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OBSERVATIONAL STUDY PROTOCOL CA180653

Determining Change in Cardiovascular and Metabolic Risks in Patients with Chronic Phase Chronic Myeloid Leukemia Receiving BCR-ABL Tyrosine Kinase Inhibitor First-Line Therapy in the United States

Protocol Amendment Number: 02

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DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|-----------------------|---------------|---|
| Protocol Amendment 02 | 17-Dec-2020 | <ul style="list-style-type: none">• Updated study personnel contact information• Added minor clarification for the coronary calcium scoring• Made minor revisions to the Notes of the Medical History On-Treatment table• AE section was updated to be consistent with current Protocol Model Document (PMD)• The email address for safety reporting was updated. |
| Revised Protocol 01 | 19-Sep-2018 | <ul style="list-style-type: none">• Updated study personnel contact information• Updated BMS address• Bosutinib was added as an acceptable first line drug for study inclusion.• Imaging (CT and echocardiogram) can be done within 2 weeks of starting the first TKI dose. |
| Original Protocol | 25-Oct-2016 | Not Applicable |

SYNOPSIS

Observational Study Protocol CA180653

Protocol Title: Determining Change in Cardiovascular and Metabolic Risks in Patients with Chronic Phase Chronic Myeloid Leukemia Receiving BCR-ABL Tyrosine Kinase Inhibitor First-Line Therapy in the United States

Department: US Medical

Objectives: In patients who are tyrosine kinase inhibitor (TKI)-naïve and are initiating first-line TKIs (dasatinib, imatinib, or nilotinib) in routine clinical practice in the United States, the objectives are:

Primary Objectives

- To evaluate the changes in cardiovascular risk from baseline using the Framingham Coronary Heart Disease Score
- To evaluate the changes in metabolic risk from baseline using metabolic lab values

Secondary Objectives

- To evaluate the incidence of cardiovascular or metabolic disease and/or exacerbation of comorbidity (ies)
- To assess the safety and tolerability of first-line BCR-ABL TKIs in adults with CP-CML
- To describe clinical outcomes (including survival, major molecular response [MMR], cytogenetic response [CCyR], [cCHR])
- To identify time to development of clinical outcomes
- To assess treatment patterns and management of adverse events and comorbid disease
- To determine factors associated with initial treatment choice and change of treatment

Exploratory Objectives

- To identify biomarkers that are predictive of an increased risk for cardiovascular or metabolic disease

Study Design: This non-interventional, prospective study will characterize the impact of three approved first and second generation BCR-ABL1 tyrosine kinase inhibitors on cardiovascular and metabolic risk factors in chronic phase CML (CP-CML) treated patients who are TKI naïve and initiating first-line TKIs in routine clinical practice in the US. All treatment decisions will be determined at the discretion of the treating physician(s) and data identifying the cardiovascular and metabolic risk factors will be collected. Additional fasting blood samples (collected following 8 hours of fasting) will be collected during routine, standard of care (SOC) routine office visits. Additional diagnostic imaging will be performed and will be reviewed by core imaging laboratory. As the study is collecting data on management of CML, this study will not influence the prescribing or management practices at participating sites.

Study Population: Newly-diagnosed, treatment-naïve CP-CML patients who are ≥ 18 years at the time of CP-CML diagnosis who are scheduled to initiate treatment with dasatinib, imatinib, Nilotinib or Bosutinib are eligible for enrollment. Enrolled patients (n=200) will be distributed across the 3 patient treatment groups of newly diagnosed CP-CML patients who will initiate their first-line TKI treatment.

Data Collection Methods: Data collection will include extraction of medical records via case report forms, blood and urine samples for SOC and biomarker research, and additional diagnostic imaging. No additional patient visits outside of standard of care will be required.

Data Analyses: All statistical analyses are performed with the understanding that this is a phase 4, non-interventional study, where treatment assignment is based on the investigator's judgment and there is no treatment randomization. Due to the nature of non-interventional research, confounding factors are not controlled in the real-life setting. No statistical comparisons will be performed between treatment cohorts.

Sample Size/Power: The primary objective of this study is to evaluate change in risk from baseline for specific CV and metabolic conditions (eg, change in Framingham coronary heart disease score, development of cardiovascular/metabolic risk variables and comorbidities), in the patient sample. Summary statistics will be provided around the proportion of patients who develop these specified clinical and disease characteristics.

Limitations/Strengths:

Limitations: One of the limitations of the study includes 24-months timeframe between baseline and end-of-study data collection. This time period is suitable in evaluating short term clinical outcomes but may not be sufficiently long period of time to assess longer term clinical outcomes.

A potential limitation is the sample size, which may not be sufficiently large to analyze some of the stratifying variables with sufficient statistical power. Therefore, the study will focus on select common adverse events.

Finally, all non-interventional observational data are potentially subject to unmeasured confounding limiting causal interpretation.

Strengths: This prospective study will include patient populations who suffer from the disease that physicians encounter in clinical practice and in the real world, therefore enhancing the generalizability of study results.

The collection of fasting blood and urine samples for central laboratory biomarker analysis and diagnostic imaging for core imaging laboratory evaluation will allow additional data generation on cardiac and metabolic risks without potential impact of altering treatment during study.

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1 INTRODUCTION

1.1 Study Rationale

BCR-ABL1 targeted tyrosine kinase inhibitor (TKIs) have changed the treatment landscape in chronic myeloid leukemia (CML) with age-adjusted life expectancy approaching that for similar patients without CML. Before TKI therapy approval, survival for patients with CML was poor. Only 40% of patients 20 to 44 years of age remained alive at 5 years after diagnosis. Older patients (> 65 years) had worse outcomes, with a 5-year overall survival (OS) rate of approximately 20%.¹ The FDA approval of imatinib mesylate in 2001 changed both the care of patients with CML and raised the prospect of a targeted approach to cancer therapies.² Although imatinib has dramatically altered the inevitable disease progression of CML, > 30% of patients with CML will either be unable to tolerate or will develop resistance to imatinib. As a result, newer generations of BCR-ABL kinase inhibitors including dasatinib, nilotinib, bosutinib, and ponatinib have been developed. Three BCR-ABL1 TKIs (dasatinib, imatinib, and nilotinib) are indicated for the treatment of chronic phase CML in previously untreated patients and have a Category 1 recommendation in the National Comprehensive Cancer Network (NCCN) guidelines for newly diagnosed CP-CML patients.³ Imatinib and these second-generation TKIs (dasatinib and nilotinib) now constitute the backbone of CML treatment and clinical outcomes for patients with CML have dramatically improved over the past decade.^{4,5}

With the advent of BCR-ABL targeted TKIs for CML, a novel paradigm of indefinite, continuous, uninterrupted therapy has become the standard. This regimen is different from historical regimens for other primary therapies aimed at remission induction and/or cure. While treatment-free remission is an active area of research and defined duration of treatment and ‘functional cure’ is developing as a goal of therapy, patients require several years of therapy and the current standard regimen is uninterrupted, indefinite treatment. The 4-year overall survival rate for CML patients is as high as 95%,⁶ and survival rates of CML patients who experience a complete cytogenetic response is comparable to their age-matched control subjects.⁷ With this prolonged survival, patients have the risk to develop unwanted comorbidities such as cardiovascular or metabolic complications, which have the potential to be exacerbated by targeted TKI treatment. Clinical outcomes do not solely rely on treatment efficacy but also on how well therapy is tolerated and on the development of comorbidities. Therefore, it is essential that physicians prevent or manage these complications associated with the use of these agents. Overall, TKIs have demonstrated a favorable safety profile in both the clinical trial and real world setting. Although many patients may experience adverse events, they are more often mild to moderate and usually resolve with adequate treatment management or are resolved shortly upon treatment dose reduction/discontinuation. Whenever a treatment interruption is required due to intolerance, re-treatment with the same TKI or a switch to an alternative TKI is able to control disease in the majority of the cases.⁸

The potential of long-term toxicities for individual patients on chronic therapy should be considered when a first line TKI is selected. The decision of which TKI to use must take into account disease-related, TKI-related, and patient-related variables.⁹ Disparate clinical trial

inclusion and exclusion criteria, differing patient populations, and treatment options make it difficult to perform cross trial comparisons and to evaluate the optimal treatment option in this setting. Table 1.1-1 shows a subset of reported cardiac and metabolic adverse events for first generation and second generation TKIs.

Table 1.1-1: Select Reported Cardiac and Metabolic Adverse Events, Warnings, and Precautions from Tyrosine Kinase Inhibitor

| TKI | Reported Data | Warnings and Precautions |
|-------------------------|---|---|
| Dasatinib (Sprycel®) | Cardiac ischemic events in 3.9% of dasatinib-treated patients in DASISION Transient hypoglycemia seen in small studies | Monitor symptoms and treat appropriately |
| Imatinib (Gleevec®) | Congestive heart failure and left ventricular dysfunction in 0.7% of patients in IRIS trial (most patients had previous medical history of cardiac disease) Hypoglycemia | Patients with cardiac disease or risk factors for cardiac disease should be monitored carefully |
| Nilotinib (Tasigna®) | Cardiovascular events occurred in 9.3% and 15.2% of patients who received 300 mg and 400 mg BID, respectively Transient hypoglycemia grade 3/4 (6% to 12%); hypercholesterolemia (28%); associated with peripheral occlusive disease, increased LDL fraction, hypertriglyceridemia | Cardiac and arterial occlusive events have been reported in CML patients; evaluate patient for cardiovascular risk factors and monitor/manage appropriately |

Cardiovascular and metabolic risk

Cardiovascular and metabolic complications associated with first and second generation BCR-ABL TKI treatment of chronic phase CML have been seen in registration studies. In clinical practice, evidence of elevation of risk factors for both cardiovascular and metabolic events has been shown with TKI treatment. A correlation between predictive risk factors and an increase of cardiovascular or metabolic disease will allow a vehicle to assess the safety of first and second generation BCR-TKIs and anticipate elevations of the risk for these adverse events. Due to differential off-target effects of these agents, adverse event profiles vary between BCR-ABL TKIs. Nilotinib treatment appears to have the most off-target toxicity leading to cardiovascular and metabolic adverse events, while imatinib and dasatinib have lower number of adverse events than nilotinib, but with similar incidence. Overall, the onset of these risk factors will be measurable within the first 2 years of treatment.

The Framingham Heart Study defines cardiovascular disease as a composite of coronary heart disease (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure.¹⁰ The impact of

preexisting cardiovascular risk on the development of CVEs during TKI therapy has been investigated. Hochhaus et al used baseline Framingham general cardiovascular risk scores and analyzed downstream events for all evaluable patients treated with either nilotinib or imatinib in the ENESTed trial. Using the Framingham Heart Study definition,¹¹ the majority of patients had scores in the low-risk category (ie, 10% predicted risk of experiencing a first cardiovascular disease event over 10 years with a smaller proportions of patients had scores in the intermediate-risk (ie, ≥ 10% to 20% predicted risk of experiencing a first cardiovascular disease event over 10 years) or high-risk (ie, ≥ 20% predicted risk of experiencing a first cardiovascular disease event over 10 years). During study treatment, CVEs occurred most frequently among patients in the high-risk and intermediate-risk categories, whereas patients in the low-risk category experienced fewer CVEs. Framingham general cardiovascular risk scores were evaluable for two of the three patients with deaths temporally associated with CVEs during study treatment both of these patients had scores in the intermediate-risk range.

Cardiovascular events

Atherosclerosis, the underlying cause of cardiovascular disease, results when you have a build-up of cholesterol plaque in your arteries for which LDL cholesterol is a major culprit. For this reason, the guidelines recommend therapy aimed at lowering LDL cholesterol in patients at metabolic risk to reduce risk for cardiovascular (CV) disease. In a head to head study of nilotinib versus imatinib, newly diagnosed patients with CML demonstrated higher levels of elevated total cholesterol (28% vs 4% patients) and elevated triglycerides (12% vs 8% patients) after receiving nilotinib or imatinib, respectively. Correlation of these risk factors to cardiovascular events is seen as more patients experienced a CV event, as defined by ischemic heart disease, ischemic cerebrovascular events, peripheral artery disease and other cardiovascular events at 5 years.¹² Table 1.1-2 shows CV AEs in patients treated with nilotinib and imatinib.

Table 1.1-2: Cardiovascular Adverse Events in Patients treated with TKIs in ENESTnd Trial

| | Nilotinib 300 mg twice daily (n = 279) | | Nilotinib 400 mg twice daily (n = 277) | | Imatinib 400 mg once daily (n = 280) | |
|--------------------------------|--|-----------|--|-----------|--------------------------------------|-----------|
| | Any grade | Grade 3/4 | Any grade | Grade 3/4 | Any grade | Grade 3/4 |
| Cardiovascular events | 21 (7.5) | 13 (4.7) | 37 (13.4) | 24 (8.7) | 6 (2.1) | 5 (1.8) |
| Ischemic heart disease | 11 (3.9) | 6 (2.2) | 24 (8.7) | 17 (6.1) | 5 (1.8) | 4 (1.4) |
| Ischemic cerebrovascular event | 4 (1.4) | 3 (1.1) | 9 (3.2) | 6 (2.2) | 1 (0.4) | 1 (0.4) |
| Peripheral artery disease | 7 (2.5) | 4 (1.4) | 7 (2.5) | 3 (1.1) | 0 | 0 |

When the incidence of these CV events were analyzed by year of nilotinib and imatinib treatment, events occurred within the first two years of treatment and were distributed across treatment years up to 7 years, as seen in Table 1.1-3.¹³

Table 1.1-3: Cardiovascular events by year of treatment in ENESTnd Trial

| First Cardiovascular Event by Year, n(%) | Nilotinib 300 mg BID (n = 279) | Nilotinib 400 mg BID (n = 277) | Imatinib 400 mg QD (n = 280) |
|--|-----------------------------------|-----------------------------------|---------------------------------|
| < 1 year | 4 (1.4) | 10 (3.6) | 2 (0.7) |
| ≥ 1 year to < 2 year | 4 (1.4) | 6 (2.2) | 1 (0.4) |
| ≥ 2 year to < 3 year | 7 (2.5) | 6 (2.2) | 1 (0.4) |
| ≥ 3 year to < 4 year | 4 (1.4) | 4 (1.4) | 1 (0.4) |
| ≥ 4 year to < 5 year | 1 (0.4) | 6 (2.2) | 1 (0.4) |
| ≥ 5 year to < 6 year | 5 (1.8) | 9 (3.2) | 1 (0.4) |
| ≥ 6 year to < 7 year | 3 (1.1) | 2 (0.7) | 1 (0.4) |
| ≥ 7 year to < 8 year | 0 | 1 (0.4) | 0 |

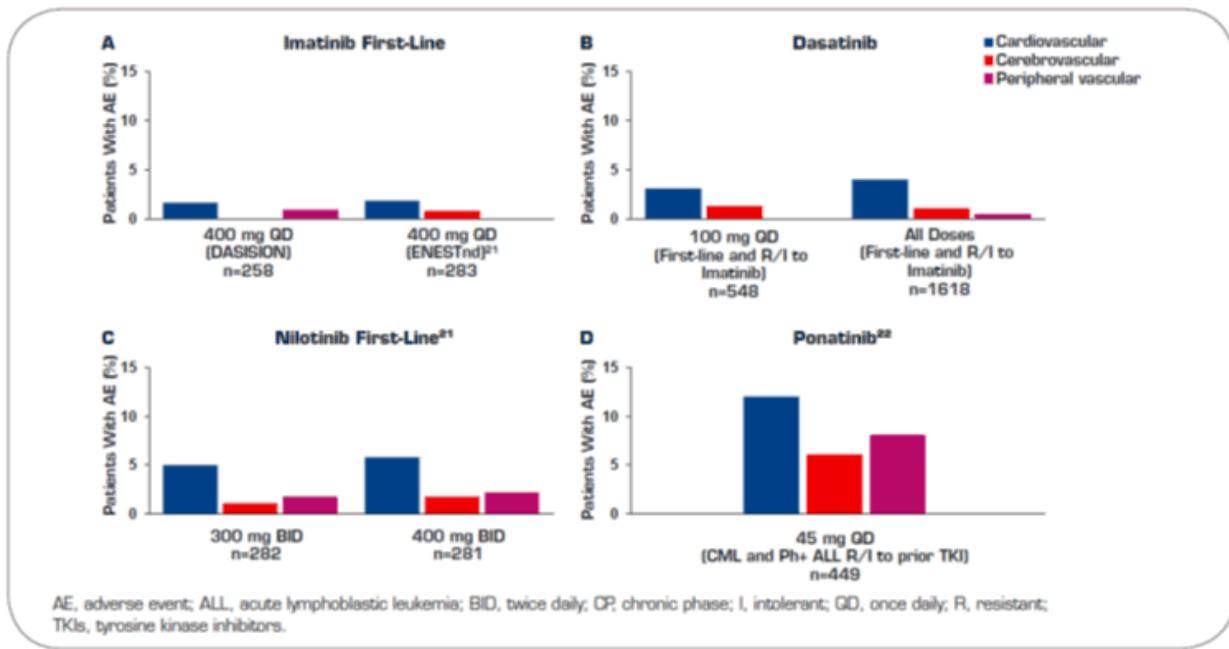
Regarding the incidence of dasatinib-associated cardiovascular events, the DASISION study (CA180056) showed that the majority of CV events occurred within the first year of treatment with few events at later treatments (see Table 1.1-4).¹⁴ This contrasts to what was seen with nilotinib and imatinib which had consistent incidences out to 6 years.

Table 1.1-4: Time to First CV Ischemic Event by Age: Pooled Ph+ Population

| | Treated patients | | | | | | Patients with event/ at risk, n/n [%] | |
|------------------------------|-----------------------|-----------|------------------------|----------|---------|--------|---------------------------------------|--|
| | Imatinib 400 mg QD | | Dasatinib 100 mg QD | | | | | |
| | Total | Total | ≤ 44 y | 45-64 y | 65-74 y | ≥ 75 y | | |
| Total patients | 258 (100) | 258 (100) | 120 (47) | 113 (44) | 18 (7) | 7 (3) | | |
| No CV ischemic event | 254 (98) | 248 (96) | 118 (98) | 108 (96) | 17 (94) | 5 (71) | | |
| CV ischemic event | 4 (2) | 10 (4) | 2 (2) | 5 (4) | 1 (6) | 2 (29) | | |
| Timing of first event | | | | | | | | |
| 0 to < 6 months | 0 | 4 (2) | 1 (1) | 2 (2) | 5 (4) | 1 (6) | 7/258 (3) | |
| 6 to < 12 months | 1 (< 1) | 3 (1) | 0 | 2 (2) | 0 | 1 (14) | | |
| 1 to < 2 years | 0 | 0 | 0 | 0 | 0 | 0 | | |
| 2 to < 3 years | 2 (1) | 2 (1) | 0 | 1 (1) | 0 | 1 (14) | | |
| 3 to < 6 years | 1 (< 1) | 1 (< 1) | 1 (1) | 0 | 0 | 0 | 1/185 (1) | |

Comparing the incidence across all BCR-ABL TKIs, nilotinib has a higher rate of cardiovascular events as compared to imatinib, while dasatinib has similar CVEs as imatinib (Figure 1.1-1).¹⁵

Figure 1.1-1: Arterial Ischemic Events Reported in Patients Treated with TKIs across CML-CP Trials



Metabolic Disease

Several risk factors are predictive of the development of metabolic disease and include:

- body mass index (BMI)
- high triglycerides (≥ 150 mg/dL) or currently taking medication to lower triglycerides
- low levels of high-density lipoprotein cholesterol (< 40 mg/dL in men or < 50 mg/dL in women), or currently taking medication to increase HDL
- high blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic) or taking blood pressure medication
- high blood glucose (fasting glucose ≥ 100 mg/dL) or currently taking medication to lower glucose levels.

The impact of first and second generation BCR-ABL TKIs and these risk factors have been directly assessed in a number of studies. In the ENESTnd study, hyperglycemia (all grades) occurred in 50% and 31% of patients in the nilotinib and imatinib arms, respectively. In a separate analysis of 168 consecutive patients with CML, Iurlo et al specifically investigated these parameters in patients currently being treated with BCR-ABL TKIs. [Table 1.1-5](#) shows demographic features.

Table 1.1-5: Clinical features of 168 CML-chronic phase patients treated with imatinib, dasatinib, or nilotinib.

| | Imatinib group (n = 92) | Dasatinib group (n = 40) | Nilotinib group (n. =36) | P-value |
|--|----------------------------|-----------------------------|-----------------------------|---------|
| Age (years), median (range) | 59.2 (21.2-87.5) | 54.9 (24.5-82.6) | 46.0 (25.1-79.0) | 0.0044 |
| Male/Female, n | 49/43 | 23/17 | 20/16 | 0.90 |
| Length of treatment (months), median (range) | 93.0 (0.4-165.5) | 41.6 (3.0-97.1) | 16.1 (0.1-70.0) | 0.0001 |

Note: P values from Kruskal-Wallis (continuous variables) or chi-squared (categorical variables) test.

Iurlo et al identified that the group treated with nilotinib had significantly higher levels of fasting plasma glucose, insulin, C-peptide, insulin resistance, and total and LDL cholesterol than the imatinib (n=92) and dasatinib (n=40) groups.¹⁶ These changes are evident within the first 16 months of treatment, as seen in Table 1.1-6 and [Table 1.1-7](#).

Table 1.1-6: Multiple regression analysis adjusted for centre, gender, age, BMI, and length of treatment, comparing dasatinib versus nilotinib group.

| | Dasatinib group (n = 40) | Nilotinib group (n = 36) | Coefficient (95% CI)* | P-value* |
|-------------------------|--------------------------|--------------------------|-----------------------|-----------|
| FPG (mg/dl) | Reference | 9.7 (2.5; 16.9) | 0.009 | |
| Insulin (%) | Reference | 22.1 (11.6; 33.6) | <0.001 | |
| C-peptide (%) | Reference | 16.2 (9.4; 24.0) | <0.001 | |
| HOMA-IR (%) | Reference | 27.1 (16.2; 40.5) | <0.001 | |
| HOMA-%B (%) | Reference | 7.3 (-4.9; 20.9) | 0.27 | |
| Total cholesterol (%) | Reference | 3.9 (-0.8; 8.3) | 0.10 | |
| HDL cholesterol (%) | Reference | 3.0 (-2.0; 8.3) | 0.24 | |
| Triglycerides (%) | Reference | -5.8 (-14.8; 4.1) | 0.23 | |
| LDL cholesterol (mg/dl) | Reference | 14.8 (-2.5; 32.1) | 0.09 | |
| | | OR (95% CI)** | | P-value** |
| DM/IFG | Reference | 1.3 (0.4; 4.1) | | 0.69 |
| MS | Reference | 0.5 (0.2; 1.9) | | 0.34 |

Note: BMI= body mass index; CI= confidence interval; OR= odds ratio; FPG= fasting plasma glucose; HOMA-IR= Homeostasis Model Assessment – Insulin Resistance; HOMA-%B= Homeostasis Model Assessment – β-cell function; DM= diabetes mellitus; IFG= impaired fasting glucose; MS= metabolic syndrome.

*From multiple linear regression models **From multiple logistic regression models

Table 1.1-7: **Multiple regression analysis adjusted for center, gender, age, BMI, and length of treatment, comparing nilotinib versus imatinib group.**

| | Imatinib group (n = 92) | Nilotinib group (n = 36) | |
|-------------------------|-------------------------|--------------------------|-----------|
| | | Coefficient (95% CI)* | P-value* |
| FPG (mg/dl) | Reference | 9.8 (1.9; 17.8) | 0.015 |
| Insulin (%) | Reference | 17.4 (6.2; 30.3) | 0.002 |
| C-peptide (%) | Reference | 11.6 (4.1; 19.7) | 0.002 |
| HOMA-IR (%) | Reference | 22.1 (9.4; 37.7) | <0.001 |
| HOMA-%B (%) | Reference | 2.0 (-9.5; 10.5) | 0.76 |
| Total cholesterol (%) | Reference | 11.6 (7.3; 16.2) | <0.001 |
| HDL cholesterol (%) | Reference | 6.2 (1.0; 11.6) | 0.02 |
| Triglycerides (%) | Reference | 3.6 (-5.8; 13.9) | 0.048 |
| LDL cholesterol (mg/dl) | Reference | 42.4 (27.0; 57.8) | <0.001 |
| | | OR (95% CI)** | P-value** |
| DM/IFG | Reference | 1.7 (0.5; 5.8) | 0.39 |
| MS | Reference | 0.6 (0.2; 2.4) | 0.46 |

Note: BMI= body mass index; CI= confidence interval; OR= odds ratio; FPG= fasting plasma glucose; HOMA-IR= Homeostasis Model Assessment – Insulin Resistance; HOMA-%B= Homeostasis Model Assessment – β-cell function; DM= diabetes mellitus; IFG= impaired fasting glucose; MS= metabolic syndrome.

*From multiple linear regression models.

**From multiple logistic regression models

Selecting a First line Therapy: Focus on Cardiovascular (CV) and Metabolic Considerations: The NCCN recommends the choice of TKI therapy in a given patient be based on the risk score, physician experience, age, ability to tolerate therapy, and the presence of comorbid conditions. A comprehensive work-up that includes multiple considerations (ie toxicity and comorbidities) to better define which patients would be ideal candidates for certain TKIs is limited to the discussion section of the NCCN guidelines and expert opinion publications.

Long-Term Considerations: CV and Metabolic Considerations: As experience with TKIs continues to evolve beyond initial clinical trials, long-term outcomes continue to be reported. Markers of long-term outcomes can include progression to accelerated or blast phase; however, more patients are dying from comorbidities rather than CML. The importance of comorbidities has been linked with an increased Charlson Comorbidities Index associated with decreased overall survival. The role of TKIs exacerbating these comorbidities or precipitating new conditions has been documented for CV and metabolic events. Further understanding to inform guideline development to increase awareness and education is needed.

The study is being conducted in an effort to better understand incidence rates of comorbidities, risk factors, and outcomes associated with adverse events in the real world setting in the United States (US).

1.2 Research Questions

In TKI- naïve chronic-phase (CP)-CML patients who are initiating first line TKIs (dasatinib, imatinib, or nilotinib) in routine clinical practice in the US:

- What are the increased risks for cardiovascular or metabolic disease?
- What are the safety and effectiveness outcomes?
- What are the treatment and management patterns of cardiovascular and metabolic disease?
- What parameters are associated with increased risk of cardiovascular or metabolic disease?

2 OBJECTIVES

In patients who are tyrosine kinase inhibitor (TKI)-naïve and are initiating first-line TKIs (dasatinib, imatinib, or nilotinib) in routine clinical practice in the US, the objectives are:

2.1 Primary Objectives

- To evaluate the changes in cardiovascular risk from baseline using the Framingham Coronary Heart Disease Score
- To evaluate the changes in metabolic risk from baseline using metabolic laboratory values

2.2 Secondary Objectives

- To evaluate the incidence of cardiovascular or metabolic disease and/or exacerbation of comorbidity(ies)
- To assess the safety and tolerability of first-line BCR-ABL TKIs in adults with CP-CML
- To describe clinical outcomes (including survival, major molecular response [MMR], complete cytogenetic response [CCyR], complete hematologic response [CHR])
- To identify time to clinical outcomes
- To assess treatment patterns and management of adverse events and comorbid disease
- To determine factors associated with initial treatment choice and change of treatment

2.3 Exploratory Objectives

- To identify biomarkers that are predictive of an increased risk for cardiovascular or metabolic disease
- To identify safety imaging parameters that are predictive of increased risk for cardiovascular disease

3 STUDY DESIGN

3.1 Overview of Study Design

This prospective, cohort study is intended to characterize the impact of three approved first and second generation BCR-ABL1 tyrosine kinase inhibitors (ie, dasatinib, imatinib, nilotinib, and

bosutinib) on cardiovascular and metabolic risk factors in CP-CML treated patients who are TKI-naïve and initiating first line TKIs in routine clinical practice in the US.

The Framingham 10-year general CVD risk prediction equations will be used as a basis for assessing risks and is shown in [Appendix 1](#). The National Heart, Lung, and Blood Institute (NHLBI) provide a Risk Score calculator and an interactive Risk Assessment Tool. The development of these CVD risk prediction equations were the outcome of extensive data from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies,^{[17,18,19](#)} and from the Framingham Original and Offspring Study cohorts.^{[20,21](#)}

Standard of care effectiveness assessments will be collected, as available. All testing for cytogenetic analysis (FISH, karyotype), molecular analysis (Q-PCR), and any mutational analysis performed at local sites will be collected. Current National Comprehensive Cancer Network (NCCN) Guidelines note that monitoring response to TKI therapy and mutational analysis should occur every 3 months after initiating treatment. After CCyR has been achieved, NCCN Guidelines notes that monitoring should occur every 3 months for 2 years and every 3 to 6 months, thereafter. CA180653 study data will be collected at all SOC routine office visits where possible.

A 24 month data collection period will include extraction of medical records via case report forms and the additional collection of fasting blood samples and urine (collected following 8 hours of fasting) for metabolic panels during routine office visits. All treatment decisions will be determined by treating physician(s) and no additional patient visits outside of standard of care will be required. As the study is collecting data on cardiovascular and metabolic risk factors in parallel with the management of CML, this study will not influence prescribing or management practices at participating sites.

Fasting blood samples will be collected as part of routine office visits for blood collection as per standard of care treatment timelines. Additional blood and urine samples for biomarker analyses will be collected for metabolic panels. Results from biomarker analyses will be analyzed and presented in the final study report. Safety imaging will be conducted as part of routine office visits as per standard of care treatment timelines. Results from diagnostic imaging will be analyzed and presented in the final study report and where possible procedures done as part of routine office visits will be analyzed and presented in the final study report.

Approximately 25 academic and community-based sites in the US will be recruited to enroll an estimated 200 patients. In order to best capture representative treatment patterns for follow-up as well as maximize the chances of capturing quality data on cardiovascular and metabolic risk, site recruitment will include academic and community-based sites. Enrollment will be competitive across all sites.

3.2 Study Population

Newly-diagnosed, treatment-naïve CP-CML patients (n = 200) who are ≥ 18 years at the time of CP-CML diagnosis who are scheduled to initiate treatment with dasatinib, imatinib, nilotinib, or bosutinib^{[22](#)} are eligible for enrollment at 12 participating sites.

No enrollment caps are planned for the four TKIs of interest (dasatinib, imatinib, nilotinib or bosutinib) and these cohorts will be filled according to natural distribution among eligible participants for this study. However, at the sponsor's discretion, enrollment into a specific cohort may be suspended to ensure equally representative cohorts are available for analysis.

3.2.1 *Inclusion Criteria*

- 1) ≥ 18 years at the time of Ph+ CP-CML diagnosis
- 2) Newly diagnosed chronic phase of Ph+ CP-CML, confirmed with cytogenetic and/or molecular testing at baseline
- 3) Treatment-naïve and initiating treatment with dasatinib, imatinib, nilotinib, or bosutinib
- 4) Willingness and ability to comply with routine office visits

3.2.2 *Exclusion Criteria*

- 1) Any other prior or active non-CML active malignancy for which the patient is receiving treatment
- 2) Participation in a therapeutic clinical trial for CML disease

3.3 *Data Source/Data Collection Process*

This study will employ prospective data collection based local sites entering data in electronic Case Report Forms (eCRFs). The investigator-accessed eCRF will be password-protected to ensure security and confidentiality. Investigators will assign a unique identifier for each patient, alive or deceased, enrolled in the study. This identifier will be used to facilitate follow-up on data queries and validation.

3.3.1 *Study Assessments*

Clinical assessments or laboratory data, as part of routine clinical care, will be collected, which normally includes visits every three months. All cardiovascular assessments (eg, EKG, vital signs, ankle brachial index, etc) will be collected. Additional fasting blood sample and urine collection for biomarker analyses will be collected to assess cardiovascular and metabolic risks. Additional diagnostic imaging (ie, echocardiogram, coronary calcium scoring) will be collected.

3.3.1.1 *Blood Sample Collection for Biomarker Assessments*

Fasting blood samples (collected following 8 hours of fasting) will be collected during routine office visits as per SOC blood testing. Additional volumes of blood will be drawn for metabolic profiling and biomarker analysis and will be required for all participants receiving treatment. These fasting blood samples will be used to test the biochemical composition and changes that evolve during treatment. Measuring these biochemical changes in the metabolome will help identify cardiovascular and metabolic risks in this treatment population. No additional visits for blood sample collection will be required. In a rare instance if patient was not fasting at baseline, the site is allowed to collect fasting samples at any visit prior to start of the TKI therapy.

The timing of blood collection for biomarker assessment will correspond with standard practice blood draw schedules at each institution with the exception that 8h fasting is required. Blood collection should occur prior to administration of therapy. All evaluations of blood samples will

be conducted within the scope of the informed consent. The contract research organization (CRO) will provide the sites with shipping kits for shipment of biomarker blood samples to the CRO. The CRO will be responsible for mailing the biomarker samples to a BMS-designated laboratory for storage until further testing and analyses.

3.3.1.2 Additional Research Collection

This protocol will include residual sample storage for additional research (AR). Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Samples kept for future research will be stored at the BMS Biorepository in Hopewell, NJ, USA or an independent, BMS-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

3.3.1.3 Urine Sample Collection

Urine tests will be administered along the same schedule as blood sample collection. Increased urinary protein excretion may be an early clinical manifestations of cardiovascular and metabolic disease, such as diabetic nephropathy or underlying cardiovascular disease.^{23,24,25,26,27}. Moderately increased albuminuria tests will be used to assess early changes in vascular endothelial function. In conjunction with the creatinine test results from SOC blood work, the albumin-to-creatinine ratio may be calculated. As the waste product, creatinine is removed and secreted, albumin levels may increase due to hypertension of metabolic disease (eg, diabetes).

The timing of urine collection for biomarker assessment will correspond with standard practice blood draw schedules at each institution. Urine collection should occur prior to administration of therapy. All evaluations of urine samples will be conducted within the scope of the informed

consent. The contract research organization (CRO) will provide the sites with urine test strips for local urinalysis.

Further details of sample collection and processing will be provided to the site in the procedure manual.

3.3.1.4 *Diagnostic Imaging*

All radiologic imaging from this study will be transmitted to a centralized imaging core lab and will be reviewed by a central review committee as determined by the Sponsor. Sites will be trained in image acquisition parameters and submission process, prior to scanning the first study subject. If required, central imaging results may be provided to local site if a patient has a cardiac event after imaging data acquisition. Local reads are done as per standard of care. Analysis of study imaging will be performed periodically during study conduct and results will be released in the final study report. These guidelines will be outlined in a separate CA1803653 Site Imaging Manual and Imaging Charter.

Non contrast cardiac CT, which provides the **coronary calcium scoring** is a non-invasive imaging test that allows high-resolution, three-dimensional visualization of the heart coronary arteries and other adjacent structures and does not require administration of iodinated contrast. Coronary calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (eg, Agatston score) and categorized as minimal (0 to 10), mild (10 to 100), moderate (100 to 400), or severe (> 400). Coronary artery calcium (CAC) scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).²⁸ Coronary calcium scoring will be done centrally, not required by the study to be done locally.

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, although current image quality lags behind two-dimensional ultrasound.

In addition to the generation of two-dimensional images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers.²⁸

3.3.1.5 *Treatment Patterns and TKI Selection*

Treating physicians select TKIs based on different criteria, such as disease characteristics, adverse event profiles, comorbidities, and patient preference.²⁹ Correlations between certain off-target

activities and AEs associated with TKI treatment are currently under investigation. To determine factors associated with initial treatment choice and change of treatment, treating physicians will complete questions within the eCRF after enrollment and THI treatment choice has been decided.

Table 3.3.1.5-1: Screening Procedural Outline (CA180653)

| Procedure | Screening | Notes |
|---|-----------|--|
| Eligibility Assessments | | |
| Informed Consent | X | |
| Inclusion/Exclusion Criteria | X | |
| Medical History | X | Including Sokal score, Framingham Coronary Heart Disease Score smoking status, history of HTN, hyperlipidemia, hyperglycemia (prediabetes) |
| Concomitant medications | X | |
| Safety Assessments | | |
| Physical Examination | X | Includes height, weight, and BMI. |
| Vital Signs | X | Includes blood pressure and heart rate. |
| Adverse Events Assessment | | |
| Efficacy Assessments | | |
| Collection of clinical assessments | X | Disease status and mutational analysis |
| Laboratory Tests | | |
| Collection of hematology and biochemistry panel results | X | All local SOC laboratory assessments |

Table 3.3.1.5-2: On Treatment Procedural Outline at Routine Office Visits (CA180653)

| Procedure | Baseline 0 M | Every 3 M | 6 M only | 24M only | Notes |
|---|--------------------------|--------------|-------------|-------------|--|
| Safety Assessments | | | | | |
| Physical Examination | X | | | | Includes height, weight, and BMI. |
| Targeted Physical Examination | | X | | | Includes weight, and BMI. HEENT, CVS, Lung, Abdomen, Endocrine |
| EKG | X | X | | | |
| Medical History | X | X | | | Baseline and updates to medical history such as new diagnosis (for example, hypertension, hyperlipidemia and hyperglycemia, etc) |
| Vital Signs | X | X | | | Includes blood pressure and heart rate. |
| Ankle-brachial index | X | X | | | |
| Adverse Events Assessment (CTCAE v4.03) | -----X continuously----- | | | | |
| Efficacy Assessments | | | | | |
| ECOG | X | X | | | |
| Collection of clinical assessments | X | X | | | Disease status and mutational analysis |
| Diagnostic Imaging | | | | | |
| Echocardiogram | X ^a | | X | X | Evaluation for functional change, elevation in pulmonary arterial pressures / pulmonary hypertension. Local read not required but can be done as per SOC |
| Non contrast cardiac CT | X ^a | | X | X | Evaluation for presence of coronary artery calcification. Local read not to be reported to study, but can be done as per SOC |
| Laboratory Tests | | | | | |

Table 3.3.1.5-2: On Treatment Procedural Outline at Routine Office Visits (CA180653)

| Procedure | Baseline 0 M | Every 3 M | 6 M only | 24M only | Notes |
|--|------------------------|---------------------|---------------------|---------------------|---|
| Collection of hematology and chemistry panel results - Local SOC labs and central labs | X | X | | | All SOC labs and other labs done centrally include fasting blood glucose, Hg A1C, fasting lipid panel (total cholesterol, HDL, LDL, triglycerides). (8 hours of fasting is required) |
| Investigational biomarker blood collection | X | X | | | Including different metabolites, cytokines, chemokines, and other biomarkers (eg, high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, and Lox-1 DNA sequencing. ^b (8 hours of fasting is required) |
| Urine collection | X | X | | | Moderately increased albuminuria (proteinuria) test to assess early changes in vascular endothelial function (8 hours of fasting is required) |

^a Imaging (CT and echocardiogram) can be done within 2 weeks of starting the first TKI dose. All other baseline procedures should be done prior to patient starting TKI treatment.

^b Lox-1 sequencing will be performed at a single time point when disease burden is at a minimum.

Note: Screening and baseline are listed separately in the protocol because of the procedures that are study specific (non SOC) that need to be done after ICF, ABI, imaging and the fasting labs. As an example if a physical exam was done during the routine office visit, but then patient signs ICF and come back the next day fasting to do the labs and imaging, the physical exam would not need to be repeated.

* Screening/baseline procedures will have different collection dates, there is no mandated window in how long screening/baseline should take but they need to be collected prior to start of the first TKI dose (except for CT, echo as described in note B).

3.4 Definitions of Study Variables

3.4.1 Outcomes/Endpoint Variables

Summary of outcomes/endpoint variables to be collected in accordance with study objectives are listed in Table 3.4.1-1 and will be collected as reported in patient medical records.

Table 3.4.1-1: Summary of Outcomes/Endpoint Variables

| Variables | Data Collected |
|------------------------------------|--|
| Treatment-related variables | Procedures and therapies received prior to study enrollment (eg, transplant) Start/end date of treatment (duration of therapy) Documented adverse events possibly caused by systemic treatment Details on adverse event management (eg, concomitant medications, treatments, and procedures) Dosing regimen, duration of treatment, discontinuation, treatment change Reason for treatment discontinuation, if documented |
| Practice pattern-related variables | Diagnostic tests, pathological diagnosis Laboratory /diagnostic tests |
| Clinical Outcomes | Overall survival (OS) Clinical response to TKI treatment (MMR, CCyR, cCHR) Time to clinical response and duration Results of mutational analyses |

3.4.2 Cardiovascular and metabolic risk variables

Summary of cardiovascular and metabolic risk variables to be collected in accordance with study objectives are listed in Table 3.4.2-1 and will be collected as reported in patient medical records.

Table 3.4.2-1: Summary of Cardiovascular and Metabolic Risk Variables

| Variables | Data Collected |
|---------------------------|--|
| Targeted cardiac events | Development of arrhythmia, cardiac dysfunction, cerebrovascular ischemic disease, coronary death, coronary insufficiency, heart failure, left ventricular systolic function, myocardial infarction, peripheral artery occlusive disease, pulmonary arterial hypertension (PAH), QT prolongation, ischemic or hemorrhagic stroke, transient ischemic attack, venous thromboembolism, other vascular occlusive events (VOEs) and the Framingham Coronary Heart Disease Score Subclinical changes that lead to development of new risk factors or exacerbation of known risk factors (newly diagnosed diabetes, newly diagnosed hypertension, progressive symptoms of disease [eg, claudication, angina, etc]) |
| Targeted metabolic events | Diagnosis of diabetes mellitus, impaired fasting glucose, elevated HbA1c, metabolic syndrome, abnormal laboratory values for events of special interest (eg, out of range) |

| Table 3.4.2-1: Summary of Cardiovascular and Metabolic Risk Variables | |
|--|---|
| Variables | Data Collected |
| Hematologic variables | Collection of fasting blood glucose, HbA1, fasting lipid panel [total cholesterol, HDL, LDL, triglycerides]). Changes from baseline will be calculated. |
| Metabolic variables | Collection of BMI, metabolites, cytokines and chemokines from biomarker panel (eg, insulin, glucose, high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, LOX-1 polymorphism), and moderately increased albuminuria levels. Changes from baseline will be calculated. |
| Diagnostic variables | Collection of echocardiogram, ankle-brachial index, and coronary calcium scoring assessments. Changes from baseline will be calculated. |

3.4.3 Exposure/Independent Variables of Interest

TKIs (ie, dasatinib, imatinib, nilotinib and bosutinib) for first line treatment of CP-CML are the exposure variables and will be the basis of three main study cohorts of interest.

3.4.4 Other Co-variates/Control Variables

Summary of demographic and clinical variables to be collected in accordance with study objectives are listed in Table 3.4.4-1 and will be collected as reported in patient medical records.

| Table 3.4.4-1: Summary of Demographic and Clinical Variables | |
|---|---|
| Variables | Data Collected |
| Patient Characteristics | Gender Race/Ethnicity Performance status (ECOG status) Previous systemic treatment, transplant Past and present smoking status Medical history (eg, obesity, pre-diabetes) Comorbidities at enrollment Geographic location by state in the US Rural/urban residence |
| Disease Characteristics | CML disease characteristics (date of diagnosis, treatment change, treatment management, response based on current NCCN guidelines) Clinical status, baseline values, and method of diagnostic (Ph+ determination) Risk scores (Sokal score, Framingham Coronary Heart Disease Score) Spleen size (if available) Concomitant medications for non-CML related diagnoses Concomitant medications for management of adverse events |

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

This is an exploratory study and the analysis will be primarily descriptive in nature.

All statistical analyses are performed with the understanding that this is a non-interventional wherein treatment assignment is based on the investigator's judgment and there is no treatment randomization. Due to the non-randomized setting and confounding factors that are not controlled in the real-life setting, no statistical comparisons will be performed between treatment cohorts without full evaluation of the data. Hence results from summary statistics should be interpreted carefully as the study was not designed or powered to support hypothesis testing. Any exploratory statistical comparisons will be two-sided and done at the 5% Type I error rate

Continuous data will be summarized using descriptive statistics: count (n), mean, standard deviation, median, 25th and 75th percentiles, minimum, maximum and count missing (n miss). If applicable, 95% confidence intervals (CI) of mean will be provided.

Categorical data will be described using frequencies and percentages, and percentages will be presented to 1 decimal place. The number and percentage of missing data will also be reported as "missing" category for each categorical variable if one or more patients had missing data. In addition, a percentage will not be presented against zero counts in the tables.

Patients will be followed continuously during and after treatment until withdrawal of consent, death, loss to follow-up, or to the end of the study, whichever comes first. For patients that discontinue the study or are lost to follow-up, every effort will be made to collect vital status at 6 month intervals.

Patients who switch from their index TKI therapy to a different TKI or other CML treatment will be summarized by initial index treatment and then broken out into subgroups for additional analyses. Time to switch and reason for switch will be evaluated and summarized. Additional details on defining the time frame for switching and additional subgroup analysis will be defined in the detailed SAP.

Patients who are lost to follow-up will be summarized for "reason of study discontinuation". These patients will be evaluated to identify differences from patients who remained on study. For clinical outcome assessments, patients lost to follow-up will be censored at the date they were last known to be alive as provided by study documentation. Additional details on handling of loss to follow-up will be defined in the detailed SAP.

All statistical analyses will be performed using SAS® v9.2 or above. All final data will be presented in listings. All tables and analyses will be provided overall and by treatment cohorts as well as other specified co-variates of interest as the population size permits.

A detailed statistical analysis plan (SAP) will be developed once the electronic case report forms and data collection guidelines have been finalized.

4.1.1 Analysis Plan for Primary Objective

For the primary study objective, risk variables for assessment of assessments for cardiovascular and metabolic disease ([Table 3.4.2-1](#)) will be described for each cohort at specified time points and stated every 3 months (baseline, 3, 6, 9, 12, 15 18, 21, and 24 months).

- Framingham Coronary Heart Disease Score
- Metabolic lab values
- Other CV and metabolic parameters of interest,

Descriptive statistics will be presented for each timepoint in addition to the change from baseline to each timepoint (baseline, 3, 6, 9, 12, 15 18, 21, and 24 months). These descriptions will be based on the observed values of patients at each time point (no last observation carried forward [LOCF]).

In addition, changes in risk assessments over time may be explored for each cohort using appropriate analyses for longitudinal data, eg, Mixed Models for Repeated Measures (MMRM) as sample size permits.

A detailed statistical analysis plan (SAP) will be developed once the electronic case report forms and data collection guidelines have been finalized.

4.1.2 Analysis Plan for Secondary Objectives

For the first secondary objectives, the incidence rates for each cardiovascular and metabolic event of interest (eg, MI, angina, stroke, diabetes mellitus, etc.) will be calculated as (N/100 patient years) and a 95% confidence interval provided by treatment cohort. Incidence rates will be reported both cumulatively and by year since initiation of treatment. Exacerbations of comorbidities will be assessed with same method.

To address the next secondary objective, descriptive data will be provided for safety and tolerability data collected on the TKI's. Frequency counts for treatment-related AEs and SAEs that occur in each of the treatment cohorts will be reported.

Data captured in medical records will be used to characterize the treatment-related AEs and to ascertain how they were treated or managed and the patient outcome. Reported AEs will be coded using MedDRA and tabulated by study cohort.

The third and fourth secondary objectives are clinical effectiveness outcomes (including survival, MMR, CCyR) and will be summarized in descriptive tables and estimated using Kaplan-Meier product limit method and medians with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will also be plotted for each of treatment cohort and additional co-variates as sample size permits. These Kaplan-Meier curves will be used in to evaluate time to event (clinical outcomes) as well. For survival analysis, death is the event, for MMR, a major molecular response is the event, and for CCyR, the event is a complete cytogenic response. Data will be censored at time of study discontinuation, end of follow-up period, switch to new therapy, discontinuation of index therapy, date of loss to follow-up or withdrawal of consent. Further explanation of event and censoring rules will be included in detail in the SAP.

To assess treatments patterns and management of treatment related AE's and comorbidities per the fifth secondary objective, descriptive summary tables will be provided. For each treatment cohort, the description will include: initial treatment regimen, treatment rationale, dosing; treatment interruptions (and reasons), change in treatment; duration of therapy, monitoring, and reason for treatment discontinuation. Discontinuation analysis will also be performed.

- To meet the final secondary objective, factors associated with initial TKI treatment choice or change in TKI treatment will be summarized and evaluated:
- Demographic and clinical patient characteristics (age, gender, comorbidities, ECOG performance status, etc.)
- Patient characteristics which may lead to a physician to recommend that a patient receive specific TKI drug treatment or change of treatment.

Descriptive statistics will be provided for patients to identify potential factors that affect physician decision-making in the treatment selection. In addition, multivariate logistic regression models may be utilized to evaluate the key patient and disease characteristics that influence treatment choice, change in treatment, or treatment discontinuation.

Participants will enter the study at the time of first TKI prescription (index date) and followed until death, leaving clinical care, or the end of the study period of two years.

A detailed statistical analysis plan (SAP) will be developed once the electronic case report forms and data collection guidelines have been finalized.

4.1.3 Analysis Plan for Exploratory Objectives

Whole blood (collected following 8 hours of fasting) and urine samples will be collected to analyze potential inflammatory molecules in CML first line treatments which may be predictive of clinical outcomes, AEs of special interest, onset of comorbidities, and survival outcomes. Blood samples will be stored and analyses will be performed as needed to assess increased risk for cardiovascular or metabolic disease after completion of sample collection. Diagnostic imaging will be collected to analyze changes in cardiovascular function in CML first-line treatments which may be predictive of clinical outcomes, AEs of special interest, onset of comorbidities, and survival outcomes.

Multivariate logistic regression models may be utilized to evaluate key patient and disease characteristics (ie, demographic differences in age, gender; prognostic characteristics, biomarkers, imaging results or co-morbidities) that influence the occurrence of CV and metabolic events in TKI treated CML patients. Confounding factors and systematic differences will be considered in any multivariate statistical models if sample size permits.

4.2 Power/Sample Size

The target enrollment for this descriptive CML study is approximately 200 patients receiving first-line TKI therapy. The primary objectives of this study is to evaluate risk for specific CV and metabolic conditions (eg, development of cardiovascular risk variables such as peripheral edema, hypercholesterolemia (event rate range from lowest to highest of 15% to 28%), and change in Framingham coronary heart disease score (approximately 15% with change over time), in the patient sample. Summary statistics will be provided around the proportion of patients who develop specified clinical and disease characteristics. With 200 CML patients receiving first line TKI therapy, the maximum width (precision estimate) of an exact 95% confidence interval around a proportion is $\pm 5.5\%$. This is based upon the maximum variance obtained when the event

proportion (based on lower event rate of cardiovascular events and similar change in Framingham score) is 15% with corresponding 95% CI: 9.5% - 20.5%.

The sample size of 200 patients should provide sufficient information to describe the primary objectives, as well as explore the secondary and additional study objectives. No formal hypothesis testing or statistical significance testing is planned. Post-hoc power calculations will be performed to determine if additional analysis and comparisons are warranted. The study is not powered for treatment comparisons or for CV events that occur at low rates, as CI intervals could become larger and often invalid.

5 STUDY LIMITATIONS/STRENGTHS

Limitations: One of the limitations of the study includes 24-months timeframe between baseline and end-of-study data collection. This time period is suitable in evaluating short term clinical outcomes but may not be sufficiently long period of time to assess longer term clinical outcomes.

A potential limitation is the sample size, which may not be sufficiently large to analyze some of the stratifying variables with sufficient statistical power. Therefore, the study will have to focus on select common adverse events.

Requesting additional fasting blood draw from patients may inhibit participation in the study, therefore create selection bias. As all blood draws will occur during routine office visits and routine blood draws, minimal inconvenience to the patient should negate any bias.

Finally, all non-interventional data are potentially subject to unmeasured confounding limiting causal interpretation.

Strengths: This prospective study will include patient populations who suffer from the disease that physicians encounter in clinical practice and in the real world, therefore enhancing the generalizability of study results.

The collection of blood and urine samples for central laboratory biomarker analysis and diagnostic imaging for core imaging laboratory evaluation will allow additional data generation on cardiac and metabolic risks without potential impact of altering treatment during study.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

The investigator must ensure that the required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation at the site.

6.1.2 *Informed Consent*

In accordance with local regulations, subjects should provide written consent before enrollment into the study. Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose of the study, potential risks, the patient's rights and responsibilities when participating in this study. If local regulations do not require an informed consent document to be signed by the patient, the site staff should document key elements of the informed consent process in the patient's chart.

6.2 *Responsibilities within the Study*

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by BMS.

6.3 *Confidentiality of Study Data*

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

6.4 *Quality Control*

Representatives of BMS and/or its delegates must be allowed to visit all study site locations to assess the data quality and study integrity. On site, they will review study files and, if allowed by local laws and regulations, patient medical charts to compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

6.5 *Database Retention and Archiving of Study Documents*

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

7 *ADVERSE EVENT REPORTING*

Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: Although not always adverse events by regulatory definition, the following events associated with a BMS product must be reported.

- Exposure (to fetus) during pregnancy, exposure (to infant) during lactation, and paternal exposure
- Overdose (defined as the *accidental* or *intentional* administration of any dose of a product that is considered both excessive and medically important)
- Lack of efficacy
- Abuse
- Misuse
- Off-label use
- Occupational exposure
- Medication error and potential medication error
- Suspected transmission of an infectious agent eg, any organism, virus or infectious particle pathogenic or non-pathogenic, via the medicinal product

The AEs under study require a causal assessment.

The causal relationship to the BMS product under study is determined by a physician and should be used to assess all adverse events under study. The causal relationship should be one of the following:

Related: There is a reasonable causal relationship between the BMS product under study and the AE.

Not related: There is not a reasonable causal relationship between the BMS product under study and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

A ***non-serious adverse event*** is an AE not classified as serious.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- 1) results in death
- 2) is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- 3) requires inpatient hospitalization or causes prolongation of existing hospitalization

Note: The following hospitalizations are not considered SAEs in BMS studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- elective surgery, planned prior to signing consent.
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
 - admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).
 - admission for administration of subsequent anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols).
- 4) results in persistent or significant disability/incapacity.
- 5) is a congenital anomaly/birth defect.
- 6) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

The following should also be classified as SAE:

- Suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the BMS product under study
- Overdose of BMS product under study
- Cancer after exposure to a BMS product under study
- Pregnancy of female patient or female partner of male patient exposed to a BMS product under study.

7.1 Adverse Event Collection and Reporting

7.1.1 Adverse Event Collection

Following the patient's consent to participate in the study, all AEs under study, as well as those meeting the definition of an adverse event (as described in [Section 7](#)), whether or not related to the product(s) under study, must be reported individually in the time frames noted below.

All AEs collected will also be reported in aggregate in the final study report. Where primary data collection practices allow, data tables should be clearly labeled to distinguish between related and non-related AE data.

7.1.2 Adverse Event Reporting

All AEs (serious and non-serious) must be recorded on the Solicited and Non-interventional Research AE/SAE Form and reported to BMS (or designee). Serious AEs must be reported within 24 hours/1 business day to comply with regulatory requirements. A form should be completed for any event where doubt exists regarding its status of seriousness. Non-serious AEs must be reported to BMS (or designee) within 7 business days. Non-serious AEs should be reported as SAEs if they become serious (see [Section 7](#) for definition of serious adverse event).

All AEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

Email Address: SafetyPV@syneoshealth.com

Facsimile Number: 1-866-880-9343

If only limited information is initially available, follow up reports may be required.

For studies capturing AEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

7.1.2.1 *Pregnancy*

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to the BMS product under study, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be recorded on a Pregnancy Surveillance Form and reported to BMS (or designee) within 24 hours/1 business day of becoming aware of the pregnancy by confirmed fax or reported via electronic mail to Worldwide.Safety@BMS.com. If only limited information is initially available, follow-up reports may be required. The original BMS forms are to remain on site. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

7.1.2.2 *Fatal Outcomes*

Adverse events with fatal outcome are reportable to BMS (or designee) as SAEs unless the fatal outcome is associated with a study endpoint. Endpoint events with fatal outcome will be summarized in the final study report.

7.1.2.3 *Other Adverse Event Reporting*

All AEs not under study that occurred while taking any BMS product should be reported to BMS or to the concerned competent authorities via the national spontaneous reporting system. Investigators/HCPs should follow local requirements for product safety reporting.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Not Applicable.

8.2 List of Abbreviations

| Term | Definition |
|-------------|--|
| AE | adverse events |
| CCyR | cytogenetic response |
| CML | chronic myeloid leukemia |
| CP | chronic phase |
| CP-CML | chronic phase chronic myeloid leukemia |
| CRF | Case Report Form |
| CV | Cardiovascular |
| DM | diabetes mellitus |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| FDA | Food and Drug Administration |
| MMR | major molecular response |
| NCI | National Cancer Institute |
| OS | overall survival |
| PAH | pulmonary arterial hypertension |
| SAE | serious adverse event |
| TKI | tyrosine kinase inhibitor |
| VOE | vascular occlusive event |

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**APPENDIX 1 ESTIMATE OF 10-YEAR RISK FOR CORONARY HEART
DISEASE FRAMINGHAM POINT SCORESFOR MEN AND
WOMEN**

1 ESTIMATE OF 10-YEAR RISK FOR MEN

Table 1: **Framingham Point Scores by Age Group for Men**

| Age | Points |
|------------|---------------|
| 20-34 | -9 |
| 35-39 | -4 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 11 |
| 70-74 | 12 |
| 75-79 | 13 |

Table 2: **Framingham Point Scores by Age Group and Total
Cholesterol for Men**

| Total Cholesterol | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
|--------------------------|------------------|------------------|------------------|------------------|------------------|
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 0 |
| 200-239 | 7 | 5 | 3 | 1 | 0 |
| 240-279 | 9 | 6 | 4 | 2 | 1 |
| 280+ | 11 | 8 | 5 | 3 | 1 |

Table 3: Framingham Point Scores by Age and Smoking Status for Men

| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
|-----------|-----------|-----------|-----------|-----------|-----------|
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 8 | 5 | 3 | 1 | 1 |

Table 4: Framingham Point Scores by HDL Level for Men

| HDL | Points |
|-------|--------|
| 60+ | -1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

Table 5: Framingham Point Scores by Systolic Blood Pressure and Treatment Status for Men

| Systolic BP | If Untreated | If Treated |
|-------------|--------------|------------|
| <120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| 160+ | 2 | 3 |

Table 6: 10-Year Risk by Total Framingham Point Scores for Men

| Point Total | 10-Year Risk |
|-------------|--------------|
| < 0 | < 1% |
| 0 | 1% |
| 1 | 1% |
| 2 | 1% |
| 3 | 1% |

Table 6: 10-Year Risk by Total Framingham Point Scores for Men

| Point Total | 10-Year Risk |
|-------------|--------------|
| 4 | 1% |
| 5 | 2% |
| 6 | 2% |
| 7 | 3% |
| 8 | 4% |
| 9 | 5% |
| 10 | 6% |
| 11 | 8% |
| 12 | 10% |
| 13 | 12% |
| 14 | 16% |
| 15 | 20% |
| 16 | 25% |
| 17 or more | ≥ 30% |

2 ESTIMATE OF 10-YEAR RISK FOR WOMEN

Table 7: Framingham Point Scores by Age Group for Women

| Age | Points |
|-------|--------|
| 20-34 | -7 |
| 35-39 | -3 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 12 |
| 70-74 | 14 |
| 75-79 | 16 |

Table 8: Framingham Point Scores by Age Group and Total Cholesterol for Women

| Total Cholesterol | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
|-------------------|-----------|-----------|-----------|-----------|-----------|
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 1 |
| 200-239 | 8 | 6 | 4 | 2 | 1 |
| 240-279 | 11 | 8 | 5 | 3 | 2 |
| 280+ | 13 | 10 | 7 | 4 | 2 |

Table 9: **Framingham Point Scores by Age and Smoking Status for Women**

| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
|-----------|-----------|-----------|-----------|-----------|-----------|
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 9 | 7 | 4 | 2 | 1 |

Table 10: **Framingham Point Scores by HDL Level for Women**

| HDL | Points |
|-------|--------|
| 60+ | -1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

Table 11: **Framingham Point Scores by Systolic Blood Pressure and Treatment Status for Women**

| Systolic BP | If Untreated | If Treated |
|-------------|--------------|------------|
| <120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| 160+ | 4 | 6 |

Table 12: **10-Year Risk by Total Framingham Point Scores for Women**

| Point Total | 10-Year Risk |
|-------------|--------------|
| < 9 | < 1% |

Table 12: **10-Year Risk by Total Framingham Point Scores for Women**

| Point Total | 10-Year Risk |
|-------------|--------------|
| 9 | 1% |
| 10 | 1% |
| 11 | 1% |
| 12 | 1% |
| 13 | 2% |
| 14 | 2% |
| 15 | 3% |
| 16 | 4% |
| 17 | 5% |
| 18 | 6% |
| 19 | 8% |
| 20 | 11% |
| 21 | 14% |
| 22 | 17% |
| 23 | 22% |
| 24 | 27% |
| 25 or more | ≥ 30% |

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.