



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

File No. CT/21/000171

To,

M/s. Roche Products (India) Private Limited,
146 B, 166 A, Unit No 7,8,9, 8th floor, R city office,
R City Mall Lal Bahadur Shastri Marg,
Ghatkopar (West) Mumbai (India) – 400086.

Sir,

With reference to your application No. GCT/CT04/FF/2021/29557 (GCT/171/21) dated 21-12-2021, please find enclosed herewith the permission in Form CT-06 for conduct of clinical trial titled, **“RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE III STUDY OF ENTRECTINIB VERSUS CRIZOTINIB IN PATIENTS WITH LOCALLYADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING ROS1GENE REARRANGEMENTS WITH AND WITHOUT CENTRAL NERVOUS SYSTEM METASTASES”**, Protocol number: MO41552 Version 4.0, dated 28-Sep-2021 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) Merely granting permission to conduct the clinical trial with the Investigational Drug Product does not convey or imply that, based on the clinical trial study data generated with the investigational drug, permission to market this drug in the country will automatically be granted to you;
- (xix) 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 G SOMANI
Dr. V. G. (Soman)
Drugs Controller General
Central Licensing Authority
SOMANI

Digitally signed by VENUGOPAL G SOMANI
DN: c=IN, o=CENTRAL DRUGS STANDARD
CONTROL ORGANIZATION, ou=DRUGS
(Dr. V. G. Soman)
pseudonym=112046a34e21727bacb255748
133c, postalCode=110092, st=DELHI,
serialNumber=971211a0c00ba11522525ff
ca0705074b4997e6b245c8d81cf282adeaf
5d, cn=VENUGOPAL G SOMANI
Date: 2022.03.14 15:29:24 +05'30'

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

1. The Central Licensing Authority hereby permits **M/s. Roche Products (India) Private Limited, 146 B, 166 A, Unit No 7, 8, 9, 8th floor, R city office, R City Mall Lal Bahadur Shastri Marg, Ghatkopar (West) Mumbai (India) – 400086** to conduct clinical trial of the new drug or investigational new drug as per **Protocol number: MO41552 Version 4.0, dated 28-Sep-2021** 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 _____

**VENUGO
PAL G
SOMANI v. G. Somani**
Drugs Controller General (India)
Central Licencing Authority
Stamp

Digitally signed by VENUGOPAL G SOMANI
DN: c=IN, o=CENTRAL DRUGS STANDARD
CONTROL ORGANIZATION, ou=DRUGS
CONTROLLER GENERAL (INDIA),
pseudonym=112046a34e21727bacb25574
87332c456d249073e5e953d9cb5b58748ee
3113c, postalCode=110002, st=DELHI,
serialNumber=e97241aa0c0bba41522525f
fca0705074b4997e6b2f4b5c8d81cf282adea
f5d, c=VENUGOPAL G SOMANI
Date: 2022.09.28 14:44:11 +05'30'

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	1. Entrectinib capsules 100mg 2. Entrectinib capsules 200mg 3. Crizotinib hard capsules 200mg 4. Crizotinib hard capsules 250mg
Therapeutic class:	Anti-neoplastic agents, protein kinase inhibitors
Dosage form:	Capsules
Composition:	<u>Capsule Fill Mass</u> Entrectinib 100.00mg In-house Active Lactose anhydrous 65.00mg USP/NF, Ph. Eur., JP In-active Microcrystalline cellulose 6.685mgUSP/NF, Ph. Eur., JP In-active Tartaric acid 29.50mgUSP/NF, Ph. Eur., JP In-active Hypromellose 9.00mgUSP/NF, Ph. Eur., JP In-active Crospovidone 11.875mgUSP/NF, Ph. Eur., JP In-active Magnesium stearate 2.375mgUSP/NF, Ph. Eur., JP In-active Colloidal silicon dioxide 0.565mgUSP/NF, Ph. Eur., JP In-active

Capsule Shell

Body

Hypromellose 35.9818mg USP/NF, EU 231/2012, Ph. Eur., JP In-active
Titanium dioxide (E171, CI77891) 0.5338mgUSP/NF, EU 231/2012, Ph. Eur., JP In-active

Yellow iron oxide (E172, CI77492) 0.084mgUSP/NF, EU 231/2012, JPE In-active

Cap

Hypromellose 23.9878mg USP/NF, EU 231/2012, Ph. Eur., JP In-active
Titanium dioxide (E171, CI77891) 0.3559mgUSP/NF, EU 231/2012, Ph. Eur., JP In-active

Yellow iron oxide (E172, CI77492) 0.0563mgUSP/NF, EU 231/2012, JPE In-active

Printing Ink Trace amount NA (In-active)

Capsule Fill Mass

Entrectinib 200.00mg In-house Active

Lactose anhydrous 130.00mg USP/NF, Ph. Eur., JP In-active

Microcrystalline cellulose 13.37mg USP/NF, Ph. Eur., JP In-active

Tartaric acid 59.00mgUSP/NF, Ph. Eur., JP In-active

Hypromellose 18.00mgUSP/NF, Ph. Eur., JP In-active

Crospovidone 23.75mg USP/NF, Ph. Eur., JP In-active

Magnesium stearate 4.75mgUSP/NF, Ph. Eur., JP In-active

Colloidal silicon dioxide 1.13mg USP/NF, Ph. Eur., JP In-active

Capsule Shell

Body

Hypromellose 56.3918mgUSP/NF, EU 231/2012, Ph. Eur., JP In-active

Titanium dioxide (E171, CI77891) 0.8756 mg USP/NF, EU 231/2012, Ph. Eur., JP In-active

FD&C Yellow #6 (E110, CI15985) 0.3326 mg 21 CFR, EU 231/2012, JFSA, In-active

Cap

Hypromellose 37.5945mg USP/NF, EU 231/2012, Ph. Eur., JP In-active

Titanium dioxide (E171, CI77891) 0.5838mg USP/NF, EU 231/2012, Ph. Eur., JP n-active

FD&C Yellow #6 (E110, CI15985) 0.2217mg 21 CFR, EU 231/2012, JSFA In-active

Printing Ink Trace amount NA (In-active)

Active ingredient-Crizotinib

Excipients-

Capsule content: Colloidal anhydrous silica, Microcrystalline cellulose, Anhydrous calcium hydrogen phosphate, Sodium starch glycolate (Type A), Magnesium stearate

Capsule shell: Gelatin, Titanium dioxide (E171), Red iron oxide (E172)

File No. CT/171/21-DCG(I)

	Printing ink: Shellac, Propylene glycol, Potassium hydroxide, Black iron oxide (E172) <u>Active ingredient</u>-Crizotinib <u>Excipients</u>- Capsule content: Colloidal anhydrous silica, Microcrystalline cellulose, Anhydrous calcium hydrogen phosphate, Sodium starch glycolate (Type A), Magnesium stearate Capsule shell: Gelatin, Titanium dioxide (E171), Red iron oxide (E172) Printing ink: Shellac, Propylene glycol, Potassium hydroxide, Black iron oxide (E172)
Indications:	For patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer Harboring ROS1 gene rearrangements with and without Central Nervous System Metastases

Annexure:

Details of clinical trial site:

Sr. No.	Names and address of clinical trial site	Ethics committee details	Name of investigator
1.	Tata Medical Center, 14-Mar (EW), New Town, Rajarhat, Kolkata-700160, West Bengal, India	Institutional Review Board, Tata Medical Center, 14-Mar (EW), New Town, Rajarhat, Kolkata-700160, West Bengal, India ECR/269/Inst/WB/2013/RR-19	Dr. Bivas Biswas
2.	Mumbai Oncocare Centre (Unit of Cellcure Cancer Centre Pvt. Ltd) 2 nd Floor, Majithia Apartments, God's Gift Premises Co-op. society Ltd, S V Road, Irla, Vile Parle (W) Mumbai-400056	Mumbai Oncocare Centre Institutional Ethics Committee, 2nd Floor, Majithia Apartments, God's Gift Premises Co-op. society Ltd, S V Road, Irla, Vile Parle (W) Mumbai-400056 ECR/1277/Inst/MH/2019	Dr. Vashishth Maniar
3.	MVR Cancer Centre and Research Institute, CP 13/516 B.C. Vellalasseri, REC (via) Poolacode, Kozhikode, Kerala-673601, India	Institutional Ethics Committee, MVR Cancer Centre and Research Institute, CP 13/516 B.C. Vellalasseri, REC (via) Poolacode, Kozhikode, Kerala-673601, India ECR/1259/Inst/KL/2019	Dr. Narayanankutty Warriar
4.	Room No. 245, Dept. Of Medical Oncology, 2 nd Floor, Dr. B. R. Ambedkar Institute Rotary cancer Hospital, All India Institute of Medical	Institute Ethics Committee, Room No. 102, 1 st Floor, Old O.T. Block, AIIMS, Ansari Nagar, New Delhi-110029	Dr. Prabhat Singh Malik

File No. CT/171/21-DCG(I)

	Sciences, Ansari Nagar, New Delhi-110029	ECR/538/Inst/DL/2014/RR-20	
5.	Department of Oncology, Christian Medical College, Ida Scudder Road, Vellore-632004, Tamil Nadu, India	Institutional Review Board (Ethics Committee-Silver) Christian Medical College, Office of Research, First Floor, Carman Block, Bagayam, Vellore-632002 ECR/326/INST/TN/2013/RR-19	Dr Anjana Joel
6.	Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research (PGIMER), Sector 12, Chandigarh, India-160012	Institutional Ethics Committee, Room No. 6006, Sixth Floor, Research Block B, PGIMER, Sector 12, Chandigarh, 160012 ECR/25/Inst/CH/213/RR-20	Dr. Navneet Singh
7.	American Oncology Institute, 1-100/1/CCH Citizens Hospital Road, Near Aparna Sarovar, Nalagandla, Hyderabad, Telangana-500019	Citizens Institutional Ethics Committee, Citizens Speciality Hospital, 1-100/1/CCH Citizens Hospital Road, Nallagandla, Serilingampally Hyderabad, Ranga Reddy, Telangana-500019, India ECR/1103/Inst/TG/2018/Rr-21	Dr. Naidu Norman Bethune