File No: BIO/CT/20/000017
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FDA Bhawan, Kotla Road
New Delhi 110 002
Date : 19-AUG-2020

To,

M/s Baxalta Bioscience India Pvt.ltd,
6th Floor, Tower C, Building No.8 DLF Cyber City,
DLF Phase II Gurgaon (India) – 122002

Subject: Application for grant of clinical trial permission to conduct a Phase IV clinical trial titled "Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-Demand or Prophylaxis Under Standard Clinical Practice", vide Protocol Number: TAK-761-4009, Dated 31-JUL-2019 under the D&C Act and Rules thereunder-Regarding

Ref: Your application no. BIO/CT04/FF/2020/18740 dated 28-FEB-2020

Sir,

Please refer to your application no. BIO/CT04/FF/2020/18740 dated 28-FEB-2020, received by this office on the above subject. Please find enclosed herewith permission to conduct Phase IV clinical trial in Form CT-06 under the New Drugs and Clinical Trials Rules, 2019 along with the details of new drug and clinical trial sites.

Please acknowledge receipt of the same

Yours faithfully,

VENUGOPAL GIRDHARILAL SOMANI

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(Dr. V.G. Somani)
Drugs Controller General (India)

File No: BIO/CT/20/000017

Government of India

Directorate General of Health Services

Central Drugs Standard Control Organization

(Biological Division)

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 to M/s Baxalta Bioscience India Pvt.ltd, 6th Floor, Tower C, Building No.8 DLF Cyber City, DLF Phase II Gurgaon (India) – 122002 to conduct clinical trial of the new drug or investigational new drug as per protocol number: TAK-761-4009, Dated 31-JUL-2019 in the below mentioned clinical trial sites.-

Details of new drug or investigational new drug:	
Name of the new drug or investigational new drug:	Coagulation Factor VIII (Recombinant) rFVIII, Plasma/ Albumin Free Method; Octocog Alfa
Therapeutic class:	Antihaemorrhagics
Dosage form:	Powder and solvent for solution for injection
Composition:	1. Target composition of the final drug product reconstituted with 5 mL of Sterile Water for Injection (SWFI)- rFVIII (Octacog alfa) INH 250 IU/ 500 IU/ 1000 IU/ 1500 IU/ 2000 IU/ 3000 IU, α,α Trehalose, Ph.Eur. 0.8% (w/v), L-Histidine, Ph.Eur.10 mM, Tris (hydroxymethyl) aminomethane, Ph.Eur.10 mM, Sodium Chloride,Ph.Eur. 90 mM, Calcium Chloride, Ph.Eur.1.7 mM, Glutathione (Reduced), Ph.Eur.0.8mg/mL, Polysorbate 80 (Vegetable-derived), Ph.Eur.0.01% w/v, Mannitol, Ph.Eur. 3.2% w/v 2. Target composition of the final drug product reconstituted with 2 mL of Sterile Water for Injection (SWFI)- rFVIII (Octacog alfa) INH- 250 IU/ 500 IU/ 1000 IU/ 1500 IU α,α Trehalose, Ph.Eur. 2.0% (w/v), L-Histidine, Ph.Eur.25 mM, Tris (hydroxymethyl) aminomethane, Ph.Eur.25 mM, Sodium Chloride,Ph.Eur. 225 mM, Calcium Chloride, Ph.Eur.4.2 mM, Glutathione (Reduced), Ph.Eur. 0.2mg/mL, Polysorbate 80 (Vegetable-derived), Ph.Eur. 0.0025% w/v, Mannitol, Ph.Eur. 8.0 % w/v
Indications:	Treatment and prophylaxis of bleeding in patients with haemophilia A (Congenital factor VIII deficiency) in all age groups.

Details of clinical trial sites-

S.No.	Name and Address of Clinical Trial Site	Ethics Committee details	Name of Principal Investigator
1	Amrita Institute of Medical Sciences and Research centre , AIMS ,, Ponekkara POM Kochi Kerala - 682041	Institutional Ethics Committee Amrita Institute of Medical Sciences AIMS-Ponekkara Kochi Edappally Ernakulam Kerala EC Reg. No: ECR/129/Inst/KL/2013/RR-19	Neeraj Sidharthan
2.	St. John's Medical College, Instituional Ethical review Board (IERB) Ground Floor , St. John's Medical College Sarjapur Road, Bnagalore Karnataka - 560034	St. Johns Medical College Hospital Sarjapur Road Koramangala Bangalore Bengaluru (Bangalore) Urban Karnataka EC Reg. No: ECR/238/Inst/KA/2013/RR-19	Ross Cecil Reuben
	UNIQUE CHILDRENS HOSPITAL Pvt Ltd. Hira Moti Fortune Opp. Police station, Pune Mumbai Road Chinchwad Pune Maharashtra	UNIQUE CHILDRENS HOSPITAL Pvt Ltd. Hira Moti Fortune Opp. Police station, Pune Mumbai Road Chinchwad Pune Maharashtra EC Reg. No: ECR/1203/Inst/MH/2019	Sunil Devichand Lohade
3.	K. J. Somaiya Hospital and Research Centre, Sathgen Lab, 2nd Floor, College Building, Somaiya Ayurvihar Complex, Behind Everard Nagar, Eastern Express highway, Sion East Mumbai Maharashtra - 400022	K J Somaiya Medical College and Research Centre Chunabhatti Sion Mumbai EC Reg. No: ECR/138/Inst/MH/2013/RR-16	Savita Rangarajan

Conditions of permission for conduct of clinical trial—

The permission granted by the Central Licencing 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 Licencing 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 Licencing 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 Licencing 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 Licencing 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 Licencing 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 Licencing 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 Licencing Authority within thirty working days of the receipt of order issued by Central Licencing 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 Licencing Authority within thirty working days of receipt of the order issued by the Central Licencing 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 Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by the Central Licencing
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) 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 Licencing 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;

(XV) 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;

(XVI) The Central Licencing 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;

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

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

(XIX)TNF-alpha levels should be measured at the time of enrollment and during the study at appropriate time points.

(XX) Patients on biological including monoclonal antibody should be excluded from the study.

XXI) Data of Secondary bacterial infection should be assessed in the study

Yours faithfully,

VENUGOPAL GIRDHARILAL SOMANI

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Date: 2020.08.19 17:27:55 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (I)
Central Licencing Authority

Place: New Delhi
Date: 19-AUG-2020

(Protocol No.: TAK-761-4009, Dated 31-JUL-2019 File No: BIO/CT/20/000017)