F. No. BIO/CT/19/000059
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

From,

The Drugs Controller General, India
Directorate General of Health Services,

FDA Bhawan Kotla Road,
New Delhi-110002

To,

M/s Aurobindo Biologics,
(A division of Aurobindo Pharma Ltd.),
Unit-17, Survey No.77&78, Indrakaran Village, Kandi Mandal,
Sangareddy District, Hyderabad-502329, Telangana, India

Subject: Application for grant of permission to conduct Phase III clinical trial entitled "A Multicenter, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Two Part, Phase III, Global Study to Evaluate the Pharmacokinetics, Efficacy and Safety of BP02 (Trastuzumab) in comparison with Herceptin-EU in Patients with HER2-Positive Early Breast Cancer (EBC) and HER2-Positive Metastatic Breast Cancer (MBC)" Protocol No: CR201-18, Version 1.0, Dated 25.06.2019 – regarding

Sir,

With reference to your application No. BIO/Form44/FF/2019/15556, dated 04.07.2019, please find enclosed herewith the permission in FORM CT-06 for conduct of subject mentioned Phase III clinical trial under the provisions of New Drugs and Clinical Trial Rules, 2019.

The permission granted by the Central Licensing Authority to conduct clinical trial under this Chapter shall be subject to following conditions, namely:

(i) Post Trial Access in both EBC (Part A) and MBC (Part B) should be ensured as per the Rules.

(ii) Clinical trial at each site shall be initiated after approval of the clinical trial protocol and other related documents by the Ethics Committee of that site, registered with the Central Licensing Authority under rule 8;

(iii) Where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial constituted in accordance with the provisions of rule 7:

Provided that the approving Ethics Committee for clinical trial shall in such case be responsible for the study at the trial site or the centre, as the case may be:

Provided further that the approving Ethics Committee and the clinical trial site or the bioavailability and bioequivalence centre, as the case may be, shall be located within the same city or within a radius of 50 kms of the clinical trial site;

(iv) In case an ethics committee of a clinical trial site rejects the approval of the protocol, the details of the same shall be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the clinical trial at the same site;

(v) The Central Licensing Authority shall be informed about the approval granted by the Ethics Committee within a period of fifteen working days of the grant of such approval;

(vi) Clinical trial shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the trial;

(vii) Clinical trial shall be conducted in accordance with the approved clinical trial protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and the provisions of these rules;

(viii) Status of enrolment of the trial subjects shall be submitted to the Central Licensing Authority on quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier;

(ix) Six monthly status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Central Licensing Authority electronically in the SUGAM portal;

(x) In case of termination of any clinical trial the detailed reasons for such termination shall be communicated to the Central Licensing Authority within thirty working days of such termination;

(xi) Any report of serious adverse event occurring during clinical trial to a subject of clinical trial, shall, after due analysis, be forwarded to the Central Licensing Authority, the chairperson of the Ethics Committee and the institute where the trial has been conducted within fourteen days of its occurrence as per Table 5 of the Third Schedule and in compliance with the procedures as specified in Chapter VI;

(xii) In case of injury during clinical trial to the subject of such trial, complete medical management and compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licensing Authority within thirty working days of the receipt of order issued by Central Licensing Authority in accordance with the provisions of the said Chapter;

(xiii) In case of clinical trial related death or permanent disability of any subject of such trial during the trial, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licensing Authority within thirty working days of receipt of the order issued by the Central Licensing Authority in accordance with the provisions of the said Chapter;

(xiv) The premises of the sponsor including his representatives and clinical trial sites, shall be open for inspection by officers of the Central Licensing Authority who may be accompanied by officers of the State Licensing Authority or outside experts as authorised by the Central Licensing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to

clinical trial and furnish reply to query raised by the said officer in relation to clinical trial;

(xv) Where the new drug or investigational new drug is found to be useful in clinical development, the sponsor shall submit an application to the Central Licensing Authority for permission to import or manufacture for sale or for distribution of new drug in India, in accordance with Chapter X of these rules, unless otherwise justified;

(xvi) The laboratory owned by any person or a company or any other legal entity and utilised by that person to whom permission for clinical trial has been granted used for research and development, shall be deemed to be registered with the Central Licensing Authority and may be used for test or analysis of any drug for and on behalf of Central Licensing Authority;

(xvii) The Central Licensing Authority may, if considered necessary, impose any other condition in writing with justification, in respect of specific clinical trials, regarding the objective, design, subject population, subject eligibility, assessment, conduct and treatment of such specific clinical trial;

(xviii) The sponsor and the investigator shall maintain the data integrity of the data generated during clinical trial.

(xix) The bulk drug to be used in the manufacturing of finished formulation intended to be used in the clinical trial and clinical trial batches of finished formulation shall be manufactured under GMP conditions using validated procedure and shall have ongoing stability programme.

Yours faithfully

V G SOMANI

Digitally signed by V G SOMANI
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Date: 2019.11.22 15:10:32 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

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 Aurobindo Biologics (A division of Aurobindo Pharma Ltd.), Unit-17, Survey No.77&78, Indrakaran Village, Kandi Mandal, Sangareddy District, Hyderabad-502329, Telangana, India** to conduct clinical trial of the new drug as per Protocol No: CR201-18, Version 1.0, Dated 25.06.2019 in the below mentioned clinical trial sites [as per Annexure].

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.

V G SOMANI

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Date: 2019.11.22 15:10:41 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Place: New Delhi
Date:

Annexure:

<table>
<tr><td>Names of the new drug or investigational new drug:</td><td>Trastuzumab powder for concentrate for solution for infusion Vial 150 mg</td></tr>
<tr><td>Therapeutic class:</td><td>Anticancer</td></tr>
<tr><td>Dosage form:</td><td>Powder for concentrate for solution for infusion</td></tr>
<tr><td>Composition:</td><td>
<table>
<tr><th>Ingredients</th><th>Quantity per vial</th></tr>
<tr><td>Trastuzumab (In house)</td><td>150 mg</td></tr>
<tr><td>L-Histidine HCL Monohydrate (BP , EP, JP, FCC)</td><td>3.4 mg</td></tr>
<tr><td>L-Histidine (BP, EP, USP, JP, FCC)</td><td>2.2 mg</td></tr>
<tr><td>α, α-Trehalose dihydrate (NF, EP, JP, ChP)</td><td>136.2 mg</td></tr>
<tr><td>Polysorbate 20 (BP,NF, EP, JP)</td><td>0.6 mg</td></tr>
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Each mL of reconstituted solution contains 21 mg/mL trastuzumab. The vial has to be reconstituted with 7.2 mL of water for injection
</td></tr>
<tr><td>Indications:</td><td>
Breast cancer
Metastatic breast cancer:
Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer: (MBC): -

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.
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.
in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer:
Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer.
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	(EBC). • following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) • following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. • in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. • in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. **Metastatic gastric cancer** Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Details of clinical trial sites:

S. No.	Names and address of clinical trial site	Ethics committee details	Name of principal investigator
1	Deenanath Mangeshkar Hospital & Research Centre, Erandawane, Pune, Maharashtra, 411004.	Institutional Ethics Committee, Deenanath Mangeshkar Hospital & Research Centre, Erandawane, Pune, Maharashtra, 411004. EC Reg No.: ECR/15/Inst/Maha/2013/RR-19	Dr. Dhananjay Kelkar
2	Noble Hospital Clinical Research Department, Noble Annex, Noble Hospital Pvt Ltd, 153, Magarpatta City Rd, Hadaspur, Pune, Maharashtra, 411013.	Noble Hospital Institutional Ethics Committee, Noble Annex, Noble Hospital Pvt Ltd, 153, Magarpatta City Rd, Hadaspur, Pune, Maharashtra, 411013. EC Reg No.: ECR/259/Inst/MH/2013/RR-16	Dr. Minish Jain
3	Department of Radiation Therapy and Oncology, Government Medical College and Hospital, Medical College Square Road, Nagpur, Maharashtra, 440003.	Institutional Ethics Committee, Department of Pharmacology, Government Medical College and Hospital, Medical College Square Road, Nagpur, Maharashtra, 440003. EC Reg No.: ECR/43/Inst/MH /2013/RR-19	Dr. Vijay Kumar Mahobia
4	Meenakshi Mission Hospital & Research	Institutional Ethics Committee, Meenakshi Mission Hospital	Dr. Ananda Selvakumar Pandy

	Centre, Lake Area, Melur Road, Madurai, Tamil Nadu, 625107.	&Research Centre, Lake Area, Melur Road, Madurai, Tamil Nadu, 625107. EC Reg No.: ECR/398/Inst/TN/ 2013/RR-19	
5	Grant Medical Foundation, Ruby Hall Clinic, 40, Sassoon Road, Pune, Maharashtra, 411001.	Poona Medical Research Foundation, E4-C to E4-F, 4th Floor, 5th Avenue, Condominium, Dhole Patil Road, Pune, Maharashtra, 411001. ECR Reg. No.: ECR/24/Inst/MH/2013/RR-19	Dr. Sadanand M Karandika
6	Jehangir Clinical Development Centre Pvt Ltd, Jehangir Hospital Premises, 32, Sassoon Road, Pune, Maharashtra, 411001.	Ethics Committee, Jehangir Clinical Development Centre Pvt Ltd, Jehangir Hospital Premises, 32, Sassoon Road, Pune, Maharashtra, 411001. EC Reg. No.: ECR/352/Inst/MH/2013/RR-16	Dr. Mangesh Mekha
7	St Theresa's Hospital, Erragadda, Sanathnagar, Hyderabad, Telangana, 500018.	Ethics Committee, St Theresa's Hospital, Erragadda, Sanathnagar, Hyderabad, Telangana, 500018. EC Reg. No.: ECR/230/Inst/AP/2013/RR-19	Dr. P. Venkata Sushma
8	Kolhapur Cancer Centre, R.S 238, Opp Mayur Petrol Pump, Gokul Shirgaon, Kolhapur, Maharashtra, 416234.	Kolhapur Cancer Centre Institutional Ethics Committee, Kolhapur Cancer Centre, R.S 238, Opp Mayur Petrol Pump, Gokul Shirgaon, Kolhapur, Maharashtra, 416234. EC Reg. No.: ECR/523/Inst/MH/2014/RR-17	Dr. Yogesh Anap
9	Health Point Hospital, 21, Prannath Pandit Street, (opp Lansdown Padmapukur), Kolkata, West Bengal, 700025.	Health Point Ethics Committee, 21, Prannath Pandit Street, (opp Lansdown Padmapukur), Kolkata, West Bengal, 700025. EC Reg. No.: ECR/284/Inst/WB/2013/RR-16	Dr. Kakali Choudhury
10	Sujan Surgical Cancer Hospital &Amravati Cancer Foundation, 52/B, Shankar Nagar, main Road, Amravati, Maharashtra	Amravati Ethics Committee, 52/B, Shankar Nagar, main Road, Amravati, Maharashtra. EC Reg. No.: ECR/432/Inst/MH/ 2013/RR-16	Dr. Rajendersingh Arora
11	North East Cancer Hospital and Research	Institutional Ethics Committee, Room No 4, Mezanine Floor,	Dr. Amit Kumar Dutta

	Institution, 11th Mile, Amerigog, Jorabat, Guwahati, Assam, 781023	North East Cancer Hospital and Research Institution, 11th Mile, Amerigog, Jorabat, Guwahati, Assam, 781023. EC Reg. No.: ECR/766/Inst/AS/ 2015	
12	Netaji Subhash Chandra Bose Cancer Hospital, 3081, Nayabad, New Garia, Kolkata, West Bengal, 700094.	Ethics Committee, Netaji Subhash Chandra Bose Cancer Hospital, 3081, Nayabad, New Garia, Kolkata, West Bengal, 700094. EC Reg No.: ECR/286/Inst/WB/2013/RR-16	Dr. Niharika Roy
13	Sahyadri Super Specialty Hospital, Hadapsar, Sr. No. 163, Bhosale Nagar, Hadapsar, Pune, Maharashtra, 411028	Sahyadri Hospitals Ltd Ethics Committee, Sahyadri Clinical Research & Development Centre, 33/34B, Makarand Bhave Path, Karve Road, Pune, Maharashtra-411004. EC Reg. No.: ECR/493/Inst/MH/2013/RR-16	Dr. Rahul Kulkarni
14	P.D.E.A's Ayurved Rugnalaya & Sterling Multispeciality Hospital, Sec No 27, Near BHEL Chowk, Nigdi Pradhikaran, Pune, Maharashtra, 411044.	Ethics Committee Sterling Hospital, P.D.E.A's Ayurved Rugnalaya & Sterling Multispeciality Hospital, Sec No 27, Near BHEL Chowk, Nigdi Pradhikaran, Pune, Maharashtra, 411044. EC Reg. No.: ECR/542/Inst/MH/2014/RR-2017	Dr. Rakesh Neve
15	Erode Cancer Centre Private Ltd, 1/393, Velavan Nagar, Perundurai Road, Thindal, Erode, Tamil Nadu, 638012.	Institutional Ethics Committee, Erode Cancer Centre Private Ltd, 1/393, Velavan Nagar, Perundurai Road, Thindal, Erode, Tamil Nadu, 638012. EC Reg. No.: ECR/319/Inst/TN /2013/RR-16	Dr. Velavan Kandappan