File No. SND/CT/20/000011
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organisation
(Subsequent New Drugs Division)

FDA Bhawan, Kotla Road,
New Delhi-110002
Dated: 02 DEC 2020

To

M/s. Bayer Zydus Pharma Pvt. Ltd.,
Bayer House, Central Avenue, Hiranandani Estate,
Thane, Maharashtra (India) – 400607.

Subject: Permission for conducting Phase IV Clinical trial "RIVACA: A phase IV study to investigate the safety and effectiveness of Rivaroxaban (Xarelto) 2.5mg [BID] + Acetylsalicylic Acid(ASA) 75mg [OD] in Indian patients with coronary or symptomatic peripheral artery disease, (Protocol No. 21269, Version No: 2.0, Dated 07/09/2020) - Reg.

CT NOC No.: CT/SND/137/2020

Sir,

With reference to your Application No. SND/CT04/FF/2020/18674 dated 22.04.2020 please find enclosed herewith the permission in Form CT-06, CT NOC No. **CT/SND/137/2020** to conduct the subject mentioned clinical trial under the provisions of New Drugs and Clinical Trial Rules, 2019.

This permission is subject to the conditions, as mentioned below.

Yours faithfully,

(Dr. V. G. Somani)
Central Licensing Authority

Conditions of Permission

(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 of the New Drugs and Clinical Trials Rules, 2019;

(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 the Chapter VI of the said Rules 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 the 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) Informed Consent Documents (ICD) viz. Patient Information Sheet (PIS) and Informed Consent Form (ICF) complete in all respect & must be got approved from the respective Ethics committee and submitted to CDSCO before enrolling first subject at the respective site.

(xix) **In the protocol, exclusion criteria should be revised to also include the patients with Hemoglobin level less than 10 gm/dl and patients with history of GI bleeding. Accordingly, you are required to submit the revised protocol to CDSCO prior to initiation of the Phase IV clinical trial.**

FORM CT-06

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

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

CT NOC NO.: CT/SND/137/2020

The Central Licensing Authority hereby permits **M/s Bayer Zydus Pharma Pvt. Ltd., Bayer House, Central Avenue, Hiranandani Estate, Thane, Maharashtra (India) – 400607** to conduct clinical trial of the new drug ~~or investigational new drug~~ as per **Protocol No. 21269, Version No: 2.0, Dated 07/09/2020** in the below mentioned clinical trial sites.

2. Details of new drug or ~~investigational new drug~~:

Names of the new drug:	Rivaroxaban Tablets 2.5 mg
Therapeutic class:	Coagulants/Anticoagulants
Dosage form:	Tablets
Composition:	Each tablets contains: Rivaroxaban .....2.5 mg
Indications:	Rivaroxaban 2.5mg tablet, Co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Details of clinical trial sites

Sr. No.	Name of Principal Investigator & Trial sites	Ethics Committee Name/Registration Number
1	Dr. Samir Dani Department of Cardiology, at Apollo Hospitals International limited, Plot IA,Bhat,GIDC Estate Gandhinagar 382428, Gujrat.	Institutional Ethics Committee- Clinical Studies (IECCS) Apollo Hospitals, Ahmedabad Apollo Hospitals International Ltd Site Office Building ,Near ICICI ATM, Bhat, GIDC Estate, Gandhinagar-382428,Gujarat India; ECR/30/INST/GJ/2013/RR-16
2	Dr. Keyur Parikh CIMS Hospital, Near Shukan Mall, Off. Science City Road, Sola, Ahmedabad-380060.	Ethics Committee of Care Institute of Medical Sciences , Near Shukan Mall, Off. Science City Road, Ahmedabad-380060, Gujarat. ECR/206/Inst/GJ/2013/RR-16
3	Dr. Kamal Sharma Sanjivanisuperspeiclaity hospital Pvt Ltd, 1- Uday, Park Society Nr Sunrise Park, Vastrapur Ahmedabad- 380015 Gujarat.	INSTITUTIONAL ETHICS COMMITTEE B.J. MEDICAL COLLEGE AND CIVIL HOSPITAL OFFICE OF MEDICAL SUPERINTENDENT CIVIL HOSPITAL Ahmedabad - 380016, Gujarat. ECR/72/Inst/GJ/2013/RR-19
4	Dr. Ramakrishna Pinjala Apollo Hospital Jubilee Hills Hyderabad OPD Room no. 9071 , 500096	Institutional Ethics Committee - Clinical Studies Apollo Hospitals Enterprise Limited, Hyderabad Apollo Research and Innovations, Jubilee Hills Apollo Health City, Hyderabad Shaikpet Hyderabad Telangana

5	Dr. V Balaji Apollo Hospital, 21,Greams Lane Off Greams Road, Chennai 600006.	Institutional Ethics Committee - Clinical Studies Apollo Hospital Enterprises Ltd. No. 21Greams Lane, Off Greams Road, Chennai 600006, Tamil Nadu. ECR/37/Inst/TN/2013/RR-16
6	Dr. Prafulla Kerkar KEM hospital & Seth GS Medical college, 4th floor, CVTC Building, Department of Cardiology, Acharya, Donde Marg, Parel 400012.	Institutional Ethics Committee-I, Seth GS Medical college, 4th floor, CVTC Building, Department of Cardiology, Acharya Donde Marg, Parel, Mumbai 400012. ECR/229/Inst/MH/2013/RR-19
7	Dr. Sandeep Bansal Safdarjung Hospital, Safdarjung Campus, Safdarjung, New Delhi, Delhi 110029.	Institute Ethics Committee, At Room No. 17A, Ground Floor,College building, VMMC and Safdarjung Hospital, New Delhi, 110029, India ECR/593/Inst/DL/2014/RR-17
8	Dr Vijayraghavan Kerala Institute of Medical, Sciences, P.B.No.1, Anayara P.O., Thiruvananthapuram 695029. Kerala, India.	Institutional Human Ethics Committee Kerala Institute of Medical Sciences, Offices of the SOCOMER, Main Building, 11th Level, Rm.No. 1119 M, P.B.No.1, Anayara P.o., Thiruvananthapuram - 695029. Kerala ECR/184/KIMS/Inst/Ker/2013/RR-16

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.

(Dr. V. G. Somani)
Central Licensing Authority
Stamp

डॉ. वी. जी. सोमानी
औषधि महानियंत्रक (भारत)
स्वास्थ्य सेवा महानिदेशालय
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
एफ.डी.ए. भवन, कोटला रोड, आई.टी.ओ
नई दिल्ली-110002

New Delhi
Date: 02 DEC 2020