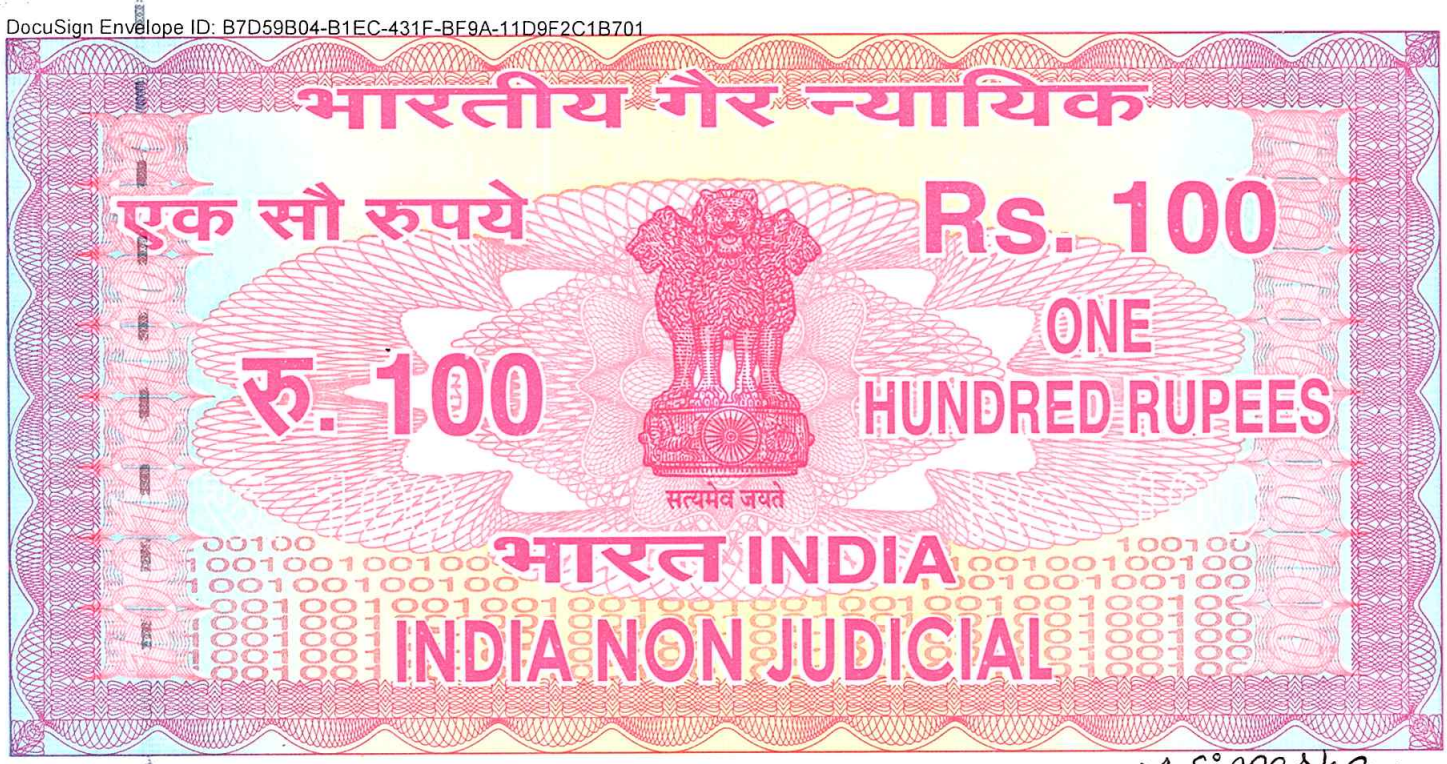


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M.Sireesha.
BD 264315

Tran Id: **240130185426648978**
Date: **30 JAN 2024, 06:56 PM**
**Purchased By:**
AZIZUDDIN MOHAMMAD
S/o VASIUDDIN MOHAMMAD
R/o HYDERABAD
**For Whom**
HETERO BIOPHARMA LIMITED

**M.SIREESHA**
LICENSED STAMP VENDOR
Lic. No. 15-10-015/2017
Ren.No. 15-10-056/2023
FLAT15,BLOCK 5,KENDRIYA VIHAR,
MAYURINAGAR,MIYAPUR,
SERILINGAMPALLY MANDAL,
RANGAREDDY DISTRICT
Ph 9441885384

## CLINICAL TRIAL AGREEMENT

This Clinical Trial Agreement ("The Agreement") is made and executed **15/04/2024** by and between

**Hetero Biopharma Limited** a company incorporated under the Companies Act 2013 with Corporate Identification No. U24290TG2016PLC111946 and having its registered office at **7-2-A2, Hetero Corporate, Industrial Estate Sanathnagar I.E., Hyderabad-500018, Telangana State, India**, (hereinafter referred to as "**SPONSOR**", which expression unless repugnant to the subject or context therein shall mean and include its assignees, affiliates, employees, subsidiaries, nominees, agents and successors-in-interest) of the ONE PART

HETERO BIOPHARMA LIMITED HYDERABAD
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**AND**

**Dr. Ankit Batra (MCI ID No: Tamil Nadu Medical Council - 158795), Consultant at Himalayan Institute of Medical Sciences (a constituent academic unit of Swami Rama Himalayan University), Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand- 248016, India** and hereinafter referred to as the "**PRINCIPAL INVESTIGATOR**" (which expression unless repugnant to the subject or context therein shall mean and include his/ her heirs, executors and successors-in-interest) of the SECOND PART,

**AND**

**Swami Rama Himalayan University (For its constituent academic unit Himalayan Institute of Medical Sciences) located at Swami Ram Nagar, Jolly Grant, Dehradun - 248 016, Uttarakhand, India.** Hereinafter referred to as the **"INSTITUTION"** (which expression unless repugnant to the subject or context therein shall mean and include its heirs, executors and successors-in-interest) of the THIRD PART,

"SPONSOR", "PRINCIPAL INVESTIGATOR" and "INSTITUTION" are hereinafter collectively referred to as 'Parties" and individually as a 'Party".

**WHEREAS**

The SPONSOR is conducting a clinical trial entitled, Study title: **A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer** (Annexure II) as permitted by the Drugs Controller General of India (DCGI) vide their approval letter dated **18/04/2023** ("the Study / Clinical Trial")

Vide Undertaking letter dated **30/06/2023** issued by the PRINCIPAL INVESTIGATOR, the PRINCIPAL INVESTIGATOR agreed to conduct the aforesaid Clinical Trial at **Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Swami Ram Nagar, Jolly Grant, Dehradun, Uttarakhand- 248016, India** in Female Patients with HER2+ Breast Cancer.

A. The SPONSOR is the owner of the Clinical Trial Protocol (as defined hereinafter) and is interested in carrying out the said Clinical Trial, through the PRINCIPAL INVESTIGATOR.

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B. PRINCIPAL INVESTIGATOR is a qualified and experienced professional in conducting the Study.

C. The INSTITUTION is equipped and qualified to undertake the Study.

D. INSTITUTION and PRINCIPAL INVESTIGATOR have agreed to perform the Study on the terms and conditions hereinafter set forth.

**NOW THEREFORE, IN CONSIDERATION OF THE PREMISES AND THE COVENANTS AND AGREEMENTS OF THE PARTIES AS HEREINAFTER SET FORTH, THE PARTIES HAVE AGREED AND DO HEREBY AGREE WITH EACH OTHER TO THE FOLLOWING:**

**1.0 Term:** The validity of the agreement is for a period of four years from the date of the Agreement or the completion of the Clinical Trial (approx. 24 months from the date of this Agreement), whichever is earlier.

**2.0 Institutional Ethics Committee (IEC):** Before the Study is initiated, Investigator will ensure that both the Study and the informed consent form are approved by an Independent Ethics Committee that complies with all applicable laws and regulations. Investigator will further ensure that the Study is subject to continuing oversight by the IEC throughout its conduct. Sponsor shall not interfere in any IEC procedures. If IEC need any assistance from Sponsor, then Sponsor shall promptly give its assistance to IEC.

**3.0 Study Disapproval:** If, through no fault of Investigator, the Study is disapproved by the IEC, this Agreement will immediately terminate with no penalty to the Investigator.

**4.0** The PRINCIPAL INVESTIGATOR will conduct the Clinical Trial strictly as per Protocol No.: HCR/IV/TRUMAB/05/2022 (Annexure II) ("Clinical Trial Protocol") and as approved by the Institutional Ethics Committee (IEC) in accordance with applicable regulatory requirements.

**4.1** The Principal Investigator will comply with the policies and procedures of the institution with which Principal Investigator is affiliated, including any applicable financial policies. Principal Investigator will notify the Sponsor promptly of any conflict between the terms of this Agreement and any such policy or procedure, and the parties will attempt to reach an appropriate accommodation.

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**4.2** The PRINCIPAL INVESTIGATOR confirms that he / she has studied and understood the Clinical Trial Protocol and has agreed to conduct the Clinical Trial according to the guidelines prescribed by the DCGI.

**4.3** The PRINCIPAL INVESTIGATOR hereunder shall perform the Study at the INSTITUTION mentioned in the aforementioned INVESTIGATOR UNDERTAKING and he/she shall be acting as the Collaborators if applicable, in the conduct of the Study and agree to be bound by the terms of this Agreement.

**4.4** The PRINCIPAL INVESTIGATOR further represents, warrants and covenants that the PRINCIPAL INVESTIGATOR is and at all times, during the Term of this Agreement, he/she shall be:

a. In good professional standing,
b. In possession of all requisite professional licenses,
c. Fully qualified to conduct the Study and to act as the PRINCIPAL INVESTIGATOR under the Agreement,
d. Fully experienced and knowledgeable with respect to all matters pertaining to the study, and
e. Responsible for the supervision of all persons who may assist the PRINCIPAL INVESTIGATOR or otherwise be engaged in the study.

**4.5** The PRINCIPAL INVESTIGATOR shall be responsible for the performance of the study as per the highest standards of medical and clinical research practices. Prior to commencing the Study, the PRINCIPAL INVESTIGATOR shall require, and each Collaborator engaged in the Study to complete and return to SPONSOR the Disclosure of Financial Interests and Arrangements, if any, in the Study.

**4.6** The PRINCIPAL INVESTIGATOR and INSTITUTION shall notify to the SPONSOR immediately by telephone and email / facsimile if the DCGI, or any other governmental or regulatory authority in India requests permission to or does inspect the PRINCIPAL INVESTIGATOR and INSTITUTION's facilities or research records relating to this Study whenever and will provide in writing to the inspecting authority copies of all materials, correspondence, statements, forms and records which the PRINCIPAL INVESTIGATOR and INSTITUTION receives, obtains, or generates pursuant to any such Study.

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**4.7** The PRINCIPAL INVESTIGATOR agrees to use his / her professional expertise to perform the Study in accordance with the Protocol and the terms and conditions of this Agreement. In the event SPONSOR does not approve, SPONSOR may terminate this Agreement in accordance with the Termination section below and INSTITUTION shall take all necessary steps to effectuate such termination.

**4.8** The PRINCIPAL INVESTIGATOR agrees to ensure that no subject in this Study may participate concurrently in any ancillary study (technique, procedure, questionnaire or observation other than those set forth in the Protocol) without prior written approval in writing from SPONSOR. In the event that SPONSOR approves such participation in any ancillary study, the PRINCIPAL INVESTIGATOR agree that the ancillary study will be conducted in accordance with all applicable Laws, Rules and Regulations, including but not limited to Schedule Y (as amendment up-to-date) to Drugs & Cosmetics Rule 1945 and other applicable rules including The New Drugs and Clinical Trials Rules 2019 under Drugs & Cosmetics Act 1940, Guidelines of Indian Council for Medical Research, India Good Clinical Practice of the Central Drugs Standards Control Organization, ICH Guidance for Good Clinical Practice (as amendment up-to-date), Declaration of Helsinki. PRINCIPAL INVESTIGATOR agrees to provide SPONSOR periodically and in a timely manner during the term of this Agreement with all Clinical Trial results and other data collected as per the Protocol on properly completed (written or electronic) Case Record Forms.

**4.9** PRINCIPAL INVESTIGATOR should prior inform the SPONSOR preferably before a month if planning to move out of the Study for any unforeseen reasons, and the PRINCIPAL INVESTIGATOR / INSTITUTION is responsible for identifying a suitable replacement in case where the PRINCIPAL INVESTIGATOR change happens in the Study. Prior approval should be obtained from the SPONSOR for all such changes and should be as per GCP and applicable regulatory requirements.

**4.10** PRINCIPAL INVESTIGATOR agrees to report to SPONSOR all Serious Adverse Events (SAEs) and important medical events, as identified in the protocol, affecting any trial subject in the Clinical trial as per applicable regulatory guidelines (including but not limited to schedule Y guidelines and New Drugs and clinical trials rule 2019).

PRINCIPAL INVESTIGATOR further agrees to follow up such report with detailed written reports in compliance with all applicable legal and regulatory requirements.

**4.11** The PRINCIPAL INVESTIGATOR / INSTITUTION undertakes to indemnify and hold harmless the SPONSOR, its directors, employees and agents from any claims, demands, costs, actions, or judgments or suits for personal injury or death directly arising out of the administration or use of the Clinical Study Drug resulting from the PRINCIPAL INVESTIGATOR's / the INSTITUTION's medical and/or professional malpractice or negligence or willful misconduct and liability thereof, including their failure and/or the failure of their employees and/or the agents of INSTITUTION to adhere to the terms of this Agreement or procedures/terms of the protocol for the trial and/or failure to comply with any/all applicable laws, regulations, guidelines and/or from the wrongful/ unauthorized use of the Clinical Trial Drug and/or from the data/information/ result/reports submitted to SPONSOR and/or from acts of negligence, malice, fraud by the PRINCIPAL INVESTIGATOR and/or the employees and/or the agents of INSTITUTION.

**4.12** The PRINCIPAL INVESTIGATOR and INSTITUTION will permit the SPONSOR to;

(a) Examine, inspect and audit the work performed here under and the facilities, systems and equipment at or with which the work is conducted.

(b) Inspect and copy all Data, documents and records related to such work and the Study.

**4.13** The obligations of this Section shall survive termination of this Agreement.

**5.0** The SPONSOR appoints Mr. Sheejith. K, DGM - Clinical Development & Medical Affairs as Monitor for the Clinical Trial and reserves its right to nominate any other person as Monitor.

The SPONSOR will supply the aforesaid Drug, case record forms, consent forms, patient information sheets and other stationery as may be required, to the PRINCIPAL INVESTIGATOR at free of cost. The SPONSOR will bear the consultation charges, Research Assistant Fee, Laboratory Investigation charges, other miscellaneous and sundry expenses as



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detailed in Annexure III. All amounts will be paid by means of RTGS/NEFT/other with available payee details.

In case of an injury occurring to the subject during the clinical trial, free medical management shall be given by the SPONSOR as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

In case of injury or death during the Clinical Trial, however not caused due to any reasons attributable to PRINCIPAL INVESTIGATOR, subject shall be given free medical management, as long as required, by the SPONSOR.

In case an injury or death occurs to the subject during the Clinical Trial, the subject or the subject's nominee(s) shall also be entitled to financial compensation as per order of the Licensing Authority defined under rule 39 of New Drugs and Clinical Trials Rules-2019 and the financial compensation will be over and above any expenses incurred on the medical management of such subject.

If a Study subject suffers an adverse reaction, illness, or injury which, in the reasonable judgment of Institution, was directly caused by a Study Drug administered in accordance with this Agreement and the Protocol or any properly performed procedures required by the Protocol, SPONSOR shall provide reimbursement for the reasonable and necessary medical costs of diagnosis and medical treatment of any Study subject injury, including hospitalization, but only to the extent such expenses are not attributable to (I) INSTITUTION's negligence or willful misconduct, (ii) INSTITUTION's breach of this Agreement or (iii) the natural progression of an underlying or pre-existing condition or events, unless exacerbated by participating in the Study.

The expenses on medical management and financial compensation in the case of injury or death of the subject shall be borne by the SPONSOR as per the provisions of New Drugs and Clinical Trials Rules, 2019.

The SPONSOR undertakes to indemnify and hold harmless PRINCIPAL INVESTIGATOR, and INSTITUTION who are directly involved in the Clinical Trial under their supervision, from any claims, demands, costs or judgments arise from the participation in and/or performance of the subject Study or arising out of adverse reactions to the subjects on



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Clinical Trial involving the Clinical trial Drug provided, however, the SPONSOR shall not be responsible for any liability, loss or damages resulting from a failure by PRINCIPAL INVESTIGATOR , IEC and/or the employees and/or the agents of INSTITUTION to comply with the terms of this agreement or any/all applicable laws, regulations, guidelines and/or acts of malice, negligence, or fraud.

All the obligations related to subject injury & indemnity shall survive termination of this Agreement.

**6.0** **Governing law and Dispute Resolution**: This Agreement shall be governed by and shall be construed in accordance with Indian Laws and the Courts at Dehradun, Uttarakhand shall have exclusive jurisdiction to resolve any dispute under this Agreement. The Parties agree that they shall in good faith work towards implementation of this Agreement and any dispute arising out of or in relation to this Agreement shall be first attempted to be resolved amicably by mutual negotiations, failing which such dispute shall be referred to Arbitration in terms of Arbitration & Conciliation Act, 1996 and rules thereof as amended upto date and further amendments if any. All disputes, controversies or claims arising out of or relating to this Agreement including interpretation thereof, or breach, termination or invalidity thereof shall be referred to arbitration to a sole arbitrator to be appointed mutually by the SPONSOR and the INSTITUTION. In circumstance parties fail to appoint a sole arbitrator then the Parties shall appoint one arbitrator each who shall in turn jointly appoint the third arbitrator. The venue of Arbitration shall be at Dehradun, Uttarakhand State and the Arbitration proceedings shall be conducted in English language. The decision of such Arbitrator shall be final, binding and conclusive on the Parties.

**7.0** **Termination: This agreement may be terminated-**

**7.1** By either party if the other party commits breach and fails to remedy such breach within 30 days from the date of receipt of written notice detailing the same. The other party on receipt of the notice shall immediately take all steps to cease conduct of the trial as soon as possible to protect the welfare of subjects participating in the trial. Further, either party may terminate this Agreement with immediate effect by written notice to the respective party if the PRINCIPAL INVESTIGATOR is no longer

available and INSTITUTION and the SPONSOR fail to appoint a PRINCIPAL INVESTIGATOR mutually.

**7.2** By SPONSOR with 30 days' prior written notice: SPONSOR, in its sole discretion, shall have the right to terminate agreement and stop the conduct of the trial at any time by giving notice to the PRINCIPAL INVESTIGATOR accordingly.

**7.3** Termination:

This Agreement may be terminated by any party upon giving at least a thirty (30) days written notice to that effect to the other parties. The day following the 30th day of such notice shall be "Effective Date of Termination". A reasonable adjustment will be made between the Parties to ensure the PRINCIPAL INVESTIGATOR and INSTITUTION is reimbursed for project costs incurred to the date of termination of this Agreement for completing the Study as per protocol or already enrolled subjects.

SPONSOR may terminate this Agreement, in whole or in part, with or without cause, immediately upon written notice to Institute subject to the discharge of their respective obligations under the terms of the Agreement. PRINCIPAL INVESTIGATOR/INSTITUTION shall have the right to terminate the conduct of the immediately upon notification to the SPONSOR, if requested to do so by the IEC or if such termination is required to protect the health/welfare of the study subjects.

1. ***Respective obligation in the event of early termination*:**

a) Upon notice of termination of this Agreement by either INSTITUTION or SPONSOR or PRINCIPAL INVESTIGATOR, INSTITUTION shall cease enrolling Clinical Trial Subjects into the Study and shall discontinue conduct of the Study as soon as is medically practicable.

b) If the trial is terminated prior to its completion, the SPONSOR shall pay to the remuneration detailed in the Agreement by the milestones that have been duly achieved to the date of termination. In the case of early termination of the trial for any reason, the INSTITUTION / PRINCIPAL INVESTIGATOR shall provide all such assistance as SPONSOR shall reasonably require to ensure an efficient handover of conduct of trial to a third party and with due regard for the welfare of the subjects.

c) If, upon the Effective Date of Termination, SPONSOR has advanced funds which remain unutilized or surplus, INSTITUTION shall repay such funds within thirty (30) days of the Effective Date of Termination. In the event INSTITUTION fails to repay such funds in a timely manner, SPONSOR may deduct an equivalent amount from any payment then or later due from SPONSOR to INSTITUTION under this or any other arrangement between the Parties.

2. ***Return of Material***: Upon termination of this Agreement, PRINCIPAL INVESTIGATOR shall return to SPONSOR any unused Study Drug, materials and all SPONSOR Confidential Information, as defined in the Confidentiality Section of this Agreement, on the conclusion of the Study or termination of this Agreement as the case may be or, at Sponsor's option, destroyed with the destruction certified in writing.

**8.0 <u>Ownership of Data, Confidentiality and Publication:</u>**

**8.1 <u>Ownership:</u>** All case report forms and other data (including without limitation, written, printed, graphic, video and audio material and information contained in any computer data base or computer readable form) generated by the PRINCIPAL INVESTIGATOR in the course of conducting the Study (the "Data") shall be property of SPONSOR, which may utilize the Data in any way it deems appropriate, subject to and in accordance with all applicable (a) Indian laws and regulations and (b) privacy and security laws of India and other countries. Any copyright work created in connection with performance of Study and contained in the Data (except any publication by the PRINCIPAL INVESTIGATOR as provided for hereinafter) shall be property of SPONSOR as the author and the owner of copyright in such work

**8.2 <u>All information</u>**, including, but not limited to, the Study Drug or SPONSOR operations, such as SPONSOR's patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data and formulation information supplied by SPONSOR to and/or PRINCIPAL INVESTIGATOR and not previously published (the "SPONSOR Confidential Information") are considered confidential and shall remain the sole property of SPONSOR. Both during and after the term of this Agreement, and PRINCIPAL INVESTIGATOR will use diligent efforts to maintain in confidence and use only for the



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purposes contemplated in this Agreement (i) the information which is identified in the preceding sentence as confidential or which a reasonable person would conclude as confidential and proprietary property of SPONSOR and which is disclose by or on behalf of PRINCIPAL INVESTIGATOR and (ii) Data which is generated as a result of this Study. The preceding obligations shall not apply to data or information (i) which has been published through no fault of PRINCIPAL INVESTIGATOR, or (ii) which SPONSOR agree, in writing, may be used or disclosed, or (iii) which is published in accordance this Section 7. The provisions in this paragraph shall survive the termination or expiration of this Agreement for a period of ten years.

**8.3 Publication:** The Parties acknowledge that the SPONSOR shall retain ownership of all original Data that result from this Study. Data generated during the Clinical Trial Study is the sole property of the SPONSOR. Further, the INSTITUTION and the PRINCIPAL INVESTIGATOR acknowledges that all the intellectual property rights in the Confidential Information of and belonging to Sponsor which is disclosed to the PRINCIPAL INVESTIGATOR is and shall always remain the sole and exclusive property of Sponsor. The primary right in the data generated during and in connection with the conduct of the trial, including publication rights, rests with the Sponsor. Therefore, PRINCIPAL INVESTIGATOR agrees not to publish or present the results or any information derived from the study but his name should to be included in any publication either author or as participant in the Study.

**8.4 Patents:** All rights to any discovery or invention conceived and reduced to practice as a result of the work conducted under this Agreement shall belong to SPONSOR. The PRINCIPAL INVESTIGATOR agrees to assign to SPONSOR, the sole and exclusive ownership thereto, upon the payment of costs by SPONSOR, if any, incurred by PRINCIPAL INVESTIGATOR in assisting SPONSOR in their filing, prosecution, or maintenance of any patent application or patent issued thereon. Such patent applications, if any, shall be filed and prosecuted by SPONSOR. PRINCIPAL INVESTIGATOR shall promptly disclose to SPONSOR any invention or discovery arising under this Agreement. PRINCIPAL INVESTIGATOR shall execute and shall have its employees execute all documents necessary to transfer all rights, titles and interests in and to any such invention or discovery to SPONSOR.



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## 9.0 Data Use Agreement:

**9.1 Encoding study data:** PRINCIPAL INVESTIGATOR shall ensure that the patient identifiable information that is disclosed during the study and provided to the SPONSOR under this study fulfilled all privacy obligations under applicable legislations and regulations.

**9.2 SPONSOR use of data set:** SPONSOR shall not use or disclose information that would violate the requirements of any privacy legislation. SPONSOR will limit access to the data to personnel responsible for research and development function within their respective organization or within affiliated companies of SPONSOR. SPONSOR may also provide access to contract research organizations and other consultants or agents working with the research and development functions of these entities on the research activities detailed above. SPONSOR will ensure that all such parties assume the data protection responsibilities of SPONSOR as set forth in this section.

**9.3** Protection of the data: Sponsor shall comply with all applicable laws and regulations regarding subject data privacy. In addition, Sponsor will review and approve the Informed Consent and Authorization documents (collectively, the "Authorization Documents") relating to the use and disclosure of individually identifiable health information of subjects enrolled in the Study ("Health Information"), including receipt and use of Health Information by Sponsor. Further, SPONSOR shall, with respect to the information continued in the data (i) not use or further disclose the information other than as permitted or required by this agreement or as otherwise required by law; (ii) use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this Agreement; (iii) report to PRINCIPAL INVESTIGATOR any use or disclosure of information not provided for by this agreement of which it becomes aware; (iv) ensure that any agent or assignee, including a subcontractor, to whom it provides the information agrees to the same restrictions and conditions that apply to SPONSOR with respect to the data and (v) not identify the information or contracts of the individuals to whom it pertains.

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## 10.0 Insurance:

**10.1** SPONSOR shall secure and maintain in full force and effect, through the performance of the study (and following termination of the study to cover any claims arising from the study) Insurance coverage for general liability in amounts appropriate to the conduct of business activities and the services contemplated by the study.

**10.2** INSTITUTION shall maintain medical professional liability insurance with limits in accordance with local standards for each medical professional involved in the Study, or require that each medical professional maintain such insurance.

**10.3** PRINCIPAL INVESTIGATOR shall secure and maintain in full force and effect, through the performance of the study (and following termination of the study to cover any claims arising from the study) Insurance coverage for medical, professional and medical malpractice liability, in amounts appropriate to the conduct of business activities and the services contemplated by the study.

**10.4** Upon request, each party shall provide to the other party a copy of the insurance certificate setting forth the foregoing coverage.

## 11.0 Debarment / Financial Disclosure:

a) PRINCIPAL INVESTIGATOR shall not employ, contract with or retain any person directly or indirectly to perform service under this Agreement if such a person incurs any disqualification of any nature under any statute in force either in India. Upon written request from SPONSOR, PRINCIPAL INVESTIGATOR shall, within ten days, provide written confirmation that it has complied with the foregoing obligation. PRINCIPAL INVESTIGATOR shall also provide to SPONSOR all information necessary to comply with any disclosure requirements mandated Drugs & Cosmetics Act 1940 and rules thereof, including any information required to be disclosed in connection with any financial relationship between SPONSOR and PRINCIPAL INVESTIGATOR. This disclosure requirement shall require disclosure of information involving immediate family members of those involved in the study.

b) The INSTITUTION certifies that to its knowledge neither it, nor any of the Study Personnel, including the PRINCIPAL INVESTIGATOR, is



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currently debarred, suspended, or excluded under any applicable laws including the Food & Drugs Act, Drug and Cosmetic Act, as amended,. In the event that the PRINCIPAL INVESTIGATOR or any Study Personnel becomes debarred or disqualified during the term of this Agreement or within 1 year after termination of the Study, the INSTITUTION agrees to promptly notify SPONSOR after learning of such event. INSTITUTION certifies that it is not excluded from any of the government program. In the event, INSTITUTION becomes excluded during the term of this Agreement or within 1 year after termination of the Study, the INSTITUTION agrees to promptly notify Sponsor after learning of such event.

**12.0** **Force Majeure:** Any delay or failure of a party hereto to perform its obligations hereunder will be excused if and to the extent that it was caused by an event or occurrence beyond such party's reasonable control and without its fault or negligence ("Force Majeure"). Force Majeure includes, but is not limited to, acts of God, actions by any government authority, fires, floods, windstorms, explosions, riots, natural disasters, wars, sabotage or acts of terrorism, pandemic. A party claiming Force Majeure must provide the other party with written notice of such delay (including the anticipated duration of the delay) within ten (10) days of the occurrence of Force Majeure. If the delay lasts more than ninety (90) days, either Party may terminate this Agreement upon written notice. Regardless of whether this Agreement is terminated or naturally expires, Sponsor shall be responsible for payment for all services or procedures actually performed in compliance with the study protocol and all non-cancellable Institution expenses incurred or obligated prior to termination or expiration and shall remit such total within thirty (30) days of Institution's written request for final payment. In the event of any overpayment by Sponsor, Institution shall refund such overpayment to Sponsor.

**13.0** **Non-Referral/Anti-Corruption:**

a. The Parties agree that it is not their intent under this Agreement to induce or encourage the unlawful referral of subjects or business between the Parties, and there shall not be any requirement under this Agreement that either Party, its employees or affiliates, including its medical staff, engage in any unlawful referral of subjects to, or order or purchase products or services from, the other Party.

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b. Each Party shall require that their employees, who are involved in the conduct of the Study, will not offer, pay, request or accept any bribe, inducement, kickback or facilitation payment, and shall not make or cause another to make any offer or payment to any individual or entity for the purpose of influencing a decision for the benefit of the other Party.

**14.0 Use of Name:**

a. Neither INSTITUTION nor SPONSOR may use the name, trademark, logo, symbol, or other image or trade name of the other Party or its employees and agents in any advertisement, promotion, or other form of publicity or news release or that in any way implies endorsement without the prior written consent of an authorized representative of the other Party whose name is being used. Such approval will not be unreasonably withheld or delayed.

b. Each Party understands that the amount of any payment made hereunder may be disclosed and made public by the other Party as required by law or regulation, provided that the disclosure clearly designates the payment as having been made to INSTITUTION for research and not to the physician.

**15.0 Independent Contractor**: PRINCIPAL INVESTIGATOR/INSTITUION act in the capacity of independent contractor(s) hereunder and not as agents or employees of SPONSOR. The PRINCIPAL INVESTIGATOR/ INSTITUION will make no claim against SPONSOR for compensation, vacation pay, sick leave, retirement benefits, social security benefits, workers compensation, disability or unemployment benefits or employee benefits of any kind, including right/status as an employee of SPONSOR.

**16.0 Publicity:** None of the parties shall use the name of any other party for promotional purposes without the prior written consent of the party whose name is proposed to be used nor shall either party disclose the existence or substance of this Agreement except as required by law.

**17.0 Agreement Modifications**: This Agreement or any of its Exhibits shall not be altered, amended or modified except by written document signed by all parties Hereto.

**18.0 Assignment**: SPONSOR shall have the right to assign this Agreement to an affiliate of SPONSOR upon prior written notice to PRINCIPAL INVESTIGATOR. In all other instances, neither party shall assign its rights



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or duties under this Agreement to another without prior written consent of the other party. Subject to the foregoing, this Agreement shall bind and inure to the respective parties and their successors and assigns.

**19.0** **Conflict with protocol**: If any of the provisions of this Agreement conflict with any provision of the protocol, this Agreement shall take precedence.

**20.0** **Recordkeeping**: The INSTITUTION and PRINCIPAL INVESTIGATOR shall prepare and maintain records, reports and Data provided in the Protocol, IEC requirements, and in accordance with all applicable local, state and Central laws and regulations. INSTITUTION or PRINCIPAL INVESTIGATOR shall cooperate with the SPONSOR in making records, reports and Data developed under this Agreement. INSTITUTION or PRINCIPAL INVESTIGATOR shall ensure the storage of data related to Study in accordance with the requirements of current Good Clinical Practices, in suitable and secured storage facilities and under appropriate conditions, for a period of time required under the agreement applicable laws and regulations in India or until 5 years after completion of all regulatory activity, whichever period is longer, unless to the extent that SPONSOR requires the return or destruction of this data, in which case this request shall be complied with to the extent allowed by applicable laws and regulations. Before the destruction or deletion of such data, SPONSOR's written approval shall be obtained.

**21.0** **Intellectual Property:** It is expressly agreed that Institution does not transfer by operation of this Agreement to the other party hereto any patent right, copyright, nor other proprietary right that it owns or controls. All other inventions developed under this Agreement ("Other Inventions") that are developed solely by Institution shall be owned by Institution.

**22.0** **Duty to update regarding Safety Information:** Sponsor shall notify Investigator in writing of any subject safety issues that may arise during the course of the Study and, thereafter, in accordance with concerned authorities requirements. In addition, if Sponsor becomes aware of any findings through its site monitoring process that may possibly affect the safety or welfare of subjects enrolled in the Study, sponsor will notify the Institution/investigator through the Institution's authorized representative.

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**23.0 Representation and Warranties:**

(a) Each Party represents to the other that it has the necessary right and authority to enter into this Agreement and to the best of its knowledge, it is not party to any agreement which would prevent it from fulfilling its obligations under this Agreement.

(b) Sponsor warrants to Institution that it shall have and maintain appropriate/applicable licences, approvals, permits, certifications and the like necessary to lawfully perform its obligations under this Agreement.

**24.0 Waiver:** No waiver of any term, provision or condition of this Agreement, whether by conduct or otherwise in any one or more instances, shall be deemed to be or construed as a further or continuing waiver of the same term, provision or condition, or of any other term, provision or condition of this Agreement.

**25.0 Severability:** The invalidity or unenforceability of any term or provision of this Agreement shall not affect the validity or enforceability of any other term or provision of this Agreement.

**26.0 Relationship of the Parties:** The relationship of SPONSOR to Institution and Investigator shall be that of an Independent entity and none of the parties shall hold itself out to third parties as purporting to act as, or on behalf of, the other party hereto.

**27.0 Survival of Obligations**: Obligations relating to Funding, Confidential Information, Study Records, Inventions, Publications, and indemnity survive termination of this Agreement as does any other provision in this Agreement or its Attachments that by its nature and intent remains valid after the term of the Agreement.

**28.0 Execution:** This Agreement will become effective after by the last signatory it is fully executed by all the parties hereto and shall continue in effect for the full duration of the Study according to the Protocol unless extended or sooner terminated in accordance with the provisions of this Agreement.

**29.0 Electronic Execution:** Any signature (including any electronic symbol or process attached to, or associated with, a contract or other record and adopted by a Person with the intent to sign, authenticate or accept such contract or record) hereto or to any other certificate, agreement or document related to this transaction, and any contract formation or record-keeping through electronic means shall have the same legal validity and enforceability as a manually executed signature or use of a paper-based recordkeeping system to the fullest extent permitted by

Swami Rama Himalayan University Registrar

DS SSinha

applicable law, including the DocuSign or Digital Signature or any similar and the parties hereby waive any objection to the contrary

// Signature page follows//

In witness whereof, the parties have caused this agreement to be executed by their authorized representative on the date, month and year first above mentioned

**Hetero Biopharma Limited**
**(SPONSOR)**

DocuSigned by:
Shubhadeep Sinha
0E394422E269413...

**Dr. Shubhadeep Sinha**
**Sr. Vice -President and Head-**
**Clinical Development & Medical Affairs**

**Reviewed & Approved by**

DocuSigned by:
Sudershan Pallap
7E31CE1D38774B3...

**Mr. Sudershan Pallap**
**AVP (Legal) &**
**Company Secretary**

**Swami Rama Himalayan University**
**Dehradun.**

**Dr. Mukesh Bijalwan**
**Registrar**

**Principal Investigator**

Dr. Ankit Batra (M.D.,DM)
Assistant Professor
Dept. of Medical Oncology
Cancer Research Institute, HIMS
Dehradun

**Dr. Ankit Batra (Consultant)**
**Himalayan Institute of Medical Sciences**

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SSinha

**Annexure I**
**DCGI NOC**
(Attached Separately)

## Annexure II
## CLINICAL TRIAL PROTOCOL
(Attached Separately)

## Annexure III
## PAYMENT TERMS AND SCHEDULE

**Estimated Cost Per Completed Patient with Trastuzumab Enrolled:**

| Trastuzumab Phase IV Clinical Study Budget | | | | | |
|---|---|---|---|---|---|
| **Sr. No** | **Head** | **Unit Charge** | **Visits** | **Safety** | **Efficacy & IM** |
| 1 | Investigator Charges | 3,000 | 12 | 36000 | 36000 |
| 2 | Chemotherapy Charges (Day Care) | 1,500 | 12 | 18000 | 18000 |
| 3 | CT with Contrast /MRI (Neck, Thorax, Abdomen, Pelvis) | 15,000 | 3 | - | 45000 |
| 4 | CT/MRI Brain | 6,000 | 1 | 6000 | 6000 |
| 5 | Bone Scan | 6,000 | 1 | 6000 | 6000 |
| 6 | Chest X-ray | 1,000 | 5 | 5000 | 5000 |
| 7 | 12 lead ECG | 300 | 12 | 3600 | 3600 |
| 8 | 2-D Echocardiogram | 1,500 | 5 | 7500 | 7500 |
| 9 | Haematology and Bio Chemistry local Lab | 3,500 | 5 | 17500 | 17500 |
| 10 | Patient Conveyance (All Visits) | 1,000 | 12 | 12000 | 12000 |
| 11 | Study Nurse & Coordinator Charges | 1,500 | 12 | 18000 | 18000 |
| | Institutional Charges (1 & 11 )* 20% | | | 10800 | 10800 |
| **Total Cost Per Completed Patient** | | | | **140400** | **185400** |

***Note: Any additional tests, performed by site will be reimbursed as per the actual cost.***

| Sl.No | Head | Amount Per Annum |
|---|---|---|
| 1. | Archival Fee | 20000 |

1. **Payment terms:**

1. Payments will be made preferably within 30 working days from the date of receipt of correct original invoice

2. Payment of Rs. 50,000 INR will be paid as an advance after signing the agreement before or after the site Initiation visit. This amount will be adjusted in the subsequent invoices received.

3. The final payment to the site will be paid based on the number of patients enrolled, completed, withdrawn/dropout and screen failures before the site closure visit.

4. If the site is terminated or doesn't progress in terms of recruitment for at least 6 months after Initiation / paying the advance, then the amount paid should be returned by the PRINCIPAL INVESTIGATOR / INSTITUTION to the SPONSOR after making necessary deductions and adjustments

5. The study documents after study completion should be archived under the supervision of the PRINCIPAL INVESTIGATOR as per the applicable regulatory timelines. Total archival fees of 100000 INR will be paid for 05 years. Archival charges will be applicable only when at least one subject is enrolled by the site and completes the study per protocol.

2. **Payee Details:**

The SPONSOR will make the payment after tax deduction at source. The account payee crossed Cheque/DD/RTGS/other will be issued in favor of

**Principal Investigator Payment Grant: Annexure III**

| | |
|---|---|
| **Payee Name** | Swami Rama Himalayan University |
| **Payee Address** | HIHT, Jolly Grant P.O Doiwala, Dehradun 0135 2412967 |
| **Account Number** | 33082676422 |
| **Bank Name** | State Bank of India |
| **IFSC Code** | SBIN0010580 |
| **Tax ID Number (PAN Number)** | AAAJH0463L |
| **GST Number** | 05AAAJH0463LIZC |

Swami Rama Himalayan University Registrar

DS SSinha

File. No. BIO/CT/22/000120

# FORM CT-06

(See rules 22, 25, 26, 29 and 30)

## PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licensing Authority hereby permits M/s. Hetero Biopharma Limited, H.No. 8-3-166/1 & 2, 105 to 108, 1st Floor, G Block, East Wing, Challa Estates, Erragadda, Hyderabad (India)-500018, Telephone No.: 40-23810110 FAX: 40-23810110 E-Mail : VIJAYNAG.T@HETERODRUGS.COM to conduct Phase IV clinical trial entitled – **"A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer"** as per Protocol No.: HCR/IV/TRUMAB/05/2022; Version:1.0, Date: 14th May 2022 in the below mentioned clinical trial sites.

2. Details of new drug and clinical trial site [as per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

4. It may kindly be noted that merely granting permission to conduct clinical trial with the drug does not convey or imply that based on the clinical trial data generated with the drug permission to market this drug in the country will automatically be granted to you.

Place: New Delhi
Date: 18-Apr-2023

RAJEEV SINGH RAGHUVANSHI

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India)
Central Licensing Authority

**Annexure:**

**Details of new drug or investigational new drug:**

| | |
|---|---|
| Names of the new drug or investigational new drug: | Trastuzumab 150 mg and 440 mg (r-DNA origin) |
| Dosage form: | Lyophilized Powder for concentrate for solution for Intravenous infusion in Vial |
| Composition: | Each Lyophilized vial contains: |

| Name of Ingredients | For 150 mg quantity in mg | For 440 mg quantity in mg |
|---|---|---|
| Trastuzumab (r-DNA origin) (in house) | 150 | 440 |
| α,α-Trehalose dihydrate (USP/IP) | 136.2 | 400 |
| L-Histidine HCl (USP/IP) | 3.36 | 9.9 |
| L-Histidine (USP/IP) | 2.16 | 6.4 |
| Polysorbate 20 (USP/IP) | 0.6 | 1.8 |

- For 150 mg vial, reconstitute the powder concentrate with bacteriostatic water for injection (BWFI). Reconstitution volume: 7.2mL, after adding 7.2mL of BWFI, total volume will be approximately 7.2mL.
- For 440 mg multi dose vial, reconstitute the powder concentrate with bacteriostatic water for injection. Reconstitution volume: 20 mL, after adding 20mL of BWFI, total volume will be approximately 20mL. Bacteriostatic water for injection contains 1.1% benzyl alcohol solution

| | |
|---|---|
| Indications: | Treatment of patients with HER2-positive breast cancer |

**Details of clinical trial site:**

| S. No. | Name and Address of Clinical Trial Site | Ethics Committee Details | Name of Principal Investigator |
|---|---|---|---|
| 1. | Dr.Bhimrao Ambedkar Institute of Rotary Cancer Hospital(Dr BRA IRCH), All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029 | Institute Ethics Committee All India Institute of Medical Sciences, Old OT Block, Room No.102, Ansari Nagar, New Delhi, Delhi – 110029<br><br>EC Reg. No.: ECR/538/Inst/DL/2014/RR-20 | Dr. Haresh KP |
| 2. | State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Sheikhpura,Patna-800014, Bihar, India | Institutional Ethics Committee, Indira Gandhi Institute of Medical Sciences (IGMS), Sheikhpura, Raja Bazar, Patna, Bihar – 800014<br><br>EC Reg. No.: ECR/640/Inst/BR/2014/RR-20 | Dr. Rajesh Kumar Singh |

| | | | |
|---|---|---|---|
| 3. | King George Hospital Andhra Medical College, Maharanipet, Visakhapatnam-530002, Andhra Pradesh, India | IEC King George hospital Maharanipeta Collector Office Junction Visakhapatnam Andhra Pradesh<br><br>EC Reg. No.:<br>ECR/197/Inst/KGH/2013/RR-20 | Dr.Shilpa Kandipalli |
| 4. | R G Kar Medical College and Hospital, 1 Kshudiram Bose, Sarani, Kolkata-700004, West Bengal, India | R G Kar Medical College and Hospital, 1, Khudiram Bose Sarani, Platinum Jubilee Building, 2nd Floor, Kolkata, West Bengal – 700004<br><br>EC Reg. No.<br>ECR/322/Inst/WB/2013/RR-20 | Dr. Bidisha Naskar Ghosh |
| 5. | Department of Radiotherapy, Nehru Extension, Post Graduate Institute of Medical Education and Research, Sector-12, Chandigarh-160012,India | Post Graduate Institute of Medical Education & Research (PGIMER), Room No 6006, Sixth Floor, PN Chuttani Block, Chandigarh, Punjab - 160012<br><br>EC Reg. No.<br>ECR/25/Inst/CH/2013/RR-20 | Dr. Budhi Singh |
| 6. | MNJ Institute of Oncology & Regional Cancer Centre, Red Hills, Hyderabad-500004,Telangana, India | MNJ Institute of Oncology and RCC, Lakdikapool, Red Hills, Hyderabad, Telangana - 500004<br><br>EC Reg. No<br>ECR/227/Inst/AP/2013/RR-19 | Dr. P. Radhika |
| 7. | Department of Oncology, Meenakshi Mission Hospital and Research Centre, Lake Area, Melur Road, Madurai-625107, Tamil Nadu, India | Meenakshi Mission Hospital and Research Centre, Lake Area Melur Road, Madurai, Tamil Nadu - 625107<br><br>EC Reg. No<br>ECR/398/Inst/TN/2013/RR-19 | Dr. Saju S.V |

| | | | |
|---|---|---|---|
| 8. | Mumbai Oncocare Centre(A Unit of Cellcure Cancer Centre Pvt Ltd) 1st Floor, Blue Nile Building, Almeda Rd, next to pinnacle hospital, Charai, Naka, Thane, Maharashtra-400601,India | Cellcure Cancer Centre Private Limited, Majithira Apartment, God Gift Premises, SV Road, Ville Parle West, Mumbai, Mumbai Suburban, Maharashtra - 400056<br><br>EC Reg. No ECR/1277/Inst/MH/2019 | Dr. Pritam Kalaskar |
| 9. | HCG City Cancer Centre, 33-25-33, Ch Venkata Krishnayya Street, Suryaraopet, Vijayawada-520002, Andhra Pradesh, India | HCG Curie City Cancer Centre, 44-1-1/3 Padavalarevu, Gunadala, Vijayawada, Krishna, Andhra Pradesh - 520004<br><br>EC Reg. No ECR/869/Inst/AP/2016/RR-19 | Dr. K. Lakshmi Priyadarshini |
| 10. | Unique Hospital Multispeciality and Research Institute, Opp. Kiran Motors, Nr.Canal, Civil Char rasta, Sosyo Circle lane, Off Ring Road, Surat-395002, Gujarat, India | Ethics committee, Unique Hospital Unique Hospital Opp. Kiran motors, nr. Canal, Civil Char Rasta Sosyo Circle lane, off. Ring Road, Surat Gujarat<br><br>EC Reg. No ECR/595/Inst/GJ/2014/RR-20 | Dr.Honey Chainsukh Parekh |

**CLINICAL TRIAL AGREEMENT**

**A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer**

**Annexure III**

**PAYMENT TERMS AND SCHEDULE**

**Estimated Cost Per Completed Patient with Trastuzumab Enrolled:**

| Trastuzumab Phase IV Clinical Study Budget | | | | | |
|---|---|---|---|---|---|
| **Sr. No** | **Head** | **Unit Charge** | **Visits** | **Safety** | **Efficacy & IM** |
| 1 | Investigator Charges | 3,000 | 12 | 36000 | 36000 |
| 2 | Chemotherapy Charges (Day Care) | 1,500 | 12 | 18000 | 18000 |
| 3 | CT with Contrast /MRI (Neck, Thorax, Abdomen, Pelvis) | 15,000 | 3 | - | 45000 |
| 4 | CT/MRI Brain | 6,000 | 1 | 6000 | 6000 |
| 5 | Bone Scan | 6,000 | 1 | 6000 | 6000 |
| 6 | Chest X-ray | 1,000 | 5 | 5000 | 5000 |
| 7 | 12 lead ECG | 300 | 12 | 3600 | 3600 |
| 8 | 2-D Echocardiogram | 1,500 | 5 | 7500 | 7500 |
| 9 | Haematology and Bio Chemistry local Lab | 3,500 | 5 | 17500 | 17500 |
| 10 | Patient Conveyance (All Visits) | 1,000 | 12 | 12000 | 12000 |
| 11 | Study Nurse & Coordinator Charges | 1,500 | 12 | 18000 | 18000 |
| | Institutional Charges (1 & 11 )* 20% | | | 10800 | 10800 |
| | **Total Cost Per Completed Patient** | | | **140400** | **185400** |

***Note: Any additional tests, performed by site will be reimbursed as per the actual cost.***

| Sl.No | Head | Amount per Annum for five years |
|---|---|---|
| 1. | Archival Fee | **Rs20,000** |

## 1. Payment terms:

1. Payments shall be raised within 30 working days from the date of receipt of correct original invoice

2. Payment of **Rs. 50,000** INR will be paid as an advance after signing the agreement before or after the site Initiation visit. This amount will be adjusted in the subsequent invoices received.

3. The final payment to the site will be paid based on the number of patients enrolled, completed, withdrawn/dropout and screen failures before the site closure visit.

4. If the site is terminated or doesn't progress in terms of recruitment for at least 6 months after Initiation / paying the advance, then the amount paid should be returned by the **PRINCIPAL INVESTIGATOR / INSTITUTION** to the SPONSOR after making necessary deductions and adjustments

5. The study documents after study completion should be archived under the supervision of the PRINCIPAL INVESTIGATOR as per the applicable regulatory timelines. Total archival fees of **100000 INR** will be paid for **05 years**. Archival charges will be applicable only when at least one subject is enrolled by the site and completes the study per protocol.

## 2. Payee Details:

The SPONSOR will make the payment after tax deduction at source. The account payee crossed Cheque/DD/RTGS/other will be issued in favor of

**Principal Investigator Payment Grant: Annexure III**

| | |
|---|---|
| **Payee Name** | **Swami Rama Himalayan University** |
| **Payee Address** | HIHT, Jolly Grant P.O Doiwala<br><br>Dehradun 0135 2412967 |
| **Account Number** | 33082676422 |
| **Bank Name** | State Bank of India |
| **IFSC Code** | SBIN0010580 |
| **Tax ID Number (PAN Number)** | AAAJH0463L |
| **GST Number** | **05AAAJH0463LIZC** |

| Trastuzumab Phase IV Clinical Study Budget | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Sr. No** | **Head** | **Unit Charge** | **Visits** | **Safety** | **Efficacy & IM** | **Heads** | **Payment Head** | **HSN Code** |
| 1 | Investigator Charges | 3,000 | 12 | 36000 | 36000 | Consultancy Clinical Trial | Study Budget | 998113 |
| 2 | Chemotherapy Charges (Day Care) | 1,500 | 12 | 18000 | 18000 | Investigation | | |
| 3 | CT with Contrast /MRI (Neck, Thorax, Abdomen, Pelvis) | 15,000 | 3 | - | 45000 | Investigation | | |
| 4 | CT/MRI Brain | 6,000 | 1 | 6000 | 6000 | Investigation | | |
| 5 | Bone Scan | 6,000 | 1 | 6000 | 6000 | Investigation | | |
| 6 | Chest X-ray | 1,000 | 5 | 5000 | 5000 | Investigation | | |
| 7 | 12 lead ECG | 300 | 12 | 3600 | 3600 | Investigation | | |
| 8 | 2-D Echocardiogram | 1,500 | 5 | 7500 | 7500 | Investigation | | |
| 9 | Haematology and Bio Chemistry local Lab | 3,500 | 5 | 17500 | 17500 | Investigation | | |
| 10 | Patient Conveyance (All Visits) | 1,000 | 12 | 12000 | 12000 | Patient Reimbursement | | |
| 11 | Study Nurse & Coordinator Charges | 1,500 | 12 | 18000 | 18000 | Consultancy Clinical Trial | | |
| | Institutional Charges (1 & 11 )* 20% | | | 10800 | 10800 | Institutional Charges | | |
| **Total Cost Per Completed Patient** | | | | **140400** | **185400** | | | |

Sweekriti M.K

Registrar

**Billing Cycle:**

1. The Invoice will be raised after the monitoring from the sponsor (Hetero.). The draft invoice will be shared by sponsor.
2. The final invoice will be generated by Finance department on request from the Clinical Trial Centre.
3. The Payments shall be received within 30 working days from the date of receipt of correct original invoice.
4. All invoices will be raised without GST if applicable ( SEZ exemption letter attached).
5. The invoice will be generated in single head as study budget (consisting of Consultancy Clinical Trial, Lab Investigation, Patient Reimbursement, OA etc ) using SAC code 998113.

SHEETAL.IC
Hetero Biopharma.

Himalayan University
Registrar

# CLINICAL STUDY PROTOCOL

**Study Title:** A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer.

| | |
|---|---|
| **Protocol ID:** | **HCR/IV/TRUMAB/05/2022** |
| **Phase of Study:** | **IV** |
| **Version No.:** | **1.0** |
| **Version Date:** | **14-May-2022** |
| **Supersedes:** | **NIL** |

| **Amendments** | |
|---|---|
| **No.** | **Date** |
| **NA** | **NA** |

| | |
|---|---|
| **Investigator:** | |
| **Center:** | |

| | |
|---|---|
| **Sponsor's Representative Designation and Address** | Dr. Shubhadeep Sinha, M.D.<br>Sr. Vice-President and Head<br>Clinical Development and Medical Affairs,<br>**Hetero Biopharma Limited,**<br>H. No. 8-3-166/1 & 2, 105 to 108,<br>1st Floor, G Block, East Wing, Challa Estates,<br>Erragadda, Hyderabad, Telangana, India, 500018.<br>Tel No. & Fax No.: +91-40-23810110<br>E-mail Id: sd.sinha@heterodrugs.com |

**SPONSOR: Hetero Biopharma Limited**
H. No. 8-3-166/1 & 2, 105 to 108,
1st Floor, G Block, East Wing, Challa Estates,
Erragadda, Hyderabad, Telangana, India, 500018.
Tel No. & Fax No.: +91-40-23810110

## SPONSOR'S REPRESENTATIVE SIGNATURE PAGE

I have read this protocol and I agree to conduct the study as described, in compliance with Good Clinical Practice (ICH E6), the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), Indian GCP guidelines, New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019 and the rules and regulations in force in this country at present.

I agree to maintain a list of appropriately qualified persons to whom I shall delegate significant trial-related duties. I shall ensure that all persons assisting me with the trial are adequately informed about the protocol, the investigational product(s) and their trial-related duties and functions.

**Signature of Authorized Signatory**

| | |
|---|---|
| **Name:** | Dr. Shubhadeep Sinha, M.D. |
| **Designation:** | Sr. Vice-President and Head Clinical Development & Medical Affairs |
| **Company:** | Hetero Biopharma Limited |
| **Date:** | **14-May-2022** |

## STATISTICIAN'S SIGNATURE

I have read this protocol and I agree to conduct the study as described, in compliance with Good Clinical Practice (ICH E6), the Declaration of Helsinki (2013), Indian GCP guidelines, New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019 and the rules and regulations in force in this country at present. I agree to maintain a list of appropriately qualified persons to whom I shall delegate significant trial-related duties. I shall ensure that all persons assisting me with the trial are adequately informed about the protocol, the investigational product(s) and their trial related duties and functions.

**Signature of Statistician**

**Name:** Dr. Sreenivasa Chary S

**Designation:** GM - Medical Affairs

**Date:** 14-May-2022

## INVESTIGATOR'S SIGNATURE PAGE

I have read this protocol and I agree to conduct the study as described in it, in compliance with Good Clinical Practice (ICH E6), the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), Indian GCP guidelines, New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019 and the rules and regulations in force in this country at present.

I agree to maintain a list of appropriately qualified persons to whom I shall delegate significant trial-related duties. I shall ensure that all persons assisting me with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

**Address of Institution**: _____

_____

_____

**Signature of Investigator**

**Name:**
**Designation:**
**Date:**

## Table of Contents

**1. TITLE PAGE ..... 8**
**2. VERSION CONTROL PAGE ..... 9**
**3. LIST OF ABBREVIATIONS AND DEFINITIONS ..... 10**
**4. STUDY SUMMARY (PROTOCOL SYNOPSIS) ..... 12**
**5. BACKGROUND INFORMATION ..... 20**
5.1 Introduction ..... 20
5.2 Purpose and Rationale ..... 20
**6. STUDY OBJECTIVES & ENDPOINTS ..... 21**
**7. STUDY DESCRIPTION (INVESTIGATIONAL PLAN) ..... 23**
7.1. Basic Principles and Ethical Considerations ..... 23
7.2. Study Design ..... 23
7.3. Study Population ..... 24
7.4. Patient Eligibility ..... 24
*7.4.1. Inclusion Criteria ..... 24*
*7.4.2. Exclusion Criteria ..... 24*
7.5. Treatment Duration ..... 24
7.6. Study Treatment ..... 24
7.7. Dose Modifications ..... 27
7.8. Missed Doses ..... 28
7.9. Study Drug Discontinuation ..... 28
7.10. Prior and Concomitant Therapy ..... 29
7.11. Sample Size ..... 29
7.12. Treatment Completion and Withdrawal ..... 29
**8. STUDY ASSESSMENTS ..... 32**
8.1 Patient Information and Informed Consent ..... 32
8.2 Background, Demographic and Administrative Assessments ..... 33
8.3 Safety and Tolerability Assessments ..... 33
8.4 Efficacy Assessments ..... 36
8.5 Immunogenicity Assessments ..... 37
8.6 Blood Sample Handling ..... 37
8.7 Assessment Windows ..... 37
**9. STUDY CALENDAR ..... 38**
**10. STUDY FORMULATION ..... 40**
10.1. Product Information ..... 40
10.2. Drug Storage ..... 40
10.3. Drug Supplies and Accountability ..... 40

10.4 Packaging and Labelling of Study Drug ..... 42
10.5 Dosing Schedule and Administration ..... 42
10.6 Dose Adjustments ..... 42
10.7 Drug Overdose ..... 42
10.8 Concurrent Medication ..... 42

**11. ASSESSMENT OF SAFETY ..... 43**

11.1. Definitions ..... 43
11.2. Classification of Adverse Events ..... 45
11.3. Clarification in Reporting of Deaths ..... 47
11.4. Causality of the Adverse Event ..... 47
11.5. Laboratory Abnormalities ..... 49
11.6. Adverse Events Recording and Reporting ..... 49
11.7. Follow-Up of Adverse Events and Serious Adverse Events ..... 50
11.8. Serious Adverse Events Reporting ..... 50
11.9. Pregnancies ..... 51

**12. STATISTICAL ANALYSIS PLAN ..... 52**

12.1. Sample Size Determination ..... 52
12.2. Demographic Data ..... 52
12.3. Analysis of the Main Variables ..... 52
*12.3.1 Variables ..... 52*
*12.3.2 Statistical Model and Method of Analysis ..... 52*
*12.3.3 Adverse Events/Serious Adverse Events ..... 53*

**13. DATA AND SAFETY MONITORING BOARD [DSMB] ..... 53**

**14. PROTOCOL MODIFICATIONS, DEVIATIONS and AMENDMENTS ..... 54**

14.1. Deviations for a Patient ..... 54
14.2. Amendments ..... 55
*14.2.1 Administrative Modifications ..... 55*
*14.2.2 Clinical Modifications ..... 55*

**15. ADMINISTRATIVE MATTERS ..... 56**

15.1. Regulatory Approvals ..... 56
15.2. Investigator's Agreement ..... 56
15.3. Regulatory Issues and Reporting ..... 56
15.4. Patient Confidentiality ..... 56
15.5. Ethics ..... 57

**16. DATA COLLECTION, DOCUMENTATION AND ARCHIVING OF STUDY DOCUMENTS ..... 58**

16.1. Study Initiation ..... 58

16.2. Study Monitoring and Source Data Verification ..... 58
16.3. Record Retention ..... 59
16.4. Data Management ..... 59

**17. INSURANCE AND INDEMNITY ..... 61**
**18. AUDITS AND INSPECTION ..... 62**
**19. PATIENT CONFIDENTIALITY AND DATA PROTECTION ..... 63**
**20. REPORT WRITING AND PUBLICATION ..... 64**
**21. ANNEXURES ..... 65**
**ANNEXURE - I: Summary of Product Characteristics ..... 65**
**ANNEXURE - II: Case Record Form of Hetero- Trastuzumab ..... 66**
**ANNEXURE - III: RECIST CRITERIA V1.1 FOR SOLID TUMORS ..... 67**
**22. REFERENCES ..... 68**

## 1. TITLE PAGE

A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer.

### STUDY OBJECTIVES

**Primary Objective**

- To evaluate the safety of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing the reported adverse events during the study period

**Secondary Objectives**

- To evaluate the long-term immunogenicity of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing Anti-Trastuzumab antibodies at the end of treatment/end of study.
- To evaluate the efficacy of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing tumor response evaluations during the study period

**STUDY INDICATION:** HER2+ Breast Cancer

**TARGET POPULATION:** Female Patients with HER2 Positive Breast Cancer.

**SPONSOR:**

**Hetero Biopharma Limited**
H. No. 8-3-166/1 & 2, 105 to 108,
1st Floor, G Block, East Wing, Challa Estates,
Erragadda, Hyderabad, Telangana, India, 500018.
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## 2. VERSION CONTROL PAGE

- Protocol Version 1.0; Dated 14-May-2022.
- This protocol is meant for regulatory and ethics committee submissions and approvals.

## 3. LIST OF ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate transaminase |
| ATA | Anti-Trastuzumab Antibodies |
| BWFI | Bacteriostatic Water For Injection |
| CBC | Complete Blood Count |
| CD&MA | Clinical Development and Medical Affairs |
| CHF | Congestive Heart Failure |
| CISH | Chromogenic in-situ Hybridization |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRA | Clinical Research Associate |
| CRC | Clinical Research Coordinator |
| CRF | Case Report Form |
| CRP | C- Reactive Protein |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCGI | Drug Controller General of India |
| ECD | Extracellular Domain |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | End of Treatment |
| FISH | Fluorescence in-situ Hybridization |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HER2 | Human Epidermal growth factor Receptor 2 |

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| HIV | Human Immunodeficiency Virus |
| ICH | International Conference on Harmonization |
| IHC | Immunohistochemistry |
| IMP | Investigational Medicinal Product |
| IP | Inpatient |
| IRR | Infusion-related reactions |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| LFT | Liver Function Tests |
| LVEF | Left Ventricular Ejection Fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| NYHA | New York Heart Association |
| OP | Outpatient |
| ORR | Objective Response Rate |
| PD | Progressive Disease |
| PFS | Progression free survival |
| PO | Per Oral |
| PP | Per protocol |
| PR | Partial Response |
| PSUR | Periodic Safety Update Report |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| RBC | Red Blood Cells |
| SAE | Serious Adverse Events |
| SAP | Statistical Analysis Plan |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| SWFI | Sterile Water For Injection |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cells |
| WHO-UMC | World Health Organization-Uppsala Monitoring Centre |

## 4. STUDY SUMMARY (PROTOCOL SYNOPSIS)

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| **Title of study** | A Phase IV Multi-Centric, Post-Marketing Study Evaluating the Safety, Immunogenicity and Efficacy of the Marketed Formulation of Hetero-Trastuzumab in Female Patients with HER2+ Breast Cancer |
| **Study Drug** | Hetero-Trastuzumab (150 mg or 440 mg vials)<br>Each 440 mg multi-use vial of Hetero-Trastuzumab contains 440mg trastuzumab. Reconstitution with 20 mL of the appropriate diluent, bacteriostatic water for injection (BWFI) or sterile water for injection (SWFI), yields a solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.<br>Each 150 mg multi-use vial of Hetero-Trastuzumab contains 150mg trastuzumab. Reconstitution with 7.2mL of appropriate diluent (BWFI or SWFI), after adding 7.2mL of water for injection, total volume will be approximately 7.2mL. |
| **Objectives** | **Primary Objective**<br>➢ To evaluate the safety of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing the reported adverse events during the study period<br>**Secondary Objective**<br>➢ To evaluate the long-term immunogenicity of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing Anti-Trastuzumab antibodies at the end of treatment/end of study.<br>➢ To evaluate the efficacy of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing tumor response evaluations during the study period |
| **Study Endpoints** | **Primary Endpoint:** |

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| | ➢ Incidence, severity, outcome, duration, action taken, and causality of individual adverse events [Labelled/Unlabelled and Serious/Non-Serious] reported during the study<br>o Significant clinical signs and symptoms developed during the treatment period<br>o Significant changes observed in laboratory parameters during treatment period.<br>➢ Incidence of AEs leading to dose discontinuation/ modifications/ interruption of study drug<br>**Secondary Endpoints:**<br>➢ Anti-Trastuzumab antibodies (ATA) against Hetero–Trastuzumab at baseline, 6 months, and 12 months or progression, whichever is earlier<br>➢ Objective Response Rate at the end of 6 months and 12 months or progression, whichever is earlier<br>[ORR = complete response (CR) + partial response (PR)]<br>*All the Response assessment for the enrolled patients will be based on RECIST Criteria Version 1.1 (Refer Annexure III).*<br>➢ Progression free survival (PFS) over study duration<br>PFS is defined as the time from enrollment to time of first documented disease progression or death due to any cause, whichever occurs first. |
| **Study design** | This is a prospective, non-comparative, post-marketing safety, immunogenicity, and efficacy study in Hetero-Trastuzumab indicated patients. |
| **Sample size and study duration** | The present study will gather the data of at least 200 patients. All patients will be evaluated for safety assessments and 100 out of 200 patients will be evaluated for Immunogenicity and Efficacy as well.<br>Study duration will be up to 4 years or until the relevant data |

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| | collected from 200 patients. |
| **Study population and eligibility criteria** | Patients in whom Hetero-Trastuzumab is indicated will constitute the target population.<br>**Inclusion criteria:**<br>• Female patients of age 18 and above<br>• Patients willing to give written, signed, and dated informed consent to participate in the study<br>• Patients with breast cancer with evidence of HER2-overexpression by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence in situ hybridization (FISH) or positive chromogenic in-situ hybridization (CISH) result. |
| | **Exclusion criteria:**<br>• Patients with history of hypersensitivity to the trastuzumab or to any of the excipients, or to murine proteins or any other chemotherapeutic agent planned along with Trastuzumab<br>• Male patients with breast cancer<br>• Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest<br>• Patients with a history or evidence of cardiovascular diseases including congestive heart failure (CHF) of Grade-III/IV New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia, unstable angina pectoris, myocardial infarction<br>• Patients who are pregnant or a nursing mother. |
| **Study Ethics** | This study will be conducted according to the principles of the Declaration of Helsinki, (International Conference of Harmonization- Good Clinical Practices [ICH-GCP] and New Drugs and Clinical Trials Rules, 2019 and Indian regulatory laws governing biomedical research in human patients. Each institution |

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| | will have an ethics committee approval before initiating the study. Patient's written informed consent will be taken prior to any study procedure being conducted. |
| **Dosage to be administered** | **Dosage Regimen**<br>*Metastatic breast cancer:*<br>Three-weekly schedule<br>• The recommended initial loading dose is 8 mg/kg body weight.<br>• The recommended maintenance dose is 6 mg/kg body weight, beginning three weeks after the loading dose.<br>Weekly schedule<br>• The recommended initial loading dose is 4 mg/kg body weight.<br>• The recommended weekly maintenance dose is 2 mg/kg body weight, beginning one week after the loading dose.<br>Trastuzumab can be administered as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy unless patients are unsuitable for these treatments.<br>Trastuzumab to be administered in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.<br>Trastuzumab to be administered in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.<br>Trastuzumab to be administered in combination with an aromatase inhibitor for the treatment of postmenopausal patients with |

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| | hormone-receptor positive MBC, not previously treated with trastuzumab.<br><br>*Early breast cancer*<br><br>*Three-weekly and weekly schedule*<br><br>As a three-weekly regimen the recommended initial loading dose of Trastuzumab is 8 mg/kg body weight. The recommended maintenance dose of Trastuzumab at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.<br><br>As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide. (Method of Administration is detailed in Section 7.6)<br><br>**Dose Reduction**<br><br>• No reductions in the dose of Trastuzumab are required.<br><br>• Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. (Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.)<br><br>• If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.<br><br>**Missed doses**<br><br>• If the patient has missed a dose of Trastuzumab by one week |

or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

- If the patient has missed a dose of Trastuzumab by more than one week, a re-loading dose of Trastuzumab should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

**Pre-Medication**

Pre-medication to be used to reduce risk of occurrence of Infusion related reactions (IRRs). The majority of these events occur during or within 2.5 hours of the start of the first infusion. Premedication consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine or as per institutional standard/investigator discretion should always be administered before each infusion of IMP.

Pre-medication dose administration details are presented as below:

**Day 1 Pre-Medication**

| Drug | Dose | Route | Timing before study drug administration |
|---|---|---|---|
| Paracetamol | 650 mg | PO | 30-60 minutes |
| Diphenhydramine | 50 mg | PO | 30-60 minutes |
| Ranitidine | 50 mg | IV | 30-60 minutes |
| Granisetron | 2 mg | IV | 30-60 minutes |

| | |
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| | Note: Premedication before Paclitaxel will be as per the Paclitaxel package insert or as per the institutional standards. |
| **Study Schedule** | This study will consist of a 21 day screening period, up to 12 months or until progression, whichever is earlier, followed by a one-month follow-up period.<br>**Visit 1:** Up to 21 days prior to baseline (Screening)<br>**Visit 2:** Baseline and Cycle 1 administration<br>(Study drug will be administered in either weekly or 3-weekly regimen, as per Investigator's discretion at hospital)<br>**Visit 3:** On-treatment visit at the end of 6 months for Efficacy & Safety assessments<br>**Visit 4:** End of Treatment (EOT) visit at the end of 12 months or Until progressive disease, whichever is earlier, for Efficacy & Safety assessments<br>**Visit 5:** End of Study (EOS) visit at 1-month post EOT for Safety assessments<br>The detailed study schedule is presented in the study calendar. |
| **Assessments for Safety** | • All patients will be monitored for significant clinical signs and symptoms and laboratory abnormalities during study period.<br>• Laboratory evaluations will be done at screening, at the end of 6 months and 12 months or progressive disease, whichever is earlier.<br>• Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment. |
| **Assessments for Immunogenicity** | • Immunogenicity will be evaluated by assessing serum for the presence of anti-Trastuzumab antibodies in 100 patients out of 200 patients.<br>• Whole-blood samples (3.5 ml) for detection of anti-Trastuzumab antibodies (ATA) will be drawn at baseline, at end of 6 months and 12 months or progressive disease, whichever is earlier. |

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| **Assessments for Efficacy** | • Tumor assessments will be performed at screening, end of 6 months and 12 months or progressive disease, whichever is earlier.<br>• Patients with disease progression shall be withdrawn from the study. Following such a withdrawal, patients will be treated at the investigator's discretion. |
| **Statistical Analysis** | Statistical Analysis Plan (SAP) will be prepared prior to the database lock. The SAP will include detailed statistical aspects of the study. The efficacy analysis will be performed on PP and ITT Population. |

# 5. BACKGROUND INFORMATION

## 5.1 Introduction

A pivotal phase III clinical trial to assess the safety and efficacy of Trastuzumab, in Indian patients of Breast Cancer has been conducted by Hetero Biopharma Limited.

The safety data from this clinical trial and all published phase-III clinical trials with other brands of Trastuzumab may not represent the safety data, which might be generated with the real-life usage in larger general population with due to the controlled setting of the trial including predefined inclusion and exclusion criteria and data in a limited number of patients. The safety evaluation during clinical drug development may not capture rare and/ or unexpected adverse events, e.g., those occurring in less than 1 in 1000 patients.[1]

The efficacy and safety of Hetero- Trastuzumab has been confirmed in Indian HER 2 positive Breast Cancer patients in a Phase III clinical study conducted by Hetero for marketing and manufacturing approval.

## 5.2 Purpose and Rationale

The purpose of this phase-IV study is therefore, to gather safety, immunogenicity and efficacy data in a larger Indian patient population indicated for Hetero- Trastuzumab. The complete Prescribing Information (Summary of Product Characteristics) for Hetero-Trastuzumab has been attached in Annexure I for information related to the prescribed product, primarily approved indications, and available adverse events data.

## 6. STUDY OBJECTIVES & ENDPOINTS

### Objectives

- To evaluate the safety of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing the reported adverse events during the study period
- To evaluate the long-term immunogenicity of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing Anti-Trastuzumab antibodies at the end of treatment/ end of study.
- To evaluate the efficacy of Hetero-Trastuzumab in patients with HER2-positive breast cancer in post marketing phase by assessing tumor response evaluations during the study period

### Endpoints

**PRIMARY ENDPOINT**

- Incidence, severity, outcome, duration, action taken, and causality of individual adverse events (Labelled/Unlabelled and Serious/ Non-Serious) reported during the study
  - Significant clinical signs and symptoms developed during the treatment period
  - Significant changes observed in laboratory parameters during treatment period.
- Incidence of AEs leading to dose discontinuation/ modifications/ interruption of study drug.

**SECONDARY ENDPOINT**

- Anti-Trastuzumab antibodies (ATA) against Hetero– Trastuzumab at baseline, 6 months, and 12 months or progression, whichever is earlier
- Objective Response Rate (ORR) at the end of 6 months and 12 months or progression, whichever is earlier
  [ORR = complete response (CR) + partial response (PR)]
  *All the Response assessment for the enrolled patients will be based on RECIST Criteria Version 1.1 (Refer Annexure III).*

- Progression free survival (PFS) over study duration

  PFS is defined as the time from enrollment to time of first documented disease progression or death due to any cause, whichever occurs first.

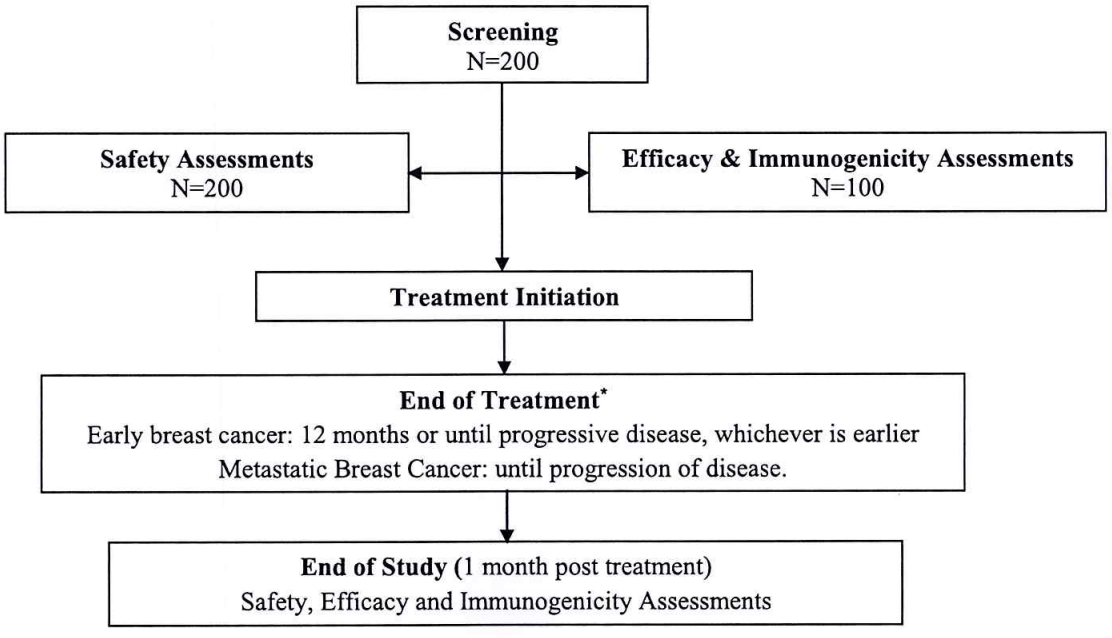
## 7. STUDY DESCRIPTION (INVESTIGATIONAL PLAN)

### 7.1. Basic Principles and Ethical Considerations

This study will be conducted according to the principles of the Declaration of Helsinki, (International Conference of Harmonization-Good Clinical Practices [ICH-GCP], New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019 and applicable regulatory laws governing biomedical research in human patients. Each institution will have an ethics committee approval before initiating the study and ethics committee will be providing continuous oversite to study conduct till completion. Patient's written informed consent will be taken prior to any study procedure being conducted.

### 7.2.Study Design

This is a prospective, non-comparative, post-marketing safety, immunogenicity, and efficacy study in Hetero-Trastuzumab indicated patients.




* The treatment duration will be up to 52 weeks as per the approved prescribing information. If required, study treatment will be continued as per investigators discretion.

### 7.3. Study Population

All patients indicated Hetero-Trastuzumab as per the prescribing information will constitute the target patient population. Each investigator will report their experience with patient(s) treated with Hetero-Trastuzumab.

### 7.4. Patient Eligibility

#### 7.4.1. Inclusion Criteria

- Female patients of age 18 and above
- Patients willing to give written, signed, and dated informed consent to participate in the study
- Patients with breast cancer with evidence of HER2-overexpression by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence in situ hybridization (FISH) or positive chromogenic in-situ hybridization (CISH) result.

#### 7.4.2. Exclusion Criteria

- Patients with history of hypersensitivity to the trastuzumab or to any of the excipients, or to murine proteins or any other chemotherapeutic agent planned along with Trastuzumab.
- Male patients with breast cancer
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest
- Patients with a history or evidence of cardiovascular diseases including congestive heart failure (CHF) of Grade III/IV New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia, unstable angina pectoris, myocardial infarction.
- Patients who are pregnant or a nursing mother.

### 7.5.Treatment Duration

For Early breast cancer: 52 weeks or until disease recurrence, whichever occurs first.
For Metastatic Breast Cancer: until progression of disease.

### 7.6. Study Treatment

Hetero-Trastuzumab is the study treatment for this study.

**Reconstitution:** Each 440 mg multi-use vial of Hetero-Trastuzumab contains 440mg trastuzumab. Reconstitution with 20 mL of the appropriate diluent, bacteriostatic water

for injection (BWFI) or sterile water for injection (SWFI), yields a solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

Each 150 mg multi-use vial of Hetero-Trastuzumab contains 150mg trastuzumab. Reconstitution with 7.2mL of appropriate diluent (BWFI or SWFI), after adding 7.2mL of water for injection, total volume will be approximately 7.2mL.

**Dosage Regimen**

**For metastatic Breast Cancer:**

Three-weekly schedule

- The recommended initial loading dose is 8 mg/kg body weight.
- The recommended maintenance dose is 6 mg/kg body weight, beginning three weeks after the loading dose.

Weekly schedule

- The recommended initial loading dose is 4 mg/kg body weight.
- The recommended weekly maintenance dose is 2 mg/kg body weight, beginning one week after the loading dose.

Trastuzumab can be administered as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy unless patients are unsuitable for these treatments.

Trastuzumab to be administered in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

Trastuzumab to be administered in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

Trastuzumab to be administered in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

**For Early Breast Cancer:**

*Three-weekly and weekly schedule*

As a three-weekly regimen the recommended initial loading dose of Trastuzumab is 8 mg/kg body weight. The recommended maintenance dose of Trastuzumab at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

**Method of administration**

Herceptin loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Herceptin intravenous infusion should be administered by a health-care provider prepared to manage anaphylaxis and an emergency kit should be available.

Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

**Pre-Medication**

Pre-medication to be used to reduce risk of occurrence of Infusion-related reactions (IRRs). The majority of these events occur during or within 2.5 hours of the start of the first infusion. Premedication consisting of an anti-pyretic and an antihistaminic, e.g., paracetamol and diphenhydramine or as per institutional standard/investigator discretion should always be administered before each infusion of IMP. Patients will be scheduled to receive pre-medication 30 to 60 minutes prior to trastuzumab infusion). Pre-medication dose administration details are presented as below:

**Day 1 Pre-Medication**

| Drug | Dose | Route | Timing before Study Drug Administration |
|---|---|---|---|
| Paracetamol | 650 mg | PO | 30-60 minutes |
| Diphenhydramine | 50 mg | PO | 30-60 minutes |

| Drug | Dose | Route | Timing before Study Drug Administration |
|---|---|---|---|
| Ranitidine | 50 mg | IV | 30-60 minutes |
| Granisetron | 2 mg | IV | 30-60 minutes |

*Note: Premedication before Paclitaxel will be as per the Paclitaxel package insert or as per the institutional standards.*

### 7.7. Dose Modifications

- No reductions in the dose of Trastuzumab will be allowed.
- **Myelosuppression**

  Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. (Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.)
- **Cardiomyopathy**

  If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
- **Infusion Reactions**
  - Decrease the rate of infusion for mild or moderate infusion reactions
  - Interrupt the infusion in patients with dyspnea or clinically significant hypotension
  - Discontinue Hetero-Trastuzumab for severe or life-threatening infusion reactions.
- **For any Adverse Event**
  - The subsequent cycle of chemotherapy will be administered once the toxic reaction improves to Grade 1 or better. The dose can be delayed up to a maximum of 3 weeks after the scheduled cycle in case of toxicity.

- If the toxic reaction is not recovered to Grade 1 or better within 3 weeks after the scheduled cycle in case of toxicity, the patient must be withdrawn from the study.

### 7.8. Missed Doses

- If the patient has missed a dose of Trastuzumab by one week or less
  - Usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle.
  - Subsequent maintenance doses should be administered 7 or 21 days later according to the weekly or three-weekly schedules, as applicable.
- If the patient has missed a dose of Trastuzumab by more than one week
  - A re-loading dose of Trastuzumab should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible.
  - Subsequent Trastuzumab maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 or 21 days later according to the weekly or three-weekly schedules, respectively.

### 7.9. Study Drug Discontinuation

Hetero-Trastuzumab may be discontinued due to any of the conditions described in the Hetero-Trastuzumab's prescribing information and as mentioned below.

- Pregnancy
- If patient develops anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome
- In case of any serious and life-threatening infusion reactions following administration of study drug
- Patients missing more than 2 consecutive doses of Trastuzumab will be discontinued from the study.
- Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis

- If LVEF has not improved within 3 weeks of study drug suspension (due to left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment), or has declined further
- If symptomatic congestive heart failure (CHF) has developed within 3 weeks of Trastuzumab
- Failure to initiate a cycle of Paclitaxel (with dose modifications) > twice

### 7.10. Prior and Concomitant Therapy

All concomitant medications not in exclusion criteria, not adversely interacting with study drugs can be given to the patient as per the investigator's clinical judgment. Concomitant medication administered must be recorded in the CRF with generic name and/or trade name of the medication, start and end dates of treatment.

If an infusion reaction occurs, the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids[2].

### 7.11. Sample Size

There is no pre-defined sample size for this study, however as per current practice, Hetero intends to submit data of at least 200 patients of Hetero-Trastuzumab.

Approximately 100 patients will also undergo immunogenicity and efficacy assessments as well.

### 7.12. Treatment Completion and Withdrawal

**Patient withdrawal and Discontinuation**

If any patient wishes to withdraw, the investigator will be informed immediately. The investigator may decide to terminate the participation and discontinue further study of any patient according to the following criteria:

1. Disease progression according to RECIST criteria Version 1.1 ( Refer Annexure III)
2. Inability to tolerate the treatment regimen as specified in section 7.10

3. The patient may be withdrawn from the trial at the discretion of the investigator or the sponsor if judged to be non-compliant with trial procedures or due to safety concerns.
4. Protocol violation: If a protocol violation occurs that in the clinical judgment of the investigator or after discussion with the sponsor may invalidate the trial (for e.g., by pharmacokinetic interference with the trial products)
5. Consent is withdrawn: Patients have the right to withdraw from the trial at any time for any reason.
6. Positive pregnancy test: A female patient with a positive pregnancy test will be withdrawn from the trial, and will be followed until termination or delivery. Children born due to failure of contraceptives under study should be followed up for any abnormalities.
7. Adverse event: Patient reports symptoms, which are considered unacceptable by the patient and/or the investigator/medical monitor and such AE precludes further participation in the trial in a safe manner. An AE form will be completed and the patient will be withdrawn from the trial.
8. Patients enrolled into the study despite meeting exclusion criteria or those with other major protocol deviations that, in investigator's/medical monitor's opinion, precludes further participation in the study should be withdrawn.

If premature withdrawal occurs for any reason, the investigator should determine the primary reason for a patient's premature withdrawal from the study. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents, steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. Patients who are withdrawn from the study will be replaced based on the number of evaluable patients at the end of the study.

If study participation is discontinued, all procedures/assessments required by end of study visit/early withdrawal visit will be performed as completely as possible. Any comments (spontaneous or elicited) or complaints made by the patient and the reason for termination, date of stopping the study medication and the total amount of study medication must be recorded in the source documents and CRFs.

**Handling of Withdrawals**

Patients who are withdrawn from this study for any reason will be requested to complete all assessments as required for the End of Study / Early Withdrawal visit within 28 days after the last dose of study visit. Reasons for early withdrawal must be recorded in the source documents.

If the patient discontinues because of an adverse event (serious or non-serious), the investigator must follow the patient's recovery until resolution or stabilization or until the investigator determines that no further follow-up is necessary. The patient will be followed-up telephonically for AEs/SAEs up to 4 weeks after the last dose of study drug.

The investigator will discuss the appropriate therapy with each patient who withdraws early from this study. Determination of the appropriate follow-up therapy will be left to the discretion of the investigator.

## 8. STUDY ASSESSMENTS

The timing of assessments required during the study is delineated in the Study Calendar. All data obtained from these assessments must be supported in the patient's source documentation. Source documentation must be available for all data collected during the study. Should it become necessary to repeat an evaluation (e.g., 12 lead ECGs, laboratory tests, vital signs, etc.), the results of the repeat evaluation should be captured.

The additional assessment will be entered in the 'Unscheduled Visit' of CRF page.

**Case Record Forms - Timelines**

A case record form (CRF) should ideally capture the entire duration of Hetero-Trastuzumab therapy (i.e., until treatment is discontinued or the patient is lost to follow-up) and up to 6 months or end of study, if it happens earlier.

A case record form (CRF) should be updated at regular intervals, preferably not exceeding 2 weeks. Case record forms (CRFs) should be updated for each administration of Hetero- Trastuzumab.

In the event of an adverse event (serious / non-serious and/ or unexpected), the case record form (Annexure-II) should be filled up immediately and sent to Hetero either by fax or email.

Investigators who are participating in the phase-IV study will dispatch the completed case record forms to Hetero through or any other monitoring or clinical research representatives appointed by Hetero.

### 8.1 Patient Information and Informed Consent

The Investigator or his / her designate will explain to the patients in their local language, through an oral presentation all relevant aspects of the study including purpose, procedures to be carried out, potential hazards, alternative treatments available, expected benefits, if any, rights of the patients before participating in the study. Patients will be encouraged to ask questions and clarify their doubts regarding any aspect of the study and the same would be documented in the source notes. Patients will be required to sign and date or give a thumb impression on informed consent form. If the patient is unable to read/write – an impartial witness should be present during the entire informed consent process who must append signatures to the consent form.

The patients will voluntarily give their written informed consent for participation in the trial by signing or by placing a thumb impression on the informed consent form, which will also be signed by the investigator or his/her designate. A photocopy of signed informed consent form will be given to the patient, while original copy will be retained at investigator site.

### 8.2 Background, Demographic and Administrative Assessments

All data regarding patient demographics (date of birth / age, gender, etc.) relevant medical history / current medical conditions will be captured in CRF. Data regarding study drug i.e., batch number, dose prescribed and dispensed to the subject during the study must be noted in the CRF.

### 8.3 Safety and Tolerability Assessments

All patients will be monitored for significant clinical signs and symptoms and laboratory abnormalities during the study.

**Vital Signs and Body Measurements**

Body weight and oral body temperature will be obtained at specified times during the study. Systolic and diastolic blood pressure and pulse rate will be assessed after the patient has rested quietly in the sitting position for at least 3 minutes.

**ECG Evaluations**

Standard 12-lead ECGs will be performed. The patient number, the date and actual time of the tracing must appear on each page of the tracing. Tracings will be dated and signed by the physician who makes the interpretation. Original 12 lead ECG tracings and a copy of the original tracings, will be appropriately signed, filed along with patient records and archived at study site. The overall interpretation will be captured and clinically significant abnormalities further explained.

**Chest X-Ray and 2D ECHO Evaluations**

Chest X-Ray and 2D-Echo will be performed at screening, at the end of 6 months and 12 months or progressive disease, whichever is earlier. The patient number, the date and actual time of the tracing must appear on each page of the tracing. Tracings will be dated and signed by the physician who makes the interpretation. The overall interpretation will be captured and clinically significant abnormalities further explained.

The overall interpretation of the 2D-Echo will be captured and clinically significant abnormalities further explained. Original reports, will be appropriately signed, filed along with patient records and archived at study site.

**Standard Clinical Laboratory Evaluations**

Laboratory evaluations will be done at screening, at the end of 6 months and 12 months or progressive disease, whichever is earlier.

- When a laboratory assessment listed in the inclusion/ exclusion criteria is outside of a protocol-specified range at screening, the assessment may be repeated once as soon as possible, and in any case, prior to enrollment to rule out lab error. If the repeat value remains outside of protocol specified ranges, the patient should be excluded from the study.
- In the case where a laboratory range is not specified by the protocol, but is outside the normal range for the central laboratory at baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once as soon as possible, and in any case, prior to enrollment to rule out lab error.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was / was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study. Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with sponsor / study medical monitor. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, sponsor / medical monitor should again be contacted.

**Hematology**

Hemoglobin, RBC count, WBC count with differential (monocytes, eosinophils, basophils, neutrophils, lymphocytes) as percentage, Absolute neutrophil count and platelet count.

**Serum Chemistry**

Blood urea, uric acid, serum creatinine, serum bilirubin (total and direct), serum albumin, total protein, AST, ALT, alkaline phosphatase, calcium, sodium, potassium, random blood glucose and CRP (C-reactive protein).

Lipid profile (triglycerides, cholesterol, HDL, LDL and VLDL) will be performed at screening visit, at the end of month 6, month 12 and EOS. Patients should give fasting sample for these visits.

**Urinalysis**

Routine urine analysis (color and appearance, pH, specific gravity, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrate and leukocytes etc.).

**HBsAg, HCV and HIV**

Patients with positive results for HBsAg, HCV and HIV at baseline will be excluded from the study.

**Adverse Events' Data Collection and Reporting**

All adverse and serious adverse events, whether previously known or unknown, will be recorded in the case record form (CRF) with clear description, severity, action taken, duration, outcome and opinion about causal relationship to Hetero- Trastuzumab.

The grading of the severity of the adverse events will be as per common terminology criteria for adverse events CTCAE (v5.0) [Section 11].

The causality assessment of the adverse events with Hetero- Trastuzumab will be done as per the WHO-UMC causality assessment system [Section 11].

Definitions of adverse events/drug reactions, serious adverse events/drug reactions & unexpected drug reaction are provided in section 11.

Whenever additional information is required in relation to a serious adverse event, Hetero representative will immediately contact the investigator for a detailed follow-up on the SAE till all relevant information is obtained.

The collected data will be reviewed for safety and tolerability of Hetero- Trastuzumab use. Each case record form (CRF) (with or without an adverse event) will be assessed by medical personnel at Hetero after data entry, coding and quality review. All adverse events will be analyzed with respect to incidence, causality, seriousness, severity,

expectedness and outcome. In case of serious adverse events, SUSARs and events of pregnancy additional follow-up information may be requested from the investigator.

After a detailed investigation of the causal relationship of the SAE to the study drug & other details, any serious unexpected suspected adverse reactions (SUSARs) will be reported to the regulatory authorities on an expedited basis and as per the applicable regulatory guidelines (New Drugs and Clinical Trials Rules, 2019).

Drugs administered for the treatment of adverse events will also be documented in the CRF

**8.4 Efficacy Assessments**

Tumor assessments will be performed at screening, end of 6 months and 12 months or progressive disease, whichever is earlier. Patients with disease progression shall be withdrawn from the study. Following such a withdrawal, patients will be treated at the investigator's discretion.

CT (with contrast) preferred; if contrast cannot be given – MRI

- Regions: Neck, thorax, abdomen, pelvis; additional sites- if clinically indicated
- Time points: Baseline, at the end of cycle 4 and end of cycle 8

Same CT/MRI modality and instrument should be used from baseline throughout all assessments

Other scans- Bone scan & Brain CT/MRI will be done at screening to rule out bone and brain metastases.

A blinded, trained and qualified radiologist shall assess radiographic change in disease state using CT/MRI scan including bone scans using centralized radiology services, as per RECIST 1.1 outlined in the imaging protocol in study reference manual.

The radiology centres at all sites participating in this study shall follow the imaging protocols outlined in the study reference manual for imaging for uniformity. All other disease activity measurements shall be completed before dosing at each visit, and entered in the CRF. For all visits, the PI shall evaluate the efficacy clinically and outcomes if any will be reported as per RECIST 1.1.

**Early EOS:** Patients who discontinue from the study early will be asked to return to the hospital within 28 days after the last dose of study drug for the end of the study visit.

### 8.5 Immunogenicity Assessments

Immunogenicity will be evaluated by assessing serum for the presence of anti-Trastuzumab antibodies in 100 patients out of 200 patients.

Whole-blood samples (3.5 ml) for detection of anti-Trastuzumab antibodies (ATA) will be drawn at baseline, at end of 6 months and 12 months or progressive disease, whichever is earlier.

### 8.6 Blood Sample Handling

Blood samples will be drawn for serum chemistry, haematology, and immunogenicity assessment.

### 8.7 Assessment Windows

Deviations within the following assessment times are acceptable based on logistical and operational considerations:

- A window period of ±3 days is allowed for visit 3, and ±7 days for visit 5 for all patients.

## 9. STUDY CALENDAR

| STUDY PHASE | Screening | Treatment Phase | | End of Treatment (EOT) | End of study (EOS) |
|---|---|---|---|---|---|
| STUDY DAYS/ TREATMENT CYCLE | -21 to 0[1] | Baseline & C1D1 | 6 Month | 12 Months | 1 month post end of treatment |
| VISIT | VISIT 1 | VISIT 2 | VISIT 3 | VISIT 4 | VISIT 5 |
| EVENTS | | | | | |
| Informed Consent Process | X | | | | |
| Inclusion/Exclusion Criteria | X | | | | |
| HER-2 assessment[2] | X | | | | |
| Demography | X | | | | |
| Medical history | X | X | X | X | X |
| Physical examination & vital signs | X | X | X | X | X |
| Prior/ Concomitant medications[3] | X | X | X | X | X |
| Tumour assessments [CT/ MRI][4] | X | | X | X | X |
| Chest X-ray | X | | X | X | |
| HBsAg, HCV and HIV | X | | | | |
| Serum/Urine pregnancy test[5] | X | | X | X | X |
| Haematology and Serum Chemistry[6] | X | X | X | X | X |
| Lipid profile and Urinalysis | X | | X | X | X |
| Cardiac assessments, 12 lead ECG[7] & 2D Echo | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X |
| Adverse Events[8] | | X | X | X | X |
| Samples for immunogenicity[9] | | X | | X | X |

1 Screening procedures can be performed up to 21 days prior to baseline
2 HER2-overexpression to be assessed by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence in situ hybridization (FISH) or positive chromogenic in-situ hybridization (CISH) result
3 Any treatment administered to the patient (excluding Hetero-Trastuzumab) from the screening visit until the end of the study is regarded as concomitant medications.

4 Tumor assessments: CT (with contrast) preferred, but if contrast cannot be given – MRI; Regions: Neck, thorax, abdomen, pelvis; additional sites- if clinically indicated

5 Serum pregnancy test for women of child-bearing potential will be done during the screening visit and during EOT visit. Urine pregnancy test will be performed at every visit as per PIs discretion. Results of the pregnancy test should be negative

6 Haematology panel would include haemoglobin, RBC count, WBC count with differential count, ANC and Platelet count; Serum chemistry includes blood urea, uric acid, serum creatinine, serum bilirubin (total and direct), serum albumin, total protein, AST, ALT, alkaline phosphatase, PT, PTT, calcium, sodium, potassium, random blood glucose, CRP; Urine analysis.

7 12-Lead ECG will be performed at screening, at each on-treatment visit and EOT

8 Adverse events (AEs) and Serious Adverse Events (SAEs) will be reported from the time of signature of the ICF. SAE must be reported until 30 days after EOT visit.

9 Whole-blood samples (3.5 ml) for detection of anti-Trastuzumab antibodies (ATA) will be drawn at baseline, EOT and EOS.

## 10. STUDY FORMULATION

### 10.1. Product Information

The Trastuzumab drug product has been developed by Hetero Biopharma Limited as the following drug product strengths of Hetero-Trastuzumab are proposed for manufacturing at clinical trials stage.

**Composition of Trastuzumab Drug Product**

| S. No. | Name of Ingredient | Specification | Function | Strength/quantity | |
|---|---|---|---|---|---|
| | | | | **440 mg** | **150 mg** |
| 1 | Trastuzumab | In-house | Active ingredient | 440 mg | 150 mg |
| 2 | α,α-Trehalose dihydrate | USP/IP | Lyoprotec tant | 400 mg | 136.2 mg |
| 3 | L-Histidine HCl | USP/IP | Buffering agent | 9.9 mg | 3.36 mg |
| 4 | L-Histidine | USP/IP | Buffering agent | 6.4 mg | 2.16 mg |
| 5 | Polysorbate 20 | USP/IP | Surfactant | 1.8 mg | 0.6 mg |

For 150 mg multi dose vial, reconstitute the powder concentrate with 7.2 mL of bacteriostatic water for injection (BWFI) or sterile water for injection (SWFI), to give a total reconstitution volume of approximately 7.2mL.

For 440 mg multi dose vial, reconstitute the powder concentrate with 20 mL of bacteriostatic water for injection or sterile water for injection (BWFI or SWFI) to give total reconstitution volume of approximately 21mL.

Bacteriostatic water contains 1.1% benzyl alcohol solution, hence might not be suitable for some patients. In such cases, sterile water for injection will be preferred.

### 10.2. Drug Storage

The product should be stored at 2°C-8°C (36°F-46°F). Do not use if frozen even if it has been thawed. Protect from exposure to light.

### 10.3. Drug Supplies and Accountability

As this is a Phase-IV study, labelled samples of Hetero- Trastuzumab will be provided by Hetero to the enrolled patients via participating investigators.

The study treatment supplied is to be used exclusively for this study according to this protocol. The pharmacist/designee is responsible for dispensing according to the dosage scheme and for ensuring proper storage.

Appropriate documentation of the subject specific dispensing process must be maintained. The trial medications which will be provided by the Sponsor or a designated CRO must be kept in a secure access controlled storage conditions until administered to the patient. Temperature logs must be maintained to make sure that the drug supplies are stored at the correct temperatures. The Sponsor should be notified in case of temperature excursion of the drugs.

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access.

**Source Documents**

These comprise the patient's hospital case sheets; laboratory investigation reports, clinical assessments etc. These will be used to transcribe data onto the case record forms. These will have to be made available to the sponsor's representative at the time of monitoring in order that the case record forms are validated.

**Case Record Forms**

A copy of the approved Phase IV protocol & printed CRF (ANNEXURE II) will be supplied to participating investigators to record patient information, safety, immunogenicity and efficacy information. The investigator's assistant will transcribe the data from the source documents onto the CRF.

Case record forms should be updated at regular intervals, to ideally capture the entire duration of Hetero- Trastuzumab therapy (i.e., until treatment is discontinued or the patient is lost to follow- up) and up to 6 months or end of study, if it happens earlier.

### 10.4 Packaging and Labelling of Study Drug

The packaging and labeling of the study drugs will be as per local regulatory requirements. The labeling of the study drugs is as follows:

| | |
|---|---|
| Protocol No. | HCR/IV/TRUMAB/05/2022 |
| Route of Administration | Intravenous infusion |
| Batch Number | NA |
| Mfg Date | NA |
| Exp Date | NA |
| Manufactured by | Hetero Biopharma Limited,<br>Survey No. 458, TSIIC Pharma SEZ,<br>Polepally (V), Jadcherla (M), Mahboobnagar,<br>Telangana, India |
| Warning | "For Clinical Trial use only"<br>Not for Sale |

### 10.5 Dosing Schedule and Administration

Scheduled dosing and details of administration are detailed in section 7.6.

### 10.6 Dose Adjustments

The dose adjustments for Trastuzumab will be done as per the approved prescribing information and as per the investigators discretion.

Dose adjustments for other concomitant medications meant for indications other than studied indication will be permitted as per the prescribing information of the respective drugs / as per institutional practices/ PI discretion.

### 10.7 Drug Overdose

Since the study drugs are administered under the supervision of the investigator, over dosage is not expected to happen. In the unlikely event of over dosage of any of the study drugs, the management will be as per the local practices at the site

### 10.8 Concurrent Medication

Drugs taken by the patient for any concurrent diseases (e.g., Diabetes, Hypertension), and underlying medical conditions (e.g., Iron deficiency, Hyperkalemia, Hypocalcemia, Cancer) will be documented as concomitant drugs and as chemotherapy drug in the relevant section of the CRF.

Data on the drugs administered for the treatment of the underlying disease will also be captured.

## 11. ASSESSMENT OF SAFETY

### 11.1. Definitions

An Adverse Event/Experience [AE] is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign [including an abnormal laboratory finding, for example], symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

In accordance with the above definition, adverse events may include:

- Worsening [change in nature, severity or frequency] of conditions present at the onset of the study
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions present or detected prior to start of the study drug administration that does not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and / or convenience admissions).
- Overdose of either study drug or concomitant medication without any signs or symptoms.

A Serious Adverse Event [SAE] is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening*
- Results in persistent or significant disabling / incapacity
- Requires in-patient hospitalization or prolongation of existing hospitalization#
- Occurrence of congenital anomaly or birth defect if relevant
- Other important medically significant events that may not result in death, be immediately life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the well-being of the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

*The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

# "Inpatient hospitalization" does not imply that the patient must have had an overnight stay in the hospital. If the patient was admitted to the hospital for less than a day for the purpose of treatment or observation, the definition of "Inpatient hospitalization" is met, provided the patient is admitted solely for treatment of the event and not admitted for any social reasons, ease of compliance, day care procedures, or for medical or hospital records (insurance reimbursement) purpose. Although, brief treatment in an outpatient clinic or Emergency department does not constitute "inpatient hospitalization", depending on the intervention/treatment required for the event, it may satisfy the criteria of inpatient hospitalization to be reported as an SAE.

An Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information [e.g., Investigator's Brochure for an unapproved investigational medicinal product].

Events previously unobserved or undocumented must be classified as unexpected on this basis, and not based on what might be anticipated from the pharmacological properties of a medicinal product.

*The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.*

### 11.2. Classification of Adverse Events

**All adverse events will be classified, MedDRA coded and documented as per the grading system presented in CTCAE version 5 (NCI).**

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

**Components and Organization**

**SOC**

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

**CTCAE Terms**

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5 term is a MedDRA LLT (Lowest Level Term).

†CTCAE v5 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

**Definitions**

A brief definition is provided to clarify the meaning of each AE term.

**Grades**

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non - invasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Each CTCAE v5 term is a MedDRA LLT (Lowest Level Term).

**Life threatening:** any adverse drug experience that places the patient or patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

The adverse event once reported will not be closed out if it is of changing severity during the course. It will be reported with changes in the severity as it upgrades in follow up reports such that each upgraded sequelae will not be recorded as a new AE but continuation of same AE. Only the highest grade of severity will be considered for analysis purpose.

### 11.3. Clarification in Reporting of Deaths

All patient deaths (regardless of relationship to study drug) should be reported for patients while on the study. This should be recorded in the adverse event page of CRF and the SAE Reporting Form (Table 5 of New Drugs and Clinical Trials Rules, 2019). If a patient dies after signing consent but before the first dose of the study drug, this will also be recorded in the CRF. Death is an outcome of an adverse event and not an adverse event itself. All reports of patient death should include an adverse event term (other than "Death") for the cause of the death. If an adverse event term is not provided, the investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an adverse event can be obtained from the investigative site, "Death-Unknown cause" will be used as the event term.

### 11.4. Causality of the Adverse Event

The investigator's causality assessment should consider the potential etiologies for the observed adverse event. An adverse event may be related to the study drug, other concomitant medications, the underlying disease pathology, inter-current illness, a procedure performed during the study, or another reason. Among the potential etiologies, the investigator should decide based on the most likely causal relationship. When a causality assessment is provided for a serious adverse event, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures.

The investigator will make a judgment considering whether, in his opinion, the adverse event was related to the drug according to the following classification. However, even if

the investigator feels that there is no relationship to the drug, the adverse event should be reported.

The likelihood of the relationship of the adverse event to the study drug is to be recorded as follows.

**Definite:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [de-challenge] should be clinically plausible. The event must be definitive pharmacologically or as a logical phenomenon, using a satisfactory re-challenge procedure if necessary.

**Probable/Likely:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal [de-challenge]. Re-challenge information is not required to fulfill this information.

**Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

**Unlikely:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

**Conditional/Unclassified:** A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination

**Unassessable/ Unclassifiable:** A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

The investigator must keep in mind the below trial related, disease related and concomitant medication related factors when performing causality assessments.

- Trial related: Planned hospitalization for administration of study drugs, evaluation of disease and other trial related procedures.
- Disease related: Known complications of the study indication/progression of disease/ death due to known complications of the disease.
- Concomitant Medication related: Adverse events known to be associated with Paclitaxel/ Paracetamol/ Diphenhydramine/Ranitidine or Granisetron.

### 11.5. Laboratory Abnormalities

Abnormal laboratory findings (e.g., clinical chemistry, haematology) or other abnormal assessments (e.g., electrocardiogram, vital signs) per se are not reported as AEs. However, abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an adverse event as described previously, as per the classifications accorded in CTCAE version 5 (NCI) for laboratory AEs. Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug administration or that are present at baseline and worsen following the administration of study drug are included as AEs. The investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant.

### 11.6. Adverse Events Recording and Reporting

For all patients who are enrolled into this study, untoward events that occur following informed consent will be recorded in the AE page of the CRF. If a pre-existing AE continues during the study period and becomes more severe in nature, the date of AE onset shall be taken as the date when it became more severe. The date of onset will distinguish the event from a treatment-emergent adverse event and baseline. If an AE that occurs after study drug treatments have begun and is related to a study required procedure, the AE should be recorded on the AE CRF with a causality assessment of "not related to study drug".

### 11.7. Follow-Up of Adverse Events and Serious Adverse Events

Any AE/SAE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e. concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the outcome of an AE must be reported in the patient's medical record and recorded on the appropriate CRF page.

### 11.8. Serious Adverse Events Reporting

To ensure subject safety, every SAE, regardless of causality, occurring **after the subject signs the informed consent and until 30 days after** last dose of the study drug shall be reported to study sponsor within 24 hours of learning of its occurrence.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The Investigator must assess the relationship to study drug, complete the SAE Report Form (as per Table 5, New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19$^{th}$ March 2019) in English, and send the completed, signed form by fax/e-mail within 24 hours to sponsor, DCGI and Ethics Committee. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the documentation at the study site.

Recurrent episodes, complications, or progression of the initial SAE shall be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. Follow-up information needs to be sent by using a new SAE Report Form (as per Table 5, New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019) stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigators and the CRO/Sponsor shall report the reportable SAEs to other participating investigator, Ethics Committees and regulatory agencies as per the local applicable regulatory requirements.

For the sites in India, the investigator and the sponsor should report the complete SAE report after due analysis to the chairman of the ethics committee, licensing authority and head of the institution where the trial is conducted within the stipulated timelines as per the current guidelines and regulatory requirements.

All SUSARs may be reported to other relevant regulatory authorities if required as part of cross-reporting whenever Hetero Biopharma Limited or collaborator initiates clinical development of Hetero- Trastuzumab in countries other than India.

The details of the personnel involved in safety reporting will be enumerated in study specific Safety Management Plan. Questions pertaining to a specific SAE occurring in a study subject should be directed to the contact persons listed in the specific Safety Management Plan.

### 11.9. Pregnancies

To ensure subject safety, each pregnancy in a subject on study drug occurring after the subject begins taking study drug and until 30 days after the last dose of the study drug must be reported to Hetero Biopharma Limited within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any pregnancy occurring after signing the informed consent and before the patient is enrolled will be an exclusion criterion.

Pregnancy should be recorded on a Pregnancy Reporting and Outcome Form provided by the CRO/Sponsor and reported by the Investigator to the designated CRO/Sponsor.

A woman who becomes pregnant during the study will be immediately discontinued from study treatment. End of study assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following-up the pregnancy every 3 months until delivery or termination, informing the Sponsor about its outcome. Although pregnancy per se is not an AE, any associated complications or adverse outcome of pregnancy (including premature termination of pregnancy) should be reported as AEs or SAEs, as appropriate.

## 12. STATISTICAL ANALYSIS PLAN

The purpose of this study is to explore the overall safety, immunogenicity and efficacy of Trastuzumab post approval in the target populations under post marketing phase and provide the systematic data on the incidence rates of selected safety-related outcomes in the target population.

Summary statistics for continuous variables will include n, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. Summary statistics for discrete variables will be presented in terms of absolute and relative frequencies.

Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA).

### 12.1. Sample Size Determination

Hetero intends to submit data of approximately 200 prescribed patients of Hetero-Trastuzumab. Out of 200 patients, up to 100 patients will be evaluated for immunogenicity and efficacy (100 – Hetero- Trastuzumab).

### 12.2. Demographic Data

Patient demographic and baseline characteristic data will be described by means of absolute and relative frequencies for categorical variables and mean, standard deviation, minimum, and maximum for continuous variables. Relevant medical history/current medical condition data and any medications taken to treat these conditions will also be summarized by frequency of these conditions and treatments.

### 12.3. Analysis of the Main Variables

#### 12.3.1 Variables

The overall safety, immunogenicity and efficacy of Trastuzumab will be assessed based on adverse events, antidrug antibodies and efficacy response.

#### 12.3.2 Statistical Model and Method of Analysis

Data for the main variables will be presented using descriptive statistics and no statistical tests are planned.

### 12.3.3 Adverse Events/Serious Adverse Events

Adverse events will be analyzed with respect to incidence, causality, seriousness, (severity), expectedness and outcome.

The incidence of AEs (new or worsened from baseline) or SAEs and suspected treatment of interest related AEs will be summarized as frequency count and percentage of patients with AEs by primary system organ class, and preferred term.

In addition, the incidence of death, SAEs, AEs leading to discontinuation, and other significant AEs will be summarized separately by primary system organ class and preferred term.

The compiled report will be submitted to Drug Controller General of India (DCGI) as per New Drugs and Clinical Trials Rules, 2019 guidelines.

## 13. DATA AND SAFETY MONITORING BOARD [DSMB]

Not Applicable

## 14. PROTOCOL MODIFICATIONS, DEVIATIONS and AMENDMENTS

### 14.1. Deviations for a Patient

When a variation from the protocol is deemed necessary for an individual patient, the Investigator must contact the medical and safety monitor. Such contact with the monitor must be made as soon as possible to permit a decision as to whether the patient is to continue the study; any departure from the protocol will be authorized only for that patient. In the event of any drug-related toxicity or hazard to the patient's well-being, all possible measures should be taken to protect well-being and life of the patient, notwithstanding the possibility of dropout from the study and regardless of contact with/permission from medical and safety monitor in the trial. A description of the departure from the protocol and the reason(s) for it must be recorded in the patients' original records and Case Report Form.

The protocol deviation is defined as follows:

1. Major Protocol Deviation - Serious non-compliance with the protocol resulting in the exclusion of a patient from the study
2. Minor Protocol Deviation - Less serious non-compliance which needs adequate documentation

Possible reasons for protocol deviation include but not limited to:

1. Use of prohibited medication.
2. Informed consent signed after study procedures performed
3. Visits arranged outside the study window
4. Participants failing to comply with study requirements

All deviations from the approved protocol should be documented. The following details will be captured:

- Description of deviation
- Date of deviation
- Date reported and by whom
- Decision of Medical Monitor/ Hetero Biopharma Limited.

All protocol deviations will be reported to Hetero Biopharma Limited immediately to confirm patient continuation or withdrawal from the study.

The Investigator should not deviate from the protocol, except in the case of safety reasons. Hetero Biopharma Limited. will not assume any resulting responsibility or liability from unapproved deviations. The Investigator, according to applicable regulations and the ethics committee's established procedures, will inform the ethics committee of protocol deviations.

## 14.2. Amendments

### 14.2.1 Administrative Modifications

Administrative or technical modifications (like change in monitor or telephone numbers), which do not interfere with the patient's health interests will be in writing and filed as amendments to the protocol. The IRB/IEC must be informed by the investigator regarding every such amendment.

### 14.2.2 Clinical Modifications

Any change to the study protocol will require approval from the IRB/IEC prior to implementation except changes involving logistical or administrative aspects of the study, which will be notified to the IRB/IEC but will not require prior approval from the IRB/IEC. Any changes to the study protocol will be notified to regulatory authority along with IRB/IEC approval letters. The Sponsor and investigator will agree to implement/adhere to such modifications.

## 15. ADMINISTRATIVE MATTERS

### 15.1. Regulatory Approvals

Hetero will undertake the relevant regulatory approval procedures with DCGI before initiating this Phase IV study. The study protocol and associated documents (including investigator's participation agreement) shall be sent to DCGI for notification and/or approval, as per regulatory requirements.

### 15.2. Investigator's Agreement

Prior to participation in study, a Hetero representative will visit the selected investigator for signing up clinical trial agreement stating the investigator's approval to conduct the study according to the study plans provided by Hetero, as per New Drugs and Clinical Trials Rules, 2019 guidelines for clinical studies and later (after start of study) to obtain a case report for each patient participating in the study till the completion

### 15.3. Regulatory Issues and Reporting

Notification to DCGI regarding the conduct of this study shall be done before study initiation. As per applicable regulatory guidelines, the patient informed consent will be taken in this phase-4 study.

A phase-4 study report will be submitted to the Regulatory Authority and the safety data shall be included in the 6-monthly Periodic Safety Update Reports (PSURs). After two years, an annual status report will be submitted till another 2 years, whichever is earlier or as per applicable New Drugs and Clinical Trials Rules, 2019 specified guidelines.

Each investigator shall receive a copy of the regulatory approved Package insert/ Product leaflet/ Summary of Product Characteristics (containing the Prescribing Information) sheet containing details of Indications, Adverse Events, Contraindications and Dosage etc.

For recording the data generated during such a study, the Hetero standardized case record form (CRF) form (Annexure-II) shall be utilized and filled in by the investigators.

### 15.4. Patient Confidentiality

Confidentiality of patients' identifier information will be maintained.

### 15.5. Ethics

This study will be conducted according to the principles of the Declaration of Helsinki, (International Conference of Harmonization-Good Clinical Practices [ICH-GCP], New Drugs and Clinical Trials Rules, 2019 Gazette G.S.R.227 (E) dated 19th March 2019 and applicable regulatory laws governing biomedical research in human patients. Each institution will have an ethics committee approval before initiating the study and ethics committee will be providing continuous oversite to study conduct till completion. Patient's written informed consent will be taken prior to any study procedure being conducted.

# 16. DATA COLLECTION, DOCUMENTATION AND ARCHIVING OF STUDY DOCUMENTS

## 16.1. Study Initiation

After the Regulatory and Institutional Ethics Committee approval is available, a ***"Site Initiation Visit"*** will be held before the first patient is enrolled in the study. The patients cannot be recruited until occurrence of such visit and its documentation. During this visit requirements of GCP, protocol procedures and all logistic issues will be discussed at length. The training of Investigator team will be documented.

## 16.2. Study Monitoring and Source Data Verification

After the study is initiated, monitor(s) will periodically visit the site for monitoring visits. These visits would be agreed with prior appointment with the investigator. These monitoring visits will take place at regular intervals during the entire study, after prior appointment with the Investigators. The routine monitoring visits will be followed by a close out visit after the completion of all study visits.

After start of recruitment, the first ***"Routine Monitoring Visit"*** would occur as soon as possible after recruitment of the first patient.

The Investigator and his/her staff are obliged to set aside a suitable amount of time and place for the monitoring visits. During each monitoring visit, the monitor will review the case report forms of each patient in the study about completeness, thoroughness and compliance to the protocol and consistency with the patient's original records, which will be reviewed to make sure:

- Patient informed consent is incorporated
- Inclusion/exclusion criteria are properly fulfilled
- The CRF data is consistent with the patient's original records, which also must clearly indicate that the patient is included in a clinical study
- All relevant clinical and laboratory findings and concomitant medication are documented in the CRFs
- Quantity and dosing schedule of the study product is in accordance with the protocol

- All relevant information *(e.g., any AE)* has been recorded in the appropriate place in the CRFs
- The study product is being stored correctly, and its supply being properly accounted for.

### 16.3. Record Retention

The sponsor/CRO should archive all the data up to clinical evaluation for a period of at least five years after marketing approval by competent authority in India. The material that needs to be archived may include test substance, vehicle, plasma / serum, tissues, paraffin blocks, microscope slides, documents, electronic material etc. and the individual durations (e.g., test material until date of expiry). The designated authority, which will be responsible for archiving and can be approached for inspection or retrieval if required, should be indicated in the study report by the applicant.

### 16.4. Data Management

The data collected from all participating investigators will be pooled for analysis.

The study case report form (paper CRF/ eCRF) is the primary data collection source for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write/enter "NID". If the item is not applicable to the individual case, write/enter "N/A".

Data entered will be verified by the monitors in the database. In case the data entered does not match with the source documents, the monitor will raise a manual discrepancy in the database and route the same to the investigator/site coordinator. Batch validation will be run daily on the entire data to check for the discrepancies and errors generated will be reviewed and addressed by site coordinators/investigators. The data reviewer and the medical reviewer will review those fields manually where errors can be generated electronically. Manual discrepancies will be raised if required. All the discrepancies in the "RESOLVED" status (electronic and manual discrepancies created by Data Reviewer/Medical Reviewer and manually closed by the site personnel) will be reviewed by the data reviewer/medical reviewer for acceptability of resolutions in the database. Where it is felt that the discrepancy is not resolved correctly, the resolved discrepancy

will be routed back to the investigator/site coordinator to obtain correct resolution. The investigator will be solely responsible for approving the pages electronically.

Prior and concomitant medications will be entered into the database and will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Coexistent diseases and AEs will be coded using MedDRA, latest version at the time of coding.

Database will be locked and frozen once all the discrepancies are closed, pages are verified by the monitors and approved by the investigator.

Laboratory data capture will be determined by individual investigators in case of treatment emergent adverse events as and when these occur.

Drug interaction information will be analyzed based on the data provided for concomitant medication for any other indication.

All safety parameters, as described in the protocol shall be entered into the database, as per Hetero's SOPs.

The compiled report will be submitted to Drug Controller General of India (DCGI) as per New Drugs and Clinical Trials Rules, 2019 guidelines.

## 17. INSURANCE AND INDEMNITY

If a subject suffers injury or death directly attributable to participation in this study, appropriate treatment and/or compensation will be provided by and/or paid to the subject by the Sponsor in accordance with applicable law.

## 18. AUDITS AND INSPECTION

In addition to the above outlined monitoring visits the investigator site may be audited or inspected. The audit may be carried out by the Quality Assurance Department of Hetero Biopharma Limited or subcontractor. In addition, competent authorities may inspect the study. Subject confidentiality will be maintained always to the extent permitted by the law. Audits and Inspections are conducted to independently assess compliance to the protocol, SOPs *(Standard operating Procedures)*, ICH guidelines, regulatory requirements and any applicable guidelines. The Investigator will expeditiously inform Hetero Biopharma Limited of an inspection requested by a regulatory authority.

## 19. PATIENT CONFIDENTIALITY AND DATA PROTECTION

Hetero Biopharma Limited will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout the study and any subsequent analysis, all data reported will be identified only by protocol number, patient number and patient initials.

## 20. REPORT WRITING AND PUBLICATION

An integrated clinical study report according to ICH-E3 guidelines will be prepared. It will be signed by the investigator after mutual consent.

Publication of the study is independent of analysis results. Authorship will be determined by mutual agreement of study sponsor and participating investigators. Monitoring alone will not be considered as a sufficient criterion for a co-authorship.

Copies of any intended publication needs to be circulated to sponsor early enough (at least 15 work days for an abstract or an oral presentation, at least 45 work days for a manuscript) to confirm the following aspects:

- Accuracy of data and findings (to avoid potential discrepancies with submissions to regulatory authorities)
- To prevent confidential information being published in error
- To give the Investigator supplementary information of which he had been unaware
- To clarify the question of co-authorship

## 21. ANNEXURES

### ANNEXURE - I: Summary of Product Characteristics

Enclosed separately.

## ANNEXURE - II: Case Record Form of Hetero- Trastuzumab

Enclosed separately.

## ANNEXURE - III: RECIST CRITERIA V1.1 FOR SOLID TUMORS

- **EVALUATION OF TARGET LESIONS**

| Response category | Criteria |
|---|---|
| CR - Complete response | Disappearance of all target lesions |
| | Reduction in short axis of target lymph nodes to < 10 mm |
| PR - Partial response | Decrease in target lesion diameter sum ≥ 30%† |
| PD - Progressive disease | Increase in target lesion diameter sum ≥ 20%‡ |
| | ≥ 5 mm increase in target lesion diameter sum |
| | New, malignant FDG uptake in the absence of other indications of progressive disease or an anatomically stable lesion, and confirmed on contemporaneous or follow-up CT |
| | Unequivocal progression of non-target lesions |
| SD - Stable disease | Does not meet other criteria‡ |

*Measurements are based on the sum of the unidimensional measurement of the greatest diameter of a maximum 5 lesions.
†Reference standard: baseline sum.
‡Reference standard: smallest recorded sum

- **EVALUATION OF NON-TARGET LESIONS**

While some Non-target lesions may actually be measurable, they need not be measured and instead they can be qualitatively evaluated.

| Response category | Criteria |
|---|---|
| CR - Complete response | Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. |
| | All lymph nodes must be non-pathological in size. |
| PD - Progressive disease | Unequivocal progression of existing non-target lesions. |
| | Appearance of one or more new non-target lesions is also considered progression. |
| Non-CR/ non-PD | Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor market level above the normal limits |

## 22. REFERENCES

1. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life –threatening conditions - E1; Version Step 4; 199

2. Summary of product characteristics of Herceptin 600 mg solution for injection, available at https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdft accessed on 24th Mar 2021.