# STUDY TITLE

An Open label, Multi-Centre, Randomized, Two-treatment, Multi dose, Parallel, Comparative Bioavailability Study of Bortezomib Injection 3.5 mg/0.2 ml and VELCADE 3.5 mg powder for solution for injection at a dose of 1.3 mg/m2 in Multiple Myeloma patients.

Country of Submission: USA

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| **CONTRACT RESEARCH ORGANIZATION** |
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# TABLE OF CONTENTS

[1.0 STUDY TITLE 1](#_Toc22992664)

[2.0 TABLE OF CONTENTS 2](#_Toc22992665)

[3.0 CONTRACT RESEARCH ORGANIZATION’S Declaration 6](#_Toc22992666)

[3.1 Project Manager 6](#_Toc22992667)

[3.2 Principal Investigator 7](#_Toc22992668)

[3.3 Bioanalytical Investigator 8](#_Toc22992669)

[3.4 Biostatistician 9](#_Toc22992670)

[4.0 SYNOPSIS 11](#_Toc22992671)

[5.0 FACILITIES 17](#_Toc22992672)

[6.0 ETHICAL CONSIDERATIONS 18](#_Toc22992673)

[6.1 Basic Principles 18](#_Toc22992674)

[6.2 Institutional Review Board/Institutional Ethics Committee 18](#_Toc22992675)

[6.3 Informed Consent 18](#_Toc22992676)

[6.4 Termination of the Study 18](#_Toc22992677)

[6.5 Termination of Study Site 19](#_Toc22992678)

[6.6 Subject Compensation 19](#_Toc22992679)

[6.7 Insurance Policy 19](#_Toc22992680)

[6.8 Confidentiality 19](#_Toc22992681)

[7.0 BRIEF PHARMACOLOGY 19](#_Toc22992682)

[7.1 Description 19](#_Toc22992683)

[7.2 Mechanism of Action 20](#_Toc22992684)

[7.3 Pharmacokinetics 20](#_Toc22992685)

[7.4 Indications 21](#_Toc22992686)

[7.5 Contraindications 21](#_Toc22992687)

[7.6 Warnings and Precautions 21](#_Toc22992688)

[8.0 INVESTIGATIONAL PLAN 24](#_Toc22992689)

[8.1 Background 24](#_Toc22992690)

[8.2 Rationale 25](#_Toc22992691)

[8.3 Study Objectives 25](#_Toc22992692)

[8.4 Study Design 25](#_Toc22992693)

[8.5 Sample Size 25](#_Toc22992694)

[8.6 Sample Size Justification 25](#_Toc22992695)

[8.7 Randomization 26](#_Toc22992696)

[8.8 Unblinding 26](#_Toc22992697)

[9.0 INVESTIGATIONAL DRUG PRODUCTS 26](#_Toc22992698)

[9.1 Test Product (T) 26](#_Toc22992699)

[9.2 Reference Product (R) 26](#_Toc22992700)

[9.3 Drug Product Distribution 26](#_Toc22992701)

[9.4 Investigational Drug Product Dispensing and Accountability 27](#_Toc22992702)

[9.5 Reconstitution Procedure for Subcutaneous Injection 27](#_Toc22992703)

[9.6 Unused Investigational Drug Products 27](#_Toc22992704)

[9.7 Retention Samples 27](#_Toc22992705)

[10.0 CLINICAL PHASE 28](#_Toc22992706)

[10.1 Screening Number 28](#_Toc22992707)

[10.2 Subject Number and Treatment Allocation 28](#_Toc22992708)

[10.3 Subject Screening 28](#_Toc22992709)

[10.3.1 Demographics 29](#_Toc22992710)

[10.3.2 Medical History 29](#_Toc22992711)

[10.3.3 Physical Examination 29](#_Toc22992712)

[10.3.4 Chest X-Ray 29](#_Toc22992713)

[10.3.5 ECG and 2D- Echo cardiogram Examination 29](#_Toc22992714)

[10.3.6 ECOG and Karnofsky Scale 29](#_Toc22992715)

[10.3.7 Pre-Study Laboratory Tests 29](#_Toc22992716)

[10.3.8 Urine Analysis 29](#_Toc22992717)

[10.3.9 Pregnancy Test 29](#_Toc22992718)

[10.4 Inclusion Criteria 30](#_Toc22992719)

[10.5 Exclusion Criteria 31](#_Toc22992720)

[10.6 Subject Housing 32](#_Toc22992721)

[10.7 Dosage Calculation 32](#_Toc22992722)

[10.8 Drug Administration 32](#_Toc22992723)

[10.9 Study Restrictions 33](#_Toc22992724)

[10.10 Blood Sampling 33](#_Toc22992725)

[10.11 Safety Monitoring 35](#_Toc22992726)

[10.11.1 Laboratory Tests 35](#_Toc22992727)

[10.11.2 Examination of Injection site 35](#_Toc22992728)

[10.11.3 Vitals and Wellbeing 35](#_Toc22992729)

[10.11.4 Handling of Adverse Event / Serious Adverse Event 36](#_Toc22992730)

[10.11.5 Serious Adverse Events Reporting 37](#_Toc22992731)

[10.11.6 Concomitant medication 38](#_Toc22992732)

[10.12 Subject withdrawal/dropout 38](#_Toc22992733)

[10.13 Post-study Laboratory Examination 39](#_Toc22992734)

[11.0 STUDY MONITORING 40](#_Toc22992735)

[12.0 BIOANALYTICAL PROCEDURES 40](#_Toc22992736)

[13.0 Data Management 40](#_Toc22992737)

[14.0 PHARMACOKINETIC & STATISTICAL ANALYSIS 40](#_Toc22992738)

[14.1 Pharmacokinetic Analysis 41](#_Toc22992739)

[14.2 Statistical Analysis 42](#_Toc22992740)

[14.2.1 Pharmacokinetic Parameters 42](#_Toc22992741)

[14.2.2 Pharmacodynamic Parameters 43](#_Toc22992742)

[14.3 Statistical Analysis for Injection Site Reactions Scoring 44](#_Toc22992743)

[15.0 CLINICAL SITE AUDITING AND INSPECTION(S) 44](#_Toc22992744)

[16.0 PROTOCOL REVISIONS / AMENDMENTs 44](#_Toc22992745)

[17.0 DEVIATIONS 44](#_Toc22992746)

[18.0 PUBLICATION POLICY 45](#_Toc22992747)

[19.0 QUALITY ASSURANCE 45](#_Toc22992748)

[20.0 ARCHIVAL 45](#_Toc22992749)

[21.0 RECORD KEEPING 45](#_Toc22992750)

[22.0 STUDY REPORT 46](#_Toc22992751)

[23.0 REVISION SUMMARY 46](#_Toc22992752)

[24.0 REFERENCES 47](#_Toc22992753)

[25.0 GLOSSARY OF TERMS 49](#_Toc22992754)

[26.0 ABBREVIATIONS 52](#_Toc22992755)

[27.0 LIST OF APPENDICES 56](#_Toc22992756)

# CONTRACT RESEARCH ORGANIZATION’S Declaration

## Project Manager

I, the undersigned, have read and understood this protocol and hereby abide to   
co-ordinate for conduct the study in accordance with the protocol, comply with all requirements regarding the obligations of Investigator, the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013), ICMR guidelines, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), USFDA guidelines and guidelines of ICH for Good Clinical Practice set forth by applicable regulatory authorities.

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## Principal Investigator

I, the undersigned, have read and understood this protocol. I agree to comply with all the obligations of the sponsor and all other pertinent requirements of the current version of the ICH ‘Guidelines for Good Clinical Practices’, “National Ethical Guidelines for Biomedical and Health Research involving Human Participants” published by Indian Council of Medical Research (ICMR), New Delhi and ‘GCP’ guidelines set up by Central Drugs Standard Control Organization (CDSCO), New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), and the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013), ICMR guidelines, USFDA guidelines, and with procedures oriented to Good Laboratory Practice and applicable regulatory requirements.

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| --- | --- | --- |
| **Name & Address of the PI** | **Signature** | **Date** |
|  |  |  |

## Bioanalytical Investigator

I, the undersigned, have read and understood this protocol, and this study will be performed in compliance with the final protocol, applicable principles of Good Laboratory Practices (GLP), relevant SOP’s and applicable regulatory guidelines.

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## Biostatistician

I, the undersigned, have read and understood this final protocol, and this study will be performed in accordance with the relevant SOP’s and applicable regulatory guidelines.

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**3.5 Sponsor’s Declaration**

I, on behalf of Shilpa Medicare Ltd., India, read, understood and approve this protocol. I agree to comply with all the obligations of sponsor and all other pertinent requirements of the current version of the ICH ‘Guidelines for Good Clinical Practices’, “National Ethical Guidelines for Biomedical and Health Research on Human Participants” published by Indian Council of Medical Research (ICMR), New Delhi and ‘GCP’ guidelines issued by CDSCO, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), USFDA guidelines and the Principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013).

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# SYNOPSIS

| **SYNOPSIS** | | | |
| --- | --- | --- | --- |
| **Study Title** | An Open label, Multi-Centre, Randomized, Two-treatment, Multi dose, Parallel, Comparative Bioavailability Study of Bortezomib Injection 3.5 mg/0.2 ml and VELCADE 3.5 mg powder for solution for injection at a dose of 1.3 mg/m2 in Multiple Myeloma patients. | | |
| **Study Design** | An Open label, Multi-Centre, Randomized, Two-treatment, Multi dose, Parallel, Comparative Bioavailability Study in Multiple Myeloma patients. | | |
| **Study Objective(s)** | *Primary Objective:*   * To compare the rate and extent of absorption between Test and Reference Products on Day 1 and Day 15. | | |
| *Secondary Objectives*:   * To assess the injection site reactions (local tolerability) of the investigational drug product(s). * To monitor adverse events and ensure the safety of subjects. | | |
| Sample Size | 102 Multiple Myeloma patients will be required for the study considering the following.   * Inter Subject CV: 35% (Considering AUC∞)21 * Expected T/R ratio 95 to 105.3% * Alpha: 5% * Power: 80%   The subjects who have been withdrawn from the study will be replaced with a new patient to get 102 evaluable patients | | |
| **Investigational Drug Products** | **Test (T)** | Bortezomib Injection 3.5 mg/0.2 mL.  ***Manufactured by*:** Shilpa Medicare Ltd., India | |
| **Reference**  **(R)** | VELCADE (Bortezomib) for Injection 3.5 mg /vial.  ***Distributed and Marketed by:***Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139 | |
| **Subject Screening** | The study is conducted in multi-centers after protocol approved by the DCGI and Institutional Ethics Committees.  Multiple Myeloma Patients will be screened for the following at the sites:   * Demographic data, Medical history, Physical examination,  12-lead ECG, 2D Echo-Cardiogram, Chest X-ray, ECOG and Karnofsky performance scale. * Hematology, Biochemistry, Urinalysis, Serology, * Urine Pregnancy test (for females).   The patients who meet all the inclusion and none of the exclusion criteria will be enrolled into the study. | | |
| **Dosing Regimen** | The patients will be on Test/Reference as per the randomization. Test/Reference drugs will be administered on Day 1, 8 and 15.  ANC and platelets will be tested a day before the dosing. The drug administration will be performed for eligible subjects only. | | |
| Subject  Housing | Day 1 and 15: The subjects will be housed from at least 13 hours before drug administration to at least 24 hours after drug administration.  Window period of up to + 2 Days will be allowed in case if the patient does not report on Day 14  Note: Based on the patient condition to facilitate the study procedure, in the opinion of the Investigator, the Patients may be housed in the study site (hospital) for additional duration. Any such decision by the Investigator will be documented in the subject case report form. | | |
| Study Duration | The total duration of the study from enrollment to end of the study is approximately 24 days. | | |
| **Dosage Calculation** | Dose will be individualized to prevent over dosage. After determining patient body surface area (BSA) in square meters, calculate the total volume of reconstituted Bortezomib based on dose of 1.3 mg/m2.  Patient’s body surface area will be determined using following formula for dose calculation.  DuBois & DuBois formula for Body Surface Area (BSA) = 0.007184 (Height(cm)0.725 X Weight(kg)0.425)  After determining patient body surface area (BSA) in square meters, using the below formula the total volume (mL) of reconstituted Bortezomib to be administered is calculated and rounded to the first decimal.  Total Bortezomib volume (mL) to be dosed =  Bortezomib dose (mg/m2) x Patient BSA (m2)  2.5 mg/mL  The dose calculation and dose administered will be recorded in the case report form. | | |
| **Reconstitution Procedure for Subcutaneous Injection** | Test Product:  For subcutaneous administration, each 3.5 mg single-use vial of Bortezomib will be reconstituted with **1.2** ml of 0.9% sodium chloride as a diluent to attain the concentration 2.5mg/ml.  Reference Product:  For subcutaneous administration, each 3.5 mg single-use vial of Bortezomib will be reconstituted with **1.4** ml of 0.9% sodium chloride as a diluent to attain the concentration 2.5mg/ml.  *Note:*   * Proper aseptic techniques should be maintained during and after the reconstitution. Reconstitute only with 0.9% sodium chloride. The reconstituted product should be a clear and colorless solution. Reconstitution will be done within 1 hour prior to dosing. * The Bortezomib should be administered within 8 hours after reconstituted. | | |
| **Drug Administration Procedure** | Patients will receive a single subcutaneous (SC) dose of Bortezomib, either Test (T) or Reference Product (R) as per the randomization schedule (1:1) in abdominal or thigh region by trained staff on Day 1, Day 8 and Day 15.  The time of administration of subcutaneous (SC) dose on each dosing days (Day 1, Day 8 and Day 15) should be normally similar  Note: On Day 22 Compassionate Medication will be given to patients at discretion of the investigator. | | |
| **Concomitant Medication** | The following concomitant medication will be administered prior/after Bortezomib administration on Day 1, 8 and 15 (with in ± 15 Minutes)   * Granisetron 1 mg – 45 minutes prior. * Dexamethasone 40mg – 10 minutes prior. * Cyclophosphamide 300mg/m2 – after 30 minutes. | | |
| **Study Restriction** | All patients will be required to fast overnight for at least  10 hours before their scheduled time of dosing (Day-1 and Day-15) and for at least 2.00 hr post-dose. | | |
| **Safety Monitoring** | Day 1 and Day 15: Blood pressure (Sitting), Pulse rate, Respiratory rate and oral temperature will be examined at the time of admission to study site, prior to drug administration (0.00 hr), 2.00, 4.00, 8.00, 12.00, 24.00,72.00,120.00 and 168.00 hours post dose (within ± 40 minutes from the scheduled time).  Day 1 and Day 15: Subject’s wellbeing will be questioned at 2.00, 4.00 and 8.00 hours post dose (within ± 40 minutes from the scheduled time).  Day 1 and Day 15: ECG will be evaluated at 1.00, and 4.00 hours post dose (within ± 40 minutes from the scheduled time).  Day 1 and Day 15: Injection site will be inspected for site reactions at 2.00, 4.00, 8.00, 24.00, and 72.00 hours post dose (within ± 40 minutes from the scheduled time) as per Appendix-III.  Day 8: Blood pressure (Sitting), Pulse rate, Respiratory Rate and oral temperature will be examined prior to drug administration (0.00 hr), ECG will be evaluated at 1.00 hours post dose (within ± 40 minutes from the scheduled time).  Day 8: injection site will be inspected at 2 hours post dose for site reactions (within ± 40 minutes from the scheduled time) as per Appendix-III.  Pregnancy Test (for female patients): will be performed during Day 0, Day 7 and Day 14.  **Note:** At the discretion of the Investigator, based on patient’s health status, additional vitals may be recorded.  **Follow-up Visit:**  Subject safety and well-being will be followed up after completion of the study at Day 24 (within + 2 Days from the scheduled time). | | |
| **Blood Sampling** | **Pharmacokinetic Assessment**  Day 1 & Day 15: Blood samples (3 mL) will be collected for PK evaluation at pre-dose (0.00 hours) and at 0.033, 0.083, 0.250, 0.500, 1.000, 1.500, 2.000, 4.000, 6.000, 12.000, 24.000, 72.000, 120.000 and 168.000hour post dose.  A total 15 blood samples will be collected in K2EDTA tubes. The blood samples will be stored in ice cold water bath till centrifugation. The plasma will be separated by centrifuging the samples at 3000 RPM at 4ºC for 10 minutes. Plasma will be transferred into two pre-labeled sample tubes. 0.8 ml of plasma in Aliquot 1 and 0.4 ml of plasma will be transferred into Aliquot 2 and will be stored upright in a box containing dry ice or in a freezer at -20ºC ± 10ºC for interim storage at study site until shipment to Bioanalytical Facility.  **Pharmacodynamic Assessment**  Day 1 & Day 15: Blood samples (2 mL) will be collected for evaluation 20s proteasome inhibition at pre-dose (0.00 hours**)** and at 0.033, 0.083, 0.250, 0.500, 1.000, 1.500, 2.000, 4.000, 6.000, 12.000, 24.000, 72.000, 120.000 and 168.000 hours post-dose.  A total 15 PD blood samples will be collected on Day 1 and Day 15. The blood samples will be collected in Sodium heparin vacutainers and stored upright in a refrigerator at 2ºC to 8ºC. The samples will be aliquoted into two and centrifuged at 3000 RPM at 4oC for 15 minutes. The plasma will be discarded and 2.5 mL of Phosphate Buffered Saline will be added and gently inverted for about 5 to 8 times. The solution will be centrifuged at 3000 RPM at 4oC for 30 minutes. The aqueous layer will be discarded and 2.5 mL of Phosphate Buffered Saline will be added and gently inverted for about 5 to 8 times. The solution will be centrifuged at 3000 RPM at 4oC for 30 minutes. The Aqueous layer will be discarded and the packed whole blood cells will be stored at -20°C ± 10°C till analysis. The entire procedure will be conducted on ice bath. | | |
| **Others** | | The total blood loss for each subject is about  188 mL and not exceeding 188 + 10 mL for the study.  The samples will be shipped from each study site to Bioanalytical facility(s) along with data logger. |
| **Bioanalytical** | **PK** | | Bortezomib will be assayed by a validated  LC-MS/MS analytical method. |
| **PD** | | 20S proteasome inhibition assay will be performed using a validate method, when the PK endpoint is not met the acceptance criteria. |
| **Statistical Analysis** | **PK Parameters** | | The statistical analysis will be done using the SAS® Software using version 9.4 or higher.  The descriptive statistics (such as mean, median, minimum, maximum, standard deviation and coefficient of variation) for the relevant pharmacokinetic parameters (Cmax, AUCt,AUC0-168h AUCinf,Tmax, t1/2,Kel,Kel\_lower and Kel\_Upper) will be estimated for both Test and Reference formulations using Phoenix® WinNonlin® version 8.1 or higher. The geometric mean and coefficient of variation will be estimated for Cmax, AUCt, AUC0-168h and AUCinf. for Day 1 & 15  90% two one sided confidence interval for the difference of the least-square means of the logarithmic transformed values of Cmax, and AUCt at 5 % level of significance will be calculated for Bortezomib of Day 1 and 15.  The 90% confidence intervals for the ratio of geometric least square means of ln-transformed pharmacokinetic parameters; Cmax and AUCt should be within 80.00 to 125.00% to conclude the test product is bioequivalent to the reference product. |
| **Injection Site Reactions Scoring** | | The descriptive statistics (such as mean, median, minimum, maximum, standard deviation and coefficient of variation) will be tabulated for Test and Reference treatments for Day 1, 8 and 15. |
| **PD Analysis** | | PD analysis is performed as per below procedure.  The statistical analysis will be done using the SAS® Software using version 9.4 or higher. The p-value will be calculated for Emax and AUEt at 5% level of significance for 20S Proteasome Inhibition.  The 90% confidence intervals for the ratio of geometric least square means of ln-transformed pharmacodynamic parameters; Emax, and AUEt should be within 80.00 to 125.00% to conclude the test product is bioequivalent to the reference product. |

# FACILITIES

|  |  |
| --- | --- |
| **Clinical Laboratory** |  |
| **Bioanalytical, Pharmacokinetic and Reporting Facility** |  |
| **Statistical Analysis** |  |
| **Drug Controller General of India (DCGI)** |  |
| **Biostatistician** |  |

# ETHICAL CONSIDERATIONS

## Basic Principles

The clinical study will be carried out in accordance with the provisions of the current version of the ICH ‘Guidelines for Good Clinical Practices’, Indian – GCP Guidelines, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), USFDA guidelines, ICMR ‘National Ethical Guidelines for Biomedical and Health Research on Human Participants’, the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013).

## Institutional Review Board/Institutional Ethics Committee

The protocol and informed consent form will be submitted to the Institutional Review Board/ Institutional Ethics Committee for review. Upon approval, the study will be conducted as per the approved protocol.

## Informed Consent

Patients will be given enough time to understand the study procedures. The potential hazards, benefits and the rights of the subject(s) during the course of the study will be explained in English or vernacular language and the patient(s) are encouraged to seek clarifications. For patient(s) who have difficulty in reading and/or understanding, thumb impression of patient along written consent will be obtained by a legally acceptable representative or impartial witness. In case of both patient and legally acceptable representative is illiterate impartial witness consent is obtained. A written informed consent signed and date and time by the subject and the investigator will be obtained for each subject in the study and a photocopy of the same will be provided to the subject.

## Termination of the Study

1. In case of termination or suspension of the study for any reason, the institution/investigator should promptly inform the trial patients, should follow-up the patients and where required switching to the appropriate therapy.
2. If Sponsor terminates the study, a written explanation for the termination must be sent to the investigator. The investigator should inform IEC/IRB.
3. If the IEC/IRB terminates the study, the investigator should provide a detailed explanation for the termination to the institution and.
4. In addition if the investigator terminates the study, the investigator must inform the institution, and IEC with a written explanation of the termination.

## Termination of Study Site

1. can pre-maturely close a site, if the site is not performing well.
2. The site can be prematurely closed-out if there is an event of breach by the investigator of the fundamental obligation under this agreement, including but not limited to breach of the clinical study protocol, breach of the applicable laws and regulations or breach of the applicable guidelines for GCP.

## Subject Compensation

The subjects will be paid an adequate compensation approved by the IRB/IEC, on account of their time, participation in the trial and for any inconvenience caused.   
In case of withdrawal of a subject before completion of the study, subject will be paid a pro-rated participation depending upon the extent of participation. Additional compensation requests, if any will be forwarded to IEC and IEC decision will be considered.

## Insurance Policy

The sponsor is responsible for obtaining liability insurance, where in all subjects participating in the study are covered for indemnity.

In the case of any injury occurring to the subject during the study, free medical management will be provided to the subjects as long as required or till such time it is established that the injury is not related to the clinical study, whichever is earlier.

## Confidentiality

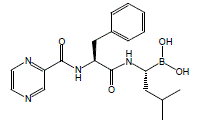
The personal and medical information of the study participants will be kept confidential. The study data is only accessible for study personnel, monitors, quality assurance auditors, IRB/IEC, sponsor representative(s) and regulatory authorities.

# BRIEF PHARMACOLOGY

## Description

VELCADE® for Injection contains bortezomib which is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1­ [[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is C19H25BN4O4. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

VELCADE is available for intravenous injection or subcutaneous use. Each single-use vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 35 mg mannitol, USP. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

## Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitinproteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma.

## Pharmacokinetics

Following intravenous administration of 1 mg/m2 and 1.3 mg/m2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (Cmax) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m2 dose and 89 to 120 ng/mL for the 1.3 mg/m2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m2 dose and 76 to 108 hours after the 1.3mg/m2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m2 and 1.3 mg/m2 , respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m2 , respectively.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m2 dose to patients (n = 14 for intravenous, n = 17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUClast) was equivalent for subcutaneous and intravenous administration. The Cmax after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUClast geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

**Dosage Regimen of Velcade for Patients with Previously Untreated Multiple Myeloma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Twice Weekly VELCADE (Cycles 1-4)** | | | | | | | | | | | | | |
| Week | 1 | | | | **2** | | **3** | **4** | | | **5** | | **6** |
| VELCADE (1.3 mg/m2 ) | **Day 1** | **--** | **--** | **Day 4** | **Day 8** | **Day 11** | **Rest period** | | **Day 22** | **Day 25** | **Day 29** | **Day 32** | **Rest period** |
| Melphalan (9 mg/m2 ) Prednisone (60 mg/m2 ) | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **--** | **--** | **Rest period** | | **--** | **--** | **--** | **--** | **Rest period** |

**Once Weekly VELCADE (Cycles 5-9 when used in combination with Melphalan and Prednisone)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Twice Weekly VELCADE (Cycles 1-4)** | | | | | | | | | | | | | |
| Week | 1 | | | | **2** | | **3** | **4** | | | **5** | | **6** |
| VELCADE (1.3 mg/m2) | **Day 1** | **--** | **--** |  | **Day 8** |  | **Rest period** | | **Day 22** |  | **Day 29** | **--** | **Rest period** |
| Melphalan (9 mg/m2) Prednisone (60 mg/m2) | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **--** | **--** | **Rest period** | | **--** | **--** | **--** | **--** | **Rest period** |

## Indications

**Multiple Myeloma:**VELCADE® (bortezomib) is indicated for the treatment of patients with multiple myeloma.

**Mantle Cell Lymphoma:** VELCADE is indicated for the treatment of patients with mantle cell lymphoma

## Contraindications

VELCADE is contraindicated in patients with known hyper sensitivity to bortezomib, boron, mannitol or to any of the excipients.

## Warnings and Precautions

**Peripheral Neuropathy:**

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous versus intravenous the incidence of Grade ≥ 2 peripheral neuropathy was 24% for subcutaneous and 39% for intravenous. Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule. In the VELCADE versus dexamethasone phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥ Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

**Hypotension**

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

**Cardiac Toxicity**

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE versus dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤ 1% for each individual reaction in the VELCADE group. In the dexamethasone group the incidence was ≤ 1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

**Pulmonary Toxicity**

Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal.

In a clinical trial, the first two patients given high-dose cytarabine (2g/m2 per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.

There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease.

In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

**Gastrointestinal Toxicity**

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting. Sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

**Thrombocytopenia/Neutropenia**

VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied.

Monitor complete blood counts (CBC) frequently during treatment with VELCADE. Measure platelet counts prior to each dose of VELCADE.

**Tumor Lysis Syndrome**

Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

**Hepatic Toxicity**

Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited rechallenge information in these patients.

# INVESTIGATIONAL PLAN

## Background

Bortezomib is indicated for the treatment of Multiple Myeloma. The following dosing regimen is approved by the USFDA:

* **Dosing regimen for previously untreated patients**: Bortezomib is administered in combination with oral Prednisone and oral Melphalan in nine cycles. In cycles 1 to 4, Bortezomib is administered weekly twice (day 1, 4, 8, 11, 22, 25, 29 & 32). In cycles 5 to 9, Bortezomib is administered once weekly (day 1, 8, 22 & 29).
* **Dosing regimen for relapsed patients**: Bortezomib is administered in combination with oral Prednisone and oral Melphalan in nine cycles. In cycles 1 to 4, Bortezomib is administered weekly twice for two weeks (day 1, 4, 8 & 11) followed by 10-day rest period. For extended therapy of more than eight cycles, Bortezomib may be administered on a standard schedule or on a maintenance schedule of once weekly for four weeks (Day 1, 8, 15 & 22) followed by a 13-day rest period.

In 2017, Indian Council of Medical Research (ICMR) published a consensus document for management of multiple myeloma4. According to this guideline, Bortezomib once a week dosing regimen is recommended as primary therapy (in combination with Cyclophosphamide and Dexamethasone and with other drugs).

The major drawback of Bortezomib containing regimens is the risk of neurotoxicity early in the disease course. The neuropathy with Bortezomib can occur abruptly and can significantly be painful and debilitating in a subset of patients.

Twice weekly Bortezomib can be associated with toxicities that may limit efficacy caused by treatment delays and/or discontinuation. In a clinical study5, 6 patients treated with weekly Bortezomib achieved responses similar to the twice weekly schedule. In addition, they experienced less grade adverse events.

Considering, ICMR guideline and current clinical practices, the current study is planned with Bortezomib (once a week) + Cyclophosphamide (300mg / m2 orally day 1, 8, 15 & 22) + Dexamethasone (40 mg orally on day 1, 8, 15 & 22) dosing regimen.

## Rationale

This study is being conducted to assess the Comparative Bioavailability by characterizing the Pharmacokinetic and Pharmacodynamic profile and assessing local tolerability of the test formulation with respect to the reference formulation in Multiple Myeloma patients.

## Study Objectives

The following are the study objectives

1. *Primary Objective*:

* To compare the rate and extent of absorption between Test and Reference Products on Day 1 and Day 15.

1. *Secondary Objectives*:

* To assess the injection site reactions (local tolerability) of the investigational drug product(s).
* To monitor adverse events and ensure the safety of subjects.

## Study Design

An Open label, Multi-Centre, Randomized, Two-treatment, Multi dose, Parallel Comparative Bioavailability Study in Multiple Myeloma patients.

## Sample Size

102 evaluable Multiple Myeloma patients will be enrolled into the study.

## Sample Size Justification

The Sample size computation was determined by considering the following assumptions:

* Inter Subject CV: 35% (Considering AUC∞)21
* Expected T/R ratio 95 to 105.3%
* Alpha: 5%
* Power: 80%

Based on the above estimates, a sample size of 102 evaluable will be sufficient for a Parallel design.

The subjects who have been withdrawn from the study will be replaced with a new patient to get 102 evaluable patients.

## Randomization

The randomization schedule is generated using Proc Plan Seed Procedure by Software using version 9.4 or higher at Pardha Analytics.

At the randomization visit after ensuring that a patient meets all eligibility criteria, the investigator will initiate randomization to study treatment. The order of receiving the test (T) or reference (R) products for each patient during the study will be determined according to a randomization schedule. Site specific randomization schedule will be generated by the biostatistician using SAS® Version 9.4 or higher (SAS Institute Inc., USA) before the commencement of the study. Block randomization of size two will be generated and balanced treatment allocation within block will be ensured at the time of randomization generation. Equal allocation of patients in each sequence (i.e. ‘T’ or ‘R’) will be ensured. A unique Patient No. will be provided to the randomized patients. The assigned patient number will be recorded in the CRF of the patient.

The personnel involved in dispensing of study drug and verification of dispensed study drugs will be accountable for ensuring compliance to randomization schedule.

## Unblinding

The bioanalytical division will be kept blinded to the randomization schedule until Pharmacokinetic, Pharmacodynamic and Statistical Analysis.

# INVESTIGATIONAL DRUG PRODUCTS

## Test Product (T)

Bortezomib Injection 3.5 mg/0.2 mL.

***Manufactured by*:** Shilpa Medicare Ltd., India.

## Reference Product (R)

VELCADE (Bortezomib) for Injection 3.5 mg /vial.

***Distributed and Marketed by:***Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139

## Drug Product Distribution

The sponsor will supply enough quantities of the test and reference products to allow the completion of the study to. The study medication will be stored at recommended storage conditions at Medical Research India Pvt. Ltd.

Pharmacist or designate will distribute enough investigational drug products along with reserved drugs to the study sites. The shipment and inventory log maintained at .

## Investigational Drug Product Dispensing and Accountability

The dispensing will be performed by a qualified pharmacist at the study site. It will be the responsibility of PI / designee at the study site to maintain the dispensing records for the administration of Investigational study products to the patients.

Each study site will maintain record for the drug accountability receipt, number of drug products dispensed to the patients and for the used / unused drug products.

The Investigator has overall responsibility for ensuring that study medication is stored in a safe, limited access location, reference medication is to be stored in below 25ºC and excursions permitted from 15ºC to 30ºC and Test medication is to be stored 02ºC to 08ºC.

## Reconstitution Procedure for Subcutaneous Injection

Test Product:

For subcutaneous administration, each 3.5 mg single-use vial of Bortezomib will be reconstituted with **1.2 ml** of 0.9% sodium chloride as a diluent to attain the concentration 2.5mg/ml.

Reference Product:

For subcutaneous administration, each 3.5 mg single-use vial of Bortezomib will be reconstituted with **1.4 ml** of 0.9% sodium chloride as a diluent to attain the concentration 2.5mg/ml.

Note: Proper aseptic techniques should be maintained during and after the reconstitution. Reconstitute only with 0.9% sodium chloride. The reconstituted product should be a clear and colorless solution. Reconstitution will be done within 1 hour prior to dosing.The Bortezomib should be administered within 8 hours after reconstituted.

## Unused Investigational Drug Products

The unused (including dispensed but not diluted), will be archived along with retention samples at the site / a third party for a period of 5 years. Leftover reconstituted and diluted but not administered products will be disposed according to the site procedures.

## Retention Samples

All the leftover or unused investigational product(s) will be archived along with retention samples at the site / a third party for a period of 5 years.

# CLINICAL PHASE

## Screening Number

Each patient is assigned a unique screening number on first cum first basis. The screening number is a combination of site code (assigned by the ) and the patient number in that site. For example 02-006 stands for 6th patient screened at Site 02. The screening number should reflect in all the laboratory records and screening documentation. Once assigned, the screening number will not be reused.

## Subject Number and Treatment Allocation

If a patient is deemed eligible for enrollment into the study, the site personnel will contact the pharmacist through e-mail for the subject number and treatment. The subject number and treatment will be allotted by the pharmacist as per the randomization schedule on first cum first basis. The e-mail of pharmacist is as follows:

There should be a source document maintained at the site which links the screening number to the randomization assignment number (once assigned). The same will be reflected in screening and enrollment log of investigator site file.

## Subject Screening

All clinical laboratory blood and urine samples will be transferred to the central laboratory under controlled temperature and in pre validated laboratory kits which will be supplied to all the sites by the central laboratory.

During enrollment/Check in day (Day 0, Day 7 and Day 14) clinical laboratory blood and urine samples will be analysed by local laboratory.

The investigator must ensure that all patients being considered for the study meet the following (All the inclusion and none of the exclusion) criteria. The investigator should apply no additional exclusions, in order that the study population will be representative of all eligible patients. Patients’ selection is to be established by checking through all inclusion/ exclusion criteria at screening,baseline and check in of each dosing. In exceptional cases, medical judgment should be exercised in deciding whether to include or exclude the patient from the study and this would be based on the condition of the patient and whole discretion of the investigator.

The following must be assessed by the Site Investigator or a delegated person prior to the enrollment normally within 20 days of the screening.

### Demographics

Name, sex, age, ethnicity, race, body weight (Kg), height (cm), BMI (Kg/m2), BSA (m2), Blood pressure, pulse rate, Respiratory Rate and oral temperature will be recorded.

### Medical History

Relevant medical history and current medication will be recorded.

### Physical Examination

Each patient will undergo a complete physical examination.

### Chest X-Ray

Each patient will undergo a chest X-ray (postero-anterior view).

### ECG and 2D- Echo cardiogram Examination

12 lead ECG and 2D- Echo cardiogram Examination.

### ECOG and Karnofsky Scale

ECOG Performance status (Appendix-I) and Karnofsky performance scale (Appendix-II) will be evaluated.

### Pre-Study Laboratory Tests

The following tests will be conducted at the central laboratory:

* + - **Hematology:** Total leukocyte count (WBC), Total erythrocyte count (RBC), Heamoglobin (Hb), HCT (PCV), Neutrophils, lymphocytes, Monocytes, Eosinophils, Basophils, Absolute Neutrophil Count (ANC) and platelet count.
    - **Clinical Chemistry**: Random blood glucose, BUN, serum creatinine, Cockcroft-Gault creatinine clearance, total bilirubin, ALT, AST, Albumin, Total Cholesterol, Triglycerides, total proteins and electrolytes (Na, K, Ca and Cl).
    - **Serology:** HIV-1, HIV-2, HbsAg and HCV.

### Urine Analysis

* **Physical Examination:** Colour, appearance and specific gravity.
* **Chemical Examination**: pH, protein/albumin, glucose, ketones, bilirubin, Leucocytes (WBC), Red Blood Cells and Urobilinogen.

### Pregnancy Test

For female subjects, a urine pregnancy test will be performed on screening, Day 0, Day 7 and Day 14 at the site.

The pre-study laboratory test results will be examined by qualified personnel and eligible patients will be enrolled into the study.

## Inclusion Criteria

Patients those who are willing to participate into this study must meet the following inclusion criteria:

1. Patient with histopathologically/cytologically confirmed multiple myeloma.
2. Adult multiple myeloma patients aged 18 to 65 years old (both inclusive) and weighing between 45 to 80 kg (both inclusive) who are naïve and/or under treatment with Bortezomib or relapsed multiple myeloma (who have previously responded to treatment with Bortezomib either alone or in combination and who have relapsed at least 6 months after the prior therapy).

Patient with ECOG (Eastern Co-operative Oncology Group) performance status 0, 1 or 2 (Refer Appendix - I).

Patient with performance ≥70% Karnofsky performance status scale (Refer Appendix - II).

Patient must have adequate bone marrow (Hemoglobin levels ≥ 8.0 g/dL, ANC ≥1500/mm3 and platelet count ≥ 1,00,000/mm3) prior to enrollment.

Patient must have adequate renal function (Serum creatinine ≤ 1.5 times of ULN). About 10% of Renal impaired patients will be enrolled who have Cockcroft-Gault creatinine clearance ≥30 ml/min.

Patient must have adequate hepatic function (Serum bilirubin ≤ 1.5 times of ULN and AST/ALT ≤ 2.0 times of ULN).

Subject who have no evidence of underlying disease which in the judgement of the investigator would not make the subject inappropriate for getting enrolled in the study (except multiple myeloma), during screening.

Patient and /or LAR or impartial witness able to give written informed consent for participation in the trial.

Patient with life expectancy of at least four months.

In the opinion of the investigator, patient should be able to comply with study procedures.

Sexually active women, unless surgically sterile (at least 6 months prior to study drug administration) or postmenopausal (females who have had a natural menopause for at least 24 consecutive months), must agree to use two effective methods of avoiding pregnancy for at least 4 weeks prior to study drug administration, during study and up to 60 days after the last dose of study drug. Cessation of birth control after this point should be discussed with a responsible physician.

*In case of male patients:* Male patients must agree to practice complete abstinence or agree to use a condom during sexual contact with a female even if they have had a successful vasectomy.

It is investigator’s responsibility to ensure that above points regarding an effective method of avoiding pregnancy are discussed with patient in detail and patient agreed for this and it is documented in source document. The investigator should ensure that the patient is using an effective method of avoiding pregnancy as per protocol.

## Exclusion Criteria

Patients will be excluded from the study if they meet one of the below exclusion criteria:

1. Known hypersensitivity to Bortezomib or to any of the excipients, Cyclophosphamide and Dexamethasone.
2. If the patient had undergone prior surgery, chemotherapy, or other anti- cancer therapy within 4 weeks (28 days), thalidomide and/or lenalidomide within 2 weeks prior to dosing in the study.
3. Patient with known human immunodeficiency virus (HIV) infection.
4. A positive hepatitis screen including HBSAg and HCV antibodies.
5. Use of any recreational drugs or history of drug addiction.
6. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds (ms)) or history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or use of concomitant medications that prolong the QT/QTc interval.
7. History of venous thromboembolism or disease that aggravate risk for thromboembolism.
8. Patient taking concurrent medications at entry that may act as inhibitors/inducers of CYP3A4 CYP2C19 and CYP1A2 as per Appendix -IV.
9. Patient with cardiac disease known and clinically significant grade 2 neuropathy, pulmonary, hepatic, gastrointestinal, endocrine, immunologic, dermatological, musculo-skeletal, psychiatric, neurological, proven amyloidosis and secondary malignancy.
10. Patient with a history of difficulty in donating blood or difficulty in accessibility of veins.
11. Patient participated in any drug intervention study and donated blood within 90 days prior to the current study.
12. Female patients with pregnancy or breast-feeding.
13. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study treatment.

## Subject Housing

Day 1 and 15: The subjects will be housed from at least 13 hours before drug administration to at least 24 hours after drug administration.

Window period of up to + 2 Days will be allowed in case if the patient does not report on Day 14.

Note: Based on the patient condition to facilitate the study procedure, in the opinion of the Investigator, the Patients may be housed in the study site (hospital) for the entire duration of the study. Any such decision by the investigator will be documented in the subject case report form.

## Dosage Calculation

Dose must be individualized to prevent over dosage. After determining patient body surface area (BSA) in square meters, calculate the total volume of reconstituted bortezomib based on dose of 1.3 mg/m2.

Patient’s body surface area will be determined using following formula for dose calculation.

|  |  |  |
| --- | --- | --- |
| DuBois & DuBois formula for Body Surface Area (BSA) | = | 0.007184 (Height(cm)0.725 X Weight(kg)0.425). |

After determining patient body surface area (BSA) in square meters, using the below formula the total volume (mL) of reconstituted Bortezomib to be administered is calculated and rounded to the first decimal.

|  |  |  |
| --- | --- | --- |
| Total Bortezomib volume (mL) to be dosed | = | Bortezomib dose (mg/m2) x Patient BSA (m2)  2.5 mg/mL |

## Drug Administration

Patients will receive a single subcutaneous (SC) dose of Bortezomib, either Test (T) or Reference Product (R) as per the randomization schedule (1:1) in abdominal or thigh region by trained staff on Day 1, Day 8 and Day 15. The investigational product should be administered to the patient only by the investigator or authorized study personnel.

The time of administration of subcutaneous (SC) dose on each dosing days (Day 1 Day 8 and Day 15) should be normally similar.

Note: Each cycle comprises 4 doses

* Day 1: Test/ Reference
* Day 8: Test/ Reference
* Day 15: Test/ Reference
* Day 22: Compassionate Medication

## Study Restrictions

All patients will be required to fast overnight of at least 10 hours (Day 1 and 15) before their scheduled time of dosing and for at least 2.00 hrs post-dose.

**Note:**

1. The subject will be abstained from grapefruit/grape fruit juice/flavonoid containing liquids during study period.
2. The subject will be abstained from xanthine containing food or beverages (like tea, coffee, chocolates and aerated drinks) and tobacco products during study period.
3. The subject will be abstained from smoking during study period.

## Blood Sampling

A heparin-lock technique will be used to prevent coagulation of the blood in the cannula. In order to reduce the fluctuation of the plasma concentration-time profiles due to the residual blood sample from the previous collection, the first 0.5 mL of blood will be discarded prior to each blood sample collection.

Blood samples (3 mL) will be collected for PK evaluation at pre-dose (0.00 hours) and at 0.033, 0.083, 0.250, 0.500, 1.000, 1.500, 2.000, 4.000, 6.000, 12.000, 24.000, 72.000, 120.000 and 168.000hour post dose on Day 1 and Day 15.

Blood samples (2 mL) will be collected for evaluation 20s proteasome inhibition at pre-dose (0.00 hours**)** and at 0.033, 0.083, 0.250, 0.500, 1.000, 1.500, 2.000, 4.000, 6.000, 12.000, 24.000, 72.000, 120.000 and 168.000 post-dose on Day 1 and 15.

The heparinized blood will be discarded for in-house samples up to 12 hours, excluding pre-dose sample.

The total volume of blood loss for the study will be as follows

|  |  |
| --- | --- |
| Screening | About 12 mL |
| ANC, Platelet count (before each dosing day) at local lab (3 X 2 mL) | About 06 mL |
| Post study Safety Assessment | About 8 mL |
| PK Sampling | About 90 mL (15 X 2 X 3 mL). |
| PD Sampling | About 60 mL (15X 2 X 2 mL) |
| Heparinized Blood | 12 mL discarded heparinized blood prior to sample collection through cannula |
| Total: | About 188 mL |

The total blood loss for each subject is about 188 mL and not exceeding 188 mL + 10 mL for the study.

Blood samples will be collected by means of intravenous cannulation/veni-puncture and transferred into pre-labeled sample tube (mentioning Study number, Subject number, Dosing Day and Sampling time point). The sample tube will be inverted gently 8 to 10 times for each sample point**.**

The pre-dose sample (0.00) will be collected prior to dosing. The post dose samples will be collected within ± 2 minutes of the schedule time for in house samples. Any blood samples drawn beyond the specified window period will be recorded. Actual time of sample collection will be considered for pharmacokinetic & statistical analysis.

A total 15 PK blood samples will be collected on Day 1 and Day 15 in K2EDTA tubes. The blood samples will be stored in ice cold water bath till centrifugation. The plasma will be separated by centrifuging the samples at 3000 RPM at 4ºC for 10 minutes. Plasma will be transferred into two pre-labeled sample tubes. 0.8 ml of plasma in Aliquot 1 and 0.4 ml of plasma in Aliquot 2 will be transferred and will be stored upright in a box containing dry ice or in a freezer at -20ºC ± 10ºC for interim storage at study site until shipment to Bioanalytical Facility.

A total 15 PD blood samples will be collected on Day 1 and Day 15. The blood samples will be collected in Sodium heparin vacutainers and stored upright in a refrigerator at 2ºC to 8ºC. The samples will be aliquoted into two and centrifuged at 3000 RPM at 4ºC for 15 minutes. The plasma will be discarded and 2.5 mL of Phosphate Buffered Saline will be added and gently inverted for about 5 to 8 times. The solution will be centrifuged at 3000 RPM at 4oC for 30 minutes. The aqueous layer will be discarded and 2.5 mL of Phosphate Buffered Saline will be added and gently inverted for about 5 to 8 times. The solution will be centrifuged at 3000 RPM at 4oC for 30 minutes. The Aqueous layer will be discarded and the packed whole blood cells will be stored at -20°C ± 10°C till analysis. The entire procedure will be conducted on ice bath.

**Transferring of Samples:**

Data loggers will be used to monitor the temperature during shipment and the recorded temperature will be maintained. After completion of the clinical phase of the study, the blood samples for analysis will be shipped to the following address:

Mr. Ramalingam

GM- Bioanalytical

QPS Bioserve India Pvt Ltd

Plot No 47, Second floor,

IDA Balanagar, Hyderabad - 500037

Telangana

Tel: +91-40-4377 0850

The samples of aliquot-II for PK analysis will be shipped only after confirming the receipt of aliquot-I samples at the bioanalytical site.

## Safety Monitoring

### Laboratory Tests

Absolute neutrophil count and platelet count will be performed prior to each dosing i.e, Day 0, Day 7 and Day 14 at local laboratory.

The Principal Investigator or designee must ensure platelet count should be at least ≥ 75,000/mm3 and ANC should be at least ≥1500/mm3 prior to dosing on Day 1, Day 8 and Day 15.

### Examination of Injection site

Day 1 and Day 15: Injection site will be inspected for site reactions at 2.00, 4.00, 8.00, 24.00, and 72.00 hours post dose (within ± 40 minutes from the scheduled time) as per Appendix-III.

On day 8 injection site will be inspected at 2 hours post dose for site reactions as per Appendix-III.

### Vitals and Wellbeing

The following will be measured:

Day 1 and Day 15: Blood pressure (Sitting), Pulse rate, Respiratory rate and oral temperature will be examined at the time of admission to study site, prior to drug administration (0.00 hr), 2.00, 4.00, 8.00, 12.00, 24.00, 72.00, 120.00 and 168.00 hours post dose (within ± 40 minutes from the scheduled time).

Day 1 and Day 15: Subject’s wellbeing will be questioned at 2.00, 4.00 and 8.00 hours post dose (within ± 40 minutes from the scheduled time).

Day 1 and Day 15: ECG will be evaluated at 1.00, and 4.00 hours post dose (within ± 40 minutes from the scheduled time).

Day 1 and Day 15: Injection site will be inspected for site reactions at 2.00, 4.00, 8.00, 24.00, and 72.00 hours post dose (within ± 40 minutes from the scheduled time) as per Appendix-III.

Day 8: Blood pressure (Sitting), Pulse rate and oral temperature will be examined prior to drug administration (0.00 hr), ECG will be evaluated at 1.00 hours post dose (within ± 40 minutes from the scheduled time).

Day 8: injection site will be inspected at 2 hours post dose for site reactions (within ± 40 minutes from the scheduled time) as per Appendix-III.

Pregnancy Test (for female patients): will be performed during Day 0, Day 7 and Day 14.

Note: At the discretion of the Investigator, based on patient’s health status, additional vitals may be recorded.

**Follow-up Visit:**

Subject safety and well-being will be followed-up after completion of the study at Day 24 (within + 2 days from the scheduled time).

### Handling of Adverse Event / Serious Adverse Event

Adverse events/serious adverse events will be recorded from the time of administration of study drug until next dose administration of Bortezomib after Day-15 (upto Day 24). Other medical events before the dose administrations but after written informed consent will be recorded on the medical history.

The relationship of the adverse event to the study medication will be judged. All adverse events encountered during the study will be recorded. Subjects experiencing adverse events will be followed up until the adverse event is resolved or lost to follow-up.

The severity of the adverse events will be graded as follows:

| **SEVERITY RELATIONSHIP** | |
| --- | --- |
| Mild | Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient. |
| Moderate | Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning. |
| Severe | Events interrupt the participant’s normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating. |

| **RELATIONSHIP TO THE STUDY DRUG** | |
| --- | --- |
| **Relationship** | **Description** |
| Certain | * Event or laboratory test abnormality, with plausible time relationship to drug intake. * Cannot be explained by disease or other drugs. * Response to withdrawal plausible (pharmacologically, pathologically) * Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) * Rechallenge satisfactory, if necessary. |
| Probable  (Likely) | * Event or laboratory test abnormality, with reasonable time relationship to drug intake * Unlikely to be attributed to disease or other drugs * Response to withdrawal clinically reasonable * Rechallenge not required. |
| Possible | * Event or laboratory test abnormality, with reasonable time relationship to drug intake. * Could also be explained by disease or other drugs. * Information on drug withdrawal may be lacking or unclear |
| Unlikely | * Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) * Disease or other drugs provide plausible explanations |
| Unassessable  (Unclassifiable) | * Report suggesting an adverse reaction * Cannot be judged because information is insufficient or contradictory * Data cannot be supplemented or verified |

### Serious Adverse Events Reporting

If any serious adverse event(s) occurred during the study, the principal investigator will provide all necessary treatment. SAE(s) will be reported to the Sponsor (Pharmacovigilance@shilpamedicare.com), , DCGI, head of the institution (study site) and Ethics Committee through E-mail within twenty-four hours of its occurrence. In case investigator fails to report any SAE within the stipulated period, he/she shall have to furnish the reason for the delay to the satisfaction of the Central Licensing authority along with the report of the SAE.

Investigator will submit detailed report of any serious adverse event to Sponsor, Central Licensing Authority, Ethics Committee, and head of the institution (study site) within 14 calendar days of its occurrence. In case investigator fails to report any SAE within the stipulated period, he/she shall have to furnish the reason for the delay to the satisfaction of the Central Licensing authority along with the report of the SAE.

Sponsor will submit detailed report of any serious adverse event to DCGI, ethics committee and head of the institution (study site) within 14 days of its occurrence.

Ethics committee will send its review report to DCGI for any serious adverse event within 30 days of its occurrence.

All serious and unexpected AEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient to be stable. The medical monitor of sponsor is:

**P. Veerendra Kumar**

Head - Clinical & Pharmacovigilance Dept.,

Shilpa Medicare Limited,

Survey No. 207, Modavalasa (V), Denkada (M),

Vizaianagram (Dist), AP, India-531 162

Email ID: veerendrap.frd@shilpamedicare.com

### Concomitant medication

The following concomitant medication will be administered prior/after Bortezomib administration on Day 1, 8 and 15 (with in ± 15 minutes).

* Granisetron 1 mg – 45 minutes prior.
* Dexamethasone 40mg – 10 minutes prior.
* Cyclophosphamide 300mg/m2 – after 30 minutes.

Adequate pre-medication will be given to avoid any adverse events as per the institutional standards. Drugs which are strong inducers and /or inhibitors of CYP3A4, CYP2C19 and CYP1A2 enzyme family and any other anti-cancer drugs (except Dexamethasone and Cyclophosphamide) will not be allowed to be used during the study. The time of administration of concomitant medications should be preferably the same for all dosing days, as possible.

## Subject withdrawal/dropout

The investigator can withdraw any subject from the study due to one or more following reasons:

1. If the subject chooses to dropout from the study with or without stating any reason.
2. Since it is not in subject’s best interest to continue in the study, as per the opinion of investigator.
3. The patient suffers from significant inter-current illness or undergoes surgery during the course of the study
4. If the subject is found to be violating the inclusion and exclusion criteria.
5. When the subject requires the use of an unacceptable concomitant medication.

The date and reason for withdrawal will be recorded in the subject withdrawal record. All the safety data normally required at the end of the study will be obtained, if possible.

Irrespective of the reason of withdrawal, the patient will be requested to complete all procedures/activities required for End of study visit assessment as far as possible. In case of consent withdrawal, the Investigator shall make serious attempts to find out the reasons behind the withdrawal. Any untoward effect reported by the patients who withdraw will be incorporated into the final study report.

## Post-study Laboratory Examination

The post-study laboratory tests will be carried out at central laboratory at the end of the clinical study (Day-22) /early withdrawal.

* **Hematology:** Total leukocyte count (WBC), Total erythrocyte count (RBC), Heamoglobin (Hb), HCT (PCV), Neutrophils, lymphocytes, Monocytes, Eosinophils, Basophils, Absolute Neutrophil count and Platelet Count.
* **Clinical Chemistry:** Random blood glucose, BUN, serum creatinine, total bilirubin, ALT, AST, Total cholesterol, Triglycerides total proteins and electrolytes (Na, K, Ca and Cl).
* **Pregnancy Test:** For female subjects, a urine pregnancy test will be performed at the End of Study visit/Early Termination procedures at the site.
* **ECG Examination:** 12 lead ECG Examination will be done at the completion of study or early withdrawal.

The Haematology, clinical chemistry will be conducted at central laboratory. The post-study laboratory results will be examined by qualified personnel. Clinically significant results will be considered as adverse events and necessary treatment and follow-up will be made.

# STUDY MONITORING

/Sponsor representatives will monitor the conduct of the study. CRA will visit the sites during the study conduction. The CRA may review all the study related documentation subject’s medical records, source documents, drug accountability records and study drugs will be made available for verification.

# BIOANALYTICAL PROCEDURES

Bortezomib will be assayed by a validated LC-MS/MS analytical method.

The bioanalysis will be conducted using a validated method in accordance with the applicable principle of Good Laboratory Practices (GLP).

The samples of all the subjects will be considered for the analysis. Samples of withdrawn or dropout subjects due to adverse events or any reasons will also be analyzed and only concentration vs. time data of that subject will be tabulated separately and reported in the bioanalytical report.

Subject samples will be quantified using a calibration curve and analytical variations during sample analysis will be evaluated using at least 5% of Quality Control samples in each run.  Samples will be reanalyzed for analytical reasons and non-analytical reasons as per SOP (SOP No: BAU010) of QPS Bioserve India Pvt. Limited.

**Incurred Sample Reanalysis (ISR):** Incurred Sample Reanalysis will be performed for Bortezomib separately as per In house SOP of QPS Bioserve India Pvt Ltd.

After completion of the analysis the biosamples will be stored at recommended storage condition for 6 months or sponsor recommendation for disposal whichever is earlier

# Data Management

Clinical Data Management will be done using Open Clinica version 3.11 or higher. An electronic case report form will be prepared in accordance with the current guidelines (CDASH). The study data will be entered into the electronic case report forms and QCed. The data will be cleaned, reconciled, approved and locked. The data will be extracted into SAS datasets. SDTM and ADaM datasets will be prepared and reviewed as per current CDISC standards.

# PHARMACOKINETIC & STATISTICAL ANALYSIS

Pharmacokinetic analyses will be performed using Phoenix® WinNonlin® 8.1 or higher. The analysis will include all the patients who have completed the study.

The missing samples (M) and Non Reportable Values (NRV) will be considered as missing and the concentration values below the limit of quantification (BLQ) will be designated as zero for analysis.

Samples of withdrawn or dropout subjects due to adverse events if analyzed, the concentration vs. time data of that subject will be tabulated separately and reported in the bioanalytical report and will not be included in Pharmacokinetic and statistical analysis.

## Pharmacokinetic Analysis

Dose normalization will be applied to calculate the pharmacokinetic parameters.

The following subjects will be excluded from the pharmacokinetic analysis:

* Subjects with three or more consecutive missing samples.
* Subjects with less than three quantifiable post dose concentrations

The subjects will be excluded from forKel, Kel\_lower andKel\_Upper and t1/2 for any one of the following reasons:

* Subjects who do not have at least three measurable concentrations after Cmax.
* Subjects who do not have log-linear relationship (i.e. last measurable concentration is more than 50% of the preceding concentration) in the terminal elimination phase.

The following pharmacokinetic parameters will be computed using non‑compartmental model.

|  |  |
| --- | --- |
| Cmax | Maximum measured plasma concentration over the time span specified. |
| AUCt | The area under the plasma concentration versus time curve, from time 0 to t (last measurable time point 168.000 hrs) concentration, as calculated by the linear trapezoidal method. |
| AUC0-168h | The area under the plasma concentration versus time curve, from time 0 to 168hrs concentration, as calculated by the linear trapezoidal method. |
| AUCinf | AUCt + Clast/Kel |
| Tmax | Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, tmax is defined as the first time point with this value. |
| t1/2 | The elimination or terminal half-life will be calculated as 0.693/Kel. |
| Kel | Apparent first order elimination rate constant calculated from a semi-log plot of plasma concentration versus time point. The regression is calculated using the last three, then the last four, last five etc., non-zero concentration points prior to Cmax. Adjusted R2 for each regression is computed and the largest adjusted R2 will be used for calculating terminal elimination rate constant. |
| Kel\_lower | Lower limit on Time for values to be included in the calculation of Kel |
| Kel\_Upper | Upper limit on Time for values to be included in the calculation of Kel |

## Statistical Analysis

### Pharmacokinetic Parameters

Statistical analysis will be performed SAS® Software using version 9.4 or higher (SAS® Institute Inc., USA).

The descriptive statistics (such as mean, median, minimum, maximum, standard deviation and coefficient of variation) for the relevant pharmacokinetic parameters (Cmax, AUCt, AUC0-168h, AUCinf, Tmax, t1/2, Kel, Kel\_lower and Kel\_Upper) will be estimated for both Test and Reference formulations using Phoenix® WinNonlin® version 8.1 or higher. The geometric mean and coefficient of variation will be estimated for Cmax, AUCt and AUCinf.

The geometric mean and coefficient of variation will be estimated for Cmax, AUCt and AUCinf. Arithmetic mean and standard deviation will be estimated for Kel, tmax, and t½.

1. **Analysis of variance**

The log transformed PK parameter values of Cmax, AUCt and AUCinf will be subjected to ANOVA. The ANOVA model will include Treatment, Site and Treatment\*Site as fixed effects.

If the Treatment\*Site interaction term is statistically not significant (p>0.05), the simple model (i.e. naïve pooling of data without Treatment\*Site term) can be applied and statistical analyses will be re‑performed excluding this interaction term.

Each analysis of variance will include calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

1. **Ratio Analysis**

The ratio of least-square means (LSMs) of Test and Reference formulations will be calculated using the least square means for log-transformed pharmacokinetic parameters of Cmax, AUCt and AUCinf. The geometric mean will be reported for the log-transformed pharmacokinetic parameters of Cmax, AUCt and AUCinf of the Test and Reference formulations.

1. **Inter-Subject Variability**

The Inter-Subject variability will be calculated using log transformed pharmacokinetic parameters of Cmax, AUCt and AUCinf.

1. **Power**

The power (i.e. probability of detection a 20% difference relative to the least square means of reference treatment at the 5% significance level under the null hypothesis) will be calculated for log-transformed Cmax, AUCt and AUCinf.

1. **Confidence Interval**

90% two one sided confidence interval for the difference of the least-square means of the logarithmic transformed values of Cmax, and AUCt at 5 % level of significance for Bortezomib of Day 1 and 15.

The 90% confidence intervals for the ratio of geometric least square means of ln-transformed pharmacokinetic parameters; Cmax and AUCt should be within 80.00 to 125.00% to conclude the test product is bioequivalent to the reference product.

1. **Graphical Presentation of Data**

Individual and Mean plasma concentration vs. time plots will be generated on both Linear and Semi-log axis for Bortezomib.

### Pharmacodynamic Parameters

The following Pharmacodynamic parameters will be computed.

|  |  |
| --- | --- |
| Emax | Observed maximum percent inhibition of 20 S proteasome activity taken directly from inhibition time profile |
| AUEt | The area under the proteasome inhibition time curve from time 0 to the last time point. |

The statistical analysis will be done using the SAS® Software using version 9.4 or higher. The p-value will be calculated for Emax and AUEt at 5% level of significance.

90% two one sided confidence interval for the difference of the least-square means of the logarithmic transformed values of Emax, and AUEt at 5 % level of significance for Bortezomib of Day 1 and 15.

The 90% confidence intervals for the ratio of geometric least square means of ln-transformed pharmacokinetic parameters; Emax, and AUEt should be within 80.00 to 125.00% to conclude the test product is bioequivalent to the reference product.

## Statistical Analysis for Injection Site Reactions Scoring

The injection site will be examined for Injection Site Reaction (ISR), Maximal Diameter of Injection Site Reaction, Duration of Symptoms, sequelae, Likely Impact on Next Dose and Activities of daily living (ADL) Limitations.

The descriptive statistics (such as mean, median, minimum, maximum, standard deviation and coefficient of variation) will be tabulated for Test and Reference treatments.

# CLINICAL SITE AUDITING AND INSPECTION(S)

The investigator will permit study-related monitoring, audits and inspections by the IEC/IRB, the sponsor, government regulatory bodies and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc. The investigator agrees to allow the auditors or inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

The investigator will ensure the capacity for inspections of applicable study related facilities (e.g. pharmacy, diagnostic laboratory, study documents etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and quality assurance offices. As soon as the investigator is notified of a future inspection by the authorities, he/she will inform the sponsor and authorize the sponsor to participate in these inspections. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the investigator to the sponsor.

# PROTOCOL REVISIONS / AMENDMENTs

Any significant change in the study procedure or study design will only be effected upon agreement with the sponsor and after obtaining a favorable opinion from the IEC.

# DEVIATIONS

All deviations from this protocol are recorded, handled and reported as per the procedures.

The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations or violation, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to observe vigilance to identify and report deviations immediately upon identification of the protocol deviation. All deviations must be promptly reported to CRO through Email. All deviations from the protocol must be addressed in study subject source documents. A completed copy of the protocol deviation form must be maintained in the regulatory file, as well as in the subject’s source document. Protocol deviations must be sent to the local IRB/IEC, if required, as per their guidelines. The site investigator / study staff is responsible for adhering to IRB/IEC requirements.

# PUBLICATION POLICY

Publication of the results of the study, whether in whole or in part, shall be within the sole and absolute discretion of Sponsor. Medical Research India Pvt Ltd., shall not be entitled to publish any of the data or information arising during or out of the provision of the services without the prior written consent of the sponsor.

# QUALITY ASSURANCE

Medical Research India Pvt Ltd., Quality assurance conducts independent study audits during the study conduction. Quality assurance has access to all the study documents, related to this study.

# ARCHIVAL

All the electronic copy of the study data will be retained by Medical Research India Pvt Ltd., for a period of 15 years after completion of the study and the paper study data will be archived for 5 years from the completion of the study or as per sponsor’s recommendation. All study related source data including treating physician’s /Investigators prescriptions, Medical Review Records, Laboratory Investigations and diagnostic reports including their images shall be archived as per recommended storage conditions at the Investigational site for a period of 15 years after site close-out.

# RECORD KEEPING

Records of patients, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, investigator’s agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site.

Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records Shilpa Medicare Ltd/ must be notified in writing and be given the opportunity to further store such records.

In the event that the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Sponsor.

# STUDY REPORT

The study report will include reports on the clinical phase, bioanalytical phase and data analysis phase of the study. the pharmacokinetic calculations, the statistical analysis of the data, and a clinical report along with raw data. The deviations from the protocol will be documented as protocol deviations and presented in the final report.

# REVISION SUMMARY

The revised protocol (version 02) includes the changes listed in Appendix VI.

# REFERENCES

1. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2006/021602s008,s009.pdf
2. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/021602s043lbl.pdf
3. https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2003/21602\_Velcade.cfm
4. Consensus Document for Management of Multiple Myeloma - 2018, Indian Council of Medical Research (http://icmr.nic.in/sites/default/files/guidelines/Multiple%20Myeloma\_0.pdf)
5. Clinical Practice guideline for Multiple Myeloma Patients, Version 3.2018-November 22, 2017, National Comprehensive Cancer Network (http://szpiczak.org/wp-content/uploads/aktualnosci/artykuly/2016/myeloma\_for\_doctors.pdf)
6. Clinical Practice guideline for Multiple Myeloma Patients, 2018, National Comprehensive Cancer Network (https://www.nccn.org/patients/guidelines/myeloma/files/assets/common/downloads/files/myeloma.pdf)
7. Reeder CB, Reece DE, Kukreti V, *et al.* (2010). Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood, 115, 3416-7.
8. Lightcap *et al*.: Ex Vivo Proteasome Assay “Proteasome Inhibition Measurements: Clinical Application. Clinical Chemistry 46:5; 673-683 (2000).
9. P. Moreau *et al*. SC *vs.* IV Bortezomib administration. “Prospective comparision of subcutaneous versus intravenous administration of Bortezomib in patients with multiple myeloma” haematologica│2008; 93(12) │1908 to 1911.
10. Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144.
11. de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320- 327. Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098.
12. O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387.
13. Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193
14. ICH (International Council for Harmonization) E6 ‘Guideline for Good Clinical Practice’ (Step 4, 2016).
15. ICH (International Council for Harmonization) E3 ‘Structure and Content of Clinical Study Reports’ (Step 4, 1995)
16. Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki (Brazil 2013).
17. The common technical document for the registration of pharmaceuticals for human use efficacy – M4E (R2) Clinical overview and clinical summary of module 2 and clinical study reports module 5 (Step 4, 2016)
18. Schedule Y (amended version 2014) of CDSCO (Central Drugs Standard Control Organization).
19. National Ethical Guidelines for Biomedical and Health Research on Human Participants, ICMR (Indian Council of Medical Research, 2017).
20. [https://www.cdisc.org](https://www.cdisc.org/)
21. Velcade (bortezomib): EMEA/H/C/000539/X/0047: EPAR Assessment report - Extension (EMA/432973/2012), first published and last updated by EMA on 17-Oct-2012.

# GLOSSARY OF TERMS

1. **Adverse Event (AE):** An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
2. **Actual Sampling Time:** The exact sampling time at which the sample was collected.
3. **Audit:** A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately, reported according to the protocol, good clinical practice (GCP), and the applicable regulatory requirements.
4. **Bioavailability:** is a measurement of the rate and extent (amount) of drug that reaches the systemic circulation from a drug product or a dosage form.
5. **Bioequivalence:** Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.
6. **Case Report Form (CRF):** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor or on each trial subject.
7. **Check-in:** The process of admitting a volunteer to a study. Normally this is done on the day before dosing.
8. **Checkout**: The process of discharging a subject on completion of housing.
9. **Compliance:** Adherence to all the study requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
10. **Essential Documents:** Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
11. **Good Clinical Practice (GCP):** A standard for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trial that provides assurance that the data and reported results are credible and accurate, and that the rights integrity, and confidentiality of trial subjects are protected.
12. **Housing:** The time during which the subject is lodged in the clinical ward, from “check-in” to “check-out” after the last in-house sample is collected.
13. **Impartial Witness:** A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends and present during the entire informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
14. **Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
15. **Investigational Product:** A pharmaceutical form of an active ingredient being tested or used as a reference in a clinical study.
16. **Investigator:** A person responsible for the conduct of the clinical trial at a trial site.
17. **Legally Acceptable Representative:** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure[s] involved in the research.
18. **Monitoring:** The act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
19. **Randomization:** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
20. **Return visits:** Blood samples collected outside the housing period, for which the subject makes scheduled visits.
21. **Sampling Time:** Time of blood collection after drug administration (in hours)
22. **Schedule Sampling Time:** The predetermined sampling time at which the same should be collected.
23. **Serious Adverse Event:** An adverse event is any undesirable experience associated with the use of a drug product in a subject. The event is serious and should be reported when the patient outcome is:

* **Death:** If the subject’s death is suspected as being a direct outcome of the adverse event.
* **Life-Threatening:** If the subject was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the subject’s death.
* **Hospitalization (initial or prolonged):** If admission to the hospital or prolongation of a hospital stay results because of the adverse event.
* **Disability:** If the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the subject’s body function / structure, physical activities or quality of life.
* **Requires Intervention to Prevent Permanent Impairment or Damage:** If you suspect that the use of a drug product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

1. **Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
2. **Standard Operating Procedures (SOPs):** Detailed, written instructions to achieve uniformity of the performance of a specific function.
3. **Study duration:** The period between start of study specific screening till the last compensation payment is made to the subject.
4. **Subject:** An individual who has been admitted into a given study.
5. **Volunteer:** A human who has shown interest in participating in a study
6. **Wellbeing (of the trial subjects):** The physical and mental integrity of subjects participating in a clinical trial.

# ABBREVIATIONS

|  |  |
| --- | --- |
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ALT | Alanine transaminase |
| ARDS | Acute Respiratory Distress Syndrome |
| ANC | Absolute Neutrophil Count |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| AUC | Area under the plasma concentration versus time curve |
| AUClast | Area under the plasma concentration versus time curve to the last measurable concentration (t) |
| AUElast | The area under the proteasome inhibition-time curve from time zero to the last sampling time point |
| BA | Bioavailability |
| BE | Bioequivalence |
| BLQ | Below Limit of Quantification |
| BP | Blood Pressure |
| BSA | Body Surface Area |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| Cm | Centimeter |
| Cmax | Maximum measured analyte concentration in the biological fluid |
| CDASH | Clinical Data Acquisition Standards Harmonization |
| CDISC | Clinical Data Interchange Standards Consortium |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organization |
| CYP1A2 | Cytochrome P450 1A2 family |
| CYP3A4 | Cytochrome P450 3A4 family |
| CYP2C19 | Cytochrome P450 2C19 family |
| CV | Coefficient of Variation |
| DCGI | Drug Controller General of India |
| ECG | Electrocardiogram |
| ECOG | Eastern Co-operative Oncology Group |
| Emax | Observed maximum percent inhibition of 20S proteasome activity, taken directly from inhibition-time profile. |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| g/dL | gram per deciliter |
| HbsAg | Hepatitis B surface antigen |
| HCT | Hematocrit |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| Hr | Hour |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation. |
| ICMR | Indian Council of Medical Research. |
| IEC | Institutional Ethics Committee |
| IRB | Independent Review Board |
| ISR | Injection Site Reaction |
| IV | Intravenous |
| K | Potassium |
| K2EDTA | Dipotassium Ethylene diamine tetra acetate |
| kel | Elimination rate constant |
| Kel\_lower | Lower limit on Time for values to be included in the calculation of Kel |
| Kel\_Upper | Upper limit on Time for values to be included in the calculation of Kel |
| Kg | Kilogram |
| LAR | Legally Acceptable Representative |
| LSM | Least-square means |
| m2 | Square meter |
| mg | Milligram |
| mg/m2 | Milligram per square meter |
| mg/dL | Milligram per deciliter |
| mg/ml | Milligram per Milliliter |
| ml/mL | Milliliter |
| mm of Hg | Millimeter of Mercury |
| mm3 | Cubic millimeter |
| mmol/L | Milimol per litre |
| MRI | Magnetic Resonance Imaging |
| Na | Sodium |
| OTC | Over the Counter |
| PA (view) | Postero-Anterior view |
| PCV | Packed Cell Volume |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PI | Principal Investigator |
| PRES | Posterior Reversible Encephalopathy Syndrome |
| R | Reference |
| RBC | Red Blood Cells |
| RPLS | Reversible Posterior Leukoencephalopathy Syndrome |
| SAS | Statistical Analysis System |
| SC | Subcutaneous |
| SDTM | Study Data Tabulation Model |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| SOP | Standard Operating Procedure |
| T | Test |
| TdP | Torsades de pointes |
| t1/2 | Elimination half-life |
| Tmax | Time to reach Emax |
| tmax | Time of the maximum measured plasma concentration |
| U/L | Units per liter |
| ULN | Upper limit of normal |
| USFDA | United States Food and Drug Administration |
| WBC | White Blood Cells |
| WMA | World Medical Association |
| % | Percentage |

# LIST OF APPENDICES

[Appendix - I ECOG PERFORMANCE STATUS](#_APPENDIX-II__POST-STUDY)

[Appendix - II KARNOFSKY PERFORMANCE SCALE](#_Appendix_-_III)

Appendix - III INJECTION SITE REACTIONS SCALE

[Appendix - IV](#_Appendix_–_IV) CYTOCHROME INHIBITORS/INDUCERS

[Appendix - V](#_Appendix_–_IV) SCHEDULE OF EVENTS

[Appendix - VI](#_Appendix_–_IV) SUMMARY OF CHANGES

**APPENDIX – I**

**ECOG Performance Status**

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

|  |  |
| --- | --- |
| **ECOG PERFORMANCE STATUS\*** | |
| **Grade** | **ECOG** |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled.  Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

\* As published in Am. J. Clin. Oncol.:  
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

**APPENDIX II**

**Karnofsky Performance Scale**

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%)

CRITERIA

|  |  |  |
| --- | --- | --- |
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal no complaints; no evidence of disease. |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| 60 | Requires occasional assistance, but is able to care for most of his personal needs. |
| 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| 10 | Moribund; fatal processes progressing rapidly. |
| 0 | Dead |

**APPENDIX III**

**INJECTION SITE REACTIONS SCALE**

|  |  |  |
| --- | --- | --- |
|  | **DESCRIPTION** | **SCORE** |
| **INJECTION SITE REACTION (ISR)** | | |
| No Evidence | None | 0 |
| Mild | Erythema or Induration or tenderness or itching | 1 |
| Moderate | As 1 and pain or swelling or signs of inflammation | 2 |
| Severe and undesirable | Ulceration or necrosis | 3 |
| **MAXIMAL DIAMETER OF INJECTION SITE REACTION** | | |
| No Evidence | None | 0 |
| Mild | Maximum 5 cm | 1 |
| Moderate | Maximum 10 cm | 2 |
| Severe and undesirable | Max 15 cm or any diameter and systemic reaction or flare-up previous IS | 3 |
| **DURATION OF SYMPTOMS** | | |
| No Evidence | ≤1 day | 0 |
| Mild | 2–14 days | 1 |
| Moderate | 2–6 weeks, reversible | 2 |
| Severe and undesirable | Permanent | 3 |
| **SEQUELAE** | | |
| No Evidence | None | 0 |
| Mild | Minimal and tolerated by patient | 1 |
| Moderate | Hardly tolerated or wish for treatment by patient | 2 |
| Severe and undesirable | Permanent despite treatment or no treatment options | 3 |
| **LIKELY IMPACT ON NEXT DOSE** | | |
| No Evidence | None | 0 |
| Mild | Injection site can be used in rotation AND no dose adaptation | 1 |
| Moderate | Injection site should be avoided in rotation OR change dose regimen | 2 |
| Severe and undesirable | Injection site cannot no longer be used OR discontinuation | 3 |
| **ADL LIMITATIONS** | | |
| No Evidence | None | 0 |
| Mild | Minimal | 1 |
| Moderate | Functional | 2 |
| Severe and undesirable | Self-care limitations | 3 |

ADL = ‘Activities of daily living’ and are defined as bathing, dressing and undressing, feeding self, using the toilet, taking medications, using the telephone, etc.

ISR = Injection site reaction

IS = Injection Site

[**APPENDIX - IV**](file:///C:\\Users\\ananth\\AppData\\Local\\Microsoft\\Windows\\Temporary%20Internet%20Files\\Content.Outlook\\WQ3M2WP4\\Borte\\CT001_19.doc#_Appendix_–_IV)

[**CY**](file:///C:\\Users\\ananth\\AppData\\Local\\Microsoft\\Windows\\Temporary%20Internet%20Files\\Content.Outlook\\WQ3M2WP4\\Borte\\CT001_19.doc#_Appendix_–_IV)**TOCHROME INHIBITORS/INDUCERS**

|  |  |  |
| --- | --- | --- |
| Atazanavir  Boceprevir  Carbamazepine  Ciprofloxacin  Clarithromycin  Cobicistat  Danoprevir  Darunavir  Diltiazem  Elvitegravir  Enoxacin  Enzalutamide | Fluconazole  Fluoxetine  Fluvoxamine  Glucocorticoids  Grapefruit  Indinavir  Itraconazole  Ketoconazole  Lopinavir  Nefazodone  Nelfinavir  Paritaprevir  Phenobarbital | Phenytoin  Posaconazole  Rifampicin/Rifampin  Ritonavir Saquinavir  St. John's Wort  Telaprevir  Telithromycin  Ticlopidine  Tipranavir  Troleandomycin  Voriconazole  Zafirlukast |

**APPENDIX-V**

**SCHEDULE OF EVENTS**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S. No.** | **Activity** | **Visit 1** |  | |  | |  | **Visit 2** | | | | |  |  | | |  | | **Visit 3** | | | **Visit 4** |
| **(Screening)**  **20 days prior to enrollment** | **Day 0 (Randomization & Check-In)** | **Day 1 (Dosing)** | | **Day 2** | | | **Day 4** | **Day 6** | **Day 7** | **Day 8 (Dosing & Check-out)** | **Day 14 (Check- In)** | | **Day-15 (Dosing)** | **Day16** | | **Day 18** | | **Day-20** | **Day 22(End of study/Early Termination)** | **Day 24 (follow-up)** |
| 1 | Informed Consent | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 2 | Demographics | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 3 | Medical History | X | X |  | |  | | |  |  |  |  | X | |  |  | |  | |  |  | X |
| 4 | Vital Signs | X | X | X | | X | | | X | X |  | X | X | | X | X | | X | | X | X | X |
| 5 | Physical Examination | X | X |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 6 | 12-lead-ECG | X |  | X | |  | | |  |  |  | X |  | | X |  | |  | |  | X |  |
| 7 | 2D-Echocardiogram | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 8 | Chest X-Ray | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 9 | ECOG and Karnofsky Performance status scale | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 10 | Hematology | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  | X |  |
| 11 | Clinical Chemistry | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  | X |  |
| 12 | Serology Tests | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 13 | Urine Analysis | X |  |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 14 | Pregnancy Test for females only (Urine) | X | X |  | |  | | |  |  | X |  | X | |  |  | |  | |  | X |  |
| 15 | ANC and Platelets |  | X |  | |  | | |  |  | X |  | X | |  |  | |  | |  |  |  |
| 16 | Evaluation of Inclusion & Exclusion Criteria | X | X |  | |  | | |  |  | X |  | X | |  |  | |  | |  |  |  |
| 17 | Randomization |  | X |  | |  | | |  |  |  |  |  | |  |  | |  | |  |  |  |
| 18 | Hospital Stay |  | X | X | | X | | | X | X | X | X | X | | X | X | | X | | X | X |  |
| 19 | Dosing |  |  | X | |  | | |  |  |  | X |  | | X |  | |  | |  |  |  |
| 20 | Concomitant Medication |  |  | X | |  | | |  |  |  | X |  | | X |  | |  | |  |  |  |
| 21 | PD Sampling |  |  | X | | X | | | X | X |  | X |  | | X | X | | X | | X | X |  |
| 22 | PK Sampling |  |  | X | | X | | | X | X |  | X |  | | X | X | | X | | X | X |  |
| 23 | Injection Site reaction Scale |  |  | X | | X | | | X |  |  | X |  | | X | X | | X | |  |  |  |
| 24 | Subject Wellbeing |  |  | X | |  | | |  |  |  |  |  | | X |  | |  | |  |  | X |
| 25 | AEs Monitoring |  |  | X | | X | | | X | X | X | X | X | | X | X | | X | | X | X | X |

**APPENDIX-VI**

**SUMMARY OF CHANGES**

| **Change Description** | **Section Affected** | **Justification** |
| --- | --- | --- |
| **Version 01 to Version 02** | | |
| Updated the study title | 1.0 and 4.0 | Updated as per sponsor suggestion |
| Updated the study design | 4.0 and 8.4 | Updated as per sponsor suggestion |
| Updated the study objectives | 4.0 | Updated as per sponsor suggestion |
| Updated the sample size and sample size justification | 4.0, 8.5 and 8.6 | Updated as per sponsor suggestion |
| Updated the Investigational drug products for standard of Care | 4.0 | Updated as per sponsor suggestion |
| Updated the dosing regimen | 4.0 | Updated as per the changed study design |
| Updated the subject housing | 4.0 and 10.6 | Updated as per the changed study design |
| Updated the study duration | 4.0 | Updated as per the changed study design |
| Updated the drug administration procedure | 4.0 and 10.8 | Updated as per the changed study design |
| Updated the concomitant medication information | 4.0 and 10.11.6 | Updated as per investigator suggestion |
| Updated safety monitoring | 4.0 and 10.11.3 | Updated as per the changed study design |
| Updated the blood sampling section | 4.0 and 10.10 | Updated as per the changed study design and prior experience |
| Updated the bioanalytical section | 4.0 | Updated as per sponsor suggestion |
| Updated the statistical section | 4.0 | Updated as per the changed study design |
| Updated the informed consent | 6.3 | Updated in line with current practice |
| Updated the rationale | 8.2 | Updated as per the changed study design |
| Updated the randomization section | 8.7 | Updated in line with current practice |
| Updated the unblinding section | 8.8 | Updated as per the changed study design |
| Updated the Retention samples | 9.7 | Updated in line with current practice |
| Updated the Pharmacist information in Subject Number and Treatment Allocation section | 10.2 | Updated in line with current practice |
| Incuded the respiratory rate | 10.3.1 | Updated as per investigator suggestion |
| Included Total Cholesterol, Triglycerides | 10.3.7 | Updated as per investigator suggestion |
| Updated inclusion criteria for points ii and vi | 10.4 | Updated as per investigator and regulatory suggestion |
| Updated exclusion criteria for point viii | 10.5 | Updated as per regulatory suggestion |
| Updated the Laboratory test | 10.11.1 | Updated as per the changed study design |
| Updated the examination injection site reactions | 10.11.2 | Updated as per the changed study design |
| Updated the bioanalytical procedures for ISR | 12.0 | In line with current practice |
| Updated the confidence interval section | 14.2 (14.2.1) | Updated as per the changed study design |
| Included the Pharacodynamic parameters | 14.2.2 | Updated as per the changed study design |
| Updated the revision summary | 23.0 | In line with current practice |
| Updated the references | 24.0 | Additional literature included |
| Updated the list of appendices | 27.0 | As per regulatory recommendation and in line with current practice |