

MINUTES OF THE 14th MEETING OF TECHNICAL COMMITTEE HELD ON 28.04.2014 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, Chairman
Director General of Health Services
2. Dr. Ranjit Roy Chaudhury, Member
National Professor of Pharmacology,
Former Member, BOG-MCI,
Y-85, Hauz Khas, New Delhi-1100 016
3. Dr. Nandini Kumar, Member
Former Dy. Director (Sr. Grade)
National Institute of Epidemiology,
ICMR, Delhi
4. Dr. Rajutitus Chacko, Member
Prof. & Head, Dept. of Medical oncology,
CMC, Vellore.
5. Dr. Kamlakar Tripathi, Member
Prof., Dept. of Medicine,
Institute of Medical Science,
Banaras Hindu University,
Varanasi-221 005
6. Dr. B.L. Shherwal, Member
DDG(M) & Director—Professor,
Dept. of Microbiology,
LHMC & Associated Hospitals,
New Delhi

From CDSCO:

1. Dr. G.N. Singh,
Drugs Controller General (India)

2. Dr.V.G.Somani
Joint Drugs Controller (India)

3. Sh. R.Chandrashekar
Deputy Drugs Controller (India)

4. Mrs. A Vishala
Deputy Drugs Controller (India)

1. Evaluation Proposals of global clinical trials/ clinical trials of NCEs recommended by NDAC / IND but yet to be approved by CDSCO

The Committee was apprised that the Hon'ble Supreme Court of India, vide its order dated 21.04.2014 in the matter of W.P. (C) No. 33/2012 of SwasthyaAdhikarManch, Indore &Anr Vs. Ministry of Health and Family Welfare &Ors. with WP(C) No. 779/2012 regarding clinical trials, had pointed as under:

- Sanjay Parikh, learned counsel for the petitioners in Writ Petition (Civil) No. 33 of 2012, with regard to non-compliance of our previous orders dated 21.10.2013 and 10.03.2014, Mr. SiddharthLuthra, learned Additional Solicitor General, prays for time to seeks instructions and file comprehensive affidavit on behalf of the Union of India through competent authority. Comprehensive affidavit shall be filed by the Union of India within eight weeks.
- From the additional affidavit dated 10.03.2014 (filed on 17.04.2014) filed by Mr. LovVerma, Secretary, Ministry of Health and Family Welfare, Government of India, it is not clear whether the Technical Committee and the Apex Technical Committee have evaluated Global Clinical Trials (GCTs)/New Clinical Trials (NCEs) having regard to three parameters, namely, (i) assessment of risk versus benefit to the patients, (ii) innovation vis-a-vis existing

therapeutic option and (iii) unmet medical need in the country as indicated in the order dated 21.10.2013.

- To obviate any controversy in future in this regard, we direct that henceforth in the Format seeking information from the applicants, three specific columns regarding the above parameters shall be inserted for the purpose of New Clinical Entities/Global Clinical Trials.

The Committee opined that they have already deliberated on these aspects in its earlier meetings, and the Committee recommended that the format of the clinical trials proposals should also include i) assessment of risk versus benefit to the patients, (ii) innovation vis-a-vis existing therapeutic option and (iii) unmet medical need in the country and the same should be asked from the applicants.

The details of the status of the total 157 Global clinical trial proposals at the time of their evaluation were as under:

S. No	Status	No. of Trials
01	Ongoing	65
02	Completed	39
03	Not initiated	13
04	Withdrawn by the respective applicant without any patient enrolment	25
05	Suspended by the respective applicant prematurely	15
06	Total	157

However, in light of the above order of Hon'ble Supreme Court dated 21.04.2014 the evaluation details with respect to i) assessment of risk versus benefit to the patients, (ii) innovation vis-à-vis existing therapeutic option and (iii) unmet medical need in the country for the GCTs which were either ongoing or not initiated are required to be mentioned.

Thereafter, the Committee deliberated the thirteen cases of fresh proposals of clinical trials. These cases have already been recommended by the NDACs.

Out of these 13 cases there were 5 cases of global clinical trials/ clinical trials of NCEs, 8 cases are related to clinical trials for approval of New Drugs including fixed dose combination, subsequent new drugs and biologicals. Detailed information on these proposals as per the prescribed format was forwarded to the members through e-mail.

In compliance with the direction of the Hon'ble Supreme Court, the Committee evaluated 05 cases of global clinical trials/ clinical trials of NCEs 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 deliberation, the Committee recommended for approval of all the 5 cases.

Details of these cases along with their evaluation in terms of the three parameters and recommendations of the Committee are mentioned in the **Annexure-I**.

Thereafter, the Committee evaluated the remaining 08 cases which were related to clinical trials for approval of New Drugs including fixed dose combination, subsequent new drugs and biologicals.

After deliberation, the Committee recommended for approval of clinical trials in 04 cases. In remaining 04 cases, the Committee has sought certain additional data/ information.

The details of 08 cases along with the recommendations of the Committee is mentioned in the **Annexure-II**.

2. Clinical trial site requirements.

CDSCO has received an application for site addition for below mentioned two studies.

CT/76/13: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events.

CT/69/13: Efficacy and safety of Semaglutide once weekly versus Sitagliptin once daily as add on to Metformin and/or TZD in subjects with Type 2 diabetes.

Site details: TOTALL Diabetes Research Hormone Institute, A unit of Diabetes Thyroid Hormone Research Institute Pvt. Ltd, BCM Health Island, PU4, Scheme 54, Behind

Prestige Management Institute, Near Bombay Hospital, Indore-452010 (Madhya Pradesh)

The Committee noted that the proposed site for inclusion under the clinical trial titled: “A trial comparing cardiovascular safety of insulin degludec versus insulin glargagine in subjects with type 2 diabetes at high risk of cardiovascular events.” and “Efficacy and safety of Semaglutide once weekly versus Sitagliptin once daily as add on to Metformin and/or TZD in subjects with Type 2 diabetes” is having 20 beds including ICU.

After deliberation, the Committee did not recommend for the addition of this site under the said study. The Committee further recommended that the clinical trials sites should have minimum 50 number of beds in the Institute / Hospital with emergency medical care facility.

The meeting ended with the vote of thanks to the Chair.

Annexure-I

A. List of 05 cases of global clinical trials/ clinical trials of NCEs alongwith their evaluations and recommendations of the Committee.

Sr. No.	Drug	Names of the Applicant	Protocol No	Evaluations in respect of three Parameters 1. Risk versus benefit to the patients 2. Innovation <i>vis-a-vis</i> existing therapeutic option. 3. Unmet medical need in the country	Recommendations
1.	UT-15C (Treprostinil Diethanolamine)	Pharmaceutical Research Associates India Private Limited	TDE-PH-310)	<p>Risk versus benefit to the patients- The risk vs benefit profile of the test drug from preclinical single dose and repeat dose toxicity studies and phasel, II and III clinical trials justify the conduct of this study with the sustained release dosage form.</p> <p>Innovation <i>vis-a-vis</i> existing therapeutic option- The test drug is an innovative therapy, not because it originates from a new therapeutic class of drug, but rather due to the route of administration and the sustained release dosage form.</p> <p>As per protocol, the purpose of the study is to compare the time to first clinical worsening of PAH in patients receiving test drug + ERA / PDE5-I therapy vs ERA/PDE5-I therapy alone.</p> <p>Unmet medical need in the country- TreprostinilSR(UT-15C) oral formulation may potentially help PAH patients due to its once weekly dosing.</p>	<p>Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.</p> <p>(NDAC recommendation - The committee reviewed the minutes of earlier NDAC held on 27/9/13 and the presentation made by the applicant during this meeting. The committee recommends for the conduct of the study at the proposed centers/trial sites.)</p>

2.	UT-15C (TreprostinilDiet hanolamine)	Pharmaceutical ResearchAssoc iatesIndiaPrivat eLimited	TDE-PH-311	<p>Risk versus benefit to the patients- The risk vs benefit profile of the test drug from the preclinical single dose and repeat dose toxicity studies and phasel, II and III clinical trials justify the conduct of this study with the sustained release dosage form.</p> <p>Innovation vis-a-vis existing therapeutic option- The test drug is an innovative therapy, not because it originates from a new therapeutic class of drug, but rather due to the route of administration and it being a sustained release dosage form.</p> <p>This is an open label study protocol to assess the long term safety of UT-15C</p> <p>Unmet medical need in the country- Treprostenil SR (UT-15C) oral formulation may potentially help PAH patients due its once weekly dosing.</p>	<p>Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.</p> <p>(NDAC recommendation - The committee reviewed the minutes of earlier NDAC held on 27/9/13 and the presentation made by the applicant during this meeting. The committee recommends for the conduct of the study at the proposed centers/trial sites.)</p>
3.	Pregabalin (Lyrica®)	Pfizer Limited	A0081105	<p>Risk versus benefit to the patients- The risk vs benefit profile of test drug from preclinical toxicity studies including acute and multiple-dose oral studies in rats and monkeys and phase I, II/III trials justify the conduct of this study.</p> <p>Innovation vis-a-vis existing therapeutic option- Pregabalin due to different mechanism of action compared to the conventional anti-epileptic drugs may potentially provide an additional choice for the control of seizures.</p> <p>The purpose of this study is to demonstrate superior efficacy of Pregabalin compared to placebo for treatment of PGTC seizures as measured by the 28 days seizure rate.</p> <p>Unmet medical need in the country- Epilepsy is a chronic disorder</p>	<p>Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.</p> <p>(NDAC Recommendation: The NDAC recommended for approval of trial protocol)</p>

				and patients usually require change in anticonvulsant therapy (with drugs such as lamotrigine, topiramate, levacetam, zonisamide, valproate, etc) due to lack of tolerability. Pregabalin may potentially benefit to such patients.	
4.	Dapagliflozin propanediol	Bristol -Myer Squibb India Pvt Limited	D1693C00001	<p>Risk versus benefit to the patients- The risk vs benefit profile of the test drug from preclinical toxicity studies including pivotal multiple dose toxicity studies in rats and dogs and Clinical data from several clinical Pharmacology studies including Phase II, III clinical trials justify the conduct of this study.</p> <p>Innovation vis-a-vis existing therapeutic option- Preliminary hypothesis-generating data from clinical studies indicate that the test drug may have CV protective effect in T2DM patients. The purpose of the study is to evaluate the effect of test drug on the incidence of cardiovascular death, MI and ischemic stroke in T2DM Patients.</p> <p>Unmet medical need in the country- The test drug may potentially provide a beneficial/ alternate option for T2DM Patients.</p>	<p>Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.</p> <p>(NDAC Recommendation: The committee has recommended for the approval of trial with dapagliflozin with the condition that all PIs should be specialist of internal medicine, diabetologist or endocrinologist instead of cardiologist and upper age limit should be 65 years. The firm will submit the details of DSMB.)</p>
5.	Eravacycline (TP 434)	PSI CRO Pharma India Pvt Ltd	TP-434-008	<p>Risk versus benefit to the patients- The risk vs benefit profile of the test drug from preclinical toxicity studies including single dose and multiple dose in rats, dogs and monkey and phase I, II Clinical trials justify the conduct of the study.</p> <p>Innovation vis-a-vis existing therapeutic option- Eravacycline has in vitro potency and spectrum to cover the intestinal flora that</p>	<p>Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.</p> <p>(NDAC recommendation - NDAC recommended for the conduct of the trial subject to the condition that the sites should be geographically distributed including north eastern and north western region of India, accordingly the applicant has submitted the list of sites for approval</p>

				<p>commonly causes cIAls.</p> <p>The purpose of the study is to compare the safety and efficacy of the test drug with a carbapenem class of drug in complicated intra-abdominal infections.</p> <p>Unmet medical need in the country-</p> <p>There is need for broad-spectrum antibiotics to empirically cover the wide range of potential pathogens seen in cIAls.</p>	<p>prior to grant of clinical trial permission.)</p>
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Annexure-II

B. List of 08 cases of clinical trial proposals other than GCT/NCE alongwith evaluations and recommendations of the Committee.

Sr. No.	Drug	Names of the Applicant	Protocol No	Recommendations
1.	Peginterferon alfa-2b	M/s Lupin Limited	LBC-P-034-13	Technical Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.
2.	Bevacizumab	M/s. Biocon Limited	BM100-CC-03-101	The Technical Committee agreed with NDAC opinion. However the names of the sites where pk-pd study will be conducted should be submitted and the PI's in the sites should be medical oncologist.
3.	AzilsartanMe doxomil	M/s Synokem Pharmaceuticals Limited	Synokem/CT/ Azilsartan/102 010	Technical Committee reiterated its earlier decision that the study in first 20 patients should be conducted in ICU setting. Based on results of 20 patients, the study can be extended on the subjects under OPD setting.
4.	AzilsartanMe doxomil	Hetero Labs Limited, Hyderabad	HCR/III/AZILE HI/10/2012	Technical Committee evaluated and recommended for the conduct of clinical trial as per the revised Clinical trial protocol.
5.	Arterolane Maleate and Piperazine Phosphate	RanbaxyLaboratories Limited	8006_APRRS _13	Technical Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.
6.	Teneligliptin and Metformin Tablets	M/s Glenmark Pharmaceuticals Limited	GPL/CT/2013/ 003/III	Technical Committee evaluated and recommended for the conduct of clinical trial as per the submitted Clinical trial protocol.
7.	Tioconazole Vaginal Tab.	Precise ChemipharmaPvt . Ltd.	CMI- PRE/T10/CT- III/070113	Technical Committee recommended resubmitting the proposal along with the opinion of Gynecologist.
8.	AzilsartanMe doxomil	M/s MSN Labs	NEX/AZL/CT- III- 5004/05/2011	Technical Committee reiterated its earlier decision that the study in first 20 patients should be conducted in ICU setting. Based on results of 20 patients, the study can be extended on the subjects under OPD setting.