सत्यमेव जयते

Government of India
Central Drugs Standard Control Organisation(Headquarter)
(Directorate General of Health Services)
FDA Bhavan, ITO, Kotla Road
New Delhi - 110002 (Delhi)
Phone No.: 91-11-23216367
Fax No.: 91-11-23236973
E-Mail: dci@nic.in

File No. BIO/CT/22/000040 Dated 06-Dec-2022

To,
M/s Bristol-Myers Squibb India Pvt. Ltd.
One International Center, 6th Floor, Tower 1,
Senapati Bapat Marg, Elphinstone (West),
Mumbai – 400013, India

Subject: Application for grant of permission to conduct Phase IV clinical trial entitled –" A Phase 4 Study to Evaluate Safety and Effectiveness of Luspatercept (ACE-536) for the Treatment of Anemia due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic SyndromeS (MDS) with Ring Sideroblasts Who Require Red Blood Cell Transfusions in Subjects Who Have Had Unsatisfactory Response to or Are Ineligible to Erythropoietin Based Therapy and in Subjects With Transfusion Dependent Anemia Due to Beta-Thalassemia" as per Protocol Number: CA056023 ,Amendment no 01 dated 02 Sep 2022- regarding

Ref.:Your Application No BIO/CT04/FF/2022/31156 dated 06-Apr-2022

Sir,

With reference to your Application No BIO/CT04/FF/2022/31156 dated 06-Apr-2022, please find enclosed herewith the permission in Form CT-06 for conduct of subject Phase IV 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) 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;

(II) 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;

(III) 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;

(IV) 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;

(V) 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;

(VI) 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;

(VII) 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;

(VIII) 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;

(IX) 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;

(X) 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;

(XI) 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;

(XII) 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;

(XIII) 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;

(XIV) 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;

(XV) 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;

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

Yours faithfully,

VENUGOPAL G SOMANI

(Dr. V.G. Somani)

Drugs Controller General (India)

Digitally signed by VENUGOPAL G SOMANI
DN: c=IN, o=CENTRAL DRUGS STANDARD CONTROL ORGANIZATION, ou=DRUGS CONTROLLER GENERAL (INDIA), pseudonym=112046a34e21727bacb2557487 32c456d249073e55e953d9cb5b58748ee3113c, postalCode=110002, st=DELHI, serialNumber=e07f241ec2b3a4c3a3ca9f5b2d4d07a6b2f4b5c8d81cf282adeaf5d, cn=VENUGOPAL G SOMANI
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File. No. BIO/CT/22/000040

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 Licencing Authority hereby permits M/s Bristol-Myers Squibb India Pvt. Ltd. One International Center, 6th Floor, Tower 1,Senapati Bapat Marg, Elphinstone (West), Mumbai – 400013, India to conduct clinical trial of the new drug or investigational new drug study titled " A Phase 4 Study to Evaluate Safety and Effectiveness of Luspatercept (ACE-536) for the Treatment of Anemia due to IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic SyndromeS (MDS) with Ring Sideroblasts Who Require Red Blood Cell Transfusions in Subjects Who Have Had Unsatisfactory Response to or Are Ineligible to Erythropoietin Based Therapy and in Subjects With Transfusion Dependent Anemia Due to Beta-Thalassemia" as per Protocol Number: CA056023 ,Amendment no 01 dated 02 Sep 2022in 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.

Place: New Delhi
Date: 06-Dec-2022

VENUGOPAL G SOMANI (V G Somani)
Drugs Controller General (India)
Central Licencing Authority

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Date: 2022.12.07 15:59:59

Annexure:

Details of new drug or investigational new drug:

<table>
<tr><td>Name of the new drug to be imported:</td><td>Luspatercept powder for solution for injection: 25 mg and 75 mg</td></tr>
<tr><td>Dosage form:</td><td>Lyophilized Powder for solution for injection in vial</td></tr>
<tr><td>Composition:</td><td>Composition of Luspatercept powder for solution for injection: 25 mg and 75 mg
<table>
<tr><th>Component</th><th>25 mg/vial
(Amt. mg/vial)</th><th>75 mg/vial
(Amt. mg/vial)</th></tr>
<tr><td>Luspatercept (In-house specification)</td><td>37.5</td><td>87.5</td></tr>
<tr><td>Citric acid monohydrate USP/NF, Ph. Eur.,JP</td><td>0.127</td><td>0.296</td></tr>
<tr><td>Tri-sodium citrate Dihydrate USP/NF, Ph. Eur., JP</td><td>2.03</td><td>4.73</td></tr>
<tr><td>Polysorbate 80 USP/NF, Ph. Eur., JP</td><td>0.15</td><td>0.35</td></tr>
<tr><td>Sucrose USP/NF, Ph. Eur., JP</td><td>67.5</td><td>158</td></tr>
<tr><td>Hydrochloric acid USP/NF, Ph. Eur., JP</td><td>As needed</td><td>As needed</td></tr>
<tr><td>Sodium hydroxide USP/NF, Ph. Eur., JP</td><td>As needed</td><td>As needed</td></tr>
<tr><td>Water for Injection USP, Ph. Eur., JP</td><td>N/A [QS (quantity sufficient) to fill volume with water which was removed during lyophilization]</td><td>N/A [QS (quantity sufficient) to fill volume with water which was removed during lyophilization]</td></tr>
</table></td></tr>
<tr><td>Indication:</td><td><u>Myelodysplastic syndromes (MDS):</u>

Luspatercept is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.</td></tr>
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	β-thalassemia: Luspatercept is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta-thalassaemia.

Details of clinical trial site:

S. No.	Name and Address of Clinical Trial Site	Ethics Committee Details	Name of Principal Investigator
1	Department of Hematology Room No.5017, 5th Floor Teaching Block, All India institute of medical sciences, New Delhi-110029, India	Institutional Ethics Committee Room No.102,1st Floor, Old O.T.Block All India institute of Medical Sciences, New Delhi-110029, India EC Reg no: ECR/538/Inst/DL/2014/RR-20	Dr. Tulika Seth
2	Hemato Oncology Clinic Ahmedabad Pvt. Ltd,Vedanta Institute of Medical Science, Ground floor & First floor,Nr. Samved Hospital Stadium Commerce College Road, Navrangpura,Ahmedabad-380009, Gujarat, India	Ethics Committee of CIMS, Care Institute of Medical Sciences,Opposite Panchamrut Bunglows,Near Shukan Mall, Off science city Road,Sola, Ahmedabad - 380060, Gujarat, India EC Reg no: ECR/206/Inst/GJ/2013/RR-20	Dr. Shah Sandip Abhaykumar
3	Healthcare Global Enterprises Ltd,Haematology Department,4th floor,Tower-1,Clinical trial department,room no 512,5th floor,Tower-4,#8,HCG Towers,P.Kalinga Rao Road,Sampangiram Nagar,Bangalore-560027	HCG Central Ethics Committee,HCG - Bangalore institute of Oncology HCG Towers- Towers-I P. Kalinga Rao Road, Sampangiram Nagar, Bangalore - 560027, Karnataka, India EC Reg. No.: ECR/386/Inst/KA/2013/RR-19	Dr. Sachin Suresh Jadhav
4	Nehru hospital, 4 floor, F block, Department of clinical Hematology and Medical Oncology,Postgraduate Institute of Medical Education and Research, Sector 12 Chandigarh-160012 India	Institutional Ethics Committee, Post Graduate Institute of Medical Education and Research, Post Graduate Institute of Medical Education and Research Room No. 6006, IEC office, 6th floor, P N Chuttani block, Chandigarh - 160012, India EC Reg no: ECR/25/Inst/CH/2013/RR-20	Dr. Pankaj Malhotra
5	Department of Clinical Haematology,3rd floor, Gauhati Medical college & Hospital, Guwahati - 781032, Assam	Institutional Ethics Committee, Gauhati Medical college & Hospital, 2nd floor, GMC main building, Narakasur, Hilltop, Guwahati - 781032, Assam EC Reg no:ECR/549/Inst/AS/2014/RR-20	Dr. Jina Bhattacharyya
6	Basavatarakam Indo American Hospital ,Road no 10, Banjara hills, Hyderabad - 500034, Telangana, India	Institutional Ethics Committee, Basavatarakam Indo American Hospital, RI Road no 10, Banjara hills, Hyderabad - 500034, Telangana, India EC Reg no: ECR/7/Inst/AP/2013/RR-20	Dr. Pavan Kumar Boyella

7	Department of Haematology,4th floor, NRS Medical college 138, A.J.C. Bose Road, Kolkata - 700014, West Bengal, India	Institutional Ethics Committee, N.R.S. Medical College & Hospital ,NRS Medical college & hospital, NRS Medical college 138, A.J.C. Bose Road, Kolkata - 700014, West Bengal, India Ec reg no: ECR/609/Inst/WB/2014/RR-20	Dr. Tuphan Kanti Dolai
8	Department of Clinical Haematology,10th floor,Ward no 42,Room number 1002,Seth GS Medical College and KEM Hospital, Acharya Donde Marg, Parel - 400012, Mumbai, India	Institutional Ethics Committee- I New UG-PG Hostel,20 storey,Hostel Building,Ground floor, Seth GS Medical College and KEM Hospital, Acharya Donde Marg, Parel - 400012, Mumbai, India Ec reg no: ECR/229/Inst/MH/2013/RR-19	Dr. S. Chandrakala
9	Department of Hemato-Oncology & BMT,Rajiv Gandhi Cancer Institute and Research Centre ,2nd floor,D-block,Sector-5, Rohini sector V, Metro station, Delhi – 110085	Institutional Review Board - Rajiv Gandhi Cancer Institute and Research Centre sector V,rohini, Delhi – 110085 Ec reg no: ECR/10/Inst/DC/2013/RR-19	Dr. Dinesh Bhurani

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
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MINISTRY OF HEALTH, GOVERNMENT OF INDIA