Statistical Analysis Plan

Protocol PCYC-1111-CA

A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma

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REVISION HISTORY

Version	Date	Version Description
1.0	05SEP2013	Original version
2.0	15APR2015	SAP was updated to reflect changes in Protocol Amendment 4.
3.0	28OCT2015	SAP was revised to update the definition of progressive disease per modified IMWG for efficacy analysis and to reflect changes in Protocol Amendment 5.
4.0	16JUN2016	SAP was revised to 1) remove detailed definition of study completion as the definition of study completion will be per protocol, and to 2) update preferred terms for CYP3A4 inhibitors in Appendix 1 per newly revised company standard.

ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
Btk	Bruton's tyrosine kinase
CBR	Clinical benefit response
CI	Confidence interval
Clcr	Creatinine clearance rate
CR	Complete response or complete remission
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCB	Duration of benefit
DILI	Drug-Induced Liver Injury
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FISH	Fluorescent in situ hybridization
Hgb	Hemoglobin
HI	Hematologic improvement
MedDRA	Medical Dictionary for Regulatory Activities
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent review committee
mITT	Modified intent-to-treat
MM	Multiple myeloma
MR	Minimal response
NCI	National Cancer Institute
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease/disease progression
PFS	Progression-free Survival
PI	Proteasome inhibitors
PK	Pharmacokinetic(s)
PR	Partial response or partial remission
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
sCR	Stringent complete response
SD	Stable disease
SFLC	Serum free light chain
SPEP	Serum protein eletrophoresis
TCB	Time to clinical benefit
TEAE	Treatment emergent adverse event
TSHI	Time to sustained hematologic improvement
TTP	Time to progression
TTR	Time to response
UPEP	Urine protein eletrophoresis
VGPR	Very good partial response

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a comprehensive description of the final statistical analyses for efficacy and safety data that have been outlined within the protocol.

This plan does not cover the analyses for pharmacokinetic (PK) and biomarker data. The PK analysis will be performed separately and included in the clinical study report. The biomarker data will be analyzed and reported separately from the clinical study report.

The SAP is based on protocol Amendment 5, dated 25 August, 2015. Any changes to the protocol analysis plan, including additional analyses are documented here.

1.1. Protocol Number and Title

Study PCYC-1111-CA: A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of this study is to determine the efficacy of ibrutinib (PCI-32765), both as a single agent and in combination with dexamethasone, in subjects with relapsed or relapsed and refractory multiple myeloma (MM) as measured by clinical benefit response (CBR) rate, defined as the proportion of subjects who achieved stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), or minimal response (MR) as assessed by the modified International Myeloma Working Group (IMWG) response criteria [1,3,6] (see protocol Appendix 6).

1.2.2. Secondary Objectives

Secondary objectives are to evaluate the efficacy, safety and pharmacokinetics of ibrutinib in this population as assessed by the following:

- Duration of clinical benefit (DCB; MR or better)
- Objective response rate (ORR) defined as the proportion of subjects who achieved sCR, CR, VGPR, or PR (ORR; PR or better)
- Duration of objective response (DOR)
- Safety (assessed by reporting of SAEs, AEs, and treatment-related discontinuations)

- Pharmacokinetics (assessed by sampling and testing for drug and metabolite levels at designated time points)

1.2.3. Exploratory Objectives

Exploratory objectives are to evaluate the following:

- Progression-free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)

1.2.4. Exploratory Analyses

- Prognostic and predictive biomarkers and genetics relative to treatment outcomes

1.3. Study Design

This is a Phase 2, open-label, nonrandomized, multi-cohort, multicenter Simon 2-stage study designed to assess the safety and efficacy of ibrutinib in subjects with relapsed or relapsed and refractory multiple myeloma.

Treatment of ibrutinib 420 mg once daily in the original protocol (hereafter referred to as Cohort 1) was designed to detect a meaningful signal of activity while minimizing risk of continuing enrollment under null conditions. Amendment 1 was designed to further explore the optimal regimen by increasing doses of ibrutinib and/or by routine combination with low dose dexamethasone. Cohorts 1 and 3 test activity of ibrutinib monotherapy; Cohorts 2 and 4 test ibrutinib in combination with dexamethasone.

Stage 1:

- Up to eleven (11) subjects were to be enrolled to Cohort 1.
- Up to eighteen (18) subjects will be enrolled to each Cohort 2, 3 and 4.
- Stage 1 enrollment to Cohorts 3 and 4 may begin concurrently after Cohort 2 Stage 1 enrollment is complete. If there is concurrent enrollment, Sponsor will implement centralized assignments into cohorts.

Stage 2:

- If $\geq$ 2 CBRs are observed among the first 11 subjects in Cohort 1, the cohort will be expanded for up to a total enrollment of 35 subjects.

- If ≥ 3 CBRs are observed within Cohorts 2, 3, or 4 in Stage 1, the cohort(s) may be selected for expansion for up to a total enrollment of 43 subjects in each cohort or until observing ≥ 8 CBRs, whichever occurs earlier.
- If there is concurrent Stage 2 enrollment to more than 1 cohort at any given time, Sponsor will implement centralized assignments into cohorts.

Sponsor maintains the prerogative to select regimen, which gives optimal efficacy and safety results at interim analysis for further development while suspending other cohorts at any time.

The expected total enrollment is between 67 (minimal) and 164 subjects. Dosages and regimens by cohort are summarized in Table 1.

Table 1: Treatment Cohorts and Planned Enrollment

Cohort	Ibrutinib (mg/day)	Dexamethasone	Planned First Stage Enrollment	CBR Criteria for First Stage	Total Enrollment (First and Second Stages)
1	420	Upon progressive disease (PD), 40 mg once weekly is allowed†	11*	≥ 2	35
2	560	40 mg once weekly#	18	≥ 3	43
3	840	Upon PD, 40 mg once weekly is allowed†	18	≥ 3	43
4	840	40 mg once weekly#	18**	≥ 3	43

* n=11 planned for Cohort 1 First Stage, n=13 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 11 subjects.
** n=18 planned for Cohort 4 First Stage, n=20 were enrolled. The decision for second stage expansion will be based on the number of CBR in the first 18 subjects.
# Dexamethasone administration starts on Cycle 1 Day 4 for Cohort 2 and 4. For Cohort 4 expansion, dexamethasone will be administered starting on Cycle 1 Day 8.
† For Cohorts 1 and 3 subjects who have confirmed PD, and who are clinically stable, without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg orally once per week in addition to continued treatment with ibrutinib, at the discretion of the investigator.

Subjects are allowed to continue study drug as long as the subject is clinically stable (stable disease [SD] or better) and the subject is not experiencing any unacceptable toxicity. Subjects in the monotherapy cohorts (1 and 3) who have PD confirmed as required by definition in the protocol, and without significant worsening of symptoms or hematologic status (ie, meet all entry criteria for the study in regard to symptoms and hematology), will be eligible to receive dexamethasone 40 mg orally once per week in addition to continued treatment with ibrutinib,

at the discretion of the investigator. Otherwise, subjects having PD will be removed from study. Note that the decision for second stage expansion of Cohorts 1 and 3 will be based on the number of subjects who achieved CBR (MR or better) prior to addition of dexamethasone.

2. STUDY ENDPOINTS

2.1. Primary Endpoint

CBR rate: defined as the proportion of subjects achieving a MR or better as assessed by investigator per the modified IMWG criteria.

2.2. Secondary Endpoints

The secondary endpoints for this study are as follows:

Safety:

- Safety parameters including the incidences and types of clinical adverse events, laboratory variables, and vital signs measurements

Efficacy:

- Duration of clinical benefit (DCB)
- Objective response rate (ORR)
- Duration of objective response (DOR)

Pharmacokinetics:

- Plasma PK of ibrutinib and metabolite PCI-45227

2.3. Exploratory Endpoints

- Progression-free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)
- Time to Clinical Benefit
- Time to Response

3. SAMPLE SIZE CONSIDERATIONS

Cohort 1 was designed to detect a meaningful signal of activity while minimizing risk of continuing enrollment under null conditions. Cohorts 2-4 were designed to further explore the optimal regimen. The sample size was estimated for each cohort without multiplicity adjustment.

3.1. Cohort 1

Full enrollment to Cohort 1 will be contingent upon Simon 2 stage design rules with a target sample size of 35 evaluable subjects based on meeting interim efficacy endpoints, i.e., if ≥ 2 CBRs are observed among the first 11 subjects within Cohort 1. This study cohort is designed to test the null hypothesis that the CBR rate of ibrutinib monotherapy at a dose of 420 mg/day is $\leq 10\%$ (not clinically compelling) versus the alternative hypothesis that CBR rate will be $\geq 30\%$, at a 1-sided significance level of 5%, with 85% power. Observation of ≥ 7 CBRs within an expanded cohort of 35 subjects will be considered consistent with the alternative hypothesis of CBR rate $\geq 30\%$.

Although the design described above is setup to detect cohort specific CBR rates of 30%, CBR rates as low as 20% is still considered clinically meaningful, as the drug may be developed in combination therapy and/or in less heavily pre-treated populations. With this 2-stage design, the probability to continue enrolling subjects for the second stage is approximately 0.68 if the true CBR rate is 20%.

3.2. Cohorts 2-4

Simon optimal 2-stage study design is utilized in Cohorts 2, 3 and 4.

Up to eighteen subjects will be enrolled to each subsequent cohort (2-4). Stage 1 enrollment to Cohorts 2, 3, and 4 will not be contingent upon results of preceding cohorts. Full enrollment to Cohort 2, 3, and 4 will be contingent upon Simon 2-stage design rules with a sample size of up to 43 evaluable subjects based on meeting interim efficacy endpoints, i.e., if ≥ 3 CBRs are observed among the first 18 subjects within the subject cohort. This design has 80% power to reject the null hypothesis of CBR rate $\leq 10\%$, at a 1-sided significance level of 5%. Observation of ≥ 8 CBRs within an expanded cohort of up to 43 subjects will be considered consistent with the alternative hypothesis of CBR rate $\geq 25\%$. The enrollment of that cohort may be closed early for success once 8 CBRs observed.

Sponsor maintains the prerogative to select regimen that gives optimal efficacy and safety results at interim analysis for further development and suspend other cohorts at any time.

This study design is not powered or intended to allow direct comparison of percent CBR among the cohorts. Results of this study will inform alternative directions for future combination and single agent development in alternative multiple myeloma study populations.

4. STUDY POPULATIONS AND ANALYSIS SETS

The analysis and summary of data for this study will be performed using the following populations:

All enrolled population: All subjects who signed the informed consent form and were enrolled to one of the treatment cohorts. This population will be used to summarize disposition information.

All treated population: All enrolled subjects who received at least one dose of study drug. This population will be used to summarize subject enrollment, demographics, baseline and disease characteristics, prior therapies, and concomitant medications. This population is referred to as the "modified intent-to-treat (mITT) population" in the protocol. This is the primary analysis population for efficacy endpoints.

Response evaluable population: All enrolled subjects who received at least one dose of study drug and underwent at least one response assessment after start of treatment. Response rates (CBR rate and ORR) will be analyzed based on response evaluable population and will be considered as sensitivity analyses.

Safety population: All enrolled subjects who received at least one dose of study drug. This population will be used for analyzing the safety (including dosing) data.

Subjects in treated, response evaluable and safety populations will be analyzed according to the actual treatment received (i.e. as treated).

5. ANALYTIC DEFINITIONS

5.1. Study Day and Duration of Treatment

Study day will be calculated in reference to the date of the first dose of study drug. Study Day 1 corresponds to the date the subject received the first dose of study drug. For assessments/events occurred on or after Study Day 1, study day is calculated as (assessment/event date – date of the first dose of study drug + 1 day). For assessments/events occurred prior to Study Day 1, study day is calculated as (assessment/event date – date of the first dose of study drug). Study Day −1 is the day before Study Day 1. There will not be a Study Day 0.

Treatment duration for ibrutinib will be calculated as the interval from the date of the first dose of ibrutinib to the date of the last dose of ibrutinib. Similarly, treatment duration for dexamethasone will be calculated.

Treatment duration (day) = date of the last dose – date of the first dose + 1 day

5.2. Time on Study

Time on study is defined as the interval between the date of the first dose of study drug and the date last known alive. Subjects who died will be censored at death date.

5.3. Baseline

Unless otherwise specified, the baseline value is defined as the last observation with a non-missing result prior to the start of study drug.

5.4. Disease Status

"Relapsed disease" is defined as the occurrence of progression following a response to a prior therapy. "Refractory" is defined as best response of SD or PD to last line of therapy while on treatment or within 60 days of last therapy.

5.5. Disease Stage

The international staging system (see Table 2) for multiple myeloma will be applied for patient classification at baseline.

Table 2: International Staging System for Multiple Myeloma

Stage	Criteria
I	Serum β_2-micoglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
II	Not Stage I or III (Serum β_2-micoglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL; or Serum β_2-micoglobulin 3.5 to <5.5 mg/L irrespective to the serum albumin level)
III	Serum β_2-micoglobulin ≥ 5.5 mg/L

5.6. ECOG and Karnofsky Performance Status Scores

For subjects in Cohort 1, Karnofsky performance status scores are measured and recorded according to the original protocol dated November 4, 2011. For those subjects, the ECOG performance status will be derived from Karnofsky performance scores (see Table 3).

Under protocol amendment 1, the decision was made to collect ECOG performance status rather than Karnofsky performance status for all subjects enrolled afterwards.

Table 3: ECOG and Karnofsky Performance Status Scores

Karnofsky Performance Status (%)	ECOG Performance Status
90, 100	0
70, 80	1
50, 60	2
30, 40	3
10, 20	4
0	5

5.7. Treatment-Emergent Period

The treatment-emergent period is defined as the period of time from the date of the first dose of study drug through 30 days after the date of the last dose of study drug (ibrutinib or dexamethasone) or the day before initiation of any subsequent anti-myeloma therapy, whichever occurs first.

The treatment-emergent period for monotherapy (Cohorts 1 and 3 only) is defined as the period of time from the date of the first dose of ibrutinib through 30 days after the date of the last dose of ibrutinib, or the day before the addition of dexamethasone, or the day before initiation of any subsequent anti-myeloma therapy, whichever occurs first.

5.8. Average Dose and Relative Dose Intensity

For ibrutinib:

Average dose administered (mg/day) = total cumulative dose administered (mg) / treatment duration (day) for ibrutinib.

For dexamethasone:

Average dose administered (mg/week) = total cumulative dose administered (mg) / treatment duration (week) for dexamethasone.

Total cumulative dose administered is the sum of dose actually taken during the treatment period. Relative dose intensity is defined as the percentage of the total expected dose that was actually administered.

Relative dose intensity (%) = total cumulative dose administered / total expected dose × 100%.

For ibrutinib:

Total expected dose (mg) = treatment duration (day) for ibrutinib × protocol assigned daily dose (e.g. 420 mg/day for Cohort 1).

For dexamethasone:

Total expected dose (mg) = treatment duration (week) for dexamethasone × protocol assigned weekly dose (40 mg/week).

5.9. Calculation of Laboratory Values

Absolute neutrophil count (ANC):

ANC (10^9/L) = (%neutrophils+%bands) × white blood cell / 100, where neutrophils and bands are in percentages and white blood cell is in 10^9/L.

Estimated creatinine clearance (Clcr) calculated using Cockcroft-Gault (C-G) formula:

$$Clcr(mL/\min) = \frac{[140 - Age(years)] \times Weight(kg) \times [0.85 \quad if \quad Female]}{72 \times Serum \quad Creatinine(mg/dL)}$$

In this calculation, if weight is not measured at the same visit as creatinine, the weight measured prior and closest to the creatinine collection time will be used.

5.10. Other General Definitions

Age:

Age in years will be calculated at the date of informed consent.

Conversions:

- 1 month = 30.4375 days.
- 1 year = 365.25 days.

6. Missing Data Handling

6.1. General Approach

In order to achieve the goal of a well conducted clinical study according to Good Clinical Practice, every effort will be made to collect all data. However, despite best efforts, it may be inevitable that some data may be missing or incomplete. Missing or partial data will be presented in the subject data listing as they are recorded on the case report forms (CRFs).

6.2. Missing and Incomplete Data

6.2.1. Efficacy Variables

No imputation of missing values will be performed for efficacy data unless otherwise specified.

6.2.2. Safety Variables

No imputation of missing values for safety data will be performed.

For missing or partial start and end dates for AEs, medical history, prior therapy and concomitant medication, no imputation will be performed. However, a conservative approach should be taken when performing the related analyses. If the available information is not enough to judge whether an event or a therapy duration has overlapped with study treatment duration, events reported on AE pages will be taken as treatment emergent AEs, events reported on medical history page will be treated as prior medical condition, prior or concomitant therapy will be considered as continuing therapy which started prior to first study treatment.

However, an intermediate imputation of partial dates may be taken in order to calculate the study day for AEs, medical history, prior therapy and concomitant medications. This is just for estimation of the timing of events relative to the study course. All missing or partial dates should remain the same values as they were recorded on the CRFs. The intermediate imputation rules are:

If only day is missing, then the 15th of that month will be used.

If only year is present, then June 30th will be used.

If such imputed date for prior therapies or initial diagnosis is on or after the date of the first dose of study drug, then date of the first dose - 1 will be used. If such imputed date for the start or end of subsequent therapies is before date of last dose of study drug, then date of last

dose of study drug +1 will be assumed. If an imputed start date of prior or subsequent therapy is after the end date, the end date will be used. If an imputed end date of prior or subsequent therapy is before the start date, the start date will be used.

If an imputed AE start date is in the same month and year as the first dose date of study drug but on an earlier date, the first dose date will be used. If an imputed AE start date is in the same month and year as the date of 30 days post the last dose of study drug but on a later date, the date of 30 days post the last dose will be used. If an imputed AE start date is after the AE end date, the AE end date will be used.

If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.

7. INTERIM and FINAL ANALYSIS

For each cohort, a futility **interim analysis** will be performed when stage 1 enrollment target met (Cohort 1; 11 subjects, Cohorts 2-4; 18 subjects) and either all enrolled subjects have evaluable response data (ie, completed 6 treatment cycles and the Cycle 7 Day 1 assessments or have discontinued treatment) or the number of clinical benefit responders met stage 2 enrollment expansion criteria (≥ 2 for Cohort 1, ≥ 3 for Cohorts 2-4), whichever occurs earlier. Further enrollment will be halted until the cohort meet stage 2 enrollment expansion criteria. All enrolled subjects will be followed to further assess their responses. Enrollment may resume earlier while waiting for the confirmation of response of the last clinical benefit responder. If a cohort failed to meet stage 2 enrollment expansion criteria when all first stage subjects have evaluable response data, the cohort will be suspended for futility.

The **final analysis** will occur upon study completion.

8. STATISTICAL METHODS

8.1. General Considerations

Unless otherwise stated, continuous variables will be summarized with descriptive statistics (mean, standard error or standard deviation, median, interquartile range, minimum, and maximum). For categorical variables, number and percentage of subjects in each category will be provided.

Time to event or duration of event endpoints will be based on the event date (or censoring date) rather than visit number or visit label.

For by-visit analysis, visit windows will be used to associate assessment with a scheduled visit and will be created in reference to the date of first dose of study drug to assign visit number based on evaluation date. If more than one assessment falls into a given visit window, the one closest to the target date will be used. If two assessments are equally close to the target day, the earlier assessment will be used.

All data collected on the CRFs will be presented in data listings upon request. All statistical analyses will be performed using SAS® version 9.2 or higher.

8.2. Analysis of the Conduct of the Study

8.2.1. Subject Enrollment and Disposition

Subject enrollment will be summarized by country, study site and treatment cohort.

The disposition of all enrolled subjects will be summarized by treatment cohort:

- Number of subjects as enrolled, number of subjects as treated, number (%) of subjects in safety and response evaluable populations
- Number (%) of subjects who are still on study treatment.
- Number (%) of subjects with dexamethasone added (Cohorts 1 and 3 only).
- Number (%) of subjects who discontinued the study treatment and reason for discontinuation
- Number (%) of subjects who exited the study and reason for study exit
- Descriptive statistics for time on study; time on study is defined in the same way as overall survival with reversed censoring, i.e., subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

The percentages will be based on the number of subjects treated.

8.2.2. Protocol Deviations

Subjects with important protocol deviations (IPDs) will be identified and documented by clinical team.

8.3. Study Periods

The whole study period is defined as the period of time from the date of the first dose of study drug until the end of the study.

The monotherapy period (Cohorts 1 and 3 only) is defined as the period of time from the date of the first dose of ibrutinib through the day before the addition of dexamethasone, or the day before initiation of any subsequent anti-myeloma therapy, whichever occurs first.

8.4. Demography and Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized for the all treated population by treatment cohort.

- Demographics: Sex, age (continuous and grouped as <65, ≥65, <70, ≥70, <75, ≥75 years), race, and ethnicity
- Baseline and disease characteristics:
  - Weight and height
  - ECOG performance status (0, 1)
  - Creatinine, estimated creatinine clearance rate (continuous and grouped as < 30, 30-<60, ≥ 60 mL/min)
  - Hematologic abnormalities (hemoglobin [Hgb] < 10 g/dL, platelets < 100×10^9/L, ANC < 1×10^9/L)
  - Hemoglobin, platelet counts and ANC
  - Time since initial diagnosis (continuous and grouped as <3, ≥3 years)
  - Disease status (relapsed, relapsed and refractory)
  - Serum β_2-microglobulin (continuous and grouped as <3.5, ≥3.5 - <5.5, ≥5.5 mg/L)
  - Serum albumin (continuous and grouped as <3.5, ≥3.5 g/dL)
  - Disease stage (I, II, III) at baseline per International Staging System (see Table 2)
  - Immunoglobulin heavy chain class (e.g. A, G, M), immunoglobulin light chain class (κ, λ)
  - Measurable disease (SPEP only, UPEP only, SPEP and UPEP, sFLC only)
  - Bone marrow plasma cell percentage
  - Cytogenetic/FISH prognostic markers [e.g. del(17p), del(13q14), t(4;14), t(11;14)]
- Prior cancer-related therapies:
  - Prior radiotherapy (yes, no), prior surgery (yes, no), prior systemic therapy (yes, no)
  - Number of prior systemic therapies (continuous and grouped as 2-3, ≥4)

- Type of prior systemic therapies: lenalidomide, thalidomide, pomalidomide, bortezomib, carfilzomib, alkylator (melphalan, cyclophosphamide), doxorubicin, corticosteroid (dexamethasone, prednisone), fludarabine, vincristine, etc.
- Type of bone marrow or stem cell transplant: autologous, allogeneic
- Refractory to last line of therapy
- Refractory to prior immunomodulatory drugs: lenalidomide, thalidomide, pomalidomide
- Refractory to prior proteasome inhibitors: bortezomib, carfilzomib
- Refractory to prior immunomodulatory drugs and proteasome inhibitors (i.e. refractory to at least one prior immunomodulatory drug and at least one prior proteasome inhibitor)
- Last prior treatment [(no PI/IMiD) vs. (PI or IMiD) vs. (PI and IMiD)]
- Last prior treatment included PI
- Last prior treatment included IMiD

8.5. Concomitant Medications

Concomitant medications are defined as medications taken during the treatment emergent period.

Concomitant medications will be summarized by the World Health Organization Drug Dictionary therapeutic class, pharmacological class, and preferred term. Concomitant use of CYP3A4 strong, moderate or weak inhibitors will be listed and/or summarized separately. The search for usage of CYP3A4 inhibitors will be based on, but not limited to the preferred terms in Appendix 1.

8.6. Study Drug Exposure

Ibrutinib and/or dexamethasone dose for a subject may be held and/or reduced according to the protocol specified criteria (see protocol Section 6.5).

For each subject the following parameters will be calculated when applicable.

- Treatment duration for each study drug (ibrutinib or dexamethasone) in month
- Time to addition of dexamethasone in month (Cohorts 1 and 3 only)
- Total cumulative dose administered for each study drug
- Average dose administered for each study drug

- Relative dose intensity for each study drug
- Number of dose missed for each study drug
- Number of dose reduction for each study drug
- Ibrutinib dose interruption ≥ 7 consecutive days (yes or no)
- Dexamethasone dose interruption ≥ 14 consecutive days (yes or no)

For each parameter, descriptive statistics (mean, standard deviation, median, and range for continuous variables; number and proportion for categorical variables) will be calculated by treatment cohort.

8.7. Subsequent Antineoplastic Therapy for Multiple Myeloma

Anti-myeloma treatments that started after discontinuation of study treatment (i.e. started after the last dose of study drug) will be considered as subsequent antineoplastic therapies for multiple myeloma. Subsequent antineoplastic therapies will be summarized by type (e.g. radiotherapy, systemic therapy, bone marrow or stem cell transplant) and preferred term.

8.8. Efficacy Analyses

Starting from Cycle 2, subjects will be evaluated by the investigators per the modified IMWG response criteria. Confirmation of investigator-assessed responses by an independent review committee (IRC) may be done as a supportive assessment. The method of independent review will be governed by an IRC charter, if needed. Some or all of the following assessments may be required to confirm the response categories: M-protein evaluations (UPEP and SPEP, serum and urine IFE, serum FLC), plasmacytoma evaluation, bone radiological assessment, bone marrow aspiration and biopsy, and serum chemistries including calcium and albumin.

The all treated population is the primary population for the efficacy endpoints. Unless specified otherwise, the all treated population will be used for all efficacy analyses. Response rates (CBR rate and ORR) will also be analyzed based on response evaluable population and will be considered as sensitivity analyses. Only adequate response assessments will be included in the analysis. An adequate response assessment is one for which the response assignment is sCR, CR, VGPR, PR, MR, SD or PD (i.e. not UE/Unknown).

IMWG criteria specify that all response categories require confirmation from a second consecutive assessment made at any time after the initial assessment with the exception of sCR and CR. The initial sCR or CR will be reported as confirmed response. However, if a subject has only one adequate post baseline assessment for which the response assignment is MR, PR or VGPR, then the best response will be summarized as SD.

In Cohorts 1 and 3, subjects will be on ibrutinib monotherapy and may convert to ibrutinib and dexamethasone combination therapy at the discretion of the investigator after a confirmed PD on ibrutinib monotherapy. Thus the efficacy endpoints (CBR, DCB, ORR, DOR, PFS, and TTP) will be presented and distinguished as with and without dexamethasone for subjects in Cohorts 1 and 3, when applicable.

No inferential statistical comparisons among treatment cohorts will be performed in this study.

8.8.1. Primary Efficacy Endpoint

The primary endpoint of the study is the CBR rate, defined as the proportion of subjects achieving a MR or better prior to initiation of new antineoplastic therapy as assessed by investigator per modified IMWG criteria.

The number and percent of subjects in each best response category (sCR, CR, VGPR, PR, MR, SD, PD) will be summarized by treatment cohort.

CBR rate and its corresponding 2-sided 90% exact binomial confidence interval (CI) will be calculated and presented by treatment cohort. For subjects in Cohorts 1 and 3, CBR will be calculated during ibrutinib monotherapy period (i.e. prior to addition of dexamethasone) as primary analysis. CBR across the whole study course (including ibrutinib and dexamethasone combination therapy period) will be calculated and presented as secondary analysis.

In addition, CBR rate will be analyzed based on response evaluable population and will be considered as sensitivity analyses.

Subgroup Analysis

Subgroup analyses may be performed for the following selected baseline characteristics and potential prognostic variables.

- Sex (male vs. female)
- Age (<65 vs. ≥65 years, <75 vs. ≥75 years)
- Race (Caucasian vs. non-Caucasian)
- Baseline ECOG score (0 vs. 1)
- Baseline hematologic abnormality (yes vs. no); hematologic abnormality: Hgb < 10 g/dL, platelets < 100×10^9/L or ANC < 1×10^9/L
- Disease status (relapsed vs. relapsed and refractory)

- Number of prior systemic therapies (2-3 vs. ≥4)
- Refractory status of last line of prior therapy (yes vs. no)
- Refractory to prior immunomodulatory drugs (yes vs. no)
- Refractory to prior proteasome inhibitors (yes vs. no)
- Refractory to prior immunomodulatory drugs and proteasome inhibitors (yes vs. no)
- FISH abnormalities
  - Del 17p (present vs. absent)
  - t(14;16) (present vs. absent)
  - t(4;14) (present vs. absent)
  - At least a presence of Del 17p, t (14;16) or t(4;14) vs. none of the three
- Last prior treatment [(no PI/IMiD) vs. (PI or IMiD) vs. (PI and IMiD)]
- Last prior treatment included PI (yes vs. no)
- Last prior treatment included IMiD (yes vs. no)

CBR rate and its corresponding 2-sided 90% exact binominal CI will be calculated within each stratum of every subgroup. Forest plot will be provided for the subgroup analyses.

8.8.2. Secondary Efficacy Endpoints

8.8.2.1. Duration of Clinical Benefit (DCB)

For all cohorts, DCB will be computed for those subjects with confirmed responses (MR or better) prior to initiation of new antineoplastic therapy. DCB will be calculated from the first observation of response (before confirmation) to the time of PD (earliest occurrence), with death from causes other than progression censored.

PD based upon changes in monoclonal protein levels requires confirmation. No minimal time interval between assessments is stipulated. PD based upon bone marrow, bone lytic lesions, or plasmacytoma changes, or upon development of hypercalcemia attributed to multiple myeloma do not require confirmation. DCB will be right-censored for subjects who meet one or more of the censoring conditions listed in Table 4 below.

Similarly, for Cohorts 1 and 3 ibrutinib monotherapy, DCB will be computed for those subjects with confirmed responses (MR or better) prior to initiation of dexamethasone or new antineoplastic therapy, whichever occurs first.

Table 4: Date of Event and Censoring Rules for DCB Analysis

Row	Situation	Date of Event or Censoring	Outcome
Events include death due to progression or first documentation of confirmed PD that occurred on or prior to the data analysis cutoff date. For Cohorts 1 and 3 ibrutinib monotherapy, events need to meet one additional criterion: occurred at or prior to initiation of dexamethasone.			
1.1	Death due to progression or confirmed PD documented at scheduled disease assessments or between two scheduled disease assessments.	Earliest date of adequate disease assessment documenting confirmed PD or date of death due to progression, whichever occurs first.	Progressed
1.2	Death before first disease assessment	Date of death	Progressed
All other cases will be censored as follows:			
2.1	No baseline assessment	Date of first study treatment	Censored
2.2	No adequate post-baseline assessment (including lost to follow-up since enrollment)	Date of first study treatment	Censored
2.3	Not known to have confirmed PD or died due to progression at the data analysis cutoff date (this includes subjects who were known to have confirmed PD or died after the data analysis cutoff date)	Date of last adequate disease assessment showing no evidence of confirmed PD on or before data analysis cutoff date	Censored
2.4	Addition of dexamethasone (Cohorts 1 and 3 ibrutinib monotherapy only)	The start date of dexamethasone	Censored
2.5	Death from causes other than progression	Date of death	Censored

For subjects who meet more than one censoring condition, DCB will be censored according to the earliest censoring condition. For subjects who meet none of the censoring conditions, DCB will be calculated using the earliest event date.

DCB Event (day) = Date of event – Date of first overall response

DCB Censor (day) = Date of censoring – Date of first overall response + 1

Kaplan-Meier curves will be used to estimate the distribution of DCB. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median DCB. A 2-sided 95% CI will be provided for this estimate. For the cases in which the median is not reached as if the study closure, the 25th percentile and its 2-sided 95% CI will be provided.

8.8.2.2. Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects achieving confirmed responses (PR or better) prior to initiation of new antineoplastic therapy as assessed by investigator per the modified IMWG criteria. ORR and its corresponding 2-sided 90% exact binomial confidence interval will be calculated and presented by treatment cohort.

Subgroup Analysis

The same subgroup analyses will be performed as those for CBR.

8.8.2.3. Duration of Response (DOR)

DOR will include only subjects with confirmed responses (PR or better). DOR will be calculated from the first observation of response (before confirmation) to the time of PD (earliest occurrence), with death from causes other than progression censored. The calculation for the time of PD and censoring rules are the same as those for DCB (see Table 3).

DOR Event (day) = Date of event – Date of first overall response

DOR Censor (day) = Date of censoring – Date of first overall response + 1

The same analyses will be done for DOR as those for DCB described in Section 8.7.2.1.

8.8.3. Exploratory Efficacy Endpoints

8.8.3.1. Progression-free Survival (PFS)

PFS is defined as the duration from the start of study treatment to PD (earliest occurrence) or death (regardless of cause of death), whichever comes first. The calculation for the time of PD will be the same as that for DCB (Section 8.7.2.1).

PFS will be right-censored for subjects who meet one or more of the censoring conditions listed in Table 5 below.

Table 5: Date of Event and Censoring Rules for PFS Analysis

Row	Situation	Date of Event or Censoring	Outcome
Events include death or first documentation of confirmed PD that occurred on or prior to the data analysis cutoff date. For Cohorts 1 and 3 ibrutinib monotherapy, events need to meet one additional criterion: occurred at or prior to initiation of dexamethasone.			
1.1	Death or confirmed PD documented at scheduled disease assessments or between two scheduled disease assessments.	Earliest date of adequate disease assessment documenting confirmed PD or date of death due to progression, whichever occurs first.	Progressed
1.2	Death before first disease assessment	Date of death	Progressed
All other cases will be censored as follows:			
2.1	No baseline assessment	Date of first study treatment	Censored
2.2	No adequate post-baseline assessment (including lost to follow-up since enrollment)	Date of first study treatment	Censored
2.3	Not known to have confirmed PD or died at the data analysis cutoff date (this includes subjects who were known to have confirmed PD or died after the data analysis cutoff date)	Date of last adequate disease assessment showing no evidence of confirmed PD on or before data analysis cutoff date	Censored
2.4	Addition of dexamethasone (Cohorts 1 and 3 ibrutinib monotherapy only)	The start date of dexamethasone	Censored

For subjects who meet more than one censoring condition, PFS will be censored according to the earliest censoring condition. For subjects who meet none of the censoring conditions, PFS will be calculated using the earliest event date.

PFS Event (day) = Date of PFS event – Date of first study treatment

PFS Censor (day) = Date of censoring – Date of first study treatment + 1

Kaplan-Meier curves will be used to estimate the distribution of PFS. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median PFS. A 2-sided 95% confidence interval (CI) will be provided for this estimate. PFS at landmark time points (e.g. 4, 8, 12, 16 months from first study treatment) will also be estimated with corresponding 2-sided 95% CI.

Subgroup Analysis

Subgroup analyses will be performed for the selected factors (see Section 8.7.1). PFS event rate, Kaplan-Meier estimates for the median and PFS at landmark time (decided by data status

at final analysis) will be provided for each stratum of the subgroups. Forest plot will be provided for PFS at landmark time.

8.8.3.2. Time to Progression (TTP)

Time to progression (TTP) is defined as the duration from start of treatment to PD (earliest occurrence), with deaths from causes other than progression not counted, but censored. The calculation for the time of PD and censoring rules are the same as those for DCB (see Table 4).

TTP Event (day) = Date of progression – Date of first study treatment

TTP Censor (day) = Date of censoring – Date of first study treatment + 1

The same analyses will be done for TTP as those for DCB described in Section 8.7.2.1.

8.8.3.3. Overall Survival (OS)

Overall survival (OS) will be measured from the date of first study drug administration until the date of death from any cause.

For subjects who have an incomplete death date, the death date will be imputed as the earliest possible date that incorporates the available death date information and that does not contradict the date last known alive in the database.

For subjects who were not known to have died prior to the analysis cutoff date, the overall survival will be right-censored based on the earliest censoring condition in Table 6.

OS Event (day) = Date of death – Date of first study treatment

OS Censor (day) = Date of censoring – Date of first study treatment + 1

Table 6: Date of Censoring for OS Analysis

Situation	Date of Censoring	Outcome
Not known to have died at the analysis cutoff date (this includes subjects who were known to have died after the data analysis cutoff date)	Date last known alive or data analysis cutoff date, whichever occurs first (specifically, for subjects who were known to have died after the data analysis cutoff date, overall survival will be censored at the data analysis cutoff date)	Censored

The date the subject was last known to be alive will be derived as follows:

- For subjects who became lost to follow-up when they were in the treatment phase, date last known alive will be derived using date of last assessment/visit, last dose date of study drug, or study exit date whichever occurs later;
- For subjects who became lost to follow-up when they were in the follow-up phase, date last known alive will be derived using date last known alive reported on the Follow-up CRF page or study exit date, whichever occurs later.

The same analyses (including subgroup analyses) will be done for OS as those for PFS described in Section 8.7.3.1.

8.8.3.4. Time to Clinical Benefit and Time to Response

Time to clinical benefit (TCB) will be analyzed for subjects achieving CBR (MR or better) prior to initiation of new antineoplastic therapy as evaluated by investigators. Time to initial response as well as best response will be derived.

Time to initial clinical benefit response is defined as the interval between the date of first dose and the date of initial documentation of a response (MR or better). Time to best response is defined as the interval between the date of first dose and the date of initial documentation of the best response that a subject achieved prior to initiation of new antineoplastic therapy.

Similarly, time to response will be analyzed for subjects achieving PR or better prior to initiation of new antineoplastic therapy as evaluated by investigators.

For Cohorts 1 and 3 ibrutinib monotherapy, time to clinical benefit and time to response will be analyzed for subjects achieving response prior to initiation of dexamethasone or new antineoplastic therapy, whichever occurs first.

Time to clinical benefit and time to response will be summarized descriptively by treatment cohort as a continuous variable.

8.9. Safety Analyses

All safety analyses will be based on the safety population.

In Cohorts 1 and 3, subjects will be on ibrutinib monotherapy and may convert to ibrutinib and dexamethasone combination therapy at the discretion of the investigator after a confirmed PD on ibrutinib monotherapy. Thus the safety data (e.g. incidence of TEAEs, laboratory values) will be presented and distinguished as with and without dexamethasone for subjects in Cohorts 1 and 3, when applicable.

Table 7: Summary of Safety Analyses to be Performed

Category	Analysis	Summarize By	Listing
Adverse Events			
General	Overall summary	Study Period	
	TEAEs	SOC+ PT+Study Period; PT+ toxicity grade+Study Period	
	Grade 3 or worse TEAE	SOC+ PT+Study Period; PT+ toxicity grade+Study Period	
	Ibrutinib Related TEAE	SOC+ PT (Whole Study Period only)	
	Dexamethasone Related TEAE	SOC+ PT (Whole Study Period only)	
	Grade 3 or worse Ibrutinib Related TEAE	SOC+ PT (Whole Study Period only)	
	Grade 3 or worse Dexamethasone Related TEAE	SOC+ PT (Whole Study Period only)	
	TEAEs leading to treatment discontinuation		✔
	TEAEs leading to Ibrutinib discontinuation	SOC+ PT (Whole Study Period only)	
	TEAEs leading to Dexamethasone discontinuation	SOC+ PT (Whole Study Period only)	
	TEAEs leading to dose reduction or dose withheld		✔
	TEAEs leading to Ibrutinib dose reduction	SOC+ PT+Study Period	
	TEAEs leading to Dexamethasone dose reduction	SOC+ PT+Study Period	
	TEAEs leading to Ibrutinib dose withheld	SOC+ PT+Study Period	
	TEAEs leading to Dexamethasone dose withheld	SOC+ PT+Study Period	
	Serious TEAEs	SOC+ PT + Study Period; PT + toxicity grade + Study Period	✔
	Ibrutinib Related Serious TEAEs	SOC+ PT (Whole Study Period only)	
	Dexamethasone Related Serious TEAEs	SOC+ PT (Whole Study Period only)	
	Treatment emergent bleeding events	PT + toxicity grade+Study Period	

Category	Analysis	Summarize By	Listing
	Treatment emergent major hemorrhage	PT + toxicity grade+Study Period	✔
	Treatment emergent atrial fibrillation and atrial flutter events		✔
Death	Death within 30 days of last study treatment	Whole Study Period	
	All Deaths		✔
Laboratory Evaluations			
Hematology	Measured values and change from baseline	Visit+Study Period	
	Treatment emergent worst post-baseline low abnormalities	Toxicity grade+Study Period	
	Shift of toxicity grade in low direction	Toxicity grade+Study Period	
Chemistry	Measured values and change from baseline	Visit+Study Period	
	Treatment emergent worst post-baseline abnormalities	Toxicity grade+Study Period	
	Shift of toxicity grade in low direction	Toxicity grade+Study Period	
	Shift of toxicity grade in high direction	Toxicity grade+Study Period	
	Shift from baseline in Creatinine Clearance	Study Period	
	DILI related lab criteria	Study Period	
	Liver function abnormalities	DILI; NCI criteria; Hy's Law	✔, only if any potential Hy's Law identified
	Treatment emergent abnormal uric acid	Study Period	
Vital Signs			
General	Measured values and change from baseline	Visit+Study Period	
	Shift of ECOG Performance Status	Study Period	
Other Safety Observations			
General	Other malignancy	Treatment Emergent Period (primary analysis) + Study Period	✔

PT = preferred term; SOC = system organ class
Study Periods refer to Whole Study Period and Monotherapy Period
DILI = drug induced liver injury

8.9.1. Adverse Events

Verbatim descriptions of AEs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be assessed using National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) Version 4.0 or higher.

Drug-related AEs are those assessed by investigator as being possible, and definitely related to study drug.

Treatment-emergent adverse events (TEAEs) are defined as those events that 1) occur after the first dose of study drug, through the treatment phase, and within 30 days following the last dose of study drug or the day prior to initiation of subsequence anti-myeloma therapy, whichever occurs earlier; 2) any event with missing onset date and its resolution date is during the treatment phase; 3) any event that is considered study drug-related regardless of the start date of the event; or 4) any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator.

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query [SMQ] excluding laboratory terms and will be tabulated. Major hemorrhage is a subset of hemorrhagic events which are grade ≥ 3 or serious or belong to central nervous system (CNS) hemorrhage/hematoma.

The causal relationship between the occurrence of an AE and study drug will be judged by the investigator as unrelated, possibly related, or definitely related. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity grade and/or strongest causal relationship to study drug will be used for purposes of incidence tabulations.

The analyses for AEs are summarized in Table 7. AEs will be summarized based on the number and percentage of subjects experiencing events by MedDRA system organ class and preferred term and by NCI toxicity grade.

Incidence of all reported deaths and deaths within 30 days after the last dose of study drug will be tabulated by cause of death.

8.9.1.1. Adverse Events of Special Interest

Major Hemorrhage: The PCYC standard definition of major hemorrhage is listed in Appendix 2. Major hemorrhage will be analyzed and listed.

8.9.2. Other Safety Observations

8.9.2.1. Other Malignancies

Other malignancies are defined as new malignant tumors including solid tumors, skin malignancies and hematologic malignancies and are to be reported by investigators for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. Malignancy events by preferred term and toxicity grade will be summarized for treatment emergent period and whole study period. A data listing will also be provided.

8.9.3. Laboratory Evaluation

Hematology and serum chemistry parameters will be measured at screening, on Days 1, 2, 8 and 15 of Cycle 1, and at each study visit thereafter. Urinalysis tests will be done at screening.

All laboratory values will be converted to standard international (SI) units and classified as normal, low, or high based on the Pharmacyclics standard reference ranges whenever local laboratory reference ranges are not available. The severity of laboratory abnormalities will be graded using NCI CTCAE version 4.0 or higher.

Number and percentage of subjects with treatment emergent laboratory abnormalities will be presented by treatment cohort for the following hematology and chemistry parameters: Hgb, ANC, platelets, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), albumin, total bilirubin, creatinine, estimated creatinine clearance (Clcr), lactate dehydrogenase (LDH), uric acid and electrolytes (sodium, potassium, calcium). Shift tables summarizing baseline CTCAE grade versus the worst post-baseline CTCAE grade will also be provided. The shift of creatinine clearance rate from baseline to the lowest post-baseline value will also be summarized by categories ($\geq$ 60, 30 - <60, and < 30 mL/min).

To conservatively evaluate potential Drug-Induced Liver Injury (DILI), the incidence of any ALT or AST > 3 × upper limit of normal range (ULN) and any total bilirubin > 2 × ULN post baseline will be reported respectively. Subjects who had both events occurred at any time post baseline (not necessary on the same lab evaluation) plus ALP < 2 × ULN at any time post baseline will be identified as potential Hy's law cases. A full listing of ALT, AST, total bilirubin and ALP values will be provided for the potential Hy's law cases. Frequency of abnormal treatment emergent uric acid will also be summarized.

Summary statistics for hematology and chemistry parameters will be calculated by treatment cohort for the measured values and for their changes from baseline at each scheduled visit of assessment.

Graphs displaying descriptive statistics over time will be provided for selected laboratory parameters including, but not limited to, Hgb, ANC, and platelets.

Laboratory values up to 30 days after the last dose of study drug will be included in the tabulations and graphs. Laboratory values after initiation of subsequence anti-myeloma therapy will be excluded.

8.9.4. Electrocardiogram

12-lead ECGs will be done at screening. ECGs will be captured on the CRFs and kept in the clinical database. No formal analysis will be performed.

8.9.5. Vital Signs and Physical Examination Findings

Vital signs (blood pressure, heart rate, respiratory rate and body temperature) and weight will be recorded at screening and each study visit. Physical examination will be done at screening and symptom-directed physical examinations will be performed during the treatment period.

Summary statistics for vital signs parameters will be calculated by treatment cohort for the measured values and for their changes from baseline at each scheduled visit of assessment.

8.9.6. ECOG Performance Status

ECOG performance status will be recorded at screening and each study visit.

A shift table will be provided for baseline score versus the maximum post-baseline score during the treatment emergent period.

9. Patient Reported Outcome

9.1. Neuropathy Assessment

The neurotoxicity (Ntx) subscale of FACT/GOG-NTX will be utilized for neuropathy assessment. The Ntx subscale scores will be derived per FACT/GOG-Ntx Scoring Guidelines[4].

Descriptive analysis (mean, standard deviation, median, and range) will be provided by cohort for baseline subscale scores and change from baseline prior to initiation of subsequent anti-myeloma therapy. Baseline value is defined as the last score collected on or prior to first dose of study drug.

9.2. Bone Pain Assessment

Brief Pain Inventory by Cleeland[2] will be utilized for bone pain assessment.

Descriptive analysis (mean, standard deviation, median, and range) will be provided by cohort for baseline scores and change from baseline prior to initiation of subsequent anti-myeloma therapy. Baseline score is defined as the last score collected on or prior to first dose of study drug.

The following parameters will be summarized:

- Pain at its worst in last 24 hrs
- Pain at its least in last 24 hrs
- Pain on the average
- Pain when assessment occurred
- Pain relief in last 24 hrs
- Activity interference caused by pain in last 24 hrs
  - General activity
  - Mood
  - Walking ability
  - Normal work
  - Sleep
  - Relations with other people
  - Enjoyment of life

10. MODIFICATIONS TO THE PROTOCOL

The following analysis modifications are made:

- Two additional exploratory endpoints, Time to Clinical Benefit and Time to Response, and the associated analysis methods are added to the SAP.

- The definition for major hemorrhage is updated in alignment with the related post marketing commitment on major bleeding and allows consistent analysis for the ibrutinib clinical development program. The updated definition is based on searching and subtyping grade ≥ 3 or serious or central nervous system (CNS) hemorrhage/hematoma by hemorrhage SMQ excluding laboratory terms. The following types of events in protocol definition were removed because they are grade ≥ 3 or serious hemorrhage events according to NCI CTCAE criteria: intraocular

bleeding causing loss of vision, the need for a transfusion of two or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of hospitalization. Intracranial hemorrhage in protocol is included in the CNS hemorrhage/hematoma as a component of major hemorrhage.

REFERENCES

1. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. Leukemia 2008; 22(2):231-239.

2. Cleeland CS. Brief Pain Inventory (Short Form), 1991.

3. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20(9):1467-1473.

4. FACT/GOG-Ntx Scoring Guidelines, Version 4, www.facit.org, 2003.

5. FDA Guidance for industry clinical trial endpoints for the approval of cancer drugs and biologics, May 2007.

6. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117(18): 4691-4695.

APPENDIX 1. PREFERRED TERMS FOR CYP3A4 INHIBITORS/INDUCERS

Strong inhibitors:	**Moderate inhibitors:**
Indinavir	Aprepitant
Nelfinavir	Amprenavir
Ritonavir	Amiodarone
Clarithromycin	Atazanavir
Itraconazole	Ciprofloxacin
Ketoconazole	Crizotinib
Nefazodone	Darunavir/ritonavir
Saquinavir	Dronedarone
Suboxone	Erythromycin
Telithromycin	Diltiazem
Cobicistat	Fluconazole
Boceprevir	Fosamprenavir
Mibefradil	Grapefruit juice
Telaprevir	Seville orange juice
Troleandomycin	Verapamil
Posaconazole	Voriconazole
	Imatinib
Strong Inducers:	**Weak Inducers:**
Avasimibe	Amprenavir
Carbamazepine	Aprepitant
Phenytoin	Armodafinil
Rifampin	Clobazam
St. John's Wort	Echinacea
Moderate Inducers:	Pioglitazone
Bosentan	Prednisone
Efavirenz	Rufinamide
Etravirine	Vemurafenib
Modafinil	
Nafcillin	

Source for inhibitors: http://medicine.iupui.edu/clinpharm/ddis/main-table/

Source for inducers: FDA Guidance for Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations February 2012.

APPENDIX 2. HAEMORRHAGE SEARCH TERMS

- Grade 3 or higher AEs using Hemorrhage Standard MedDRA (Version 17.0) Query (SMQ) without labs
- Any SAE using Hemorrhage SMQ without labs
- All Grades of CNS hemorrhage listed below:
  CNS hemorrhage Preferred Terms:
  - Acute haemorrhagic leukoencephalitis
  - Basal ganglia haemorrhage
  - Brain stem haemorrhage
  - Brain stem haematoma
  - Central nervous system haemorrhage
  - Cerebellar haematoma
  - Cerebellar haemorrhage
  - Cerebral arteriovenous malformation haemorrhagic
  - Cerebral haematoma
  - Cerebral haemorrhage
  - Cerebral microhaemorrhage
  - Encephalitis haemorrhagic
  - Epidural haemorrhage
  - Extradural haematoma
  - Haemorrhagic intracranial
  - Haemorrhagic cerebral infarction
  - Haemorrhagic stroke
  - Haemorrhagic transformation stroke
  - Intracerebral haematoma evacuation
  - Intracranial haematoma
  - Intracranial tumour haemorrhage
  - Intraventricular haemorrhage
  - Pituitary haemorrhage
  - Putamen haemorrhage
  - Ruptured cerebral aneurysm
  - Spinal cord haemorrhage
  - Spinal epidural haematoma
  - Spinal epidural haemorrhage
  - Spinal subarachnoid haemorrhage
  - Spinal haematoma
  - Spinal subdural haematoma
  - Spinal subdural haemorrhage
  - Subarachnoid haemorrhage
  - Subdural haematoma

- Subdural haemorrhage
- Subgaleal haematoma
- Thalamus haemorrhage

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Statistical Analysis Plan (SAP) Approval

Protocol Number:	PCYC-1111-CA
Protocol Title:	A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma
SAP Version:	2.0
Date:	20JUN2016

By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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