**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*.*

Part or all the information presented in this document were unpublished material and was treated as the confidential property of Laboratories Limited. The use of such information or material was restricted to the recipient for the agreed purpose and was not disclosed to any unauthorized persons, in any form, including publications and presentations, without the written consent of Laboratories Limited.

**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

| **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:** |  | |

# TABLE OF CONTENTS

[2 SYNOPSIS 4](#_Toc31298031)

[3 TABLE OF CONTENTS 13](#_Toc31298032)

[4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 18](#_Toc31298033)

[5 ETHICAL CONSIDERATIONS 20](#_Toc31298034)

[5.1 Independent Ethics Committee or Institutional Review Board 20](#_Toc31298035)

[5.2 Ethical Conduct of the Study 20](#_Toc31298036)

[5.3 Patient Information and Consent 20](#_Toc31298037)

[6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 20](#_Toc31298038)

[6.1 Investigators 20](#_Toc31298039)

[6.2 Sponsor 22](#_Toc31298040)

[7 INTRODUCTION 23](#_Toc31298041)

[7.1 Background 23](#_Toc31298042)

[7.2 Rationale 24](#_Toc31298043)

[8 STUDY OBJECTIVES 25](#_Toc31298044)

[8.1 Primary Objective 25](#_Toc31298045)

[8.2 Secondary Objectives 25](#_Toc31298046)

[9 INVESTIGATIONAL PLAN 25](#_Toc31298047)

[9.1 Overall Study Design and Plan-Description 25](#_Toc31298048)

[9.1.1 Description of study visits 26](#_Toc31298049)

[9.2 Discussion of Study Design, Including the choice of control groups 35](#_Toc31298050)

[9.2.1 Patient informed consent 35](#_Toc31298051)

[9.2.2 Study site visits 35](#_Toc31298052)

[9.2.3 Unscheduled visits/investigations 35](#_Toc31298053)

[9.2.4 Visit window period 36](#_Toc31298054)

[9.2.5 Central laboratory investigations 36](#_Toc31298055)

[9.2.6 Local laboratory investigations 36](#_Toc31298056)

[9.2.7 Patient Diary 36](#_Toc31298057)

[9.3 Selection of Study Population 37](#_Toc31298058)

[9.3.1 Inclusion criteria 37](#_Toc31298059)

[9.3.2 Exclusion criteria 37](#_Toc31298060)

[9.3.3 Removal of Patients from Therapy or Assessment 38](#_Toc31298061)

[9.4 Treatments 39](#_Toc31298062)

[9.4.1 Treatment administered 39](#_Toc31298063)

[9.4.2 Identity of investigational products 39](#_Toc31298064)

[9.4.3 Method of assigning patients to treatment groups 41](#_Toc31298065)

[9.4.4 Selection of Doses in the Study 41](#_Toc31298066)

[9.4.5 Selection and Timing of dose for each subject 41](#_Toc31298067)

[9.4.6 Blinding 41](#_Toc31298068)

[9.4.7 Prior and Concomitant Therapy 42](#_Toc31298069)

[9.4.8 Treatment Compliance 43](#_Toc31298070)

[9.5 Efficacy and Safety Variables 45](#_Toc31298071)

[9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart 45](#_Toc31298072)

[9.5.2 Appropriateness of Measurements 53](#_Toc31298073)

[9.5.3 Drug Concentration Measurements 53](#_Toc31298074)

[9.6 Data Quality Assurance 54](#_Toc31298075)

[9.6.1 Audits and Inspections 54](#_Toc31298076)

[9.6.2 Data handling 54](#_Toc31298077)

[9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size 54](#_Toc31298078)

[9.7.1 Statistical and analytical plans 54](#_Toc31298079)

[9.7.2 Determination of sample size 57](#_Toc31298080)

[9.7.3 Statistical Significance 58](#_Toc31298081)

[9.8 Changes in the Conduct of the Study or Planned Analyses 58](#_Toc31298082)

[10 STUDY PATIENTS 59](#_Toc31298083)

[10.1 Disposition of Patients 59](#_Toc31298084)

[10.2 Protocol Deviations 59](#_Toc31298085)

[10.3 Demographic and Other Baseline Characteristics 59](#_Toc31298086)

[10.3.1 Demography 59](#_Toc31298087)

[10.3.2 Medical history and disease characteristics at baseline 59](#_Toc31298088)

[10.3.3 Treatment compliance 59](#_Toc31298089)

[10.3.4 Prior and concomitant medication 59](#_Toc31298090)

[11 EFFICACY EVALUATION 60](#_Toc31298091)

[11.1 Data sets Analyzed 60](#_Toc31298092)

[11.2 Demographic and other Baseline Characteristics 60](#_Toc31298093)

[11.3 Measurements of Treatment Compliance 60](#_Toc31298094)

[11.3.1 Primary Efficacy Variable Analysis 60](#_Toc31298095)

[11.3.2 Secondary Efficacy Variable Analysis 60](#_Toc31298096)

[11.4 Efficacy Results and Tabulation of Individual Patient Data 60](#_Toc31298097)

[11.4.1 Analysis of Efficacy 60](#_Toc31298098)

[11.4.2 Statistical / Analytical Issues 60](#_Toc31298099)

[11.4.3 Tabulation of Individual Response Data 60](#_Toc31298100)

[11.4.4 Drug Dose, Drug Concentration and Relationship to Response 61](#_Toc31298101)

[11.4.5 Drug-Drug, Drug-Disease Interactions 61](#_Toc31298102)

[11.4.6 By Patient Displays 61](#_Toc31298103)

[11.4.7 Efficacy Conclusions 61](#_Toc31298104)

[12 SAFETY EVALUATION 62](#_Toc31298105)

[12.1 Extent of Exposure 62](#_Toc31298106)

[12.2 Adverse Events 62](#_Toc31298107)

[12.2.1 Brief Summary of Adverse Events 62](#_Toc31298108)

[12.2.2 Display of Adverse Events 62](#_Toc31298109)

[12.2.3 Analysis of Adverse Events 62](#_Toc31298110)

[12.2.4 Listing of Adverse Events by Patient 62](#_Toc31298111)

[12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Event 62](#_Toc31298112)

[12.3.1 Listing of Death, other Serious Adverse Events and Other Significant Adverse Events 62](#_Toc31298113)

[12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events 62](#_Toc31298114)

[12.3.3 Analysis and Discussions of Deaths, Other Serious Adverse Events and Other Significant Adverse Events 62](#_Toc31298115)

[12.4 Clinical Laboratory Evaluations 62](#_Toc31298116)

[12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value 62](#_Toc31298117)

[12.4.2 Evaluation of Each Laboratory Parameter 62](#_Toc31298118)

[12.5 Vital Signs , Physical Findings and Other Observations related to Safety 62](#_Toc31298119)

[12.6 Safety Conclusions 62](#_Toc31298120)

[13 DISCUSSION AND OVERALL CONCLUSIONS 62](#_Toc31298121)

[14 TABLE/FIGURES/GRAPHS REFERRED TO BUT NoT INCLUDED IN THE TEXT 63](#_Toc31298122)

[14.1 Demographic Data 63](#_Toc31298123)

[14.2 Efficacy Data 63](#_Toc31298124)

[14.3 Safety Data 63](#_Toc31298125)

[14.3.1 Display of Adverse Events 63](#_Toc31298126)

[14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events 63](#_Toc31298127)

[14.3.3 Narratives of Death, Other Serious and Certain Other Significant Adverse Events 63](#_Toc31298128)

[14.3.4 Abnormal Laboratory value listing 63](#_Toc31298129)

[15 REFERENCES 64](#_Toc31298130)

[16 Appendices 66](#_Toc31298131)

[16.1 Study Information 66](#_Toc31298132)

[16.1.1 Protocol and Protocol Amendments 66](#_Toc31298133)

[16.1.2 Sample Case Report Form(s) 66](#_Toc31298134)

[16.1.3 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 66](#_Toc31298135)

[16.1.4 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 66](#_Toc31298136)

[16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor’s Responsible Medical Officer, Depending on the Regulatory Authority’s Requirement 66](#_Toc31298137)

[16.1.6 Listings of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used 66](#_Toc31298138)

[16.1.7 Randomisation Scheme and Codes (Subject Identification and Treatment Assigned) 66](#_Toc31298139)

[16.1.8 Audit Certificates 66](#_Toc31298140)

[16.1.9 Documentation of Statistical Methods 66](#_Toc31298141)

[16.1.10 Documentation of Inter-Laboratory Standardisation Methods and Quality Assurance Procedures if Used 66](#_Toc31298142)

[16.1.11 Publications based on the Study 66](#_Toc31298143)

[16.1.12 Important publications referenced in the report 66](#_Toc31298144)

[16.2 Patient Data Listings 66](#_Toc31298145)

[16.2.1 Discontinued Patients 66](#_Toc31298146)

[16.2.2 Protocol Deviations 66](#_Toc31298147)

[16.2.3 Patients Excluded from the Efficacy Analysis 66](#_Toc31298148)

[16.2.4 Demographic Data 66](#_Toc31298149)

[16.2.5 Compliance and/or Drug Concentration Data 66](#_Toc31298150)

[16.2.6 Individual Efficacy Response Data 66](#_Toc31298151)

[16.2.7 Adverse Event Listings 67](#_Toc31298152)

[16.2.8 Listing of Individual Laboratory Measurements by Patient, when required by regulatory authorities 67](#_Toc31298153)

[16.3 Case Report Form 67](#_Toc31298154)

[16.3.1 CRF's for Deaths, other Serious Adverse Events, and Withdrawals for Adverse events 67](#_Toc31298155)

[16.3.2 Other CRF's Submitted 67](#_Toc31298156)

[Individual Patient Data Listings 67](#_Toc31298157)

**LIST OF TABLES**

[Table 1 List of Study Investigators 20](#_Toc31272668)

[Table 2 Details of the Investigational Products 39](#_Toc31272669)

[Table 3 Study Flow Chart 45](#_Toc31272670)

[Table 4 ECOG Performance Scale 49](#_Toc31272671)

[Table 5 List of Changes 58](#_Toc31272672)

**LIST OF FIGURES**

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

# ETHICAL CONSIDERATIONS

## Independent Ethics Committee or Institutional Review Board

## 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

## Rationale

# STUDY OBJECTIVES

## Primary Objective

## 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

### Inclusion criteria

### Exclusion criteria

### 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