MINUTES OF 28th MEETING OF THE TECHNICAL COMMITTEE HELD ON 21.08.2015 UNDER THE CHAIRMANSHIP OF DGHS FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA ON 03.01.2013.

Present:

1.	Dr. Jagdish Prasad, Director General of Health Services, Nirman Bhawan, New Delhi	Chairman
2.	Dr. Ranjit Roy Chaudhury, National Professor of Pharmacology, Former Member, BOG – MCI, Y-85, Hauz Khas, New Delhi-110 016.	Member
3.	Dr.Rajutitus Chacko, Prof. & Head, Dept. of Medical Oncology, CMC, Vellore	Member
4.	Dr. Ashok Kumar Das, Professor of Medicine & Professor and Head of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry – 605014	Member
5.	Dr. Yash Paul, Prof. & Head, Dept. of Cardiology, PGIMER, Chandigarh.	Member
6.	Dr. Kamlakar Tripathi, Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005	Member
7.	Dr. Nandini Kumar, Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, 5/1 (New) Padmalaye Apt. Chennai.	Member
8.	Dr. B.L. Sherwal, Addl. MS (T) & Director-Professor, Dept. of Microbiology, LHMC & Associated Hospitals, New Delhi.	Member
9.	Dr. Nikhil Tandon, Professor, Dept. of Endocrinology & Metabolism, AIIMS, New Delhi.	Member

From CDSCO:

1. Dr. V. G. Somani,
   Joint Drugs Controller (I)
2. R. Chandrashekar
   Deputy Drugs Controller (I),
3. Mrs. Annam Visala
   Deputy Drugs Controller (I)
4. Mrs. Rubina Bose
   Deputy Drugs Controller (I)

The Chairman welcomed the members of the meeting and Dr. V. G. Somani, JDC (I) initiated the proceedings of the Committee.

First, chairman stated to indicate date of application of proposals in the documents ,thereafter , the Committee discussed the clinical trial proposals one by one as under:

The Committee deliberated 19 cases related to approval of clinical trials. Out of these 19 cases, 03 cases were related to clinical trials of NCEs, 04 cases (03 fresh cases and 01 case for re-deliberation) were related to global clinical trials (GCT). Remaining 12 cases were related to clinical trials for approval of New Drugs, Subsequent New Drugs and biologicals.

1. <u>Proposals of Clinical Trials of NCEs recommended by SECs / IND.</u>

The Committee evaluated the 03 cases related to clinical trial of NCEs and made recommendations considering all aspects of safety, efficacy especially in terms of the three parameters viz. risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical need in the country. After detailed deliberation, the Committee recommended 02 cases out of the 03 cases of NCEs. In the remaining case **(S. No 02 at Annexure-I)**, the Committee deferred the proposal for additional information. The recommendation of the Committee is enclosed as **Annexure-I.**

2. <u>Proposals of Clinical Trials of GCT recommended by SECs / IND.</u>

Thereafter, the Committee evaluated 04 cases related to global clinical trial. After detailed deliberation, the Committee recommended all the four cases. The recommendation of the Committee is enclosed as **Annexure-II.**

3. <u>Proposals of Clinical Trials other than GCT/ NCEs recommended by SECs / IND.</u>

The Committee evaluated the remaining 12 cases of other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of all 12 cases. Of the 12 cases, 02 cases **(S. No 06 and 10 at Annexure-III)** were recommended subject to certain condition. The recommendations of the Committee in respect of these 12 cases are enclosed as **Annexure-III.**

Thus, the Committee recommended for approval of 18 cases, out of total 19 cases of clinical trial proposals.

4. Others:

a) Re-deliberation of the proposal of M/s Bharat serum based on the recommendation of the Committee.

Name of the Drug : Ulinastatin Injection (50,000 IU/1,00,000 IU)
Name and Address of the Applicant: M/s Bharat Serum and Vaccine Pvt. Ltd

The Committee noted that M/s Bharat Serum and Vaccine Pvt. Ltd has submitted an application to conduct phase IV clinical trial of the drug Ulinastatin Injection as per the condition imposed by this Directorate while granting permission for manufacturing and marketing of the drug Ulinastatin Injection indicated for the treatment of Severe Sepsis.

Study title: "A Phase IV, Prospective, Multicentric, Double-blind, Comparative, Clinical Study to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects with severe sepsis"

Recommendation of the SEC dated 07.04.2015
The proposal was deliberated upon by the SEC on 07.04.2015 wherein the Committee recommended as under:
The firm submitted the application for conducting a Phase IV trial. The firm presented the proposed protocol to be conducted in 300 patients. The Committee deliberated the proposal in detail and recommended for grant of permission to conduct the clinical trial.

Recommendation of the Technical Committee dated 06.05.2015

There after the proposal was deliberated upon by the technical Committee in its meeting held on 06.05.2015. After detailed deliberation, the Committee noted that it is not clear in the protocol as what is meant by standard supportive care. Therefore, the Committee recommended that the firm shall clarify it and provide a proper protocol within 15 days from receipt of letter, failing which the marketing authorization which was granted subject to the conduct of phase-IV trial in 200 patients shall be made invalid. Further, whether standard care of treatment will be provided in Placebo arm needs to be clarified. Hence the Committee did not recommend the trial as per protocol submitted.

Accordingly, the firm has submitted the reply in respect of the recommendation of the Technical Committee as follows:

Meaning of standard supportive care: Standard supportive care would be as per recommendations of 'Surviving Sepsis Campaign International Guidelines for Management of Sever Sepsis and Septic Shock: 2012 to which the Indian Society of critical care Medicine

is also a signatory. On the basis of this guideline, the firm has included the details in the protocol.

Revised version of protocol: 150 subjects in Group A- Ulinastatin will be administered in a dose of 200,000 IU diluted in 100 ml of 0.9% saline given IV over one hours every 12 hours for 5 days along with standard supportive care.

150 subjects in Group B- Placebo will be administered identical appearing placebo diluted in 100 ml of 0.9% saline given IV over one hour every 12 hours for 5 days along with standard supportive care.

Standard supportive care would be as per recommendations of surviving sepsis campaign international Guidelines for Management of severe sepsis and septic shock: 2012 and standard treatment protocols of individual hospitals.

Whether standard care of treatment will be provided in Placebo arm: The firm has confirmed that Standard supportive care will be provided to placebo arm and it will be same as that provided to Ulinastatin arm.

Recommendation of the Committee: After detailed deliberation, the Committee recommended to conduct the study.

b) Appeal by M/s Maya Clinical to waiver of the 3 trial per investigator condition imposed by Technical Committee in its 12th meeting.

The Committee in its 12th meeting recommended that ***"as per actions taken on the recommendations of Prof. Ranjit Roy Chaudhury Expert Committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs, it was made mandatory that the sponsor shall ensure that the number of clinical trials an investigator can undertake should be commensurate with the nature of the trial, facility available with the investigator etc. However, under no circumstances the number of trials should be more than three at a time"***

The M/s Maya Clinical has granted the CT NOC dated 09/06/2015 for phase 3 clinical trial titled ***"A prospective, multicenter, randomized, open-label, active controlled, two-parallel groups, phase 3 study to compare the efficacy and safety of masitinib at 7.5 g/kg/day to dacarbazine in the treatment of patients with non-resectable or metastatic stage 3 or stage 4 melanoma carrying a mutation in the juxta membrane domain of c-kit"***

Now the firm appeal for waiver for 3 trials per investigator for above cited study based on the following justifications;

1. **Melanoma as orphan indication in Indian Context**: Melanoma of the skin is rare in the Asian population. Melanoma in India is one of the lowest incidence regions of the world. Cancer registries in India report that the age specific incidence rates for cutaneous

malignant melanoma are less than 0.5 per 1,000,000. There are only few reports in the literature on CMM in the Asian population. The regional cancer centre at Trivandrum registers about 6000 new cancer cases per year and CMM forms 0.5% of them.

The main consideration to treat this indication as an orphan is because the investigators are opting out of opening their sites even after they agreed to conduct study.

2. The investigators want to participate in studies in indications with rapid recruitment instead of melanoma with fewer patients.
3. Out of approved 13 sites unable to open the sites due to lack of interest form the investigators.
4. Due to limitating 3 trials per investigator as per present practice , investigators are reluctant to take up melanoma study.

Because of the above reason firm designate melanoma as rare or orphan status and allow the investigator to take this up as a fourth study and request to allot a special status for this study and allow investigators to take up this study in addition to three other studies.

Recommendation of the Committee: After detailed deliberation the committee considered the appeal made by the firm and recommended that since melanoma is rare disease therefore investigators can undertake the study in addition to three other studies.

b1) While deliberating on this agenda committee additionally taken up for deliberations, as whether shall it be compulsory to have 50 beds for any site to be considered as acceptable for conduct of clinical trial and whether the limit of only 3 clinical trials per investigator shall be continued ?

Recommendations of the Committee: The Committee deliberated the matter in detail and recommended that clinical trial site shall have emergency care and all necessary arrangement required for conduct of clinical trial. However, the number of bed is not specified in Drugs and cosmetics Rules as a limiting criteria for site approval and specifically for OPD based trial. Similarly , it was opined by the Committee that how many clinical trials, an investigator can undertake depends on the capacity of investigator and complexity of clinical trial and it is also not specfied in said rules .Therefore, suitability of the site with respect to beds and other facilities and the number of clinical trials, any investigator can undertake at any given point of time shall be examined and approved by Ethics Committee. The Committee further opined that the guidance documents for Ethics Committee in this regard may be prepared by the experts.

c) Appeal by M/s Astra Zeneca to include subject aged up to 75 years in the study.

The Committee noted that M/s Astra Zeneca has granted the CT NOC dated 05/03/15 for phase IIIb trial titled **"A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor 90 mg twice daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus [THEMIS - effect of Ticagrelor on Health outcomes in Diabetes Mellitus patients Intervention Study]"**

It may please be informed that the proposal was examined by the Subject Expert Committee (SEC) and Technical committee details of deliberation as placed below:

- **SEC Recommendation Dated 21-08-2014:**

After detailed deliberation the committee recommended the conduct of study subject to condition that there is an upper age limit for recruitment should be 75 yrs and the revised protocol should be submitted to CDSCO before permitting the trial.

- **21st Technical Committee Recommendation Dated 21-01-2015:**

After detailed deliberation the committee recommended for the conduct of trial subject to condition that

1. Upper age limit should be 60 yrs.
2. The dose of aspirin should be 75 mg

- **Appeal by the firm to include subject aged up to 75 years in the study:**

Now the firm appeal to include subject aged up to 75 years in the study based up on the following justification;

1. This is phase 3b study and includes approximately 17000 randomized patients, recruited from 40 countries worldwide and in approximately 950 study centers. **The above mentioned has been approved in all the participating country without any restriction.**
2. Study in special populations under Schedule Y which is recommends inclusion of geriatrics patients in certain specific studies. As the proposed phase IIIb study falls under this category, the firm request to consider age restriction up to 75 years.
3. Patients with T2DM and documented coronary artery atherosclerosis have a particularly high risk of major CV events (as evidenced by having had a PCI, CABG or angiographic evidence of >50% lumen stenosis of at least one coronary artery). Since age is an additional risk for cardiac events, the THEMIS study will recruit patients aged 50 years or above without a specific upper age limit. THEMIS study is designed to evaluate the

effects of ticagrelor on MI, stroke, CV death and bleeding events in the long-term management of patients with T2DM at high risk of CV events.

4. Ticagrelor is approved in India for the management of ACS since 2012 and is available for use in ACS patients. The conduct of THEMIS study in India (as part of a global clinical trial) will help to generate supportive data in the widely prevalent patient population of Type 2 Diabetes with high risk of cardiovascular events.
5. In a study conducted by CSIR-NEERI in India on elderly patients to find out the exact prevalence of Diabetes the prevalence rate was 30.42%
6. Another study conducted by National Urban Diabetes Survey covering the 6 major metropolitan cities in India the prevalence of Diabetes in elderly age groups, 60-69 is 29.1% & over 69 years of age is 25.9%.
7. Ticagrelor has shown significant benefits over Clopidogrel in both elderly patients, age>75 years of age, (n=2878) as well as Diabetic patients (n=4662). Overall there were 809 patients in the PLATO trial who were over 75 years of age & were diabetic.
8. The safety and efficacy data of Ticagrelor available to date, according to the sponsor does not reveal any difference in the safety and efficacy profile of patient below or above the age of 65 years.
9. Based on the Indian epidemiological data available and in addition the current safety and efficacy data of Ticagrelor for patient above the age of 65 as displayed in this document, the sponsor believes that Indian patients above the age of 65 years could potentially benefits from Ticagrelor therapy.
10. Furthermore the current Guidelines from EMA, ICH, recommend to include patients above the age of 65 years old in pivotal studies.

Therefore taking all these points into consideration, the sponsor hereby requests, to allow Indian patients age 65 years and older to participate in the THEMIS study.

Recommendation of the Committee: After detailed deliberation the committee considered the appeal made by the firm and recommended the conduct of the study with upper age limit for recruitment as 75 years, subject to the condition that the dose of aspirin should be 75 mg.

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Annexure-I

List of 03 cases of clinical trial of NCEs along with their evaluations and recommendations of the Technical Committee in its 28th Meeting.

Proposal No	Details of the proposal	Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Subject Expert Committee 2. Technical Committee
1.	**Name of the Drug:** FG-3019 **Protocol No** : FGCL-3019-067 **Phase of the Study:** Phase II **Name of the Applicant :** Excel Life Sciences Pvt. Ltd. D-62, 1st floor, Sector2, Noida-201301 Uttar Pradesh, India **Name of the Sponsor:** FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA **Name of the Manufacturer:** Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Str. 65 88397 Biberach/Riss Germany. **Title:** A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis	**Assessment of Risk vs. Benefit to the patients**: The safety profile of the test drug from various preclinical pharmacokinetic, repeat dose toxicity, phase I and ongoing phase II clinical study justify the conduct of the study. **Innovation *vis-à-vis* Existing Therapeutic Option**: The purpose of the study is to evaluate safety and efficacy of FG-2019 in patients with idiopathic pulmonary fibrosis. **Unmet Medical Need in the country**: The test drug may provide an additional treatment option in patients with idiopathic pulmonary fibrosis.	**1. SEC Recommendation on 30-06-15:** After detailed deliberation the committee recommended the conduct of the study subject to the conditions that the failure and intolerance to perfinedone (only approved drug for IPF) should be carefully assessed by the investigator before including them in to the trial. The reasons for the failure shall be explicitly documented in source document. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

2.	**Name of the Drug:** ZYAN1 **Protocol no:** ZYAN1**1001** **Phase of the Study:** Phase I **Name of the Applicant:** Zydus Research Centre, Cadila Healthcare Limited, Survey No. 396/403, Opp. Sarvottam Hotel, Nr. Nova Petrochemicals, Sarkhej-Bavla N.H. No. 8A, Moraiya, Ahmedabad-382213 Gujarat, India, **Name of the Sponsor:** Same as above. **Name of the manufacturer:** Cadila Healthcare Limited Survey No. 417, 419 & 420, Sarkhej Bavla, N. H. No. 8A, Moraiya, Tal. Sanand, Ahmedabad - 382 210. India. **Title:** A randomized, double-blind,placebo-controlled Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of ZYAN1, a novel PHD-2 Inhibitor, following oral administration in healthy volunteers.	**Risk versus benefit to the patients** As this is a first in human trial, safety and tolerability yet to be defined, though considered safe on basis of pre-clinical results. Subjects taking part in this phase I study might not have any direct benefit from this study other than the benefit of free medical checkup but they will contribute to the medical science by helping us generate the safety and tolerability data on this new chemical entity which will be helpful for many other people in future. **Innovation *vis-a-vis* existing therapeutic option:** Oral route of administration instead parentral route for the treatment of anemia of chronic diseases **Unmet medical need in the country:** Treatment of anemia of chronic diseases, and other hypoxia related disorders.	**1. Recommendation of the IND Committee** : The Committee noted from the firm's presentation that the proposed study is multicentric in Australia and India and the firm has received permission from the regulatory authorities of Australia to conduct the study. After detailed deliberation the Committee recommended the proposed study subject to the following conditions:- ➢ Study should be conducted under the full time monitoring of a Cardiologist. ➢ Upper limit of Haemoglobin should be less than 15 g/dL. ➢ Complete chemical structure should be submitted to CDSCO. ➢ DSMB should be constituted to monitor the study. Accordingly, revised protocol etc. should be revised and submitted to DCGI. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee sought the clarification and presentation on following observation. 1. Animal details indicating the pharmacology and mechanism of action of the NCE are not explained clearly. The details of proof of pharmacological action in the given therapeutic indication, which justify further trials in human are not given. 2. The hypoxia related disorder which is mentioned as one of the proposed indication is too general and needs to be specified.

3.	**Name of the Drug:** ZYDPLA1 **Protocol no: ZYDPLA1 1001** **Phase of the Study:** Phase I **Name of the Applicant:** Zydus Research Centre, Cadila Healthcare Limited, Survey No. 396/403, Opp. Sarvottam Hotel, Nr. Nova Petrochemicals, Sarkhej-Bavla N.H. No. 8A, Moraiya, Ahmedabad-382213 Gujarat, India, **Name of the Sponsor:** Same as above. **Name of the manufacturer:** Cadila Healthcare Limited Survey No. 417, 419 & 420, Sarkhej Bavla, N. H. No. 8A, Moraiya, Tal. Sanand, Ahmedabad - 382 210. India. **Title:** A randomized, double-blind, placebo-controlled Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of ZYDPLA1, a novel DPP- IV inhibitor, following oral administration in healthy volunteers	**Risk versus benefit to the patients** As this is a first in human trial, safety and tolerability yet to be defined, though considered safe on basis of pre-clinical results. Subjects taking part in this phase I study might not have any direct benefit from this study other than the benefit of free medical checkup but they will contribute to the medical science by helping us generate the safety and tolerability data on this new chemical entity which will be helpful for many other people in future. **Innovation *vis-a-vis* existing therapeutic option** Oral route of administration with dosing frequency once a week only **Unmet medical need in the country:** Better compliance for diabetic patients as the dosing frequency will be once a week	**1. Recommendation of the IND Committee** : The Committee noted from the firm's presentation that the proposed study is a multicentric trial in USA and India and pK study in USA commenced with the approval of the FDA and is currently under progress. After detailed deliberation the Committee recommended the proposed study subject to following conditions:- • Cardiac monitoring should be monitored by Cardiologist. • Upper limit of Haemoglobin should be less than 15 g/dL. • Complete chemical structure should be submitted to CDSCO. • DSMB should be constituted to monitor the study. Accordingly, revised protocol etc. should be revised and submitted to DCGI **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the IND recommendation.

Annexure-II

List of 04 cases of Clinical Trial proposals of GCT along with evaluations and recommendations of the Technical Committee in 28th Meeting.

Proposal No.	Details of the proposal	Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Subject Expert Committee 2. Technical Committee
1.	**Name of the Drug:** Linaclotide Capsules **Protocol No**: CR039-14 **Phase of the study:** Clinical Bioequivalence – Clinical End Point Study **Applicant Name and Address**: AXIS Clinicals Ltd, 1-121/1, Miyapur, Hyderabad-500 049, Andhra Pradesh Sponsor Name and Address**:** APL Research Center Aurobindo Pharma Limited Survey No -313, Bachupally Village, Qutubullapur Mandal, Hyderabad -500 090, India, **Manufacturer Name and Address**: Aurobindo Pharma Limited, Unit VII, SEZ, APIIC, Plot No. S1, Svy no. 411, 425, 434,435 & 458, Green Industrial Park, Polepally Village, Jedcherla Mandal, Mahaboobnagar District, Andhra Pradesh **Title**: A Randomized, Double Masked, Parallel Group, Placebo Controlled, Multicentric Study To Evaluate The Efficacy And Safety Of Linaclotide Capsules-290 mcg in Subjects Of Irritable Bowel Syndrome with Constipation	**Risk versus Benefit to the patients**- The safety profile of the test drug from various pre clinical studies including single dose, repeat dose, reproductive and development toxicity, genotoxicity study and clinical phase II, III studies justify the conduct of the study. **Innovation *vis a vis* existing therapeutic option**- The purpose of the study is to assess the efficacy of Linaclotide 290 mcg capsules when administered for 12 weeks to patients with irritable bowel syndrome with constipation. **Unmet need**- The test drug may provide an additional treatment option in patients with irritable bowel syndrome with constipation.	**SEC recommendation dated 01-05-2015:** After detailed deliberation the committee recommended the conduct of trial subject to the following 1. The standard of care should be defined and 2. The trial centers should be evenly distributed across the country. **Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

	[Group-I: Linaclotide Capsules -290 mcg (Test), Group-II: Linzess Capsule® 290 mcg –(Reference) and Group –III: Placebo]		
2.	**Name of the Drug:** Mylan Adalimumab (MYL-1401A) **Protocol No**: **MYL-1401A-3001** **Phase of the Study: Phase-III** **Applicant Name and Address**: PPD Pharmaceutical Development India Private Limited, 01-Dynasty B-Wing (Kanakia Spaces), Andheri-Kurla Road, Andheri East, Mumbai-400 059, India **Sponsor Name and Address**: Mylan GmbH (Mylan) Thurgauerstrasse, 40 CH-8050 Zürich, Switzerland **Manufacturer Name and Address**: Biocon Ltd Plot no 2-4, Phase –IV Bommasandra, Jigani Link Road, Bangalore-560099, India **Title**: Multicenter, Double-Blind, Randomized, 2-Arm, Parallel-Group, Equivalence Study Evaluating Efficacy and Safety Similarity of Mylan Adalimumab (MYL-1401A) Compared With Humira® in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis (MYL-1401A-3001)	**Risk Versus Benefit to the Patients**: The risk vs benefit profile of the test drug from preclinical repeated dose toxicity studies and single dose PK studies justify the conduct of this study. **Innovation *vis-a-vis* Existing Therapeutic Option:** The purpose of the study is to assess the equivalence of MYL-1401A to Humira with regards to efficacy at week 16 in subjects with moderate-to-severe chronic plaque psoriasis. **Unmet Medical Need in the Country:** The test drug may potentially provide alternative treatment option in patients with moderate-to-severe chronic plaque psoriasis.	**1. SEC recommendation:** After the detailed deliberation the committee recommended the conduct of study subject to the following conditions 1. Unblinded Phase I safety data should be submitted prior to conduct of proposed phase III study. 2. Trial sites should have more than or equal to 50 bedded facility with emergency services. 3. The investigators must possess MD (Dermatology) qualification. 4. The trial sites should be geographically distributed equitably between Govt and private. **2. Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

3.	**Name of the Drug:** LCZ696 **Protocol No: CLCZ696D2301** **Phase of the study**: Phase-III **Applicant Name and Address:** Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai – 400 018 **Sponsor Name and Address**: Novartis Healthcare Private Limited, **Manufacturer Name and Address:** Novartis Pharma AG, Lichtstrasse 35, CH-4056, Stein Basel, Switzerland. **Title:** A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction	**Assessment of Risk vs. Benefit to the patients:** The safety profile of the study drug from preclinical pharmacology, repeat dose toxicity, reproductive toxicity, genotoxicity, juvenile toxicity studies and phase I, II clinical studies justify the conduct of the trial. **Innovation *vis-à-vis* Existing Therapeutic Option**: The purpose of the study is to evaluate efficacy and safety of LCZ 696 compared to valsartan on morbidity and mortality in heart failure patients (NYHA II-IV) with preserved ejection fraction. **Unmet Medical Need in the country**: The test drug may potentially provide treatment option in patients with heart failure with preserved ejection fraction.	**1.Recommendation of the SEC:** After the detailed deliberation the committee recommended the conduct of the study subject to the following condition 1. Serum potassium levels should be assessed at 1 week post dose escalation to 160 mg BD. 2. Ejection fraction assessment should be performed by 2D volumetric methods. **2.Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation with the condition that the patients who have eGRF less than 45 ml/min should be excluded from the study.
4.	**Name of the Drug: Pregabalin** **Protocol No: A0081041** **Phase of the Study: III** **Name of the Applicant and**	**Risk versus benefit to the patients**- In light of the fact that the test drug is already marketed in India, the safety profile of the test drug, justify the conduct of the trial. **Innovation *vis-a-vis* existing therapeutic option**- The purpose	**1. Recommendation of the SEC:** The firm presented safety data in different age groups from global clinical trials. After detailed deliberation the committee opined that the phase II data of safety & efficacy of Pregabalin in pediatric

	address: Pfizer Ltd, Pfizer Centre, Patel Estate, Off S. V. Road, Jogeshwari (W), Mumbai – 400 102 **Sponsor Name and Address**: **Same as above** **Manufacturer Name and Address**: Pfizer Manufacturing Deutschland GmbH – Freiburg Site, Mooswaldallee 1, D-79090, Freiburg **Title:** A Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Of The Efficacy And Safety Of Pregabalin As Adjunctive Therapy In Children 4 -16 Years Of Age With Partial Onset Seizures.	of the study is to evaluate the efficacy and safety of pregabalin as adjunctive therapy in children 4-16 years of age with partial onset seizures. **Unmet medical need in the country**- The test drug may be an alternative treatment option as adjunctive therapy in children age of 4-16 years with partial onset seizures.	age group not available from India. The committee also opined that the data generated from this study cannot be the base for marketing authorization for this age group. However as per existing rules this global clinical trial may be permitted. **2. Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

Annexure III

List of 12 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 28th Meeting.

Sl No	Name of the Drug	Firm Name	Recommendations: 1. Subject Expert Committee 2. Technical Committee
1.	Paclitaxel Oral Liquid 50 mg/ml	M/s Cadila Pharmaceuticals Limited	**1.Recommendation of the SEC:** Firm presented the proposal before the committee. After detailed deliberation the committee recommended to conduct proposed Phase I trial with the following conditions. • Standard 3X3 design shall be followed at all dose level • Modify the Inclusion criteria ie ➢ all solid tumour except GI cancer ➢ Patients should have progressed after at least two lines of chemotherapy and standard of care option is not available • Additional PK sample shall be taken at 36 and up to 48 hr • At least one more site shall be included Accordingly revised protocol shall be submitted to O/o DCG (I) for the approval. **2.Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
2.	Norethisterone 10 mg Controlled Release tablet	M/s Synokem Pharmaceuticals Ltd.	**1.Recommendation of the SEC:** Firm presented revised Phase III clinical trial protocol before the Committee as per previous recommendation by the committee. The Committee noted that firm has also submitted BE study protocol. After detailed deliberation the Committee recommended for conducting proposed BE study and CT study with the condition that pelvic sonography shall be performed at visit 1 during the clinical trial **2.Recommendation of the Technical Committee** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
3.	Progesterone (Micronized) SR oral tablets	M/s Synokem Pharmaceuticals Ltd.	**1. Recommendation of the SEC:** Firm presented revised Phase III clinical trial protocol before the committee as per previous recommendation by the committee. The

			committee noted that firm has also submitted BE study protocol. After detailed deliberation the committee recommended for conducting proposed BE study and CT study with the condition that PAP smear test shall be performed at visit 1 during the clinical trial. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
4.	Insulin Aspart	M/s BioGenomics Limited	**1.Recommendation of the SEC:** After detailed deliberation the Committee recommended for the conduct of the study, subject to the condition that the firm submits names of qualified PI and Co-I having adequate qualification to conduct the clamp study. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
5.	Bevacizumab (r-DNA origin)	M/s Dr Reddy's Laboratories Ltd	**1.Recommendation of the SEC:** Part A- • Primary end point should be PFS-9 and not PFS-6. • Sample size should be recalculated, accordingly. • A copy of bio-statistician certificate shall be submitted. • The study will continue in open label phase after completion of the primary end point and generic Bevacizumab will be provided to all responding patients in this open label phase with continuation of safety and toxicity assessment. Part-B- • Disease assessment will be done after every 2 cycles of the treatment. • The study will continue in open label phase after completion of the primary end point and generic Bevacizumab will be provided to all responding patients in this open label phase with continuation of safety and toxicity assessment. After submission of the revised protocol with inclusion of above said points, proposal may be considered for the approval without further discussion in SEC. **2.Recommendation of the Technical Committee:**

			After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
6.	Tenecteplase (TNK-tPA)/ R-TPR-012	M/s Reliance Life Sciences Pvt. Ltd.	**1.Recommendation of the SEC:** After detailed deliberation the committee recommended the proposed Phase III study with following conditions: 1. Major and minor bleeding criteria should be specified. 2. Telephonic Interview questionnaire should be designed. 3. Patient consent form should explicitly mention about the need of the angiography. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation with further condition that patient wise data to be generated for platelets/bleeding. The incidence of bleeding in geriatric population with this drug needs to carefully monitored and evaluated.
7.	Measles, Mumps, Rubella & Varicella Vaccine	M/s Cadila Healthcare Ltd.,	**1.Recommendation of the SEC:** The committee deliberated the proposal in detail and recommended for the conduct of study as per submitted protocol. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
8.	Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension (1% w/v + 0.15% w/v), 5 ml	M/s Unimed Technologies Limited	**1.Recommendation of the SEC:** The Committee recommended to conduct the proposed clinical trial. The results of the trial shall be presented before the Committee for considering marketing approval. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
9.	Typhoid Vi Capsular Polysaccharide-Tetanus Toxoid Protein Conjugate Vaccine	M/s Bharat Biotech International Limited	**1.Recommendation of the SEC:** The Committee deliberated the proposal in detail and recommended for the conduct of study as per submitted protocol. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee

			recommended to conduct the study as per the SEC recommendation.
10.	Rabies Vaccine, Human (Cell Culture) I.P.	M/s Bio-Med (p) Ltd	**1.Recommendation of the SEC:** The committee reviewed the proposed sample size and recommended for approval. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation. However, firm shall measure the immunogenicity of the subjects within 48 hours of vaccination and incase sufficient titre is not reached, rescue treatment (alternative vaccine) to be given to the subjects which shall be provided in the protocol.
11.	Japanese Encephalitis Vaccine	M/s Human Biologicals Institute Ltd.,	**1.Recommendation of the SEC:** The committee deliberated the proposal in detail and recommended the protocol for the conduct of Phase I/II study subject to the condition that the firm shall conduct the study in the adult age group of 18-49 years only. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
12.	Inactivated Japanese encephalitis vaccine	M/s Bharat Biotech International Limited	**1Recommendation of the SEC:** The committee deliberated the proposal in detail and recommended for approval. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

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