**CLINICAL STUDY REPORT**

# TITLEPAGE

**A Prospective, Multicenter, Randomized, Double-blind, Parallel group Study to Compare the Efficacy and Safety of GBR 200 (similar biologic of Trastuzumab) versus Innovator Trastuzumab both when Given in Combination with Paclitaxel in Patients Diagnosed with HER2 Positive Metastatic Breast Cancer**

**Investigational Product:**

**Indication:**

**Sponsors:**

**Study Number:**

**Phase of Development:**

**Date of first patient first visit (FSFV):**

**Date of last patient last visit (LSLV):**

**Sponsor’s Representative:**

**Date of Final Report:**

This study was conducted in compliance with Good Clinical Practice

**CONFIDENTIALITY STATEMENT**

This study was performed in compliance with Good Clinical Practices, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996*.*

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**CLINICAL STUDY REPORT PREPARED BY**

|  |  |
| --- | --- |
| I have prepared or read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. | |
| Medical Writing responsible person |  |
| Biostatistician: |  |

**CLINICAL STUDY REPORT APPROVED BY**

|  |  |
| --- | --- |
| I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. | |
| Sponsor Representative: |  |

# SYNOPSIS

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. |

| **Name of Sponsor/Company:**  Laboratories Limited |  | *(For National Authority Use Only)* |
| --- | --- | --- |
| **Name of Finished Product:**  GBR 200/ Similar biologic of Trastuzumab |
| **Name of Active Ingredients:**  Trastuzumab |
| **Title of the study:** | | |
| **Study centers:**  The | | |
| **Publications (reference):** | | |
| **Study period**: 21 Weeks per patient | Date first patient enrolled: 27 Aug 2017  Date last patient completed: 13 Jan 2020 | |
| **Phase of development:** | Phase III | |
| **Objectives:** |  | |
| **Endpoints:** |  | |
| **Methodology:** | This was a prospective, multicenter, randomized, double-blind, parallel-group study to compare the efficacy and safety of GBR 200 versus Innovator Trastuzumab both when given in combination with Paclitaxel in patients diagnosed with HER2+ MBC.  The study was planned to be conducted at 25 centers across India  One-hundred and sixty-four (164) patients (82 patients in each treatment group) were planned to be enrolled in the study. These patients were stratified based on number of tumor lesions (i.e. < 4 tumor lesions and ≥ 4 tumor lesions). Of these 164 patients, a total of 24-evaluable patients (i.e. 12 patients in each treatment group) were planned to be considered for PK assessments in the study.  A total of 164 patients who met the eligibility criteria were randomized in a ratio of 1:1 to either of the treatment groups:   * + Group A: GBR 200 + Paclitaxel   + Group B: Innovator Trastuzumab + Paclitaxel   The study involved the following study periods:   * + Screening period (Up to 21 days/Visit 1): It was up to 3 weeks duration, during which the patients were screened to confirm the eligibility for study participation   + Double-blind treatment period (Days 1 to 106/Visits 2 to 7): It was of 15 weeks duration. It consisted of 6 cycles (Cycle 1 to Cycle 6). Each cycle was of 3 weeks duration. The patients were randomized at Visit 2 and received the first dose of the IP on the same day.   + Post-treatment follow-up period (Days 107 to 127/Visit 8): It was of 3 weeks duration after Cycle 6 (i.e. after the last dose of the IP)   The investigator made every effort to follow the schedule of study assessments and procedures. The screening procedures were completed up to 21 days from the signing of the informed consent form (ICF). A window period of ± 3 days visit window was allowed from Visit 3 to Visit 8.  In patients participating in the PK sub study, blood samples for PK assessments were collected pre-and post IP –infusions as per the timepoints as mentioned in protocol.  In all randomized patients, blood samples for anti-trastuzumab antibody assessments were collected prior to start of the IP infusion at Cycle 1 (i.e. at Visit 2) and at the end of the study (EOS) visit (i.e. at Visit 8).  **Study drugs administration details**  GBR 200 or Innovator Trastuzumab were administered to the patient at a loading dose of 8 mg/kg of body weight for the first cycle followed by maintenance dose of 6 mg/kg of body weight for subsequent 5 cycles (Cycle 2 to Cycle 6) as an IV-infusion over 90-minutes (min) (± 10 min).  Paclitaxel was administered at a dose of 175 mg/m2 of body surface area (BSA) every 3 weeks for 6 cycles as an IV-infusion over 3-hours (± 10 min). The first dose of Paclitaxel was administered the day following the first dose administration of GBR 200 or Innovator Trastuzumab. For subsequent cycles (i.e. Cycle 2 to Cycle 6), Paclitaxel was administered on the same day of IP dosing i.e. 30 min (±10 min) after IP infusion was complete.  The patients were free to withdraw at any time during the study. In case of premature treatment withdrawal/discontinuation, the reason for treatment discontinuation was recorded in the electronic case report form (eCRF) and the end of study (EOS) visit (Visit 8) procedures were conducted for the patient.  **Data Safety Monitoring Board**  A data safety monitoring board (DSMB) was responsible for oversight of the patient’s safety during the trial. At each DSMB meeting, the committee reviewed the accumulated safety data from the trial.  The data reviewed included adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory investigations. The committee had to determine if the investigational therapy poses an unacceptable risk to the patient’s safety and had the authority to prematurely halt/terminate the study. The frequency of meetings and quorum of the safety monitoring board were described in the DSMB Charter. | |
| **Number of patients:** | Planned: 164  Screened:363  Screen failures: 199  Eligible: 164  Enrolled/Randomized:164 | |
| **Diagnosis and criteria for inclusion:** | A patient was eligible for inclusion in the study if he/she fulfilled all the following criteria:   1. Female patients between 18-65 years of age (both inclusive) at the time of signing the ICF 2. Had life expectancy of at least 6 months from screening 3. Histologically confirmed diagnosis of breast cancer 4. Presence of metastatic disease as per Tumor Node Metastasis staging at screening 5. Had at least 1 measurable target lesion (tumor/lymph node) as per RECIST version 1.1 at screening 6. HER2 overexpression confirmed by immunohistochemistry (IHC) (IHC3+ or IHC2+ with positive fluorescent in situ hybridization [FISH] test result at screening 7. Eastern cooperative oncology group (ECOG) status 0 to 2 at screening 8. Left ventricular ejection fraction (LVEF) > 55 % at screening 9. Willing to provide written informed consent | |
| **Diagnosis and criteria for exclusion:** | The patients meeting any of the following criteria were not enrolled:   1. History of known severe hypersensitivity reaction to Trastuzumab or Paclitaxel or any of its excipients 2. Prior systemic therapy for metastatic disease, including cytotoxic chemotherapy, or previous anticancer therapy with signal transduction inhibitors (e.g. Lapatinib), biological drugs (e.g. Trastuzumab and Bevacizumab), experimental drugs (not approved for breast cancer therapy, anticancer drugs (except hormonal therapy) 3. Prior Trastuzumab or Taxane for adjuvant/neoadjuvant therapy for breast cancer within 12 months prior to randomization 4. Had received cumulative doses of anthracycline, exceeding 360 mg/m2 of BSA for doxorubicin, 720 mg/m2 of BSA for epirubicin, 120 mg/m2 of BSA for mitoxantrone, and 90 mg/m2 of BSA for idarubicin 5. Had metastases to central nervous system 6. Had bone or skin metastasis as the only measurable tumor 7. Had history of congestive heart failure of any New York Heart Association class, serious cardiac arrhythmia requiring treatment, unstable angina pectoris, and/or myocardial infarction within 12 months prior to screening 8. Had uncontrolled hypertension at screening (i.e. systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg) 9. Had severe dyspnea at rest or requiring supplementary oxygen therapy 10. Had undergone any prior mediastinal irradiation (except internal mammary node irradiation) for the present breast cancer 11. Had undergone surgery or radiation therapy within 4 weeks prior to randomization 12. Patients who had the following laboratory results at screening 13. Absolute neutrophil count (ANC) < 1,500/mm3 14. Hemoglobin (Hb) < 9 g/dL 15. Platelet count < 100,000/mm3 16. Total bilirubin level > 1.25 times the upper limit of the normal laboratory range (ULN) 17. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels ≥ 10 X ULN 18. Serum Creatinine level > 1.5 X ULN 19. Positive serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) at screening 20. Patients of childbearing potential not willing to implement adequate non-hormonal contraceptive measures during the study period 21. Patients who were pregnant or nursing 22. Patients suffering from acute or chronic infection(s) 23. Preexisting Grade 3 or higher sensory or motor peripheral neuropathy 24. Had any concurrent disease or condition, which in the opinion of the investigator does not allowed participation of the patient in this study 25. Had participated in any other clinical trial and received experimental medications within 4 weeks prior to screening 26. Not willing and unable to comply with all aspects of the protocol | |
| **Withdrawal criteria** | The patient might be withdrawn/discontinued from the study due to the following reasons:   1. Progressive disease 2. Patient’s voluntary withdrawal of consent 3. Patient non-compliance 4. Protocol violation 5. Any AE or SAE requiring patient withdrawal in the opinion of the investigator 6. Requirement of prohibited medication 7. Study termination by the sponsor 8. Any, other reason | |
| **Investigational products** | | |
| **Test product:** | Similar biologic of Trastuzumab/ GBR 200 | |
| **Dose:** | A loading dose of 8 mg/kg of body weight for the first cycle followed by maintenance dose of 6 mg/kg of body weight for subsequent 5 cycles (Cycle 2 to Cycle 6) | |
| **Administration:** | IV-infusion over 90-min (± 10 min) | |
| **Batch number:** |  | |
| **Duration of treatment:** | Once every 3 weeks for 6 cycles. Each cycle was of 3-weeks duration | |
| **Reference product:** | Innovator Trastuzumab | |
| **Dose:** | A loading dose of 8 mg/kg of body weight for the first cycle followed by maintenance dose of 6 mg/kg of body weight for subsequent 5 cycles (Cycle 2 to Cycle 6) | |
| **Administration:** | IV-infusion over 90-min (± 10 min) | |
| **Batch number:** |  | |
| **Duration of treatment:** | Once every 3 weeks for 6 cycles. Each cycle was of 3-weeks duration | |
| **Non-Investigational product** | Paclitaxel | |
| **Dose** | It was administered at a dose of 175 mg/m2 of BSA every 3-weeks for 6 cycles | |
| **Administration:** | The 1st dose of Paclitaxel was administered the day following the 1st dose administration of IP. For all subsequent cycles (Cycle 2 to Cycle 6), the Paclitaxel dose was administered on the same day of IP dosing i.e. 30 min (± 10 min) after IP infusion was completed | |
| **Batch number** |  | |
| **Duration of treatment:** | Once every 3 weeks for 6 cycles. Each cycle was of 3-weeks duration | |
| **Criteria for evaluation:** | | |
| **Efficacy:** |  | |
| **Pharmacokinetics:** | **Pharmacokinetic Assessments**  A comparative PK assessment was performed to evaluate PK parameters of GBR 200 versus innovator Trastuzumab in a total of 24-evaluable patients (i.e. 12 patients in each treatment group).  The following PK parameters were evaluated in the study:   * + Cmax: Maximum drug concentration achieved in systemic circulation following drug administration   + Ctrough: Drug concentration achieved in systemic circulation at the end of dosing   + AUC0-t: The area under the plasma concentration-time curve from, from time 0 hr to the last measurable concentration, where t = time of last identifiable concentration   + AUC(0-tau)ss: The area under the plasma concentration time curve over one dosing interval in multiple dose study at steady state   The following were the pre-and post IP-infusion time-points for collection of blood samples for PK assessments:  **Cycle 1 and Cycle 6**   * + Pre- infusion: 0 minute (min) (i.e. within 30 min prior to start of IP-infusion at Cycle 1 and Cycle 6)   + End of infusion: upon completion of IP-infusion at Cycle 1 and Cycle 6   + Post-infusion (time points were calculated from the end of IP-infusion):   4 hours (±5 min)  6 hours (±5 min)  24 hours (±15 min)  168 hours (±1 hour)  336 hours (±1 hour)  504 hours (±1 hour)  **Cycle 4 and Cycle 5:**  Pre-infusion: 0 min (within 30 minutes prior to start of IP-infusion at Cycles 4 and 5)  Any blood sample drawn before or after the window period to the scheduled time point was noted as “late blood draw”. Actual blood sampling time points was recorded in source documents and electronic case record form (eCRF). Blood samples collected before or later to scheduled time point were appropriately corrected for time point value during the calculation of PK. | |
| **Safety:** | The following were the safety assessments:   * + AEs and SAEs were collected for relatedness, severity, seriousness, and outcome   + Vital signs: Pulse rate, respiratory rate, SBP and DBP (in supine position after 5 minutes of rest), and body temperature   + Body weight   + Physical examination   + 12-Lead electrocardiogram (ECG)   + 2D-echocardiography   + LVEF   + Laboratory investigations   + Hematology: Hb, platelet count, red blood cells, white blood cells with differential count, and ANC * Blood chemistry: ALT, AST, alkaline phosphatase (ALP), total bilirubin, serum creatinine, and potassium * Urinalysis: Routine and microscopic examination * Urine pregnancy test: Only for females of childbearing potential or who are ≤ 1 year postmenopausal prior to enrollment into the study * Immunogenicity assessment: Anti-trastuzumab antibodies were assessed across both treatment groups. Blood samples were collected at the start of the IP-infusion at Cycle 1 (i.e. at Visit 2) and at the EOS visit (i.e. at Visit 8)   The following laboratory investigations were done at screening visit only:   * + IHC test: Documentation of HER2 overexpression (IHC3+ or IHC2+ with positive FISH result) and hormone receptor status (ER/PR +/-)   + Serology: HIV, HBV, HCV | |
| **Bioanalytical Methods** |  | |
| **Statistical methods:** |  | |
| **Summary of results:** | | |
| **Demographic and baseline characteristics:** |  | |
| **Efficacy results:** | **Primary endpoint:** | |
| **Secondary endpoints:** | |
| **Safety results:** |  | |
| **Conclusions:** |  | |
| **Date of report:** |  | |

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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 |

**Note:** Terminologies like Subject and Patient; ALT and SGPT; AST and SGOT are interchangeable

# ETHICAL CONSIDERATIONS

## Independent Ethics Committee or Institutional Review Board

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.

## Ethical Conduct of the Study

## Patient Information and Consent

# INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

## Investigators

Table 1 List of Study Investigators

## Sponsor

The contact details are as follows:

# INTRODUCTION

## 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

## Primary Objective

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.

## Secondary Objectives

# INVESTIGATIONAL PLAN

## Overall Study Design and Plan-Description

### Description of study visits

#### Visit 1/Up to 21 days

#### Visit 2/Cycle 1/Day 1 (no window period is allowed)

#### Visit 3/Cycle 2/Day 22 (±3 days)

#### Visit 4/Cycle 3/Day 43 (±3 days)

#### Visit 5/Cycle 4/Day 64 (±3 days)

#### Visit 6/Cycle 5/Day 85 (±3 days)

#### Visit 7/Cycle 6/Day 106 (±3 days)

#### Visit 8/Day 127 (±3 days)

## Discussion of Study Design, Including the choice of control groups

Figure 1: Study Design

### Patient informed consent

### Study site visits

### Unscheduled visits/investigations

### Visit window period

### Central laboratory investigations

### Local laboratory investigations

### Patient Diary

## Selection of Study Population

Table 14.2.2.3.4 Summary of 6 Minute Walk for the Distance Covered -ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 275 | 296 | 285 |
|  | SD | 73.6 | 58.7 | 67.2 |
|  | Q1 | 214 | 285 | 255 |
|  | Median | 307 | 309 | 309 |
|  | Q3 | 323 | 329 | 323 |
|  | Range (Min.: Max.) | (140: 440) | (80.0: 361) | (80.0: 440) |
|  | 95% CI | (245: 305) | (270: 321) | (265: 304) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 2 (7.69 %) | 2 (8.70 %) | 4 (8.16 %) |
|  | No | 24 (92.3 %) | 21 (91.3 %) | 45 (91.8 %) |
| **9 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 22 | 18 | 40 |
|  | n | 21 | 18 | 39 |
|  | Mean | 353 | 323 | 339 |
|  | SD | 48.7 | 50.0 | 50.9 |
|  | Q1 | 330 | 300 | 315 |
|  | Median | 347 | 323 | 343 |
|  | Q3 | 366 | 363 | 365 |
|  | Range (Min.: Max.) | (245: 480) | (175: 393) | (175: 480) |
|  | 95% CI | (331: 375) | (299: 348) | (323: 356) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 20 (90.9 %) | 18 (100 %) | 38 (95.0 %) |
| **12 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 366 | 335 | 352 |
|  | SD | 68.4 | 50.4 | 62.2 |
|  | Q1 | 325 | 300 | 310 |
|  | Median | 366 | 328 | 353 |
|  | Q3 | 389 | 360 | 373 |
|  | Range (Min.: Max.) | (194: 500) | (234: 480) | (194: 500) |
|  | 95% CI | (338: 394) | (312: 358) | (333: 370) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 24 (96.0 %) | 21 (100 %) | 45 (97.8 %) |
| **24 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 21 | 19 | 40 |
|  | n | 20 | 19 | 39 |
|  | Mean | 377 | 331 | 355 |
|  | SD | 58.9 | 91.1 | 78.7 |
|  | Q1 | 333 | 310 | 318 |
|  | Median | 374 | 351 | 371 |
|  | Q3 | 415 | 375 | 390 |
|  | Range (Min.: Max.) | (270: 481) | (0.00: 425) | (0.00: 481) |
|  | 95% CI | (349: 404) | (287: 375) | (329: 380) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 20 (95.2 %) | 18 (94.7 %) | 38 (95.0 %) |
| **Note:** [1] Respective visit counts is used as denominator for percentage calculation.  **General Note:** > Baseline value was defined as average of the all baseline 6-minute walk tests. If those values are within 10% of each other, otherwise   the last available 6-minute walk test was used. | | | | |

### 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).
3. Patient with ECOG (Eastern Co-operative Oncology Group) performance status 0, 1 or 2 (Refer Appendix - I).
4. Patient with performance ≥70% Karnofsky performance status scale (Refer Appendix - II).
5. 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.
6. 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.
7. Patient must have adequate hepatic function (Serum bilirubin ≤ 1.5 times of ULN and AST/ALT ≤ 2.0 times of ULN).
8. 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.
9. Patient and /or LAR or impartial witness able to give written informed consent for participation in the trial.
10. Patient with life expectancy of at least four months.
11. In the opinion of the investigator, patient should be able to comply with study procedures.
12. 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.
13. *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.

### Removal of Patients from Therapy or Assessment

## Treatments

### Treatment administered

### Identity of investigational products

#### *Dosage Form, Dose, Dosage Frequency, Dosing Schedule, and Mode of Administration*

#### *Non-Investigational Product*

#### *Distribution, Packaging and Labeling*

#### *Handling and Dispensing of the Study Treatment*

#### *Study Drug Number*

#### *Storage and Disposal of the Study Treatment Error: Reference source not found,Error: Reference source not found,Error: Reference source not found*

### Method of assigning patients to treatment groups

### Selection of Doses in the Study

.

### Selection and Timing of dose for each subject

### Blinding

#### *Maintenance of Study Treatment Randomization Codes and Procedures for Breaking Codes*

#### *Emergency Unblinding of an Individual Patient in the Study*

### Prior and Concomitant Therapy

#### *Pre-medications*

#### *Prior Medications*

#### *Concomitant Medications*

### Treatment Compliance

#### *Procedure(s) for Monitoring Patient Compliance to the Study Drugs*

#### *Dose Interruption, Modifications and Delays*

## Efficacy and Safety Variables

### Efficacy and Safety Measurements Assessed and Flow Chart

Efficacy and safety assessments were carried as depicted in the study flow chart Table 2

Table 2 Study Flow Chart

* + - 1. *Primary Endpoint*
      2. *Secondary Endpoints*
      3. *Efficacy Assessments*
      4. *Computed Tomography Scan*
      5. *Performance Status*
      6. Safety Assessments
      7. Adverse events

* + - 1. Serious Adverse Events
      2. Vital Signs
      3. Body weight
      4. Physical Examination
      5. 12-Lead Electrocardiograms
      6. 2D-Echocardiography
      7. Laboratory Investigations
      8. Immunogenicity Assessment

### Appropriateness of Measurements

All the measurements were considered standard and reliable.

### Drug Concentration Measurements

* + - 1. *Pharmacokinetic Assessments*

## Data Quality Assurance

### Audits and Inspections

### Data handling

## Statistical Methods Planned in the Protocol and Determination of Sample Size

### Statistical and analytical plans

#### *Study Analyses Sets*

#### *Demographic and Other Baseline Characteristics*

#### *Decoding of Randomization*

#### *Study Treatments and Compliance*

#### *Efficacy analysis*

#### *Pharmacokinetic Analyses*

#### *Safety analysis*

### Determination of sample size

### Statistical Significance

## Changes in the Conduct of the Study or Planned Analyses

The detailed list of changes made to the study planned, are attached as an appendix 16.1.1

Table 3 List of Changes

|  |  |  |
| --- | --- | --- |
|  | | |
| **S. No.** | **Change** | **Rationale** |
|  |  |  |

# STUDY PATIENTS

## Disposition of Patients

## Protocol Deviations

## Demographic and Other Baseline Characteristics

### Demography

### Medical history and disease characteristics at baseline

### Treatment compliance

### Prior and concomitant medication

# EFFICACY EVALUATION

## Data sets Analyzed

## Demographic and other Baseline Characteristics

## Measurements of Treatment Compliance

### Primary Efficacy Variable Analysis

### Secondary Efficacy Variable Analysis

## Efficacy Results and Tabulation of Individual Patient Data

### Analysis of Efficacy

### Statistical / Analytical Issues

#### Adjustments for Covariates

#### Handling of drop-outs or missing data

Missing data points were dealt using appropriate statistical techniques, depending on the nature of the data

#### Interim analysis and data monitoring

No interim analysis was planned for this study.

#### Multicenter studies

There were approximately 20-25 centers in the study.

#### Multiple comparison/ multiplicity

No adjustments were made for multiple comparisons.

#### Use of an Efficacy Subset of Patients

#### Active control studies intended to show equivalence

#### Examination of sub-groups

### Tabulation of Individual Response Data

Discussed in listing.

### Drug Dose, Drug Concentration and Relationship to Response

### Drug-Drug, Drug-Disease Interactions

### By Patient Displays

### Efficacy Conclusions

**Primary Endpoint:**

**Secondary Endpoints:**

# SAFETY EVALUATION

## Extent of Exposure

## Adverse Events

### Brief Summary of Adverse Events

### Display of Adverse Events

### Analysis of Adverse Events

### Listing of Adverse Events by Patient

## Deaths, Other Serious Adverse Events, and Other Significant Adverse Event

### Listing of Death, other Serious Adverse Events and Other Significant Adverse Events

#### Death

#### Other Serious Adverse Events

#### Other Significant Adverse Events

### Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

### Analysis and Discussions of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

## Clinical Laboratory Evaluations

### Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

### Evaluation of Each Laboratory Parameter

#### Laboratory values over time

#### Individual patient changes

#### Individual Clinically Significant Abnormalities

## Vital Signs , Physical Findings and Other Observations related to Safety

## Safety Conclusions

# DISCUSSION AND OVERALL CONCLUSIONS

**Conclusion**

# TABLE/FIGURES/GRAPHS REFERRED TO BUT NoT INCLUDED IN THE TEXT

## Demographic Data

## Efficacy Data

## Safety Data

### Display of Adverse Events

### Listing of Deaths, Other Serious and Significant Adverse Events

### Narratives of Death, Other Serious and Certain Other Significant Adverse Events

### Abnormal Laboratory value listing

# REFERENCES

# Appendices

## Study Information

### Protocol and Protocol Amendments

### Sample Case Report Form(s)

### List of Independent Ethics Committees or Institutional Review Boards, and Sample Consent Forms Plus the Name of the Committee Chair if Required by the Regulatory Authority) -Representative Written Information for Subject, and Sample Consent Forms

### List and Description of Investigators and Other Important Participants in the Study, Including Brief (one Page) CV’s or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

### Signatures of Principal or Coordinating Investigator(s) or Sponsor’s Responsible Medical Officer, Depending on the Regulatory Authority’s Requirement

### Listings of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used

### Randomisation Scheme and Codes (Subject Identification and Treatment Assigned)

### Audit Certificates

### Documentation of Statistical Methods

### Documentation of Inter-Laboratory Standardisation Methods and Quality Assurance Procedures if Used

### Publications based on the Study

### Important publications referenced in the report

## Patient Data Listings

### Discontinued Patients

### Protocol Deviations

### Patients Excluded from the Efficacy Analysis

### Demographic Data

### Compliance and/or Drug Concentration Data

### Individual Efficacy Response Data

### Adverse Event Listings

### Listing of Individual Laboratory Measurements by Patient, when required by regulatory authorities

## Case Report Form

### CRF's for Deaths, other Serious Adverse Events, and Withdrawals for Adverse events

### Other CRF's Submitted

## Individual Patient Data Listings