File No. CT/55/21-DCG(I)

GOVERNMENT OF INDIA
CENTRAL DRUGS STANDARD CONTROL ORGANISATION (Headquarter)
(Directorate General of Health Services)
Ministry of Health & Family Welfare
FDA Bhavan
ITO, Kotla Road
New Delhi - 110002 (Delhi)
Phone No.: 91-11-23216367
Fax No.: 91-11-23236973
E-Mail : dci@nic.in

सत्यमेव जयते

File No. CT/21/000055

To,

M/s Pharmaceutical Research Associates India Private Limited,
A 603, The Qube, CTS No 1498, A/2, MV Road Marol,
Andheri (East) Mumbai (India) - 400059

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Sir,

With reference to your application No. GCT/CT04/FF/2021/24796 (GCT/55/21) dated 19-05-2021, please find enclosed herewith the permission in Form CT-06 for conduct of clinical trial titled, "**A Phase 3, Multi-center, Randomized Study Evaluating Efficacy of TAR-200 in Combination With Cetrelimab Versus Concurrent Chemoradiotherapy in Participants With Muscle-Invasive Urothelial Carcinoma (MIBC) of the Bladder who are not Receiving Radical Cystectomy", Protocol Number: 17000139BLC3001, Amendment 1 dated 18/September/2020** under the provisions of New Drugs and Clinical Trial Rules, 2019

The permission granted by the Central Licensing Authority to conduct clinical trial 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 permission to initiate clinical trial granted under rule 22 in form CT-06 or automatic approval under rule 23 in Form CT 4A shall remain valid for a period of **two years** from the date of its issue, unless extended by the Central Licencing Authority.

Yours faithfully,

VENUGOPAL GIRDHARILAL SOMANI

Digitally signed by VENUGOPAL GIRDHARILAL SOMANI
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Date: 2021.09.03 16:54:44 +05'30'

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

File No. CT/55/21-DCG(I)

FORM CT-06

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

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

1. The Central Licensing Authority hereby permits **M/s. Pharmaceutical Research Associates India Pvt Ltd, The Qube, A-603, C.T.S. No. 1498 A/2 M.V. Road, Marol, Andheri (East) Mumbai, 400 059, India** to conduct clinical trial of the new drug or investigational new drug as per **Protocol Number: 17000139BLC3001, Amendment 1 dated 18/September/2020** in the below mentioned clinical trial sites [As per Annexure].-

2. Details of new drug or investigational 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 _____

VENUGOPAL GIRDHARILAL SOMANI

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

Note: The permission to initiate clinical trial granted under rule 22 in form CT-06 shall remain valid for a period of **two years** from the date of its issue, unless extended by the Central Licencing Authority.

Annexure:
Details of new drug or investigational new drug:

Names of the new drug or investigational new drug	JNJ-17000139 Gemcitabine 225 mg intravesical delivery system (TAR-200) JNJ-63723283 (Cetrelimab)
Therapeutic class:	Anticancer agent
Dosage form:	JNJ-17000139 Gemcitabine 225 mg intravesical delivery system (TAR-200) – Intravesical Drug Delivery System (225 mg of gemcitabine) JNJ-63723283 (Cetrelimab)– Lyophilized product for reconstitution (240mg/vial in 30mL)

Composition:	JNJ-17000139 Gemcitabine 225 mg intravesical delivery system(TAR-200) is a passive, non-resorbable investigational drug-device combination product, whose primary mode of action is the controlled release of gemcitabine into bladder urine during the indwelling period. The TAR-200 product is a co-packaged drug device combination product consisting of two components. • The first component is a single integral drug-device combination product that is being developed as an intravesical drug delivery system for controlled release of a drug constituent into the bladder. As such, the single integral drug-device combination product drug delivery system is anticipated to be regulated with a drug primary mode of action The drug constituent of TAR-200 consists of gemcitabine mini tablets (225 mg, free base equivalent), and osmotic mini tablets containing Urea as the osmotic agent. The device constituent of TAR-200 is comprised of a dual lumen silicone part with a single laser machined orifice and a super elastic nitinol wire. The large lumen of the silicone part contains the gemcitabine and urea mini tablets and serves as an elementary osmotic pump to release drug in a controlled manner. The smaller lumen contains the nitinol wire in a predefined form to provide retention of the system in the bladder during the indwelling period. • The single integral drug-device combination product is co-packaged with an accessory device (the second component of the TAR-200 product), the Urinary Placement Catheter (also called the inserter), to allow nonsurgical transurethral placement of the intravesical drug delivery system into the bladder. The inserter is considered as an accessory to the drug delivery system, designed specifically to be used with the integral drug device combination product only, for transient use. The inserter will not be commercialized as a stand-alone device. Please refer to the enclosed Instructions to Reviewers for reference to technical documents and essential information pertaining to the inserter. TAR-200 is packaged within 2 pouches. The product is first sealed in a Tyvek pouch which serves as the primary sterile barrier, sterilized by gamma irradiation, then followed by a foil over-pouch that is used to provide moisture control. The Urinary Placement Catheter is packaged in a Tyvek pouch and sterilized using ethylene oxide. Tables 2 and 3 (page 44) of the IMPD (v4.0 dated 23Oct2020) lists the compositions of the drug constituents gemcitabine and osmotic mini tablets in TAR-200 and Table 1 (page 43) of the IMPD lists the components of the device constituent. *JNJ-63723283 Cetrelimab* is a novel fully human immunoglobulin G4 (IgG4) kappa monoclonal antibody (mAb) containing the hinge-stabilizing S228P mutation. Cetrelimab binds to programmed cell death protein-1 (PD-1) with high affinity and specificity, blocks binding to the programmed-cell death

	ligands 1 and 2 (PD-L1 and PD-L2), enhances pro-inflammatory cytokine production from ex-vivo stimulated T-cells, and reduces tumor volume in human PD-1 knock-in (hPD-1KI) mice bearing MC38 murine colon carcinoma tumors. Cetrelimab will be packaged as a final lyophilized product for reconstitution, in 30mL Type I borosilicate glass vials. Each vial contains 240mg of lyophilized product. Table 1(page233of the IMPD(v5.0)lists the composition of the Cetrelimab 240 mg Lyophilized Drug Product
Indications:	Muscle invasive urothelial carcinoma of the bladder

Annexure:

Details of clinical trial site:

Sr. No.	Names and address of clinical trial site	Ethics committee details	Name of investigator
1.	Dept. of Urology, Uro-Science Centre, S.P. Medical College & A.G. of Hospitals, Bikaner-334003, Rajasthan	Ethics Committee, S.P. Medical College & A.G. of Hospitals, Pawanpuri, Bikaner-334003, Rajasthan ECR/27/Inst/RJ/2013/RR-16	Dr. M.C. Arya
2.	Apex Wellness Hospital Sarvey No. 799, Plot no 187, Behind Prakash Petrol Pump, Govind nagar, Nashik-422009, Maharashtra, India	Apex Wellness Ethics Committee (AWEC) C/o Apex Wellness Hospital, Survey 799, Govindnagar, Nashik Maharashtra-422009 ECR/1500/Inst/MH/2021	Dr. Shailesh Arjun Bondarde
3.	Aakash Healthcare Pvt. Ltd., Hospital Plot, Road No. 201, Sector 3, Dwarka, New Delhi-110075	Aakash Healthcare Super Speciality Hospital Institutional Ethics Committee, Department of Academic & Research Development, Basement 1, Near Ultrasound, Hospital Plot, Road No. 201, Sector 3, Dwarka, New Delhi-110075, India ECR/1265/Inst/DL/2019	Dr. Chandragouda Dodagoudar
4.	Department of Medical Oncology & BMT, R K Birla Cancer Center, SMS Hospital, Jaipur-302004	Ethics Committee of SMS Medical College & Attached Hospitals, Office of Ethics Committee, Allergy Clinic, SMS Hospital, JLN Marg, Jaipur-302004 ECR/26/Inst/RJ/2013/RR-19	Dr. Sandeep Jasuja

5.	Post Graduate Institute of Medical Education and Research, Chandigarh, Sec-12, Pin-160012	Institutional Ethics Committee, Room No. 6006, Sixth Floor, PN Chutani Research Block B, PGIMER, Sector-12, Chandigarh-160012 ECR/25/Inst/CH/2013/RR-20	Dr. Shrawan Kumar Singh
6.	Jehangir Clinical Development Centre Pvt. Ltd., Jehangir Clinical Premises 32, Sassoon Road, Pune-411001, Maharashtra, India	Ethics Committee Jehangir Clinical Development Centre Pvt. Ltd., Jehangir Hospitall Premises 32, Sassoon Road, Pune-411001, Maharashtra, India ECR/352/Inst/MH/2013/RR-19	Dr. Balchandra Dattatraya Kashyapi
7.	State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar-800014,India	Institutional Ethics Committee, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna 800014,Bihar ECR/640/Inst/BR/2014	Dr. Rajesh Kumar Singh
8.	Rajiv Gandhi Cancer Institute and Research Centre, Sector-5, Rohini, New Delhi 110085, India	Institutional Review Board, Rajiv Gandhi Cancer Institute and Research Centre Sector-5, Rohini, New Delhi -110085 ECR/10/Inst/DC/2013/RR-19	Dr. Sudhir Kumar Rawal