MINUTES OF 23rd MEETING OF THE TECHNICAL COMMITTEE HELD ON 19.03.2015 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	Chairman
2.	Dr. Nandini Kumar, Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, 5/1 (New) Padmalaye Apt. Chennai.	Member
3.	Dr. Kamlakar Tripathi, Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005.	Member
4.	Dr. Ashok Kumar Das, Professor of Medicine & Professor and Head of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry - 605014	Member

From CDSCO:

1. Dr.V.G.Somani,
   Joint Drugs Controller (India)
2. R. Chandrashekar
   Deputy Drugs Controller (India), CDSCO HQ
3. Mrs. A Visala
   Deputy Drugs Controller (India)
4. Mrs. Rubina Bose
   Deputy Drugs Controller (India)
5. Mrs. Swati Srivastava
   Asst. Drugs Controller (India)

Dr. V.G. Somani, JDC (I) welcomed the members of the meeting and initiated the proceeding of the Committee as per the agenda.

The Committee then discussed the clinical trial proposals one by one as under:

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

The Committee deliberated 20 cases related to approval of clinical trials. Out of these 20 cases, 03 cases were related to clinical trials of NCEs (02 cases of GCT and 01 case of Biological) and 03 cases were related to global clinical trials (GCT). Remaining 14 cases were related to clinical trials for approval of New Drugs, medical devices and biologicals.

The Committee evaluated the 03 cases related to clinical trial of NCEs one by one 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 deliberations, the Committee recommended for approval of 02 cases (01 case of GCT and 01 case of Biological) out of 03 cases. In the remaining one case, the Committee recommended that the proposal is to be further reviewed by the experts of gastroenterology and the firm should inform whether the study has been initiated in Belgium and Slovak Republic, if so number of patients enrolled in the study for further deliberation in the Technical Committee meeting. The recommendations of the Committee in respect of these 03 cases related to clinical trial of NCEs are enclosed as **Annexure-I.**

Thereafter, the Committee evaluated 03 cases related to global clinical trial. After detailed deliberations, the Committee recommended for approval of 02 cases out of 03 cases. In the remaining one case, the Committee recommended that the firm shall make detail presentation on the proposal in the forthcoming Technical Committee meeting. The recommendations of the Committee in respect of these 03 cases related to GCTs are enclosed as **Annexure-II**

The Committee also evaluated the remaining 14 cases of other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of 12 out of 14 cases. Out of 12 recommended cases, the Committee recommended 01 case subject to certain conditions. The Committee did not recommend the remaining 02 cases and deferred the proposals for seeking clarification and to hold further discussion to decide on policy matter related to stem cell product along with experts. The recommendations of the Committee in respect of these 20 cases are enclosed as **Annexure-III.**

Thus, the Committee recommended for approval of 16 cases, out of total 20 cases of clinical trial proposals.

2. Others:

i) Appeal of M/s INC Research for waiver of the Clinical Trial condition imposed by Technical Committee and Apex Committee in its 21st and 20th meeting respectively.

Study title: "A Randomized, Double-Blind, Placebo- and Active-Controlled Study of DS-5565 in subjects with Pain Associated with Fibromyalgia"

It may please be informed that the proposal was deliberated in Technical Committee and Apex Committee in its 21st and 20th meeting respectively.

The trial was recommended by the Technical Committee and Apex Committee. The details of the deliberations by these Committees are given below:-

1. Deliberation of proposal by SEC:-

The proposal was deliberated in the meeting of SEC (Neurology and Psychiatry) held on 28.08.2014.

The Committee after deliberation recommended as under:-

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

1. The investigator should be Orthopaedics or rheumatologist. The team include clinical psychiatric/psychologist for the assessment of inclusion and exclusion criteria.
2. The number of proposed subjects from India is 105. Considering drop out 50% as per protocol statistical analysis, therefore this cannot be applicable for marketing permission in India.
3. The pk rational for trying the drug OD or BD should be provided.

2. Deliberation of proposal by Technical Committee (TC):-

The proposal was placed before the Technical Committee along with the recommendations of the SEC in the 21st Technical Committee meeting held on 21-01-2015.

The Committee after deliberation recommended as under:-

"The Committee recommended for the conduct of trial as per the SEC recommendation subject to the condition that all the 105 subjects should be treated in hospitalized setting only with complete cardiac monitoring for duration of one month. If AEs are not reported after the period of one month, trial can be conducted on OPD setup."

3. Deliberation of proposal by Apex Committee:-

The proposal was then deliberated in 20th Apex Committee meeting held on 30.01.2015, wherein Committee agreed with the recommendations of Technical Committee.

4. Appeal by M/s INC Research for waiver on the condition imposed under CT NOC:-

There after the applicant represented the matter to DCG (I) for waiver on the condition imposed under CT NOC based upon following justifications;

A. Pre- clinical and clinical data for DS-5565 do not support the need for intensive cardiac monitoring, as summarized below:

- **Preclinical cardiac safety studies:**
  - hERG assay (HEK 293 cells)- DS-5565 had no effect on the 1Kr potassium current at 3.0, 100 and 300uM.
  - Action potential duration (APD) assay using guinea pig papillary muscle – DS-5565 was tested at 30, 100 and 300uM and found to produce statistically significant shortening in the APD30 and APD90 at 30uM and higher. This change ranged from -4.2% to -8.4% with no observed dose response.

  - In view using conscious cynomolgus monkeys – DS 5565 was administered at 30, 300 and 2000mg/kg and was found to decrease SBP, DBP and mean BP at 200mg/kg from 4h post done until 7h post-dose.
    As below, see note regarding clinical relevancy of findings at 2000mg/kg doses. No effects on ECG parameters and HR were noted.

- **Toxicology**: Repeated dose toxicity studies in rats (26 weeks) and monkeys (39 week) at doses up to 100mg/kg/day are summarized in section 4.3.2 of the investigators brochure, Notably, abnormal clinical signs related to CNS depression, such as hypoactivity and staggering gait, were observed in rats given 30 mg/kg or more and cynomolgus monkeys given 100 mg/kg or more and were considered due to an excessive pharmacological action. From a cardiac standpoint, a decrease in heart rate observed in male cynomolgus monkeys at 100mg/kg or more was considered to be a change secondary to the CNS depression (and in contrast to the supratherapeutic dose described in the cardiovascular safety pharmacology studies above); also, a few rats and a cynomolgus monkey dosed at 2000 mg/kg showed myocardial necrosis and degeneration, respectively. These effects, were observed at exposures not considered to have clinical relevancy as they far exceed those reached at the highest dose (15mg BID) administered in the Phase 3 program.

- **Clinical data**:
  - A thorough QT study was conducted in healthy human subjects by the sponsor to assess the effects of two doses of DS-5565 (therapeutic and supratherapeutic dose) on cardiac repolarization and the various ECG intervals (PR, QRS and QT). In this study, there were no clinically significant changes in 12-lead electrocardiogram (ECG) parameters; neither the therapeutic dose (15 mg of DS-5565 displayed no effects on the cardiac repolarization at 15mg & 50mg dosages.
  - The Phase 1 and 2 clinical studies shows no cardiac events related to the study drug.
  - In India the sponsor has completed one phase 1 study (DS5565-A-E114) in twenty one (21) healthy subjects, all of whom were monitored in a hospitalized (CPU) setting and in whom no cardiac adverse events were reported during the

conduct of the study. Globally, across the three ongoing double blind studies, 118 subjects have been randomized as of 26 Feb 2015, 3 of which have completed the 13 week double blind treatment period. All of these subjects have been treated as per protocol specified visits, in an outpatient setting. As of 26 February 2015. No SAE's have been reported.

B. Safety experience from other compounds in the class (Pregabalin and Gabapentin) in class do not suggest a cardiac safety concern:

- Labeling for Pregabalin[1], an approved alpha-2-delta (a28) ligand, includes language in the warnings and precautions section stating that "LYRICA treatment was associated with PR interval increase was 3-6 msec at LYRICA doses ≥300 mg/day." But it also notes that "this mean change difference was not associated with an increased risk of PR mean change difference was not associated with and increased risk of PR increase ≥ 200 msec, or an increased risk of adverse reactions of second or third degree AV block.".
- Similarly, US labeling for Gabapentin[2] Has A Notable Absence Of Any Warning Or Precaution Regarding Cardiac safety, with cardiovascular adverse events being mentioned as infrequent and rare in nature.
- Given the lack of apparent significant cardiovascular findings, there is no additional cardiac monitoring recommended for either gabapentin or Pregabalin. This is supported by extensive post-marketing safety exposure, with Gabapentin approved in the US in 1913 and Pregabalin approved in 2004. There is no scientific or medical reason to suggest that DS-5565 would confer any additional risk from a cardiovascular standpoint when used in an outpatient setting that would justify requiring additional cardiac monitoring.

C. The sponsor has put in place robust and extensive measures to safeguard the patients enrolled in the study and global program, including:

- All the study investigators will critically evaluate all patients during screening (as designated in the study protocol). As per exclusion criteria #1 of the study protocol, patients with unstable cardiovascular disease (e.g. severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) or any other concurrent disease within 12 months prior to screening that in the opinion of the investigator would interfere with study participation or assessment of safety and tolerability are excluded from the study and will not be considered for study participation.
- Patients will be evaluated in an ongoing manner during the course of the study:
  - All randomized subjects will have a 12-lead ECG conducted at the Screening visit and at the End of Treatment/Early Termination visit.
  - All randomized subjects will visits the investigator sites every two weeks for the duration for the study. At each visit, the investigator will perform a thorough physical examination, including cardiovascular evaluation, of the patient and also question for any adverse events since the last visit.
- Ongoing review of blinded, individual subject safety data will take place by a team of experienced medical monitors, throughout the course of the study, including review of both adverse event and laboratory data.

- Ongoing review of unblended, aggregate safety data (including both adverse event data and labs), across the entire global program and indications, will take place quarterly, by a multifunctional Safety Management team including but not limited to clinical physicians, biostaticians, and clinical pharmacologists.
- An independent Data Safety Monitoring Board (DSMB) is in place and charged with overseeing patient safety across the global program via the review of unblended, aggregate safety data in a periodic manner (Every 3- 6 months) or ad-hoc if the sponsor of DSMB chair determines the need. The DSMB is comprised of independent, medical experts with vast experience in their respective specialties (including the chair, a Rheumatologist, 2 Psychiatrists (one in the US and one in Japan), 1 Hepatologist, 1 clinical trial specialist with experience in rheumatology/analgesia/cardiovascular and an independent biostatistician). These independent medical experts are well suited to evaluate safety across the intended patient population will make recommendations to the sponsor regarding continuing the studies without change, recommending amendments to the protocols based upon safety concerns or stopping study (ies) due to the same.

D. The study will be conducted in patients with pain due to fibromyalgia, an indication for which patients are routinely treated in the out-patient department setting (OPD). Treating fibromyalgia patients in a hospitalized, in-patient, setting would inconvenience the patients and further their psychological distress, and extended hospitalization may put subjects at risk of acquiring nosocomial, or hospital-acquired, infections. Additionally, these patients require no other procedures that need to be administered in a hospitalized setting.

This study is one of the three identical Phase 3 double – blind parallel group studies conducted as part of the global DS-5565 fibromyalgia program. These identical protocols have been submitted across thirty eight (38) countries globally and have been approved in nineteen (19) countries so far, including USA, UK, Germany, France and Australia. Recruitment is commencing in countries where all regulatory approvals have been attained. Additionally, studies with similar doses of DS-5565 in patients with Diabetic Peripheral Neuropathic Pain (DPNP) or Post Herpetic Neuralgia (PHN) have been approved and are ongoing in Japan. All of the above studies are being conducted in an outpatient setting globally, and the sponsor would like to maintain consistent conduct in Indian Studies to allow for uniformity in study design, conducted a reproducibility of results.

Recommendations: The Committee discussed the matter. After detailed deliberation and review of the firm's representation the Committee was of the opinion that the trial can be conducted subject to the condition that all the 105 subjects should be treated in hospitalized settings only, with complete cardiac monitoring for duration of one week as various adverse events including acute transmuralinfero-lateral myocardial infarction was reported in the phase-I study. If AEs are not reported after the period of one week, trial can be conducted on OPD setup.

ii) Request to reconsider the application from M/s LV Prasad Eye Institute, Andhra Pradesh regarding to conduct clinical study titled "A proof of concept study to evaluate the clinical safety and efficacy of a Poly Lactide-co-Glycolic Acid (PLGA) biodegradable, synthetic carrier membrane, used to regenerate epithelium using autologous limbal tissue as a single step procedure in patients having total unilateral limbal stem cell deficiency (LSCD).

An application from M/s LV Prasad Eye Institute, Andhra Pradesh to conduct clinical study titled "A proof of concept study to evaluate the clinical safety and efficacy of a Poly Lactide-co-Glycolic Acid (PLGA) biodegradable, synthetic carrier membrane, used to regenerate epithelium using autologous limbal tissue as a single step procedure in patients having total unilateral limbal stem cell deficiency (LSCD)," was received on 17.10.2013 by this Directorate.

The proposal of M/s. LV Prasad Eye Institute, Hyderabad regarding permission to conduct Phase-I clinical study for PLGA membrane was discussed in 5th CBBTDEC held on 30.04.2014 and committee recommended for approval of the study with the condition to follow-up for one year.

The proposal of M/s LV Prasad was deliberated in 18th meeting of the Technical Committee held on 13.10.2014 and the Committee recommended that one more level of animal study in rabbit has to be done replicative of human study with the same membrane and submit the report to the Committee and 17th meeting of the Apex Committee held on 15.10.2014 recommended that the therapy using autologous limbal tissue in limbal stem cell deficiency (LSCD) is standard therapy. Therefore, the Technical Committee should relook the matter and the applicant may be asked for further clarification.

A query letter was issued to the applicant on 1st Dec 2014 on the basis of recommendation of 18th meeting of the Technical committee held on 13.10.2014 and 17th meeting of the Apex committee held on 15.10.2014.

On the request of the firm, the proposal was again put up for deliberation in the Technical Committee meeting held on 21.01.2015 in presence of Corneal Expert Dr. Rohit Saxena, Associate Professor, AIIMS, New Delhi as per directives of the DGHS and 20th meeting of the Apex Committee held on 30.01.2015. After deliberation, the Technical Committee recommended that the study should be conducted in one more animal species for duration of 6 weeks or till the duration for which the membrane under study is not visible or completely disintegrates. The Apex Committee has concurred with the recommendation of the Technical Committee

A query letter was issued to the firm on 24th Feb. 2015 on the basis of recommendation of 21st meeting of the Technical Committee held on 21.01.2015 and 20th meeting of the Apex Committee held on 30.01.2015.

In query response, the firm has submitted the following:

1) In the very first animal study that they did in rabbits for 28 days, the PLGA membrane disintegrated completely at 14 days without causing any adverse

effects locally (on the eye) or systemically. In Schedule Y, to the Drugs and Cosmetics Rules, the preferred animal model is rabbit for occular toxicity studies.

2) Further as per Schedule Y, to the Drugs and Cosmetics Rules, they would not need to do the ocular toxicity study in another animal species, until they plan to go to the Phase III study. As per Schedule Y, in Phase I and II studies for products meant for ocular instillation, the toxicity study needs to be done only in one species for duration of 4 weeks where it is proposed to give one single dose or multiple doses for duration of up to two weeks. Currently, they are proposing to do only a Phase I study in 10 patients and they shall be using one membrane per patient per procedure. The use of the membrane is similar to the one time use of sutures in eye surgeries.

3) The material used for building the membrane is PLGA (polyactic acid: polyglycolic acid). This copolymer is already in the market in India in the form of sutures used in eye surgeries, and is being marketed by the firm Johnson & Johnson, duly approved by DCGI

4) The PLGA membrane is not a drug with therapeutic properties and is being planned to be used as a scaffold to provide support for the growth of the transplanted limbal tissue grafts in the proposed clinical trial.

In view of above, firm has mentioned that a second animal study in another species for longer duration of six weeks or more is not warranted for Phase I study of 10 patients.

As desired by DGHS, the proposal has been submitted again to the Technical Committee. Accordingly the proposal was presented by Dr. Virendar Singh Sangwan, Director, LV Prasad Institute and Dr. Nitin Reddy, Toxicologist.

Recommendation: The Committee noted the conclusions of animal toxicity studies and also the requirement of number of species required for occular toxicity study in phase-I as per Schedule Y of Drugs and Cosmetics Rules, and the same were taken into the consideration by the Committee which were not presented categorically by the firm during last presentation in the Technical Committee meeting. The conclusion on the animal toxicity study was that the polyactic acid: polyglycolic acid (PLGA) membrane completely disintegrated on day 14 with no local or systemic toxicity. Similarly, as per Schedule Y only one species is required for occular toxicity study in phase I. Therefore, after detailed deliberation, the Committee recommended to conduct Phase I trial with a condition to submit copy of Informed Consent Documents clearly stating that the patient on trial will be apprised of the fact that this membrane is used for the first time and duly signed by all the study subjects and the Investigator.

The meeting ended with vote of thanks to the Chair.

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Annexure-I

List of 03 cases of clinical trials of NCEs along with their evaluations and recommendations of the Technical Committee in its 23rd Meeting.

Sr No.	Name of the Drug	FIRM	PROTOCOL	Parameters 1. risk versus benefit to the patients 2. innovation vis-a-vis existing therapeutic option 3. unmet medical need in the country	Recommendation
1	Masitinib	Maya Clinicals	AB11003	**Risk vs Benefit to the patients:** The risk versus benefit of the test drug from various preclinical pharmacology and toxicity studies including repeat dose, reproductive and development toxicity studies, genotoxicity, carcinogenicity studies and phase I, II, and III clinical studies justifies the conduction of the trial. **Innovation vis a vis against existing therapy**: The purpose of the study is to evaluate and compare the efficacy and safety of masitinib to placebo, in the treatment of moderate Crohn's disease in patients intolerant or with unsatisfactory response to immunosuppressive drug and/or TNF-inhibitor. **Unmet need**: The data from the study may provide an alternative treatment option in Crohn's disease patients intolerant or with unsatisfactory response to immunosuppressive drug and/or TNF inhibitor.	**Recommendation:** The Committee recommended that the proposal is to be further reviewed by the experts of gastroenterology and the firm should inform whether the study has been initiated in Belgium and Slovak Republic, if so number of patients enrolled in the study for further deliberation in the Technical Committee meeting. **SEC Recommendation** After detailed deliberation the committee opined that there can be only two arms in the study i.e. 1. Masitinib and azathioprine/6- mercapto purine/ methotrexate 2. Placebo and azathioprine/6-mercaptopurine/methotrexate and no other sub sets/arms within the above group are permitted. The study duration can be only for 12 wks and the requested extension phase is not granted at this stage. In view of the above the applicant is required to submit the revised protocol for further deliberation by the committee. The firm now submitted the revised protocol wherein the third arm where placebo alone was to be given has been deleted and the study duration is restricted to 12 weeks at this stage. The committee reviewed the revised protocol in view of the previous recommendation dated 28-11-2014 and recommended the conduct of the study in its presented form.

2	LEE011	Novartis	**CLEE011E2301**	**Assessment of Risk vs. Benefit to the patients**: The safety profile of the study drug from preclinical pharmacology, general toxicity, single dose, repeat dose toxicity, genotoxicity and phase I, II clinical studies justify the conduct of this study. **Innovation vis-à-vis Existing Therapeutic Option:** The purpose of the study to determine whether treatment tamoxifen or a NSAI + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR + HER2-negative advanced breast cancer **Unmet Medical Need in the country:** The test drug may potentially provide alternative option for the treatment of premenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer.	**Recommendation:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation. **SEC Recommendation dated 24.02.2015** After detailed deliberation observe that. 1. As per the schedule Y pre clinical re-productive toxicity data is mandatory. However the present study is being conducted in subject with stage IV advanced breast cancer who will be receiving; in addition to IP goserelin; these subjects have less chance of becoming pregnant. Also protocol ensures absence of pregnancy at inclusion and strict contraception during the study. 2. Further the firm has initiated animal reproductive toxicology studies and has assured the committee that the data will be submitted as soon as possible. In view of the above the committee opined that the study may be conducted with strict enforcement of contraception and the preclinical reproductive toxicological data should be submitted as soon as possible. **SEC Recommendation dated 14.01.2015** After detailed deliberation the committee recommended for conduct of the trail with the subject to the condition that pre-clinical reproductive toxicity data shall be submitted to this Directorate before final approval.
3.	Allogenic Pancreatic Cancer	Cadila Pharma ceutical	CRSC11004, 01	**Assessment of risk versus benefit to the patients:** Being active immunotherapy, no systemic risk to the	**Recommendation:** After detailed deliberation, the

		s		patient is expected. All patients are likely to have local injection site reaction which is common to the class and is seen with any other active immune therapy (vaccine). Patients are expected to generate immune response against pancreatic cancer leading to an improved overall survival by more than 60%, based on preclinical data. Being active immunotherapy it is expected that few of the patients will have significantly prolonged overall survival. The product also offers advantage of combining with existing therapy to improve efficacy of existing therapy without adding any additional systemic side effect. **Innovation vis-a-vis existing therapeutic option:** Use of gemcitabine which improves survival by one month and cannot be used in patient with Karnofsky below 50 Karnofsky score below 50 is seen in more than 50% of the patient diagnosed to have pancreatic cancer and so gemcitabine cannot be used. Innovative product can be given to all patient diagnosed with pancreatic cancer irrespective of Karnofsky score. It can also be give along with gemcitabine. **Unmet Medical Need in the country:** Pancreatic cancer is an unmet medical need around the world including India. The number of patients dying because of pancreatic cancer is same as those who are diagnosed with pancreatic cancer. In economically developed countries one year survival following diagnosed pancreatic cancer is only 12% and 5 year survival is only 6%. Median overall survival with Gemcitabine (approved chemotherapy) is 5.0-7.2 months.	Committee recommended to conduct the study as per the IND recommendation. **IND Recommendation**: The Committee recommended the proposal in line with the recommendations of SEC-Oncology and recommended that the data of Stage I part of Phase I trial may be placed before the committee for consideration of next stage of the trial.

Annexure-II

List of 03 cases of Global Clinical Trials along with their evaluations and recommendations of the Technical Committee in its 23rd Meeting.

Sr No.	Name of the Drug	Name of Firm	PROTOCOL	Parameters 1. risk versus benefit to the patients 2. innovation vis-a-vis existing therapeutic option 3. unmet medical need in the country	Recommendation
1	Dabigatran	Boehringer	**1160.186**	**Assessment of Risk vs. Benefit to the patients:** In light of the fact that the test drug is already approved and marketed in India, the safety profile of the test drug justify the conduct of the trial **Innovation vis-à-vis Existing Therapeutic Option:** The purpose of the study is to compare a dual antithrombotic regimen of 110mg dabigatranetexilateb.i.d. plus clopidogrel or ticagrelor (110mg DE-DAT) and 150mg dabigatranetexilateb.i.d. plus clopidogrel or ticagrelor (150mg DE- DAT) with a triple antithrombotic therapy (TAT) of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin-TAT) in patients with non valvular atrial fibrillation (NVAF) that undergo a PCI with stenting. **Unmet Medical Need in the country**: The test drug may potentially provide alternative treatment option in patients with non valvular atrial fibrillation (NVAF) that undergo a PCI with stenting.	**Recommendation:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation. **SEC Recommendation:** The said proposal was deliberated in SEC on 25/11/14. After detailed deliberation the committee opined that two confounding variables cannot be compared at the same point. The rationale behind comparing control arm having Triple Antihrombotic Therapy as against the treatment arm with Dual Antihrombotic Therapy should be justified and presented to the committee. .

					The applicant presented the data and current guidelines emphasizing the lack of evidence for clear strategy for treating patients with AF with coronary stents. Further the three anti platelet drugs are to be given for 1 to 3 months. In view of the lack of adequate data in this subset of patients, the committee was of the view that the trial can be conducted in its presented form subject to the condition that the results of trial must be analyzed separately for initial 3 months and the rest of the time to identify the effects of 3 Vs 2 drugs and reported separately. Accordingly the firm should submit undertaking to CDSCO
2.	*Triple Pill-Strength 1: Optidoz* (Telmisartan 20mg +Amlodipine 2.5mg + Hydrochlorothiazide 6.25 mg) *Triple Pill-Strength 2: Telsartan Trio* (Telmisartan 40mg + Amlodipine	George Institute	**1041052**	**Risk vs Benefit to the patients**: The risk versus benefit of the test drug combination in mild hypertension as a first line therapy is not justified. **Innovation vis a vis existing therapy**: The purpose of the study is to evaluate a fixed dose combination blood pressure lowering pill (Triple Pill) based strategy as a first line therapy compared to usual care among individuals with mild to moderate hypertension on no or minimal drug therapy with step care therapy. **Unmet need**: The study proposes to provide new treatment strategy for management of patients with mild to moderated hypertension.	**Recommendation:** After detailed deliberation on the appeal, the Committee recommended that the applicant shall make detail presentation in the forthcoming Technical Committee meeting.

	5mg + Hydrochlorothiazide 12.5 mg)				**SEC Recommendation** **1st NDAC Deliberation dated 24-01-2014:** **Recommendations**: The committee opined that at present there is no scientific justification for use of these drugs combination pill as starting therapy in stage 1 hypertension. Therefore the NDAC does not recommended approval of study **2nd SEC/NDAC Deliberation dated 21-08-2014:** **Recommendation:** After detailed deliberation the committee opine d that at present there is no scientific justification for the use three drugs combination pill as starting /first line therapy in stage 1 hypertension/mild hypertension. The investigators suggested submitting the published documents on this specific issue of triple drug therapy, as first line approach in mild hypertension. The

					committee opined that the submitted documents should be forwarded to cardiologist for their opinion. **3rd SEC Deliberation dated 25-11-2014: (In presence of Cardiology experts)** **Recommendation:** After detailed deliberation the committee did not recommended the conduct of the trial.
3.	BenzaClin® Gel, (Clindamycin phosphate 1% and Benzoyl peroxide 5%, topical gel)	Cliantha Research Ltd	CRL/CT/05/12-13	**Risk Versus Benefit to the patients** In light of the fact that the FDC is already approved, the safety profile of the test drugs justifies the conduct of the study. **Innovation Vis-A-Vis Existing Therapeutic Option** The purpose of the study is to compare the efficacy and safety of clindamycin 1% / benzoyl peroxide 5% topical gel (of cadila healthcare limited, india) versus benzaclin® topical gel (of valeant pharmaceuticals international, inc.) versus placebo topical gel in the ratio of 2:2:1 respectively, in patients with acne vulgaris. **Unmet Medical Need In The Country** The test drug may potentially be an additional option to the existing formulation in the market	**Recommendation:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation. **SEC Recommendation** **18th Apex Committee Recommendation dated 25-12-2014 :** The committee deliberated upon the proposals and agreed with the recommendations of the Technical Committee. **19th Technical Committee recommendation dated 17-12-2014:**

					The committee agreed with the recommendations of the SEC and has not recommended the conduct of trial **SEC Recommendation dated 22-12-2014:** The committee reviewed the proposal and opined that the reference cited in the presentation regarding reduction in resistance of P. acne with use of this combination needs to be submitted in original articles (not as cross references) and circulated to all the experts for further review based on which final decision will be taken by CDSCO. If submitted information is found to be adequate the recommends the conduct of the trial with the following conditions: 1. Rescue medication (including score going from 1 to 2, score worsens or crosses 3) for placebo group is required after two weeks and 2. The storage condition of the

					IMP should be recorded. **The articles submitted by the firm forwarded to SEC members for review. After review experts opined that the literatures are adequate and there is enough evidence that the combination yield better results than alone. Hence recommended approval for the conduct of trial.** **SEC Recommendation dated 23/09/2014:** The committee reviewed the proposal and opined that for a bio-equivalence study placebo arm is not required. But the company claims th at to market the drug in USA it is required to fulfill the condition of placebo arm, hence placebo arm is required; if it is so then trial should be conducted in USA only. The committee opined that the rationale of combination of two antibiotics still could not be explained by the applicant**. Hence the committee did not recommend the conduct of the**

					study in India. **SEC Recommendation dated 27/06/2014:** After detailed deliberation the committee opined that the data on synergistic efficacy, safety and tolerability of the proposed FDC Vs the individual products is to be presented to the committee. Acne patients receiving no treatment in the placebo group may be a issue of concern the committee did not approve the conduct of study

Annexure-III

List of 14 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 23rd Meeting.

Sl No	Name of the Drug	Firm Name	Recommendation
1.	Recombinant Human Chorionic Gonadotropin Hormone	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
2.	Trastuzumab, powder for concentrate for solution for infusion 150 mg single dose vial and 440 mg multidose vial	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
3.	Denosumab solution for injection 60 mg/mL in vial/PFS	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
4.	Pegfilgrastim (PEG-GCSF) Pegylated Granulocyte Colony Stimulating Factor	M/s Biocon Limited	The Committee reviewed the protocol of PK/PD study submitted as a part of the Marketing Authorization of their indigenously developed Peg-GCSF. The Committee recommended for the proposed PK/PD study. However, the Committee opined that, the firm shall submit undertaking that, they will carry out Phase III clinical trial with suitable protocol and submit the report for seeking Marketing Authorization, as the proposed study on healthy human volunteers does not support the use in patients for "reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapeutics for malignancies".

5.	Rhoclone 300 mcg (monoclonal Anti Rho (D) immunoglobulin	M/s Bharat serum and Vaccine Ltd.,	After detailed deliberation, the Committee agreed for the proposed conduct of study.
6.	Measles, Mumps and Rubella vaccine (Live)	M/s Cadila Healthcare Pvt Ltd,	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
7.	Hepatitis B (r DNA) IP.	M/s Cadila Healthcare Pvt Ltd,	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
8.	Autologous Dendritic Cell Product	M/s Apac Biotech Pvt. Ltd,	The Committee raised question on which solid tumor it is going to treat? How it is going to act? And precise purpose of the study. After detailed deliberation, the Committee deferred the proposal for seeking clarification and to hold further discussion to decide on matters related to such stem cell product along with experts.
9.	Quadrivalent Inactivated Influenzae Vaccine	M/s Sanofi Pasteur India Private Limited.	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
10.	Adult Human Bone Marrow derived, Cultured, Pooled, Allogenic Mesenchymal Stromal Cells	M/s Stempeutics Research Private Limited	The Committee noted that the study is going to be conducted in patients with CLI with burger's disease, therefore the Committee deferred for seeking clarification and to hold further discussion to decide on matter related to such stem cell product along with experts.
11.	Cabazitaxel (JEVTANA™)	Dr Kumar Prabhash	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
12.	Hydroxy-progesterone	Dr. Rajendra A.Badwe	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
13.	Arterolane (RBx11160) Maleate and Piperaquine Phosphate Dispersible tablets	M/s Ranbaxy Laboratories Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

14.	SRAVAN' – Cochlear implant system	Dr V Bhujanga Rao, Chief Designer	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

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