Minutes of IND Committee meeting held on 24.01.2017 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

List of Participants:

1. Dr. Soumya Swaminathan, Secretary, Dept. of Health Research & Director General, Chairperson, IND Committee.
2. Dr. Y.K. Gupta, Prof. & Head, Dept. of Pharmacology, AIIMS, New Delhi.
3. Dr. A.K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
4. Dr. C. D. Tripathi, Prof. & Head, Department of Pharmacology, VMMC, New Delhi.
5. Dr. Nilima Kshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
6. Dr. Bikash Medhi, Prof. Dept. of Pharmacology, PGIMER, Chandigarh.
7. Dr. S.K. Sharma, Ex-Prof. & Head, Dept. of Medicine, AIIMS, New Delhi

ICMR Representative:

1. Dr. Vijay Kumar, Scientist G, Division of BMS-Co-ordinator, ICMR, New Delhi

CDSCO Representatives:

1. Dr. V. G. Somani, Joint Drugs Controller (India), CDSCO.
2. Mrs. Rubina Bose, Deputy Drugs Controller (India), CDSCO (HQ).

Following members could not attend the meeting:

1. Dr.Deepak Kaul, Prof. & Head, Deptt. Of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
2. Dr. Chandishwar Nath, Ex. Scientist-G & Scientist –in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
3. Prof. Dinesh Puri, Head, Department of Medical Bio-Chemistry, GTB Hospital, Shahdara, New Delhi.

Dr. Soumya Swaminathan, Chairperson of the Committee welcomed the members to the meeting. She then apprised the Committee about the order of the Hon'ble Supreme Court of India, dated 21.10.2013 in the matter of W.P. (C) No. 33/2012 of Swasthya Adhikar Manch, Indore & Anr Vs. Ministry of Health and Family Welfare &Ors. with WP(C) No. 779/2012 regarding clinical trials wherein it was directed that the Technical Committee and the Apex Committee while evaluating the cases shall keep in view all relevant aspects of safety and efficacy particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic option and unmet medical need in the country.

In view of this the Chairperson requested the members for their critical evaluation of applications considering various scientific and ethical parameters of the proposals, specially all relevant aspects of safety and efficacy particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic option and unmet medical need in the country. The minutes of the last IND meeting held on 15.12.2016, which was already circulated to the members were taken as approved.

S.No.01

Phase III clinical trial with Remogliflozin Etabonate Tablets 100mg and 250mg of M/s Glenmark Pharmaceuticals Limited.

This office has received an application from M/s Glenmark Pharmaceuticals Limited for the grant of permission to manufacture and market Remogliflozin Etabonate bulk drug and Remogliflozin Etabonate Tablets 100mg/ 250mg and conduct a Phase III clinical trial with Remogliflozin Etabonate Tablets entitled, "A 24-week randomized, double-blind, double-dummy, parallel-group, multi-centre, active-controlled study to evaluate efficacy and safety of Remogliflozin Etabonate in subjects with type-2 diabetes mellitus".

Remogliflozin Etabonate is a Novel SGLT2 inhibitor.

This is a 24-week randomized, double-blind, double-dummy, active-controlled, three-arm, parallel-group, multi-center study to evaluate the efficacy and safety of Remogliflozin Etabonate in comparison to Dapagliflozin in subjects with T2DM who have inadequate glycemic control with diet and exercise alone or with stable dose of Metformin as monotherapy.

Subjects with HbA1c ≥ 7% but ≤ 10% at Screening will be considered eligible for randomization, on fulfilling other study inclusion criteria.

Eligible subjects will be randomized to receive one of the following treatments in a double blind, double dummy design. Matching placebo(s) will be used to blind the three treatment arms and every subject will receive a total of 3 tablets twice daily including one of the following active study drugs along with matching placebo(s) for the other two study drugs.

Arm 1: Remogliflozin Etabonate 100 mg, administered as 1 tablet BID for 24 weeks

Arm 2: Remogliflozin Etabonate 250 mg, administered as 1 tablet BID for 24 weeks.

Arm 3:Dapagliflozin 10 mg, administered as 1 tablet QD in morning + Placebo, administered as 1 tablet QD in evening, for 24 weeks.

In addition, subjects who have received Metformin at stable doses of > 1500 mg per day (> 1000 mg per day in subjects not tolerating), will continue to receive the same dose throughout the study period in an open label manner. 612 subjects at 5 sites will be enrolled.

Primary objective of the study is to evaluate the glycemic efficacy of Remogliflozin Etabonate compared to Dapagliflozin after 24 weeks in subjects with type 2 diabetes mellitus.

Secondary objective of the study is to evaluate effect of Remogliflozin Etabonate on total body weight compared to Dapagliflozin after 24 weeks of treatment and to evaluate the safety and tolerability of Remogliflozin Etabonate in comparison to Dapagliflozin.

Discussion, observations and recommendations of the Committee: -

Based on the statement of the firm, the committee noted that firm has taken the ownership of the product and the chemical, non-clinical and clinical data generated on the product outside India. When enquired by the committee about the product ownership and development plan, firm informed that they have acquired the product and the chemical (CMC),preclinical and clinical data generated on it from the parent companies (GSK and Kissei, Japan).

Further it was also informed that the raw data of all the development is available with the firm, as may be required for examination purposes. Also it was informed by the firm that this drug though discovered in Japan and partly developed/studied in Europe, will be further manufactured (API

and formulation, in India by the applicant firm that is M/s Glenmark) and will be taken into further phases of trial i.e phase III trial, India and subsequently in other countries (for which other partners may also be involved).

As the proposed phase III trial is not a global clinical trial but a clinical trial in India specific population for the NCE, which has undergone clinical development upto phase II in other countries, the committee examined the rule position as in Schedule Y of Drugs and Cosmetics Rules, wherein it is stated that 'for new drug substances discovered in countries other than India, phase I data from other countries as per Appendix 1 of Schedule Y should be submitted along with the application. After submission of phase 1 data generated outside India, permission may granted to repeat the phase I trials and/or to conduct phase II trials and subsequently phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted.'

The Committee further examined the proposal as per the three criteria- (1) Risk vs benefit (2) innovations-vis-a -vis existing therapy (3) unmet medical need and opined that as the NCE has shown adequate efficacy and initial result for improved safety upto phase II level than the existing therapeutic option within the class of drug glifozins at the dose of 100 mg and 250 mg, therefore it was decided to examine the protocol for further development in India.

When enquired about why GSK has stopped further development of this drug, the representatives of the firm replied that, against the once daily dose available for this class of drug, twice daily dose of the said drug and the anticipated commercial reasons, GSK might have discontinued the further development of the drug and it was further stated that there were no other reasons related to the safety, efficacy and quality of this IND/NCE.

CDSCO approved three gliflozins viz. Canagliflozin, Dapagliflozin and Empagliflozin based on Global Clinical Trials conducted in India. A total of 12795, 11000 and 16395 global patients were enrolled in these trials out of which 1038, 414 and 498 were Indian patients in the clinical studies with Canagliflozin, Dapagliflozin and Empagliflozin respectively.

Global clinical trial conducted with Empagliflozin was on 2477 global patients, out of which 332 were Indian and it was randomised, double-blind, 3 parallel groups study comparing Empagliflozin 10 mg once daily (830 patients), Empagliflozin 25 mg/once daily (822 patients) and placebo (825 patients) as add-on to standard of care treatment of patients with T2DM.

The Committee enquired that whether 612 subjects having three arms of approximately 200 subjects in each arms - Remogliflozin etabonate 100 mg, Remogliflozin etabonate 250 mg and Dapagliflozin 10 mg is sufficient number for considering approval of Remogliflozin for first time in the world in India, based on the safety and efficacy outcome of this trial. For which the firm informed proposed number of subjects is sufficient for approval of the indication T2DM as an add on to Metformin.

Thereafter, committee deliberated in detail the Phase III protocol presented by the firm and opined as follows:

1. Only diabetic patients who are on Metformin 1000 - 1500 mg doses and are not controlled should be included in the study and the investigational drug Remogliflozin should be given as add-on drug only. Accordingly the committee suggested removing the treatment naïve arm of Remogliflozin.
2. The data presented by the firm suggested that 50 mg dose of Remogliflozin was more effective in reducing the Hb1Ac levels than the 100 mg dose. Further, there was a dose response relationship between 100 and 1000 mg dose at 12 weeks duration. The firm

explained this by stating that in totality the efficacy of 100 mg was better than 50 mg in which they considered Hb1Ac, fasting blood glucose and body weight as efficacy parameters. However, the data of the latter two parameters was not presented.

3. Since the important safety concerns stated by the firm are Urinary Tract Infections/Genital Fungal Infections, atleast once in 4 weeks clinical and bacteriological analysis of the urine should be carried out to detect any such infections.
4. It was presented by the firm that three active metabolites have been detected [GSK189075, GSK189074, GSK279782] for Remogliflozin. However, no report of degradation pathway and the toxicity of the said metabolites were submitted by the firm.
5. Pre-clinical toxicological studies were conducted in dogs at a dose range of 60, 100, 250, 300, 650 and 1000 gm for different durations [2 weeks, 4 weeks, 13 weeks, 52 weeks]. The results shown that, at dose of ≥250 mg/Kg for 4 weeks duration, slight microscopic changes were observed in Kidneys in addition to atrophy of seminiferous tubules (in recovery group), whereas, no such findings were noted in higher doses and at higher duration studies. However, justification for the same was not furnished by the firm except for the statement that said changes were reversed on long duration of exposure.
6. The data presented of three trials of Phase II were not done in India, and although Asian populations represented at 7% of the sample size, none of these were of Indian origin. The firm stated that the metabolizing enzyme/metabolic pathway is unlikely to be different between the population studied in Phase II and the Indian subjects, however no supportive evidence for the same were presented. Further, it was stated that the mechanism of action of the drug is not through the route which is influenced by ethnic variation.
7. It was opined by the Committee that pharmacokinetics studies should be conducted in Indian populations, since the pharmacokinetics of the formulation of the investigational drug in Phase I/II is not available in Indian subjects and new API and formulation is going to be manufactured in India by M/s Glenmark Pharmaceuticals by way of technology transfer.
8. The committee also deliberated in detail the adequacy of sample size (204+204+204: Total 612) for the proposed study. The firm presented that the study isone sided non-inferiority trial with active comparator evaluating efficacy with a margin of 0.35 for reduction in HbA1c in 24 weeks assuming a SD = 1% with 90% power (assuming a dropout rate of 15%). Based on this, the committee opined that this number may be inadequate if the efficacy of the two doses show variability in the subjects having differential Hb1Ac. With this background it was suggested by the committee that the firm should submit the data in a stratified manner according to Hb1Ac ranges of 7-7.9, 8.8.9 and 9-10. Therefore, it was opined that as phase II studies are carried out upto 12 weeks only, the firm should submit data/report of 12 weeks with pharmacokinetics, initially for evaluation by the Committee, and then after 24 weeks with stratified analysis of data, for evaluation of adequacy of the sample size by the committee so that based on the report, decision on whether further trials are needed to grant marketing approval or will it be sufficient and the prescribing information shall also be submitted by the firm at the time of submission of Phase III results for examination of context in it vis-à-vis evidence.
9. The firm also stated that the API and formulation shall be manufactured in India with technology transfer from the innovator. Therefore, the firm should establish pharmaceutical equivalence and bioequivalence of the said formulation. Accordingly

the firm should submit bioequivalence study protocol and conduct BE study of the formulation developed in India in comparison with the formulation used for Phase I/II study in a minimum of 24 normal healthy volunteers and similarly at least, repeat dose toxicity should be conducted for the drug developed in India (by technology transfer) as per Appendix III of Schedule Y of Drugs and Cosmetics Rules, 1945.

Considering these facts and that no concurrent Phase III trial is ongoing and similar class of drug is already in the market, the Committee recommended that the firm should submit study data/report of 12 weeks with pharmacokinetics initially and then after 24 weeks with stratified analysis of data, for evaluation of adequacy of the sample size by the committee so that based on the report, decision on whether further, non-inferiority phase III trial are needed shall be taken by the committee. The present permission of Phase III trial will not be construed as per only study for grant of marketing authorization after completion of trial and submission of report unless the above facts are examined to the satisfaction of the committee. Accordingly the firm should submit (i) revised clinical trial protocol with Pk study in Indian subjects by removing the treatment naïve patients & only including add on arm to Metformin (ii) BE study protocol for BE study of the formulation developed in India in comparison with formulation used for Phase I/II study outside India in a minimum of 20 normal healthy volunteers to CDSCO for re-deliberation in the next IND committee meeting.

Sr. No. 02

Phase II clinical trial with CPL-2009-0031 Tablets of M/s Cadila Pharmaceuticals Limited.

This Directorate has received an application from M/s Cadila Pharmaceuticals Limited for the grant of permission to conduct a Phase II clinical trial with CPL-2009-0031 entitled “Prospective, randomized, double blinded, parallel group, multicentric, comparative clinical study to compare efficacy and safety of oral CPL-2009-0031 of Cadila Pharmaceuticals Limited, India against innovator Sitagliptin in patients with Uncontrolled Type 2 Diabetes Mellitus (T2DM).

The proposal of the firm to conduct Phase II/ III clinical study was deliberated in IND Committee meeting dated 08.11.2016, wherein the firm presented the Phase I clinical study report and Phase II/ III clinical study protocol. After detailed deliberation, the Committee accepted the Phase I clinical study report and recommended that firm shall conduct Phase II clinical study with dose of 70mg and 140mg subject to following conditions:-

1. Uncontrolled T2DM shall be clearly defined in the inclusion criteria as subjects with HbA1c > 7 and those on oral hypoglycaemic agents other than Insulin and Gliptins.
2. Time point shall be defined in the protocol for rescue therapy.
3. Firm shall constitute an independent DSMB for evaluation of Phase II results and report to be submitted to the Committee for review before consideration of Phase III protocol.

Accordingly, revised protocol to be submitted. Further, the firm shall submit the complete developmental history of the drug with the mechanism of cleavage into Sitagliptin in the duodenum as presented by the firm.

Now, firm has submitted revised Phase II clinical trial protocol to conduct clinical study in 60 subjects at 5 sites in India.

This is a prospective, randomized, double-blinded, parallel group, three arm, multicentric, comparative, dose finding study of oral CPL-2009-0031 (70 & 140 mg) in comparison to Sitagliptin 50mg among patients with Uncontrolled Type 2 Diabetes Mellitus (T2DM) for the determination of safety, efficacy and tolerability.

Following 2-weeks of placebo run-in period and, diet and exercise counseling, patients will be randomized in 1:1:1 to receive CPL-2009-0031 (70 & 140 mg) once daily or oral Sitagliptin 50 mg once daily for a period of 12 weeks. Safety and tolerability will be evaluated through- out the study period. Additionally, follow-up visit at week 6 will be scheduled to evaluate the safety & treatment compliance of the patient. After end of 12 weeks study, phase II results and report will be submitted to IND committee for review before phase III study protocol. Based upon the DSMB recommendation phase III will be initiated.

Rescue therapy will be considered in case of medical emergencies which needs hospitalization. Investigator can use his discretion for the patient's well being during study period.

Recommendations of the Committee:-The applicant presented the Phase II clinical study protocol as suggested by the IND Committee dated 08.11.2016. After detailed deliberation, the committee recommended the Phase II study as per protocol with the recommendations that the firm needs to clearly define the time point of rescue therapy and the criteria for deciding the same.

Accordingly, revised protocol shall be submitted to CDSCO and if above parameters are included it may be approved.

Further the firm shall submit Animal toxicity report as per Appendix III of Schedule Y of Drugs and Cosmetics Rules, 1945. The committee also recommended that the firm shall conduct the following studies concurrently with the Phase II study and the result shall be submitted by the firm along with the Phase II Clinical study report:-

1. Mechanism of cleavage of the drug CPL 2009-0031 to Sitagliptin in animal models.
2. Effect of food on the Pharmacokinetics of the drug in humans.

S.No.03

Phase I clinical trial with FDC of HT61 HCl 0.75%w/w + Mupirocin 1.0% w/w + Neomycin sulphate 0.5% w/w of M/s Cadila Pharmaceuticals Limited.

This Directorate has received an application from M/s Cadila Pharmaceuticals Limited for the grant of permission to conduct a Phase I/II clinical trial with FDC of HT61 HCl 0.75%w/w + Mupirocin 1.0% w/w + Neomycin sulphate 0.5% w/w entitled "A Randomized, Double blind, Active Controlled, Parallel group Study to Evaluate the Safety and Efficacy of FDC of Mupirocin calcium, Neomycin Sulfate & HT61 HCL in Patients with infected skin lesions by Staphylococcus aureus including Methicillin-resistant Staphylococcus aureus (MRSA) and/or S. pyogenes".

The proposal of the firm to conduct Phase I/ II clinical study was deliberated in IND Committee meeting dated 08.11.2016, wherein the firm presented the Phase I/ II clinical study protocol. After detailed deliberation, the Committee recommended that firm shall initially conduct Phase I clinical study in minimum 30 patients to ascertain the safety at different wound sizes based on the preclinical toxicity study report. Further, the Committee decided that the Phase II clinical study protocol will be considered based on the results of Phase I clinical study. Accordingly, the firm shall submit revised Phase-I protocol to the Committee.

Now, firm has submitted revised Phase I clinical trial protocol entitled, "A prospective, randomized, parallel group Study to Evaluate the Safety and Efficacy of FDC of Mupirocin calcium, Neomycin Sulfate & HT61 HCL in Patients with infected skin lesions by Staphylococcus aureus including Methicillin-resistant Staphylococcus aureus (MRSA) and/or S. Pyogenes" to conduct clinical study in 30 subjects at Bodyline Hospitals, Ahmedabad, Gujarat.

This is a prospective, multicentric, randomized, parallel group, clinical trial is designed to evaluate safety and efficacy of FDC of Mupirocin 1% + Neomycin 0.5% + HT61 HCL 0.75%) of Cadila pharmaceutical Limited in patients with infected skin lesions by Staphylococcus aureus including MRSA and/or S. pyogenes. A total of 30 patients fulfilling eligibility criteria will be randomized in a ratio of 1:1:1 (10 patients in each group) to receive study treatment as per randomization schedule in three patient groups based on wound length as below:

- 1 – 4 cm Wound length
- 5 – 7 cm Wound length
- 8 – 10 cm Wound length.

Recommendations of the Committee:- The firm presented the Phase I clinical study protocol as suggested by the IND Committee dated 08.11.2016.

After detailed deliberation, the committee recommended the Phase I study as per protocol.

The meeting ended with vote of thanks by the Chair

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