1 (1244.60)	-22.27 (50.305)
	Median		193	-62	-37

Time point	Statistics	n	Value	Change from baseline	% change from baseline
	Q1;Q3		93; 373	−291; 3	−58; 5
	Min; Max		12.5; 2660.0	-10375.0; 326.0	-95.5; 115.7
C6D28	Mean (SD)	60	273.68 (278.125)	-269.7 (1361.55)	-15.04 (77.046)
	Median		200	-83	-41
	Q1;Q3		98; 349	−260; 13.5	−64; −7
	Min; Max		12.7; 1599.0	-10470.0; 648.0	-95.5; 257.1
C12D28	Mean (SD)	46	231.32 (233.369)	-119.5 (279.024)	-20.61 (82.527)
	Median		155	-109	-49
	Q1;Q3		66; 290	−250; 25	−71; −14.5
	Min; Max		11.0; 1050.0	-925.2; 672.0	-94.9; 266.7
NA=not applicable					

Patient-reported outcomes/quality of life measurements

The Total MSAS score (TMSAS) is the average of the symptom scores of all 32 symptoms in the MSAS instrument. The results regarding the TMSAS assessments are summarised in Table 81.

Table 79 Patients with MSAS scores improved for at least 168 days (PEP) - study D2201

	Midostaurin
	N =89
Categories	n (%)
≥ 50% decrease in TMSAS score relative to baseline	20 (22.5)
In evaluable patients	20/52 (38.5)
≥ 50% decrease in MSAS GDI score relative to baseline	25 (28.1)
In evaluable patients	25/49 (51.0)
≥ 50% decrease in PHYS score relative to baseline	19 (21.3)
In evaluable patients	19/51 (37.3)
≥ 50% decrease in PSYCH score relative to baseline	21 (23.6)
In evaluable patients	21/47 (44.7)

80 patients had baseline scores recorded.

Evaluable patients: baseline score >0, and evaluable for at least 168 days

The overall response rate by PRO response category (MSAS) is resented in **Table 82**.

Table 80. Overall response rate by PRO response category (MSAS) in Study D2201 (PEP)

	ORR in patients with at least 50% reduction in PRO score	ORR in patients with less than 50% reduction in PRO score	p-value [1]
PRO instrument and subscales	**n/N (%)**	**n/N (%)**	
TMSAS	15/20 (75.0)	31/57 (54.4)	0.1211
MSAS-GDI	17/25 (68.0)	27/48 (56.3)	0.4505
MSAS-PHYS	17/19 (89.5)	29/57 (50.9)	0.0028
MSAS-PSYCH	14/21 (66.7)	27/46 (58.7)	0.5976
P-value based on a Fisher exact test.			

Ancillary analyses

NA

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 81 Summary of efficacy for Study A2301 (pivotal phase 3 study)

Title: A randomised phase III study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in treatment-naive patients with *FLT3* mutated acute myeloid leukaemia (AML)		
Study identifier	RATIFY; CALGB 10603; CPKC412A2301, EudraCT No. 2006-006852-37	
Design	Randomised, double-blind, placebo-controlled, phase III study	
	Study start date:	03-Jul-2008 (first patient randomised)
	Study completion date:	Data cut-off for this primary clinical study report was 01-Apr-2015;
Hypothesis	Superiority	
Treatments groups	Induction/consolidation + midostaurin	Induction phase: 200 mg/m2/day cytarabine (Days 1-7) and 60 mg/m2/day daunorubicin (Days 1-3) and 50 mg b.i.d. midostaurin/placebo (days 8-21) (up to 2 cycles). Consolidation phase: 4 cycles of with high-dose cytarabine (3 g/m2 iv every 12 h on Days 1, 3 and 5 of each cycle) followed by

	Induction/consolidation + placebo		midostaurin/placebo (50 mg twice a day on Days 8-21). Continuation therapy: patients who continued to maintain a CR after consolidation therapy received continuation therapy with midostaurin 50 mg or placebo b.i.d. for 28 days according to their initial assignment (until relapse or for 12 cycles of 28 days each maximum).
Endpoints and definitions	Primary endpoint	OS (non-censored for SCT)	The period from the date of randomisation until death by any cause.
	Secondary endpoint	OS (censored for SCT)	OS analysis with censoring at the time of SCT.
	Key secondary endpoint	EFS (non-censored for SCT)	A failure to obtain a CR within 60 days of initiation of protocol therapy, or relapse, or death from any cause, whichever occurred first.
	Key secondary endpoint	EFS (censored for SCT)	EFS analysis with censoring at the time of SCT.
	Secondary endpoint	DFS (non-censored for SCT)	The analysis for DFS included patients who achieved CR by Day 60. DFS was measured from the date of first CR to relapse or death from any cause, whichever occurred first.
	Secondary endpoint	DFS (censored for SCT)	DFS analysis with censoring at the time of SCT.
	Secondary endpoint	CR rate	The summary of the CR rate within 60 days of study treatment start, and the difference in CR rates with 95%CIs obtained from the Wald asymptotic confidence limits were provided. CRs occurring later than within 60 days were not counted as CRs in the primary analysis.
	Secondary endpoint	SCT rate	The overall number and percentage of patients who received SCT during the study was summarised by treatment arm and *FLT3* mutation strata for each type of SCT: allogeneic related SCT, allogeneic unrelated SCT, autologous SCT, cord blood and other.

	Secondary endpoint	DFR rate 1 year after completing continuation therapy	DFS was assessed for all patients who had completed continuation therapy and were still in CR.		

Database lock	April 1st 2015

Results and Analysis

Analysis description	Primary Analysis

Analysis population and time point description	Full analysis set (FAS, N=717)

Descriptive statistics and estimate variability	Treatment group	Placebo	Midostaurin	
	Number of subjects	N=357	N=360	
	OS (non-censored for SCT), median (95%CI)	25.6 months (18.63-42.87)	74.7 months (31.54-NE)	P=0.0078
	OS (censored for SCT), median (95%CI)	9.95 months (7.85-14.39)	17.08 months (12.39-26.94)	
	EFS (non-censored for SCT), median (95% CI)	2.99 months (1.91-5.91)	8.18 months (5.42-10.68)	P=0.002
	EFS (censored for SCT), median (95% CI)	2.83 months (1.91-5.91)	8.31 months (5.78-10.68)	
	DFS (non-censored for SCT), median (95% CI)	15.51 months (11.33-23.46)	26.74 months (19.35-NE)	P=0.0051
	DFS (censored for SCT), median (95% CI)	14.49 months (9.23-21.75)	20.70 months (16.43-NE)	
	CR rate, N (%)	191 (54%)	212 (59%)	P=0.073
	SCT rate, N (%)	197 (55%)	214 (59%)	P=0.250

Effect estimate per comparison	OS (non-censored for SCT) (primary endpoint)	Comparison groups	Midostaurin versus placebo
		HR	0.77
		95%CI	0.629-0.953
		Log-rank P value	P=0.0078
	OS (censored for SCT)	Comparison groups	Midostaurin versus placebo
		HR	0.75

		95%CI	0.544-1.031
		Log-rank P value	P=0.0373
	EFS (non-censored for SCT)	Comparison groups	Midostaurin versus placebo
		HR	0.78
		95%CI	0.662-0.930
		Log-rank P value	P=0.0024
	EFS (censored for SCT)	Comparison groups	Midostaurin versus placebo
		HR	0.81
		95%CI	0.677-0.975
		Log-rank P value	P=0.0124
	DFS (non-censored for SCT)	Comparison groups	Midostaurin versus placebo
		HR	0.71
		95%CI	0.545-0.923
		Log-rank P value	P=0.0051
	DFS (censored for SCT)	Comparison groups	Midostaurin versus placebo
		HR	0.72
		95%CI	0.536-0.970
		Log-rank P value	P=0.0150

Table 82. Summary of efficacy for pivotal trial D2201

Title: A single arm, Phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukaemia +/- an associated haematological clonal non-mast cell lineage disease	

Study identifier	PKC412D2201; D2201			
Design	Single-arm, non-randomised, open-label, multi-center Phase II study using an adapted Fleming two-stage design followed by an extension phase			
	First patient enrolled:		6-Jan-2009	
	Analysis cut-off date:		1-Dec-2014	
Hypothesis	Null hypothesis of an ORR ≤ 30%			
Treatments groups	Midostaurin (N=116, FAS; N=89, PEP, N=86, PPS)	100 mg b.i.d. continuous		
Endpoints and definitions	Primary endpoint	ORR	Proportion of patients in the PEP with a best response of MR or PR that initially occurred in the first 6 cycles of treatment as assessed by the SSC using modified Valent/Cheson criteria and that was confirmed at least 56 days later.	
	Secondary endpoint	DOR	Time from the start of the first confirmed response occurring before the end of cycle 6 until the date of first confirmed PD or death due to ASM or MCL.	
	Secondary endpoint	OS	Time from the start of treatment to the date of death due to any cause.	
	Secondary endpoint	PFS	Time from the start of treatment to the date of the first confirmed progression or death due to any cause.	
Database lock	01-Dec-2014			

Results and Analysis				
Analysis description	The primary efficacy analysis was performed on the primary efficacy population (PEP)			
Analysis population and analysis description	Best overall response per SSC adjudication in the primary efficacy population (PEP)			
Primary endpoint, ORR	Treatment group	Midostaurin		
	Number of subjects (all patients evaluated)	N=89	C. I. 95%	P-value
	ORR (95%CI)	59.6%	(48.6-69.8%)	<0.001 (two sided)
Secondary endpoints, DOR	Treatment group	Midostaurin		

	Number of subjects	N=89		
	DOR, median (months)	18.6	(9.9 – 34.7)	
Secondary endpoints, OS	Treatment group	Midostaurin		
	Number of subjects	N=89		
	OS, median (months)	26.8	17.6-34.7	
Secondary endpoints, PFS	Treatment group	Midostaurin		
	Number of subjects	N=89		
	PFS, median (months)	17.0	10.2-24.8	
Sensitivity analysis	Response rate based on IWG criteria			
	Treatment group	Midostaurin		
	Number of subjects	N=115		
	ORR (95%CI)	37.4%	(28.5-46.9%)	
Sensitivity analysis	ORR in the FAS			
	Treatment group	Midostaurin		
	Number of subjects	N=116		
	ORR (95%CI)	45.7%	(36.4-55.2%)	
Sensitivity analysis	ORR in the per-protocol set			
	Treatment group	Midostaurin		
	Number of subjects	N=86		
	ORR (95%CI)	58.1%	(47.0-68.7%)	
Sensitivity analysis	**ORR in the PEP by Valent/Cheson criteria, without consideration of the clinical context (i.e. algorithm-based calculation of ORR)**			
	Treatment group	Midostaurin		

	Number of subjects	N=89		
	ORR (95%CI)	46.1%	(35.4-57.0%)	
Sensitivity analysis	**ORR in the PEP by investigator assessment**			
	Treatment group	Midostaurin		
	Number of subjects	N=89		
	ORR (95%CI)	52.8%	(41.9-63.5%)	

Clinical studies in special populations

AML indication

Table 83. Number of elderly patients in Novartis-sponsored studies in the AML program

	Age 65 to <75 years n/N (%)	Age 75 to <85 years n/N (%)	Age ≥ 85 years n/N (%)
Controlled Trials	0/717	0/717	0/717
Non Controlled trials	50/233 (21.5)	34/233 (14.6)	3/233 (1.3)

n= number of older subjects, N=total number of subjects
Controlled trials: A2301
Non Controlled trials: A2106, A2104, A2104E1, A2104E2, A2114
Source: [AML Appendix 1-Table HAQEU.1-86.1]

Advanced SM (ASM/SM-AHN/MCL) indication

Table 84. Number of elderly patients in the advanced SM program

	Age 65 to <75 years n/N (%)	Age 75 to <85 years n/N (%)	Age ≥ 85 years n/N (%)
Controlled Trials	No controlled trials have been conducted in advanced SM		
Non Controlled trials Total	48/142 (33.8)	16/142 (11.3)	0
Study D2201 (FAS)	37/116 (31.9)	14/116 (12.1)	0
Study A2213 (FAS)	11/26 (42.3)	2/26 (7.7)	0

n= number of older subjects, N=total number of subjects
Source: [AdSM Appendix 1-Table HAQEU.2-109.1]

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison of OS data from studies D2201 and A2213 with those from a registry of patients with ASM

Exploratory analyses were performed to further assess the clinical benefit of midostaurin in the studied population by comparing the OS observed with midostaurin to the OS observed in an independent German Registry (Heidelberg University), including patients with ASM or MCL +/- AHNMD who never received midostaurin. However it is considered that these analyses are methodologically unsound, and severely biased in favour of the midostaurin group (data not shown).

Supportive studies

Acute myeloid leukaemia indication

Study ADE02T

An interim analysis was conducted on the first cohort of 145 patients enrolled into study ADE02T, which was a phase 2, single-arm, multicentre, investigator-initiated study evaluating the efficacy and safety of midostaurin in combination with intensive induction therapy (daunorubicin and cytarabine) and as single agent maintenance therapy after allogeneic haematopoietic stem cell transplantation (ASCT) or high-dose cytarabine in patients with newly diagnosed *FLT3*-ITD positive AML. Patients aged 18-70 years old are enrolled in this study.

In study ADE02T, after achieving CR patients proceed to ASCT as the preferred treatment option, and if ASCT was not feasible then patients received four cycles of age-adapted high-dose cytarabine (day 1, 3, and 5) in combination with midostaurin (day 6 onwards). All patients were to receive 1 year of midostaurin maintenance therapy post-SCT or cytarabine consolidation. The primary endpoint was EFS. Secondary endpoints included CR rate, relapse free survival (RFS), OS, and the cumulative incidences of relapse (CIR) and death (CID) in CR.

ADE02T differed in some critical aspects of study design from the pivotal study (A2301). In the pivotal study patients receiving SCT discontinued midostaurin, while in study ADE02T patients received 1 year maintenance treatment with midostaurin after SCT. In the pivotal study patients received midostaurin on days 8-21, while in study ADE02T patients received midostaurin from day 8 until 48 hours prior to start of the next cycle of chemotherapy or conditioning therapy for SCT (effectively this means patients were intended to receive midostaurin on days 8-26 in contrast to days 8-21 as in the pivotal study). In study ADE02T patients older than 60 years of age were enrolled.

In study ADE02T, patients had a median age of 53.6 years (range: 20 to 69 years; 32% of patients were >60 years of age), and the age groups (≤ 60, >60) were well matched with respect to gender and ECOG status. The median follow-up was derived taking the Kaplan-Meier estimate of median time to censoring and was 25.2 months (95%CI: 24.4-27.4). The primary efficacy endpoint was EFS after 2 years. The 2 year EFS of the whole cohort was 34.6% (95%CI: 27.4-43.6), which was higher than historical cohort of 588 *FLT3*-ITD AML patients used for comparison (2 year EFS 25%). Improved 2 year EFS rates were notable for patients >60 years with 27.1% (95%CI: 16.6-44.1) compared to 14% in the historical control. The median EFS was 10.7 months (95%CI: 7.7-19.7) for the whole population; 13.8 months (95%CI: 7.9, 23.3) in younger patients and 9.3 months (95%CI: 3.5-21.1) in older patients.

The CR rates (CR/CRi) were 77% (age ≤ 60 years) and 67% (age>60 years); 50% of the younger patients and 23% of those >60 years proceeded to SCT in CR1. Relapse free survival after 2 years was 51.3% and 36.6% for the younger and older age groups respectively. The median OS after 2 years was 24.7 months; 28.5 months for patients ≤ 60 years, and 15.5 months for those >60 years.

Additional comparison analysis of study ADE02T with historical controls

The Applicant has provided data on a comparison between efficacy of midostaurin in patients >60 years of age from ADE02T with efficacy in historical controls. The historical controls were selected from 5 successive clinical trials conducted by AMLSG enrolling AML patients treated with intensive chemotherapy (Tassara et al 2014, Schlenk et al 2016b, Schlenk et al 2006a, Schlenk et al 2006b, Schlenk et al 2004a, Schlenk 2004b, Schlenk 2003). Only limited information was provided on baseline characteristics. Propensity score matching

was applied for the following baseline variables: age, gender, NPM1 mutation status, white blood cell count and percentage of bone marrow blasts, in an effort to control for prognostic variables. In the analysis no correction for time/year of initiation of treatment (while prognostic for outcome) was performed. Based on this analysis the HR (95%CI) for OS was 0.49 (0.316, 0.753) for patients >60 years of age (data not shown).

Aggressive systemic mastocytosis / Mast cell leukaemia indication

Study A2213 (PKC412A2213)

This was a single-arm, Phase II, open-label study using Simon's two-stage design to assess the efficacy of oral midostaurin at a dose of 100 mg b.i.d. in patients with ASM or MCL with or without associated haematological clonal non-mast cell lineage disease (AHNMD). Midostaurin was administered in cycles of 28 days duration.

Initially, 10 patients were to be enrolled in Stage I, and each patient was to be evaluated for at least 2 months for efficacy, safety, tolerability, PK and pharmacodynamic endpoints. Any patient who discontinued treatment for reasons other than toxicity, death or disease progression was to be replaced. If at least one of the first 10 patients from the Stage I had a response, an additional 15 patients were to be enrolled into the Stage II of the study. If none of the first 10 patients had a clinical response, the study was to be closed. The Stage I and Stage II portions of the Simon's two-stage design was conducted under the leadership of the Principal Investigator and Novartis received the data (data up to 3 December 2012) after all patients were enrolled in Stage I and Stage II portions of the study.

Patients were followed for survival for one year after they stopped treatment.

Midostaurin was administered at a dose of 100 mg b.i.d., beginning on Day 1. Each patient could receive up to 12 cycles of midostaurin; each cycle was 28 days in duration. At the end of each cycle the patient was evaluated for response. After the first 2 cycles of therapy, patients without a documented MR or PR according to the Valent criteria (Valent et al. 2003) were to be discontinued from the study. This is different from the main study where patients received treatment until documented progression or discontinuation for other reasons such as unacceptable toxicity.

The primary objective was to evaluate the efficacy of twice-daily oral doses of PKC412 (midostaurin) when administered to patients with ASM/MCL ± AHNMD (associated haematological clonal non-mast cell lineage disease) by measuring ORR.

Secondary objectives included PKs of twice-daily oral doses of PKC412, evaluation of the effect of PKC412 on survival, investigation of ASM/MCL specific DNA mutations and comparison of gene expression changes in blood and bone marrow cells, and investigation of the effects of genetic variation in drug metabolism genes. The first 2 secondary objectives presented above were evaluated in this study. Secondary objectives 3 and 4 were not evaluated in this study, because the format of data collection did not allow for the generation of summary statistics.

The inclusion and exclusion criteria were highly similar to the main study (study A2213).

The primary efficacy endpoint of the study was ORR based on investigator assessment, over the first 2 cycles. The response assessments in patients with ASM and MCL were based on the response criteria of Valent et al. (2003).

Results

A total of 26 patients were enrolled from 7 July 2005 to 26 April 2010 at 3 centres in the United States. At the time of the data cut-off date (3 December 2012), 7 patients were continuing to receive study drug, and 19 patients had discontinued study drug. Among the 26 patients enrolled in the study, all patients were included in all analysis sets.

The median duration of study follow-up was 73 months (range: 31 – 89 months). Twenty (76.9%) patients had ASM (17 [85%] with AHNMD) and 6 patients (23.1%) had MCL (2 [33.3%] with AHNMD). The median age was 64.5 years with half of the patients ≥ 65 years). At baseline, 88.5% had >1 C finding and 69.2% had received at least one prior anti neoplastic regimen (SmPC, section 5.1).

Table 85. Best overall response as per Investigator assessment (full analysis set) - Study A2213

	All Patients N=26 n (%)
Best overall response	
Major Response (MR)	13 (50.0)
Complete Remission (CR)	0
Incomplete Remission (IR)	5 (19.2)
Pure Clinical Response (PCR)	8 (30.8)
Partial Response (PR)	6 (23.1)
Good Partial Response (GPR)	4 (15.4)
Minor Response (MinR)	2 (7.7)
No Response	7 (26.9)
Stable Disease (SD)	6 (23.1)
Progressive Disease (PD)	1 (3.8)
Not Evaluable	0
Overall Response Rate (ORR=MR+PR)*	19 (73.1)
95% CI for ORR	[52.2, 88.4]

*Overall response rate (ORR) was defined as the proportion of patients in FAS with an overall best response of major response (MR) or partial response (PR) in the first 2 cycles of treatment as assessed by Investigator using Valent criteria.
The 95% CI for ORR was computed using an exact binomial confidence interval

Median overall survival was 40.0 months (patients were only followed up for one year after treatment discontinuation for survival) (SmPC, section 5.1).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

AML indication

In phase I and II studies, the OS and EFS were similar between 50 mg bid and 100 mg bid dosage regimens and together with the acceptable safety profiles, the dose of 50 mg in AML patients was considered acceptable.

The overall design of the study was considered adequate. The target patient population (patients with ≥ 5% FLT3-mutated alleles), the comparator (standard induction and consolidation chemotherapy plus placebo), and the sequential dosing regimen of midostaurin were considered acceptable and have been previously agreed upon in an SAWP scientific advice (EMEA/H/SA/764/1/2006/PA/III). The inclusion and exclusion criteria were considered adequate and the enrolled patient population was considered to be a clinically

representative population of patients with FLT3 positive AML. The patient population in the pivotal study was restricted to patients younger than 60 years of age. This reflects the standard of care at the time that the pivotal study was initiated, i.e., at that stage patients older than 60 years of age were deemed ineligible for standard induction and consolidation chemotherapy. As current practice is that AML patients older than 60 who are fit should also treated with standard induction and consolidation chemotherapy, an indication is proposed by the applicant without restriction of age (see efficacy data and additional analyses below).

A relatively high number of major protocol violations occurred in the pivotal study. The nature of the protocol deviations and the distribution across treatment arms is such that they do not impact the conclusions regarding efficacy and safety drawn from the submitted data to a relevant extent. The main amendments to the study protocol did not impact the interpretation of the efficacy or safety results.

Three GCP inspections were performed at three centres participating in the pivotal study. The three sites were assessed as compliant, despite a few critical findings that were noted. Considering the nature of these critical findings (they were mainly related to the informed consent process and drug accountability) however, it is concluded that they do not impact the reliability of the submitted efficacy and safety data.

Signs of monotherapy activity of midostaurin have been observed in patients with FLT3 mutated as well as wild type AML in early clinical studies, although the activity might be higher in patients with mutated FLT3. These findings are supported by data from *ex vivo* studies indicating higher activity in cell lines with FLT3 mutation. At this stage, therefore, there is an acceptable rationale for the proposed target population of FLT3-mutated patients (although the favourable findings observed in patients with mutated FLT3 might support further studies to be conducted in FLT3 wild type AML). The cut-off for FLT3 status is considered acceptable and was agreed upon in a previous scientific advice (EMEA/H/SA/764/1/2006/PA/III). Quality control regarding FLT3 screening during conduct of the pivotal study was adequate. The CHMP agreed that in view of the availability of a FLT3 mutation test at multiple commercial and academic centres, co-development of a commercially available Health Authority-approved FLT3 mutation detection kit would not be considered necessary.

Regarding the choice for the induction and consolidation chemotherapy regimens, in clinical practice, different varieties of regimens are used, using slightly different doses and/or e.g. different types of anthracyclines. It is unclear to which extent different induction and consolidation regimens could interact differently with midostaurin from a PK/PD perspective and in regard to the treatment effect of midostaurin. Therefore, the chemotherapy to be used in combination with Rydapt is specified in the wording of the indication.

The chosen primary endpoint, OS, was considered adequate to demonstrate clinical benefit in the context of first-line treatment of AML. In the primary analysis patients receiving SCT were not censored. This is considered appropriate. The secondary endpoints, EFS (with and without censoring for SCT), DFS, CR rate, and SCT rate are considered adequate endpoints which are relevant in the context of the studied population.

Patient and disease characteristics were balanced between treatment arms, with the exception of a small imbalance in gender (females accounted for 51.7% vs. 59.4% of patients in the midostaurin and placebo arms, respectively). Subjects with a history of cardiac problems, including symptomatic congestive heart failure, were excluded from the pivotal study. Taking into account the proposed target population, exclusion of risk groups such as these from the pivotal study is described in the SmPC.

The pivotal study in AML did not include MRD assessment, because, at the time this study was initiated (2008) there was no universal, robust, regulatory authority-approved technology available to measure MRD. However the results of study E2301, a randomised, double-blind study of midostaurin versus placebo in combination with chemotherapy during induction and consolidation, followed by 12 months of midostaurin

monotherapy in adult patients (aged ≥ 18 years) with newly diagnosed AML, without FLT3 mutation, will provide information on MRD assessment (see Annex II conditions).

<u>*ASM/SM-AHN/MCL indication*</u>

No dose-finding studies were conducted in ASM/SM-AHN/MCL. The dose of 100 mg b.i.d was selected based on the same phase I and II studies in AML patients (i.e. A2104 and A2104E1). Since there were no data in ASM/SM-AHN/MCL patients after 50 mg b.i.d, and the safety profile with 100 mg b.i.d was acceptable in ASM/SM-AHN/MCL patients the dose of 100 mg b.i.d was considered acceptable.

Issues related to the conduct of the main study such as a large proportion of ineligible patients were enrolled in the study, an amendment affecting the statistical analysis plan and the primary analysis introduced halfway during the study and also concerns regarding potential bias in the assessment of the primary endpoint ORR by the SSC were further discussed. There were issues related to the accuracy of the ORR as primary endpoint including the use of Valent and Cheson criteria, the heterogeneity observed in the degree of responses, the assessment of the responses, the primary efficacy on a subset of population and the discordance in the analysis of best overall response (by the investigator vs by the SSC). These concerns were relieved based on a post-hoc analysis provided by the applicant, in which ORR was determined using the most recent response criteria (IWG-MRT & ECNM criteria), and in which an algorithm-based assessment is performed without the potentially subjective nature of assessment by the SSC.

The lack of a comparative design as the pivotal results obtained in a single arm trial (D2201), was of concern. Adequate justification for why a randomized clinical trial is not feasible in the ASM, SM-AHN, and MCL indication was provided. Considering that these are rare life-threatening conditions with large unmet medical need, the lack of a randomized controlled trial was considered acceptable. Study D2201 is the largest prospectively conducted clinical trial in this population. Recruitment was completed in three years (January 2009 to June 2012) and the study is still ongoing. A controlled trial with a relevant size to perform appropriate statistical comparison would take a very long time to complete.

Duration of response (DOR) and the remaining secondary endpoints, including OS, MC improvement, and spleen volume were considered relevant endpoints. Quality of life data are highly relevant, but interpretation of the quality of life measurements that were performed in the main study was problematic in view of the single-arm, open-label design of the study.

Efficacy data and additional analyses

<u>*AML indication*</u>

The primary endpoint OS (without censoring for SCT) was met, with a HR of 0.774 (95% CI: 0.629-0.953, p=0.0078), corresponding to a relative risk reduction of 23% in favour of midostaurin. The midostaurin arm had a higher plateau, with 51% (95%CI: 45-56) of the patients surviving at the 5-year time point, versus 43% (95%CI: 38-49) of the patients in the placebo arm. Comparison of the median OS values (midostaurin: 75 months; placebo: 26 months) is not informative since the Kaplan-Meier curves plateau around the median and estimates of the median are therefore not precise. The difference in OS, and the higher plateau for patients treated with midostaurin, are considered to be of clinical relevance for the target population, although the treatment effect as determined by the HR was considered to be of moderate magnitude. Censoring for SCT did not affect the results regarding OS, confirming the robustness of the OS benefit conferred by midostaurin in the overall population. Multivariable analysis also confirmed the OS benefit in the overall population.

Most subgroups showed a similar OS benefit as in the overall population. However, while males had a clear OS benefit in the pivotal study (HR 0.53, 95%CI: 0.39-0.72), females appeared to have no OS benefit from treatment with midostaurin relative to placebo (HR 1.01, 95%CI: 0.76-1.34). Review of the publicly available literature for potential gender differences in outcome in newly diagnosed/untreated AML adult patients receiving intensive chemotherapy, indicated that in most studies no significant differences between males and females are observed. No apparent gender effect in OS was seen in supportive study A2106 in FLT3+ AML patients, while a trend towards longer OS for males was noted in supportive study ADE02T. However, while a gender difference has not consistently been observed, study A2301 is not the first study in the published literature reporting a (potential) difference in gender. This somewhat alleviates the concern regarding the lack of internal consistency.

A gender difference in OS was evident in the placebo arm and was statistically significant (HR=0.66; 95% CI 0.49, 0.90 in a multivariate analysis). Additional analyses of SCT by gender and treatment arms showed that censoring for SCT diminished the effect of gender on OS (HR 0.812, 95% CI 0.520, 1.269) in the placebo arm, while the SCT rates and timing of SCT did not reveal major differences between these groups. This was due to better survival of males (shift in the KM curve) when censoring for SCT while censoring had only limited effect on the survival curve for females. This apparent gender-related difference was confirmed in the OS analysis of the subgroups who received SCT. Additional censoring analysis (for SCT in CR1 only or SCT in salvage) seemed to indicate that this is mainly caused by a gender difference between patients receiving SCT as salvage therapy. While, in the midostaurin arm, the impact of SCT censoring on the survival curves also seems to be larger for males than females, this effect seems less than what is noted in the placebo arm. Notably, due to this differential effect of SCT on the male and female survival curve, a separation of these curves seems to be occurring but this did not result in a statistical significant difference in OS (HR 1.192, 95% CI 0.745, 1.908) in the midostaurin arm. Although all these censoring and subgroup analyses should be interpreted with caution as they are post-hoc, and may be subject to informative censoring or are based on a post-baseline parameter and therefore bias cannot be excluded they do suggest that the observed difference in OS benefit between the sexes may, at least in part, be SCT-related and thus to a post-midostaurin treatment event. The data also indicated that midostaurin treatment may have played a role in the impact of SCT on the survival of males and females in this study, as the impact differs between the treatments arms (thus there might be a potential carry-over effect). As it is likely that SCT has substantially contributed to the apparent gender effect, it is important to note that censoring for SCT (sensitivity analysis) in the ITT population (HR 0.75, 95%CI: 0.54-1.03) confirmed the observed OS benefit conferred by midostaurin observed in the primary analysis (HR 0.774 (95% CI: 0.629, 0.953). Based on this observation, together with the fact that for females a benefit of treatment was seen in the secondary endpoints EFS, CR and CIR, it is considered that there is sufficient evidence of benefit, and no safety signal, to collectively outweigh the uncertainty on the effect size and concern regarding the internal consistently, provided that the observed effects between the sexes are adequately described in the SmPC. Confirmation or refutation of this gender difference is expected from the planned ongoing study in newly diagnosed FLT3 wild type AML patients (E2301), and as this study includes a more substantial biomarker analysis, also a more mechanistical explanation might be found.

In current clinical practice, three genetic alterations are routinely determined as prognostic markers in AML, i.e. FLT3, NPM1, and CEBPA. Like FLT3, alterations in NPM1 and CEBPA affect outcome of patients with AML, and in the 2016 revision to the WHO classification of myeloid neoplasms and acute leukaemia, "AML with mutated NPM1" and "AML with biallelic mutations of CEBPA" have become separate clinical entities. In additional analysis, NPM1 status did not affect the treatment effect of midostaurin, as midostaurin was

effective both in NPM1 mutated and NPM1 wildtype FLT3-mutated AML. CEBPA alterations were too infrequent (2.5%) in FLT3-mutated AML patients for analyses to be performed.

The effect of midostaurin on EFS was concordant with the effect on OS, with a HR of 0.784 favouring midostaurin (p=0.0024). Similar to OS, a higher plateau for EFS was observed for the midostaurin treatment arm. The effect of midostaurin on EFS was homogeneous across the investigated subgroups, including males/females and multivariable analysis confirmed the EFS benefit in the overall population. The EFS benefit is supportive of the overall result on OS.

The CR rate was higher in the midostaurin arm in the analysis that considered all CRs (including those that occurred outside of the 60-day window) further confirming the anti-AML activity of midostaurin. Also the results regarding DFS were in line with the primary endpoint: HR 0.71, 95%CI: 0.55-0.92 (one-sided p=0.0051), confirming the efficacy of midostaurin.

Slightly more patients in the midostaurin arm (59.4%) received SCT throughout the study as compared to the placebo arm (55.2%) possibly indicating that more patients receiving midostaurin became eligible/fit for SCT. In addition, more patients achieved CR in the midostaurin arm vs. the placebo arm. The proportion of patients who died after SCT in their first CR was lower in the midostaurin arm (HR 0.638) than in the placebo arm, but the 95%CI was relatively wide (0.373-1.091). Thus, so far the data indicated that midostaurin prior to SCT does not impair the results of SCT. The comparison of survival data in the subgroup of all patients who received SCT was performed and confirmed the efficacy of midostaurin in this subgroup.

The added value of maintenance treatment is difficult to establish based on the design of the pivotal study. While two deaths (total events nine) were reported in the placebo arm in this phase, no deaths of 16 events were reported the midostaurin arm, which is reassuring. Interpretation of the exploratory analyses is difficult due to the following reasons: lack of re-randomisation of the midostaurin patients to either placebo or midostaurin at the start of continuation therapy, the fact that the efficacy analyses performed to support the effect of midostaurin given as continuation therapy was based on a small sample size (less than 30% of the randomised patients) and the highly selected population included in the analysis. Therefore, at present the available data did not allow a firm conclusion regarding the added value of the 12 months midostaurin continuation therapy. However, there is a clear scientific rationale for following the induction and consolidation phases by a period of maintenance therapy in FLT3-mutated AML, which has a high relapse rate that can be partly attributed to FLT3 clones (although other clones also contribute to relapse). Furthermore, the efficacy of midostaurin has been demonstrated only when a continuation/maintenance phase is applied. In addition, the safety profile of midostaurin monotherapy is favourable. For these reasons, the proposed indication which includes a postremission maintenance phase is considered acceptable.

In the pivotal study, only patients <60 years of age were enrolled. During the initial evaluation, the CHMP raised a major objection about the indication needing to be further discussed, with reference to patients ≥ 60 years of age. Several post-hoc analyses were conducted to evaluate effect of age on efficacy outcome (CR, EFS, DFS and OS) in study A2301. CR, EFS, DFS and OS were also reviewed by 5-year intervals. These post-hoc analyses do not support a hypothesis where efficacy of midostaurin would decrease with increasing age, and no conclusions can be drawn regarding specific age cutoffs for treatment. The biology of AML may differ between young and old AML patients, but not in the subset of patients with FLT3 mutations eligible to intensive chemotherapy. The main change of biology of AML related to age is an increase in complex cytogenetics in older patients, which is not relevant to patients with a FLT mutation. Therefore there are no reasons to expect that the mode of action differs between older and younger FLT3-positive AML patients and the age is not expected to affect the PK of midostaurin. In addition, the safety profile of midostaurin appears

similar in patients >60 vs those <60 years of age based on the analysis in the ADE02T study. Regarding the comparison with historical controls it is considered that interpretation of the data is strongly hampered as a result of different factors i.e. the time of treatment and the frequency of SCT.

In conclusion, in spite of the limited experience in patients ≥ 60 years of age, the preliminary findings of the supportive study ADE02T indicated a beneficial effect also in this population. Furthermore, the results from the post-hoc analyses (study A2301) did not demonstrate that the efficacy of midostaurin would decrease with increasing age, which is reassuring. Therefore the CHMP agreed that the observed survival benefit in the population of the pivotal study (<60 years of age) can be extrapolated to the ≥ 60 years of age population. However, until further data become available the limited experience in the elderly should be taken into account in clinical decision-making, therefore the limited experience in elderly and additional guidance on selecting eligible patients has been included in the product information (sections 4.2 and 5.1). To further resolve this, the applicant will submit the updated results of study ADE02T and the results of studies A2408 and E2301 when available in order to confirm the benefit of midostaurin in patients ≥ 60 years of age (see Annex II conditions).

The molecular genetic alterations that were determined as part of clinical practice (NPM1 and to a limited extent CEBPA) did not appear to affect the treatment effect of midostaurin (e.g., OS, EFS). In addition, no obvious relation between the genetic markers and the subgroup of gender was found. Additional efforts to identify biomarkers that could be relevant in relation to the treatment effect of midostaurin based on samples that were banked as part of local protocols are under discussion between the Applicant and the cooperative groups. A Biomarker study (targeted gene panel sequencing) of pre-treatment samples from patients in Study A2301 will evaluate the prognostic and predictive value of specific gene mutations, patterns of gene mutations, and key pre-treatment variables, for response to treatment with midostaurin and the CHMP recommended the applicant to submit the results upon completion of the study.

ASM/SM-AHN/MCL indication

The initial indication proposed by the applicant included the use of midostaurin as monotherapy for the treatment of adult patients with advanced systemic mastocytosis. However, the CHMP considered that the wording of the indication should be amended in order to clearly and specifically reflect the enrolled patient population in line with the WHO classification. Based on this, the indication was revised to include aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN) or mast cell leukaemia (MCL).

The ORR was 59.6% (95%CI: 48.6-69.8, p<0.001) in the PEP, a subset of the overall population (N=89 out of 116). In the analysis conducted using the new, more stringent response criteria for ASM published in 2013 by the IWG-MRT/ECNM (IWG criteria) the ORR was lower using (28%). An ORR analysis according to IWG criteria was performed for ASM, SM-AHN, and MCL patients separately following CHMP's request. The overall ORR was 28.3% (with 32/113 patients having a response of CR, PR, or CI), and 60.0%, 20.8% and 33.3%, respectively, in patients with ASM, SM-AHNMD and MCL. Overall, it was considered that the observed responses are unlikely to be 'spontaneous', or related to the natural course of disease of mastocytosis, since prolonged improvement of C-findings (>12 weeks as required according to the IWG response criteria used) and durable reductions of mast cell burden (and serum tryptase) are not expected based on the natural course of the disease. Therefore, the observed responses were considered to be a treatment effect of midostaurin.

Clinically relevant durations of response were observed in patients who achieved response according to IWG criteria. This analysis showed that responses to midostaurin treatment were most durable among patients who achieved a CR or PR (median not reached, 95% CI: 27.0 – NE), and less durable in patients with clinical improvement alone. Thus, the magnitude of response was correlated with duration of response.

In total 26.7% of these patients had a best decrease in spleen volume of at least 35%. Further data on changes in spleen volume during the course of treatment and spider plots of changes in bone marrow mast cell burden for all individual patients provided better insight into the course of changes in pharmacodynamic parameters over the course of treatment with midostaurin. Durable improvements in mast cell burden are expected to be of benefit to the patient as reduced mast cell burden leads to reduction of the symptoms related to aberrant mast cell activity.

Patient-reported outcomes were measured as an exploratory endpoint. Updated analyses showed that response according to Valent criteria was associated with superior PROs and provided additional insight into the clinical relevance of the PRO data. The analyses remain, however, considered exploratory, in view of the single-arm open-label nature of the study and of limited value in guiding treatment decisions.

An ORR of 23.1% (3/13) was observed in KIT-wild type patients vs. 30.5% (29/95) in KIT-mutated patients. Among the three KIT-wild type patients who responded, all patients had substantial reductions in mast cell burden, in addition to improvement of their C-findings. Thus, despite the fact that KIT-wild type receptor is not expected to be inhibited to a relevant extent based on in vitro IC50 values (in contrast to KIT-D816V-mutated receptor), these response data are a strong suggestion that both patients with or without detectable levels of the KIT-D816V mutation may benefit from midostaurin therapy. The large difference in OS between KIT-mutated and KIT-wild type patients, with KIT-mutated patients having much longer OS, remains however unexplained, and a potential impact of KIT status on therapeutic efficacy of midostaurin cannot be excluded. It is therefore considered relevant to describe the OS data according to KIT status in the product information of Rydapt to adequately inform clinicians about the potential impact of KIT status (SmpC section 5.1).

No comparative data were available for the ASM/SM-AHN/MCL indication. However, the specific circumstances such as the extreme rarity of the diseases and the great unmet medical need in systemic mastocytosis patients should be considered. Furthermore, it is considered that the provided efficacy data for midostaurin are compelling relative to what is historically known for available (but non-approved) therapies. Midostaurin conferred durable responses which correlated with survival benefit, and the responses were further corroborated by durable reductions in bone marrow mast cell burden). For other available therapies such as interferon-α and cladribine, the evidence for efficacy is much weaker, and comes mostly from retrospective investigations (and some small single-arm studies).

2.5.4. Conclusions on the clinical efficacy

AML indication

The pivotal study in AML showed a clinically relevant improvement of OS by addition of midostaurin to standard induction and consolidation chemotherapy, followed by continuation therapy with midostaurin for 12 cycles. This was supported by improvements on all relevant secondary endpoints. Therefore, clinically relevant efficacy of midostaurin in newly diagnosed FLT3 positive AML was demonstrated in the overall studied population.

The CHMP considers the following measures necessary to address issues related to efficacy in the elderly:

The applicant should submit by September 2021 the final results of study ADE02T, a phase II, single-arm, investigator-initiated study of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single agent maintenance in patients aged 18-70 with FLT3 ITD mutated AML.

The applicant should submit by December 2022 the final results of study A2408, a single-arm multi-centre study to assess safety and efficacy of midostaurin in combination with standard chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients (aged ≥ 18 years) with newly diagnosed FLT3-mutated AML.

The applicant should submit by June 2023 the results of study E2301, a randomised, double-blind study of midostaurin versus placebo in combination with chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients (aged ≥ 18 years) with newly diagnosed AML, without FLT3 mutation. The protocol includes a comprehensive collection of baseline data (including biomarkers), post-study treatments, and evaluation of MRD.

ASM/SM-AHN/MCL indication

Objective and durable responses according to IWG criteria were observed in 28.3% of the patients, with 60%, 21% and 33% of the patients with ASM, SM-AHNMD, and MCL, respectively, having a response. The responses were durable in a relevant proportion of patients and durability correlated with the magnitude of response. Furthermore, the responses are supported by solid evidence of pharmacodynamic activity, i.e., clear improvements in mast cell burden and further supported by reductions in serum tryptase.

Based on the benefit in ORR and duration, it is considered that the efficacy of midostaurin for the treatment of patients with ASM, SM-AHNMD, and MCL has been demonstrated.

2.6. Clinical safety

Midostaurin has been evaluated in an extensive clinical program including more than 1800 subjects, including one large, placebo-controlled study of midostaurin in combination with chemotherapy in FLT3-mutated AML, two Phase 2 studies in the ASM/SM-AHN/MCL indication, nine Phase 1-2 studies conducted in various indications (advanced solid tumours, chronic lymphocytic leukaemia (CLL), non-Hodgkin's lymphoma (NHL)), and 11 clinical pharmacology studies.

The AML safety database consists of 345 patients from Study A2301 who received midostaurin in combination with chemotherapy, and 164 patients with AML/advanced MDS from Studies A2106 (midostaurin in combination with chemotherapy) and A2104E1 (single agent midostaurin). The focus of the safety evaluation of midostaurin in AML is primarily based on the results of Study A2301, with the other studies as key supportive studies for the AML indication.

The evaluation of safety of midostaurin in ASM/SM-AHN/MCL is based on pooled safety data from patients in Study D2201 and Study A2213 who received at least one dose of single agent midostaurin at a dose of 100 mg b.i.d. (ASM/SM-AHN/MCL, pooled dataset, N=142).

In addition, 349 other patients with AML (Study A2104 and A2104E2; not dosed at 50 mg b.i.d. midostaurin), other haematological malignancies, solid tumours and diabetes and 504 healthy subjects contribute to the overall safety assessment for both indications.

Specific safety studies have been performed to evaluate the effect of midostaurin on cardiac conduction intervals (Study A2113) and the use of midostaurin in patients with hepatic impairment (Study A2116).

Patient exposure

Of the 717 patients enrolled in study A2301, 680 patients were included in the safety set; 345 patients in the midostaurin group and 335 patients in the placebo group. Of note, 2 patients who were randomised to the placebo arm received only midostaurin during the study and were therefore analysed in the midostaurin group for the safety analysis, and patients who were never treated with study drug were excluded from the safety analyses.

Of the whole patient population, 120 patients in the midostaurin arm and 85 patient in the control arm entered the continuation phase. The median duration of exposure was 34 days (range 1-465 days), and 73 patients (21.2%) in the midostaurin group and 51 patients (15.2%) in the control group were exposed to study drug for at least 12 months. The median time of follow-up (i.e. from the date of randomisation to data cut-off) was 60.2 months (range 42 to 81 months) overall, and similar in both treatment arms.

The exposure to chemotherapy (daunorubicin, induction phase only and cytarabine, induction and consolidation phase), was similar in both treatment arms throughout the induction and consolidation phases. Almost all patients (98.5%) received at least 1 concomitant medication. During induction phase no clear differences in co-medication was noted. Some differences in co-medications were present during consolidation (higher frequency of use of levofloxasin (50 vs 41%) and dexamethasone 54 vs 47%) in the midostaurin arm) and continuation (slightly higher frequency in the midostaurin arm of paracetamol (13% vs 4%) sulfamethoxazole/trimethoprim (12 vs 6%) and ondansetron (13% vs 2.5%)).

A summary of study drug exposure overall and by treatment phase is dispayed in Table 88.

Table 86 Summary of study drug exposure overall and by treatment phase (Safety set) - study A2301

Exposure	MIDOSTAURIN N=345	PLACEBO N=335
Overall		
Cumulative dose (mg), n	345	335
Mean (SD)	12763.0 (15703.30)	9874.5 (13764.54)
Median (min, max)	4150.0 (50, 80800)	2800.0 (50, 43250)
ADI (mg/day), n	345	332
Mean (SD)	99.4 (248.28)	83.8 (24.58)
Median (min, max)	95.1 (4, 4667)	94.8 (2, 107)
Missing	0	3
RDI (%), n	345	332
Mean (SD)	99.4 (248.28)	83.8 (24.58)
Median (min, max)	95.1 (4, 4667)	94.8 (2, 107)
Missing	0	3
Induction – Cycle 1		
Cumulative dose (mg), n	345	335
Mean (SD)	1626.9 (5239.94)	1162.8 (407.67)
Median (min, max)	1400.0 (50, 70000)	1400.0 (0, 1600)
ADI (mg/day), n	345	334
Mean (SD)	114.0 (361.94)	82.5 (28.97)
Median (min, max)	100.0 (4, 5000)	96.4 (0, 114)
Missing	0	1
RDI (%), n	345	334
Mean (SD)	114.0 (361.94)	82.5 (28.97)
Median (min, max)	100.0 (4, 5000)	96.4 (0, 114)
Missing	0	1
Induction - Cycle 2		
Cumulative dose (mg), n	81	101
Mean (SD)	1223.5 (364.36)	1305.2 (264.32)
Median (min, max)	1400.0 (0, 1600)	1400.0 (0, 1700)
ADI (mg/day), n	81	101
Mean (SD)	86.6 (26.25)	92.6 (18.95)
Median (min, max)	100.0 (0, 114)	100.0 (0, 121)
RDI (%), n	81	101
Mean (SD)	86.6 (26.25)	92.6 (18.95)
Median (min, max)	100.0 (0, 114)	100.0 (0, 121)
Consolidation – overall		
Cumulative dose (mg), n	232	209
Mean (SD)	3847.1 (1893.44)	3643.5 (1822.14)
Median (min, max)	4650.0 (0, 7000)	4200.0 (0, 5900)
ADI (mg/day), n	232	207
Mean (SD)	88.8 (21.55)	87.9 (22.05)
Median (min, max)	98.2 (0, 125)	96.6 (0, 107)
Missing	0	2
RDI (%), n	232	207
Mean (SD)	88.8 (21.55)	87.9 (22.05)
Median (min, max)	98.2 (0, 125)	96.6 (0, 107)
Missing	0	2

Continuation - overall

Cumulative dose (mg), n	120	85
Mean (SD)	23752.7 (11271.45)	23824.4 (12522.13)
Median (min, max)	29050.0 (1250, 36350)	31200.0 (450, 35500)
ADI (mg/day), n	120	85
Mean (SD)	89.8 (14.48)	91.5 (16.50)
Median (min, max)	96.5 (47, 108)	97.9 (16, 116)
RDI (%), n	120	85
Mean (SD)	89.8 (14.48)	91.5 (16.50)
Median (min, max)	96.5 (47, 108)	97.9 (16, 116)

Cumulative dose (mg) for a period = total dose taken during the considered period.
ADI = Actual Dose Intensity. ADI (mg/day) for a cycle (in induction/ consolidation) = Cumulative dose during the cycle / max (duration of study drug exposure during the cycle, planned duration of study drug exposure during the cycle). ADI (mg / day) for continuation = Cumulative dose during continuation phase / duration of study drug exposure during continuation phase.
RDI = Relative Dose Intensity. RDI (%) for a period = (ADI (mg/day) for the period / planned dose intensity (mg/day) for the period) *100.
In a given cycle, the cumulative dose, ADI and RDI are equal to zero for patients who entered the cycle but did not take the study drug during this cycle. It is missing when the dose/duration cannot be determined, as applicable.
Only patients entering the considered cycle/phase were considered (n+missing).

ASM/SM-AHN/MCL

All patients enrolled in Study D2201 and Study A2213 received at least one dose of midostaurin and were included in the safety set. Per protocol in Study D2201 patients received midostaurin at a dose of 100 mg b.i.d. continuously in cycles of 28 days until disease progression, intolerable toxicity or withdrawal due to any other cause, whichever occurred first. In Study A2213 per protocol patients could receive up to 12 cycles of midostaurin, each cycle was 28 days in duration; however, if a patient did not achieve a major or partial response in first two months treatment was to be discontinued.

The median duration of exposure was 11.4 months (longest duration of exposure was 81 months), and 48.6% and 33.8% of patients had at least 12 months and 24 months of exposure, respectively. The mean relative dose intensity was 90% of the intended daily dose, the dose intensity was slightly higher in study A2213 than in study D2201.

All patients had at least 1 concomitant medication. In Study D2201 following Amendment 2, prophylaxis for the prevention of nausea and vomiting was to be administered to all patients. In Study A2213, prophylaxis for the prevention of nausea and vomiting was also recommended to be taken prior to each dose of midostaurin.

Table 87 Summary statistics of exposure of study drug (Safety set)- Study D2201

Exposure variable	Midostaurin N=116
Cumulative dose (mg)	
Mean (standard deviation)	101330 (99069.18)
Median (Range)	63450.0 (1800.0-408800.0)
Average daily dose (mg)	
Mean (standard deviation)	183.6 (30.84)
Median (Range)	198.7 (66.9-271.4)
Actual dose intensity (mg/week)	
Mean (standard deviation)	1285.1 (215.86)
Median (Range)	1391.2 (468.4-1900.0)
Relative dose intensity, n (%)	
<70%	12 (10.3%)
70-90%	19 (16.4%)
>90%	85 (73.3%)
Mean (standard deviation)	91.8% (15.42%)
Median (Range)	99.4% (33.5-135.7%)

Actual dose intensity=cumulative dose (mg)/duration of exposure (weeks)

Relative dose intensity= actual dose intensity/planned dose intensity*100

Adverse events

AML

In Study A2301 the collection of safety data, i.e. the collection of AEs and SAEs differed between the North America (NA) and non-North America (NNA) regions due to the difference in sponsorship. In NA region Grade 1 and 2 events were not collected, with the exception of 13 pre-specified groups of AEs (neutrophils/granulocytes, platelets, haemoglobin, febrile neutropenia, ataxia (incoordination), rash/desquamation, diarrhoea, nausea, vomiting, keratitis, fatigue, left ventricular systolic dysfunction and mucositis/stomatitis), whereas in NNA (where Novartis is the sponsor), all AEs regardless of grade were collected. Due to the difference in the way AEs were collected in NA, compared to other regions (NNA), the safety data are presented separately as well as combined for the two regions. One third (236 patients, 32.9%) were randomised in the NA region, and 481 patients in the NNA region.

All patients in Study A2301 experienced at least one AE of any grade. All but one patient in the midostaurin group experienced at least one grade 3/4 AE. The majority of events were reported during the induction and consolidation phases and events were less frequently reported during the continuation phase.

Table 88. Common adverse events (grade 3-4 with overall incidence >10% in the midostaurin group) (Safety set) - Study A2301

Preferred term	Non-North American sites (N=455)		All sites (N=680)	
	MIDOSTAURIN N = 229	PLACEBO N = 226	MIDOSTAURIN N = 345	PLACEBO N = 335
	All grades n (%)	All grades n (%)	Grade 3-4 n (%)	Grade 3-4 n (%)
Overall	**N = 229**	**N = 226**	**N = 345**	**N = 335**
Any PT	229 (100.0)	226 (100.0)	344 (99.7)	335 (100.0)
Platelet count decreased*	224 (97.8)	220 (97.3)	337 (97.7)	325 (97.0)
Neutrophil count decreased*	221 (96.5)	221 (97.8)	329 (95.4)	326 (97.3)
Haemoglobin decreased*	224 (97.8)	220 (97.3)	321 (93.0)	297 (88.7)
Febrile neutropenia*	191 (83.4)	182 (80.5)	287 (83.2)	279 (83.3)
Diarrhoea*	161 (70.3)	162 (71.7)	54 (15.7)	51 (15.2)
Dermatitis exfoliative*	141 (61.6)	137 (60.6)	47 (13.6)	26 (7.8)
Leukopenia	54 (23.6)	58 (25.7)	92 (26.7)	101 (30.1)
Lymphopenia	38 (16.6)	42 (18.6)	68 (19.7)	76 (22.7)
Device related infection	55 (24.0)	39 (17.3)	56 (16.2)	34 (10.1)
Hypokalaemia	65 (28.4)	63 (27.9)	47 (13.6)	57 (17.0)
Pneumonia	39 (17.0)	39 (17.3)	45 (13.0)	47 (14.0)
Alanine aminotransferase increased	81 (35.4)	75 (33.2)	44 (12.8)	32 (9.6)
Induction phase	**N = 229**	**N = 222**	**N = 345**	**N = 329**
Any PT	229 (100.0)	222 (100.0)	344 (99.7)	329 (100.0)
Platelet count decreased*	219 (95.6)	213 (95.9)	332 (96.2)	315 (95.7)
Neutrophil count decreased*	210 (91.7)	209 (94.1)	317 (91.9)	311 (94.5)
Haemoglobin decreased*	221 (96.5)	210 (94.6)	304 (88.1)	267 (81.2)
Febrile neutropenia*	172 (75.1)	171 (77.0)	259 (75.1)	259 (78.7)
Diarrhoea*	148 (64.6)	150 (67.6)	43 (12.5)	43 (13.1)
Dermatitis exfoliative*	123 (53.7)	108 (48.6)	40 (11.6)	22 (6.7)
Leukopenia	42 (18.3)	51 (23.0)	78 (22.6)	86 (26.1)
Lymphopenia	23 (10.0)	32 (14.4)	47 (13.6)	55 (16.7)
Device related infection	26 (11.4)	24 (10.8)	22 (6.4)	20 (6.1)
Hypokalaemia	45 (19.7)	54 (24.3)	37 (10.7)	43 (13.1)
Pneumonia	27 (11.8)	27 (12.2)	32 (9.3)	33 (10.0)
Alanine aminotransferase increased	44 (19.2)	51 (23.0)	21 (6.1)	18 (5.5)
Consolidation phase	**N=154**	**N=132**	**N=227**	**N=205**
Any PT	154 (100.0)	132 (100.0)	225 (99.1)	204 (99.5)
Platelet count decreased*	152 (98.7)	129 (97.7)	223 (98.2)	199 (97.1)
Neutrophil count decreased*	149 (96.8)	129 (97.7)	218 (96.0)	201 (98.0)
Haemoglobin decreased*	152 (98.7)	129 (97.7)	194 (85.5)	167 (81.5)
Febrile neutropenia*	95 (61.7)	75 (56.8)	141 (62.1)	120 (58.5)
Diarrhoea*	57 (37.0)	48 (36.4)	12 (5.3)	13 (6.3)
Dermatitis exfoliative*	54 (35.1)	55 (41.7)	6 (2.6)	4 (2.0)

Preferred term	Non-North American sites (N=455)		All sites (N=680)	
	MIDOSTAURIN N = 229	PLACEBO N = 226	MIDOSTAURIN N = 345	PLACEBO N = 335
	All grades n (%)	All grades n (%)	Grade 3-4 n (%)	Grade 3-4 n (%)
Leukopenia	30 (19.5)	29 (22.0)	54 (23.8)	60 (29.3)
Lymphopenia	21 (13.6)	25 (18.9)	46 (20.3)	53 (25.9)
Device related infection	36 (23.4)	15 (11.4)	39 (17.2)	16 (7.8)
Hypokalaemia	37 (24.0)	24 (18.2)	14 (6.2)	19 (9.3)
Pneumonia	18 (11.7)	19 (14.4)	16 (7.0)	22 (10.7)
Alanine aminotransferase increased	54 (35.1)	36 (27.3)	22 (9.7)	13 (6.3)
Continuation phase	**N=84**	**N=56**	**N=120**	**N=85**
Any PT	83 (98.8)	56 (100.0)	50 (41.7)	40 (47.1)
Platelet count decreased*	40 (47.6)	35 (62.5)	2 (1.7)	13 (15.3)
Neutrophil count decreased*	31 (36.9)	25 (44.6)	10 (8.3)	8 (9.4)
Haemoglobin decreased*	49 (58.3)	39 (69.6)	1 (0.8)	0
Febrile neutropenia*	1 (1.2)	0	1 (0.8)	0
Diarrhoea*	21 (25.0)	13 (23.2)	1 (0.8)	2 (2.4)
Dermatitis exfoliative*	10 (11.9)	10 (17.9)	1 (0.8)	0
Leukopenia	13 (15.5)	8 (14.3)	3 (2.5)	0
Lymphopenia	14 (16.7)	5 (8.9)	8 (6.7)	2 (2.4)
Device related infection	0	1 (1.8)	0	0
Hypokalaemia	2 (2.4)	5 (8.9)	0	1 (1.2)
Pneumonia	2 (2.4)	0	0	0
Alanine aminotransferase increased	26 (31.0)	12 (21.4)	5 (4.2)	4 (4.7)
* Pre-specified AEs in the NA region Preferred terms are sorted with first the expected AEs, then the non-expected AEs, and then in descending frequency, as reported in the MIDOSTAURIN – Grade 3-4 – All sites column. A patient with multiple occurrences of an AE is counted only once in the AE category. AEs with a missing grade are excluded from the table but appear in [Study A2301].				

The most frequent AEs overall were those associated with myelosuppression and these AEs comprised also the most frequent grade 3-4 AEs.

Adverse events of any grade occurring more frequently (difference of ≥ 5% in the overall population) in the midostaurin group than in the placebo group at all sites included nausea (82% vs 73%) and stomatitis (19% vs 12%). Of note, the frequency of grade 3/4 nausea was lower in the midostaurin group than in the placebo group (5.8% vs 10.1%, respectively). The increase in device-related infections in the midostaurin arm, as noted in the frequencies in grade 3/4 events (16 vs 10%), is also evident from the overall frequencies of device related infections (24% vs 17%, NNA sites only). Based on the AE collection in the NNA sites also headache (46% vs 38%), back pain (22% vs 16%) and petechiae (36% vs 27%) occurred more frequent in the midostaurin arm.

Bleeding events occurred in similar proportion of patients in the midostaurin (59.0%) and placebo (57.5%) groups in NNA sites; however grade 3/4 events were slightly more common in the midostaurin group. The

most frequently reported events were petechiae (35.8% vs 27.0%, midostaurin vs control arm respectively), epistaxis (27.5% vs 23.5%) and hematoma (16.2% vs 16.8%) among patients in NNA sites. The majority of bleeding events occurred during the induction (48.9% vs 44.6%) and consolidation (42.2% vs 53.8%) phases, with few events occurring in the continuation phase (6.0% vs 10.7%) in NNA sites.

Grade 3/4 AEs occurring more frequently (>5%) in the midostaurin group than in the placebo group at all sites included exfoliative dermatitis (14% vs 8%, mostly due to a higher incidence in the induction phase) and device related infections (16% vs 10%, due to a higher incidence in the consolidation phase).

Over 75% of patients in either treatment group experienced at least one grade 3/4 AE suspected to be related to midostaurin/placebo treatment. Most of these AEs occurred at similar frequencies in both treatment groups.

Table 89. Adverse drug reactions observed in the AML clinical study (safety set) Study A2301

Adverse drug reaction	All grades	Grades 3/4	Frequency category
	Rydapt + chemo n=229[1] %	Rydapt + chemo n=345[1] %	
Infections and infestations			
Device-related infection	24	15.7	Very common
Upper respiratory tract infection	5.2	0.6	Common
Neutropenic sepsis	0.9	3.5	Uncommon
Blood and lymphatic system disorders			
Febrile neutropenia	83.4	83.5	Very common
Petechiae	35.8	1.2	Very common
Lymphopenia	16.6	20	Very common
Immune system disorders			
Hypersensitivity	15.7	0.6	Very common
Metabolism and nutrition disorders			
Hyperuricaemia	8.3	0.6	Common
Psychiatric disorders			
Insomnia	12.2	0	Very common
Nervous system disorders			
Headache	45.9	2.6	Very common
Syncope	5.2	4.6	Common
Tremor	3.9	0	Common
Eye disorders			
Eyelid oedema	3.1	0	Common
Cardiac disorders			
Hypotension	14.4	5.5	Very common
Sinus tachycardia	9.6	1.2	Common
Hypertension	7.9	2.3	Common
Pericardial effusion	3.5	0.6	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	27.5	2.6	Very common
Laryngeal pain	11.8	0.6	Very common
Dyspnoea	10.9	5.5	Very common
Pleural effusion	5.7	0.9	Common
Nasopharyngitis	8.7	0	Common
Acute respiratory distress syndrome	2.2	2.3	Common

Gastrointestinal disorders			
Nausea	83.4	5.8	Very common
Vomiting	60.7	2.9	Very common
Stomatitis	21.8	3.5	Very common
Abdominal pain upper	16.6	0	Very common
Haemorrhoids	15.3	1.4	Very common
Anorectal discomfort	7	0.9	Common
Abdominal discomfort	3.5	0	Common
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative	61.6	13.6	Very common
Hyperhidrosis	14.4	0	Very common
Dry skin	7	0	Common
Keratitis	6.6	0.3	Common
Musculoskeletal and connective tissue disorders			
Back pain	21.8	1.4	Very common
Arthralgia	14	0.3	Very common
Bone pain	9.6	1.4	Common
Pain in extremity	9.6	1.4	Common
Neck pain	7.9	0.6	Common
General disorders and administration site conditions			
Pyrexia	34.5	3.2	Very common
Catheter-related thrombosis	3.5	2	Common
Investigations			
Haemoglobin decreased*	97.3	78.5	Very common
ANC decreased*	86.7	85.8	Very common
ALT increased*	84.2	19.4	Very common
AST increased*	73.9	6.4	Very common
Hypokalaemia*	61.7	13.9	Very common
Hyperglycaemia	20.1	7	Very common
Hypernatraemia*	20	1.2	Very common
Activated partial thromboplastin time prolonged	12.7	2.6	Very common
Hypercalcaemia*	6.7	0.6	Common
Weight increased	6.6	0.6	Common

[1]For trial sites in North America, all grades were collected for 13 pre-specified adverse events. For all other adverse events, only grades 3 and 4 were collected. Therefore all grade AEs are summarised only for patients in non-North American trial sites, whereas Grades 3 and 4 are summarised for patients in all trial sites.
* Frequency is based on laboratory values.

ASM/SM-AHN/MCL

In the ASM/SM-AHN/MCL pool, all patients had at least 1 AE.

Table 90. Overview of frequency of adverse events in ASM/SM-AHN/MCL (Safety set)

Category	D2201 N=116 n (%)	A2213 N=26 n (%)	AdSM pool N=142 n (%)
On-treatment deaths	22 (19.0)	4 (15.4)	26 (18.3)
Adverse events (AEs)	116 (100)	26 (100)	142 (100)
Suspected to be drug-related	108 (93.1)	25 (96.2)	133 (93.7)
Grade 3-4 AEs	103 (88.8)	16 (61.5)	119 (83.8)
Suspected to be drug-related	51 (44.0)	8 (30.8)	59 (41.5)
Clinically notable AEs	116 (100)	26 (100)	142 (100)
Suspected to be drug-related	106 (91.4)	25 (96.2)	131 (92.3)
Serious adverse events (SAEs)	85 (73.3)	12 (46.2)	97 (68.3)
Suspected to be drug-related	27 (23.3)	4 (15.4)	31 (21.8)
AEs leading to discontinuation	30 (25.9)	4 (15.4)	34 (23.9)
Suspected to be drug-related	15 (12.9)	1 (3.8)	16 (11.3)
AEs requiring dose interruption and / or reduction	67 (57.8)	13 (50.0)	80 (56.3)
AEs requiring additional therapy	116 (100)	25 (96.2)	141 (99.3)

The most frequently reported AEs in the pooled dataset were those related to GI toxicity (nausea, vomiting, and diarrhoea), infections, and myelosuppression (anaemia, thrombocytopenia, neutropenia). Other frequent AEs (>25% of patients) were oedema peripheral, fatigue, pyrexia, and headache . The most frequent grade 3-4 AEs were those related to myelosuppression (anaemia, thrombocytopenia, and neutropenia). All other grade 3-4 AEs were reported in <10% of patients each.

The nature and incidence of AEs reported was similar (< 15%) across the 2 studies (D2201 vs A2213) with the exception of diarrhoea (all grade 56.0 vs 30.8%), fatigue (26.7% vs 50.0%), constipation (25.0% vs 46.2%), musculoskeletal pain (15.5% vs 0%), abdominal distention (5.2% vs 23.1%), abdominal pain (29.3% vs 11.5%).

Table 91. Frequent adverse events (>10% in pool) in ASM/SM-AHN/MCL (Safety set)

	D2201		A2213		Advanced SM pool	
	N=116		N=26		N=142	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	116 (100)	103 (88.8)	26 (100)	16 (61.5)	142 (100)	119 (83.8)
Nausea	93 (80.2)	8 (6.9)	24 (92.3)	0	117 (82.4)	8 (5.6)
Vomiting	77 (66.4)	8 (6.9)	19 (73.1)	0	96 (67.6)	8 (5.6)
Diarrhoea	65 (56.0)	9 (7.8)	8 (30.8)	0	73 (51.4)	9 (6.3)
Oedema peripheral	40 (34.5)	5 (4.3)	10 (38.5)	0	50 (35.2)	5 (3.5)
Anaemia	38 (32.8)	29 (25.0)	9 (34.6)	4 (15.4)	47 (33.1)	33 (23.2)
Fatigue	31 (26.7)	10 (8.6)	13 (50.0)	2 (7.7)	44 (31.0)	12 (8.5)
Constipation	29 (25.0)	1 (0.9)	12 (46.2)	0	41 (28.9)	1 (0.7)
Pyrexia	33 (28.4)	6 (5.2)	5 (19.2)	0	38 (26.8)	6 (4.2)
Abdominal pain	34 (29.3)	5 (4.3)	3 (11.5)	0	37 (26.1)	5 (3.5)
Headache	28 (24.1)	2 (1.7)	9 (34.6)	0	37 (26.1)	2 (1.4)
Thrombocytopenia	22 (19.0)	14 (12.1)	8 (30.8)	3 (11.5)	30 (21.1)	17 (12.0)
Pruritus	25 (21.6)	4 (3.4)	4 (15.4)	0	29 (20.4)	4 (2.8)

Preferred term	D2201 N=116		A2213 N=26		Advanced SM pool N=142	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Arthralgia	23 (19.8)	3 (2.6)	4 (15.4)	0	27 (19.0)	3 (2.1)
Back pain	25 (21.6)	2 (1.7)	2 (7.7)	0	27 (19.0)	2 (1.4)
Dyspnoea	19 (16.4)	6 (5.2)	7 (26.9)	2 (7.7)	26 (18.3)	8 (5.6)
Cough	21 (18.1)	1 (0.9)	2 (7.7)	0	23 (16.2)	1 (0.7)
Neutropenia	17 (14.7)	13 (11.2)	2 (7.7)	2 (7.7)	19 (13.4)	15 (10.6)
Nasopharyngitis	18 (15.5)	0	1 (3.8)	0	19 (13.4)	0
Urinary tract infection	15 (12.9)	3 (2.6)	4 (15.4)	1 (3.8)	19 (13.4)	4 (2.8)
Dizziness	15 (12.9)	0	4 (15.4)	0	19 (13.4)	0
Musculoskeletal pain	18 (15.5)	1 (0.9)	0	0	18 (12.7)	1 (0.7)
Pleural effusion	14 (12.1)	5 (4.3)	4 (15.4)	1 (3.8)	18 (12.7)	6 (4.2)
Epistaxis	15 (12.9)	4 (3.4)	2 (7.7)	0	17 (12.0)	4 (2.8)
Upper respiratory tract infection	10 (8.6)	2 (1.7)	6 (23.1)	0	16 (11.3)	2 (1.4)
Hypokalaemia	12 (10.3)	5 (4.3)	4 (15.4)	1 (3.8)	16 (11.3)	6 (4.2)
Electrocardiogram QT prolonged	13 (11.2)	1 (0.9)	2 (7.7)	0	15 (10.6)	1 (0.7)
Insomnia	12 (10.3)	0	3 (11.5)	0	15 (10.6)	0
SM=systemic mastocytosis						

Among the ASM/SM-AHN/MCL patients haematological events at baseline were reported; anaemia in 51.4% of patients thrombocytopenia in 40.1%, neutropenia in 7.7%, leukopenia in 7.0%, and eosinophilia in 7.0%. Also in ASM/SM-AHN/MCL patients, GI related events have been consistently reported at high rates in published literature. Bleeding events were reported in 38% of patients. The most commonly reported were epistaxis (12%), contusion (6.3%) and hematoma (6.3%). Grade 3/4 events were reported in 20 (14.1%) patients; the most commonly reported were gastrointestinal haemorrhage (5 patients) and epistaxis (4 patients). Psychiatric disorder-related events were reported in 34.5% of patients in the ASM/SM-AHN/MCL pool. Depression was reported in 14 patients (9.9%) and anxiety in 9 patients (6.3%). Symptoms of psychiatric disorders at baseline were reported in 35.9% in advanced SM pool; depression in 18.3%, major depression in 0.7% and anxiety in 14.1% of patients and appears to be consistent with literature reports. Left ventricle ejection fraction (LVEF) was monitored for 64 patients during treatment. LVEF changes over time show that around month 3 there is a decrease in the mean LVEF, and 3 patients had clear LVEF changes (reduction) from baseline.

AEs related to study drug were reported in 93.7% of patients; 93.1% in Study D2201 and 96.2% in Study A2213. The most commonly occurring AEs suspected to be study drug related were gastrointestinal-related, and the majority of these were grade 1 or 2 in severity. Among the patients with nausea and vomiting, the majority of the events were suspected to be related to study drug.

Table 92. Adverse events (> 5% patients in pool) suspected to be related to study drug (Safety set)

Preferred term	D2201 N=116 All grades n (%)	D2201 N=116 Grade 3/4 n (%)	A2213 N=26 All grades n (%)	A2213 N=26 Grade 3/4 n (%)	AdSM pool N=142 All grades n (%)	AdSM pool N=142 Grade 3/4 n (%)
Any preferred term	108 (93.1)	51 (44.0)	25 (96.2)	8 (30.8)	133 (93.7)	59 (41.5)
Nausea	84 (72.4)	7 (6.0)	24 (92.3)	0	108 (76.1)	7 (4.9)
Vomiting	71 (61.2)	7 (6.0)	19 (73.1)	0	90 (63.4)	7 (4.9)
Diarrhoea	33 (28.4)	3 (2.6)	7 (26.9)	0	40 (28.2)	3 (2.1)
Lipase increased	11 (9.5)	6 (5.2)	3 (11.5)	2 (7.7)	14 (9.9)	8 (5.6)
Thrombocytopenia	9 (7.8)	4 (3.4)	4 (15.4)	1 (3.8)	13 (9.2)	5 (3.5)
Fatigue	9 (7.8)	5 (4.3)	4 (15.4)	1 (3.8)	13 (9.2)	6 (4.2)
Headache	7 (6.0)	0	6 (23.1)	0	13 (9.2)	0
Anaemia	8 (6.9)	4 (3.4)	4 (15.4)	2 (7.7)	12 (8.5)	6 (4.2)
Neutropenia	8 (6.9)	6 (5.2)	1 (3.8)	1 (3.8)	9 (6.3)	7 (4.9)
Electrocardiogram QT prolonged	7 (6.0)	1 (0.9)	2 (7.7)	0	9 (6.3)	1 (0.7)
Abdominal pain	6 (5.2)	0	2 (7.7)	0	8 (5.6)	0

AEs of special interest

Gastrointestinal disorders

In AML GI-related AEs were common among patients in Study A2301 (95.6% vs 91.6% for midostaurin vs. placebo, all grades at NNA sites). Grade 3-4 GI events were reported for 22.7% vs 22.6% (midostaurin vs placebo, NNA sites). The incidence and severity of diarrhoea was similar for midostaurin vs placebo (70.3% vs 71.7%, all grades at NNA sites, and 16.2% vs 13.3%, grade 3-4 AEs, NNA sites). In contrast, the incidences of nausea and vomiting of any grade were slightly higher in the midostaurin group (nausea: 83.4% vs 70.4%; vomiting 60.3% vs 52.7%, NNA sites), whereas grade 3-4 events were infrequent and were slightly more common in the placebo group (nausea 6.6% vs 8.4%; vomiting 2.2% vs 3.1%, NNA sites).

In the ASM/SM-AHN/MCL pool, the most frequently reported events were nausea, vomiting and diarrhoea, and the majority were of mild severity with a low proportion of patients experiencing grade 3 or 4 AEs or SAEs of any grade.

The GI-related adverse events reported from the midostaurin treatment groups in ASM/SM-AHN/MCL and AML studies were mainly nausea, vomiting and diarrhoea. The majority of events were reported by investigators to be related to the administration of midostaurin or treatment regimen, mild to moderate in severity, not serious, and occurred within the first 6 months of treatment. These events were generally manageable with anti-emetic therapy and supportive measures. Dose adjustment or interruption was less commonly required and permanent discontinuation of therapy was infrequent (<2%). Similar findings have been seen in other studies in the midostaurin programme.

Hematologic adverse events

In the ASM/SM-AHN/MCL population, many patients had cytopenias at baseline associated with their disease. In study A2301 (AML) there was a high frequency of haematological-related events; however, this was likely attributable to the combination of treatment with chemotherapy.

In AML patients the majority of patients had anaemia-related events (NNA: midostaurin 97.8% vs placebo 97.3%) and most were grade 3 or 4 (93.9% vs. 89.4%). No clear difference was observed between the midostaurin group and the control group. No discontinuations due to anaemia were reported. Anaemia-related events were reported in 33.1% of ASM/SM-AHN/MCL patients, (grade 3 or 4 in 23.2% and considered related to study drug in 8.5% of patients). Treatment-emergent or worsening grade 3 or 4 haemoglobin laboratory values were reported in 40.2% of patients. SAE of anaemia was reported in 6 patients and 4 patients required dose adjustment or interruption; however, no patient discontinued treatment due to anaemia.

All AML patients in study A2301 reported leukopenia-related events and all were grade 3/4 in severity. The most commonly occurring were neutrophil count decreased (96.5% vs 97.8%) and febrile neutropenia (83.4% vs 80.5%). There was no discernible difference in the incidence of leukopenia-related events including neutropenia (grade 4) or in the time to resolution between midostaurin and placebo treatment groups. Leukopenia-related events were reported in 32 (22.5%) ASM/SM-AHN/MCL patients. Neutropenia was reported in 19 patients (13.4%) and febrile neutropenia was reported in 11 patients (7.7%). Dose adjustment or interruption was required in 8 patients for neutropenia and 2 patients for febrile neutropenia. The absolute neutrophil count decreased during the first 2 weeks on midostaurin treatment, and then remained stable between 3-4 x 10^9/L during the remainder of the study.

Thrombocytopenia-related events: In the AML study 97% of patients in each treatment group reported at least 1 event of platelet count decreased (grade 3/4 97.8% vs 96.9%). The incidence of thrombocytopenia was similar in the two treatment groups, although there was a slight trend towards an increased number of units of transfused platelets with midostaurin treatment. In the ASM/SM-AHN/MCL population thrombocytopenia –related events were reported by 31 (21.8%) patients. Dose adjustment/ interruption was required in 6 patients, 2 patients discontinued due the an event of thrombocytopenia.

Infections

In Study A2301 (AML), the incidence infections (SOC) was similar in the treatment arms (NNA all grades, midostaurin 69.9% and placebo 69.0%). The most commonly reported events in all sites were device related infections (16.2% vs 10.1%), pneumonia (13.0% vs 14.0%) and sepsis (7.0% vs 7.5%). AEs related to infection leading to discontinuation were reported for 2 patients in each group. Deaths due to infection occurred less frequently in the midostaurin (4 sepsis, 1 infectious colitis,1 septic shock) compared to the placebo group (6 sepsis, 1 infectious colitis, 1 septic shock).

Infections were reported in 63.4% of ASM/SM-AHN/MCL patients. Grade 3/4 infections (SOC) were reported in 28.9% of patients; the most commonly reported were sepsis (n=10; 7.7%) and pneumonia (n=10; 7.0%). Urinary tract infections were reported in 19 patients. Infection-related events lead to study drug discontinuation in 3 patients (pneumonia, sepsis and urinary tract infection). Six on-treatment deaths were related to infections and infestations (5 sepsis and 1 pneumonia) in the ACM/MCL population.

Cardiac dysfunction

In the AML study cardiac failure AEs (any grade) were reported for 1.3% of patients in both the midostaurin and placebo groups (NNA sites). Cardiac related deaths (cardiac arrest (related), myocardial infarction

(possibly related)) occurred in the midostaurin group and myocardial ischemia (related; placebo) occurred in the placebo group.

In the ASM/SM-AHN/MCL pool, events related to cardiac failure were reported in 10 patients (8.6%), the most commonly reported events were cardiac failure in 5 patients (4.3%) and pulmonary oedema in 3 patients (2.6%). No patients discontinued due to events of cardiac failure, 5 patients died due to a cardiac disorder-related events (see Table 98). Cardiac failure events were more commonly reported among elderly patients (≥ 60 years; 8.9% vs < 60 years; 3.8 %).

LVEF

In the AML study LVEF was only assessed at baseline. In the ASM/SM-AHN/MCL pool baseline and at least one post-baseline LVEF assessment were available for 64 patients. Echocardiography was not centrally read. The LVEF changes over time show that around month 3 there is a decrease in the mean LVEF. Three patients had notable LVEF changes from baseline (defined as a new LVEF compared to baseline of < 50% or < 45% with/without a decrease by > 10% or > 20%):

1 patient (aged 58) had a baseline LVEF of 50% which decreased at Cycle 6 to 41%. No subsequent LVEFs were reported; 1 patient (aged 68) had a baseline LVEF of 65% which decreased to 49% at Cycle 3. Subsequent LVEFs were >60% (Cycle 6), and 59% (Cycle 12); 1 patient (aged 72) had a baseline LVEF of 60% which decreased to 45% at Cycle 3. At Cycle 6, the LVEF was reported to be >60%.

None of these patients had reported cardiac AEs concurrent with the LVEF nadirs.

QTc prolongation

Notable QTcF events reported inStudy A2301 are shown in Table 95.

Table 93. Notable QTcF abnormalities by treatment phase and overall (Safety set) - Study A2301

Notable ECG abnormalities	Midostaurin n/n* (%)	Placebo n/n* (%)
Induction	**N=345**	**N=329**
QTcF (ms)		
New >450	38/232 (16.4)	32/212 (15.1)
New >480	11/249 (4.4)	10/222 (4.5)
New >500	5/251 (2.0)	6/224 (2.7)
Increase from baseline >30	79/252 (31.3)	62/226 (27.4)
Increase from baseline >60	25/252 (9.9)	15/226 (6.6)
Heart rate (bpm)		
Increase from baseline >25% and to a value >100	18/257 (7.0)	13/231 (5.6)
Decrease from baseline >25% and to a value < 50	5/257 (1.9)	5/231 (2.2)
Pulse rate (ms)		
Increase from baseline >25% and to a value >200	1/244 (0.4)	1/219 (0.5)
Consolidation	**N=227**	**N=205**
QTcF (ms)		
New >450	38/158 (24.1)	27/139 (19.4)
New >480	13/173 (7.5)	5/145 (3.4)
New >500	9/175 (5.1)	0/146 (0.0)
Increase from baseline >30	63/176 (35.8)	52/147 (35.4)
Increase from baseline >60	24/176 (13.6)	14/147 (9.5)
Heart rate (bpm)		
Increase from baseline >25% and to a value >100	29/178 (16.3)	28/150 (18.7)
Decrease from baseline >25% and to a value < 50	8/178 (4.5)	10/150 (6.7)
Pulse rate (ms)		
Increase from baseline >25% and to a value >200	13/171 (7.6)	6/142 (4.2)
Continuation	**N=120**	**N=85**
QTcF (ms)		
New >450	11/76 (14.5)	8/61 (13.1)
New >480	2/84 (2.4)	0/64 (0.0)
New >500	2/86 (2.3)	0/64 (0.0)
Increase from baseline >30	28/86 (32.6)	17/65 (26.2)
Increase from baseline >60	8/86 (9.3)	1/65 (1.5)
Heart rate (bpm)		
Increase from baseline >25% and to a value >100	8/88 (9.1)	4/65 (6.2)
Decrease from baseline >25% and to a value < 50	3/88 (3.4)	3/65 (4.6)
Pulse rate (ms)		
Increase from baseline >25% and to a value >200	7/85 (8.2)	1/61 (1.6)
Overall	**N=345**	**N=335**
QTcF (ms)		
New >450	70/239 (29.3)	54/219 (24.7)
New >480	26/258 (10.1)	13/229 (5.7)
New >500	16/260 (6.2)	6/232 (2.6)
Increase from baseline >30	115/261 (44.1)	93/234 (39.7)
Increase from baseline >60	48/261 (18.4)	25/234 (10.7)

In Study A2301, QTc prolongation AEs (any grade) were reported in 24.0% vs 21.2% of patients in the midostaurin vs. control groups, respectively (NNA sites), primarily ECG QT prolonged (19.2% vs. 16.8%) and syncope (5.2% vs. 4.9%). The proportion of patients with notable abnormalities in cardiac conduction intervals on ECGs was higher overall in the midostaurin vs placebo groups (QTcF >480 ms: 10.1% vs 5.7%; QTcF >500 ms: 6.2% vs 2.6%; >60 ms increase from baseline: 18.4% vs 10.7%, PR > 25% increase from baseline and > 200 ms: 0.4% vs 0.5% and HR > 25% increase from baseline and > 100 ms: 7.0% vs 5.6%).

ASM/SM-AHN/MCL QT prolongation-related events were reported in 16.2% of patients; the most commonly reported event was ECG QT prolonged (15 patients; 10.6%) and resulted in discontinuation in 3 patients. A further 2 patients discontinued due to events of cardiac arrest and ventricular tachycardia (events included in the QT prolongation standard MedDRA query). Notable QTcF events are shown in Table 96.

Table 94. Notable QTc values in ASM/SM-AHN/MCL safety pool

	D2201 N=116			A2213 N=26			AdSM pool N=142		
	Total	n	%	Total	n	%	Total	n	%
QTcF (ms)									
New >450	103	28	27.2	23	4	17.4	126	32	25.4
New >480	105	5	4.8	23	1	4.3	128	6	4.7
New >500	105	0	0	23	0	0	128	0	0
Increase from baseline > 30	105	41	39.0	23	5	21.7	128	46	35.9
Increase from baseline > 60	105	8	7.6	23	0	0	128	8	6.3

Source: [SCS Appendix 1-Table 5-17.1]

In Study D2201, there were specific criteria for dose adjustment or study drug discontinuation with regard to QT interval values. In 10 patients (8.6%) dose reduction/interruption due to QT prolonged events was reported.

A linear mixed effects model was used to fit the change from baseline in QTcF as a response variable, with log-transformed concentration (of midostaurin and both metabolites), baseline QTcF and relevant covariates (identified through backwards selection) fitted as fixed effects. A negative effect of concentration was observed on ΔQTcF for all three analytes.

Pulmonary toxicity

In AML, in Study A2301 pulmonary toxicities were assessed based on 2 groupings of events: interstitial lung disease (ILD), and pulmonary edema. ILD cases were balanced between the treatment groups (13.5% midostaurin vs 14.2% placebo; NNA sites); primarily pneumonitis (11.4% vs 12.8%). Seven patients (3.1% midostaurin group) and 15 patients (6.6%, placebo group) had an event of pulmonary toxicity which was suspected to be related to study treatment. SAEs were reported in 14 midostaurin-treated patient and 13 placebo treated patients, with 11 patients in each group having pneumonitis. One on-treatment death due to pneumonitis was recorded in the midostaurin group.

Pulmonary oedema was experienced by 1 patient in the midostaurin group; the event was grade 1-2 in severity and did not lead to discontinuation.

In Study ADE02T (n=145), pulmonary haemorrhages were reported in 21 patients, 1 died; in 5 patients events were suspected to be related to study drug by the investigator of which 1 was grade 3/4. Most of these occurred in the induction and early consolidation phases. One event each pneumonitis and pulmonary haemorrhage were reported as serious adverse events and both were assessed as not related. No treatment discontinuation resulted from events of pneumonitis or pulmonary haemorrhage.

In Study A2104 (n=20), 1 patient died due to grade 4 SAE of bronchopneumonia and 1 patient experienced a grade 2 SAE of alveolar haemorrhage that was not suspected to be related to study drug.

For the ASM/SM-AHN/MCL studies patients were excluded from enrolment if they had evidence of pulmonary infiltrates and were not considered for study inclusion unless all the pulmonary infiltrates had resolved. In Study A2301, dose adjustment/interruptions were recommended if a patient experienced a ≥ grade 3 pulmonary infiltration event.

In the ASM/SM-AHN/MCL safety pool interstitial lung disease (pulmonary toxicity) was reported in 5 (3.5%) patients, of which 1 was suspected to be treatment-related. No deaths were related to pulmonary toxicity.

Skin toxicity

In Study A2301 (AML), the incidence of any grade skin toxicities was similar in the treatment groups, overall and in the induction phase. However, during the induction phase, grade 3/4 skin toxicities were reported at a higher incidence in the midostaurin arm than in the placebo arm (14.0% midostaurin vs. 7.2% placebo; 10.9% vs 4.1% dermatitis exfoliative). The high proportion of patients with rash and desquamation may partially be explained by concomitant use of vancomycin. Among patients from all sites, 4 patients in the midostaurin group had an AE of skin toxicity which led to discontinuation of study treatment (3 during the induction phase, 1 during the consolidation phase). No case of severe or fatal skin toxicity (e.g. Stevens-Johnsons syndrome) was reported.

Sporadic cases of skin toxicity were observed in ASM/SM-AHN/MCL patients; in Study D2201, 4 patients reported grade 3 toxic skin eruption and in Study A2213 1 patient reported grade 2 erythema multiforme.

In supportive studies skin-related events were also commonly reported, but as control groups are lacking treatment relationship cannot be determined. There was one case of discontinuation due to Stevens-Johnson syndrome reported in Study A2104E1. No other severe skin reactions were reported across the midostaurin development programme.

Serious adverse event/deaths/other significant events

Deaths

<u>AML</u>

Of all deaths, 36 patients died on treatment: 15 patients (4.3%) in the midostaurin group and 21 (6.3%) patients in the placebo group. All but one on treatment deaths in the midostaurin group occurred during the induction phase, the other patient died during consolidation. In the control arm, 11 died during the induction phase and 9 during the consolidation phase and 1 in the continuation phase. The causes of on-treatment deaths are presented in Table 97. On-treatment deaths suspected to be related to study drug were balanced between the treatment groups: 9 patients (2.6%) versus 7 patients (2.1%) in the midostaurin and placebo group, respectively.

To evaluate if midostaurin treatment had an adverse effect on the outcomes for patients who received an SCT, mortality was analysed at 30 days and at 100 days post SCT for patients who received an SCT within 2 months of study drug discontinuation. The proportion of patients who died within 30 days from their SCT was similar in the midostaurin and placebo groups (3/88 (3.4%) and 3/86 (3.5%) patients respectively). The proportion of patients who died within 100 days from their SCT was slightly lower in the midostaurin group (6/88 (6.8%)) than the placebo group (11/86 (12.8%)).

Table 95. On-treatment deaths in study A2301

Preferred term	MIDOSTAURIN n (%)	PLACEBO n (%)
Overall	N=345	N=335
Total	15 (4.3)	21 (6.3)
Sepsis	4 (1.2)	6 (1.8)
Multi-organ failure	2 (0.6)	3 (0.9)
Acute myeloid leukaemia	1 (0.3)	1 (0.3)
Infectious colitis	1 (0.3)	1 (0.3)
Pulmonary haemorrhage	1 (0.3)	1 (0.3)
Septic shock	1 (0.3)	1 (0.3)
Acute respiratory distress syndrome	1 (0.3)	0
Acute respiratory failure	1 (0.3)	0
Cardiac arrest	1 (0.3)	0
Colitis	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Neutropenic sepsis	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Vomiting	1 (0.3)	0
Cerebellar haemorrhage	0	1 (0.3)
Cerebral haemorrhage	0	1 (0.3)
Disease progression	0	1 (0.3)
Haemorrhagic stroke	0	1 (0.3)
Hypokalaemia	0	1 (0.3)
Large intestine perforation	0	1 (0.3)
Myocardial ischaemia	0	1 (0.3)
Opportunistic infection	0	1 (0.3)
Sudden death	0	1 (0.3)

ASM/SM-AHN/MCL

In the pooled dataset there were 26 on-treatment deaths reported (i.e. deaths occurring on treatment and up to 28 days after the last dose of study drug; see Table 98). None of the deaths were considered related to study drug by the investigators.

Seven (7) additional on-treatment deaths were reported after the cut-off dates of the individual studies up to 30 April 2016 (i.e. deaths occurring on treatment and up to 28 days after the last dose of study drug, 4 deaths in Study D2201, and 3 deaths in Study A2213) Four of these deaths (3 in Study D2201 and 1 in Study A2213) occurred in the context of disease progression. The causes of deaths for the 3 other patients were: liver and kidney failure subsequent to disseminated intravascular coagulation; progression of general decline in health secondary to an inflammatory disorder of the central nervous system, and sepsis related to complications of an infection. None of these deaths were considered to be related to study drug by the investigators.

Table 96. On-treatment deaths (ASM/SM-AHN/MCL pool)

Primary system organ class Cause of death	D2201 N=116 n (%)	A2213 N=26 n (%)	AdSM pool N=142 n (%)
-Any primary system organ class	22 (19.0)	4 (15.4)	26 (18.3)
Blood and lymphatic system disorders	10 (8.6)	1 (3.8)	11 (7.7)
Systemic mastocytosis	9 (7.8)	1 (3.8)	10 (7.0)
Splenic infarction	1 (0.9)	0	1 (0.7)
Cardiac disorders	5 (4.3)	0	5 (3.5)
Cardiac arrest	2 (1.7)	0	2 (1.4)
Cardiac disorder	1 (0.9)	0	1 (0.7)
Cardiac failure	1 (0.9)	0	1 (0.7)
Cardiac failure congestive	1 (0.9)	0	1 (0.7)
General disorders and administration site conditions	2 (1.7)	1 (3.8)	3 (2.1)
Multi-organ failure	2 (1.7)	1 (3.8)	3 (2.1)
Infections and infestations	4 (3.4)	2 (7.7)	6 (4.2)
Sepsis	3 (2.6)	2 (7.7)	5 (3.5)
Pneumonia	1 (0.9)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	0	1 (0.7)
Acute myeloid leukaemia	1 (0.9)	0	1 (0.7)

Deaths occurring on treatment and up to 28 days after the last dose of study drug.
Source: [SCS Appendix 1-Table 5-21.1]

Serious adverse events

AML

Table 97. Serious adverse events (grade 3/4 with overall incidence greater than and equal to 2% in the midostaurin group) regardless of midostaurin/placebo relationship in Study A2301

Preferred term	Non-North American sites (N=455)		All sites (N=680)	
	MIDOSTAURIN All grades n (%)	PLACEBO All grades n (%)	MIDOSTAURIN Grade 3/4 n (%)	PLACEBO Grade 3/4 n (%)
Overall	N = 229	N = 226	N = 345	N = 335
Any PT	106 (46.3)	117 (51.8)	162 (47.0)	163 (48.7)
Febrile neutropenia*	38 (16.6)	37 (16.4)	54 (15.7)	53 (15.8)
Neutrophil count decreased*	19 (8.3)	21 (9.3)	28 (8.1)	33 (9.9)
Platelet count decreased*	14 (6.1)	18 (8.0)	24 (7.0)	28 (8.4)
Haemoglobin decreased*	7 (3.1)	3 (1.3)	12 (3.5)	9 (2.7)
Dermatitis exfoliative*	6 (2.6)	4 (1.8)	10 (2.9)	1 (0.3)
Device related infection	17 (7.4)	10 (4.4)	23 (6.7)	13 (3.9)
Pneumonia	20 (8.7)	22 (9.7)	23 (6.7)	23 (6.9)
Sepsis	7 (3.1)	10 (4.4)	16 (4.6)	14 (4.2)
Pneumonitis	11 (4.8)	11 (4.9)	11 (3.2)	8 (2.4)
Hypotension	6 (2.6)	3 (1.3)	10 (2.9)	1 (0.3)
Aspartate aminotransferase increased	6 (2.6)	0	9 (2.6)	1 (0.3)
Neutropenic infection	2 (0.9)	0	9 (2.6)	6 (1.8)
Alanine aminotransferase increased	7 (3.1)	3 (1.3)	8 (2.3)	3 (0.9)
Infection	7 (3.1)	3 (1.3)	8 (2.3)	3 (0.9)
Leukopenia	5 (2.2)	3 (1.3)	8 (2.3)	7 (2.1)
Neutropenic sepsis	2 (0.9)	1 (0.4)	8 (2.3)	1 (0.3)
Renal failure	4 (1.7)	1 (0.4)	8 (2.3)	2 (0.6)
Colitis	6 (2.6)	8 (3.5)	7 (2.0)	9 (2.7)
Continuation phase	N=84	N=56	N=120	N=85
Any PT	17 (20.2)	12 (21.4)	14 (11.7)	9 (10.6)
Neutrophil count decreased*	4 (4.8)	2 (3.6)	3 (2.5)	1 (1.2)
Platelet count decreased*	1 (1.2)	3 (5.4)	0	2 (2.4)
Haemoglobin decreased*	0	1 (1.8)	0	0
Pneumonia	1 (1.2)	0	0	0
Hypotension	0	1 (1.8)	0	0
Aspartate aminotransferase increased	2 (2.4)	0	1 (0.8)	0
Alanine aminotransferase increased	3 (3.6)	1 (1.8)	0	0
Infection	1 (1.2)	0	1 (0.8)	0
Leukopenia	1 (1.2)	0	1 (0.8)	0
Colitis	0	1 (1.8)	0	0

SCT = Stem cell transplantation
* In North America, 13 expected AEs had all grades collected. For all other AEs, only grades ≥ 3 were collected.
For this reason unexpected all grade cells are empty in NA and overall.
Expected AEs are associated to more than 13 preferred terms.
Preferred terms are sorted with first the expected AEs, then the non-expected AEs, and then in descending frequency, as reported in the MIDOSTAURIN – Grade 3/4 – All sites column.
A patient with multiple occurrences of an AE is counted only once in the AE category.
AEs with a missing grade are excluded from the table but appear in Listing 16.2.7-1.2.

Source: Table 14.3.1-2.1

Approximately half of all patients in Study A2301 experienced an SAE, with similar incidences in the midostaurin and placebo groups, with the exception of grade 3/4 exfoliative dermatitis and grade 3/4 hypotension. Device related infections occurred more often in the midostaurin arm than in the control arm (23 (6.7%) vs 13 (3.9%).

In study A2301 an analysis was provided for all AEs leading to hospitalization. The proportion of patients requiring additional or prolonged hospitalization during Cycle 1 of the induction phase was similar in the midostaurin and placebo groups (53.3% vs 50.4%). For patients who had a second cycle of induction treatment (n=81 vs n=101), the proportion of hospitalised patients was slightly higher in the midostaurin group (56.8%) than the placebo group (44.6%).

ASM/SM-AHN/MCL

In the pooled dataset, 68.3% of the patients had an SAE; the events were mostly grade 3 or 4 (62.7%) (see Table 100). Infections were among the most commonly reported SAEs: pneumonia and sepsis (each reported in 7.0% of patients) and urinary tract infection (4.2%). Other commonly reported SAEs were pleural effusion (4.9%), dyspnoea (4.2%), pyrexia (4.9%) and ascites (3.5%). Acute myeloid leukaemia occurred in 5 patients (3.5%). All other SAEs were reported in 3 or fewer patients.

Table 98. Serious adverse events (>2% in pool) in advanced SM (Safety set)

	D2201		A2213		Advanced SM pool	
	N=116		N=26		N=142	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	85 (73.3)	79 (68.1)	12 (46.2)	11 (42.3)	97 (68.3)	90 (63.4)
Pneumonia	8 (6.9)	7 (6.0)	2 (7.7)	2 (7.7)	10 (7.0)	9 (6.3)
Sepsis	8 (6.9)	8 (6.9)	2 (7.7)	2 (7.7)	10 (7.0)	10 (7.0)
Diarrhoea	8 (6.9)	4 (3.4)	0	0	8 (5.6)	4 (2.8)
Febrile neutropenia	6 (5.2)	6 (5.2)	1 (3.8)	1 (3.8)	7 (4.9)	7 (4.9)
Pyrexia	7 (6.0)	4 (3.4)	0	0	7 (4.9)	4 (2.8)
Pleural effusion	6 (5.2)	4 (3.4)	1 (3.8)	1 (3.8)	7 (4.9)	5 (3.5)
Anaemia	6 (5.2)	5 (4.3)	0	0	6 (4.2)	5 (3.5)
Gastrointestinal haemorrhage	6 (5.2)	5 (4.3)	0	0	6 (4.2)	5 (3.5)
Vomiting	6 (5.2)	3 (2.6)	0	0	6 (4.2)	3 (2.1)
Urinary tract infection	5 (4.3)	2 (1.7)	1 (3.8)	1 (3.8)	6 (4.2)	3 (2.1)
Dyspnoea	5 (4.3)	3 (2.6)	1 (3.8)	1 (3.8)	6 (4.2)	4 (2.8)
Ascites	5 (4.3)	3 (2.6)	0	0	5 (3.5)	3 (2.1)
Acute myeloid leukaemia	5 (4.3)	5 (4.3)	0	0	5 (3.5)	5 (3.5)
Upper gastrointestinal haemorrhage	4 (3.4)	3 (2.6)	0	0	4 (2.8)	3 (2.1)
Leukocytosis	3 (2.6)	2 (1.7)	0	0	3 (2.1)	2 (1.4)
Coronary artery disease	3 (2.6)	1 (0.9)	0	0	3 (2.1)	1 (0.7)
Fatigue	3 (2.6)	2 (1.7)	0	0	3 (2.1)	2 (1.4)
General physical health deterioration	3 (2.6)	3 (2.6)	0	0	3 (2.1)	3 (2.1)
Acute kidney injury	3 (2.6)	2 (1.7)	0	0	3 (2.1)	2 (1.4)
Renal failure	3 (2.6)	3 (2.6)	0	0	3 (2.1)	3 (2.1)
Epistaxis	3 (2.6)	2 (1.7)	0	0	3 (2.1)	2 (1.4)
Toxic skin eruption	3 (2.6)	3 (2.6)	0	0	3 (2.1)	3 (2.1)
Hypotension	2 (1.7)	1 (0.9)	1 (3.8)	0	3 (2.1)	1 (0.7)
SM=systemic mastocytosis						

After the cut-off dates for the individual studies, 22 additional SAE cases were reported (up to 30 April 2016). Six cases were related to infections, 3 cases each were related to haematological events, gastrointestinal events and respiratory events, 1 case of osteonecrosis of the jaw (patient receiving alendronate), left ventricular failure (patient with history aortic valve stenosis and valve replacement) and cellulitis (condition unchanged). Other cases included events that were as expected for the patient population with ASM as judged by the investigators/Applicant.

For the ASM/SM-AHN/MCL safety pool an analysis was provided of AEs requiring additional therapy. All but 1 patient (99.3%) in the advanced SM pool had additional therapy to manage AEs.

Laboratory findings

Haematology parameters

AML

In study A2301 the collection of safety laboratory values was initiated after the start of the study (amendment 2), therefore some of the data were collected retrospectively for non-North America (NNA) but not for North America (NA). Overall, shifts in haematological abnormalities were similar in the midostaurin and placebo group. The majority of patients experienced grade 3 and 4 cytopenias in the induction and consolidation treatment phases. In the continuation phase, the frequencies of newly occurring or worsening haemoglobin, platelets and WBC counts were similar between the treatment groups. Median time to ANC recovery ($\geq$ 500/μl) was similar in both treatment groups; in induction phase cycle 1 (27 and 26 days in midostaurin and placebo patients, respectively) and in consolidation phase cycle 1 (27 and 25 days, in midostaurin and placebo patients, respectively).

ASM/SM-AHN/MCL

In the pooled dataset, newly occurring or worsening in haematology parameters were reported in $\geq$ 50% of patients. Newly occurring or worsening from baseline to grade 3 or 4 for lymphocytes and haemoglobin was reported for more than 40% of patients.

An increase was seen in haemoglobin level over time, but this is confounded by red blood cell transfusions in a number of patients for disease-related anaemia or bleeding episodes. The median time to onset of new grade 3 or worse neutrophil decrease was 0.76 months. The ANC over time demonstrated a decrease within the first month of midostaurin treatment that remained stable thereafter.

Clinical chemistry

AML

Newly occurring or worsening biochemistry abnormalities were balanced between the two treatment groups. Elevations to newly occurring or worsening grade 3/4 abnormalities occurred in $\geq$ 10% of patients in both treatment groups for low potassium, total bilirubin and ALT.

ASM/SM-AHN/MCL

Newly occurring and worsening biochemistry abnormalities were mostly mild in severity (grade 1 or 2). The most commonly reported biochemistry abnormality was glucose increased (all grades: 79.6% of patients; grade 3 and 4: 18.6%), however a significant proportion of the patients had received corticosteroids on study (>60%). Patients with grade 3-4 glucose increases included diabetic patients and patients already hyperglycaemic at baseline and/or with risk factors for diabetes. Uric acid elevations were reported in 37.9% of patients and shifts to grade 3 or 4 were seen in 10.7% of patients, hyperuricaemia was reported as AE in 4 patients. Newly occurring or worsening laboratory abnormalities of creatinine increased were reported in 35 (24.6%) patients, with AEs of creatinine increased reported in 8 patients. Newly occurring or worsening shifts in magnesium (decreased) were reported in 29 patients; however, no shifts occurred to grade 3 or 4. Newly occurring or worsening shifts in amylase was experienced in 19.7% of patients in the pooled dataset and grade 3 or 4 events were reported in 6.4% of patients. Lipase elevations were reported in 37.3% of patients in the pooled dataset and grade 3 or 4 events were reported in 17.6% of patients. Elevations in amylase and lipases have been reported as AEs.

Safety in special populations

Age

A subgroup analysis based on age was not conducted for patients in Study A2301, as patients ≥ 60 years of age were not eligible for the study.

Two age subgroup analyses were conducted for the ASM/SM-AHN/MCL safety pool: < 65 years and ≥ 65 years and < 60 years and ≥ 60 years. 52 patients were < 60 years and 90 patients were ≥ 60 years. The median duration of exposure was higher in the patients < 60 years (18.6 months) compared to patients ≥ 60 years (9.1 months);

The number of patients who experienced AEs and SAEs were generally similar in the two age groups, while Grade 3/4 AEs/SAEs were reported more frequently in patients ≥ 60 years (89%/68%) than in those < 60 years (75.0%/58%). In the ≥ 60 years there were more AEs leading to discontinuation (29 vs 15%) and to dose adjustment/interruption (62 vs 46%). Results were similar in patients when 65 years was chosen as cut-off (< 65 years: n=78 patients) and ≥ 65 years: n=64 patients).

Table 99 Summary of adverse events by age (Safety Set Studies D2201/A2213)

	Age <65	Age 65-74	Age 75-84
	N=78	N=48	N=16
	n (%)	n (%)	n (%)
Total AEs	78 (100)	48 (100)	16 (100)
Serious AEs - Total	55 (70.5)	34 (70.8)	8 (50.0)
Fatal	8 (10.3)	14 (29.2)	4 (25.0)
Hospitalization/prolong existing hospitalization	53 (67.9)	33 (68.8)	8 (50.0)
AE leading to drop-out	14 (17.9)	13 (27.1)	7 (43.8)
Psychiatric disorders	25 (32.1)	16 (33.3)	8 (50.0)
Nervous system disorders	38 (48.7)	21 (43.8)	11 (68.8)
Accidents and injuries	17 (21.8)	14 (29.2)	3 (18.8)
Cardiac disorders	12 (15.4)	19 (39.6)	5 (31.3)
Vascular disorders	19 (24.4)	13 (27.1)	6 (37.5)
Cerebrovascular disorders	3 (3.8)	2 (4.2)	0
Infections and infestations	50 (64.1)	34 (70.8)	6 (37.5)
Anticholinergic syndrome	0	0	0
Quality of life decreased	0	0	1 (6.3)
Sum of postural hypotension, falls, black outs, syncope, dizziness,ataxia, fractures	13 (16.7)	10 (20.8)	3 (18.8)
The cut off date used in this analysis is 01DEC2014 for D2201 and 03DEC2012 for A2213. Fatal events are deaths recorded in the study evaluation completion CRF page. A patient with multiple occurrences of an AE is counted only once in the AE category. Source: The cut off date used in this analysis is 01DEC2014 for D2201 and 03DEC2012 for A2213. Fatal events are deaths recorded in the study evaluation completion CRF page. A patient with multiple occurrences of an AE is counted only once in the AE category.			

The Applicant has provided an analysis of grade 3/4 AEs by age group (<40 years, 40 - <50 years, and >50 years) in pivotal AML study A2301 (Figure 24).

Figure 23. Grade ¾ AEs by age reported in all age groups with a frequency of at elast 10% oin the midostaurin arm in study A2301(Safety Set)
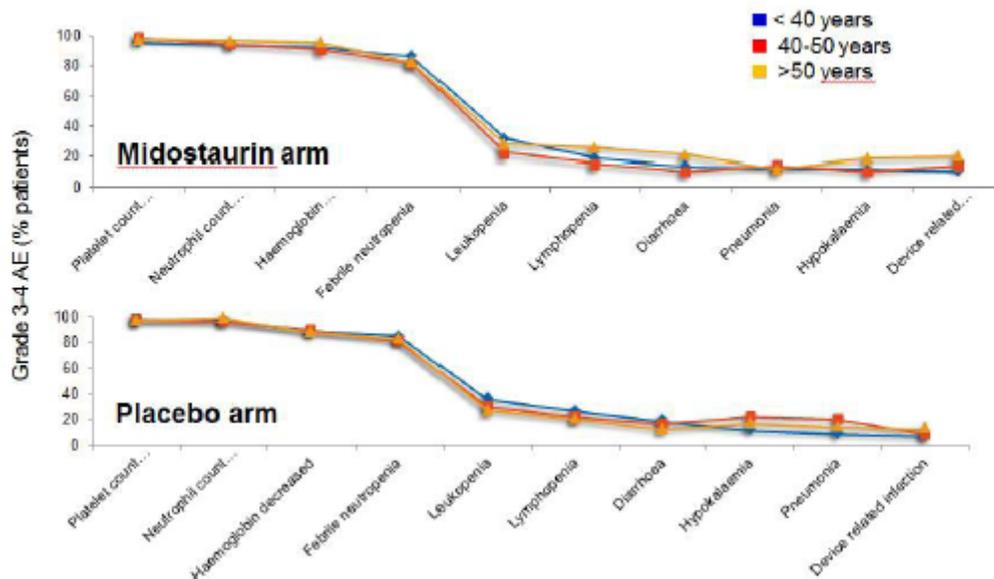
Gender

AML

Overall the proportion of patients with AEs was similar among male and female patients in both treatment groups. In the continuation phase, among the patients in the midostaurin group the incidence of grade 3 or 4 AEs was higher in male patients (48.4%) compared to female patients (33.9%). No difference was seen in the incidence of events in the SOCs of blood and lymphatic disorders, infections, or gastrointestinal disorders. A difference was noted in the incidence on cardiac disorder grade 3/4 events (male: 18 patients; 10.7% and female: 6 patients; 3.4%); among the male patients grade 3 or 4 events of left ventricular dysfunction occurred in 6 patients and atrial fibrillation in 4 patients; however, in female patients these events occurred in 2 patients and 0 patients, respectively. In females diarrhoea and vomiting occurred more frequently.

ASM/SM-AHN/MCL

Some differences between the genders in AE reporting were noted: A higher frequency of reporting in males was seen for SAEs (71.4% vs. 62.7%), grade 3/4 AE (65.9% vs 58.8%), AEs leading to discontinuation (all grades: 29.7% vs 13.7%; grade 3/4 23.1% vs 9.8%). AEs reported more often (>10% difference) in males were anaemia, peripheral oedema, rash and insomnia. AEs reported more often in females were vomiting (all grades 80.4% vs 60.4%; grade 3/4 11.8% vs 2.2) and nausea (all grades 92.2% vs 76.9%; grade 3/4 11.8% vs 2.2%) and (with >10% difference) tremor, blood alkaline phosphatase increased, urinary tract infection, flushing, and back pain.

Notably, there is an imbalance in overall exposure with respect to gender (median duration of exposure was 17.0 months in female patients and 11.3 months in male patients).

The Applicant concludes that no gender-related pattern could be discerned related to the proportion of patients with AEs overall, those requiring dose adjustment/interruption, or those requiring addition therapy overall.

ECOG

In study A2301 (AML patients) the incidence of AEs was similar regardless of ECOG status (ECOG 0-1 vs ≥ 2). The proportion of patients with AEs was similar regardless of ECOG status both overall and in the continuation phase alone.

Hepatic function

For the ASM/SM-AHN/MCL population a subgroup analysis was performed between patients with AEs among the normal hepatic function (n=106) and mild (n=23) hepatic impairment subgroups. As there were few patients with moderate (n=8) and severe (n=2) hepatic impairment, no meaningful conclusions could be made for these subgroups. There were no major differences between the proportion of patients with AEs, deaths, AEs leading to discontinuation or dose reduction/interruption. The incidence of SAEs was somewhat higher in patients with mild hepatic function impairment (65 vs. 78%).

Safety related to drug-drug interactions and other interactions

Strong CYP3A4 inhibitors increase the exposure of midostaurin (see PK section of this report). In the AML pivotal Phase 3 study A2301, patients receiving concomitant strong CYP3A4 inhibitors had 1.44-fold higher exposure to midostaurin compared to all remaining patients in the study. For the sum of active moieties at steady state the increase is relatively small changes consisting of 1.22 fold higher exposure in patients receiving strong CYP3A4 inhibitors. An overview of AEs, in patients who were treated and those were not treated with strong CYP3A4 inhibitors for both treatment arms are presented in Table 102 and

Table 103).The comparison of the AE profile of subjects known to have concomitant treatment with a strong CYP3A4 inhibitor with that of subjects who did not, showed that in both arms the frequency of infections is increased in the group treated with strong CYP3A4 inhibitors when compared to those not receiving CYP3A4 inhibitors, but that the difference in the placebo arm is less than what is seen in the midostaurin group.

Table 100 Adverse Events with an incidence rate of 10% or more in either treatment arm regardless of midostaurin/placebo relationship by primary SOC, preferred term, maximum CTC grade, and strong CYP3A4 inhibitor: Yes - study A2301 (SS)

Primary SOC Preferred term	All sites (N=415)			
	MIDOSTAURIN N=214		PLACEBO N=201	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any primary SOC		**214 (100.0)**		**201 (100.0)**
Blood and lymphatic system disorders		**196 (91.6)**		**175 (87.1)**
Febrile neutropenia*	183 (85.5)	183 (85.5)	164 (81.6)	164 (81.6)
Leukopenia		54 (25.2)		57 (28.4)
Lymphopenia		37 (17.3)		42 (20.9)
Gastrointestinal disorders		**70 (32.7)**		**68 (33.8)**

| | All sites (N=415) | | | |
| | MIDOSTAURIN N=214 | | PLACEBO N=201 | |
Primary SOC Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Diarrhoea*	160 (74.8)	31 (14.5)	148 (73.6)	34 (16.9)
General disorders and administration site conditions		**36 (16.8)**		**31 (15.4)**
Infections and infestations		**124 (57.9)**		**112 (55.7)**
Device related infection		36 (16.8)		18 (9.0)
Pneumonia		33 (15.4)		36 (17.9)
Investigations		**214 (100.0)**		**200 (99.5)**
Platelet count decreased*	209 (97.7)	209 (97.7)	195 (97.0)	194 (96.5)
Neutrophil count decreased*	208 (97.2)	206 (96.3)	195 (97.0)	194 (96.5)
Haemoglobin decreased*	209 (97.7)	201 (93.9)	196 (97.5)	180 (89.6)
Alanine aminotransferase increased		30 (14.0)		21 (10.4)
Metabolism and nutrition disorders		**67 (31.3)**		**64 (31.8)**
Hypokalaemia		30 (14.0)		33 (16.4)
Respiratory, thoracic and mediastinal disorders		**36 (16.8)**		**29 (14.4)**
Skin and subcutaneous tissue disorders		**36 (16.8)**		**18 (9.0)**
Dermatitis exfoliative*	139 (65.0)	28 (13.1)	130 (64.7)	11 (5.5)
Vascular disorders		**25 (11.7)**		**12 (6.0)**

* In North America, only 13 expected AEs had all grades collected. For all other AEs, only grades >=3 were collected. For this reason unexpected all grade cells are empty in NA and overall. Expected AEs are associated to more than 13 Preferred terms. Primary system organ classes are presented alphabetically; preferred terms are sorted within Primary system organ class with first the expected AEs, then the non expected AEs, and then in descending frequency,
As reported in the MIDOSTAURIN – Grade 3/4 – All sites column.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.
Only AEs recorded with a report start date lower or equal to the last study drug intake + 30 days are summarized.
AEs with a missing grade are excluded from the table.

Table 101.Adverse Events with an incidence rate of 10% or more in either treatment arm regardless of midostaurin/placebo relationship by primary system organ class, preferred term, maximum CTC grade, and strong CYP3A4 inhibitor: No - study A2301 (SS)

| | All sites (N=265) | | | |
| | MIDOSTAURIN N=131 | | PLACEBO N=134 | |
Primary SOC Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any primary SOC		**130 (99.2)**		**134 (100.0)**
Blood and lymphatic system disorders		**116 (88.5)**		**121 (90.3)**
Febrile neutropenia*	105 (80.2)	105 (80.2)	115 (85.8)	114 (85.1)
Leukopenia		39 (29.8)		44 (32.8)

Primary SOC Preferred term	All sites (N=265)			
	MIDOSTAURIN N=131		PLACEBO N=134	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Lymphopenia		32 (24.4)		34 (25.4)
Gastrointestinal disorders		**43 (32.8)**		**44 (32.8)**
Diarrhoea*	102 (77.9)	22 (16.8)	104 (77.6)	17 (12.7)
Nausea*	106 (80.9)	7 (5.3)	100 (74.6)	19 (14.2)
General disorders and administration site conditions		**15 (11.5)**		**28 (20.9)**
Fatigue*	99 (75.6)	10 (7.6)	97 (72.4)	16 (11.9)
Infections and infestations		**61 (46.6)**		**64 (47.8)**
Device related infection		18 (13.7)		15 (11.2)
Investigations		**129 (98.5)**		**134 (100.0)**
Platelet count decreased*	128 (97.7)	128 (97.7)	132 (98.5)	132 (98.5)
Neutrophil count decreased*	125 (95.4)	123 (93.9)	133 (99.3)	133 (99.3)
Haemoglobin decreased*	128 (97.7)	121 (92.4)	131 (97.8)	118 (88.1)
Alanine aminotransferase increased		15 (11.5)		11 (8.2)
Metabolism and nutrition disorders		**44 (33.6)**		**57 (42.5)**
Hypokalaemia		18 (13.7)		24 (17.9)
Hyponatraemia		14 (10.7)		15 (11.2)
Hypophosphataemia		11 (8.4)		23 (17.2)
Respiratory, thoracic and mediastinal disorders		**19 (14.5)**		**25 (18.7)**
Skin and subcutaneous tissue disorders		**22 (16.8)**		**17 (12.7)**
Dermatitis exfoliative*	89 (67.9)	19 (14.5)	95 (70.9)	14 (10.4)
* In North America, only 13 expected AEs had all grades collected. For all other AEs, only grades >=3 were collected. For this reason unexpected all grade cells are empty in NA and overall. Expected AEs are associated to more than 13 Preferred terms. Primary system organ classes are presented alphabetically; preferred terms are sorted within Primary system organ class with first the expected AEs, then the non expected AEs, and then in descending frequency, As reported in the MIDOSTAURIN – Grade 3/4 – All sites column. A patient with multiple occurrences of an AE is counted only once in the AE category. A patient with multiple AEs within a primary system organ class is counted only once in the total row. Only AEs recorded with a report start date lower or equal to the last study drug intake + 30 days are summarized. AEs with a missing grade are excluded from the table but appear in [Study A2301]				

Discontinuation due to adverse events

AML

The rate of discontinuation for the entire study was 79.4% in the midostaurin group, and 84.6% in the placebo group.

Table 102. Adverse Events leading to midostaurin/placebo discontinuation- Study A2301

Preferred term	Non-North American sites (N=455)		All sites (N=680)	
	MIDOSTAURIN All grades n (%)	PLACEBO All grades n (%)	MIDOSTAURIN Grade 3/4 n (%)	PLACEBO Grade 3/4 n (%)
Overall	N = 229	N = 226	N = 345	N = 335
Any PT -Total	19 (8.3)	12 (5.3)	21 (6.1)	15 (4.5)
Dermatitis exfoliative	3 (1.3)	0	4 (1.2)	0
Alanine aminotransferase increased	4 (1.7)	1 (0.4)	3 (0.9)	1 (0.3)
Aspartate aminotransferase increased	4 (1.7)	1 (0.4)	2 (0.6)	0
Renal failure	1 (0.4)	0	2 (0.6)	0
Atrioventricular block	1 (0.4)	0	1 (0.3)	0
Central nervous system leukaemia	1 (0.4)	0	1 (0.3)	0
Cervical vertebral fracture	1 (0.4)	0	1 (0.3)	0
Chloroma	1 (0.4)	0	1 (0.3)	0
Device related infection	0	0	1 (0.3)	0
Febrile neutropenia	1 (0.4)	1 (0.4)	1 (0.3)	2 (0.6)
Hypercholesterolaemia	1 (0.4)	0	1 (0.3)	0
Hypertriglyceridaemia	1 (0.4)	0	1 (0.3)	0
Jaundice	1 (0.4)	0	1 (0.3)	0
Jaw fracture	1 (0.4)	0	1 (0.3)	0
Myocardial ischaemia	0	0	1 (0.3)	0
Neutrophil count decreased	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Pregnancy	0	0	1 (0.3)	0
Pulmonary haemorrhage	0	0	1 (0.3)	0
Rib fracture	1 (0.4)	0	1 (0.3)	0
Staphylococcal infection	1 (0.4)	0	1 (0.3)	0
Troponin T increased	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)

Adverse events of any grade leading to treatment discontinuation were observed in 8.3% of patients in the midostaurin group and in 5.3% patients in the placebo group. Information on AEs leading to study drug interruption or dose adjustment was not collected for Study A2301, however reasons for missed/reduced doses were provided in the study report. The number of missed/reduced doses due to cardiac toxicities is numerically higher in the midostaurin group (49 (15%) vs 41 (13%).

ASM/SM-AHN/MCL

At the time of data cut-off for each study, 28 patients (19.7%) in the pooled ASM/SM-AHN/MCL dataset continued to receive study treatment, 21 in study D2201 and 7 in study A2213.

Table 103. Reason for treatment discontinuation in ASM/SM-AHN/MCL (Safety set)

Study number	D2201	A2213	Advanced SM pool
Nr of discontinued patients	**N=95**	**N=19**	**N=114**
Primary reason for end of treatment	**n (%)[a]**	**n (%)[a]**	**n (%)[a]**
Disease Progression	44 (46)	6 (32)	50 (44)
Adverse Event(s)	28 (29)	4 (21)	32 (28)
Other	15 (16)	8 (42)	23 (20)
Death	8 (8)	1 (5)	9 (8)
Missing	21 (22)	7 (37)	28 (25)

a: percentage of all *discontinued* patients

The most frequent reasons for discontinuation of study drug were disease progression (n=50) and AEs (n=32, 23.9%). Death was the primary reason for discontinuation in 9 of patients. The most frequent AEs leading to discontinuation were nausea (n=3), ascites (n=3), and ECG QT prolonged (n=3), all other AEs leading to discontinuation were reported in no more than 2 patients each.

Dose interruptions were reported for 67 patients (47.2%) in the pooled safety set: 29 patients (20.4%) had 1 dose interruption and 38 patients (26.8%) had more than 1 dose interruption. Dose reductions were reported for 84 patients (59.2%) in the pooled safety set: 38 patients (26.8%) had 1 dose reduction and 46 patients (32.4%) had more than 1 dose reduction. AEs were the most frequent reason for dose interruptions (59 of 67 interruptions) and dose reductions (63 of 84 reductions), followed by dosing error. AEs leading to dose interruption/adjustment were most commonly related to GI events: nausea (n=12, 12.0%), vomiting (n=13, 9.2%) and diarrhoea (n=7, 4.9%); ECG QT prolonged events (n=10, 7.0%); haematological events: neutropenia (n=8, 5.6% patients), thrombocytopenia (n=6, 4.2% patients) and anaemia (n=4, 2.8% patients); pyrexia (n=6 4.2%), and fatigue (n=5 3.5%).

Supportive safety studies

Study A2106

Study A2106 was a phase 1b, open-label, multi-centre study to evaluate the safety, tolerability and PK of twice daily oral dosing of midostaurin in newly diagnosed, previously untreated AML patients with *FLT3*-mutated and *FLT3*-WT AML aged 18-60 years. Midostaurin was administrated either sequentially (Arm 1) or concomitantly (Arm 2) with standard induction therapy. Patients were treated with midostaurin at 100 mg b.i.d. (29 patients) or 50 mg b.i.d. (40 patients).

After completion of consolidation therapy, patients were to continue to receive midostaurin as single-agent maintenance therapy according to the schedule assigned during induction. In the absence of safety concerns, midostaurin could be continued until relapse or for up to 3 years from the time of diagnosis.

Overall the incidence of AEs was similar in each dose group; however AEs suspected to be related to study drug, SAEs, AEs leading to discontinuation were reported at a higher incidence in the 100 mg b.i.d. group compared to the 50 mg b.i.d. group.

Table 104. Overview of adverse events (safety set) Study A2106

Category	Midostaurin 100 mg bid N=28		Midostaurin 50 mg bid N=40		All patients N=68	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
AEs	28 (100)	28 (100)	40 (100)	36 (90.0)	68 (100)	64 (94.1)
Suspected to be drug-related	25 (89.3)	17 (60.7)	32 (80.0)	22 (55.0)	57 (83.8)	39 (57.4)
SAEs	20 (71.4)	20 (71.4)	26 (65.0)	25 (62.5)	46 (67.6)	45 (66.2)
Suspected to be drug-related	10 (35.7)	9 (32.1)	6 (15.0)	6 (15.0)	16 (23.5)	15 (22.1)
AEs leading to discontinuation	5 (17.9)	3 (10.7)	3 (7.5)	3 (7.5)	8 (11.8)	6 (8.8)
Suspected to be drug-related	4 (14.3)	1 (3.6)	1 (2.5)	1 (2.5)	5 (7.4)	2 (2.9)
Other significant events	28 (100)	28 (100)	39 (97.5)	35 (87.5)	67 (98.5)	63 (92.6)
Suspected to be drug-related	24 (85.7)	17 (60.7)	31 (77.5)	17 (42.5)	55 (80.9)	34 (50.0)

The most frequent AEs (100 mg b.i.d. vs 50 mg b.i.d.) were those associated with myelosuppression (thrombocytopenia 67.9% vs 75.0%; febrile neutropenia 60.7% vs 65.0%, anaemia 28.6% vs 45.0%, neutropenia 28.6% vs 52.5%), gastrointestinal events (nausea 75.0% vs 77.5%, diarrhoea 71.4% vs 67.5%, vomiting 67.9% vs 65.0%), infections (pneumonia 28.6% vs 12.5%), LFTs (AST increased 39.3% vs 25.0%, ALT increased 35.7% vs 27.5%, bilirubin increased 28.6% vs 20.0%), psychiatric disorders (insomnia 25.0% vs 42.5%, depression 14.3% vs 25.0%), skin toxicities (alopecia 35.7% vs 27.5%, petechiae 32.1% vs 40.0%, rash 28.6% vs 35.0%) and vascular disorders (hypotension 42.9% vs 30.0%).

Study A2104E1

Study A2104E1 was an open label, randomised study in patients with AML (*FLT3* wild type or mutated) and in patients with high risk MDS who were relapsed or refractory. Patients were randomised to receive continuous oral dosing of either 50 mg b.i.d. or 100 mg b.i.d. midostaurin in a 28-day cycle regimen during the treatment period. Eighty-five (89.5%) patients with AML and 10 patients (10.5%) with MDS were included. The median duration of exposure was 48.0 days and was slightly higher in patients treated at 50 mg b.i.d. (59.0 days) compared to the 100 mg b.i.d. dosage (42 days).

Table 105. Overview of adverse events (safety set) Study A2104E1

Category	Midostaurin 50 mg bid N=51		Midostaurin 100 mg bid N=44		All patients N=95	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
AEs	51 (100)	44 (86.3)	44 (100)	37 (84.1)	95 (100)	81 (85.3)
SAE	39 (76.5)	36 (70.6)	33 (75.0)	31 (70.5)	72 (75.8)	66 (69.5)
AEs leading to discontinuation	8 (15.7)	7 (13.7)	12 (27.3)	8 (18.2)	20 (21.1)	15 (15.8)
AEs leading to dose adjustment/interruption	13 (25.5)	13 (25.5)	15 (34.1)	11 (25.0)	28 (29.5)	24 (25.3)
AEs leading to hospitalization/prolonged hospitalization	38 (74.5)	35 (68.6)	32 (72.7)	30 (68.2)	70 (73.7)	65 (68.4)
Deaths	5 (9.8)		2 (4.5)		7 (7.4)	

Source: [SCS-Appendix1-Table 10.2-1s], [SCS Appendix 1- Table 10.2-2s], [SCS Appendix 1-Table 10.1-2s], [SCS Appendix 1-Table 10.2-5s], [SCS Appendix 1Table 10.2-7s], [SCS Appendix 1Table 10.2-9s]

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

Midostaurin has been evaluated in an extensive clinical program including more than 1800 subjects comprising ~20 studies in various indications.

AML

All demographic characteristics and relevant disease characteristics were balanced between the two treatment arms with the exception of gender (more male patients in the midostaurin arm, 48.3% vs 40.6% in the placebo arm) and extramedullary disease (a higher proportion in the placebo arm, 15.8% vs 23.5%).

The collection of data on concomitant treatments was initiated after study initiation. Almost all patients (98.5%) received at least 1 concomitant medication. During the induction phase no clear differences in co-medication were noted. During consolidation therapy, a (slight) imbalance in levofloxacin and use of

dexamethasone seems to be apparent, with more use in the midostaurin arm (50 vs 41% and 54 vs 47% respectively). During the continuation phase, an imbalance in the use of ondansetron is noted with 13% (14 of 106) patients using this substance in the midostaurin arm vs 2.5 % (2 of 80) in the control arm, with apparent limited use of other anti-emetics.

The safety evaluation of Rydapt (50 mg twice daily) in patients with newly diagnosed FLT3 mutated AML was based on a phase III, randomised, double blind, placebo controlled study with 717 patients. The overall median duration of exposure was 42 days (range 2 to 576 days) for patients in the Rydapt plus standard chemotherapy arm versus 34 days (range 1 to 465 days) for patients in the placebo plus standard chemotherapy arm. For the 205 patients (120 in Rydapt arm and 85 in placebo arm) who entered the maintenance phase, the median duration of exposure in maintenance was 11 months for both arms (16 to 520 days for patients in the Rydapt arm and 22 to 381 days in the placebo arm) (SmPC, section 4.8).

All patients in Study A2301 experienced at least one AE of any grade regardless of relation with study drug. All but one patient in the midostaurin group experienced at least one grade 3/4 AE. The majority of events were reported during the induction and consolidation phases and events were less frequently reported during the continuation phase. Notably, the absence of chemotherapy administration is the most likely reason for the lower frequency of AEs in the continuation phase (=monotherapy midostaurin vs. placebo). However, selection of patients with lower sensitivity for AEs/toxicity might have contributed as well.

The most frequent AEs overall were those associated with myelosuppression and these AEs comprised also the most frequent grade 3-4 AEs (occurring in >95% of the study population). The myelosuppression is most likely due to the chemotherapy, however a potential contribution of midostaurin to haematological toxicity cannot be ruled out. Of note, also for the myelosuppression events frequencies in the continuation phase were low.

Over 75% of patients in either treatment group experienced at least one grade 3/4 AE suspected to be related to treatment. These AEs occurred at similar frequencies in both treatment groups.

The most frequent adverse drug reactions (ADRs) in the Rydapt arm were febrile neutropenia (83.4%), nausea (83.4%), exfoliative dermatitis (61.6%), vomiting (60.7%), headache (45.9%), petechiae (35.8%) and pyrexia (34.5%). The most frequent Grade 3/4 ADRs were febrile neutropenia (83.5%), lymphopenia (20.0%), device related infection (15.7%), exfoliative dermatitis (13.6%), hyperglycaemia (7.0%) and nausea (5.8%) (SmPC, section 4.8).

Bleeding events occurred in similar proportions of patients in the midostaurin (59.0%) and placebo (57.5%) groups in NNA sites; however, grade 3/4 events were slightly more common in the midostaurin group. The most frequently reported events were petechiae (35.8% vs 27.0%), epistaxis (27.5% vs 23.5%), haematoma (16.2% vs 16.8%).

GI events were among the most commonly reported AEs (diarrhoea, nausea and vomiting > 55%). This high incidence was attributed to chemotherapy treatment. The incidence and severity of diarrhoea was similar for midostaurin vs. placebo, but the incidences of nausea and vomiting of any grade were slightly higher in the midostaurin group (nausea: 83.4% vs 70.4%; vomiting 60.3% vs 52.7%, NNA sites). Also stomatitis occurred more frequently in the midostaurin group than in placebo (19% vs 12%). Based on the AE collection in the NNA sites only, headache (46% vs 38%), back pain (22% vs 16%) and petechiae (36% vs 27%) occurred more frequent in the midostaurin arm.

Approximately half of all patients experienced an SAE with similar incidences in the midostaurin and control group, except for grade 3/4 exfoliative dermatitis (10 vs 1 pt), grade 3/4 hypotension (10 vs 1 pt) and

possibly also device related infections (23 vs 13 pt) which were reported more often in the midostaurin group.

In Study A2301, a total of 36 patients died on treatment: 15 patients (4.3%) in the midostaurin group and 21 (6.3%) patients in the placebo group. Of these on-treatment deaths 16 were suspected to be related to study drug: 9 patients (2.6%) in the midostaurin and 7 patients (2.1%) and control group. Among the 14 patients who died on-treatment in the midostaurin group due to causes other than disease progression it is noted that there was one case of cardiac arrest and 2 patients for whom QTc > 450 ms was recorded (1 died due to myocardial infarction, the other due to colitis). An analysis of the mortality early post SCT (within 30 days or 100 days) did not provide a cause for concern on a possible effect of midostaurin treatment on SCT treatment-related mortality.

The most frequent laboratory abnormalities were haemoglobin decreased (97.3%), ANC decreased (86.7%), ALT increased (84.2%), AST increased (73.9%) and hypokalaemia (61.7%). The most frequent Grade 3/4 laboratory abnormalities were ANC decreased (85.8%), haemoglobin decreased (78.5%), ALT increased (19.4%) and hypokalaemia (13.9%) (SmPC, section 4.8).

Discontinuation due to any adverse reaction occurred in 3.1% of patients in the Rydapt arm versus 1.3% in the placebo arm. The most frequent Grade 3/4 adverse reaction leading to discontinuation in the Rydapt arm was exfoliative dermatitis (1.2%)(SmPC, section 4.8).

When the maintenance phase (single agent Rydapt or placebo) was assessed separately, a difference in the type and severity of ADRs was observed. The overall incidence of ADRs during the maintenance phase was generally lower than during the induction and consolidation phase. Incidences of ADRs were, however, higher in the Rydapt arm than in the placebo arm during the maintenance phase. ADRs occurring more often in the midostaurin arm versus placebo during maintenance included: nausea (46.4% versus 17.9%), hyperglycaemia (20.2% versus 12.5%), vomiting (19% versus 5.4%) and QT prolongation (11.9% versus 5.4%)(SmPC, section 4.8).

Most of the haematological abnormalities reported occurred during the induction and consolidation phase when the patients received Rydapt or placebo in combination with chemotherapy. The most frequent Grade 3/4 haematological abnormalities reported in patients during the maintenance phase with Rydapt were ANC decrease (20.8% versus 18.8%) and leukopenia (7.5% versus 5.9%)(SmPC, section 4.8).

ADRs reported during the maintenance phase led to discontinuation of 1.2% of patients in the Rydapt arm and none in the placebo arm (SmPC, section 4.8).

Subgroup analysis based on age was not conducted for patients in Study A2301, as patients ≥ 60 years of age were not eligible for the study. In study ADE02T two age groups were studied: patients aged ≤ 60 and patients aged >60, however an analysis of differences in the AE profile between these groups was not provided. An analysis of the data in the study report did not reveal major differences, except treatment related mortality, which occurred at a higher frequency in the >60 years of age population. Most of the deaths were early or hypoplastic deaths and were observed during the first or second induction cycles. While age might have contributed to the apparent reduced capability to recover from the effects of high dose chemotherapy (some of the) older patients, also the more aggressive disease in the elderly may also have played a role. However given the MoA of midostaurin and its safety profile, a contribution of midostaurin to thease early death, in particular those attributed to the inability to restore haematopoiesis cannot be excluded.

In this analysis of grade 3/4 AEs by age group (<40 years, 40 - <50 years, and >50 years) there appeared to be no notable differences in the safety of midostaurin across age groups. High level analyses of data on

the safety profile of midostaurin in older patients collected in the monotherapy setting were also provided. In AML study A2104E1, the majority of the enrolled patients were ⩾ 60 years of age (80 of 95 patients). The results of subgroup analyses by age groups <60 years vs ⩾ 60 years showed that there were no clinically relevant differences in the incidences of AEs, SAEs, discontinuations and other clinically significant events in the two age subgroups. Similarly also the results for subgroup analyses conducted using pooled data from studies A2104, A2104E1, A2104E2, and A2114 (patients with AML/MDS/ALL), which included 57 patients <60 years of age and 107 patients ⩾ 60 years of age, were consistent with these findings.

The proportion of patients with AEs was similar among male and female patients in both treatment groups. The frequency of vomiting and diarrhoea was higher in females than in males (81% vs. 70% for diarrhoea and 68% vs. 54% for vomiting), which is in part explained by the longer exposure in females. A difference was noted in the incidence of cardiac disorder grade 3/4 events (male: 18 patients; 10.7% and female: 6 patients; 3.4%); among the male patients grade 3 or 4 events of left ventricular dysfunction occurred in 6 patients and atrial fibrillation in 4 patients; however, in female patients these events occurred in 2 patients and 0 patients, respectively.

ASM/SM-AHN/MCL

In the pooled population 90 (63%) patients were ≥ 60 years of age and 39 (28%) were ≥ 70 years of age. The majority of patients were Caucasian, and there was a higher proportion of males (64.1%). The majority of patients had an ECOG status of 1 or 2. In total 102 patients had a diagnosis of SM with AHNMD and 25 patients had a diagnosis of SM without AHNMD. Overall, 27 patients were diagnosed as having MCL and among those 12 had a co-existing AHNMD. The most commonly occurring AHNMD subtypes were chronic myelomonocytic leukaemia (CMML) (32.4%) and MDS/myeloproliferative neoplasms-unclassifiable (MPN-U) (23.2%).

All but 1 patient in the pooled dataset had at least 1 comorbidity at study start, and all patients had at least 1 concomitant medication.

The safety of Rydapt (100 mg twice daily) as a single agent in patients with ASM, SM AHN and MCL was evaluated in 142 patients in two single arm, open label, multicentre studies. The median duration of exposure to Rydapt was 11.4 months (range: 0 to 81 months) (SmPC, section 4.8).

All patients had at least 1 AE of any grade. The most frequently reported AEs in the pooled dataset were those related to GI toxicity (nausea, vomiting, diarrhoea), infections, and myelosuppression (anaemia, thrombocytopenia, neutropenia). Other frequent AEs (>25% of patients) were peripheral oedema, fatigue, pyrexia, and headache. The most frequent grade 3/4 AEs were those related to myelosuppression (anaemia, thrombocytopenia, and neutropenia).

The most common AEs are those that are also associated with the disease. As in ASM/SM-AHN/MCL only single arm studies have been performed by the Applicant, the analysis of AEs is severely complicated by the (evolution of) the underlying condition and also the co-morbidities of the patients.

Bleeding events were reported in 38% of patients. The most commonly reported bleeding events were epistaxis (12%), contusion (6.3%) and haematoma (6.3%). Grade 3/4 events were reported in 20 (14.1%) patients; the most commonly reported were gastrointestinal haemorrhage (5 patients) and epistaxis (4 patients).

Psychiatric disorder-related events were reported in 34.5% of patients in the ASM/SM-AHN/MCL pool. Depression was reported in 14 patients (9.9%) and anxiety in 9 patients (6.3%). Symptoms of psychiatric disorders at baseline were reported in 35.9% in the ASM/SM-AHN/MCL pool.

Pleural effusion was seen in 18 patients (13%) of which 8 patients (4%) had pleural effusion grade 3/4. Interstitial lung disease was reported in 5 patients (3.5%), of which 1 was suspected to be treatment-related.

Skin toxicities were observed in ASM/SM-AHN/MCL patients with 4 cases (2.8%) of grade 3 toxic skin eruption and 1 grade 2 erythema multiforme.

QT prolongation-related adverse events were reported in 16.2% of patients. An increase from baseline with > 30 msec was observed in 46 (36%) of the patients and of > 60 msec in 8 (6.3%) patients.

AEs related to study drug were reported in 133 (93.7%) patients. The most commonly occurring AEs suspected to be study drug related were gastrointestinal-related (nausea, vomiting diarrhoea), and the majority of those were grade 1 or 2 in severity.

The most frequent ADRs were nausea (82%), vomiting (68%), diarrhoea (51%), peripheral oedema (35%) and fatigue (31%). The most frequent Grade 3/4 ADRs were fatigue (8.5%), sepsis (7.7%), pneumonia (7%), febrile neutropenia (7%), and diarrhoea (6.3%). The most frequent non haematological laboratory abnormalities were hyperglycaemia (93.7%), total bilirubin increased (40.1%), lipase increased (39.4%), aspartate aminotransferase (AST) increased (33.8%), and alanine aminotransferase (ALT) increased (33.1%), while the most frequent haematological laboratory abnormalities were absolute lymphocyte count decreased (73.2%) and ANC decreased (58.5%) (SmPC, section 4.8).

Serious ADRs occurred at similar rates in patients in the Rydapt versus the placebo arm. The most frequent serious ADR in both arms was febrile neutropenia (16%) (SmPC, section 4.8).

In the pooled safety dataset there were 26 (18%) on-treatment deaths reported. While no clear pattern in the cause of the on-treatment deaths was noted, 5 were due to cardiac disorders (2 cardiac arrest, 1 disorder, 1 failure and 1 congestive failure). This seems rather high, but given the age of the patients, the absence of a control group and variability in the type of cardiac disorders no definitive conclusions can be drawn from the provided data.

The most frequent Grade 3/4 laboratory abnormalities were absolute lymphocyte count decreased (45.8%), ANC decreased (26.8%), hyperglycaemia (19%), and lipase increased (17.6%) (SmPC, section 4.8).

The safety data collected in the ASM/SM-AHN/MCL population is of limited value for assessment of possible effects of midostaurin on haematological parameters because of the uncontrolled nature of the trial and the fact that the disease is accompanied by haematological abnormalities. Of note, during study D2201, 59 of 116 patients received RBC transfusions, 27 of which did not have transfusion-dependent anaemia at baseline. Platelet transfusions were given to 17 patients. However, it cannot be determined whether this increase in transfusion-dependent subjects is caused by midostaurin or due to progressive disease. In addition, newly occurring and worsening biochemistry abnormalities were commonly seen, but most were mild in severity. The most commonly reported biochemistry abnormality was glucose increased (all grades: 79.6% of patients; grade 3 and 4 : 18.6%). An additional analysis was made using the broad Pancreatitis SMQ to identify potential cass of pancreatitis by looking for patients in whom an event of lab abnormality and a clinical symptom indicative of pancreatits occurred within the time frame of 1 days. Several cases were found with events that may be seen as indicative for pancreatitis (lab abnormality + at least clinical symptom) (10 from ASM trials and 19 in Novartis Argus safety database). Importantly, none of these cases were diagnosed as pancreatitis. In addition a search of the Novartis Argus safety database revealed 8 cases with a diagnosis of acute pancreatitis/pancreatitis. Only in 1 case of pancreatitis a relationship to midostaurin treatment was suspected. Overall, in the absence of a plausible mechanism supporting a causal relationship between midostaurin treatment and pancreatitis, and with only 1 case of a suspected relationship, it is agreed that thus far the data are not indicative of a causal relationship between midostaurin and pancreatitis.

Dose modifications (interruption or adjustment) due to ADRs occurred in 31% of patients. The most frequent ADRs that led to dose modification (incidence ≥5%) were nausea and vomiting (SmPC, section 4.8).

ADRs that led to treatment discontinuation occurred in 9.2% of patients. The most frequent (incidence ≥1%) were febrile neutropenia, nausea, vomiting and pleural effusion (SmPC, section 4.8).

The number of patients who experienced AEs and SAEs were generally similar in patients < 60 years and patients ≥ 60 years. Results were similar in patients < 65 years (n=78 patients) and ≥ 65 years of age (n=64 patients). Also in this population an increased mortality in the elderly (>65 years) is noted.

The frequency of SAEs, grade 3/4 AEs and AEs leading to discontinuation were higher in males. Vomiting and nausea were more commonly reported in females, as were tremor, blood alkaline phosphatase increased, urinary tract infection, flushing, and back pain. Anaemia, peripheral oedema, rash and insomnia were more commonly reported in males. Of note, median exposure in females was higher than in males which may partly explain the increased AEs seen in females.

There were no apparent differences in AE profile in populations with different ECOG status (ECOG 0-1 vs ≥2) in the AML population. Among patients with normal vs those with mild hepatic impairment, apart from a somewhat higher frequency of SAEs in the hepatic impaired (65% vs. 78%), no major differences were observed in the proportion of patients with AEs, deaths, AEs leading to discontinuation or dose reduction/interruption.

Safety on both indications
Neutropenia has occurred in patients receiving Rydapt as monotherapy and in combination with chemotherapy. Severe neutropenia (ANC <0.5 x 10^9/l) was generally reversible by withholding Rydapt until recovery and discontinuation in the ASM, SM-AHN and MCL studies. White blood cell counts (WBCs) should be monitored regularly, especially at treatment initiation. In patients who develop unexplained severe neutropenia, treatment with Rydapt should be interrupted until ANC is ≥1.0 x 10^9/l. Rydapt should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to Rydapt (SmPC, section 4.4).

All AML patients in study A2301 reported leukopenia-related events and all were grade 3/4 in severity. The most commonly occurring were neutrophil count decreased (96.5% vs 97.8%) and febrile neutropenia (83.4% vs 80.5%). There was no discernible difference in the incidence of leukopenia-related events including neutropenia (grade 4) or in the time to resolution between midostaurin and placebo treatment groups. Leukopenia-related events were reported in 32 (22.5%) ASM/SM-AHN/MCL patients. Leukopenia has been categorized as identified risk (see Risk Management Plan).

Because of the observed neutropenia and leukopenia, any active serious infection should be under control prior to starting treatment with Rydapt monotherapy. Patients should be monitored for signs and symptoms of infection, including any device-related infections, and if a diagnosis of infection is made appropriate treatment must be instituted promptly, including, as needed, the discontinuation of Rydapt (SmPC, section 4.4). Severe infections have been categorized as identified risks (see Risk Management Plan).

Patients with symptomatic congestive heart failure were excluded from clinical studies. In the ASM, SM-AHN and MCL studies cardiac dysfunction such as congestive heart failure (CHF) (including some fatalities) and transient decreases in left ventricular ejection fraction (LVEF) occurred. In the randomised AML study no difference in CHF was observed between the Rydapt + chemotherapy and placebo + chemotherapy arms. In patients at risk, Rydapt should be used with caution and the patient closely monitored by assessing LVEF

when clinically indicated (at baseline and during treatment) (SmPC, section 4.4). Cardiac dysfunction has been categorized as potential risk (see Risk Management Plan).

An increased frequency of QTc prolongation was noted in midostaurin–treated patients (see section 4.8), however, a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by ECG should be considered if Rydapt is taken concurrently with medicinal products that can prolong QT interval (SmPC, section 4.4).

Interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in patients treated with Rydapt monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis and Rydapt discontinued in patients who experience pulmonary symptoms indicative of ILD or pneumonitis that are ≥Grade 3 (NCI CTCAE) (SmPC, section 4.4). Pulmonary toxicity (including pleural effusion and interstitial lung disease) has been categorized as identified risk (see Risk Management Plan).

Caution is warranted when considering the administration of midostaurin in patients with severe hepatic impairment and patients should be carefully monitored for toxicity (SmPC, section 4.4). Use of midostaurin in patients with severe hepatic impairment is classified as missing information in the risk management plan.

Caution is warranted when considering the administration of midostaurin in patients with severe renal impairment or end-stage renal disease and patients should be carefully monitored for toxicity (SmPC, section 4.4).

Rydapt contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea. A 100 mg dose of Rydapt contains approximately 14 vol. % ethanol anhydrous, which corresponds to 333 mg alcohol. This is equivalent to 8.4 ml beer or 3.5 ml wine. Alcohol may be harmful in patients with alcohol-related problems, epilepsy or liver problems or during pregnancy or breast-feeding (SmPC, section 4.4).

The safety of Rydapt in children and adolescents below 18 years has not been established (section 4.2). This has been adequately reflected in the SmPC and is reflected in the Risk Management Plan.

In AML patients the incidence of any grade skin toxicities was similar in the treatment groups except for grade 3/4 skin toxicities which were reported at a higher incidence in the midostaurin arm than in the placebo arm (overall:14.0% midostaurin vs. 7.2% placebo; dermatitis exfoliative: 10.9% vs 4.1%). In 4 patients in the midostaurin group skin toxicity was reported as an AE leading to treatment discontinuation. Sporadic cases of skin toxicity were observed in ASM/SM-AHN/MCL patients with 4 cases of grade 3 toxic skin eruption and 1 grade 2 erythema multiforme. In supportive studies skin-related events were also commonly reported. No case of severe or fatal skin toxicity (e.g. Stevens-Johnsons syndrome) was reported across the midostaurin studies. A cumulative search for photosensitivity reports in the Novartis Safety Database (ARGUS) with a data lock of 16-April-2017 and using the MedDRA (version 19.1) HLT "Photosensitivity and photodermatosis conditions" revealed a total of 11 cases. The limited data that was available suggested confounding by multiple co-suspect drugs known to cause photosensitivity (providing alternative causal factors), had an unreasonable time-to-onset making a causal relationship unlikely, or had a prior history of photosensitivity indicating other unknown causal factors.

With regard to basal cell carcinoma (BCC), the review of the eight reports did not justify the addition of BCC to the label or the RMP considering confounding factors; two patients had prior history of BCC; one had prior radiotherapy, which was a more likely trigger for the reported event of Bowen's disease. Two patients presented with BCC more than two years after the last dose of midostaurin, and among the remaining three

poorly documented cases one was not suspected to be related to midostaurin and the remaining two were too poorly documented to be assessed properly.

Overall it is considered that the addition of photosensitivity or basal cell carcinoma to the label/ RMP is not warranted at this time.

Strong CYP3A4 inhibitors increase exposure of midostaurin (see discussion on clinical pharmacology). In A2301, up to 62% of the patients received midostaurin concomitantly with strong inhibitors of CYP3A4 in the induction phase. Comparison of the AE profile in the midostaurin arm of subjects known to have concomitant treatment with a strong CYP3A4 inhibitor (n=170) with that of subjects who did not (n=59), showed that the frequencies of grade 3/4 pneumonia, sepsis, febrile neutropenia, and infections were all increased in patients treated concomitantly with CYP3A4 inhibitors. Analysis, of patients who were treated and those were not treated with strong CYP3A4 inhibitors for both treatment arms indicated that also in the placebo group the frequency of infections is increased in the placebo group treated with strong CYP3A4 inhibitors when compared to those not receiving CYP3A4 inhibitors, albeit that the difference is a bit less than what is seen in the midostaurin group. Drug-drug interactions with strong CYP3A4 inhibitors and drug-drug interactions with strong CYP3A4 inducers have been categorized as identified risks (see Risk Management Plan).

Reported experience with overdose in humans is very limited. Single doses of up to 600 mg have been given with acceptable acute tolerability. Adverse reactions observed were diarrhoea, abdominal pain and vomiting.

There is no known specific antidote for midostaurin. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated (SmPC, section 4.9).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of midostaurin is manageable with gastrointestinal and haematological toxicity being the most common observed toxicity.

2.7. Risk Management Plan

Safety concerns

Table 106 Summary of the Safety Concerns

Important identified risks	Leukopenia
	Severe infections
	Pulmonary toxicity (including pleural effusion and interstitial lung disease)
	Drug-drug interactions with strong CYP3A4 inhibitors
	Drug-drug interactions with strong CYP3A4 inducers
Important potential risks	Cardiac dysfunction
	Reproductive and developmental toxicity
	Use during lactation
	Effect of genomic polymorphisms of CYP3A4/CYP3A5 on

Important identified risks	Leukopenia
	Severe infections
	Pulmonary toxicity (including pleural effusion and interstitial lung disease)
	Drug-drug interactions with strong CYP3A4 inhibitors
	Drug-drug interactions with strong CYP3A4 inducers
	pharmacokinetics of midostaurin and potential risk of treatment-related toxicity
	Drug-drug interactions with OATP1B1, P-gp, BCRP and BSEP transporter substrates
	Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and oral contraceptives
Missing information	Use in pediatric population
	Use in patients with severe hepatic impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
PKC412E2301 is a Phase III trial currently under preparation in newly diagnosed AML patients with wild-type FLT3. Additional pharmacogenetics samples will be collected in a subset of patients in this study to inform on the impact of CYP3A4 and CYP3A5 polymorphism on the exposure of midostaurin, CGP52421 and CGP62221 and on treatment-related toxicity. Category 3	To determine the impact of CYP3A4 and CYP3A5 polymorphisms on the exposure of midostaurin, and on treatment-related toxicity.	Effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2019 (planned)
Study to determine the impact of a single dose of midostaurin on the PK of substrates of the transporters P-gp and BCRP. Category 3	To assess the impact of a single dose of midostaurin on the PK of substrates of P-gp and BCRP transporters.	Drug-drug interactions with OATP1B1, P-gp and BCRP and BSEP transporter substrates	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2019 (planned)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
Addition of a sensitive substrate of CYP2D6 to evaluate the inhibitory effect of midostaurin in a single dose study Category 3	To assess the inhibitory effect of a single dose of midostaurin on the PK of a single dose of a CYP2D6 substrates	Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9 CYP2C19 and oral contraceptives	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2019 (planned)
To study the impact of midostaurin on the PK of a cocktail of CYP2B6, CYP2C8 and CYP3A4 substrates. Category 3	To assess the impact of multiple doses of midostaurin on the PK of a single dose of a cocktail of CYP2B6, CYP2C8 and CYP3A4 substrates.	Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and oral contraceptives	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2020 (planned)
Impact of midostaurin on oral contraceptives Category 3	To assess the impact of midostaurin on the PK of a single dose of oral contracep-tives after 28 days of treatment	Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and oral contraceptives	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2020 (planned)
Impact of midostaurin on the PK of a substrate of OATP1B1 transporters based on dynamic modeling of the steady-state concentrations of midostaurin, CGP52421 and CGP62221 Category 3	To assess the impact of steady-state midostaurin on the PK of a single dose of substrates of OATP1B1 transporter.	Drug-drug interactions with OATP1B1, P-gp and BCRP and BSEP transporter substrates	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2020 (planned)
PKC412A2116 An open label, multiple dose study to evaluate	To evaluate the PK of midostaurin in subjects with mild,	Use in patients with severe hepatic	Ongoing	Final study report: Jun-2020

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
the PK of midostaurin in subjects with mild, moderate and severe hepatic impairment compared to matched healthy subjects. Category 3	moderate and severe hepatic impairment compared to matched healthy subjects.	impairment		(planned)
PK data on the impact of midostaurin, CGP62221 and CGP52421 on BSEP in-vitro Category 3	To assess the impact of midostaurin, CGP62221 and CGP52421 on BSEP in-vitro	Drug-drug interactions with OATP1B1, P-gp and BCRP and BSEP transporter substrates	Planned Protocol submission: 6 months after approval of MA	Final study report: Dec-2017 (planned)

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 107 Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Leukopenia	This item is appropriately communicated through current labeling in: SmPC Section 4.8 Undesirable effects Relevant preferred terms are included as ADRs in SmPC Section 4.8, Undesirable effects	None.
Severe Infections	This item is appropriately communicated through current labeling in: SmPC Section 4.4 Special warnings and precautions for use Relevant preferred terms are included as ADRs in SmPC Section 4.8, Undesirable effects	None.
Pulmonary toxicity (including pleural effusion and interstitial lung disease)	This item is appropriately communicated through current labeling in: SmPC Section 4.4 Special warnings and precautions for use	None.
Drug-drug interactions with strong CYP3A4	This item is appropriately communicated through current	None.

Safety concern	Routine risk minimization measures	Additional risk minimizatio n measures
inhibitors	labeling in: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction	
Drug-drug interactions with strong CYP3A4 inducers	This item is appropriately communicated through current labeling in: SmPC Section 4.3, Contraindications SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction	None.
Cardiac dysfunction	This item is appropriately communicated through current labeling in: SmPC Section 4.4 Special warnings and precautions for use	None.
Reproductive and developmental toxicity	This item is appropriately communicated through current labeling in: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.6 Fertility, pregnancy and lactation	None.
Use during lactation	This item is appropriately communicated through current labeling in: SmPC Section 4.6 Fertility, pregnancy and lactation	None
Effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity	Prescription only medicine, should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products	None
Drug-drug interactions with OATP1B1, P-gp, BCRP and BSEP transporter substrates	This item is appropriately communicated through current labeling in: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 5.2 Pharmacokinetic properties	None.
Drug-drug interactions with substrates for CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and oral contraceptives	This item is appropriately communicated through current labeling in: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 5.2 Pharmacokinetic properties	None.
Use in pediatric population	This item is appropriately communicated through current labeling in: SmPC Section 4.2, Posology and method of administration SmPC Section 5.1 Pharmacodynamic properties	None.

Safety concern	Routine risk minimization measures	Additional risk minimizatio n measures
	SmPC Section 5.2 Pharmacokinetic properties	
Use in patients with severe hepatic impairment	This item is appropriately communicated through current labeling in:	None.
	SmPC section 4.2 Posology and method of administration	
	SmPC section 4.4 Special warnings and precautions for use	
	SmPC Section 5.2 Pharmacokinetic properties	

Public summary of the RMP

The public summary of the RMP does not require revision.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5, dated 20 July 2017, is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.04.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant compared the structure of midostaurin with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers midostaurin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rydapt (midostaurin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indications are as follows:

- Midostaurin is indicated in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy and for patients in complete response followed by Rydapt single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive

- Midostaurin is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

3.1.2. Available therapies and unmet medical need

FLT3 positive AML

Standard of care therapy of AML has not changed substantially in the past 30 years and consists of a combination of an anthracycline and continuous-infusion of cytarabine in the classic '3+7' regimen, i.e., 3 days of intravenous administration of an anthracycline combined with 7 days of continuous intravenous cytarabine as induction chemotherapy, followed by consolidation therapy with intermediate or high-dose cytarabine-based chemotherapy, and/or stem cell transplantation, depending on risk group. Despite the currently available treatment options, around 60% of adult AML patients who are 60 years of age or younger

and 90% of patients who are older than 60 years of age are not cured with available treatment options. Therefore, there is a need for new treatment options in patients with AML.

ASM / SM-AHN / MCL

Patients with ASM, SM-AHN, or MCL have limited treatment options, and to date there are no approved therapies in the EU for ASM, SM-AHN, or MCL. However, there are several therapies available which are considered standard and are commonly used in clinical practice. In addition to therapies intended to control MC mediator-related symptoms (including histamine antagonists, corticosteroids, proton-pump inhibitors, and sodium cromolyn), cytoreductive therapy with either interferon-α (often considered first-line cytoreductive therapy in ASM/SM-AHN/MCL) or cladribine (often considered second-line cytoreductive therapy in ASM/SM-AHN/MCL) are used in clinical practice in order to reduce symptoms and with the aim to prolong survival. Despite these available treatment options, response is limited to 30-60% of the patients. Patients with ASM, SM-AHN, or MCL have a shortened survival (median survival 3.5 years in patients with ASM, 2 years in SM-AHN, and ~6 months in MCL), indicating that there is a need for new treatment options in patients with ASM/SM-AHN/MCL.

3.1.3. Main clinical studies

The clinical package of midostaurin for the AML indication was primarily supported by data from a randomised phase III study (A2301) of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy + midostaurin (N=294) or placebo (N=269) in newly diagnosed patients younger than 60 years of age with FLT3-mutated AML.

The main study for the ASM/SM-AHN/MCL indication was study D2201, a single arm, phase II, open-label study designed to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients (N=116) with ASM or MCL with or without an AHNMD.

3.2. Favourable effects

FLT3 positive AML

In study A2301 the addition of midostaurin to standard induction and consolidation chemotherapy significantly improved OS for the overall studied population: HR 0.774 (95%CI: 0.629-0.953, p=0.0078), corresponding to a relative risk reduction of 23% in favour of midostaurin. In an updated analysis of OS with 15 months additional follow-up, the HR was 0.79 (95%CI: 0.64-0.97), p=0.011. At around 24-30 months OS curves reached a plateau with roughly 10% difference in survival rates between the curves. Subgroup analyses showed a consistent OS benefit across most investigated subgroups, including FLT3-high and low ITD/TKD allelic ratio with the exception of the gender subgroup.

In terms of secondary endpoints, the median EFS was significantly longer for patients in the midostaurin arm compared to patients in the placebo arm (8.2 vs. 3.0 months) with a HR = 0.784 (95%CI: 0.662-0.930, p=0.0024). Subgroup analyses showed a consistent EFS benefit across most investigated subgroups, including according to gender (females: HR 0.81, 95%CI: 0.65-1.02; males: HR 0.79, 95%CI: 0.61-1.03).

Subgroup analyses in patients with known NPM1 status showed that OS benefit from midostaurin occurred in all subgroups of patients according to NPM1 status: NPM1 mutated, HR 0.72 (95%CI: 0.52-1.01); NPM1 wildtype, HR 0.74 (95%CI: 0.54-1.03). Subgroup analyses according to age on efficacy outcomes showed that the effect of midostaurin on CR, EFS and DFS was rather similar across the different age categories.

Sensitivity analyses for OS and EFS in the ITT population in which patients receiving SCT were censored showed a consistent treatment effect in line with the primary analysis.

The secondary endpoint DFS was also consistent with the primary endpoint (HR 0.71, 95%CI: 0.55-0.92; p=0.0051) and complete response rate was numerically but not significantly higher in the midostaurin arm (58.9% vs. 53.5%, one sided p=0.073).

Analyses of exposure-response relationships showed a trend towards increased risk of death with lower exposure to midostaurin (HR 1.18, 95%CI: 0.98-1.43, p=0.083) and a significantly increased risk of death with lower exposure to the metabolite CGP2221 (HR 1.37, 95%CI: 1.08-1.74, p=0.009).

ASM / SM-AHN / MCL

In the main study D2201, midostaurin conferred an ORR of 59.6% (95%CI: 48.6-69.8; p<0.001) assessed by the SSC and based on modified Valent/Cheson criteria, with 45% of the patients achieving a major response, and 15% of the patients achieving a partial response. There were no complete responses.

Subgroup analyses showed similar response rates (ORR according to modified Valent/Cheson criteria) in patients with ASM/SM-AHN (61.6%, 95%CI: 49.5-72.8) and MCL (50%, 95%CI: 24.7-75.3). In KIT mutation positive patients the response rate was higher than in KIT mutation negative patients (63.0% for KIT positive, n=73; versus 43.8% for KIT negative or unknown, n=16 of which 2 unknown).

Sensitivity analyses on ORR resulted in ORR values between 28% (ORR according to IWG-MRT-ECNM IWG criteria) and 65% (ORR in the PEP including late responders).

The results of the overall ORR based on the most recent response criteria (IWG-MRT-ECNM criteria, 2013) was 28.3% (with 32/113 patients having a response of CR, PR, or CI), and 60.0%, 20.8% and 33.3%, respectively, in patients with ASM, SM-AHNMD, and MCL.

Median DOR according to IWG-MRT-ECNM criteria was 36.8 months (95%CI: 20.5-NE). In addition, responses to midostaurin treatment were most durable among patients who achieved a CR or PR (median not reached, 95%CI: 27.0-NE), and were less durable in patients with 'clinical improvement' alone (23.5 months, 95%CI: 10.9-36.8). Thus, the magnitude of response was correlated with duration of response.

An ORR analysis in subgroups of patients with and without KIT mutations based on IWG-MRT-ECNM criteria showed that activity of midostaurin is observed in both subgroups, with an ORR of 23% (3/13) in KIT-wild type patients vs. 39% (38/97) in KIT-mutated patients. Overall survival was 26.8 months (95%CI: 17.6-34.7). OS differed between patients with KIT positive disease (33.9 months) versus KIT negative disease (7.8 months).

Mast cell improvement (≥ 50%) was seen in 16/89 patients (18%). Serum tryptase reductions (>50% decrease relative to baseline) were seen in 58% of the patients. In 27% of the patients a best decrease in spleen volume of at least 35% was seen.

A ≥ 50% decrease in TMSAS score (symptom burden) for at least 168 days was seen in 20 out of 52 patients in whom TMSAS score was measured (38%).

3.3. Uncertainties and limitations about favourable effects

There is limited experience in patients ≥ 60 years of age. However, the preliminary findings of the supportive study ADE02T indicated a beneficial effect also in this population. Based on the similar disease biology

between the age subgroups, the results of several post-hoc analyses of the pivotal study, the results of the supportive study and the safety profile of patients ≥ 60 years of age it was concluded that the observed survival benefit in the population of the pivotal study (<60 years of age) can be extrapolated to the ≥ 60 years of age population. The results from on-going and planned studies will further quantify the OS benefit of midostaurin in midostaurin in patients ≥ 60 years of age (see discussion on clinical efficacy and section 4).

A difference in treatment effect was observed in the pre-defined subgroups according to gender, with the large group of females found to have no OS benefit by addition of midostaurin to chemotherapy in study A2301. Although a gender difference has not consistently been observed in previous studies in newly diagnosed AML, study A2301 is not the first study reporting a (potential) difference in gender which somewhat alleviates the concern regarding the lack of internal consistency. As it is likely that SCT has substantially contributed to this apparent gender effect, it is important to note that censoring for SCT (sensitivity analysis) in the ITT population (HR 0.75, 95%CI: 0.54 to 1.03) confirmed the observed OS benefit conferred by midostaurin in the overall population observed in the primary analysis (HR 0.774, 95% CI: 0.629 to 0.953). This, combined with the fact that for females a benefit of treatment was seen in the secondary endpoints EFS, CR and CIR, there is sufficient evidence of benefit and no safety signal to collectively outweigh the uncertainty on the effect size and concern regarding the internal consistently. In the SmpC it is highlighted that in a subgroup analysis, no apparent OS benefit was observed in females, however, a treatment benefit was observed in females in all secondary efficacy endpoints.

The uncertainties that were identified during the assessment for the ASM / SM-AHN / MCL indication, primary analyses of ORR, the absence of comparative efficacy data and the initially proposed indication were satisfactorily addressed (see discussion on clinical efficacy).

3.4. Unfavourable effects

FLT3 positive AML

Gastrointestinal (GI) events were among the most commonly reported AEs (diarrhoea, nausea and vomiting occurred in >55% of the patients). The incidences of nausea, vomiting and stomatitis of any grade were slightly higher in the midostaurin group compared to placebo group (nausea: 83.4% vs 70.4%; vomiting 60.3% vs 52.7%, stomatitis 19% vs 12% (NNA sites only). Grade 3/4 AEs occurring more frequently (>5%) in the midostaurin group than in the placebo group at all sites included exfoliative dermatitis (14% vs 8%) and device-related infections (16% vs 10%).

Regarding haematological toxicitiy, the most frequent treatment-related grade 3/4 AEs were decreased platelet counts (60%), neutrophil counts (61%), haemoglobin (54%), and febrile neutropenia (44%), and these occurred at similar frequencies in both treatment groups.

Approximately half of all patients experienced a SAE with similar incidences in the midostaurin and placebo group for most SAEs, except for grade 3/4 exfoliative dermatitis (10 vs 1 patients), grade 3/4 hypotension (10 vs 1 patients) and device-related infections (23 vs 13 patients) which were reported more often in the midostaurin group.

QTc abnormalities were seen in both treatment arms; an increase of >30 msec was seen in 115 patients (44%) and 93 patients (40%) in the midostaurin and placebo arms, respectively, and an increase of >60 msec was observed in 48 patients (18%) and 25 patients (11%) in the midostaurin and placebo arms, respectively. The frequency of >60 msec increase in QTc interval during the continuation phase (when

midostaurin is administered as monotherapy) was 9.3% vs. 1.5%, for the midostaurin and placebo arms, respectively.

A total of 36 patients died on treatment: 15 patients (4.3%) in the midostaurin group and 21 patients (6.3%) in the placebo group. Of these on-treatment deaths, 16 deaths were suspected to be related to study drug (9 patients (2.6%) in the midostaurin arm and 7 patients (2.1%) in the placebo group). In the midostaurin treatment arm there was one case of cardiac arrest and 2 patients for whom QTc > 450 msec was recorded (1 patient died due to myocardial infarction, the other patient due to colitis).

ASM / SM-AHN / MCL

All patients had at least 1 AE of any grade regardless of causality. The most frequently reported AEs in the pooled dataset were those related to GI toxicity (nausea, vomiting, diarrhoea), infections, and myelosuppression (anaemia, thrombocytopenia, neutropenia). Other frequent AEs (occurring in >25% of patients) were peripheral oedema, fatigue, pyrexia, and headache. The most frequent grade 3-4 AEs were those related to myelosuppression (anaemia, thrombocytopenia and neutropenia).

AEs related to study drug were reported in 133 patients (93.7%). The most commonly occurring AEs suspected to be study drug-related were gastrointestinal-related (nausea, vomiting, diarrhoea), and the majority of these were grade 1 or 2 in severity.

In the pooled dataset, 68.3% of the patients had an SAE; the events were mostly grade 3 or 4 (62.7%). Infections were among the most commonly reported SAEs (pneumonia: 7%, sepsis: 7%, and urinary tract infection: 4.2%). GI events were reported in 23.9% of patients overall (gastrointestinal haemorrhage: 4.2%, upper gastrointestinal haemorrhage: 4.2%, diarrhoea: 5.6%, and vomiting: 4.2%). Haematological events most commonly reported were febrile neutropenia (4.9%) and anaemia (4.2%).

In the pooled safety dataset there were 26 (18%) on-treatment deaths reported with 5 (3.5% of pooled population) due to cardiac disorders (2 cardiac arrest, 1 cardiac disorder, 1 heart failure and 1 congestive heart failure).

Left ventricular ejection fraction was monitored for 64 patients during treatment. LVEF changes over time showed that around month 3 there was a decrease in the mean LVEF, and 3 patients had clear LVEF reductions compared to baseline: in 1 patient an LVEF of 50% decreased to 41%, in another patient 65% decreased to 49%, and for third patient a decrease from 60% to 45% was seen.

The most frequent reasons for discontinuation of study drug in the ASM/SM-AHN/MCL safety pool were disease progression (n=50, 35%) and AEs (n=32, 23%). Death was the primary reason for discontinuation in 9 patients (6%). Of these 9 deaths, for 6 patients death was considered to be due to adverse events.

In study A2301, 62% of the patients received midostaurin concomitantly with strong inhibitors of CYP3A4. Comparison of the AE profile in 214 patients known to have had concomitant treatment with a strong CYP3A4 inhibitor with 131 patients who did not, showed that the frequencies of grade 3/4 pneumonia (15.4% vs 9.2%), sepsis (9.3% vs 3.1%), febrile neutropenia (85.5% vs 79.4%) and infections (5.1% vs 0.8%) were all increased in patients treated concomitantly with CYP3A4 inhibitors. However, also in the placebo group the frequency of these AEs was increased in patients treated with strong CYP3A4 inhibitors, indicating that confounding by indication resulted in the higher frequency of AEs in patients treated with strong CYP3A4 inhibitors (albeit that the differences in frequencies of AEs in the placebo group were somewhat less than in the midostaurin group).

3.5. Uncertainties and limitations about unfavourable effects

The apparent midostaurin-related increase in QT prolongation events and in a >60ms shift from baseline QTc values in terms of exposure/dose-effect relationships has not been explained. QT prolongation (mainly) occurred in the presence of other confounding factors (concomitant medication and/or e.g. electrolyte imbalances). While it may be unlikely that midostaurin treatment on its own has the potential to induce QT prolongation, a possible contribution of midostaurin to QT prolongation in patients at risk for this event cannot be excluded. Therefore caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances) and interval assessments of QT by ECG should be considered if midostaurin is taken concurrently with medicinal products that can prolong QT interval. These have been adequately reflected in the SmPC (see section 4.2, 4.4, and 5.1) and are reflected in the Risk Management Plan.

Data on potential drug-drug interactions was limited. Midostaurin and metabolites are mainly substrate for CYP3A4, and large differences in exposure to midostaurin and metabolites have been observed upon concomitant administration of strong CYP3A4 inhibitors/inducers. Based on the discussion of clinical consequence of the co-medication with strong 3A4 inhibitors and inducers, warnings on using inhibitors have been added in the SmPC, and using strong 3A4 inducers has been contra-indicated. The available PK data indicated that the risk of midostaurin affecting other drugs due to induction of CYP enzymes is high (including induction of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2B6), and is thus likely to affect the efficacy of many co-medications. A number of planned studies will be conducted by the applicant in order to address this safety concern (see Risk Management Plan).

3.6. Effects Table

Table 108 Effects Table for midostaurin in acute myeloid leukaemia (Study A2301, cut-off date: 1 April 2015)

Effect	Short Description	Unit	Midostaurin	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Acute myeloid Leukaemia						
OS (non-censored for SCT)	Median time from randomisation until death by any cause	months	74.7 (31.5, NE)	25.6 (18.6, 42.9)	Benefit in elderly (>60 years) Benefit in females	See ''clinical efficacy'' section
EFS	Median time between randomisation and the date of event/censoring	months	8.2 (5.4, 10.7)	3.0 (1.9, 5.9)		
DFS	Median time of first CR to relapse or death from any cause, whichever occurred first	months	26.7 (19.4, NE)	15.5 (11.3, 23.5)		

Effect	Short Description	Unit	Midostaurin	Placebo	Uncertainties/ Strength of evidence	References
CR	Complete remission rate	%	58.9	53.5		
Unfavourable Effects						
ADRs	Grade 3-4	%	78	75.2		See ''clinical safety section''
QTc prolongation	Proportion of patients with > 60 msec increase	%	18.4	10.7	QTc effects seen in both AML AND ASM/SM-AHN/MCL studies	
Device related infection	Grade 3-4	%	16.2	10.1		
Nausea	Grade 3-4	%	5.8	10.1	Nausea all grades was reported in 83.4% in midostaurin group vs 70.4 % in the placebo group	
Vomiting	Grade 3-4	%	2.9	4.5		

Abbreviations: CR = complete response; DFS = disease-free survival; DOR = duration of response; EFS = event-free survival; HR = hazard ratio; IWG = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MO = major objection; ORR = overall response rate; OS = overall survival

Table 109 Effects Table for midostaurin in ASM / SM-AHN / MCL: (Study D2201, cut-off date: 1 December 2014)

Effect	Short Description	Unit	Midostaurin	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR (modified Valent/Cheson criteria)	Proportion of patients with a best response of MR or PR	%	59.6	-		See ''clinical efficacy'' section
ORR (IWG criteria)	ORR according to IWG criteria	%	28.3	-		
DOR (IWG criteria)	Median time from the first confirmed response until the date of first confirmed PD or death due to ASM or MCL	months	NE (27.0-NE)	-		

Effect	Short Description	Unit	Midostaurin	Placebo	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
ADRs	Grade 3-4	%	93.1			See ''clinical safety section
QTc prolongation	Proportion of patients with > 60 msec increase	%	6.3	-	QTc effects seen in both AML AND ASM/SM-AHN/MCL studies	
Neutropenia	Grade 3-4	%	5.2	-		
leukopenia	Grade 3-4	%	4.3	-		
Nausea	Grade 3-4	%	6.0	-	Relationship to treatment plausible	
Vomiting	Grade 3-4	%	6.0	-		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FLT3 positive AML

The pivotal study convincingly demonstrated that addition of midostaurin to standard of care induction, consolidation chemotherapy followed by maintenance in newly diagnosed patients with *FLT3* positive AML was associated with OS benefit, with an overall reduction in the risk of death of 23%. The higher plateau in the EFS and OS Kaplan-Meier curves suggested that addition of midostaurin lead to a higher proportion of the patients having long-term benefit. The effect of midostaurin on outcome is considered clinically relevant, and addition of midostaurin to chemotherapy is considered to be a therapeutic advantage compared to available standard of care therapy. All secondary endpoints are in support of the observed OS benefit, with a strong degree of statistical significance, and the treatment effect is therefore considered robustly demonstrated.

Although the safety evaluation of midostaurin is complicated by the administration of concomitant chemotherapy (AML) overall, the safety profile of midostaurin is relatively well characterised.

ASM / SM-AHN / MCL:

In the updated ORR analysis according to the more recent and more clinically relevant IWG-MRT-ECNM criteriathe overall ORR was 28.3% (with 32/113 patients having a response of CR, PR, or CI), and 60.0%, 20.8% and 33.3%, respectively, in patients with ASM, SM-AHNMD, and MCL. The magnitude of response was correlated with duration of response and this is considered a clinical benefit in terms of delaying worsening of the disease. Overall, quality of life data and OS data did not highlight any potential detriment, albeit based on indirect comparisons.

The safety evaluation of midostaurin is complicated by the lack of a control arm (ASM/SM-AHN/MCL) and/or the underlying condition (ASM/SM-AHN/MCL), however, overall, the safety profile of midostaurin is relatively well characterised.

3.7.2. Balance of benefits and risks

FLT3 positive AML

Given the poor prognosis of patients with AML, the treatment effect of midostaurin is considered clinically relevant, and has been robustly demonstrated in the overall population in the single pivotal study that was submitted. The safety profile of midostaurin was manageable and is acceptable in view of the therapeutic context and given the observed benefits.

ASM / SM-AHN / MCL

It is considered that the ORR analyses submitted based on IWG-MRT-ECNM criteria provided compeling evidence for the efficacy of midostaurin and demonstrated that midostaurin provides clinical benefit to patients who achieve a treatment response. The safety profile of midostaurin in ASM/SM-AHN/MCL is acceptable in view of the severity of the disease and the benefits observed.

The lack of comparative data is unfortunate but understandable given the specific circumstances which pertain to the extreme rarity of the diseases and the great unmet medical need in systemic mastocytosis patients. Midostaurin conferred durable responses, and the responses were further corroborated by durable reductions in bone marrow mast cell burden). For other available therapies such as interferon-α and cladribine, the historical evidence for efficacy is much weaker and comes mostly from retrospective investigations (and some small single-arm studies).

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Rydapt is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Rydapt is not similar to Ceplene, Vidaza and Dacogen within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Rydapt is favourable in the following indication:

- in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive (see section 4.2);

- as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

Description	Due date
PAES: In order to investigate the efficacy in elderly patients, the MAH should submit the final results of a phase II ADE02T study of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single agent maintenance in patients aged 18-70 with FLT3 ITD mutated AML	Final CSR: September 2021
PAES: In order to investigate the efficacy in elderly patients, the MAH should conduct and submit the results of A2408, a study to assess the efficacy and safety of midostaurin in combination with standard chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients (aged ≥18 years) with newly diagnosed FLT3-mutated AML	Final CSR: December 2022
PAES: In order to investigate the efficacy in elderly patients, the MAH should conduct and submit the results of a randomised, double-blind E2301 study of midostaurin versus placebo in combination with chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients (aged ≥18 years) with newly diagnosed AML, without FLT3 mutation. The protocol includes a comprehensive collection of baseline data (including biomarkers), post-study treatments, and evaluation of minimal residual disease (MRD).	Final CSR: June 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that midostaurin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

References

Ciolli, S., Vannucchi, A. M., Leoni, F., Nozzoli, C., Longo, G., Salati, A., Bosi, A. (2004). Internal tandem duplications of Flt3 gene (Flt3/ITD) predicts a poor post-remission outcome in adult patients with acute non-promyelocytic leukemia. Leuk Lymphoma, 45(1), 73-78.

Cohen, S. S., Skovbo, S., Vestergaard, H., Kristensen, T., Moller, M., Bindslev-Jensen, C., Broesby-Olsen, S. (2014). Epidemiology of systemic mastocytosis in Denmark. Br J Haematol, 166(4), 521-528. doi:10.1111/bjh.12916

Dohner, H., Estey, E. H., Amadori, S., Appelbaum, F. R., Buchner, T., Burnett, A. K., European, L. (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood, 115(3), 453-474. doi:10.1182/blood-2009-07-235358

Ferrara, F., & Schiffer, C. A. (2013). Acute myeloid leukaemia in adults. Lancet, 381(9865), 484-495. doi:10.1016/S0140-6736(12)61727-9

Frohling, S., Schlenk, R. F., Breitruck, J., Benner, A., Kreitmeier, S., Tobis, K., leukemia, A. M. L. S. G. U. A. m. (2002). Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood, 100(13), 4372-4380. doi:10.1182/blood-2002-05-1440

Georgin-Lavialle, S., Lhermitte, L., Dubreuil, P., Chandesris, M. O., Hermine, O., & Damaj, G. (2013). Mast cell leukemia. Blood, 121(8), 1285-1295. doi:10.1182/blood-2012-07-442400

Gilliland, D. G., & Griffin, J. D. (2002). The roles of FLT3 in hematopoiesis and leukemia. Blood, 100(5), 1532-1542. doi:10.1182/blood-2002-02-0492

Haenisch, B., Nothen, M. M., & Molderings, G. J. (2012). Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. Immunology, 137(3), 197-205. doi:10.1111/j.1365-2567.2012.03627.x

Kottaridis, P. D., Gale, R. E., Frew, M. E., Harrison, G., Langabeer, S. E., Belton, A. A., Linch, D. C. (2001). The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood, 98(6), 1752-1759.

Kristensen, T., Vestergaard, H., & Moller, M. B. (2011). Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn, 13(2), 180-188. doi:10.1016/j.jmoldx.2010.10.004

Lim, K. H., Pardanani, A., Butterfield, J. H., Li, C. Y., & Tefferi, A. (2009). Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol, 84(12), 790-794. doi:10.1002/ajh.21561

Lim, K. H., Pardanani, A., & Tefferi, A. (2008). KIT and mastocytosis. Acta Haematol, 119(4), 194-198. doi:10.1159/000140630

Lim, K. H., Tefferi, A., Lasho, T. L., Finke, C., Patnaik, M., Butterfield, J. H., Pardanani, A. (2009). Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood, 113(23), 5727-5736. doi:10.1182/blood-2009-02-205237

Molderings, G. J. (2015). The genetic basis of mast cell activation disease - looking through a glass darkly. Crit Rev Oncol Hematol, 93(2), 75-89. doi:10.1016/j.critrevonc.2014.09.001

Orfao, A., Garcia-Montero, A. C., Sanchez, L., Escribano, L., & Rema. (2007). Recent advances in the understanding of mastocytosis: the role of KIT mutations. Br J Haematol, 138(1), 12-30. doi:10.1111/j.1365-2141.2007.06619.x

Pardanani, A., Lasho, T., Elala, Y., Wassie, E., Finke, C., Reichard, K. K., Tefferi, A. (2016). Next-generation sequencing in systemic mastocytosis: Derivation of a mutation-augmented clinical prognostic model for survival. Am J Hematol. doi:10.1002/ajh.24426

Pardanani, A., Lim, K. H., Lasho, T. L., Finke, C., McClure, R. F., Li, C. Y., & Tefferi, A. (2009). Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. Blood, 114(18), 3769-3772. doi:10.1182/blood-2009-05-220145

Pemmaraju, N., Kantarjian, H., Ravandi, F., & Cortes, J. (2011). FLT3 inhibitors in the treatment of acute myeloid leukemia: the start of an era? Cancer, 117(15), 3293-3304. doi:10.1002/cncr.25908

Portenoy, R. K., Thaler, H. T., Kornblith, A. B., Lepore, J. M., Friedlander-Klar, H., Kiyasu, E., et al. (1994). The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer, 30A(9), 1326-1336.

Schnittger, S., Schoch, C., Dugas, M., Kern, W., Staib, P., Wuchter, C., Hiddemann, W. (2002). Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. Blood, 100(1), 59-66.

Sotlar, K., Colak, S., Bache, A., Berezowska, S., Krokowski, M., Bultmann, B., Horny, H. P. (2010). Variable presence of KITD816V in clonal haematological non-mast cell lineage diseases associated with systemic mastocytosis (SM-AHNMD). J Pathol, 220(5), 586-595. doi:10.1002/path.2677

Thiede, C., Steudel, C., Mohr, B., Schaich, M., Schakel, U., Platzbecker, U., Illmer, T. (2002). Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood, 99(12), 4326-4335.

Ustun, C., Gotlib, J., Popat, U., Artz, A., Litzow, M., Reiter, A., Valent, P. (2016). Consensus Opinion on Allogeneic Hematopoietic Cell Transplantation in Advanced Systemic Mastocytosis. Biol Blood Marrow Transplant, 22(8), 1348-1356. doi:10.1016/j.bbmt.2016.04.018

Valent, P., Horny, H. P., Escribano, L., Longley, B. J., Li, C. Y., Schwartz, L. B., Bennett, J. M. (2001). Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res, 25(7), 603-625.

Valent, P., Spanblochl, E., Bankl, H. C., Sperr, W. R., Marosi, C., Pirc-Danoewinata, H., et al. (1994). Kit ligand/mast cell growth factor-independent differentiation of mast cells in myelodysplasia and chronic myeloid leukemic blast crisis. Blood, 84(12), 4322-4332.

Valent, P., Sperr, W. R., & Akin, C. (2010). How I treat patients with advanced systemic mastocytosis. Blood, 116(26), 5812-5817. doi:10.1182/blood-2010-08-292144

Visser, O., Trama, A., Maynadie, M., Stiller, C., Marcos-Gragera, R., De Angelis, R., Group, R. W. (2012). Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer, 48(17), 3257-3266. doi:10.1016/j.ejca.2012.05.024