Minutes of IND Committee meeting held on 27.11.2019 at ICMR (HQ), V. RamalingaSwamiBhawan, Ansari Nagar,New Delhi.

List of Participants:

1. Prof. BalramBhargava, Secretary, Department of Health Research & Director General, Chairman, IND Committee.
2. Dr. Y. K. Gupta, Ex. Dean, AIIMS, New Delhi.
3. Dr. S. K. Sharma, Ex-Prof. & Head, Department of Medicine, AIIMS, New Delhi.
4. Dr. C. D. Tripathi, Prof.& Head, Department of Pharmacology, VMMC, New Delhi.
5. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
6. Dr.ChandishwarNath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.

ICMR Representative:

1. Dr. Vijay Kumar, Scientist G, Division of BMS-Co-ordinator, ICMR, New Delhi.
2. Dr. RajniKaul, Scientist G, Division of BMS, ICMR, New Delhi.
3. Dr. Monika Pahuja, Scientist C, ICMR, New Delhi.

CDSCO Representatives:

1. Dr. S. Eswara Reddy, Joint Drugs Controller (India).
2. Mr. A. K. Pradhan, Deputy Drugs Controller (India), CDSCO (HQ).
3. Mr. R. Chandrasekhar, Deputy Drugs Controller (India), CDSCO (HQ).
4. Mr. Sanjeev Kumar, Deputy Drugs Controller (India), CDSCO (HQ).

Following members could not attend the meeting:

1. Dr. Deepak Kaul, Prof.& Head, Department of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
2. Prof. Dinesh Puri, Head, Department of Medical Bio-Chemistry, GTB Hospital, Shahdara, New Delhi.
3. Dr. NilimaKshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
4. Dr. BikashMedhi, Prof., Department of Pharmacology, PGIMER, Chandigarh.

Prof. BalramBhargava, Secretary, DHR and DG ICMR, Chairman of the Committee welcomed the members and informed the committee that since he has to attend another important meeting, in his absence Dr. Y. K. Gupta would Chair the meeting. Thereafter, the agenda items were discussed one by one.

Sr. No. 1

Proposal for marketing authorization of PMZ-2010 (Centhaquine citrate)

This isrelated to an application for grant of marketing authorization of Centhaquine Citrate bulk drug and Centhaquine Injection 1mg/vial indicated as a resuscitative agent for Hypovolemic shock.

Firm was granted permission to conduct the Phase III clinical trial, "A Prospective, Multi-Centric, Randomized, Double-Blind, Parallel, Phase-III Study to Assess Efficacy of PMZ-2010 as a Resuscitative Agent for Hypovolemic Shock to be Used as an Adjuvant to Standard Shock Treatment" on 24.12.2018.

Now, firm has submitted the Phase III clinical study report.

As per application submitted by the firm:-

PMZ-2010 (Centhaquine citrate) is targeted to be used as a "Regenerative agent for hypovolemic shock". The proposed mechanism of action of Centhaquine suggests that in low doses it acts on α2B adrenergic receptors to produce venous constriction and a consequent increase in venous return to the heart, and stimulation of sodium sense in the brain to increase the intravascular blood volume. These effects lead to an increase in cardiac output and tissue perfusion which may be responsible for its resuscitative action.

Preclinical toxicological studies of PMZ-2010 indicate a high safety margin. Single intravenous injection of PMZ-2010 in mice, rats and rabbits showed LD50>100 mg/kg, 79.43 mg/kg and 9.55 mg/kg, respectively. The No Observed Adverse Effect Level of PMZ-2010 in mice, rats, rabbits and dogs was found to be at the dose of 1.0 mg/kg, determined after repeated intravenous injections of different doses of PMZ-2010 for 28 days. Repeated administration of PMZ-2010 (0.45 mg/kg) was well tolerated by pregnant rats that gave birth to normal pups. PMZ-2010 did not affect postnatal development of rats. PMZ-2010 did not produce any effect on male fertility of rats when administered by intravenous route at and up to 1.0 mg/kg body weight. Also, repeated application of PMZ-2010 did not induce any skin sensitization as tested in guinea pigs. PMZ-2010 was found to be non-mutagenic as studied using bacterial reverse mutation assay, in-vitro mammalian chromosome aberration test, in-vivo mammalian bone marrow chromosome aberration test, and in-vivo mammalian erythrocyte micronucleus test. To evaluate the potential of PMZ-2010 to prolong QT interval, its binding affinities with hERG receptor was accessed in presence of [3H] dofetilide using radio-ligand binding method. In the binding assay, the IC50for PMZ-2010 obtained was 3.17 μM. This IC50value of PMZ-2010 is several folds higher than its maximum plasma concentration observed in rats and humans, thus indicating its wide safety margin.

Phase I clinical trial

Firm was granted Phase I clinical trial permission as per recommendation of IND Committee, Technical Committee and Apex Committee on 09.04.2014 and has conducted Phase I study entitled, "A randomized, double-blind, placebo-controlled Phase I study to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of PMZ-2010 in healthy male volunteers" in 25 healthy volunteers.

The primary objective of this phase I study was to determine the safety and tolerability of PMZ-2010 after Single ascending dose (SAD) and Multiple ascending dose (MAD) administration in healthy male volunteers. The secondary objective was to evaluate the pharmacokinetics (PK) of PMZ-2010after SAD and MAD administration and to determine exploratory pharmacodynamic markers of PMZ-2010 in the study population. This study was a double-blind, randomized and placebo controlled. The study drug was provided labeled as Lyophilized Centhaquinecitrate Injection (PMZ-2010)/Placebo (100 mL Normal Saline). Dose of PMZ-2010 for respective subject was calculated as per the Cohort and subject weight and then was administered in 100 mL of normal saline as IV infusion over one hour. The group details and treatments are given in the table below:

Study Groups	Treatment
	Single Ascending Dose (SAD)
Cohort I	A single dose of 0.005 mg/kg of PMZ-2010 (n=3) or placebo (n=1)
Cohort II	A single dose of 0.01 mg/kg of PMZ-2010 (n=3) or placebo (n=1)
Cohort III	A single dose of 0.05 mg/kg of PMZ-2010 (n=3) or placebo (n=1)
Cohort IV*	A single dose of 0.1 mg/kg of PMZ-2010 (n=3) or placebo (n=1)
	Multiple Ascending Dose (MAD)
Cohort V	0.033 mg/kg of PMZ-2010 (n=3) or placebo (n=1) administered every 8 hourly for 02 days
Cohort VI	0.067 mg/kg of PMZ-2010 (n=3) or placebo (n=1) administered every 8 hourly for 02 days

* An intermediate dose of PMZ-2010 (0.10 mg/kg, N=3) was used after noticing adverse event at 0.15 mg/kg dose (N=1).

PMZ-2010 was well tolerated and found safe when administered intravenously as SAD and MAD. A total of five non-serious adverse events were reported by 2 subjects among 25* dosed subjects (*One subject was dosed at 0.15 mg/kg dose level) during the study. The subject dosed with 0.15 mg/kg experienced expected adverse reactions of hypotension and high lactic acid while another subject experienced fall in respiratory rate, dryness of mouth

and drowsiness with an IV dose of 0.10 mg/kg. The events were mild in nature and resolved without sequelae and any intervention in about an hour. These adverse events occurred at more than ten folds higher than therapeutic dose of 0.01 mg/kg indicating a wide safety margin. None of the subject had experienced SAE in any cohort. Pharmacokinetic Analysis (PK):For single ascending dose of PMZ-2010, the maximum plasma concentration observed was between 0.59 ng/mL to 30.64 ng/mL (Cmax); time to reach Cmax was 0.08 h to 0.17 h (Tmax); elimination half-life was 0.71 h to 1.62 h (T1/2) and elimination rate constant was 0.983 to 0.438 (Kel) for doses ranging between 0.005 mg/kg to 0.1 mg/kg, administered singly. For multiple ascending doses, PMZ-2010 was administered every 8 hourly for 02 days. For 0.033 mg/kg dose, the Cmax of 8.891 ng/mL and 7.973 ng/mL was reached in 0.08 h of administration of first and last dose and for 0.067 mg/kg dose the Cmax of 10.472 ng/mL and 13.019 ng/mL was reached in 0.08 h of administration of first and last dose. In Phase I Study, PMZ-2010 was well tolerated and found safe after SAD and MAD administration. In SAD cohorts, a dose range of 0.005 mg/kg to 0.15 mg/kg was administered as IV infusion to healthy subjects and 0.1 mg/kg dose of PMZ-2010 was found to be maximum tolerated dose (MTD). In MAD cohorts, a dose range from 0.1 mg/kg/day to 0.2 mg/kg/day, calculated from MTD was administered every 8 hourly in three divided doses for 2 days. PMZ-2010 was found to be safe and well tolerated.

Phase II clinical trial

Firm was granted permission to conduct the Phase II clinical trial, "A prospective, multicentric, randomized, double blind, parallel, placebo controlled Phase-II safety and efficacy study of PMZ-2010 as a resuscitative agent for Hypovolemic Shock due to excessive blood loss to be used along with standard shock treatment" on 29.12.2016.

This was a prospective, multicentric, randomized, double- blind, parallel, saline controlled Phase II safety and efficacy clinical study of PMZ-2010 therapy in patients with Hypovolemic shock due to blood loss with systolic arterial blood pressure ≤ 90 mmHg at presentation and continues to receive standard Shock Treatment.

A total of 137 patients were screened, of which 50 patients met inclusion and exclusion criteria and were included in the study. All patients received standard treatment for shock and were randomly assigned to either control group (N=26) that received standard treatment for shock along with normal saline or PMZ-2010 group (N=24) that received standard treatment along with PMZ-2010. From control group, 22patients completed the study (2 patients withdrawn by the investigator, 2 patients withdrawn the consent) and from PMZ-2010 group 23 patients completed the study (1 patient withdrawn by the investigator). Demographics ofpatients in both cohorts were comparable. SBPin control did not reach statistical significance ($p=0.0795$) 12 hours after resuscitation compared to baseline (before resuscitation) on the other hand in PMZ-2010 cohort extremely significant ($p<0.0001$) increase in SBPwasobserved. Similarly, an extremely significant ($p<0.0001$) increase was observed in DBPin PMZ-2010 cohort compared to control. Blood lactatelevels (mmol/L) decreased from 4.30±0.96 at baseline to 3.28±1.12 ($p=0.4929$) at

day 3 in control and from 4.34±0.78 at baseline to 1.44±0.13 (p=0.0012) at day 3 in PMZ-2010 cohort. Total amount of vasopressors administered in the first 48 hours of resuscitation were 9.84±4.47 mg in the saline group, and 3.12±2.18 mg in PMZ-2010 treated patients (p=0.1868). Serum creatinine (mg/dL) decreased from 0.93±0.11 at baseline to 0.57±0.03 (p=0.0030) at end of study in control and from 1.13±0.10 at baseline to 0.72±0.05 (p=0.0012) at end of study in PMZ-2010 cohort. Time spent on ventilator was 0.89±0.45 days in patients from PMZ-2010 group while it was 2.05±1.15 days in patients from control group. Two out of 22patients died in control and none in PMZ-2010 cohort. Three (3) adverse events were reported inthreepatients of control group (N=21). Out of these three, two events were serious (death), and one was moderate (Hepatitis) which was resolved with medical intervention. Two (2) adverse events (Diarrhea and AcuteKidney Injury) were reported in two patients of PMZ-2010 group (N=23) which were moderate in severity and were resolved with medical intervention. All these adverse events in control and PMZ-2010 groups were not related to study drug or study procedures and were completely associated with patient's disease progression. No clinically significant effect of study drug was observed on vital signs, ECGs and laboratory parameters. PMZ-2010 was found to be safe and was well tolerated in patients of hypovolemic shock due to blood loss. The results indicate that, PMZ-2010 is a highly effective resuscitative agents and is likely to improve the outcome of patients of hypovolemic shock.

Phase III clinical trial

Firm was granted permission to conduct the Phase III clinical trial, "A Prospective, Multi-Centric, Randomized, Double-Blind, Parallel, Phase-III Study to Assess Efficacy of PMZ-2010 as a Resuscitative Agent for Hypovolemic Shock to be Used as an Adjuvant to Standard Shock Treatment" on 24.12.2018.

This was prospective, multi-centric, randomized, double-blind, parallel, controlled phase-III efficacy clinical study of PMZ-2010 therapy conducted in patients with hypovolemic shock with systolic arterial blood pressure ≤ 90 mmHg at presentation and continue to receive standard treatment for hypovolemic shock. The study was conducted with the following objectives:

- **Primary Objectives:-**
  - Change in systolic and diastolic blood pressure, Mean through 48 hours [Time frame: first 48 hours].
  - Change in blood lactate, Mean through 48 hours [Time frame: first 48 hours].
  - Change in Base-deficit, Mean through 48 hours[Time frame: first 48 hours].

A total of 197 patients were assessed for eligibility, out of which 105 patients were enrolled in the study and 92 patients did not meet the eligibility criteria and were excluded. Out of 105 patients, 71 were randomized in PMZ-2010 group and 34 in control group. In PMZ-2010 group 1 patient withdrew consent and 2 patients were excluded by the investigator. A total of

34(22 male and 12female) patients in control and 68 (41 male and 27 female) patients in PMZ-2010 group completed the study. In both treatment groups, patients were provided the standard of care. PMZ-2010 or Normal Saline was administered intravenously after randomization to hypovolemic shock patients with systolic arterial blood pressure ≤ 90 mmHg at presentation and who continued receiving standard treatment for hypovolemic shock.

In PMZ-2010 group, dose of PMZ-2010 (0.01 mg/kg) was administered as an IV infusion over 1 hour in 100 mL of normal saline. Second dose of PMZ-2010 was administered only if SBP falls below or remained below or equal to 90 mmHg but not before 4 hours of previous dose and total doses per day (in 24 hours) was not exceeded3 doses. PMZ-2010 administration if needed was continued for two days (only if needed) post randomization. Minimum 1 dose or maximum 6 doses of PMZ-2010 was administered within first 48 hours post randomization. In control group, single dose of equal volume of normal saline was administered as IV infusion over 1 hour in 100 mL of normal saline post randomization. Condition of administration remained same as for PMZ-2010 group. Each patient was monitored closely throughout his/her hospitalization and was followed until discharge from randomization.

Now, firm has submitted the report of Phase III clinical trial and requested for manufacturing and marketing permission of Centhaquine Citrate bulk drug and Centhaquine Injection 1mg/vial.

Firm has also submitted the Phase IV clinical trial protocol entitled, "A prospective, multi-centric, open-labeled, phase-IV study to assess safety and efficacy of LYFAQUIN™(Centhaquine citrate)as a resuscitative agent for hypovolemic shock to be used as an adjuvant to standard treatment of shock". 400 patients will be enrolled in the study. Approximately 50 study centers in India will participate in the study.

In light of recommendation of IND Committee dated 08.12.2018, the firm presented their proposal along with results of the Phase III clinical trial data.

Recommendation of the Committee:-

The Committee after detailed deliberation recommended for grant of permission to manufacture and market Centhaquine Injection1mg/vial as addon resuscitative agent for Hypovolmic Shock subject to fulfillment of following conditions:-

1. The manufacturing facility should be inspected to verify GMP compliance.
2. Some of the trial site should be inspected to verify the GCP compliance.
3. Proposed Package insert, Label, Carton to be adopted should be got approved fromCDSCO as per the requirements of the Rules.
4. The firm shall submit Phase IV clinical trial protocol before launching the product.
5. The firm shall submit the background information as available regarding earlier development and discontinuation of the product, as well as the difference in terms of salts, dosage form etc., if any developed earlier vis-à-vis the proposed product.

Sr. No. 02

Marketing authorization of Saroglitazar tablets 2mg and 4mg

This isrelated to an application for grant of permission to manufacture and marketing of Saroglitazar tablets 2mg and 4mg (Additional indication).

Additional Indication: Type 2 Diabetes Mellitus -as an add-on therapy to Metformin.

CDSCO approval status:-

Drug Name	Strength	Indication	Date of approval
Saroglitazar 2mg/4mg Tablets	Each uncoated tablet contains; Saroglitazar 2mg, 4mg.	For the treatment of diabetic dyslipidemia and hypertriglyceridemia with type-2 diabetes mellitus not controlled by statin therapy.	25.02.13 to M/s Cadila healthcare Ltd.

CDSCO had granted permission dated January 09, 2015 (F. No. 12-05/05-DC (Pt-C) to conduct Phase III clinical trial entitled "A multi-centric, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2mg and 4mg as compared to Pioglitazone in Type 2 Diabetes Mellitus",

Protocol No.: SAR0.14.002.01.01. PROT, version No. 1.1, dated December 12, 2014.

Firm stated that they have completed the above mentioned Phase-III study as per approved protocol (Protocol No.: SAR0.14.002.0l.0l.PROT, version No. 1.1). This phase III study was planned to evaluate the efficacy and safety of Saroglitazar 2mg and 4mg as compared to Pioglitazone 30 mg in type 2 diabetes mellitus.

Results of the present study showed that statistically significant reduction from baseline in each treatment group (Saroglitazar 2mg group, Saroglitazar 4mg group and Pioglitazone 30 mg group) at Week 24 (p-value <0.016) when administered along with metformin. The within group mean(± SD) change in HbA1c (%)from baseline of the Saroglitazar (2mg and 4 mg) and Pioglitazone 30mg treatment groups at week 24were: -1.38 ± 1.99 for Saroglitazar 2mg; 1.4 7 ± 1.92 for Saroglitazar 4mg and -1.41± 1.86 for Pioglitazone 30 mg, respectively

Overall, the treatment with Saroglitazar 2mg and 4mg improved glycemic control over 56 weeks in patients oftype II Diabetes mellitus receiving background Metformin therapy. Both the strengths of Saroglitazar met the primary objective of the study and led to a clinically meaningful reduction of HbA1c levels. This reduction which was evident by week 12 was consistently sustained through week 24 till week 56. Saroglitazar was well tolerated by the patients. Most of

the adverse events were mild to moderate in severity and were resolved. There were no safety concerns with the laboratory evaluations.

Now, firm submitted application for approval of new indication as **Type 2 Diabetes Mellitus-as an add-on therapy to Metformin**by taking into consideration the results of Saroglitazar in this study wherein it has beneficial effects on the glycemic parameters and diabetic dyslipidemia, and without safety concerns.

Firm has submitted Therapeutic Rationale and Justification for the Proposed Additional Indication as under:

Thiazolidinedione drugs are widely used to lower blood glucose levels in subjects with type 2 diabetes mellitus. In the United States, three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity; rosiglitazone (Avandia, GlaxoSmithKline), which recently received black-box warning from Food and Drug Administration (FDA) for its adverse effects on heart and the currently available Pioglitazone (Actos, Takeda).Thiazolidinediones act as agonists for PPAR-γ receptors, receptors which are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues. Similarly, fibric acid analogs, known to be PPAR-α agonists, are in clinical practice for lowering lipids in hyperlipidemic subjects albeit not very effectively. On the other hand, statin class of compounds is the most successful therapeutic agent for the management of dyslipidemia and hypercholesteremia. However, no single therapy is able to reach desirable clinical endpoint for Syndrome X.Several research groups have or are attempting to develop dual PPARα/γ agonist, some whichmay eventually reach desirable clinical efficacy and safety endpoint. But if the agonist has higher PPARγ binding properties then several of the side effects such as edema, weight gain, bone effect and cardiovascular complication may occur. Therefore, there has been an increasing interest to develop new molecular entities, which can treatinsulin resistance, lower plasma glucose in diabetic subject, improve lipid profile without weight gain and cardiovascular risk. New chemical entity having a superior PPAR-α agonist activity with a moderate PPAR-γ agonist activity is developed; it might have desirable clinical profile with having no edema or weight gain effects. Based on this assumption, Saroglitazar (LipaglynTM; Code:ZYH1) having a preferential PPARα agonist property with a moderate PPARγ agonist activity has been developed by Cadila Healthcare Limited (CHL).Thus, Saroglitazar belongs to a new class of NME having predominantly PPAR α agonist activity.

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The proposal was deliberated in IND Committee meeting dated 10.10.2019.

Recommendation of the IND Committee dated 10.10.2019:- The firm presented their proposal alongwith Phase III clinical study report. The Committee noted that the drug is already approved for diabetic dyslipidemia and hence, this proposal should be deliberated in the next meeting in presence of Cardiologists and Diabetologists. The firm should also present details in respect of dosage, recommendation, precautions, warning etc. for the drug.

As advised by the Committee, the Diabetologist and Cardiologist from the panel were invited for attend the meeting. However, because of pre-occupation they could not attend.

In light of recommendation of the Committee dated 10.10.2019, the firm presented the details about dosage recommendations, precaution, warning etc.

Recommendation of the Committee:-

After detailed deliberation, the Committee recommended for grant of permission to manufacture and market the drug Saroglitazar 2mg and 4mg for Type 2 Diabetes Mellitus – as an add-on therapy to Metformin, subject to condition that the firm should clearly mention the recommendation about the dose titration and conditionsregarding use of 4mg strength in the package insert of the product. The Package insert, Label, Carton to be adopted should be got approved fromCDSCO as per the requirements of the Rules.

Sr. No. 3

Phase III clinical trial of FDC of Remogliflozin 100mg + Vildagliptin 50mg Tablets

This is related to an application for conduct of the Phase III clinical trial protocol as well as BE study Protocol of fixed dose combination of Remogliflozinetabonate and Vildagliptin in subjects with type-2 diabetes mellitus. For the indication of Fixed dose combination of Remogliflozin Etabonate &Vildagliptin is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- To improve glycaemic control when Metformin and one of the mono-components of fixed dose combination of RemogliflozinEtabonate&Vildagliptin do not provide adequate glycaemic control
- When already being treated with the free combination of RemogliflozinEtabonate&Vildagliptin.

Based on IND committee recommendations, detailed documents submitted by the firm, CDSCO has granted permission to manufacture and market RemogliflozinEtabonate bulk and RemogliflozinEtabonate tablets 100mg on 26.04.2019 to be indicated in adults aged 18 years and older with type2 diabetes mellitus to improve glycaemic control as:-

1. Monotherapy when diet and exercise alone do not provide adequate glycaemic control.
2. Add on therapy with Metformin, together with diet and exercise, when these do not provide adequate glycaemic control with following conditions.
    I. The firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.
    II. Proposed Package Insert, Label, Carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.

Further, CDSCO has also granted permission to manufacture and market RemogliflozinEtabonate + Metformin Hydrochloride IP (100mg + 500mg & 100mg + 1000mg) on 14.08.2019 to be indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control:

I. In patients insufficiently controlled on their maximally tolerated dose of Metformin alone
II. In patients already being treated with the combination of Remogliflozin and Metformin as separate tablets.

Brief of Pre-clinical information:

Glenmark Pharmaceuticals Limited, India has developed a fixed dose combination of Remogliflozinetabonate + Vildagliptin (100/50 mg) tablet. The recommended daily dose is 100/50 mg twice daily (200/100 mg/day). To support the Marketing authorization of the proposed fixed dose combination, Glenmark Pharmaceuticals Limited, India has conducted acute (mice and rats) and repeat dose (13-week study in rats) oral (gavage) toxicity studies with a combination of Remogliflozinetabonate + Vildagliptin.

Nonclinical data included in this overview are based on the information generated by the Applicant, obtained following a literature search during the month of May 2019 using the primary databases TOXLINE and PubMed or from regulatory review documents. Only the relevant nonclinical data in the public domain have been cited in this nonclinical overview.

Animal Toxicology:

RemogliflozinEtabonate + Vildagliptin Combination:

Glenmark Pharmaceutical Limited, India has conducted single dose toxicity study in mice and rats where animals were dosed orally with 750 (500+250), 1500 (1000+500) and 2100 (1400+700) mg/kg with Remogliflozinetabonate + Vildagliptin combination. No mortality and clinical signs were noted. No treatment related effect on body weight and body weight gain were noted. Gross pathology examination did not reveal any abnormality. The maximum tolerate dose (MTD) was 2100 (1400+700) mg/kg in mice [Study No. BIO-ATX 745, 2019] and rats [Study No.

BIO-ATX 744, 2019] which is about 34 and 68 times, respectively the MRHD of 200+100 mg/day (100+50 mg BID) of Remogliflozinetabonate + Vildagliptin. Additionally Sponsor is also conducting a 13-week repeat dose oral (Gavage) toxicity study with Remogliflozinetabonate + Vildagliptin combination in rats. The final report of the study will be submitted to the Agency as the earliest.

Based on the above non clinical data of Remogliflozinetabonate and Vildagliptin alone or in combination, adequate safety to support the human use of a fixed dose combination of Remogliflozinetabonate + Vildagliptin up to daily doses of 200+100 mg/day (100 + 50 mg twice daily) has been established.

Brief of Clinical Information:

The pathogenesis of T2DM is complex and involves multiple metabolic defects. As a result, the use of combination therapy with glucose lowering drugs with different mechanisms of action has the advantage of preventing compensatory mechanisms and has the potential to produce an additive reduction in HbA1c.. Thus, the combination of SGLT2i plus DPP-4i has the potential to produce a robust reduction in HbA1c. Also, due to differences in mechanism of action, the potential for adverse effects is expected to be less with the use of combination than with increasing the doses of monotherapy. A systematic review and meta-analysis of 14 randomized controlled trials demonstrated greater reduction in HbA1c with the combination compared to mono-components (Li D, et al, Diabetes ObesMetab. 2018).

Remogliflozin and Vildagliptin are twice daily SGLT2i and DPP4i respectively, approved in India for the treatment of diabetes as monotherapy and add-on therapy with Metformin. Many patients are likely receiving Remogliflozin and Vildagliptin concomitantly as separate tablets. A fixed dose combination of Remogliflozin and Vildagliptin will reduce the pill burden and help improve treatment compliance.

Thus a second-line oral dual add-on therapy with Vildagliptin plus Remogliflozinetabonate could be a new option, as part of a triple combination that only includes drugs with complementary mechanisms of action, a low risk of hypoglycaemia and also has the potential for moderate weight loss, thus contributing in a useful and complementary fashion to a more effective, patient friendly management of T2DM.

Efficacy and safety of Remogliflozin and Vildagliptin has been established and both the mono-component products are approved in India and Europe

Phase III CT Protocol Details:

Study Design:

A Randomized, double-blind, double-dummy, active-controlled, two-arm, parallel group, multi-centre study to evaluate the efficacy and safety of concurrent administration of FDC of Remogliflozinetabonate and Vildagliptin with Metformin in comparison with concurrent administration of FDC of Empagliflozin and Linagliptin with Metformin in subjects with T2DM who have inadequate glycemic control with stable dose of Metformin as monotherapy.

Study duration: 16 weeks treatment period

Sample size: A total of 400 subjects with T2DM will be enrolled (randomized) in the study.

Primary Objective:

To evaluate the efficacy of concurrent administration of FDC of Remogliflozinetabonate and Vildagliptin with Metformin in comparison with concurrent administration of FDC of Empagliflozin and Linagliptin with Metformin in change from baseline in glycosylated haemoglobin (HbA1c) after 16 weeks of double-blind treatment in subjects with type 2 diabetes mellitus.

Secondary Objective:

To evaluate the efficacy of concurrent administration of FDC of Remogliflozinetabonate and Vildagliptin with Metformin in comparison with concurrent administration of FDC of Empagliflozin and Linagliptin with Metformin in:

- change from baseline in fasting plasma glucose and
- change from baseline in post-prandial plasma glucose
- change from baseline in Body weight
- proportion of patients achieving therapeutic glycaemic response defined as HbA1c <7%
- proportion of subjects requiring rescue medication

To evaluate the safety and tolerability of concurrent administration of FDC of Remogliflozin and Vildagliptin with Metformin in comparison with concurrent administration of FDC of Empagliflozin and Linagliptin with Metformin over 16 weeks of double-blind treatment.

No of sites proposed: 09 Sites details was submitted by the firm.

Bioequivalence protocol details:

Study Design: An Open-label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single dose oral bioequivalence study of Fixed dose combination oral tablet of RemogliflozinEtabonate 100 mg and Vildagliptin 50 mg of Glenmark Pharmaceuticals Limited., India with RemogliflozinEtabonate Tablet 100 mg of Glenmark Pharmaceuticals Limited., India and Galvus® (Vildagliptin) 50 mg Tablet of Novartis Farmaceutica S.A., in healthy, adult, male subjects under fed conditions.

Study Population: 28 healthy male adult subjects will be enrolled in this study

Wash out period: There will be a washout period of at least 05 days between the successive dosing of the study.

The proposal was deliberated in IND Committee meeting dated 18.09.2019.

Recommendation of the IND Committee dated 18.09.2019:- The firm presented their proposal to conduct Phase III clinical trial, bioequivalence study along with the rationale for the proposed FDC. During the presentation, the firm mentioned that many patients do not achieve glycaemic control by single drug and require combination treatment, and ~60% patients receiving Remogliflozin require co-administration of DPP4.

After detailed deliberation, the Committee recommended for grant of permission to conduct the proposed BE study. As regards permission to conduct the Phase III Clinical trial, the committee recommended that the firm should submit following details for further review:-

1. The prescription audit data/report in respect of the claim that ~60% patients receiving Remogliflozin requires co-administration of DPP4i.
2. PSURs for RemogliflozinEtabonate & FDC of Remogliflozinetabonate + Metformin HCl which are already approved for manufacturing and marketing in the country.

The above information shall be reviewed by the committee to consider the matter further.

The firm had submitted the prescription audit data/report in respect of the claim that ~60% patients receiving Remogliflozin requires co-administration of DPP4i and PSUR data of RemogliflozinEtabonate Tablets 100mg and requested for grant of Phase III clinical trial.

In light of recommendation of the Committee dated 18.09.2019, the firm presented the documents/ information in support of the claim that ~60% patients receiving Remogliflozin requires co-administration of DPP4i alongwith PSUR data of Remogliflozin 100mg.

Recommendation of the Committee:-

After detailed deliberation, the Committee recommended for grant of permission to conduct the Phase III clinical trial with the proposed FDC as per protocol submitted.

Sr. No. 4

Phase I clinical trial of ChikunGunya Vaccine

This is related to application for conduct of the Phase I clinical trialof ChikunGunya Vaccine.Earlier based on the recommendations of IND committee dated 06.08.2015, 16.12.2015 and Apex Committee recommendations dated 29.04.2016, CDSCOhad granted phase I clinical trial permission titled "A Phase I Open label, dose escalation clinical trial to evaluate the safety, tolerability and immunogenicity of Inactivated Chikungunya Vaccine in healthy adults of 18 to 50 years of age" (protocol no. BBIL/CHIKV/I/2014) to M/s Bharat Biotech Int. Ltd., Hyderabad (BBIL) vide CT No. 15/2016 dated 13.07.2016.

On 19.06.2019, BBIL requested to CDSCOfor a Pre-submission meeting as provided under Rule 98 of chapter XIII of New Drugs and Clinical Trials Rules, 2019 for seeking guidance about the requirements of law and procedure of such licence or permission of manufacturing process, clinical trial and other requirements for Inactivated Chikungunya vaccine.

Accordingly, a pre-submission meeting was convened on 24.07.2019 by CDSCOon clinical development and regulatory strategy of Inactivated Chikungunya wherein experts from the relevant fields such as SEC Vaccine committee, Indian Council of Medical Research (ICMR) and Department of Biotechnology (DBT) were invited for giving their recommendations. In the said meeting, the following regulatory pathway was decided:-

Conclusion of the Pre-submission meeting:

a) Firm should submit amendment in current phase I clinical trial protocol to evaluate the safety of 40 µg dose of Inactivated Chikungunya vaccine with limited number of subjects.
b) Simultaneously, firm may submit a phase II/III clinical trial protocol with 20 µg and 40 µg doses in target population, wherein both sero-negative and sero-positive subjects would be evaluated along with subjects receiving placebo, which may also be simultaneously reviewed by CDSCO.
c) Firm may initiate phase I clinical trial with 40µg dose and simultaneously Phase II/III clinical trials with 20µg dose. The Phase II/III with 40µg dose has to be carried out after submission of immunogenicity/safety data arising out of Phase I of 40µg dose & its clearance by Data Safety Monitoring Board (DSMB) and submission of CSR to CDSCO & subsequent approval.
d) Based on satisfactory review, firm may continue to conduct phase II/III clinical trial using 40 µg dose, depending upon the results of phase I trial.
e) Subjects participating in the phase II/III trial will be followed for at least 12 months, post full vaccination with the 2 doses series.
f) The trial results will be evaluated for further need of trial or approval based on results of seroconversion, seroprotection, results of epidemiological and other data at the point of submission of report by the firm.

Accordingly, M/s BBIL has submitted an amendment in the approved Phase-I clinical trial protocol to evaluate the safety of 40 µg dose of Inactivated Chikungunya vaccine with 20 subjects along with Phase I clinical trial report to this office. The Phase I clinical trial was conducted at 4 sites i.e. (1) KEM Hospital, Mumbai, (2) Medanta-The Medicity Hospital, Gurgaon, (3) Panchsheel Hospital, Delhi & (4) King George Hospital, Visakhapatnam.

Study Vaccine: Inactivated Chikungunya virus vaccine (10µg/0.5ml, 20 µg/0.5ml and 30 µg/0.5ml)

The Phase I clinical study report is placed below:

Safety result:

Out of 45 subjects in the vaccine group, 40 events were reported in 20 subjects (which had one or more adverse events). Out of 15 subjects in the placebo group, 12 events were reported in 6 subjects (which had one or more adverse events). There was no significant difference in the percentage of adverse events between the vaccine and placebo groups. 40 adverse events were observed among 135 doses administered in the vaccine group (29.63%) and 12 adverse events were observed among 45 doses administered in the placebo group (26.67%). No adverse event was reported.

Immunogenicity result:

Neutralization antibody titres post vaccine administration were estimated by PRNT50 i.e. the post vaccination PRNT50 titre should be ≥1:20 within each dose and in each study group.

The geometric mean titres before vaccination was 0.32, at 10 µg after dose 1 is 5.79 with 95% CI (1.92,17.46), after dose 2 is 65.38 with a 95% CI(53.79,79.47) and after dose 3 is 287.52 with a 95% CI (243.25, 339.86), there is a steady rate of increase in the titres after each dose.

The geometric mean titres before vaccination was 0.47, at 20 µg after dose 1 is 21.88 with 95% CI (18.51, 25.88), after dose 2 is 98.35 with a 95% CI(81.61,118.53) and after dose 3 is 430.13 with a 95% CI (397.05, 488.09), there is a steady rate of increase in the titres after each dose with a big boost after dose 3.

The geometric mean titres before vaccination was 1.23, at 30 µg after dose 1 is 23.17 with 95% CI (19.09, 28.2), after dose 2 is 133.70 with a 95% CI(11.01, 159.58) and after dose 3 is 546.34 with a 95% CI (471.63, 632.88), there is a steady rate of increase in the titres after each dose and massive boost after dose 3.

The geometric mean titre at 10µg, 20 µg and 30 µg after dose 1 shows a relatively small increase in the titre, but after dose 2 & 3 the increase in substantial in the three groups. From the result, it has concluded that the group which received 30 µg vaccine has achieved the highest antibody titre after dose 3. All the three concentrations (10 µg, 20 µg and 30 µg) show 100% seroconversion after two doses of the vaccine.

There was 100% seroconversion (>=1:20) after 2ndnad 3rd dose of vaccine (day 56 & day 84) for all three dose strengths (10 µg, 20 µg and 30 µg).

Overall Conclusion:

1. In vaccine group, 40 adverse events were reported in 20 subjects (44.44%) and in placebo group, 12 adverse events were reported in 6 subjects (40.00%).
2. GMT for 10 µg, 20 µg and 30 µg after dose 1 shows relatively small increase in the titre but after dose2 & dose 3, the increase was reported to be substantial in the three groups.
3. Based on seroconversion and GMT, it was concluded that 20 µg and 30 µg shows better response than 10 µg.

Amendment in Phase-I clinical trial proposal:-

Protocol Title: Phase-I, open label, clinical trial to evaluate the safety, tolerability and immunogenicity of Chikungunya vaccine in healthy adults of 18 to 50 years age.

Protocol no.: BBIL/CHIKV/I/2014, version 1.4; dated 14.09.2019.

Investigational product: Chikungunya virus vaccine

Placebo: 0.5 ml vial containing Alum, 2-PE and Phosphate-buffered saline

Study population: 20 healthy adult (Male & Female) (15 [test group]:5[Control group])

Primary Objective: To assess the safety & tolerability of CHIKV vaccine developed by Bharat Biotech in terms of adverse events (e.g. fever, arthralgia, myalgia), physical examination, vital signs and laboratory tests including complete biochemical and haematological tests. Any serious adverse events will also be recorded and reported during the study period.

Secondary Objective: To assess the immune response elicited by the CHIKV vaccine in terms of CHIKV neutralizing antibodies by $PRNT_{50}$.

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Primary endpoints:

1. Occurrence of immediate adverse events and adverse events within 7 days post each dose (Reactogenicity)
2. Occurrence of AEs (including SAEs) till follow up post 2nd dose of vaccination.

Secondary endpoints:

1. Proportion of subjects that seroconvert i.e. post vaccination PRNT50 titres ≥1:20 after each dose. Participants who are seronegative at baseline (<1:20) will need to achieve a PRNT50 titre of ≥1:20 to meet the criteria for seroconversion.
2. Proportion of subjects that demonstrate ≥ 3-fold rise in antibody titres.

Blood Collection: Blood samples of 10 ml will be collected from subjects for safety investigations on the day of screening, as well as 56 and blood samples of 5 ml will be collected from subjects for end point immunological assays on day 0, day 28 & day 56.

Clinical trial site & Investigators details: King George Hospital, Vishakhapatnam.

In view of the above,the firm presented the proposed amendment to the Phase I Clinical Trial protocol with higher dose (40mcg).

Recommendation of the Committee:-

After detailed deliberation, the Committee recommended for grant of permission to conduct the Phase I clinical trial as per the amended protocol submitted by the firm.

Meeting ended with thanks to the Chair.

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