# Minutes of IND Committee meeting held on 10.06.2019 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

**List of Participants:**

1. Prof. Balram Bhargava, Secretary, Department of Health Research & Director General, Chairman, IND Committee.
2. Dr.Nilima Kshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
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.Bikash Medhi, Prof., Department of Pharmacology, PGIMER, Chandigarh.

**ICMR Representative:**

1. Dr.Rajni Kaul, Scientist G, Division of BMS, ICMR, New Delhi.
2. Dr. Monika Pahuja, Scientist C, ICMR, New Delhi.

**CDSCO Representatives:**

1. Mr. A. K. Pradhan, Deputy Drugs Controller (India), CDSCO (HQ).
2. Mr. R. Chandrasekhar, Deputy Drugs Controller (India), CDSCO (HQ).
3. Mr. Sanjeev Kumar, Deputy Drugs Controller (India), CDSCO (HQ).

**Following members could not attend the meeting:**

1. Dr. Y.K. Gupta, Ex. Dean, AIIMS, New Delhi.
2. Dr. Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
3. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
4. Dr. Deepak Kaul, Prof.& Head, Department of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
5. Prof. Dinesh Puri, Head, Department of Medical Bio-Chemistry, GTB Hospital, Shahdara, New Delhi.

Prof. Balram Bhargava, 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. Nilima Kshirsagar would Chair the meeting. Thereafter, the agenda items were discussed one by one: Committee took into consideration the comments sent on email by Dr. Y.K. Gupta who could not attend the meeting.

Agenda No. 1

**Phase I clinical trial with AT-10 of M/s IPCA Laboratories, Limited**

This is related to an application for grant of permission to conduct a Phase I clinical trial entitled, "A Phase 1 Open Label, Randomized, Two-Period, Single and Multiple-Dose, Safety,

Tolerability, Pharmacokinetic and Pharmacodynamic, Study of AT-10 in Healthy Human Subjects considered as Extensive and Poor Metabolizers of CYP2C19 based on Genotyping."

As per the proposal submitted by the applicant:-

M/s Ipca Laboratories, Ltd. has developed an antiplatelet agent AT-10 (2-oxoclopidogrel bisulfate) of different strengths i.e. Tablets 7.5 mg, 10 mg, 30 mg and 40mg which is one of the intermediate metabolite in the metabolic pathway of Clopidogrel that is further metabolically converted in one CYP-dependent step (instead of two step process as observed in Clopidogrel metabolism) to produce the pharmacologically active metabolite (MP-H4) that is same as formed in the metabolic pathway of the approved listed drug Clopidogrel (Plavix). It means if firm administer AT-I0 to humans, it doesn't represent the first exposure of AT-I0 to humans; however it's a first direct administration of AT-I0 to humans which should results in administration of much lower dose of AT-I0 as compared to Clopidogrel.

Firm has submitted Phase I Clinical trial Study Protocol Number CBCC/2019/003, Version: 1.0, 08/Mar/2019. This study is an open label, two-period, crossover study wherein each subject will receive a single loading dose followed by 5 daily doses (maintenance dose) of either AT-10 or Clopidogrel in Period 1 and then crossover to receive the other therapy (AT-10 or Clopidogrel) in Period 2.

40 subjects are planned to be randomized into the study. Out of this, 20 subjects would be extensive CYP2C19 metabolizers and 20 would be poor CYP2C19 metabolizers. The 20 extensive metabolizers will be randomized on a 1:1 basis into Groups 1 and 3. The 20 poor metabolizers will be randomized on a 1:1 basis into Groups 2 and 4. Subjects who withdraw or are removed from the study will not be replaced.

The study duration will be Considering the minimum washout period of at least 14 days, expected study duration of clinical phase is at least 27 days (excluding screening period) from the day of check-in of period-I to the visit for the last study sample of period - II. This study will be conducted by M/s CBCC Global Research LLP, Ahmedabad (CRO) & sponsored by M/s IPCA Laboratories Limited, Mumbai.

The Primary objectives of the study are as follows:

- To determine the safety and tolerability of AT-10 compared to Clopidogrel administered orally to humans.
- To compare the platelet aggregation effect of AT -10 (loading and maintenance doses) to the approved doses of Clopidogrel (loading and maintenance doses) in poor and extensive metabolizers.
- To confirm the AT-10 loading dose (PD equivalent dose to the Clopidogrel 300 mg) and the AT -10 maintenance dose (PD equivalent to the Clopidogrel 75 mg) given as a loading dose followed by 5 days of maintenance dose

The Secondary objectives of the study is to determine the single and multiple dose pharmacokinetics (PK) of Clopidogrel, AT -10, and active metabolite MP-H4.

**Pharmacodynamics:** Pharmacodynamic assessment will be performed using ADP-induced platelet aggregation with plasma produced from whole blood treated with sodium citrate as an anti-coagulant. ADP induced platelet aggregation will be assessed for change from baseline in each treatment group at each time point assessed on each dosing day (0.5, 2, and 6 hours post dose) and 24 hrs post dosing of last dosing day in each period. The change over time for each parameter will also be assessed. The data from Groups 1 and 3 will be combined in the analysis and Groups 2 and 4 will be combined in the analysis.

The following assessments will also be performed and reviewed observationally to further assess the PD of AT -10:

1. Liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase) measured as part of clinical chemistry.
2. Abbreviated physical examination focused on signs of bleeding including but not limited to echymosis, petechiae, and bleeding gums

Statistical comparison will be made between the change from baseline at each time point between the Groups 1 and 3 (extensive metabolizers) versus Groups 2 and 4 (poor metabolizers) for each treatment (AT -10 and Clopidogrel). The incidence of signs of bleeding from the abbreviated physical examination and the incidence of abnormal liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase) will be tabulated for the treatment groups. The incidence of these events will not be formally tested and the comparison will be observational only. The observational comparisons will be made between the AT-10 and Clopidogrel in the extensive metabolizers and poor metabolizers

**Pharmacokinetics:** Pharmacokinetic parameters (AUCt, AUCinf, Cmax, tmax, t½, kel, Cl/F, Vd/F) will be estimated following noncompartmental analysis of plasma concentration time-course data for Clopidogrel, AT -10 (2-oxo-clopidogrel), and MP-H4. PK parameters at steady-state will be estimated for Clopidogrel, AT-10 (2-oxo-clopidogrel), and MP-H4. Statistical comparison of the single-dose and multiple-dose PK parameters of peak (Cmax) and total (AUCt, AUCinf) exposure for the AT-10 and MP-H4 will be made between the AT-10 and Clopidogrel dose groups; between and within metabolizers groups. Although this is not a bioequivalence study following PK comparison will be made:

- PK comparisons will be made for AT-10 and MP-H4 from AT -10 treatment in extensive metabolizers versus Clopidogrel treatment in extensive metabolizers.
- PK comparisons will be made for AT-10 and MP-H4 from AT -10 treatment in poor metabolizers versus Clopidogrel treatment in poor metabolizers.
- PK comparisons will be made for AT-10 and MP-H4 from AT-10 treatments in extensive metabolizers versus AT-10 treatments in poor metabolizers.

**Safety Assessment:** Tolerability and safety will also be assessed. Safety assessments will include screening, pre-dose and post-dose vital signs, ECGs, clinical laboratory testing (hematology, blood chemistry, and urinalysis), documentation of AEs and clinical examinations. Coagulation parameters (PT and PTT) will also be assessed at screening, at check-in during each period, at 8 hrs post-dose on each dosing day and at exit or early termination.

**Pre-clinical Studies:** Following pre-clinical studies have been conducted by Ipca with AT-10 so far;

**A. Pharmacodynamic studies of AT-10**

1. Inhibition of platelet aggregation in ex-vivo studies in wistar rats and cynomolgus monkeys.
2. PK-PD study in cynomolgus monkey
3. Antithrombotic activity in FeCl3 induced arterial thrombosis model in rats
4. P-Glycoprotein interaction study

**B. Pharmacokinetic studies of AT-10**

1. Mass balance and tissue distribution kinetics study in Cynomolgus monkeys
2. Drug metabolism studies in Clopidogrel in rat, dog, monkeys and humans hepatocytes
3. Enzyme Inhibition studies.

**C. Safety Pharmacology studies**

1. Single dose acute toxicity study in Cynomolgus monkeys.
2. 5 days repeat dose toxicity study in Cynomolgus monkeys.
3. 28 days repeat dose toxicity study in Cynomolgus monkeys.

D. **Genotoxicity studies:**
   1. AMES Test (evaluated the mutagenic potential of AT-10 at different concentrations.
   2. In-vitro Chromosomal aberration:
   3. In vivo micronucleus assay

**Clinical Studies:** Following clinical studies have been conducted by Ipca in USA with AT-10 so far;

1. A phase 1, single ascending dose (SAD) and multiple ascending dose (MAD), PK-PD study in healthy human volunteers who were specifically genotyped for CYP2C19 (extensive metabolizers) -dose finding study.
2. Drug-drug interaction study with Omeprazole.
3. Study the effect of AT-10 in heavy smokers.

**Recommendation of the Committee:-** The firm presented their proposal including the protocol for conduct of Phase I clinical trial in India.. The results of various pre-clinical including animal toxicological and clinical data generated with AT-10 were presented. During the presentation, the firm mentioned that they have generated pre-clinical data following 505 (b) (2) regulatory pathway of USFDA and based on the same they have conducted three Phase I clinical trials which include a Phase I SAD & MAD, PK-PD study in healthy human volunteers, drug-drug interaction study with Omeprazole and study to assess the effect of AT-10 in heavy smokers in USA.

After detailed deliberation, the Committee recommended for grant of permission to conduct the Phase I clinical trial. However, the firm should submit the detailed justification in writing for generating toxicity studies in one species of animals in light of regulatory requirements under the New Drugs and Clinical Trials Rules, 2019 and the method to be adopted for determination of Extensive and Poor Metabolizers of CYP2C19 based on Genotyping before grant of the Clinical Trial permission by CDSCO.

**Agenda No. 2**

**Phase I clinical trial with PNB-001 of M/s Lambda Therapeutics Research Limited**

This is related to an application for grant of permission to conduct a Phase I clinical trial with PNB-001 entitled, "A placebo-controlled, randomized, double blind, multiple ascending dose, multiple cohort, multicentre study to assess safety, tolerability, pharmacokinetic & efficacy of PNB-001 (Test manufactured by PNB Vesper Life Sciences Pvt. Ltd., India)".

As per the proposal submitted by the applicant:-

PMB-001 is the racemic mixture of 4-Chloro-5-hydroxy-1-phenethyl-5-phenyl-1,5-dihydropyrrol-2-one. PNB-001 a cholecystokinin (CCK) receptor antagonist that binds to CCKA and CCKB with an $IC_{50}$ of 20 nM, respectively. In cell-based functional assays, PNB-001 inhibited CCKA and CCKB function by 5-6 fold greater than the positive control, proglumide. PNB-001 at a dose as low as 0.25mg/kg, administered intra-peritoneally, and a dose of 20 mg/kg, administered orally, alleviated pain induced by hot plate, surgery, inflammation and neuropathy in mice and rats. In addition, PNB-001 at 20 mg/kg p.o. reversed the inflammatory bowel syndrome (IBS) or Chron's disease caused by indomethacin in a rodent model of IBS. The results in the IBS model were comparable to a highly potent glucocorticoid, prednisolone.

PNB-001 was subjected to various in vivo studies in mice and rats to determine its ability to alleviate pain response, IBS, anxiety, and depression. In all studies animals administrede with PNB-001 did not show any toxic signs. PNB-001, in mice hot plate theramla nociceptive study elicited anti-nociceptive actions at 30 min and the effect was sustained until the end of the study. The effect of PNB-001 was dose dependent. As expected, in the same study, the

positive control, Tramadol, provided with sustained pain relief. PNB-001, in thermal nociceptive effects starting from 5 mg/kg p.o. with maximum effect obtained at 20 mg/kg p.o.

PNB-001 was tested in formalin-induced inflammatory pain and neuropathic pain models in rats. The formalin test differs from the hot-plate and tail-flick assays in several ways: the noxious stimulus is a chemical, little or no restraining of experimental animals is needed during testing, and the response to chemical stimuli (formalin) is persistent rather than transient. These features make the formalin assay, classified as a model of persistent pain, a good way to determine the potential analgesic activity of test compounds. The nociceptive response produced by formalin is biphasic, and the two phases can be distinguished pharmacologically. For example, NSAIDs are ineffective in attenuating the Phase I response, but are effective in attenuating Phase 2. Phase 1 of the formalin test begins immediately after the formalin injection and lasts for about 10 in. This initial response is thought to be caused by a burst of activity from pain fibers (particularly C fibers). Phase 2 typically begins 15 to 20 min after the formalin injection and continues for 40 min. Phase 2 is mediated by peripheral inflammation and can be attenuated by NSAIDs. In addition, the second-phase behavioral response is also believed to be mediated by so-called central sensitization. This facilitation of central nociceptive processing (e.g., increased sensitivity of spinal cord neurons) is thought to be result of the prolonged afferent input to be spinal cord following the formalin injection. Both the peripheral (inflammation) and central sensitization are thought to mediate the clinical symptoms, including hyperalgesia, associated with tissue injury.

PNB-001 at 1.5 mg/kg s.c. and at 5 and 20 mg/kg p.o. was effective in reducing pain induced ny formalin. PNB-001 reduced significantly the number of licks or bites concentration dependently both in phase I and phase II, indicative of its ability to reduce pain induced by neuropathy and inflammation.

PNB-001 was tested in indomethacin-induced IBS model in rats. Indomethacin, administered subcutaneously at 10 mg/kg, clearly induced inflammation in alll the regions of the gastrointestinal tract. PNB-001 dose dependently (5 and 20 mg/kg) reduced the inflammation scores and the results with PNB-001 were comparable to the results obtained with positive control prednisolone. The histopathological sections clearly demonstrate the reversal of ulcerative colitis and inflammation by PNB-001 with efficacy comparable to positive control, prednisolone.

**Applicant has submitted the following Animal Toxicity studies:-**

**Acute oral toxicity study of PNB001 was conducted in Swiss Albino Mice:-**Acute oral toxicity study of PNB001 was conducted in Swiss Albino Mice at dose of 2000 mg/kg/day. PNB001 at 1000 mg/kg bid (i.e. 2000 mg/kg/day) and control vehicle at 0 mg/kg body weight were administered orally to 24 healthy Swiss Mice (6 males + 6 females/ group). The animals were observed for clinical signs, occurrence of morbidity/ mortality, body weight change and treatment related behavioral changes during the 14 day observation period. Animals from both groups were sacrificed on Day 15 and were subjected to detailed gross pathological examination. No incidence of mortality or treatment related abnormal clinical signs in either sex were noticed when treated with PNB001 at 2000 mg/kg/day. Maximum Tolerated Dose (MTD) of PNB001 in Swiss Mice for both the sex, was found to be 2000 mg/kg body weight and LD50 was found to be >2000 mg/kg/day.

Acute oral toxicity study of PNB001 was conducted in Sprague Dawley Rats:-Acute oral toxicity study of PNB001 was conducted in Sprague Dawley rats at dose of 2000 mg/kg/day. PNB001 at 1000 mg/kg bid (i.e. 2000 mg/kg/day) and control vehicle at 0 mg/kg body weight were administered orally to 24 healthy rats (6 males + 6 females/ group). The animals were observed for clinical signs, occurrence of morbidity/ mortality, body weight change and treatment related behavioral changes during the 14 day observation period. Animals from both groups were sacrificed on Day 15 and were subjected to detailed gross pathological examination. No incidence of mortality or treatment related abnormal clinical signs in either sex were noticed when treated with PNB001 at 2000 mg/kg/day. Maximum Tolerated Dose

(MTD) of PNB001 in Sprague Dawley Rats for both the sex, was found to be 2000 mg/kg body weight and LD50 was found to be >2000 mg/kg/day.

**90-Day Repeated Dose Oral Toxicity and Toxicokinetic Study of PNB-001 with 28-Day Recovery Period in Beagle Dogs:-**The study was conducted at 0 (vehicle control), 50 (low), 100 (mid) and 200 (high) mg/kg B.wt. There were 6 groups (4 main and 2 recovery groups), each main group consisted of 4 male and 4 female dogs and recovery groups consisted of 3 males and 3 females. Test item was administered by oral gavage as suspension. No treatment related mortality and clinical signs and changes in body weights, food consumption, ophthalmology, hematology, coagulation and urine parameters were observed following 90-day repeated dose oral administration of PNB-001 up to 200 mg/kg B. w.t/day in Beagle dogs. Significant increase in liver enzymes was observed in animals treated with PNB-001 at 50 mg/kg B. wt/day. NOAEL will be decided after having histopathology and TK study.

**90-Day Repeat Dose Toxicity Study of PNB001 in Sprague-Dawley Rats by Oral Route with 28 Day Recovery Period:-** The study was conducted at 0 (vehicle control), 75 (low), 150 (mid) and 300 (high) mg/kg B.wt. No treatment related mortality or clinical signs, changes in body weight, food consumption, ophthalmology, hematology, clinical chemistry, coagulation, urine parameters, organ weights, gross and histopathology were observed in Spargue Dawley rats of either sex following 90 days repeated oral administration at and up to 300 mg/kg b.w. Therefore, it is concluded that the NOAEL of PNB001 is 300 mg/kg b.w. in rats of either sex.

**Genotoxicity:-** PNB-001 was tested up to the highest concentration 250 µg/ml. The results of chromosome aberrations, including and excluding gap, in presence and absence of metabolic activation did not show any significant

PNB-001 induction of chromosome aberrations over the concentrations range tested compared to vehicle control. Confirmatory Chromosome Aberration Assay: The negative results obtained in the initial chromosome aberration assay were confirmed by the assay wherein the cultures were continuously exposed for approximately 22 hours in the absence of metabolic activation.Ames test: The Ames test was performed to evaluate the ability of PNB-001to induce point mutations at the histidine locus in five tester strains of Salmonella typhimurium(TA1537, TA1535, TA98, TA100 and TA102). On the basis of preliminary cytotoxicity study results the test item, PNB-001, was tested in the Mutagenicity study at different test concentrations. On the basis of the results of this study, it is concluded that PNB-001 did not induce point mutations at the histidine locus up to 2500 µg/plate in the presence (5 % v/v S9) and absence of metabolic activation system in all five tester strains of Salmonella typhimurium.In vivo chromosomal aberration study was conducted in Swiss Albino mice with PNB-001. PNB-001 administered orally at 2000 mg/kg and bone marrow chromosomal aberration was evaluated 24 hrs and 48 hrs after administration of the drug. PNB-001 did not cause any changes in chromosomal aberration indicating that it is not genotoxic to mice.

M/s PNB Vesper Life Science Pvt. Ltd., India was granted permission to conduct Phase I clinical study entitled, "A placebo-controlled, randomized, double blind, single ascending dose study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of PNB-001 in healthy, adult, human male subjects under fasting conditions" on 21.03.2014. Now, M/s Lambda Therapeutics has submitted protocol for Phase I multiple dose study alongwith report of single ascending dose.

In the single ascending dose study primary objective was to assess the safety, tolerability and pharmacokinetic of PNB-001 after single ascending dose in healthy, adult, human male subjects under fasting conditions.

Secondary objective was to assess pharmacodynamic effect of PNB-001 in healthy, adult, human male subjects under fasting conditions by measuring Lipase, Amylase.

Subjects were recruited in 7 Cohorts, Cohort I - PNB-001 25mg, Cohort II - PNB-001 50mg, Cohort III - PNB-001 100mg, Cohort IV - PNB-001 300mg, Cohort V - PNB-001 1000mg, Cohort VI - PNB-001 1500mg, Cohort VII - PNB-001 300mg. The study consisted of 5 active and 2 placebo subjects in each cohort (Cohort I to Cohort VII). One subject did not report in Cohort VII.

Five (05) significant adverse events (AEs) were reported by three (03) subjects during the conduct of the study.

Now, M/s Lambda Therapeutics has submitted an application to conduct Phase I clinical trial protocol entitled, "A Placebo-controlled, randomized, double blind, multiple ascending dose, multiple cohort, multicentre study to assess safety, tolerability, pharmacokinetic & efficacy of PNB-001 (Test manufactured by PNB Vesper Life Sciences Pvt. Ltd., India). The study is a placebo-controlled, randomized, double blind, multiple ascending dose, multicentre study. The study will be conducted in multiple cohorts. Cohort 1 to 4 will consist of healthy volunteers wherein the objective of the study is to safety, tolerability & pharmacokinetics of PNB-001.Cohort 5 and 6 will consist of patients wherein objective of the study is to assess efficacy of PNB-001.Cohort 5 will consist of patients with inflammatory bowel disease (ulcerative colitis). Cohort 6 will consist of surgically sterilized females with dysmenorrhoea. 52 subjects/patients will be enrolled in the study. [32 Healthy Adult subject (24 Healthy Male & 08 healthy surgically sterilized female subjects), 08 Adult Male patients with inflammatory bowel disease & 12 surgically sterilized female patients with dysmenorrhoea]. The Primary objective of the study is to assess the safety and tolerability of study drug and Secondary objective is to assess pharmacokinetics and efficacy of study drug. Safety assessments will be based on review of recorded adverse events, vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests.

**Recommendation of the Committee:-** The firm presented their proposal along with report of Single Ascending Dose (SAD) Phase I clinical trial and protocol for Multiple Ascending Dose (MAD), multiple cohort, multicentre study to assess safety, tolerability, pharmacokinetic & efficacy of PNB-001.

From the results of SAD Phase I clinical trial it was observed that in presence of high fat high calorie meal, $C_{max}$ and $AUC_{0-t}$ for PNB-001 was increased by approximately 5-fold and 4-fold, respectively and one subject in Cohort VII (300 mg Fed) reported Sinus Tachycardia as an adverse event. It was also observed that in Cohort II, one subject had very low concentration profile and hence, PK cannot be reliably estimated which lead to the very long half-life of ~55 hours and very low $C_{max}$ as compared to other subjects.

After detailed deliberation, the Committee recommended that the firm should determine the expected anticipated effective dose of PNB-001in human considering the food effect, PK-PD and toxicokinetic data generated, and propose justified dose to be used in the MAD Phase I clinical trial. The firm should analyse the results of the outlier in the Cohort II and also do causality analysis of Sinus Tachycardia observed in one subject. Accordingly, the detailed information on above points along with revised MAD Phase I clinical trial protocol should be submitted for further review by the Committee.

**Agenda No. 3**

**Phase III clinical trial with PMZ1620 of M/s Pharmazz India Private Limited**

This is related to an application for grant of permission to conduct "A prospective, multicentric, randomized, double-blind, parallel, phase III clinical study to assess efficacy of PMZ-1620 along with standard treatment in patients of acute ischemic stroke" with protocol no. PMZ 1620/CT-3.1/2019 Version 1.0/ 29 APRIL 2019."

Firm was granted Phase II clinical trial permission as per recommendation of IND Committee, on 25.07.2017. Accordingly, firm has conducted Phase I study entitled, "A Prospective, Multicentric, Randomized, Double Blind, Parallel, Saline Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 therapy along with Standard Supportive Care in Subjects of Acute Ischemic Stroke."

This was a prospective, multi-centric, randomized, double-blind, parallel, saline controlled phase II clinical study (CTRI/2017/11/010654) was conducted in forty patients with cerebral ischemic stroke, of which 36 completed 90-day follow-up. All patients received standard treatment and were randomly assigned to either control (saline; n=18; 11 male and 7 female) or PMZ-1620 group (n=18; 15 male and 3 female). Clinical outcome parameters such as National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Barthel Index (BI), EuroQol Index and Stroke-Specific Quality-of-life (SSQoL)Index for cerebral stroke were determined. Standard treatment and care were provided to all the patients. All the patients received saline or PMZ-1620within 24 hours of onset of stroke. Number of patients that received saline within 20 hours of onset of stroke were 14 out of 18, whereas those that received PMZ-1620were 10out of 18.NIHSS on day 6 when compared to day 1 showed significance value of P=0.0495in saline and P=<0.0001 in PMZ-1620cohorts. Similarly, mRSon day 6 when compared to that observed on day 1 showed significance value of P=0.0859 in saline cohort, while in PMZ-1620cohort it was P<0.0001. BI on day 6 when compared to day 1 was similar (P=0.3948) in saline cohort, whereas it significantly (P<0.0001) improved in PMZ-1620cohort.

It is reported that, PMZ-1620 produced a significantly quicker recovery in patients with acute cerebral ischemic stroke. In saline 12.50% while in PMZ-1620cohort 87.50% (odds ratio 10.18; 95% CI 10.18 to 120.50; P=0.0201) patients showed an improvement of ≥6 in NIHSS from baseline (enrollment time) at day 6 of treatment, while at 90 day 43.48% in saline and 56.52% patients in PMZ-1620 cohort (odds ratio 2.275; 95% CI 0.5785 to 8.310; P=0.2714) showed an improvement of ≥6 in NIHSS. An improvement of ≥2 in mRS was observed in 39.13% and 60.87% patients in saline and PMZ-1620cohorts, respectively at 30 day of treatment. Similar improvement in mRS was observed at 90 day of treatment (odds ratio 5.250; 95% CI 1.00 to 27.63; P=0.0519). An improvement of ≥40 in BI in saline cohort was 30.00% while it was 70.00% patients in PMZ-1620cohort at 30 days of treatment (odds ratio 5.833; 95% CI 1.217to 21.26; P=0.0172). At 90 days of treatment 36.00% and 64.00% patients in control and PMZ-1620cohorts, respectively showed an improvement of ≥40 in BI (odds ratio 12.44; 95% CI 1.502 to 147.10; P=0.0112). A change of 80 or more in EuroQol scale was 0% of patients in saline and 100% of patients in PMZ-1620cohort at 60 days (odds ratio ∞; 95% CI 0.9391 to ∞; P=0.0389) and at 90 days (odds ratio ∞; 95% CI 1.00 to ∞; P=0.0332). Similarly, a change of 150 or more in SSQoL scale was 22.22% of patients in saline and 77.78% of patients in PMZ-1620cohort at 60 days (odds ratio 4.773; 95% CI 0.9278 to 25.06; P=0.0665) and at 90 days (odds ratio 5.250; 95% CI 1.00 to 27.63; P=0.0519).Number of patients with 100% recovery achieving NIHSS score of 0 (P=0.04791), mRS of 0 (P=0.1193) and BI of 100 (P=0.02795) were more in PMZ-1620cohort compared to saline. PMZ-1620 treatment did not have any effect on hemodynamic, biochemical or hematological parameters. No incidence of drug related adverse event was reported. There was no mortality and no incidence of recurrent ischemic stroke occurred in any of the enrolled patient.

Firm concluded on the Phase II Clinical Trial Study that, PMZ-1620 was found to be safe and was well tolerated in patients of ischemic stroke. PMZ-1620 has the potential to be a first-in-class neuronal progenitor cell therapeutics that promotes quicker recovery and significantly improves neurological outcome in cerebral ischemic stroke patients compared to standard of care.

Now, firm has submitted an application for grant of permission to conduct a Phase III clinical trial entitled, "A prospective, multicentric, randomized, double-blind, parallel, phase III clinical study to assess efficacy of PMZ-1620 along with standard treatment in patients of acute ischemic stroke" with protocol no. PMZ 1620/CT-3.1/2019 Version 1.0/ 29 APRIL 2019."

This is a prospective, multicentric, randomized, double- blind, parallel, Phase III efficacy study of PMZ-1620 therapy along with standard treatment in patients with acute ischemic stroke. A minimum of 100 patients (50 in each treatment arm) are to be evaluated as per the protocol, considering a discontinuation rate of approximately 10 %, approximately 110 patients will be enrolled in the study. This study will be conducted at approximately 20 study centres in India will participate in the study.

The enrolment period of the study will be approximately 15 months and total duration of the study will be approximately 18 months. For an individual patient, duration of the study will be 3 months (90 days), including 5 study visits: visit 1/Day 1 (screening/baseline/treatment visit), visit 2 (Day 12 + 2), visit 3 (Day 30 + 5), visit 4/telephonic visit (Day 60 ± 7), and visit 5/End of Study (Day 90 ± 7). At visit 1, approximately 110 patients will be randomized 1:1 into 2 treatment groups after meeting the eligibility criteria:

- Group 1: PMZ-1620 + Standard treatment
- Group 2: Normal Saline (Dose: Equal volume) + Standard treatment

PMZ-1620 or Normal Saline will be administered as an intravenous (IV) bolus over one minute within the window of 24 hours after the onset of stroke. In PMZ group, three doses of PMZ-1620 (each dose of 0.3 µg/kg body weight) will be administered as an IV bolus over one minute at an interval of 3 hours ± 1 hour on day 1, day 3, and day 6 (total dose/day: 0.9 µg/kg body weight). In control group, three doses of equal volume of normal saline will be administered as an IV bolus over one minute at an interval of 3 hours ± 1 hour on day 1, day 3 and day 6 post randomization. In both treatment groups, patients will be provided the standard treatment for stroke. Standard treatment to be provided to the patients shall be the one used in the particular hospital setup. Each patient will be monitored closely throughout his/her hospitalization for the qualifying stroke and will be followed for 3 months from randomization. Each patient will be assessed for efficacy parameters over 3 months from randomization at a clinic visit. Every effort will be made to have drug administration at the same time on day 1, day 3 and 6.

**The primary objectives of the study are to determine the following points:**

- Increases the proportion of ischemic stroke patients with National Institute of Health Stroke Scale (NIHSS) score <6; modified Rankin Scale (mRS) score <2 and Barthel index (BI) score >60 at day 6, 1 month and 3 months.
- Improves the functional outcome as assessed by NIHSS, mRS and BI at day 6, 1 month and 3 months post-randomization.
- Improves the overall clinical outcome (as assessed by the global statistical test of NIHSS, mRS, and Barthel index [BI] scores) at day 6, 1 month and 3 months post-randomization.

**The secondary objectives of the study are to determine the following points:**

- Quality-of-life (QoL) as assessed by EuroQol and Stroke-Specific Quality of Life (SSQOL) instruments at 1 month and 3 months post-randomization.
- Incidence of recurrent ischemic stroke within 1 month and 3 months post-randomization, as assessed by Questionnaire to Validate Stroke-Free Status (QVSFS) .
- Mortality within 3 months post-randomization.
- Incidence of radiographic or symptomatic Intra Cerebral Hemorrhage (ICH) within 24 (± 6) hours of randomization.
- Cognition measured at 1 month and 3 months by Montreal Cognitive Assessment (MoCA) Test.

- Proportion of patients with adverse events (AEs) and serious adverse events (SAEs).

**Parameter for efficacy evaluation of the study is as follows:**

- Increase in proportion of patients with NIHSS score <6, mRS<2 and BI >60 at day 6, 1 month and 3 months post randomization
- Increase in proportion of patients with improvement in NIHSS score ≥6, mRS ≥2 and BI ≥40 from baseline to day 6, day 12, 1 month, and 3 months post randomization
- Proportion of patients with overall clinical outcome as assessed by the global statistical test of NIHSS, mRS, and BI scores at 1 month and 3 months post randomization
- Change in QoL score from baseline to 1 month, 2 months and 3-months post randomization
- Proportion of patients with recurrent ischemic stroke within 1 month and 3 months
- Number of deaths within 3 months post-randomization
- Proportion of patients with radiographic or symptomatic ICH within 24 (±6) hours of randomization
- Change in MoCA score at 1 month and 3 months post-randomization
- Proportion of patients with adverse events (AEs) and serious adverse events (SAEs)

**The Safety evaluation parameter of this study is as follows:**

- All AEs will be listed and categorized by AEs before dosing and treatment emergent adverse events (TEAEs) i.e. AEs with onset date on or after dosing.

**Recommendation of the Committee:-** The firm presented their proposal along with report of Phase II clinical trials conducted in India and Phase III clinical trial protocol. After detailed deliberation, the committee recommended for grant of permission to conduct the Phase III clinical trial ensuring proper randomization of the subjects.

**Agenda No. 4**

**Marketing Authorization of FDC of Remogliflozin and Metformin of M/s Glenmark Pharmaceuticals Limited**

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

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

Now firm submitted the Phase III clinical trial report of Remogliflozin Etabonate along with justification of Bioequivalence study wavier for FDC Remogliflozin Etabonate + Metformin HCL (100 mg + 500mg & 100mg + 1000 mg) tablets.

**Remogliflozin Etabonate - A Novel SGLT2 Inhibitor:**SGLT2 inhibitors are novel anti-diabetic drugs that help achieve glycaemic control by acting on the SGLT2 receptors in the proximal tubule of the kidney, thereby preventing renal re-absorption of glucose and promoting excretion of glucose in the urine. Remogliflozin Etabonate (RE) is the ester prodrug of Remogliflozin (active entity) that selectively inhibits SGLT2. Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to be effective in the management of T2DM as monotherapy as well as in combination with other anti-diabetic agents. By inhibiting SGLT2 receptors it inhibits re-absorption of glucose and enhances urinary glucose excretion and thus reduces the blood glucose levels. SGLT2 inhibitors are indicated where diet and exercise alone do not provide adequate glycaemic control and in patients for whom use of Metformin is considered inappropriate due to intolerance. SGLT2 inhibitors are also indicated in combination with other glucose-lowering medicinal products including insulin.

As per the proposal submitted by the firm:-

**Clinical Development Summary:** Remogliflozin has been evaluated in 26 clinical studies (phases I, II and III). These studies provide information about the safety, efficacy, pharmacokinetics, pharmacodynamics, drug interaction and evaluation in special populations of Remogliflozin Etabonate (RE). Pharmacokinetic profiles of Remogliflozin Etabonate and its metabolites are generally proportional to the dose administered and similar between healthy subjects and individuals with T2DM. Pharmacodynamic studies with GSK189075 have demonstrated dose-related increases in urine glucose excretion and decreases in plasma glucose as determined by 24-hour profiles. Single and multiple dose treatment at doses up to 1000 mg BID and 4000 mg QD have been administered and have generally been well tolerated.

Studies evaluating PK suggested that RE is rapidly and extensively absorbed and converted to active moiety Remogliflozin. The plasma exposures were generally dose proportional. No accumulation has been observed with multiple dosing. Based on the radiolabelled study, Remogliflozin is extensively metabolized with only about 11% is recovered as Remogliflozin in urine; majority of the drug related material was eliminated in urine as inactive glucuronides. No clinically meaningful effect of food on the pharmacokinetic and Pharmacodynamic properties of RE was observed. The exposure to Remogliflozin was increased by < 2-fold when dosed with ketoconazole (potent inhibitor of CYP3A4) indicating a week interaction. Given the wide therapeutic index with RE, no dose adjustment is needed when administered with CYP3A4 inhibitors. There was no PK interaction between RE 500 mg or 750 mg BID and Metformin in humans and co-administration of Metformin with RE did not diminish the PD effect of RE. No sex or age related effect was identified in glucose lowering effect of RE. Concomitant administration of RE and bupropion does not affect the steady state PK of RE or bupropion. Co-administration of RE appeared to have a potential for a sporadic lack of absorption of oral contraceptives. As the effectiveness of oral contraceptive may be impacted, it is recommended that an appropriate alternative method for avoiding pregnancy should be utilized. No clinically meaningful difference in PK characteristics of RE in Indian healthy subjects was observed in comparison to the PK characteristics of RE in healthy volunteer of foreign origin. The PK

characteristics of RE was comparable between healthy volunteers and T2DM patients. Concomitant administration of RE and diuretic does not affect serum sodium and potassium concentrations and urine glucose excretion. There is no clinically significant alteration in urine glucose excretion in patients with mild to moderate renal insufficiency and no dose adjustment of RE is required in such patients. In a repeat dose study, no clinically relevant effect of RE was found on cardiac repolarization, up to doses of 4000 mg QD.

Dose range, regimen, efficacy and safety of multiple doses of RE was evaluated in phase II studies. In these studies, RE doses were administered up to 12 weeks in subjects with type 2 diabetes mellitus. All the doses of RE demonstrated efficacy in terms of reduction in HbA1c, fasting plasma glucose and post prandial plasma glucose. All the doses were well tolerated and safe. Based on the data from these studies, doses of RE 100 mg BID and RE 250 mg BID were chosen for phase III study.

The phase III clinical study was designed to provide confirmatory evidence of efficacy and safety of Remogliflozin Etabonate 100 mg BID and Remogliflozin Etabonate 250 mg in comparison with Dapagliflozin 10 mg over 24 weeks of treatment in subjects with T2DM who were inadequately controlled with Metformin monotherapy, to support marketing authorization.

**Summary of Phase III Clinical Trial Results of Remogliflozin:**

Firm conducted a phase III study in India to evaluate the efficacy and safety of Remogliflozin Etabonate 100 mg & 250 mg tablet BID as add-on to Metformin in comparison to Dapagliflozin 10 mg OD as add-on to Metformin in subjects with T2DM who had inadequate glycaemic control with stable dose of Metformin as monotherapy. In this study along with Remogliflozin or Dapagliflozin tablets patients also received Metformin at stable dose of >1500 mg per day (>1000 mg per day in subjects not tolerating) throughout the study period. In this study, Remogliflozin 100 mg added-on to Metformin was found to be non-inferior to Dapagliflozin 10 mg added-on to Metformin in reducing HbA1c at week 24. There was significant reduction in fasting plasma glucose and post-prandial plasma glucose with Remogliflozin 100 mg. Plasma glucose reduction, proportion of patient achieving glycaemic control and proportion of patients requiring rescue medication in the Remogliflozin 100 mg group were comparable to those in the Dapagliflozin group. The overall safety of Remogliflozin 100 mg added-on to Metformin was comparable to that of Dapagliflozin added-on to Metformin.

In the randomized, double blind, double dummy, active comparator, parallel group phase III study, Remogliflozin 100 mg and Remogliflozin 250 mg twice daily were evaluated in subjects with type 2 diabetes and in comparison with Dapagliflozin 10 mg once daily. All the subjects were receiving Metformin at doses of ≥1500 per day (≥1000 mg per day in subjects not tolerating) at screening and continued treatment with same baseline dose of Metformin throughout the study. Subjects were randomized to receive one of the 3 treatment arms for period of 24 weeks.

Remogliflozin 100 mg reduced HbA1c % by 0.68 compared to a reduction by 0.59 in the Dapagliflozin group. These improvements were statistically highly significant and are more

than the minimal clinically important difference of 0.40. In the Remogliflozin 100 mg group, reduction in fasting blood sugar was 12.29 mg/dL reduction in post prandial blood sugar was 24.3 mg/dL. Proportion of subjects achieving glycaemic control defined as HbA1c <7 % at 24 weeks was 40.7% with Remogliflozin 100 mg compared to 40.4% with Dapagliflozin. Proportion of subjects requiring treatment with rescue medication was 21.6% with Remogliflozin compared to 22.0% with Dapagliflozin. These changes were statistically not different from the changes found in the Dapagliflozin group.

Safety of Remogliflozin 100 mg was comparable to that of Dapagliflozin 10 mg (as tabulated below). The overall rate of treatment emergent adverse event (TEAEs) was comparable in the Remogliflozin Etabonate 100mg group (29.5%) compared to the Dapagliflozin group (27.4%). TEAEs reported in ≥ 2% of subjects were diarrhoea, pyrexia, bacteriuria, headache, ketonuria and urinary tract infection (UTI) in the Remogliflozin Etabonate 100mg arm and bacteriuria dyslipidemia and headache in the Dapagliflozin 10mg arm. The incidence of TEASs causing the permanent discontinuation of the study drug was 1.4% in Remogliflozin Etabonate 100mg arm and 1.5% in Dapagliflozin 10mg arm.

| | **Dapagliflozin 10 mg** | **Remogliflozin 100 mg** |
|---|---|---|
| TEAE, % | 27.4 | 29.5 |
| Serious Adverse Events, n | 1 | 0 |
| AE leading to Death, n | 0 | 0 |
| Hypoglycemia, % | 1.0 | 1.2 |
| Genital Mycotic Infections, % | 2.5 | 1.7 |
| Urinary Tract Infections, % | 1.5 | 2.9 |

Hypoglycemic events were comparable between the treatment arms: Remogliflozin Etabonate 100mg 1.2% and Dapagliflozin 10mg 1.0%. No subject had severe hypoglycemic event. Incidence of UTI in the Remogliflozin Etabonate 100mg arm was 10 (2.9%, females: 4 [1.2%], males: 6 [1.7%]), and in the Dapagliflozin 10mg arm was 3 (1.5%, females: 2 [1.0%], males: 1[0.5%]). The incidence of genital fungal infection events was 1.7% in the Remogliflozin Etabonate 100mg arm, and 2.5% in Dapagliflozin 10 mg arm.

<u>Regulatory Status of Drug Products</u>:

***Remogliflozin Etabonate 100 mg tablets:***

Remogliflozin Etabonate 100 mg tablet is approved for manufacturing and marketing in India on 26.04.2019 and which is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control.

- Add on therapy with Metformin, together with diet and exercise, when these do not provide adequate glycaemic control.

***Metformin HCL 500 mg & 1000 mg tablets:*** Metformin HCL 500 mg / 100 mg tablet is approved in India as monotherapy and in combination with other anti-diabetic agents for the treatment of Diabetes Mellitus.

**Justification for BE wavier:** Firm requested a waiver of in-vivo Bioavailability (BA) / Bioequivalence (BE) study of FDC tablet of Remogliflozin Etabonate + Metformin HCl (100/500mg and 100/1000mg) on the following grounds:

1. Both the individual drugs i.e. Remogliflozin Etabonate and Metformin HCL belongs to BCS Class I as per Biopharmaceutical Classification system (BCS).
2. Both the drugs release more than 85% of labeled amount within 15 minutes in the test as well as reference product.
3. The mono tablets (Remogliflozin 100mg tablets as well as Metformin HCl 500mg/ 1000mg tablets) and the FDC tablets, both are manufactured by Glenmark Pharmaceuticals Ltd

**Recommendation of the Committee:-** The firm presented their proposal along with results of the Phase III clinical trial data of 906 subjects, toxicology data, clinical evidence of safety & efficacy of Metformin and Remogliflozin used concomitantly ,drug-drug interaction study along with physicochemical compatibility, dissolution profile of the FDC, justification for BE waiver etc

.

After detailed deliberation, the committee recommended for grant of permission to manufacture and market of FDC Remogliflozin Etabonate + Metformin HCL (100 mg + 500mg & 100mg + 1000 mg) tablets indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:-

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in patients already being treated with the combination of remogliflozin and metformin as separate tablets

subject to following conditions:-

1. The firm should submit protocol for active Post Marketing Surveillance of the FDC to CDSCO before launching the product in the market.
2. Proposed package insert, label, carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.

Agenda No. 5

Active Post Marketing Surveillance of Remogliflozin 100 mg Tablets of M/s Glenmark Pharmaceuticals

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

1. Monotherapy when diet and exercise alone do not provide adequate glyceamic control.

2. Add on therapy with metformin, together with diet and exercise, when these donot provide adequate glyceamic control with following conditions:-
   - The firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.
   - Proposed Package Insert, Label, Carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.

The firm has submitted Phase III clinical study report after analysis of 906 subjects vides its application no. GRA/Ind/2019-05/582 dated 07.05.2019 and protocol for active Post Marketing Surveillance study of Remogliflozin etabonate 100 mg tablets vide application ref. no: GRA/Ind/2019-05/579 dated 03.05.2019.

Summary of the submitted CSR is as follows.

**Subject Disposition:**
In this clinical study report, results of analysis for 906 randomized subjects are presented. Of the 1865 subjects screened, 911 (48.8%) were considered eligible for randomization in the study.

The 906 randomized subjects were assigned to 1 of the 3 treatment arms: 347 in the remogliflozin etabonate 100 mg arm, 362 in the remogliflozine tabonate 250 mg arm, and 197 in the dapagliflozin 10 mg arm.

The first subject was enrolled in the study on 01-Dec-2017 and the last subject completed the end-of-study assessments on 05-Mar-2019. A total of 671 subjects (74.1%) completed the study: 267 (76.9%) in the remogliflozin etabonate 100 mg arm, 260 (71.8%) in the remogliflozin etabonate 250 mg arm, and 144 (73.1%) in the dapagliflozin 10 mg arm. A total of 234 subjects (25.8%) were withdrawn from the study: 79 (22.8%) in the remogliflozin etabonate 100 mg arm, 102 (28.2%) in the remogliflozin etabonate 250 mg arm, and 53 (26.9%) in the dapagliflozin 10 mg arm.

The reasons for discontinuation from the study reported for >5.0% of subjects in any treatment arm were withdrawal by subject (45 [13.0%] in the remogliflozin etabonate 100 mg arm, 61 [16.9%] in the remogliflozin etabonate 250 mg arm, and 35 [17.8%] in the dapagliflozin 10 mg arm) followed by eGFR<60 mL/min/1.73 m2
   - pre-dose eGFR<60 mL/min/1.73 m2: 7 [2.0%] in remogliflozin etabonate 100 mg arm, 6 [1.7%] in remogliflozin etabonate 250 mg arm, and 1 [0.5%] in dapagliflozin 10 mg arm
   - post-doseeGFR<60 mL/min/1.73 m2: 10 [2.9%] in remogliflozin etabonate 100 mg arm, 13 [3.6%] in remogliflozin etabonate 250 mg arm, and 2 [1.0%] in dapagliflozin 10 mg arm.

**Baseline Demographics:**
The mean (standard deviation [SD]) age of subjects was similar across the treatment arms (50.49 years in remogliflozin etabonate 100 mg arm, 51.03 years in remogliflozin etabonate 250 mg arm,

and 50.23 years in dapagliflozin 10 mg arm). All subjects enrolled in the study were Indian. The distribution of men and women was similar across the treatment arms and >50.0% of subjects in each treatment arm were men. Subject body weight and height were similar across the treatment arms.

The mean (SD) HbA1c level at screening was 8.28% (0.835%) in the remogliflozin etabonate 100 mg arm, 8.22% (0.796%) in the remogliflozin etabonate 250 mg arm, and 8.29% (0.796%) in the dapagliflozin 10 mg arm.

**Efficacy Results:**

**Primary Efficacy Endpoint**

The primary efficacy endpoint of mean change from baseline in HbA1c levels at Week 24 was analyzed using the MMRM method in the PP population. Mean baseline levels of HbA1c were generally comparable across the treatment arms and ranged from 8.19% to 8.25%. Reduction in the mean HbA1c levels was seen at all visits and in all the treatment arms. The primary endpoint assessment, least squares mean (LSM) change from baseline in HbA1c levels at Week 24 was -0.68% in the remogliflozin etabonate 100 mg arm, -0.61% in the remogliflozin etabonate 250 mg arm, and -0.59% in the dapagliflozin 10 mg arm. The difference in change from baseline in HbA1c level at Week 24, between remogliflozin etabonate 100 mg and dapagliflozin 10 mg arms was -0.08% (90% CI: -0.30 , 0.13) and was NI to dapagliflozin with high statistical significance (P<0.001). The difference in change from baseline in HbA1c level at Week 24 between remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms was -0.02% (90% CI: -0.24, 0.19) and was NI to dapagliflozin with high significance (P= 0.002). Thus, the primary endpoint was achieved with both doses: remogliflozin etabonate 100 mg and remogliflozin etabonate 250 mg demonstrating NI to dapagliflozin 10 mg.

Similar observations were noted for secondary analysis using the MMRM method in the mITT population and all sensitivity analyses by the methods analysis of covariance (ANCOVA) with observed cases (OC), ANCOVA with last observation carried forward (LOCF), and ANCOVA with IR including values on rescue medication in both PP and mITT populations for the primary efficacy endpoint.

**Secondary Efficacy Endpoints**

**Change in HbA1c Levels at Week 12:** In the PP population, the LSM (SE) change from baseline in HbA1c levels at Week 12 was -0.45% (0.074%) in remogliflozin etabonate 100 mg arm, -0.55% (0.076%) in remogliflozin etabonate 250 mg arm, and -0.44% (0.099%) in dapagliflozin 10 mg arm.

The LSM difference in change from baseline in HbA1c levels at Week 12 between remogliflozin etabonate 100 mg and dapagliflozin 10 mg arms was -0.01% (90% CI: -0.20, 0.18) and was NI to dapagliflozin with statistical significance (P =0.001). The LSM difference in change from baseline in HbA1c levels at Week 12 between remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms was -0.11% (90% CI: -0.31 , 0.08) and was NI to dapagliflozin with statistical significance (P <0.001).

**Change in FPG Concentrations:** Reduction in mean FPG concentrations from baseline was observed at Week 1, Week 12, and Week 24 in all the treatment arms. Statistically significant differences favouring remogliflozin were observed between remogliflozin etabonate 250 mg and dapagliflozin 10 mg for change from baseline in FPG at Week 1, in both PP and mITT populations for (P=0.003; P=0.044), respectively. No statistically significant difference was observed between remogliflozin etabonate 100 mg and dapagliflozin 10 mg arms at Week 1 in change from baseline in FPG concentrations. No statistically significant difference was observed between remogliflozin etabonate 100 mg or remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms at Week 12, and Week 24 in change from baseline in FPG concentrations.

**Change in PPG Concentrations:** Reduction in mean PPG concentrations from baseline was observed at Week 1, Week 12, and Week 24 in all the treatment arms. No statistically significant difference was observed between remogliflozin etabonate 100 mg or remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms at Week 1, Week 12, and Week 24 in change from baseline in PPG concentrations.

**Body Weight:** Reduction in body weight was similar in the treatment arms. Change from baseline in body weight was -2.56 (0.20) kgs in remogliflozin etabonate 100 mg arm, -2.83 (0.20) kgs in remogliflozin etabonate 250 mg arm, and -2.66 (0.26) kgs in dapagliflozin 10 mg arm in the PP population. No statistically significant difference in change from baseline in total body weight was observed between the treatment arms except a statistically significant difference was observed for Remogliflozin etabonate 250 mg compared with dapagliflozin 10 mg for change from baseline in total body weight at Week 12 (P=0.030) in the mITT population.

**HbA1c Levels Stratified At Baseline:**

Change in HbA1c Levels with Remogliflozin Etabonate 250 mg versus Remogliflozin Etabonate 100 mg at Week 24: The difference between 250 mg and 100 mg doses of remogliflozin etabonate in HbA1c level reduction did not appear to be related to HbA1c level strata at baseline. No effect of the 3 strata (7% to 7.9%, 8% to 8.9%, and 9% to 10%) of HbA1c level at baseline on the difference between 2 doses of remogliflozin etabonate with regard to change from baseline in HbA1c level was observed. In the PP population, the LSM difference in change from baseline HbA1c levels at Week 24 between remogliflozin etabonate 250 mg and remogliflozin etabonate 100 mg stratified for screening HbA1c levels (7% to 7.9%, 8% to 8.9%, and 9% to 10%) was not statistically significant (P>0.05).

**Fasting Lipids:** No statistically significant difference in change from baseline in TC, LDL-C, HDL-C, and triglycerides was observed between the treatment arms except for 2 significant differences observed for TC (remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms; Week 24 [P= 0.040] mITT population) and LDL-C (remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms; Week 24 [P= 0.040] mITT population).

**Therapeutic Glycaemic Response:** 40.7% subjects in the remogliflozin etabonate 100 mg arm, 46.0% subjects in the remogliflozin etabonate 250 mg arm, and 40.4% subjects in

the dapagliflozin 10 mg arm in the PP population achieved therapeutic glycemic response defined as HbA1c <7% at Week 24. However, the difference between remogliflozin etabonate 100 mg versus dapagliflozin 10 mg arms and between remogliflozin etabonate 250 mg and dapagliflozin 10 mg arms was not statistically significant.

**Rescue Medication:** 27.0% subjects in the remogliflozin etabonate 100 mg arm, 17.2% subjects in the remogliflozin etabonate 250 mg arm, and 27.7% subjects in the dapagliflozin 10 mg arm in the PP population used rescue medication. Lesser proportion of subjects in the remogliflozin etabonate 250 mg arm used rescue medication compared with dapagliflozin 10 mg arm. In both PP and mITT populations for remogliflozin etabonate 250 mg compared with dapagliflozin 10 mg statistically significant differences were observed for proportion of subjects using rescue medication at Week 24 (P=0.015; P=0.006), respectively. However, the difference between remogliflozin etabonate 100 mg compared with dapagliflozin 10 mg was not statistically significant for proportion of subjects using rescue medication at Week 24.

**Pharmacokinetic Results:**

Following oral administration of Remogliflozin etabonate tablets at 100 and 250 mg, the plasma concentrations of the prodrug (RET) generally reached Cmax faster than other analytes with a median Tmax ranging from 1.00 to 2.00 hours post dosing on both day 1 and day 8. The active moiety remogliflozin (REMO) reached the Cmax relatively at later time points with median Tmax ranging from 1.50 to 2.51 hours on both day 1 and day 8. The metabolite (GSK 279782) generally reached Cmax later than that of REMO with median Tmax ranging from 2.00 to 3.00 hours on both day1 and day 8. After Cmax, the plasma concentrations generally declined for all 3 analytes. The prodrug (RET) showed fastest decline with plasma concentrations falling below quantifiable limit (BQL) before 12 hours in most subjects. REMO and metabolite had quantifiable concentrations until the end of dosing interval in all subjects at both dose levels. There were no considerable increase in plasma concentrations of all 3 analytes on day 8 in comparison to day 1. This is consistent with the short half-lives observed for all 3 analytes.

Among the 3 analytes, the active Moiety (Remogliflozin) showed the highest Cmax and AUC, followed by the metabolite (GSK 279782). The lowest Cmax and AUC was observed for the prodrug (Remogliflozin Etabonate), suggesting rapid conversion of the prodrug to the active moiety. The geometric mean GSK 279782 exposures were around 22-25% of the remogliflozin exposure. The Cmax and AUC of both active moiety and metabolite appeared to be nearly proportional between 100 mg and 250 mg on both days. The geometric mean t1/2 was shortest for the prodrug (0.759 to 1.16 hours), followed by that of remogliflozin (1.49 to 2.18 hours), and in general the longest t1/2 among 3 analyte was of metabolite (2.06 to 2.30 hours). Consistent with the short half-lives, all 3 analytes showed only minimal accumulation in plasma exposure with repeat dosing. The minimal accumulation on day 8 also indicates rapid attainment of steady state levels.

**Safety Results:**

- Overall, the safety profile of both 100 mg and 250 mg doses of remogliflozin etabonate was comparable to that of dapagliflozin 10 mg over 24 weeks treatment in subjects with type

2 diabetes mellitus. Both 100 mg and 250 mg doses of remogliflozin etabonate were found to be safe and well tolerated.

- The incidence of TEAEs was also low and comparable across the 3 treatment arms; the incidence of TEAEs was 29.5% in the remogliflozin etabonate 100 mg arm, 28.7% in the remogliflozin etabonate 250 mg arm, and 27.4% in the dapagliflozin 10 mg arm.
- The incidence of study drug-related TEAEs was comparable across the 3 treatment arms (8.1% in the remogliffozin etabonate 100 mg arm, 11.6% in the remogliflozin etabonate 250 mg arm, and 6.6% in the dapagliflozin 10 mg arm).
- There was 1 subject with 1 serious AE of vertigo in the dapagliflozin 10 mg arm which was considered study drug related and the study drug was temporarily interrupted due to the event.
- Overall, TEAEs which led to permanent discontinuation of study drug were reported in 16 subjects (1.4% in the remogliflozin etabonate 100 mg arm, 2.2% in the remogliflozin etabonate 250 mg arm, and 1.5% in the dapagliflozin 10 mg arm).
- With regards to TEAEs of special interest of hypoglycaemia, genital fungal infection, and UTI, no clinically-relevant difference was found in the incidence of hypoglycaemia, genital fungal infections, and UTI in remogliflozin etabonate 100 mg and 250 mg arms compared with the dapagliflozin 10 mg arm.
- No treatment-related trends were noted in the clinical biochemistry, haematology, urinalysis, and vital signs data during the study.
- No clinically-relevant difference was found in the vital signs, physical examination, 12-lead ECG, haematology, clinical biochemistry, and urine analysis in remogliflozin etabonate 100 mg and 250 mg arms compared with the dapagliflozin 10 mg arm.

**Conclusion:**

Overall, this study demonstrated that both 100 mg and 250 mg doses of remogliflozin etabonate reduced HbA1c levels at 24 weeks and demonstrated non-inferiority when compared with dapagliflozin 10 mg. Remogliflozin etabonate 100 mg and 250 mg doses were found to be non-inferior to dapagliflozin 10 mg with statistical significance in subjects with type 2 diabetes mellitus.

The secondary endpoints showed no significant differences between 100 mg or 250 mg dose of remogliflozin etabonate and dapagliflozin 10 mg, except remogliflozin etabonate 250 mg achieved statistically significant improvements with reductions in FPG, total body weight, TC, LDL-C and proportion of subjects using rescue medication compared with dapagliflozin 10 mg in this study.

Following oral administration of remogliflozin etabonate tablet at 100 mg and 250 mg, the active moiety (Remogliflozin) showed the highest plasma exposure, followed by the metabolite (GSK 279782). The inactive prodrug (Remogliflozin Etabonate) showed the lowest plasma exposure.

The metabolite (GSK 279782) AUC was about 22-25% of that of remogliflozin. Between 100 mg to 250 mg, the plasma Cmax and AUC of remogliflozin and GSK 279782 showed near dose proportional increase on both day 1 and day 8. In general, all the 3 analytes showed short

halflives. Consistent with short half-lives, no considerable accumulation in plasma exposures was observed for any of the analytes.

Remogliflozin etabonate 100 mg and 250 mg doses were well tolerated and the safety profile was comparable to that of dapagliflozin 10 mg.

Further, the firm has also submitted protocol for active Post Marketing Surveillance study of Remogliflozin etabonate 100 mg tablets titled, "A Prospective Active Post Marketing Surveillance Study to Assess Safety & Effectiveness of Remogliflozin in Management of Type 2 Diabetes Mellitus in Real World Setting (REFORM-INDIA)" vide application ref. no: GRA/Ind/2019-05/579 dated 03.05.2019 as per the condition that the firm should submit protocol for active post marketing surveillance of the drug to CDSCO before launching the product in the market.

The primary objective of the study is to assess the safety profile & effectiveness of Remogliflozin in management of patients with Type 2 Diabetes Mellitus in real world setting and the secondary objective is to study the characteristics of Remogliflozin usage in Type 2 Diabetes Mellitus, in terms of

- Clinical profile of patients
- Patterns of its usage

The study is planned to recruit 10,000 patients from ~100 sites across India over period of one year. Each participant would be followed up for 12 months.

**Recommendation of the Committee:-** The firm presented the protocol for conducting Active Post Marketing Surveillance(PMS) study of Remogliflozin 100 mg Tablets on 10,000 patients. After detailed deliberation, the committee recommended for grant of approval of active PMS study of Remogliflozin 100 mg Tablets subject to conditions that, firm should also capture data related to concomitant use of other drugs and incidence of progression/ regression of DM related complications

**Agenda No. 6**

**Phase II clinical trial with GRC27864 of M/s Glenmark Pharmaceuticals**

This is related to an application for grant of permission to conduct Phase II clinical trial entitled, "A Phase 2 dose- range finding 12-week, double-blind, randomized, parallel group study to evaluate safety and efficacy of GRC 27864 in patients with moderate to severe osteoarthritis pain", as per the amended clinical trial protocol submitted.

As per information submitted by the firm:-

GRC 27864, known chemically as N-(4-chloro-3-(5-oxo-1-(4-(trifluoromethyl) phenyl)-4, 5 dihydro-1H-1, 2,4-triazol-3-yl) benzyl) pivalamide, is a novel potent, selective, orally bioavailable inhibitor of mPGES-1. It has demonstrated good efficacy in various preclinical disease models of pain and inflammation, such as lipopolysaccharide (LPS)-induced PGE2

release, inflammatory hyperalgesia, osteoarthritic pain and monoarticular arthritis in guinea pigs.

Safety and tolerability of single and multiple ascending doses of GRC 27864 administered as granules in suspension and tablet (single dose) has been evaluated in Phase 1 studies in healthy volunteers (GRC 27864-101 and GRC 27864-102). The highest tested doses of a single oral dose up to 1000 mg and multiple oral doses up to 130 mg/day (for 28 days) have been well tolerated in these studies. Further pharmacodynamic biomarker (PGE2) data generated in phase 1 studies demonstrated adequate target engagement and PK/PD correlation.

GRC 27864 has been studied in a first-in-man phase I single ascending dose (SAD) study (GRC 27864-101), multiple ascending dose (MAD) study (GRC 27864-102) and a formulation bridging study (GRC 27864-103).

GRC 27864 was well tolerated up to 1000 mg single dose and up to 130 mg per day for 28 days. In a SAD study (GRC 27864-101) in healthy subjects (age <55 years), the most commonly reported treatment-emergent adverse events (TEAEs) considered possibly related to study drug were dizziness, headache, and diarrhea. One SAE (upper GI bleeding) was reported in a 67-year-old female who took a single dose of 250 mg GRC 27864. The subject was found to be H. pylori positive and the SAE was resolved with anti H. pylori treatment. However, this SAE was considered possibly related to study drug due to temporal association. In the multiple ascending dose (MAD) study for 28 days (GRC 27864-102) in healthy subjects of age < 55years and elderly subjects (age > 65 years), the most commonly reported TEAEs that were considered related to study drug were abdominal pain, diarrhea, and nausea. No SAEs were reported in the MAD study in healthy adult subjects (<55 years) as well as elderly subjects (>65 years). The pharmacokinetics and relative bioavailability of tablet formulation of GRC 27864 was evaluated in healthy volunteers (GRC 27864-103). None of the TEAEs in clinical study GRC 27864-103 were considered to be related to study drug.

GRC 27864 is a first in class, potent, selective, orally bioavailable inhibitor of mPGES-1 enzyme which is up-regulated under inflammatory conditions. There is strong and consistent evidence of a novel mechanism of selective prostaglandin E2 (PGE2) inhibition with GRC 27864 while preserving prostanoid balance including prostacyclin (PGI2) and thromboxane (TXA2). This evidence comes from evaluation of the effect of GRC 27864 on prostanoidinhibition pattern in in vitro, urinary prostanoidbiomarker studies in dogs and human healthy volunteers. GRC 27864 is thus a new class of analgesic compound, devoid of impact on the gastrointestinal (GI) and cardiovascular (CV) systems based on the animal studies conducted so far, thus suitable for chronic treatment of pain. This is in contrast to the NSAID class comprising of cyclooxygenase (COX)-1inhibitors and COX-2 inhibitors that have documented GI and CV safety concerns. An increasing degree of selectivity towards COX-2 is implicated in augmentation of CV risk while increasing selectivity towards COX-1 augments GI risk as reflected in their respective relative risk values.
Selective inhibition of mPGES-1 is an attractive and novel approach under development for pain therapy. mPGES-1 enzyme is solely involved in PGE2 production during pain and inflammation. PGE2, derived from mPGES-1 has a proven pathological role in several painful, inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and dysmenorrhea and is also implicated in the development of atherosclerosis. Blocking the mPGES-1 enzyme is expected to selectively inhibit increased PGE2 production during inflammation, without inhibiting other physiologically important prostanoids such as PGI2 and TXA2. Selective mPGES-1 inhibitors are thus expected to relieve pain while mitigating the dose limiting side effects of currently used analgesics (traditional NSAIDs and selective COX inhibitors) on the GI, renal and CV systems.

As per recommendation of IND Committee dated 25.07.2017, the firm was granted permission to conduct Phase II clinical trial entitled, "A Phase II dose- range finding 12-week, double-blind,

randomized, parallel group study to evaluate safety and efficacy of GRC 27864 in patients with moderate to severe osteoarthritis pain" on 07.12.2017.

A total of 624 (156 per arm) subjects will be enrolled in the study.

Eligible subjects will be randomly assigned to one of the following arms in double-dummy, double blind design with 1:1:1:1 ratio. Randomization across the treatment arms will be balanced for subjects having received previous NSAIDs as well as those who receive background treatment with chondroprotective agents.

Arm 1: GRC 27864, 10 mg, QD for 12 weeks.
Arm 2: GRC 27864, 25 mg, QD for 12 weeks.
Arm 3: GRC 27864, 75 mg, QD for 12 weeks.
Arm 4: Placebo, QD for 12 weeks.

Now, the firm has revised the Phase II clinical trial protocol with certain protocol amendments. These amendments are related to exclusion criteria, secondary efficacy end points and assessment of safety. Changes are summarized below:-

| **Present**<br><br>**Protocol Version 3.0 dated 31.10.2017** | **Proposed**<br><br>**Protocol Version 4.0 dated 11.04.2019** | **Rationale for Amendment** |
|---|---|---|
| **Subject Exclusion Criteria** | | |
| a. eGFR< 80 ml/min/1.73m2 as determined by MDD method | eGFR< 60ml / min/1.73m2 as determined by MDRD method | The prevalence of osteoarthritis (OA) increase with age However; because of exclusion criteria of eGF<80ml/min/1.73m2 as determined by MDRD method; many subjects in older age group are being excluded. This may lead to recruitment of relatively younger population and may affect the generalizability of the results. The available safety data from the ongoing study does not suggest any adverse impact of investigational proudct (IP) on eGFR.<br><br>The modification in exclusion criteria will not jeopardize the safety of the subjects as subjects with eGFR> 60ml / min/1.73m2 can be considered as having normal renal function in the absence of any other markers of renal damage like albuminuria or haematuria. (Ref: https://renal.org/information-resources/the-uk-eckd-guide/normal- |

| | | |
|---|---|---|
| | | gfr/) |
| **Secondary efficacy end points** | | |
| Mean change from baseline in the Patient Global Assessment of Response to Therapy (PGART) using 0-4 point Likert scale at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) | Change in Patient Global Assessment of Response to Therapy (PGART) using 0-4 point Likert scale at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) | Editorial changes as PGART is being recorded at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) and not at baseline. |
| Mean change from baseline in the Investigator Global Assessment of Responses to Therapy (IGART) using 0-4 point Likert scale at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) | Change in Investigator Global Assessment of Response to Therapy (IGART) using 0-4 point Likert scale at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) | Editorial changes as PGART is being recorded at the end of 2, 4, 8 and 12 weeks of treatment and at follow up (14 weeks) and not at baseline. |
| **Protocol Synopsis and throughout the document for consistency** | | |
| In addition, urine will be collected for estimation of prostanoid metabolites for up to 24h, at baseline visit (Day -2 and / or Day -1), and Visits 4 and 6 from subjects who have consented for PK sampling. | In addition, urine will be collected for estimation of prostanoid metabolites for up to 24h, up to 2 days (voluntary for day -2 and mandatory for day -1) prior to visit 2 (day 1) and on two occasions at visit 4 i.e. day 29±3 (voluntary) and visit 6 i.e. day 85±3 (mandatory) | As per requirement of the exploratory end - point for estimation of urinary biomarker; urine collection will be voluntary for day -2 and day 29±3. Changes have been made throughout the documents for the same. |
| **Assessment of Safety, X-ray** | | |
| Not applicable | Kellgren and Lawrence (K-L) | As per recommendation from DSMB . |

| | | |
|---|---|---|
| | grading will be determined based on screening X-ray | |

**Recommendation of the Committee:**-The firm presented their proposal for amendment of Phase II clinical trial protocol. After detailed deliberation, the committee recommended for grant of approval of the protocol amendment.

**Agenda No. 7**

**Application for grant of Marketing Authorization of Recombinant Rabies G Protein Vaccine of M/s CadilaPharmaceuticals Limited**

M/s Cadila Pharmaceuticals has submitted an application for grant of market authorization for Recombinant Rabies G protein Vaccine, 50µg/0.5ml, 0, 3, 7 days schedule.

**Clinical trial Data:**

- Phase I/II clinical trial:

Firm's protocol for conduct of phase I/II clinical trial titled "open label, randomized comparative clinical trial to assess safety and immunogenicity of Recombinant Rabies G protein Vaccine administered as a simulated post exposure immunization in healthy volunteers of 18 to 65 years of age group" was deliberated in IND committee meeting as and based on the recommendation of IND committee meeting, this office had granted phase- I/II clinical trial NOC to firm on 09.10.2013. (Doses: 5, 10, 20 & 50µg per 0.5ml, schedule: On days: 0, 3 / 0, 3, 7 / 0, 7 / 0, 7, 10).

- **Phase III clinical trial protocol:**

**Objective of Phase III clinical trial:**

- The primary objective of the Phase III trial was to demonstrate the non-inferiority of the investigational vaccine relative to the comparator vaccine in terms of seroprotection rate attained at 14 days post first of study vaccine.
- The Secondary Objective was to compare subjects with seroprotection at day 42 post first of study vaccine and safety by monitoring subjects with adverse events [Time frame: 0-180 days].
- [Test vaccine: Rabies G protein vaccine (Purified G-protein recombinant nanoparticle rabies vaccine) (3-doses intramuscular injection (50 mcg/0.5ml, Day 0, 3 & 7)] [Reference vaccine: Rabipur Vaccine (5-doses Intramuscular (2.5 IU/ml, day 0, 3, 7, 14 & 28)].
- The trial was to evaluate the immunogenicity and safety of Rabies G protein vaccine (Purified G-protein recombinant nanoparticle rabies vaccine, the investigational vaccine) compared to an approved Comparator Rabipur Vaccine to be administered as a simulated post-exposure (PEP) immunization in healthy volunteers.

Accordingly, firm's proposal to conduct Phase III clinical trial titled "Immunogenicity and safety study of Recombinant Rabies G protein Vaccine administered as post-exposure immunisation in healthy volunteers" along with phase I/II report was deliberated in SEC vaccine dated 30.09.2015 and based on the recommendations of SEC vaccine, this office had granted clinical trial permission vide CT no.-CT-03/2016 dated 15.02.2016 for

conducting the clinical trial at 10 centres located at Gujarat, Chandigarh, Karnataka, Hyderabad, Odisha, Rajasthan, Ahmadabad and Chennai.

**Amendment in Phase III CT protocol with respect to dose and dosage regimen:**
Firm had applied for grant of amendment in change in dose and dosage regimen from 10µg/0.5 ml, Day 0,3 to 50µg/0.5ml at 0, 3 and 7 days due to long term sustainability of the antibody titre and the same amended protocol was deliberated in SEC vaccine dated 29.04.2016 and based on the recommendations SEC vaccine, this office acknowledges the change in dose and dosage regimen as 50µg/0.5ml at 0, 3 and 7 days.

- **Phase III clinical trial report summary:**
  **Results:**
  **Efficacy Results:**

➢ Primary efficacy: Subjects with seroprotection at 14 days post 1st dose of study vaccine:

- The primary efficacy endpoint was to evaluate the efficacy by seroprotection at 14 days post 1st dose of Test vaccine: Rabies G protein Vaccine (Dose: 50 µg/0.5 ml, Day 0, 3, 7) compared to Reference vaccine: Rabipur Vaccine (Dose: 2.5 IU/ml, Day 0, 3, 7, 14 & 28) as intra-muscular injection.
- Out of Total 800 randomized subjects, 779 samples (522 in test vaccine arm and 257 in reference vaccine arm) were seropositive (RVNA Titer ≥ 0.5 IU/ml), while 10 samples (04 in test vaccine arm and 06 in reference vaccine arm) were seronegative (RVNA Titer<0.5 IU/ml).There is no statistically significant difference (p=0.1607, 95% CI: 0.9602-0.9837) between test and reference vaccine arms for day 14 seroprotection.

➢ Secondary efficacy: Subjects with seroprotection at 42 days post 1st dose of study vaccine:

- The secondary efficacy endpoint was to evaluate the efficacy by seroprotection at 42 days post 1st dose of Test vaccine: Rabies G protein Vaccine (Dose: 50 µg/0.5 ml, Day 0, 3, 7) compared to Reference vaccine: Rabipur Vaccine (Dose: 2.5 IU/ml, Day 0, 3, 7, 14 & 28) as intra-muscular injection.
- Out of total 800 randomized subjects, 576 samples were collected and analyzed, while 224 samples (146 in test vaccine arm and 78 in reference vaccine arm) were unsatisfactory, hence not analyzed. Out of 576 samples, 564 samples (375 in test vaccine arm and 189 in reference vaccine arm) were seropositive (RVNA Titer ≥ 0.5 IU/ml), while 12 samples (12 in test vaccine arm) were seronegative (RVNA Titer<0.05 IU/mL). There is no statistically significant difference (p=0.8999, 95% CI: 0.6721-0.7364) between test and reference vaccine arms for day 42 seroprotection.

**Safety Results**:
No Serious adverse event or anaphylactic reaction was observed during the trial. Total 170 AEs were reported by 99 subjects. Out of 85 AEs in test vaccine arm, 79 AEs were local and 06 AEs were systemic. However, Out of 85 AEs in reference vaccine arm, 77 AEs were local and 08 AEs were systemic.

SEC (vaccine) recommendation:
Based on submission of request of firm for Market Authorization of Recombinant Rabies G protein Vaccine, the proposal along with Phase III CT report was deliberated in the SEC vaccine dated 14.05.2019 wherein the committee noted that out of 800 randomized subjects only 576 (72%) samples could be analysed while 224 samples (28%) could not be analysed due to various reasons which is much higher than the proposed 20% dropout rate. The committee also noted that, it is an IND molecule and Phase I/II clinical trial protocol have

been evaluated by that committee. After detailed deliberation, the committee recommended that the proposal may also be referred to the IND committee.

**Recommendation of the Committee:-** The firm presented their proposal along with Phase III clinical trial report. The committee observed that there are many discrepancies in the clinical data and the results presented were not in accordance with GCP. Therefore, the Committee recommended that the firm should submit the actual results of the clinical trials with proper interpretation including details of no. of subjects screened, randomized, drop out/ lost to follow up, details of no. of samples analyzed etc. along with the raw data of the Phase III clinical trial.

**Agenda No. 8**

**Application for grant of Marketing authorization of Rabimabs ( Docaravimab 62-713 and Miromavimab M777-16-3) of M/s Cadila Healthcare Limited.**

M/s Cadila Healthcare Limited has submitted their application for grant of permission to manufacture and market their Investigational drug product, Rabimabs**( Docaravimab 62-713 and Miromavimab M777-16-3)** liquid solution (sterile) for injection in vial with proposed strengths 3000IU/10mL, 3000IU/5mL, 1500IU/5mL, 1500IU/2.5mL & 600IU/1mL.

After successful completion of Phase I/II clinical trial, firm had obtained permission to conduct Phase III study entitled "Randomized, multi-centric, open-label, comparator-controlled study to evaluate the efficacy and safety of RABIMABs administered in conjunction with Vaxirab N for post-exposure prophylaxis in patients following potential rabies exposure" from this office. Firm has completed the Phase III study and has submitted the clinical study report for obtaining permission to manufacture and market the drug product, Rabimab liquid solution (sterile) for injection in vial.

**Indication:** Rabimab is proposed to be indicted in combination with rabies vaccine for rabies post-exposure prophylaxis.

**Results of Phase III clinical trial report as submitted by the firm -**

- Firm was accorded permission for conduct of Phase III CT by this office on 17th March 2017.
- The purpose of this Phase III study was to evaluate the efficacy and safety of Rabimabs (Test product, Zydus) vs. Reference product, Imogam in conjunction with Vaxirab N for post-exposure prophylaxis in patients following potential rabies exposure.
- Based on the results of Phase I/II clinical study with RABIMABs, 40 IU/Kg dose was selected for Phase III clinical study.
- A total of 308 subjects were randomized in this study in the ratio of 1:1.
- 154 subjects each in RABIMABs and Imogam® treatment arm.
- The safety population comprised 308 subjects.

- In total, 286 subjects qualified for the per protocol population analysis and 299 subjects qualified for the mITT population analysis.
- In total, 277 subjects completed the study, 13 7(88.96%) subjects from RABIMABs treatment arm and 140 (90.91%) subjects from Imogam® treatment group.
- The major reasons for withdrawal included: 22(7.14%) subjects lost to follow-up and 9(2.92%) subjects withdrew their consent.
- In total, 31(10.06%) subjects discontinued the study: 17 (11.04%)in the RABIMABs group and 14 (9.09%) in the Imogam® group.
- Similar percentages of subjects in both the treatment group completed the study.

**Efficacy Conclusions:**

**Primary endpoints:**

- Of 144, 130(90.28%) participants in the RABIMABs group and 134 (94.37%) from 142 participants in Imogam® group had RFFIT titre ≥0.5 IU/ml on day 14 in PP population.
- Of 148, 133 (89.86%) participants in the RABIMABs group and 137 (90.73%) from 151 participants in Imogam® group had RFFIT titre ≥0.5 IU/mlon day 14in mITT population.
- Based on the results obtained for PP and mITT populations non-inferiority of RABIMABs compared to Imogam®for responders with RFFIT titre ≥0.5 IU/ml on Day 14 is established.

**Secondary endpoints:**

- The upper bound of 95% CI of responder (RFFIT titre ≥0.5 IU/mL) difference in the two treatment groups at Day 28, 42 and 84 is <0.10 in PP and mITT populations with statistically not significant one-sided p-value >0.025.
- The responder rate obtained at Day 28, 42 and 84statistically supports the non-inferiority of RABIMABs compared to Imogam® for responders with RFFIT titre ≥0.5 IU/ml.
- The upper bound of 95% CI of responder (RFFIT titre ≥0.1 IU/mL) difference in the two treatment groups at Day 3 is <0.10 in PP and mITT populations with statistically not significant one-sided p-value >0.025. The upper bound of 95% CI of responder (RFFIT titre ≥0.1 IU/mL) difference in the two treatment groups at Day 7 is ≥0.10 in PP and mITT populations with statistically significant one-sided p-value <0.025.
- There was no statistically significant difference in occurrence of local reactions between the treatment groups. In systemic reactions, fever was experienced in RABIMABs group at screening and enrolment visit.
- Thus, safety and tolerability of RABIMABs is comparable to Imogam®.
- By Day 84, 98 participants in PP population and 101 in mITT populations in RABIMABs treatment group had tested for positive ADA for 62-71-3 compared with baseline.

- By Day 84, 53 participants in PP population and 55 in mITT populations in RABIMABs treatment group had tested for positive ADA for M777-16-3 compared with baseline.

**Safety Conclusion:**

- After 28 days of treatment, the following can be concluded regarding the safety of RABIMABs in the treatment of post-exposure prophylaxis in patients following potential rabies exposure.
- In total, 113 subjects reported 170 AEs during the treatment duration: 92 AEs in RABIMABs and 78 AEs in Imogam® treatment group.
- Number of subjects experiencing AEs during the study do not significantly differ ($p>0.05$) in both the treatment groups.
- 68 subjects had AEs that were considered by investigators to be related(Possibly related and related)to study medication: 42 (27.27%) subjects in the RABIMABs groups and 26 (16.88%) subjects in the Imogam® treatment group.
- Most of the AEs were mild in severity. No clinically relevant treatment differences were observed in ECG findings between treatment groups throughout the study duration.
- None of the subjects were discontinued from the study due to AEs in any of the treatment group.
- There were no deaths and SAEs during the treatment period.
- In total, the reported TEAEs were: General disorders and administrative site conditions 69 (22.40%); followed by infections and infestations 14 (4.55%); skin and subcutaneous tissue disorders 13 (4.22%); blood and lymphatic system disorders 12 (3.90%); renal and urinary disorders 11 (3.57%); musculoskeletal and connective tissue disorders 10 (3.25%);investigations 9(2.92%); metabolism and nutrition disorders 5 (1.62%); hepatobiliary disorders 4 (1.30%);respiratory, thoracic and mediastinal disorders 3 (0.97%); injury, poisoning and procedural complications1 (0.32%) and gastrointestinal disorders1 (0.32%).
- In total, 113 (36.69%) subjects had at least one TEAE during the treatment period: 63 (40.91%) subjects in RABIMABs and 50 (32.47%) subjects in Imogam® treatment group.
- In total, the most frequently reported TEAEs experienced by ≥1% of subjects in both the treatment groups were pain 38 (12.34%); pyrexia 15 (4.87%); urinary tract infection 13 (4.22%); swelling 11 (3.57%); haematuria 8 (2.60%); erythema 8 (2.60%); tenderness 5 (1.62%); hyperbilirubinaemia 4 (1.30%) and myalgia 4 (1.30%).
- 68 had AEs that were considered by investigators to be related(Possibly related and related)to study medication: 42 (27.27%) subjects in the RABIMABs groups and 26 (16.88%) subjects in the Imogam® treatment group.

- Adverse events reported by most of the subjects [113(36.69%)] were resolved or recovered by end of the study.
- In total, 4(1.30%) subjects had AEs which are not recovered or resolved. There were no deaths and SAEs during the study. None of the subjects were discontinued from the study due to AEs in any of the treatment group.
- No clinically relevant treatment differences were observed in ECG findings between treatment groups throughout the study duration.

**The proposal was deliberated in IND Committee in its meeting held on 15.03.2019. Recommendation of the Committee dated 15.03.2019:-**The firm presented their proposal along with Phase III clinical trial report. The committee observed that certain data presented before the committee was not in consonance with that submitted along with their application and therefore, the firm should present their proposal with full clarity before the committee to consider the matter further.

**Recommendation of the Committee:-** The firm presented their proposal along with results of the Phase III clinical trial. The committee noted that in the Phase III clinical trial results, there is no much variation in terms of efficacy and safety of Rabimab's (Test product, Zydus) vs. Rabies Immunoglobulins (Reference product, Imogam) in conjuction with Vaxirab N for post-exposure prophylaxis in patients following potential rabies exposure.

After detailed deliberation, based on detailed data generated, the committee recommended for grant of permission to manufacture and market Rabimabs (Docaravimab 62-713 and Miromavimab M777-16-3) to be indicated for in combination with rabies vaccine for rabies post-exposure prophylaxis subject to condition that, the firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.

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

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