**Table of Contents**

[Abbreviations 3](#_Toc118796081)

[Timetable 4](#_Toc118796082)

[Directions 4](#_Toc118796083)

[Guidelines used 4](#_Toc118796084)

[Product Overview 5](#_Toc118796085)

[Product details 5](#_Toc118796086)

[Preclinical and clinical trials overview 6](#_Toc118796087)

[Part A: Preclinical Plan 8](#_Toc118796088)

[Dylan: Acute toxicity 8](#_Toc118796089)

[Dylan: Dosage 8](#_Toc118796090)

[Mouna: Pharmacodynamic 9](#_Toc118796091)

[Mouna: Pharmacokinetic and toxicokinetic studies: 9](#_Toc118796092)

[Raluca: Toxico-pharmacological aspects 9](#_Toc118796093)

[Raluca: Pharmacodynamics 10](#_Toc118796094)

[Raluca: Toxicology Single Dose 10](#_Toc118796095)

[Raluca: Exploratory Clinical Trials 10](#_Toc118796096)

[Raluca: Local Tolerance Clinical Trials 10](#_Toc118796097)

[Priya: Combinational Study 10](#_Toc118796098)

[Priya: Genotoxicity 11](#_Toc118796099)

[Part B: Clinical Plan 12](#_Toc118796100)

[Dylan: Trial design 12](#_Toc118796101)

[Dylan: Clinical trial dosage 12](#_Toc118796102)

[Mouna: PK/PD 13](#_Toc118796103)

[Raluca: Clinical plan 13](#_Toc118796104)

[Priya: Clinical plan 13](#_Toc118796105)

[Part C: Chemistry, Manufacturing and Controls, CMC 14](#_Toc118796106)

[Dylan: Description of Manufacturing Process and Process Controls 14](#_Toc118796107)

[Dylan: Design spaces 14](#_Toc118796108)

[Dylan: Process Risk Assessment 15](#_Toc118796109)

[Dylan: Specifications 15](#_Toc118796110)

[Dylan: Control strategy 15](#_Toc118796111)

[Dylan: Regulatory Filing and Process Monitoring 16](#_Toc118796112)

[Raluca 16](#_Toc118796113)

[Raluca: Chemistry, Manufacturing and Controls 16](#_Toc118796114)

[Priya: Chemistry, Manufacturing, and Controls 16](#_Toc118796115)

[Priya: Control of Drug substances and Drug products – Characterization 16](#_Toc118796116)

[Priya: Manufacturing process - Purification 17](#_Toc118796117)

[Part D: Scientific Advice 19](#_Toc118796118)

[Dylan: EMA Scientific Advice overview 19](#_Toc118796119)

[Dylan: Parallel scientific advice 20](#_Toc118796120)

[Dylan: Application timetable 20](#_Toc118796121)

[Dylan: Dose response studies 20](#_Toc118796122)

[Dylan: Non-clinical aspects 20](#_Toc118796123)

[Priya: Pre-IND Meeting 21](#_Toc118796124)

[Priya: Scientific Advice 22](#_Toc118796125)

[Priya: Parallel scientific advice 22](#_Toc118796126)

[Part E: Inspection Readiness 23](#_Toc118796127)

[Dylan Reasons and readiness key points. 23](#_Toc118796128)

[Priya: Inspection Readiness (IR) 23](#_Toc118796129)

[Overall strategy 24](#_Toc118796130)

[Dylan: Strategy key points 24](#_Toc118796131)

[Priya: Overall strategy 24](#_Toc118796132)

[Advice to Management 25](#_Toc118796133)

[Dylan: Achievements, next steps and outcome reasoning 25](#_Toc118796134)

[Priya: Advice to Management 25](#_Toc118796135)

[Conclusion 26](#_Toc118796136)

[Dylan: Summary 26](#_Toc118796137)

[Priya: Summary 26](#_Toc118796138)

[Supplemental 26](#_Toc118796139)

[References 27](#_Toc118796140)

[Raluca References 28](#_Toc118796141)

[Priya References 29](#_Toc118796142)

# Abbreviations

AC, anthracycline-cyclophosphamide;

CHMP, Committee for Medicinal Products for Human Use;

CTD, common technical document;

EGFR, epidermal growth factor receptor;

EMA, European Medicines Agency;

FDA, Food and drug administration;

FIH, first in human;

FMECA, failure modes effects and criticality analysis;

GCP Good clinical practice;

GLP Good laboratory practice;

GMP, Good manufacturing practice;

HER, human epidermal growth factor receptor;

IV, Intravenous;

IR, inspection readiness;

MABEL, minimal anticipated biological-effective level;

MAPK, mitogen-activated protein kinase;

MED, minimum effective dose;

MEK, MAPK/extracellular signal–related kinase kinase;

MFD maximal feasible dose;

MSRD, maximum recommended starting dose;

MTD, maximum tolerated dose;

NDA, new drug application;

NOAEL, no-observed-adverse-effect level;

PAD, pharmacologically active dose;

PI3K, phosphoinositide 3-kinase;

PRA, process risk assessment;

PSA, parallel scientific advice;

QbD, quality by design;

REC, response evaluation committee;

RPN, risk priority number;

SAWP, Scientific Advice Working Part;

SmPC, summary of product characteristics;

SOS, son of sevenless;

TTF, time to treatment failure;

VEGF, vascular endothelial growth factor.

# Timetable

[x] 20 Thursday - Assign responsibility (Word).

[x] 24 Monday - Check the skeleton is being filled in (Word). Final vote on presentation style.

[x] 27 Thursday - Check all sections filled (Word, slides). - Not completed

[x] 31 Monday - Review slides and practice (slides). - waiting for word completion.

[ ] 03 Thursday - Edits complete, practice (Word, slides).

[ ] 07 Monday - Practice (slides).

[ ] 10 Thursday - Present.

Word = MSword file containing the presentation material, references, discussion.

Slides = powerpoint slide for presentation.

# Directions

1. Use your individual report to fill in the points you have covered in parts A-E. Together we will have covered serval different topic to make up a complete report.

2. You will be assigned responsibility for curating on specific part. Check that sufficient descriptions have been provided for your part. Check that regulatory guidelines have been followed for each topic in your part.

**Required form everyone:**

We have each written something unique for parts A-E in the individual reports. Copy your unique topics from every part A-E into the master MSword document. Write your name next to your input part. Reduce to the key point and reference the regulatory guidance that applies.

**Individual responsibility:**

Dylan - Part A: Preclinical Plan

Raluca - Part B: Clinical Plan

Mouna - Part C: Chemistry, Manufacturing and Controls, CMC

Priya - Part D: Scientific Advice

Olivia - Part E: Inspection Readiness

You have been assigned one part which you will curate. Check that everyone contributes their topic to your part. Check that guidance literature is cited (ICH, EMA, Eudralex). Example, for part A do we have a realistic number of preclinical trials? Have several guidelines been referenced to show that we have the required studies done?

ICH <https://www.ich.org/page/quality-guidelines>

EMA <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines>

Eudralex <https://health.ec.europa.eu/medicinal-products/eudralex_en>

# Guidelines used

[ICH M3](https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (R2) [1]

[ICH E6](https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice): Guideline for good clinical practice (R2),

[ICH Q8](https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development) Pharmaceutical development [2, p. 8].

[ICH Q9](https://www.ema.europa.eu/en/ich-q9-quality-risk-management) Quality risk management[3, p. 9].

[ICH Q6B](https://www.ema.europa.eu/en/ich-q6b-specifications-test-procedures-acceptance-criteria-biotechnologicalbiological-products) Specifications: test procedures and acceptance criteria for biotechnological/biological products[4],

[ICH Q10](https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system) Pharmaceutical quality system[5, p. 10], the

[ICH M4](https://www.ema.europa.eu/en/ich-m4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd) Common technical document (CTD) for the registration of pharmaceuticals for human use - organisation of CTD (R4) [6, p. 4]

[EudraLex Volume 10 clinical trials guidelines](https://ec.europa.eu/health/documents/eudralex/vol-10_en) [7].

Good manufacturing practice: [(EMA GMP)](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice)

Good laboratory practice compliance ([EMA GLP](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-laboratory-practice-compliance))

Good clinical practice ([EMA GCP](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice))

# Product Overview

**Product Profile**: Our product is a monoclonal antibody to be used in a phase 1 clinical trial in oncology. The company is named VaudBioTech with headquarters located in Switzerland. This company is the discoverer of the product in question. The planned phase 1 clinical trial will be conducted in Germany at [Heidelberg University Hospital](https://www.heidelberg-university-hospital.com/). Additional information is provided to summarize the potential phase 2 and 3 clinical trials.

**Company:** VaudBioTech

**Product name**: Hertumig.

**Treatment**: Treatment of HER2 receptor positive breast cancer.

**Delivery**: Intravenous administration.

**Mechanism/target**: Similar to the mode of action from Pertuzumab and Herceptin (as illustrated in Figure 1), Hertumig targets a newly defined antigen of HER2 which inhibits the [dimerization](https://en.wikipedia.org/wiki/Protein_dimer) with other HER receptors, thereby preventing [signaling](https://en.wikipedia.org/wiki/HER2/neu#Signal_transduction) in ways that promote cell growth and proliferation. HER2 positive breast cancer is caused by *ERBB2* gene amplification that results in overexpression of HER2 in approximately 15-30% of breast cancer tumors. Stimulates cell proliferation and cell growth. It is a bispecific monoclonal antibody (BsMAb) which targets two epitopes.

**Discussion**: This drug is reminiscent of the classical mAb anticancer treatments; (i) similar to [Pertuzumab](https://en.wikipedia.org/wiki/Pertuzumab) (RG6264, Perjeta) from [Genentech](https://en.wikipedia.org/wiki/Genentech) which was first approved in 2012, Europe in 2013, etc. (ii) similar to [Trastuzumab](https://en.wikipedia.org/wiki/Trastuzumab), Herceptin from Genentech very well known, approval US 1998, EU 2000, WHO essential medicine, as illustrated in Figure 1.

## Product details

**Chemical Name**: Immunoglobulin G1 (human-mouse monoclonal rhuMAb HER2γ1- chain anti-human P185c-erB2 receptor) disulphided with human-mouse monoclonal rhuMAb HER2 light chain, dimer. Molecular Formula/Molecular Weight: C6460H9972N1724O2014S44 / 148 kDa (without the N-glycan moiety). Structure or Biochemical Description: SB3 (hertumig) contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) modified to bind to two epitopes of HER2. SB3 consists of 1,328 amino acids. The amino acid sequences for the heavy and light chains of SB3 are listed in the following fasta format:

>Hertumig\_Heavy\_Chain

EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR IYPTNGYTRY

ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG GDGFYAMDYW GQGTLVTVSS

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS

GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG

PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE

MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW

QQGNVFSCSV MHEALHNHYT QKSLSLSPG

>Hertumig\_Light\_Chain:

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS

RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKRTV AAPSVFIFPP

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

Composition: Hertumig is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial contains 440 mg of Hertumig, 6.4 mg L-histidine, 9.9 mg L-histidine HCl, 1.8 mg polysorbate 20, and 400 mg α,α-trehalose dihydrate. Reconstitution with 20 mL of the supplied BWFI, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL Hertumig, at a pH of approximately 6.

**Availability**: Hertumig is supplied as a lyophilized, sterile powder containing 440 mg Hertumig per vial under vacuum. BWFI is supplied as a 20 mL vial of sterile solution containing 1.1% benzyl alcohol as an antimicrobial preservative. Each carton contains one vial of 440 mg Hertumig and one 20 mL vial of BWFI containing 1.1% benzyl alcohol.

Map

Description automatically generated

Figure 1 Cryo-EM structure of HER2 bound by mAb

HER2 (cyan) extracellular domain, Trastuzumab Fab (Herceptin - red and pink), and Hertumig Fab complex (Perjeta - yellow and orange). Derived from PDB 6OGE <https://doi.org/10.1371/journal.pone.0216095>.

## Preclinical and clinical trials overview

Hertumig was produced as a humanized anti-HER2 mAb to target HER2-overexpressing breast tumors. The design was based on the body of work since the original development of Trastuzumab (Herceptin) [8] and the advent of modern mAb treatments [9], [10], more than 100 of which have now been approved by FDA [11].

Our *in vitro* **preclinical** data has demonstrated the effect of Hertumig equal to or surpassing trastuzumb (Herceptin) due to its bispecific epitope binding activity to produce antiproliferative and antitumor effects in ovarian and breast cancer cell lines. Additional evidence was demonstrated using human breast cancer xenograft models. The design of these experiments reflects those demonstrated previously by Baselga et al. 1998; Carter et al. 1992; Lewis et al. 1993; Pegram et al. 1999 [8], [12]–[14] and thus support the proposed functional mechanism of action compared to drugs currently on the market. With our successful *in vitro* demonstration of the scientific bases, **preclinical** and clinical trials have been planned. The **preclinical** trials quantified pharamacokinetic and toxicology outcomes and returned favorable results (Figure 2). Therefore, a clinical trial program will be established in small numbers of patients.

**Phase 1** clinical trials will be performed to show that the antibody is safe and confined to the tumor. Two open-label **phase 1** dose escalation trials will be carried out, consisting of single and weekly-repeated doses of Hertumig monotherapy for patients with advanced refractory HER2-positive metastatic breast cancer [15], [16]. **Phase 2** trials will assess whether women with HER2-positive metastatic disease who had relapsed after chemotherapy will respond to Hertumig. Results should support the **preclinical** data to demonstrate the efficacy of Hertumig when given with chemotherapy as superior to its effectiveness when used alone. **Phase 2** trials of Hertumig monotherapy [17] and Hertumig in combination with cisplatin (50 or 100 mg/m2) [18] will be undertaken. As in the **phase 1** trials, the patient population will consist of pretreated HER2-positive metastatic breast cancer patients of European ancestry. These studies will assess the appropriate dosage, safety and potential efficacy of Hertumig as a single agent and in combination with concomitant chemotherapy in humans. Based on these data, progression to pivotal clinical trials can be pursued in order demonstrate the efficacy and subsequently obtain its marketing approval by regulatory authorities.

If **phase 1** and **2** trials produce successful end points, pivotal trials will be conducted in large numbers of HER2-positive metastatic breast cancer patients: a phase 2 trial of second-/third-line Herceptin monotherapy [19] and a **phase 3** first-line Hertumig combination trial [20]–[22]. **Phase 3** trials are expected to be carried out in women with cancers that overexpressed HER2 who have not previously received chemotherapy for metastatic disease. They will be randomly assigned to receive either chemotherapy alone or chemotherapy plus Hertumig. The primary end points of the study will be the time-to-disease-progression and the incidence of adverse effects. Secondary end points will be the rates and the duration of responses, the time-to-treatment-failure, and overall survival.

Details used for the planning of these trials are described elsewhere and use additional evidence derived from similar studies [15], [22]–[24]. Dosages will be defined based on **phase 1** outcomes, however, Hertumig administration is currently estimated as a 4-mg/kg initial dose followed by a 2-mg/kg IV weekly maintenance dose (to be modified based on the preceding outcomes). In the combination trial, patients will be randomized to receive Hertumig with anthracycline-cyclophosphamide (AC) versus AC alone or, if they had previously received adjuvant anthracyclines, Hertumig plus paclitaxel versus paclitaxel alone.

An independent Response Evaluation Committee (REC) will be employed to determined tumor responses in the intent-to-treat-population (n = 200) of the pivotal **phase 2** trial. They will measure the overall response rate (e.g. 20%), duration of response (e.g. 12 months) and a median survival (e.g. 24 months). The median time to treatment failure (TTF) (e.g. 24 months) will be compared with that for the prior regimens of chemotherapy (e.g. 6 months). Similarly, independent evaluation will be performed for **phase 3** trials to quantify the expected increase the clinical benefit of first-line chemotherapy. Statistical analysis will be carried out as reported in preregistration throughout. Data will be collected and analyzed according to the statistical analysis plan by our contract research organization.

Timeline

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Figure 2 Nonclinical evaluation for small molecules.

Figure reproduced from Nürnberg and Pierre 2017 [25]. Biologics may require fewer nonclinical studies than small molecules but can be complicated due to novelty and lack of relevant model species. Often the rodent species by be omitted if they are not representative of the expected human response. However, transgenic murine models may be required. Immunogenicity can produce both a lack of efficacy or severe adverse outcomes (PD and PK). Extensive immunogenicity testing may be required. Only major steps are illustrated; e.g. carcinogenicity may require dose testing and subsequent two-year rodent study and six-month transgenic mouse study.

# Part A: Preclinical Plan

## Dylan: Acute toxicity

In accordance with [ICH M3](https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals) R2 [1], acute toxicity was assessed using single-dose toxicity studies in two mammalian species (one non-rodent):

1. Intravenous (IV) bolus administration in mice (M+F) at 0, 10, 50 and 100 mg/kg [*H0030\_preclinical\_acute\_toxicity\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
2. IV bolus administration in rhesus monkeys (M+F) at 0, 5, 25 and 50 mg/kg [*H0031\_preclinical\_acute\_toxicity\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*

Studies were performed under good laboratory practice (GLP) ([ICH GLP](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-laboratory-practice-compliance)). Additional preclinical studies were repeated in rhesus monkeys to validate the progressive changes towards clinical trial production formats: liquid formulation process change from Hertumig H2 to Hertumig H13 (study H0031a), manufacturing processing change (study H0031b), and production of clinical-grade lyophilized Hertumig (study H0031c).

The presence or absence of toxicity of several different preparations and formulations of hertumig was be measured based on standard parameters including food consumption, body weight, antibody formation, clinical chemistry and macro- and microscopic examination of standard organs/tissues. The no-observable-effect-level (NOEL) was obtained which, based on other similar products, was 100 and 50 mg/kg in mice and rhesus monkeys, respectively. In these studies (H0030, H0031a-c), both the clinical and parenteral route of administration were used; intravenous (IV) bolus. The minimum and maximum dosages (5 - 50 mg/kg) were administered over 90 minutes without short-term adverse effects. Each study was conducted under GLP ([ICH GLP](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-laboratory-practice-compliance)). All subjects were evaluated for antibody production. No anti-hertumig antibodies were detected, precluding subsequent allergic manifestations which would be a concern for further clinical testing. Acute toxicity results will be used in combination with the known toxicity for other mAbs to assess the potential consequences of human overdose and will be available to support Phase III.

Table 1Overall Summary of Nonclinical Acute Toxicity Studies with Hertumig

*F, female; GLP, Good laboratory practice; M, male. a This study was conducted to support a liquid formulation process change from Hertumig H2 to Hertumig H13. b This study was conducted to support the clinical use of Hertumig produced by a scaled-up manufacturing process, Hertumig (H13-12K). c This study was conducted to support the clinical use of lyophilized Hertumig.*

Table

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## Dylan: Dosage

In accordance with [ICH M3](https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals) R2 [1], dosage was assessed for non-clinical trials. The maximum recommended starting dose (MSRD) is required as the first step in first-in-human (FIH) testing. This determination is based on *in vitro* and *in vivo* pharmacological, pharmacodynamic, pharmacokinetic, physiological, and toxicological data. Preclinical dosages were guided based on functionally similar mAb [8], [12]–[14] and based on our successful *in vitro* studies. Additional non-anti-HER2 mAb treatments were assessed to estimate potential dosage variations for preclinical testing [9], [10],

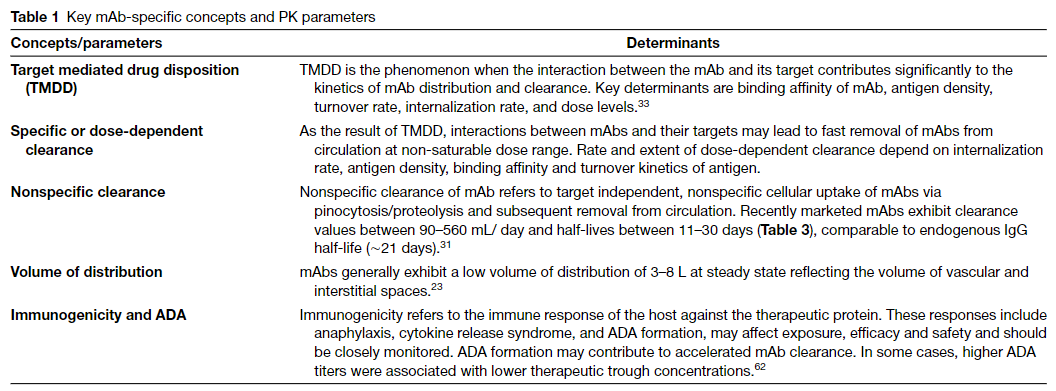
The no-observed-adverse-effect level (NOAEL) dose was be determined from the GLP toxicology study. The pharmacologically active dose (PAD) was quantified in the preclinical trials and based on other similar mAb, defined for the FIH clinical trials [9], [10]. MSRD was calculated from the NOAEL and additionally compared with the PAD and the minimal anticipated biological-effective level (MABEL). Lastly, based on the multiple measurements (MABEL, PAD, NOAEL) the lowest estimate will used in phase 1 clinical trials [26]. After IV administration the initial plasma concentration is typically approximately 50mL/kg. The mAb is initially confined to circulation in the vasculature with eventual extravasation into tissue [26]–[28].

## Mouna: Pharmacodynamic

In vitro studies will be performed on HER2 overexpressing cells such as *SK-BR-3, MCF7* to study the pharmacodynamic effect of Hermitug. To do so, parameters such as proliferation, adhesion, metastatic potential of the tumour cells, vascular endothelial growth factor will be studied. Levels of Her2 expression on the cell surface will also be measured. Cross reactivity with frozen human or cynomolgus monkey tissue will be performed to study the immunoreactivity and identify the non-specific and specific binding of the mAb. In vivo studies using a nude mouse model transplanted with human breast tumor xenografts will also be performed to study the pharmacodynamic effects of hermitug. Tumor size will be measured to assess the efficacy of the treatment.1

## Mouna: Pharmacokinetic and toxicokinetic studies:

According to ICH M3 R2, In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data in the species used for repeated-dose toxicity studies should be evaluated before initiating human clinical trials 2. Therefore, Pharmacokinetic studies of Hermitug will be performed on mice, rhesus and cynomolgus monkeys. ADME parameters will be measured after administration of Hermitug to these models my measuring the analytes Int samples using using ELISA and LC -MS.

<https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1111/cts.12567>: 

*Table 1**Overall Summary of Nonclinical Acute Toxicity Studies with Hertumig*

Table

Description automatically generated

## Raluca: Toxico-pharmacological aspects

Hertumig is directed against HER2, which is part of a family of membrane-bound phosphoglycoproteins with tyrosine kinase activity. The proteins coded by the oncogens, the oncoproteins, are all involved in the signalling cascades that control cell proliferation and differentiation [12].

## Raluca: Pharmacodynamics

In vitro studies Hertumig inhibited proliferation of HER2 overexpressing cells and induced loss of intrinsic resistance of cells that overexpress HER2. Furthermore, reduction in synthesis of cellular components affecting cell adhesion and the metastatic potential of tumour cells in treatment with Hertumig.

Although Hertumig has been shown to bind to HER2 on several breast adenocarcinoma cell lines and activate the complement cascade [12].

In cross-reactivity studies with frozen human or Cynomolgus monkey’s tissues, Hertumig and muMAb 4D5 showed similar patterns of immunoreactivity.

The nonlinear PK observed at lower doses of Hertumig in monkey is consistent with specific, saturable binding. The tissue cross reactivity and nonclinical PK studies and the demonstrated specificity for HER2, support the conclusion that Hertumig recognised monkey HER2 [12].

Several studies on the pharmacokinetic profiles of Hertumig after a single administration revealed a terminal half-life ranging from 8 to 15 days determined in mice, and cynomolgus monkeys. The presence of free extracellular domains (ECD) of HER-2 in the serum of cynomolgus resulted in an increased clearance and thus a shorter half life of Hertumig. ECD clearance was also decreased in the presence of Hertumig in both the mouse and the monkey indicating that ECD can be maintained in circulation when complexed with Hertumig.

In single-dose studies in mice Cmax was 18, 2800, 2250 µg/ml for the doses of 1, 10, 100 mg/kg respectively. The dose response in terms of Cmax or AUC in the rhesus monkey was non-linear.

## Raluca: Toxicology Single Dose

Toxicity Single-dose acute studies were undertaken using iv bolus administration in mice (M+F) at 0, 9.5, 49 and 94 mg/kg and in rhesus monkeys (M+F) at 0, 4.7, 23.5 and 47 mg/kg. The absence of toxicity of several different preparations and formulations of Hertumig could be demonstrated.

## Raluca: Exploratory Clinical Trials

The draft revision of the ICH M3 (R2) guideline [10] describes five approaches, including two that use microdoses (objective: receptor occupancy and biodistribution) and three with pharmacological doses as a single dose or with up to 14 days of repeated dosing [objective: pharmacodynamic activity (PD) and/or pharmacokinetics (PK, PK/PD)].

## Raluca: Local Tolerance Clinical Trials

Pharmacodynamics

In alignment to ICH M3 (R2) [10], no specific pharmacodynamic study has been performed. The data gained from the exploratory pharmacodynamic analysis of the pivotal trial are too limited to draw any conclusion concerning trends between shed HER2 extracellular domain (ECD) and clinical response. It remains open whether ECD concentrations at baseline > 200 ng/mL are predictive of a worse clinical outcome.

## Priya: Combinational Study

ICH M3 R2, ICH S9, and guidelines for fixed combination medicinal products suggest combination studies are usually not warranted for oncology drugs unless there is a significant toxicological concern. However, preclinical combination study enhances the confidence of combinational clinical trial. In addition to patient safety, the combined efficacy of the drug combination was also evaluated in the studies. Therefore, preclinical general toxicity and pharmacology studies were systematically designed for Hertumig combined therapy. Existing mAbs Herceptin® and Perjeta® and chemotherapeutic with Taxotere® were selected to evaluate the efficacy of the Hertumig combined therapy.

In vitro combination studies were conducted in SK-BR-3, HER2-transfected MCF7, and BT-474 cell lines. Molecular assays were developed to analyze the antitumor and antiproliferative activity of Hertumig (HT1 to HT15). In vitro cytokine stimulation assay was performed to assess immune stimulation in the case of the mAb combination. In vivo combinational studies were performed for 90 days in the rhesus monkey that evaluated efficacy with safety endpoints.

In combination studies, synergistic effects were observed in cell culture with Herceptin® and Perjeta®, whereas a combination with Taxotere® has shown additive interactions. Combinations with Perjeta® and Taxotere® were most effective *in vivo*. The combination with Taxotere® has the most significant tumor regression in vivo with the BT-474 cell line.

## Priya: Genotoxicity

As per guidelines ICH M3 (R2) and ICH S9, for oncology studies genotoxicity not warranted by health regulatory unless any significant health concerns. Like combination therapy, Antibody-drug conjugates (ADC) are proven more efficient for treating HER2-overexpressing breast cancer. A classic example of ADC is Herceptin/Trastuzumab emtansine (Kadcyla™), effectively used in the HER2-positive breast cancer regimen. Genotoxicity studies for Hertumig alone and conjugated to DM1 were performed. DM1 is a cytotoxic derivative of maytansine, a highly potent microtubule inhibitory drug. Genotoxicity for Hertumig was evaluated under the ICH S6(R1) guideline (‘Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals’ 1997, later complemented by an addendum ICH S6 R1, 2011)

The genotoxicity of Hertumig (HT1 to HT15) has been investigated by *in vitro* and *in vivo* preclinical studies. Hertumig (HT1 to HT15) concentrations up to 5 mg/ml were used in both *in vitro and in vivo* assays. No significant genotoxic effects were observed for Hertumig alone, whereas conjugation to DM1 makes it genotoxic.

*In vitro* studies:

1. Ames test in *Salmonella typhimurium* (strains TA 98, 100, 1535, and 1537),

2. *E. coli* assays (strains WP2pKM101 and WP2uvrApKM101),

3. Chromosome aberration assay in human peripheral lymphocytes.

In vivo test was a mouse micronucleus assay involving a single iv injection of Hertumig (HT1 to HT15) at 29.5, 59, and 118 mg/kg.

Timeline

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Figure 2 – Preclinical studies in the drug development pipeline. Figure modified (Andrade et al., 2016)

# Part B: Clinical Plan

## Dylan: Trial design

Clinical Trial Protocol was drafted for inclusion in the application of Hertumig. In this we define the main points of the clinical trial protocol and consider a master protocol. In addition to regulatory guidelines, we

include protocol aims for cancer trials from [Ledford 2013](http://www.nature.com/news/master-protocol-aims-to-revamp-cancer-trials-1.13176) [29] and [Woodcock and LaVange 2017](http://www.nejm.org/doi/full/10.1056/NEJMra1510062#t=article) [30]. We additionally considered [PRIME](https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines) (EU) and [Breakthrough Designations](https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies) (US).

In accordance with [ICH M3](https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (R2) [1] and [ICH E6](https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice): Guideline for good clinical practice (R2) [32], phase 1 acute toxicity will be assessed using single-dose toxicity studies. Two studies will be performed:

1. IV bolus single dose administration to women who have not received chemotherapy within 30 days at 10, 50, 100, 250 mg [*HC1030\_clinical\_acute\_tox\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
2. IV bolus single dose administration to women are receiving chemotherapy at 10, 50, 100, 250 mg [*HC1031\_preclinical\_acute\_tox\_with\_chemo\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*

Upon successful outcomes, phase 2 and phase 3 studies are expected to follow (with duration and dosages to be adjusted as appropriate based on outcomes of MABEL, PAD, NOAEL in phase 1 trials:

1. IV bolus administration initially at 4 mg/kg followed by 1 mg/kg weekly for 9 weeks total to women who have not received chemotherapy within 3 weeks [*HC2030\_clinical\_multi\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
2. IV bolus administration initially at 250 mg followed by 100 mg weekly for 9 weeks total to women who will received chemotherapy in combination [*HC2031\_clinical\_multi\_with\_chemo\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
3. IV bolus administration initially at 4 mg/kg followed by 2 mg/kg weekly for 9 weeks total to women who initially received chemotherapy and have incurred relapse of disease [*HC2032\_clinical\_mutli\_with\_chemo\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*
4. Women will receive chemotherapy with or without IV bolus administration of initially 4 mg/kg followed by 2 mg/kg weekly [*HC3030\_clinical\_multi\_with\_chemo\_study\_handbook.pdf*](file:///Volumes/GoogleDrive/My%20Drive/E4Ldrugdevice/dylan_notes_docs/dylan_case_study/demo)*.*

## Dylan: Clinical trial dosage

Accurate dosages for our FIH studies are required to measure a true therapeutic effect. The initial studies will assess the tolerance for the MABEL, PAD, and aim to stay below the NOAEL. Severe adverse outcomes have be reported in published cases of mAb therapies, which have been blamed on poor adherence to regulatory guideline such as [ICH E6](https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice) (R2) [32], as seen in the TGN1412 study [31]. Therefore, we have followed the regulatory guidelines closely in design of our protocol. We have included information on reasons why dosage will vary for mAb [26], considerations on the safety and side effects of monoclonal antibodies [33], risk of cytokine storm in FIH study [31], and protocols in development of mAb for therapeutic use [26].

Table 2 Overall Summary of Planned Clinical Studies with Hertumig

Table

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## Mouna: PK/PD

Clinical trial will be conducted in Germany and therefore should be approved by the competences in of the study country i.e Paul Ehrlich Institute. The phase 1 trial will be performed on 15 cancer patients to avoid endangering healthy volunteers and will aim to evaluate the safety of the mAb.

The objectives of the clinical pharmacology program are to evaluate the pharmacokinetic profile of hermitug. The pharmacokinetics (absorption, distribution and elimination) will be characterised during single-dose and steady-state conditions in patients.3

Following successful results with phase 1, the cohorts of the phase 2 and 3 will have more and will evaluate the efficacy of the drug in inhibiting the progress of the disease, along with additional side effects.

*Table 2 Overall Summary of Planned Clinical Studies with Hertumig*

Table

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## Raluca: Clinical plan

In accordance with ICH E6 (R2) [2], three open-label, phase I clinical trials in patients with refractory (grade 4) HER2-positive meta-static breast cancer, which will be primarily designed to determine the safety, maximum tolerated dose and pharmacokinetics of Hertumig. The weekly schedule of i.v. infusion is based on the expected clearance calculated from preclinical studies and was continued until disease progressed. As is usual in such studies, relatively low numbers of patients will be recruited in these phase I clinical trials (n =15-18) and the enrolment can be completed in a short period of time.

## Priya: Clinical Plan

Preclinical studies have demonstrated the efficacy and safety of Hertumig. A multifactorial preclinical study provides a stronger foundation for establishing phase I clinical trials in the Hertumig drug development program. Phase I clinical studies' main objectives are evaluating safety and tolerability, determining biomarkers, proof of concept, and the first human-safe dose. Further details about the trial are mentioned below -

* Site - Heidelberg University Hospital, Germany.
* Duration - 15 months
* Cohort size - 24
* Inclusion criteria –
  + - Advanced refractory HER2-positive metastatic breast cancer
    - HER2 overexpression at a 3+ level (determined by immunohistochemistry)
    - No chemotherapy treatment in the last 30 days
* Exclusion criteria –
* History of adverse reactions, cardiac dysfunction, or symptomatic and asymptomatic cardiotoxicity, autoimmune diseases
* Ongoing viral infection
* Pregnancy and breastfeeding
* Study design - two open labeled
* Phase I A - SAD (single ascending dose)
* Phase I B - MAD (multiple ascending doses) weekly repeated
* Concentration for dose escalation study- 10/50/100/ 250/500 mg
* Safety factor for dose - 10
* Medical supervision - 24 hours after administration
* Endpoints- Safety and PK (Pharmacokinetics)

Clinical studies are designed in agreement with (ICH M3) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (R2) and (ICH E6: Guideline for good clinical practice (R2).

# Part C: Chemistry, Manufacturing and Controls, CMC

Our CMC plan on the work that needs to be done and included in the application for Hertumig is summarized. Regulations were followed according to European Commission:([EudraLex Volume 10 clinical trials guidelines](https://ec.europa.eu/health/documents/eudralex/vol-10_en)) [7]. Multiple ICH guidelines are followed as referenced throughout. Good manufacturing practice (GMP) [(ICH GMP)](https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice) was followed.

## Dylan: Description of Manufacturing Process and Process Controls

Hertumig is produced using a mammalian cell line expanded in bioreactor cultures followed by a drug substance purification process that includes various steps designed to isolate and purify the protein product. Residual levels of process-related impurities (e.g., host cell proteins [HCP], host cell DNA [HCD], and those specific to the Hertumig manufacturing process) were evaluated as part of the Hertumig drug substance in-process and release testing. The data provided demonstrated that the Hertumig drug substance manufacturing process sufficiently reduces the impurities to very low levels (e.g., ppm for HCP and pg/ml for HCD). The Hertumig drug product was developed as a multi-dose vial containing 440 mg of lyophilized powder, to reflect the same strength, presentation and route of administration as EU-Herceptin (440 mg). The manufacturing process for Hertumig drug substance was scaled-up over the course of development, and comparability studies between the scales demonstrated consistency of the product. The drug product manufacturing process remained essentially the same. The drug product intended for commercial use was demonstrated to be analytically comparable to the drug product manufactured for clinical use, and combined data were included in the analytical similarity assessment. Analytical assessments have been carried out as listed in Table 3.

Table 3 Quality attributes and methods used to evaluate Hertumic production

Table

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## Dylan: Design spaces

Based on similar drugs (Herceptin, Perjeta), we have proposed the design space (input variables [e.g., material attributes] and process parameters that have been demonstrated to provide assurance of quality) which is subject to regulatory assessment and approval, as advised by [ICH Q8](https://www.ema.europa.eu/en/ich-q8-r2-pharmaceutical-development) [2, p. 8]. Working within the design space is not considered as a change but any additional changes will initiate a regulatory postapproval change process. Critical quality attributes (CQAs) have been assigned to control the impact of each unit operation.

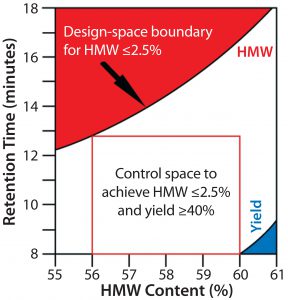


Figure 3 Example design space

*Example of our design space for a hydrophobic-interaction chromatography (HIC) step used to purify an Fc fusion protein as determined by Jiang et al. [34]*

## Dylan: Process Risk Assessment

We have identified, explored, and optimized (and will produce eventual specification) multiple operating parameters. A process risk assessment (PRA) has been carried out for the operating parameters (inputs) for each process step, e.g., cell density and viability for an upstream process or load temperature, load pH, and load conductivity for a column chromatography step. PRA was carried out using failure modes effects and criticality analysis (FMECA), based on [ICH Q9](https://www.ema.europa.eu/en/ich-q9-quality-risk-management) [3, p. 9]. Each operating parameter was assessed to calculate a risk priority number (RPN), the severity score of the level of harm to patients should failure occur, based on prior-knowledge therapeutic mAbs.

## Dylan: Specifications

Specifications for design spaces of in-process, drug substance, and drug product attributes were produced. Which, in accordance with [ICH Q6B](https://www.ema.europa.eu/en/ich-q6b-specifications-test-procedures-acceptance-criteria-biotechnologicalbiological-products) [4], include a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described”;

[ICH Q6B](https://www.ema.europa.eu/en/ich-q6b-specifications-test-procedures-acceptance-criteria-biotechnologicalbiological-products) [4]. They establish “the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use”; [ICH Q6B](https://www.ema.europa.eu/en/ich-q6b-specifications-test-procedures-acceptance-criteria-biotechnologicalbiological-products) [4]. These specifications we defined based on operations with CQAs in safety and efficacy using published literature other mAb drugs, and in-house nonclinical and public clinical reports.

## Dylan: Control strategy

Our control strategy was designed to ensure product quality and control product and process variability. A combination of traditional control strategy elements and quality by design (QbD) for CQAs. In accordance with [ICH Q10](https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system) [5, p. 10], the control strategy is “a planned set of controls, derived from current product and process understanding that assures process performance and product quality” and include “parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished-product specifications, and the associated methods and frequency of monitoring and control” [ICH Q10](https://www.ema.europa.eu/en/ich-q10-pharmaceutical-quality-system) [5, p. 10]. An example of our control strategy risk assessment is illustratedin Figure 4, which shows **t**he formula for our risk assessment for mAb development.

Diagram

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Figure 4 Control strategy risk assessment for mAb

*Control strategy risk assessment combines criticality assessment of quality attributes with process capability and testing strategy to determine the risk priority number (RPN) for a control strategy, reprinted from CMC BWG [35].*

## Dylan: Regulatory Filing and Process Monitoring

The regulatory filing includes detailed descriptions of the product design space, process design space, and control strategy. In accordance with [ICH M4](https://www.ema.europa.eu/en/ich-m4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd) (R4) [6, p. 4], the regulatory filings can be submitted using the common technical document (CTD) format, a harmonized approach to filing a new drug application (NDA) in all regions that are signatory to the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use; [ICH M4](https://www.ema.europa.eu/en/ich-m4-common-technical-document-ctd-registration-pharmaceuticals-human-use-organisation-ctd) (R4) [6, p. 4]. Following approval of our product, we will continually monitor the manufacturing process to ensure that variability remains within limits defined by the process design space. The QbD protocol will allow us to modify the process without needing further review or regulatory approval.

## Raluca

Overall, description of the upstream (cell expansion and main fermentation) and downstream process will be provided. The steps, control parameters, test methods used for control, and acceptance criteria to be indicated, in addition to information about buffer volumes, flow rates, in process controls, maximum target mass, and collection mode.

Each step in the filling, storage, and shipping steps will be described adequately, along with in-process controls and tests. The specifications for the raw materials used for purification, and the bulk formulation process will be provided.

## Raluca: Chemistry, Manufacturing and Controls

Overall, description of the upstream (cell expansion and main fermentation) and downstream process will be provided. The steps, control parameters, test methods used for control, and acceptance criteria to be indicated, in addition to information about buffer volumes, flow rates, in process controls, maximum target mass, and collection mode.

Each step in the filling, storage, and shipping steps will be described adequately, along with in-process controls and tests. The specifications for the raw materials used for purification, and the bulk formulation process will be provided.

## Priya: Chemistry, Manufacturing, and Controls

Drug discovery has identified the lead compound Hertumig. We aim to produce the Hertumig required for the consecutive clinical trial phases under GMP compliance.

## Priya: Control of Drug substances and Drug products – Characterization

As shown in the following table, the structural and functional characterization (also termed an analytical assessment) of Hertumig was carried out. We have determined physicochemical properties of the Hertumig (e.g., size, charge, isoelectric point, amino acid sequence, hydrophobicity, post-translational modifications -glycosylation).

Table 1. Analytical items and analytical methods for the analysis of mAb characterization.Graphical user interface, application, table

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## Priya: Manufacturing process - Purification

For the large-scale production of the Hertumig, we have developed (optimized) a manufacturing process to yield drug substances and products per specifications needed for human use. During the manufacturing process, product-related and process-related impurities are generated. These impurities are host-cell-derived proteins, nucleic acid, viruses, and other impurities, including media-derived compounds and undesirable chemicals introduced by the purification process itself. A combination of orthogonal methods generates the Hertumig purity/impurity profile. These methods generally include determining physicochemical properties such as molecular weight or size, isoform pattern, extinction coefficient, electrophoretic profiles, chromatographic data, and spectroscopic profiles. Further validation of the Hertumig purification process was performed, and a reduction factor at each stage of purification was established.

The following guidelines are used for Hertumig

* European Commission: (EudraLex Volume 10 clinical trials guidelines),
* Eudralex Volume 3 PRODUCTION AND QUALITY CONTROL OF MEDICINAL PRODUCTS DERIVED BY RECOMBINANT DNA TECHNOLOGY
* Production and Quality Control of medicinal products derived by recombinant DNA technology” (3AB1A),
* ICH guidelines - ICH Q6B “Test Procedures and Acceptance Criteria for Biotechnological/Biological Products” (CPMP/ICH/365/96) Good manufacturing practice (ICH GMP).
* Guideline on development, production, characterization, and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008

# Part D: Scientific Advice

## Dylan: EMA Scientific Advice overview

The European Medicines Agency (EMA) can provide scientific advice at any stage of a medicine's development.

The purpose of this process is to answer VaudBiotech’s questions which are not fully answered by guidance documents and other publicly available resources and provide information that will assist in preparing our market approval application and reduce the risk of a clinical hold. The process ensures that appropriate tests and studies are designed, so that no major objections regarding the design of the tests are likely to be raised during the evaluation of the marketing authorisation application. For Hertumig, scientific advice and protocol assistance are given by the [Committee for Medicinal Products for Human Use](https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp) (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP).

Requesting scientific advice or protocol assistance from EMA will be completed using the [IRIS platform](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/requesting-scientific-advice-protocol-assistance-ema). The briefing document has be drafted using the EMA template ([direct download of template](https://www.ema.europa.eu/documents/template-form/chmp-protocol-assistance-scientific-advice-briefing-document-template_en.doc)). Regulatory and procedural guidance on applying for scientific advice, was derived from [EMA guidance for applicants](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/scientific-advice-protocol-assistance-regulatory-procedural-guidance#standard-operating-procedures-and-work-instructions-section).

Diagram

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Figure 5 Scientific Advice and Protocol Assistance procedure from EMA

*Standard operating procedure 01-DEC-15 SOP/H/3037 from* [*EMA regulatory and procedural guidance for scientific advice*](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/scientific-advice-protocol-assistance-regulatory-procedural-guidance#standard-operating-procedures-and-work-instructions-section)*.*

Our completed briefing application documentation ([ema\_scientific\_advice\_submission.pdf](https://www.ema.europa.eu/en/documents/assessment-report/perjeta-epar-public-assessment-report_en.pdf)) includes:

* Introduction including background information on the disease, the product, regulatory status, and rational for seeking advice.
* Overview of product development including quality information, non-clinical information (pharmacology, PK, PD, toxicology), known clinical pharmacology of similar drugs and those predicted for Hertumig (clinical pharmacology, PK, PD, efficacy, and safety).
* Questions on quality development; both non-clinical and clinical development, significant benefit, and other CHMP comments.

## Dylan: Parallel scientific advice

Phase 1 trials will be conducted in Germany and subject to EMA regulations. For expansion into the US market, it is advisable to conduct joint EMA-FDA parallel scientific advice (PSA). Information can be found by request for PSA from either the EMA or FDA ([general principles information](https://www.ema.europa.eu/en/documents/other/general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf)). Further information specific to EMA only can be obtained from the section: EMA [Scientific advice](https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#how-scientific-advice-works-section). Further information specific to FDA only (for US application) can be obtained under the section: FDA [Pre-IND](https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otat-pre-ind-meetings).

## Dylan: Application timetable

Dates of 2023 SAWP meetings and submission deadlines can be found from EMA ([direct download](https://www.ema.europa.eu/en/documents/other/dates-2022-scientific-advice-working-party-sawp-meetings-submission-deadlines-scientific-advice/eunethta-parallel-consultation-requests_en.pdf)). Table 4 lists the planned application deadlines.

Table 4 2023 Submission deadlines - Scientific advice, protocol assistance, qualification of biomarkers

*Dates of 2023 SAWP meetings and submission deadlines. Dates shown are the first available dates. Monthly meetings are held and as such, application can be adjusted to start at any of the available monthly meetings.*

Table

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## Dylan: Dose response studies

We will receive advice to ensure that we have complete the requirements for our dose response studies. Two of the Phase I studies will consist of ascending dose studies in which Hertumig will be administered as a single agent to patients with advanced solid tumors, in doses of 10 up to 250 mg/kg administered as an IV infusion once. Both will be conducted in patients of European ancestry. The studies will be conducted for women who have not received chemotherapy and women who are receiving chemotherapy.

After determining tolerance under both of these conditions, efficacy and toxicity will be assessed in further multidose trials. This will consist of administration of a fixed initial loading dose of 250mg and 100mg weekly doses for 9 weeks. These studies will be conducted for those with and without additional chemotherapy to assess repossesses. PK analysis based on the data from Phase I studies with single-agent Hertumig will quantify the frequency of patients who receive the fixed, non-weight-based dosing regimen (250 mg loading dose with a 100 mg maintenance dose) that achieve steady-state trough serum concentrations that are higher than the target serum concentration (> 20 μg/mL, the target for efficacy predicted from nonclinical models). If the target concentrations are achieved by this dosing regimen, higher doses will not be selected.

## Dylan: Non-clinical aspects

We will receive advice to ensure that we have complete the requirements for our non-clinical studies. Based on *in vitro* and *in vivo* PD data, there is a clear rationale for the inclusion of Hertumig in a drug combination regimen in the treatment of breast cancer. No effects on safety pharmacology end points (respiratory and cardiovascular) are expected in the repeat-dose toxicity studies. The major finding made from our pre-clinical trials from rhesus monkey repeat-dose toxicity studies was severe diarrhoea which led to the need for intensive supportive care and in one case it was necessary to euthanize the animal. In line with ICH guidance, [ICH S6](https://www.ema.europa.eu/en/ich-s6-r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals): Preclinical safety evaluation of biotechnology-derived pharmaceuticals [36] and [ICH S9](https://www.ema.europa.eu/en/ich-s9-non-clinical-evaluation-anticancer-pharmaceuticals): Non-clinical evaluation for anticancer pharmaceuticals [37], no studies on genotoxicity and carcinogenicity have been performed.

According to the [ICH S9](https://www.ema.europa.eu/en/ich-s9-non-clinical-evaluation-anticancer-pharmaceuticals) guidance [37], fertility studies were not required for medicinal products indicated for late-stage cancer. The risk of effects on fertility were obtained from the examination of reproductive organs in our repeat-dose toxicity studies. In the present application, the large majority of male rhesus monkeys used in the repeat-dose toxicity studies were sexually immature. Only one of the male subjects undergoing high-dose (50 mg/kg) Hertumig treatment was sexually mature. Therefore, no information could be obtained on the potential effect of Hertumig on the male reproductive organs. However, evidence of menses was noted for 7 out of 8 female monkeys treated with Hertumig hence the large majority of the female monkeys were sexually mature during the treatment period.

No effects on the female reproductive organs were seen in the repeat-dose toxicity studies performed with Hertumig. Findings made in the rhesus monkeys embryo-fetal development study (HP0031d), consisted of low amniotic fluid volume, high fetal lethality, retarded development, and external (paw hyperextension, paw hyperflexion and microtia), visceral (small lungs, thin ventricular wall and ventricular septum defect, hypoplasia of the collecting glomeruli, renal tubules, collecting tubules and pelvis) and skeletal abnormalities (reduced length of ossified bones). The observed external, visceral and skeletal abnormalities were considered secondary to intrauterine restriction resulting from the oligohydramnios (low amniotic fluid volume).

In humans oligohydramnios may be associated with marked deformation and growth restriction of the fetus due to intrauterine constraint. Moreover, oligohydramnios adversely affects fetal lung development resulting in pulmonary hypoplasia. Histopathologically, kidney hypoplasia was observed in all treated fetuses and this was associated with a dose-dependent increase in severity. HER-family members play an important role in the regulation of growth, differentiation and morphogenesis of renal tissue and the interaction of these receptors may be perturbed by inhibition of HER2 dimerisation by Hertumig. Moreover, it is likely that the ventricular abnormalities in the fetuses were the result of a direct treatment-related effect. As no NOAEL for fetal toxicity was established in this study, it cannot be excluded that the observed fetal toxicity may occur at therapeutic Hertumig concentrations in humans.

In line with guidance [ICH S6](https://www.ema.europa.eu/en/ich-s6-r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals) [36] and [ICH S9](https://www.ema.europa.eu/en/ich-s9-non-clinical-evaluation-anticancer-pharmaceuticals) [37], no studies on genotoxicity and carcinogenicity have been performed. No specific fertility studies in animals have been performed to evaluate the effect of Hertumig. No definitive conclusion on adverse effects can be drawn on the male reproductive organs in rhesus monkey repeated dose toxicity study. Based on the review of the data on non-clinical aspect the following statements to address the potential risk of Hertumig in pregnant women have been included the summary of product characteristics (SmPC).

## Priya: Pre-IND Meeting

VaudBiotech SA. considers the pre-IND (investigational new drug) meeting an excellent opportunity to meet representatives of the regulatory bodies.

Pre-IND meeting objectives –

* Purpose of the study /unmet medical need
* Represent preclinical data
* Represent the proposed plan for the clinical phase and CMC
* Drug development timeline
* Guidance and advice on the IND application

In the following steps of drug development, we aim to get approval to evaluating the efficacy and safety of Hertumig in humans.

## Priya: Scientific Advice

Getting advice and guidance at the early stage of drug development significantly improves the chances of success in drug approval. CHMP (Committee for Medicinal Products for Human Use) on SAWP (the Scientific Advice Working Party) provides scientific advice and protocol assistance to the Hertumig Drug development process. EMA guidance for applicants is a one-stop solution for regulatory and procedural guidelines. A brief progress report and milestones of the drug development process are summarized in the application.

## Priya: Parallel scientific advice

Convincing datasets from preclinical studies encouraged us to introduce Hertumig in the US market. We plan to get approval for the drug in the EU first. Additionally, we would like to initiate the FDA approved process in parallel. We are in the process of getting joint scientific advice (PSA).

# Part E: Inspection Readiness

## Dylan Reasons and readiness key points.

Inspection may be carried out for a number of reasons including:

* Verification of data accuracy that has been submitted
* complaint about a study conduct at any site
* concerns from the sponsor
* termination of any clinical site
* real-time assessment of the investigator’s conduct of the trial
* assessment of protection of human subjects at the request of EMA

Readiness will be prepared by

* Forming an inspection readiness (IR) committee
* IR committee prepares for inspections EMA
* Ensure key documents are listed and available
* Note any deficiency in regulation compliance and provide immediate action
* Form an independent mock inspection team and carry out assessment

Key responsibilities by the IR committee include the review of protocols, ethics and regulatory approval, quality assurance and sops, investigator master file, personnel, facilities, sampling, recruitment and consent, contracts, insurance and indemnity, confidentiality, and adverse events.

Preparations have been made in accordance with European Commission[EudraLex Volume 10](https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en) clinical trials guidelines: Guidance documents containing the common provisions on the conduct of GCP inspections by competent authorities of the different member states (see chapter 4 Inspections); Guidance for the conduct of good clinical practice inspections([pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2008_11/vpl10_an5_10-2008_en.pdf)). [7].

## Priya: Inspection Readiness (IR)

Health authorities (HA), ethical committees (EC), and institutional review boards (IRB) closely follow the process of drug development. Inspection from the regulatory authorities ensures that the drug development process is being conducted as per guidelines, regulations, and compliances. Inspections are an integral part of the drug development process and are carried out for numerous reasons regularly and might be without any intimation. For the preparation of European Commission EudraLex Volume 10 clinical trials Guidelines, Guidance for the conduct of good clinical practice inspections were used.

We have an internal quality management system (QMS) that manages change control, risk management, and corrective action preventive action (CAPA) processes. We also run an inspection readiness program that consists of cross-functional subject matter experts.

* Keep updated with current regulations, guidance, and compliances
* It organizes mock inspections, audits
* Provide unbiased reviews
* Provide formal training to make competent to handle inspections

In VaudBiotech SA, inspection readiness is considered the state of the operation. We are confident and fully equipped to welcome inspectors and satisfactorily answer their questions.

# Overall strategy

## Dylan: Strategy key points

To accelerate the submission process in Germany, with minimum questions from the health authorities and EC/IRB, and obtain rapid HA and EC/IRB approvals we will conduct scientific advice sessions at the earliest possible date with EMA. We will collaborate with experts in this technology who have a proven track record for completing timely regulatory submissions.

We will use our direct connections to regulators to ensure a swift completion. The management plan will allow team leaders to accurately estimate and follow through with their deliverables. CMC and manufacturing control processes have identified key areas that require the most attention and will be continuously monitored in order to avoid delays. We will adhere to our inspection readiness requirements to ensure that all key documents are prepared, listed, and available for review. Team leaders will be assessed for their ability to review such documentation.

We will closely report based on ICH guidelines and validate documentation against EudraLex guidelines. Our reporting format will be assessed during thorough scientific advice and protocol assistance by CHMP with EMA and we will confirm that members of the advice committee can accurately assess our documentation by following the recommendations of SAWP.

## Priya: Overall strategy

We aim to provide safe, effective, and quality drugs to patients. We have strictly and stringently monitored the drug development process to ensure the study is carried out under the regulations, guidance, and compliance. Therefore, we have designed well defined, robust regulatory strategy to ensure Hertumig gets approval to treat HER2+ breast cancer.

The regulatory strategy for Hertumig consists of the following components -

* Literature review for critically and carefully designing studies
* Learn from the past submission in the same category
* Consistent, clear, and precise datasets generated from studies
* Practical and feasible timeline for deliverables
* Timely crosstalk among stakeholders
* Dedicated team for handling documentation, submission
* Dedicated team for CMC and manufacturing (most critical)
* Dedicated IP- patenting team
* Consultation from an expert in the field
* Organize a pre-submission meeting with health agencies for feedback and guidance
* Update on global regulatory requirements
* Streamline strategy
* Strategic and operational outsourcing
* Scientific advice and Protocol assistance from the Scientific Advice Working Party (SWAP)

A robust regulatory strategy will assist in a smooth and swift transition from the preclinical to the clinical phase. We will choose a centralized marketing authorization application (MAA). A single application to EMA is valid for all the members of the EU. We have filed a patent application and aim to get market exclusivity rights for ten years.

# Advice to Management

## Dylan: Achievements, next steps and outcome reasoning

Hertumig has been designed to ameliorate a serious and common disease. Based on a strong background of scientific evidence, this project was carefully developed to rapidly complete key milestones in development and market approval. Using knowledge gained from three decades since the first anti-HER2 mAb development, we have produced a potent and safe therapeutic that offers a promising treatment for patients.

Successful studies *in vitro* and *in vivo* have allowed us to quickly move through the planned pre-clinical trials.

The outcomes in each trial were withing the expected tolerable ranges based on pre-registered statistical analysis plans. Therefore, we are confident that we are on track for progressing to clinical trials in a small number of human participants. After completing these tolerance studies, which due to similarity to existing mAb therapeutics and existing evidence are likely to successfully complete, we will be prepared to increase testing in our pivotal phase 2 studies.

Due to our careful manufacturing design process, we are prepared for large scale production without any further modification for regulatory requirements. Risk assessments are continuously being monitored with several major milestones already complete.

Market authorization is likely to be successful based on our adherence to regulatory guidelines and collaboration with the authorities during scientific advice phases. The key documentation used is this process is included in the references section.

We look forward to updating you at our next meeting to report on phase 1 clinical trials.

## Priya: Advice to Management

A Hertumig drug development process has been planned considering the limitations of the currently available treatment for breast cancer. Per current regulations and guidelines, the Hertumig drug discovery and development plan has been carefully and critically drafted by our team.

In a preclinical and clinical phase I studies, safety and efficacy were evaluated in the first place. Convincing robust datasets from our preclinical studies established a reliable platform for clinical phase I studies. Simultaneous optimization of the manufacturing design process prepared us for the large-scale production of the drug. Regulatory guidelines were followed strictly and stringently for the large-scale production of Hertumig. In addition, the necessary documentation supporting our studies has been completed and submitted on time.

In summary, we will deliver a safe, efficacious, quality drug, Hertumig, which can be a crucial player in HER2+ breast cancer treatment. Datasets from our preclinical and phase I clinical study give us the impression that we will complete subsequent phases of the drug development process in time.

# Conclusion

## Dylan: Summary

Based on a strong scientific background of anti-HER2 mAb production and delivery, we are confident that Hertumig will successfully complete phase 1 clinical trials. Our manufacturing process has been design based on best principles derived from over 100 FDA-approved mAb therapies [9]. The CMC and production plan has been developed to ensure adherence to regulatory guidelines. We have worked with regulatory authorities to receive scientific advice about our submission package and have thus far fulfilled all requirements without challenge. All questions about ambiguity in regulatory documentation have been answered. Our pre-clinical trials have completed on schedule without any unplanned events. Therefore, we are confident about completing the next phase on target.

## Priya: Summary

In this study, we are explicitly targeting the HER+ positive subtype of breast cancer. Hertumig drug discovery, development, and production were planned and executed according to current regulatory guidelines and compliances. So far, we have completed preclinical studies in time without any adverse events. We have determined the First- in- human dose and evaluated the safety and efficacy of the Hertumig by *in vivo* and *in vitro* assays. In addition, a combinational study with existing therapies was carried out. We are confident to enter the next stage of the drug development process

# Supplemental

Dylan: introduction on therapeutic mAb.

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