Minutes of IND Committee meeting held on 15.03.2019 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. Y.K. Gupta, Ex. Dean, 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.
6. Dr. Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
7. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.

ICMR Representative:

1. Dr. Vijay Kumar, Scientist G, Division of BMS-Co-ordinator, ICMR, New Delhi.
2. Dr. Rajni Kaul, Scientist G, Division of BMS, ICMR, New Delhi.
3. 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).

Following members could not attend the meeting:

1. Dr. S.K. Sharma, Ex-Prof. & Head, Department of Medicine, AIIMS, New Delhi.
2. Dr. Deepak Kaul, Prof. & Head, Department of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
3. 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. The Chairman also informed the committee that since he has to attend another important meeting after some time, in his absence Dr. Nilima Kshirsagar and Dr. Y. K. Gupta would Chair the meeting. Thereafter, the agenda items were discussed one by one:

Agenda No. 1

Phase II clinical trial with TRC160334 of M/s Torrent Pharmaceuticals

This office has received an application for the grant of permission to conduct a Phase II clinical study entitled “A Phase II randomized, double blind, placebo controlled, parallel group, multi-

centre study to evaluate the efficacy, safety and tolerability of TRC160334 as an add-on to mesalamine in subjects with mild to moderate Active Ulcerative Colitis".

As per the proposal submitted by the firm:-

TRC160334 is reported to be a novel synthetic HIF hydroxylase inhibitor, the resulting HIF activation is known to induce transcription of genes to adapt and to recover from hypoxic/ischemic conditions including those involved in maintenance of intestinal barrier function and dampening of inflammation. Improving barrier function mid dampening inflammation, HIF-1 seems to target several pathways involved in UC by promoting ulcer healing and reducing intestinal secretary responses.

TRC160334 inhibits the HIF-hydroxylase enzyme. Under hypoxic condition in UC, HIF-alpha does not degrade and make HIF alpha/beta complex which accumulates in the nucleus and activates several genes responsible for regaining haemostasis in hypoxic tissues. TRC160334 facilitates stabilization of HIF by inhibiting its hydroxylase enzyme and causing certain genes to regulate angiogenesis, cell survival, metabolism and vascular tone. In vitro studies have supported the fact that TRC160334 dose dependently increase HIF-α level and inhibits the HIF-hydroxylase enzyme. In vivo data suggests thatTRC160334 has positive effect on TNBS and DSS induced UC. These studies have reported improvement in disease activity index (DAI), survival rate, macroscopic evaluation and loss in body weight in animals with ulcerative colitis.

TRC160334 has medium intestinal permeability and it is found to be weak substrate of efflux transporter BCRP. TRC160334 is rapidly absorbed (Tmax< 0.5 hour) in male SD rats with an absolute oral bioavailability of 54%. The in vitro metabolism studies with liver microsomes and hepatocytes from various species have demonstrated the metabolic stability of TRC160334. However, two major metabolites (hydroxylation and methylation or ketone formation) were identified in plasma samples of rats and dogs during toxicity studies. TRC160334 did not show inhibition or induction potential against major CYPs. The tissue distribution of TRC160334 in rat was rapid and wide after its single oral administration. After repeated administration in mice with DSS induced colitis, it was observed that more amount of TRC160334 was present in target tissues through oral and ir administration in comparison to IP route. The mean elimination half-life is 2.6 hr in rats after oral administration. The major route of excretion is urine after IV administration and major fraction of administered dose was recovered from faeces after oral administration. Higher exposure of TRC160334 in female BALB/c mice in comparison to male can be attributed to sex related difference in BCRP expression in liver. The exposure in male mice with TNBS induced colitis was half of that observed with healthy male mice, whereas no such difference observed in females with DSS induced colitis. Dose related increase in exposure of TRC160334 was observed at several fold higher pharmacological doses across the species and gender without accumulation after its repeated dose oral administration.

TRC160334 was evaluated extensively to understand the toxicological profile after oral route of administrations. An array of toxicity studies including single dose, repeat dose (up to 26 weeks), genotoxicity (standard test battery),Segment I fertility studies and Segment II Teratology studies were conducted as part of human clinical Phase trial

enabling toxicology program of TRC160334. A guinea pig skin sensitization test was also performed to explore possible health hazards likely to arise in humans due to hypersensitivity.TRC160334 has been evaluated for repeat dose toxicity up to 26 weeks in Wistar rats and up to180 days in Beagle dogs to identify the target organ toxicity studies and define no observed adverse effect levels (NOAELs). Reproductive toxicology studies to assess the effect on reproductive performance, as well as embryo foetal and pre-natal development were studied in Wistar rats and rabbits. Two in vitro and two in vivo genotoxicity studies have been performed to observe the mutagenic activity and effect on micronuclei induction of TRC160334. Allergenicity/hypersensitivity studies were performed to evaluate skin sensitization potential of TRC160334 by guinea pig maximization test.

Single dose toxicity studies have been performed on Wistar rats and Swiss albino mice with oral and IV administration. The dose of 2000 mg/kg in rats and 1500 mg/kg in mice by oral gavage was well tolerated, whereas, 20 mg/kg by intravenous was found to be well tolerated by rats and mice. No clinical signs and mortality was observed up to 2000 mg/kg in both genders.

Repeated dose toxicity studies were conducted in rats (IV route for 2 weeks and oral route for 28 days) and dogs (oral route for 28 days). TRC160334, on repeated IV (10 minutes' infusion) administration for 2 weeks to Wistar rats, did not cause any adverse effect on health, growth, survivability, injection site (no local tissue reaction), food consumption, ophthalmoscopy, clinical pathology, gross and histopathology up to the maximum feasible dose (and NOAEL) of 10 mg/kg/day, with a safety of ~ 126x, compared to efficacy exposure.

Wistar rats received the TRC160334, a novel HIF-1 stabilizer, for 26 Weeks by oral route at doses of 20, 40, 80 and 120 mg/kg/day did not show treatment related clinical signs during entire period of experiment. No any treatment related adverse effects noticed in body weight, percent body weight change, food consumption, ophthalmoscopic examination, functional observations parameters at any of the dose level tested. During post treatment haematology analysis, significant increase in reticulocyte count was noticed in both male and female animals at 120 mg/kg/day.

TRC160334 administered to the Beagle dogs up to the dose of 80mg/kg/day orally for 4 weeks, did not cause any effect on health, growth and food consumption, ECG parameters, clinical chemistry, gross pathology. Histopathologically, minimal to mild basophilic and dilated kidney tubules were observed at 40 and 80mg/kg/day with partial reversibility. The NOAEL was established to be 20mg/kg/day.

TRC160334 when administered orally once a day to Beagle dogs for a minimum period of 180 days, and to assess a delay in toxicity and/or recovery after a 28-day recovery period at 1,3, 9 and 18 mg/kg. Various parameters evaluated for the assessment of toxicity ophthalmic examinations, electrocardiographic analysis, haematology, serum chemistry, coagulation, urinalysis, physical examinations, and histopathology did not show any effects related to the test article. Test article related clinical observations were noted: the number of stool events increased with increasing dosage of test article. This incidence plateaued at doses over 3 mg/kg (mid-level dose). Furthermore, during recovery the stool observation frequency persisted in the dosed group. The stool incidence was not considered

toxicologically relevant since it had no apparent effect on food consumption, body weight, clinical observations, clinical pathology, histology, or findings at gross necropsy. TRC160334 following once daily administrations to Beagle dogs for 180 days is considered to be 18 mg/kg which was giving safety margin of 158 times with respect to efficacy exposure.

Genotoxic potential of TRC160334 was evaluated by standard battery of tests. TRC160334 was not mutagenic up to the highest concentration of 2500 µg/plate for a range of Salmonella typhimurium bacterial strains in the presence and absence of metabolic activation. Positive responses were obtained with TRC160334 in the absence and presence of S9 in an in vitro assay for cytogenetic damage in human lymphocytes. Although not linked to excessive cytotoxicity, the clastogenic damage is likely due to the effects of HIF-activation, namely production of reactive oxygen species and inhibition of DNA repair. TRC160334 did not induce micronuclei in mouse or rat bone marrow in acute or 14-day infusion studies, or induce DNA damage (Comet assay) in multiple rat tissues at plasma and tissue exposures that were several orders of magnitude higher than human therapeutic exposures. There were small increases in micronucleus frequency in rat bone marrow (only in males at highest dose of 480 mg/kg/day, multiples of exposure being more than 6000x) following 28 days oral dosing, but these are likely to be due to erythropoietic responses resulting from HIF activation and would therefore exhibit a threshold, as evidenced by the haematological changes reported. At doses where there were no increases in micronuclei i.e., 240 mg/kg/day in both genders (and 480 mg/kg/day in females), systemic exposures were at least 2067 times (and 4329 times) greater than desired therapeutic exposure in humans. In in-vivo Comet Assay in rat TRC160334 did not cause increase in DNA damage in liver, stomach, duodenal, jejunal, spleen, kidney and bone marrow cells relative to the concurrent and respective vehicle controls, up to the maximum tolerated dose of 1500 mg/kg/day. Thus, it is concluded that TRC160334 does not pose a genotoxic risk.

Firm had conducted the three Phase I clinical trial outside India. Details are as under:-

1. A Double-blind, Placebo-controlled, Randomised, Single dose, Dose-ascending Study to Evaluate the Safety, Tolerability and Pharmacokinetics of TRC160334 administered intravenously to male and female healthy subjects (Part A) and elderly subjects with renal impairment (Part B).Intravenous TRC160334 powder for solution for injection/infusion has been evaluated in Caucasian healthy human volunteers during its first in man (FIM) study. During this FIM single ascending dose (SAD) escalation study, total 33 volunteers were enrolled to assess the safety and pharmacokinetic (PK) of TRC160334. The drug was found to be safe and well tolerated from dose 1 mg to 27 mg administered intravenously in healthy volunteers and 9 mg in elderly subjects with renal function impairment. There were no deaths, serious adverse events (SAEs) or significant adverse events (AE) reported as related to the study drug. The most frequent treatment emergent adverse event (TEAE) was headache reported in 4 subjects (12.12 %). Plasma concentrations of TRC160334 as reflected in Cmax, AUC0-lastand AUC0-infvalues increased in a dose proportional manner across 5 dose levels starting from 1 mg to 27 mg. The amount of TRC160334

excreted in urine within 48 hours following single 9mg IV dose was 73.2 % in healthy and 55.1 % in elderly renally impaired subjects; showing that renal excretion plays a significant role in TRC160334 elimination. Mean renal clearance was decreased by approximately 50 % in elderly renal impaired subjects.

2. A double-blind, placebo-controlled, randomized, single-dose (Part A) and multiple dose (Part B), dose-ascending study to evaluate the safety, tolerability and pharmacokinetics after oral administration of TRC160334 in young healthy adult male and female subjects under fasting and fed conditions, with a single cohort of patients in Part A. Delayed release TRC160334 tablets were evaluated in Phase I study among Caucasian healthy and UC subjects. In Part A of the study, single oral administration of 5 mg (fasting conditions), 30 mg (fasting and fed conditions) and 80 mg (fasting conditions) ofTRC160334 was carried out among healthy male and female subjects and 30 mg (fasting conditions) among UC subjects. Multiple ascending dose (MAD) (Part B) study at 10, 30 and 60 mg/day (in two divided daily doses) for 7 days was carried out in young healthy male and female subjects. The drug was found to be safe and well tolerated in both studies. There were no deaths, SAEs or significant AEs reported as related to the study drug. The most frequently reported TEAE was headache in 3 subjects in SAD, and sensation of heaviness in both legs in 3 subjects in MAD study. With delayed release tablets, the exposure of TRC160334 increased in a dose proportional manner in the range of 5 to 80 mg in healthy subjects. The maximum average systemic exposure achieved was 8166.9 ng*h/ml after 80 mg administration. Following 30 mg TRC160334 administration, a delay by approximately 2 hrs in TRC160334 absorption was observed in UC subjects compared to healthy subjects. No statistically significant difference in plasma peaks and exposure was observed between healthy and UC subjects. TRC160334 oral exposure reduces when taken with food. On repeat dose administration for 7 days, no accumulation was observed.

3. An open label, single strength, multiple dose administration study to evaluate pharmacokinetics and safety of TRC160334 in subjects with mild to moderately active ulcerative colitis. This study was designed to evaluate pharmacokinetic of immediate release (IR) formulation and its interaction with food, 8 subjects with mild to moderately active UC were recruited. It was found that IR formulation had better plasma PK profile i.e., AUC0-12of 4617.6 ng*h/mL for IR formulation compared to AUC0-12 of 3315.8 ng*h/mL, than delayed release formulation. Around 20 % free fraction of TRC160334 was available in faeces. Presence of free TRC160334 in faeces is expected to act locally on luminal lesions in colon and contribute to overall efficacy outcome with TRC160334 treatment. Similar to earlier observation with delayed release formulation, significant food interaction was observed when TRC160334 IR formulation was administered along with food in subjects with mild-to-moderately active UC, where a reduction in plasma Cmax and exposure was observed by approximately 68 % and 46 %, respectively. This observation clearly warrants the need for TRC160334 to be administered empty stomach to avoid its interaction with food and maximise its availability. In this study repeat administration of

TRC160334 to mild to moderately active UC subjects for 7 days was found to be well tolerated, only 3 TEAEs were reported in 3 subjects out of the 8 subjects exposed to treatment: only two cases of nausea (one mild, one moderate) reported in 2 subjects were considered possibly and probably related to treatment. The other TEAE was a single case of moderate toothache, not related to treatment.

The proposed study is a Phase II randomized, double blind, placebo controlled, parallel group, multi-centre study to evaluate the efficacy, safety and tolerability of TRC160334 as an add-on to mesalamine in subjects with mild to moderately Active Ulcerative Colitis". Approximately 261 patients will be enrolled in this study. In the proposed Phase II clinical study the efficacy, safety and tolerability of molecule TRC160334 will be evaluated in subjects with mild to moderately active ulcerative colitis (UC) as an add-on to mesalamine. All the eligible subjects will be randomized in a ratio of 1:1:1 to receive either 4 mg or 8 mg/day in two divided doses or matching placebo twice a day. Phase II clinical study being the first efficacy study in humans, two dose levels of TRC160334 is proposed to be evaluated in this study, 4 mg/day and 8 mg/day.

Recommendation of the Committee:-The firm presented their proposal along with reports of Phase I clinical trials conducted outside India and Phase II clinical trial protocol. After detailed deliberation, the committee recommended for grant of permission to conduct the Phase II clinical trial subject to following conditions:-

1. The inclusion criteria “Subjects on stable dose of oral mesalamine of at least 2.4 gm/day for 2 weeks prior to screening” should be revised to - “Subjects on stable dose of oral mesalamine at 2.4 gm/day or higher recommended dose as tolerated for 2 weeks prior to screening”.
2. The haematological analysis of the patients should also include the assessment of Erythropoetin at 4, 12 and 13 weeks of the study.
3. Biochemical and Urine analysis of the patients should be done at 2, 4, 12 and 13 weeks of the study.

Agenda No. 2

Phase III clinical trial with ZYAN1 of M/s Cadila Healthcare Limited

This office has received an application for the grant of permission to conduct a Phase III clinical study entitled “A randomized, double-blind, placebo controlled, parallel group, Phase II multicentric trial to assess safety, tolerability and efficacy of PHD-2 Inhibitor, ZYAN1 in the treatment of anaemia in pre-dialysis chronic kidney disease patients".

As per the proposal submitted by the firm:-

Desidustat (ZYAN1) is reported to be a novel, small organic molecule and orally bioavailable prolylhydroxylase (PHD) inhibitor for the treatment of anaemia. Chemically, ZYAN1 is a quinolone derivative.

To evaluate the pharmacodynamics of ZYAN1, seven studies were carried out wherein ZYAN1inhibited prolyl hydroxylase, stabilized HIF, and improved release of EPO, which was translated into increased haematopoiesis in normal rats and mice, and normalized the haemoglobin concentration in anaemic (nephrectomized or cisplatin treated) rat and mice models. General and safety pharmacological studies were conducted in mice, rats, and dogs to support the use ofZYAN1 in humans. ZYAN1 was also evaluated on Eurofins Panlabs Lead Profile Screen panel containing 68 targets that have been associated with unwanted off target activities, including enzymes, GPCR's, transporters, nuclear hormone receptors and ion channels.

A total of twenty six studies were conducted for assessment of pharmacokinetic of ZYAN1 in non-clinical species. In vivo studies were carried out in C57 mice, Wistar rats, beagle dogs and rhesus monkey. The preclinical pharmacokinetic data indicate that following oral administration, ZYAN1 is well absorbed in all species tested, and it shows dose-linear absorption over a widedose range. ZYAN1 is well-distributed and it is partially excreted as unchanged compound in the urine (28% of dose orally administered). It showed minimal excretion unchanged compound in faeces and bile. At the pharmacokinetically relevant dose tested (2 mg/kg), ZYAN1concentrations in most organs/tissues in rats declined at 24 h post dose when compared 0.5 h (Tmax). ZYAN1 was metabolically stable in vitro and in vivo, and the compound shows minimal potential to inhibit the major CYP isozymes based on in vitro data.

Phase I study was conducted to evaluate the safety, tolerability and pharmacokinetics ofZYAN1 following oral administration in healthy volunteers. The study was randomized, double blind, placebo controlled, multi-centric trial. In plan I (10 mg to 300 mg) and II (100 mg to 300 mg), at each dose level, ZYAN1 and placebo was planned to be given randomly to 6 and 2 volunteers, respectively. To avoid the potential risk to larger number of subjects, each dose panel of eight subjects was divided into two blocks. In first block two subjects were enrolled (01 placebo+01 ZYAN1). Second block were consist of six subjects (01 placebo + 05 ZYAN1). Second block of each panel was initiated after 24 hrs post dose safety analysis of first block. In plan III (150 mg), six male and six female volunteers were enrolled in the study. All twelve healthy volunteers were administered a single oral dose of ZYAN1 in the overnight fasting condition.

The test product has been found safe and well tolerated when administered as a single oral dose up to 300 mg under fasting condition and multiple dose up to 300 mg (on alternate days i.e. Day 1, Day 3 & Day 5) in healthy human subjects. No adverse event was observed in 150 mgZYAN1 treatment arm in any of the populations. i.e. Australian and Indian. No drug-related serious adverse events were reported.

The pharmacokinetic evaluations indicated that the active drug is well absorbed on oral administration in both male and female subjects. There is no any significant difference between pharmacokinetic parameters of centre 1: Australia's 150 mg single dose and centre 2: India's 150mg single dose.

In Phase II,A total of 117 subjects were assigned randomly in a ratio of 1:1:1:1 treatment groups: 29 to the each of ZYAN1 group (i.e. 100 mg, 150 mg and 200 mg) and 30 to the placebo group, of which103 subjects completed the study.

Efficacy: The significant increase was observed in Hb levels from Week 2 to Week 6 in ZYAN1 100 mg,150 mg and 200 mg treatment groups vs. placebo. This trend was observed in both mITT and PP populations. Greater than 80% responders were observed in ZYAN1 200 mg and >60% responders were observed in ZYAN1 100 mg and 150 mg treatment groups in both mITT and PP populations during the study. The significant increase was observed in TIBC levels from Week 2 to Week 6 in ZYAN1 150mg and 200 mg treatment groups vs. placebo in mITT and PP populations. The significant increase was observed in TIBC levels at Week 6 in ZYAN1 100 mg treatment group vs. placebo. The significant decrease was observed in Transferrin saturation at Week 6 in ZYAN1 150 and 200 mg treatment groups vs. placebo at $p < 0.025$ in both mITT and PP populations.

The significant decrease was observed in LDL levels from Week 2 to Week 6 in ZYAN1 200 mg treatment group vs. placebo in mITT and PP populations. The significant decrease was observed in LDL levels at Week 6 in ZYAN1 150 mg treatment group vs. placebo in mITT population. The significant increase was observed in EPO levels in ZYAN1 150 and 200 mg treatment groups compared to placebo from 6 hrs post-dose to 10 hrs post dose at Week 0 and Week 6visits.Iron, TG and CRP were stable during the study with no significant change in both mITT and PP populations. The significant decrease was observed in hepcidin levels at Week 2 in ZYAN1 150 and 200 mg treatment groups compared to placebo and at Week 6, the change from baseline in hepcidin levels was statistically significant in ZYAN1 treatment groups in mITT and PP populations. A dose-related increase in Cmax and AUC0-t was observed in ZYAN1 100 mg to 200 mg dose after single and multiple doses. Fluctuation (%) is similar in all the three treatment arms. Drug doesn’t seem to accumulate with multiple doses with accumulation index of ZYAN1 100 mg:1.028, ZYAN1 150 mg: 1.008 and ZYAN1 200 mg: 1.034. Similar trend was observed for both metabolites. Mean half-life after first dose (Week 0) of ZYAN1 treatment groups was observed in the range of 6.563 to 13.786 hrs and mean half-life after last dose (Week 6) of ZYAN1 treatment groups was observed in the range of 6.343 to 8.702 hrs. Similar trend was observed in the populations, mITT and PP for primary and most of the secondary endpoints.

Safety: A total of 31 AEs were reported from 18 (15.38%) subjects during the study. In total, the most commonly reported TEAEs (PTs) during the study were abdominal pain, vomiting and headache. These TEAEs were observed in total approximately 4% of subjects. No serious adverse events and deaths were reported in ZYAN1 treatment group and no persistent change in laboratory parameters. No clinically relevant treatment differences were observed in ECG findings between treatment groups after 6 weeks of treatment.

The proposed study is A phase 3, multicenter, multi-country, open-label, randomized, active-controlled clinical trial to evaluate the efficacy and safety of Desidustat versus Darbepoetin for the treatment of anaemia in patients with chronic kidney disease (CKD) who are not on dialysis".

The purpose of the study is to assess the efficacy of Desidustat tablet versus Darbepoetin injection based on haemoglobin (Hb) levels (evaluation versus baseline) (Duration: Week 24).

Around 588 subjects will be enrolled in the study with 1:1 treatment allocation ratio to Desidustat and Darbepoetin.

Recommendation of the Committee:-The firm presented their proposal along with Phase II clinical trial report and Phase III clinical trial protocol. After detailed deliberation, the committee recommended for grant of permission to conduct the Phase III clinical trial as per the protocol submitted.

Agenda No. 3

Application for marketing authorization of Remogliflozin of M/s Glenmark Pharmaceuticals.

M/s Glenmark Pharmaceuticals Limited was granted permission to conduct Phase III clinical trial titled, “A 24-Week, Randomised, Double-blind, Double-dummy Parallel-group, Multi-centre, Active-controlled Study to Evaluate Efficacy and Safety of Remogliflozin etabonate in subjects with Type-2 Diabetes Mellitus" on 09.06.2017 and PK studies titled, "Single oral dose pharmacokinetic study of Remogliflozin etabonate tablet 250 mg under fasting condition” on 09.06.2017 and “Single oral dose pharmacokinetic study of Remogliflozin etabonate tablet 100 mg and 250 mg under fasting and/or fed condition” on 06.10.2017.

Subsequently, the firm vide their application dated 04.10.2018 had proposed amendments in the clinical trial protocol related to the statistical analysis of safety and efficacy and reconsideration of the sample size for doing PK analysis in the sub-population as follows:

1. To conduct the statistical analysis in 2 steps which allows a provision of analysis of data of first 612 subjects, followed by eventual analysis with complete 906 subjects’ data after completion of clinical trial.
2. Revise PK sample size from 48 to 30 subjects, considering the challenge of availability of recruitable subjects for PK subset due to unwillingness of the subjects to provide PK blood samples and concurrently also because there is availability of adequate PK data in healthy volunteers.

The proposal was deliberated in IND meeting dated 03.12.2018 wherein the committee after detailed deliberation, recommended for approval of the proposed amendments. Accordingly, approval for the amendments was issued by CDSCO to the firm on 24.12.2018

The firm has now submitted the results of statistical analysis of data after completion of 612 subjects of Phase III clinical study along with Pharmacokinetic study reports as per approved protocol version 03 dated 26 September 2018 and requested for permission to manufacture and market the product in the country.

As per the proposal submitted by the firm:-

Remogliflozin etabonate - A Novel SGLT2 Inhibitor:

SGLT2 inhibitors are novel anti-diabetic drugs that help achieve glycemic 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.

The data submitted by the firm is as follows:

Non-clinical Development Summary:

Pharmacology:-RE is the prodrug of Remogliflozin, a potent and selective inhibitor of the human SGLT2. Remogliflozin is ~100-1000 fold more active against human SGLT2 than SGLT1, with weak inhibitory effects on human SGLT1 and no effects on human SGLT3. RE caused a concentration-dependent increase in urinary glucose excretion in normal mice, rats and dogs. Oral administration with pharmacological doses of RE reduced postprandial glucose excursions in normal animals, without inducing hypoglycemia. Plasma glucose and HbA1c levels were reduced in diabetic models although the insulin response varied depending on the model studied. Single oral doses of RE (up to 1000 mg/kg) produced no treatment-related effects on behaviour or spontaneous loco motor activity in rats or on respiratory or cardiovascular function in dogs. The IC50 concentrations for hERG inhibition for RE and Remogliflozin was 77.3 µg/mL (147.9 µM) and 187.8 µg/mL (416.9 µM), respectively. The IC50 concentrations for hERG inhibition for non-protein bound RE and Remogliflozin are approximately 6184 and 179 times the projected Cmax values (~10% of 0.125 µg/mL for RE and ~35% of 3.00 µg/mL for Remogliflozin) following the administration of a total clinical daily dose of 500 mg (given as a single dose). Overall, these data indicate that RE and Remogliflozin is not likely to alter human cardiac electrophysiology.

Pharmacokinetics:- The pharmacokinetics of RE (prodrug) and Remogliflozin (active moiety) have been investigated through a series of oral and intravenous studies in CD-1 mice, Sprague Dawley rats, Dutch Belted rabbits and Beagle dogs and in a series of in vitro studies using tissue fractions prepared from the rat, dog, monkey and human. Several studies were also conducted with metabolites GSK279782, GSK333081, GSK1997711, GSK1997714 and GSK355993. Non-radio labelled and radio labelled compounds were used in the studies. Remogliflozin generally showed high volume of distribution and moderate to high clearance in preclinical species. Radio labelled studies in rats indicated high absorption, wide distribution of radioactivity followed by nearly complete excretion. No selective association of radioactivity

with any tissues were observed. Moderate plasma protein binding (47 to 76%) of GSK 189074 was observed across the species and no preferential distribution into blood cells.

Toxicology:-RE has been evaluated in repeat dose oral toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 52 weeks in dogs. Genetic toxicology, carcinogenicity assays and reproductive toxicology studies have also been conducted. The no-observed-adverse effect levels (NOAELs) established in 13-, 26- and 52-week oral toxicity studies in mice, rats and dogs were 2000, 1200 and 650 mg/kg/day, respectively (the highest dose tested in each species). The systemic exposure (AUC) obtained at the NOAEL dose (650 mg/kg/day) in 52-week dog (most sensitive species) study are315 to 366-fold for RE (prodrug), ~14 to 17-fold for Remogliflozin (active entity) and ~4 to 5-fold for GSK279782 (a metabolite) when compared to human AUC values for RE, Remogliflozin and GSK279782 (AUC0-24hr200, 9220 and 2050ng.h/mL, respectively) achieved at maximum recommended clinical dose of 500 mg/day (250 mg BID) in a 24-week clinical study with RE in type 2 diabetes mellitus patients (GPL/CT/2016/009/III). RE was non-genotoxic in various in vitro and in vivo genotoxicity assays and was non-carcinogenic in a 2-year oral (gavage) carcinogenicity study conducted in rats and mice. RE had no effect on male or female fertility in rats, was not teratogenic in rats and rabbits and showed no developmental effects in Segment III reproductive toxicity study in rats. RE did not produce anaphylactic reactions and was found to be non-sensitizer in animal studies and non-irritant to skin and eye in vitro.

The NOAELs doses established in animal toxicity studies, provides sufficient safety margins to support the bulk drug approval and market authorization of Remogliflozin etabonate at maximum recommended clinical doses up to 500 mg/day (250 mg BID).

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. 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 radio labelled 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 pharmacodynamics 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.

Pharmacokinetic studies in Indian subjects:

An open label, single treatment, single period, single oral dose PK study of Remogliflozin etabonate Tablet 250 mg of Glenmark Pharmaceuticals Ltd., India was conducted in 30 normal, healthy, adult, human male Indian subjects under fasting condition. Results from Study 0355 – 17 indicate that no formal conclusion was drawn.

An open label, two stage, single period, single oral dose PK study of Remogliflozin etabonate Tablet 100 mg and Remogliflozin etabonate Tablet 250 mg of Glenmark Pharmaceuticals Ltd., India was conducted in 65 normal, healthy, adult, human male Indian subjects under fasting and/or fed condition. The pharmacokinetics of GSK189075 (prodrug: Remogliflozin etabonate), GSK189074 (active moiety: Remogliflozin) and GSK279782 (metabolite) was evaluated in 65 healthy adult volunteers of Indian origin, following single oral administration of Remogliflozin etabonate tablet at 100 mg and 250 mg under fasted state and fed state. In general, under fasted state, the maximum plasma concentrations were achieved rapidly for all 3 analytes with median Tmax ranging between 0.5 to 1.5 hours. With food, there was a slight delay in the Tmax (1.50 to 3.00 hours) for all 3 analytes. In general, the Cmax was generally comparable for all 3 analytes between fasted and fed state across both the dose levels. The AUC was largely comparable for the active moiety (GSK189074) between fasted and fed state, and were slightly higher under fed state for the

inactive prodrug and the metabolite. The observed difference in Cmax or AUC of the active moiety, metabolite or the inactive prodrug between fasted and fed state is not anticipated to be of clinical significance. When a 250 mg of Remogliflozin etabonate tablet was administered in presence of glucose solution, the plasma concentration profiles showed considerably prolonged absorption, indicating glucose solution could be impacting the absorption probably by interfering with solubility of the prodrug. The dose proportional increase in Cmax and AUC, and similar half-lives at 100 mg and 250 mg indicate linear pharmacokinetics. Data from this study demonstrated that the test products were well tolerated.

Summary of Phase III Clinical Trial Results:

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. Subjects were randomized to receive one of the 3 treatment arms for a period of 24 weeks. Primary endpoint was change from baseline in HbA1c% at 24 weeks. Total sample size for the study is 906. Sample size assumptions suggested a sample size of 612 subjects to establish non-inferiority of remogliflozin 100 mg and 250 mg with dapagliflozin 10 mg with sufficient (90%) power. Sample size was increased to 906 for comparison between the two doses of remogliflozin in the three strata of HbA1c at baseline. Analysis was planned and conducted on completion of 612 subjects. Remaining subjects are being continued in the study and on completion, analysis will be conducted to update the results.

As per approved protocol version 03 dated 26 September 2018, statistical analysis was conducted after completion of 612 subjects. Total 581 subjects were included in the mITT and 430 subjects were included in the per protocol population. At 24 weeks change from baseline in HbA1c% in the Dapagliflozin group was -0.58, in the Remogliflozin 100 mg group it was -0.72 and in the Remogliflozin 250 mg group it was -0.77. The p-value for Non-inferiority test was highly significant for Remogliflozin 100 mg (p-value <0.001) and Remogliflozin 250 mg (p-value <0.001), confirming non-inferiority of both the doses of Remogliflozin with Dapagliflozin 10 mg. Thus, the primary endpoint of the study was achieved. These results were confirmed by all the sensitivity analyzes of the primary endpoint.

The change from baseline in fasting plasma glucose (FPG) at week 24 was significant in all the 3 groups: Dapagliflozin 10 mg -20.45 mg/dL, Remogliflozin 100 mg -17.54 mg/dL and Remogliflozin 250 mg -20.51 mg/dL. There was no difference between the 2 doses of Remogliflozin versus Dapagliflozin in FPG reduction (all p values >0.05). In all the 3 groups, post prandial plasma glucose (PPG) reduced from baseline at week 24 groups: Dapagliflozin 10 mg -31.1 mg/dL, Remogliflozin 100 mg -37.2 mg/dL and Remogliflozin 250 mg -39.0 mg/dL. There was no difference between the 2 doses of Remogliflozin versus Dapagliflozin in PPG reduction (all p values >0.05).

Proportion of subjects achieving glycemic control defined as HbA1c <7% at 24 weeks was more with Remogliflozin than Dapagliflozin:30.3% in Dapagliflozin group, 36.4% in the Remogliflozin 100 mg group and 37.1% in the Remogliflozin 250 mg group. However, the difference between the 3 groups was not statistically significant. Proportion of subjects

requiring treatment with rescue medication was less with Remogliflozin than Dapagliflozin: 21.2% in Dapagliflozin group, 17.5% in the Remogliflozin 100 mg group and 12.1% in the Remogliflozin 250 mg group. However, the difference between the 3 groups was not statistically significant. There was 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 in change from baseline in HbA1c level.

Safety of Remogliflozin 100 mg and Remogliflozin 250 mg was comparable to that of Dapagliflozin 10 mg (Table 1). No SAE or death was reported in the 612 subjects during the trial. Incidence of male and female genital mycotic infections and urinary tract infection was comparable between the remogliflozin 100 mg or 250 mg and dapagliflozin 10 mg groups and in line with that of reported incidence with dapagliflozin. Incidence of hypoglycemia was low and comparable between the remogliflozin 100 mg or 250 mg and dapagliflozin 10 mg group. No severe hypoglycemia was reported in the 612 subjects. There was no clinically relevant difference between Dapagliflozin and the 2 doses of Remogliflozin in ECG parameters and laboratory test parameters. Overall, both the doses of Remogliflozin were found to be safe and well tolerated.

Table 1: Safety of Remogliflozin 100 mg and Remogliflozin 250 mg versus Dapagliflozin 10 mg

	Dapagliflozin 10 mg	Remogliflozin 100 mg	Remogliflozin 250 mg
TEAE, %	29.5	32.6	34.4
Serious Adverse Events, n	0	0	0
AE leading to Death, n	0	0	0
Hypoglycemia without rescue medication, %	5.5	5.4	6.2
Hypoglycemia with rescue medication, %	1.4	0.9	1.2
Female Genital Mycotic Infections, %	1.4	1.3	1.2
Male Genital Mycotic Infections, %	1.4	0.4	0
Female Urinary Tract Infections, %	1.4	0.9	5.0
Male Urinary Tract Infections, %	0.7	2.2	1.7

The results of phase III clinical trial in Indian subjects with type 2 diabetes, confirm the efficacy and safety of Remogliflozin 100 mg and Remogliflozin 250 mg and non-inferiority with dapagliflozin 10 mg.

Overall Efficacy & Safety Summary of Remogliflozin etabonate 100mg/250mg Tablets: Overall evidence of efficacy and safety of Remogliflozin etabonate is supported by 3 phase II clinical trials and a large phase III clinical trial. 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. Remogliflozin administered as BID regimen was well tolerated in the phase II clinical studies at doses up to 1000 mg BID with low incidence of glycosuria related adverse events such as urinary tract infections (0-4%) and genital fungal infections (0-8.5%).

The results of phase III clinical trial in Indian subjects with type 2 diabetes, confirm the efficacy and safety of Remogliflozin 100 mg and Remogliflozin 250 mg and non-inferiority with dapagliflozin. Considering, confirmation of efficacy and safety of Remogliflozin etabonate100 mg and 250 mg, with consistency across the results we seek marketing authorization of Remogliflozin etabonate 100 mg and 250 mg administered as BID dosing regimen for the treatment of Type 2 Diabetes Mellitus (T2DM) as monotherapy and in combination with existing anti-diabetic therapies.

Based on all the efficacy and safety data, Remogliflozin etabonate is expected to be an important, effective and safe SGLT2 inhibitor for use in Indian subjects with type 2 Diabetes Mellitus.

Recommendation:-In light of the recommendation of the IND committee meeting dated 03.12.2018, the firm presented their proposal along with results of the Phase III clinical trial data of first 612 subjects. The committee noted that in the Phase III clinical trial results, there is no much variation in terms of efficacy between Remogliflozin etabonate tablets 100 mg and 250 mg. After detailed deliberation, based on detailed non-clinical and clinical data (Phase I,II,III) generated, the committee recommended for grant of permission to manufacture and market Remogliflozin etabonate tablets of 100mg strength for the treatment of Type 2 Diabetes Mellitus (T2DM) as monotherapy and in addition to the existing anti-diabetic therapies subject to the following conditions:-

1. The firm should submit protocol for active Post Marketing Surveillance of the drug 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. 4

Application for marketing authorization of Levonadifloxacin (Oral and Intravenous) of M/s Wockhardt Limited.

M/s Wockhardt Limited was granted permission to conduct Phase III clinical trial entitled, " A Phase III, Multi-centre, Randomized Study to Compare the Efficacy and Safety of Levonadifloxacin (IV and Oral) with Linezolid (IV and Oral) in Acute Bacterial Skin and Skin Structure Infections (ABSSSI)" on 09.06.2017.

Now, firm has submitted the Phase III clinical study report and requested for manufacturing and marketing permission of Levonadifloxacin Injection 800 mg/100 ml and Levonadifloxacin tablets 100mg.

As per the proposal submitted by the firm:-

Levonadifloxacin intravenous injection contains L-arginine salt of Levonadifloxacin, a novel broad spectrum synthetic benzoquinolizine fluoroquinolone antibacterial agent. Emrok injection is for intravenous administration as a 90 minute infusion. The chemical name of Levonadifloxacin L-arginine salt is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid L-arginine salt tetrahydrate. The molecular weight of Levonadifloxacin arginine tetrahydrate salt is 606.6 g/mol and the molecular weight of Levonadifloxacin free acid is 360.4 g/mol.

Alalevonadifloxacinmesylate; the water soluble prodrug of Levonadifloxacin, is a mesylate salt of L-alanine ester of the active parent drug Levonadifloxacin, a synthetic broad spectrum benzoquinolizine fluoroquinolone antibacterial agent for oral administration. Alalevonadifloxacin is rapidly and completely hydrolysed by esterase enzymes during oral absorption, and is distributed in the circulating blood as active Levonadifloxacin. The chemical name of Alalevonadifloxacin mesylate is (S)-(-)-9-Fluoro-8-(4-L-alaninyl oxypiperidin-1-yl)-5-methyl-6,7-dihydro-1-oxo-1H,5H-benzo[i,j] quinolizine-2-carboxylic acid, methane sulfonic acid salt and its structure is shown below.

The molecular formula of Alalevonadifloxacin mesylate is C22H26FN3O5•CH3SO3H and the molecular weight is 527.6 g/mol. Alalevonadifloxacin mesylate is freely soluble in water at 25°C across a pH range of 2-8 encountered in the gastrointestinal tract. The molecular weight of Levonadifloxacin free acid is 360.4 g/mol.

Mechanism of Action:- Levonadifloxacin demonstrates bactericidal activity through dual inhibition of DNA gyrase and topoisomerase IV, with primary affinity towards DNA gyrase. DNA gyrase and topoisomerase IV enzymes are essential for DNA replication, transcription, repair and recombination. Owing to high affinity to DNA gyrase, Levonadifloxacin demonstrates potent cidal action even against high density S. aureus cultures. Substitution of 4-hydroxy piperidine side chain at C-8 position of benzoquinolizine tricyclic core resulted in lower pKa (6.8), which contributes to better permeation, enhanced target affinity and a lower

potential to select resistant mutants of methicillin-resistant Staphylococcus aureus (MRSA) and quinolone-resistant Staphylococcus aureus (QRSA).Levonadifloxacin due to its anionic nature demonstrates enhanced bactericidal activity against Gram-positive and Gram-negative organisms even under an acidic environment. Levonadifloxacin is not a substrate of multidrug efflux pumps, including Nor A pump associated with quinolone resistance in Staphylococcus aureus.

Mechanism of Resistance:-Levonadifloxacin resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV, termed the Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux. In vitro resistance to Levonadifloxacin develops by multiple-step mutations in the QRDRs of Gram-positive and Gram-negative bacteria. Levonadifloxacin-resistant mutants were selected in vitro at a frequency of <10-9. The mechanism of action of fluoroquinolones, including Levonadifloxacin is different from that of macrolides, aminoglycosides, β-lactam, glycopeptides, tetracyclines and oxazolidinones; therefore, microorganisms resistant to these classes of drugs may still be susceptible to Levonadifloxacin. Levonadifloxacin mutant prevention concentration (MPC) for MRSA/QRSA is just 2x of MIC demonstrating its superior resistance suppression feature.

Levonadifloxacin intravenous injection:-

Distribution:-The mean steady state volume of distribution of Levonadifloxacin is 32.7 L which approximates total body water. The serum protein binding of Levonadifloxacin is in the range of 70-90% and is independent of its concentrations in serum. Following oral administration of Emrok O (alalevonadifloxacin mesylate tablets 500 mg) to healthy volunteers, the Day 5 Levonadifloxacin AUC(0-12h) in lung epithelial lining fluid (ELF) (172.6 µg·h/mL) was 1.15-fold of plasma AUC(0-12h).The maximum Levonadifloxacin concentration in ELF was 26 µg/mL (Cmax) and its concentration at 12 hours was 4.28 µg/mL (Clast), resulting in 24 hours lung ELF AUC of 345.2 µg·h/mL. Intracellular concentration of Levonadifloxacin in alveolar macrophage exceeded the MIC90 values of S. aureus and atypical respiratory pathogens. Such high exposures of Levonadifloxacin in lung would have significant therapeutic benefit for the treatment of respiratory infections.

Excretion:-Following multiple intravenous dose administrations, the mean elimination half-life of Levonadifloxacin (800 mg BID infused over 90 minutes) is approximately 6.8 hours and mean serum clearance (CL) of Levonadifloxacin is 4.2 L/h and steady state is achieved on Day 2. There is no evidence of accumulation of Levonadifloxacin after multiple dose administrations for a period of 5 days. After intravenous administration, approximately 16.2% of Levonadifloxacin dose is excreted as unchanged Levonadifloxacin (2.3% in urine and 13.9% in faeces) and 72.0% of Levonadifloxacin dose is excreted as Levonadifloxacin sulphate metabolite (50.3% in urine and 21.6% in faeces). A total of 88.2% of the intravenous dose is recovered as unchanged Levonadifloxacin and Levonadifloxacin sulphate metabolite in urine and faeces. Levonadifloxacin sulphate is devoid of antibacterial activity.

Metabolism:-Levonadifloxacin sulphate is the predominant circulating metabolite accounting for nearly half of the serum exposure (AUC) of Levonadifloxacin. Approximately 72% of intravenous Levonadifloxacin is excreted as Levonadifloxacin sulphate metabolite

(approximately 50.3% in urine and 21.6% in faeces). Other Levonadifloxacin metabolites detected in trace amounts in urine are glucuronide conjugated metabolites along with three oxidative metabolites. Trace amount of glucuronide metabolite is also detected in faeces. The drug disposition profile of Levonadifloxacin indicates very little involvement of cytochrome P450 system in the metabolism of Levonadifloxacin.

Levonadifloxacin Tablets:-

Absorption:-Following oral administration, alalevonadifloxacin mesylate undergoes esterase mediated bio-transformation to release active drug Levonadifloxacin in systemic circulation. Prodrug alalevonadifloxacin mesylate does not appear in systemic circulation after oral administration. As esterases are widely distributed in diverse tissues such as intestinal mucosa, liver and blood, there is a rapid and complete conversion of prodrug into Levonadifloxacin. The day 5 serum concentration time profile of Levonadifloxacin after oral multiple doses of 1000 mg was almost comparable to that of Levonadifloxacin 800 mg intravenous infusion. The absolute oral bioavailability of Levonadifloxacin was approximately 90 % under fasting condition and the peak serum concentrations of Levonadifloxacin were usually attained at 0.5 to 2 hours after tablet administrations suggesting a rapid and almost complete oral absorption of alalevonadifloxacinmesylate. Administration of Levonadifloxacin tablets (1000 mg) following high-calorie-high-fat diet delayed the time of Levonadifloxacin to achieve peak concentration (Tmax) by 2 hours and decreased Levonadifloxacin peak concentration (Cmax) by approximately 27% without significantly affecting the area under the plasma concentration-time curve (AUC) values. Food has little effect on the oral absorption of alalevonadifloxacinmesylate.

Distribution:-The mean steady state apparent volume of distribution of Levonadifloxacin after oral administration is 55.44 L which approximates total body water. The serum protein binding of Levonadifloxacin is in the range of 70-90% and is independent of its concentrations in serum. Following oral administration of Levonadifloxacin tablets to healthy volunteers, the Day 5 Levonadifloxacin AUC (0-12h) in lung epithelial lining fluid (ELF) (172.6 µg·h/mL) was 1.15-fold of plasma AUC (0-12h). The maximum Levonadifloxacin concentration in ELF was 26 µg/mL (Cmax) and its concentration at 12 hours was 4.28 µg/mL (Clast), resulting in to 24 hours lung ELF AUC of 345.2 µg·h/mL. Intracellular concentration of Levonadifloxacin in alveolar macrophage exceeded the MIC90 values of S. aureus and atypical respiratory pathogens. Such high exposures of Levonadifloxacin in lung would have significant therapeutic benefit for the treatment of respiratory infections.

Metabolism:-Levonadifloxacin sulphate is the predominant circulating metabolite accounting for nearly half of the serum exposure (AUC) of Levonadifloxacin. Approximately, 66.77 % of oral total dose of Levonadifloxacin is excreted as Levonadifloxacin sulphate metabolite. Significant portion of Levonadifloxacinsulphate metabolite is excreted through urine (37.2% of the dose) and faeces (29.5% of dose). Other metabolites of Levonadifloxacin detected in trace amount in urine are glucuronide conjugated metabolites along with three oxidative metabolites. Trace amount of a glucuronide metabolite is also detected in faeces. The drug disposition profile of Levonadifloxacin indicates very little involvement of cytochrome P450 system in the metabolism of Levonadifloxacin.

In the phase III study, Levonadifloxacin tablets administered at 1000 mg BID, active drug (levonadifloxacin) appears rapidly in plasma with Tmax (Mean ± SD) of 2.68 ± 1.27 h. The maximum mean plasma concentration (Cmax) achieved was 21.48 ± 8.82 µg/mL and the minimum mean plasma concentrations (Cmin) observed was 6.13 ± 3.62 µg/mL. The mean plasma exposure (AUC0-6) was 94.8 ± 37.95 µg.h/mL.

Oral and IV administration of Levonadifloxacin (Alalevonadifloxacinmesylate equivalent to Levonadifloxacin, oral tablet) and Levonadifloxacin respectively a showed similar pharmacokinetic profile (Cmax and AUC). This supports the option for IV to oral switch for the treatment of patients.

Excretion:- Following multiple oral dose administrations, the mean elimination half-life of Levonadifloxacin is approximately 7.35 hours and mean serum clearance (CL) is 5.2 L/h and steady state is achieved on Day 2.There is no evidence of accumulation of Levonadifloxacin after multiple oral dose administrations of Levonadifloxacin tablets for a period of 5 days. After oral administration, approximately 30.8 % of alalevonadifloxacinmesylate dose is excreted as unchanged Levonadifloxacin (0.8% in urine and 30.0% in faeces) and 66.7% of Levonadifloxacin dose is excreted as Levonadifloxacinsulphate metabolite (37.2% in urine and 29.5% in faeces). A total of 97.6% of oral dose is recovered as unchanged Levonadifloxacin and Levonadifloxacinsulphate metabolite in urine and faeces. Levonadifloxacinsulphate is devoid of any antibacterial activity.

In monkeys following a 90-minute intravenous infusion of Levonadifloxacin at a dose of 100 mg/kg (C_{max} was 4.7-fold of clinical C_{max}), there was no effect on the various cardiovascular parameters like systolic and diastolic blood pressure, heart rate and cardiac conduction time (PQ, QRS, QTc interval duration). In vitro studies reveal that Levonadifloxacin does not have the potential to inhibit human ether-a-go-go-related gene (hERG) potassium channels at concentrations 27-fold higher than free clinical C_{max}. No seizures potentials were observed in mice administered Levonadifloxacin at supratherapeutic concentrations in combination with theophylline or fenbufen (non-steroidal anti-inflammatory drug), thus demonstrating no interaction of Levonadifloxacin with these agents. In 28- and 90-day repeat dose IV toxicity studies with Levonadifloxacin in rat, no indication of toxicity was noticed in liver, kidney, haematology and clinical chemistry up to 245 and 670 mg/kg/day dose(5-10x therapeutic dose), respectively. In IV 28-day dog and 90-day monkey long term studies, no evidence of any morbid or target organ toxicity was noticed at doses as high as 80 and 225mg/kg/day, respectively (approximately 5x therapeutic dose). Dose dependent emesis was noticed in dogs which were ascribed to bolus administration of Levonadifloxacin.

Levonadifloxacin did not affect the fertility of male or female rats up to the highest intravenous dose tested (240 mg/kg/day) corresponding to approximately 3 times the recommended maximum human dose based on body surface area. Female rats were dosed 2 weeks prior to mating and through cohabitation, gestation and lactation and male rats were treated for 28 days prior to mating and 14days during cohabitation. The serum AUC of Levonadifloxacin in male and female (non-pregnant and pregnant) rats at 240 mg/kg/day was 297 µg·h/mL.

Levonadifloxacin was not mutagenic in a bacterial reverse mutation (Ames) assay, and was not clastogenic in a mouse bone marrow micronucleus test up to 475 mg/kg/day dose. In an *in vitro* clastogenicity assay using isolated human lymphocytes, Levonadifloxacin was negative. In a chromosomal aberration study in mice, at 475 mg/kg/day, no mutagenic effect was observed.

Long-term studies in animals to determine the carcinogenic potential of Levonadifloxacin have not been performed considering the relatively shorter duration of Emrok therapy in patients.

Phase III study in Acute Bacterial Skin and Skin Structure Infections (ABSSSI):A total of 501 adults with clinically documented acute bacterial skin and skin structure infection were enrolled in a randomised, multi-centre, open-label, non-inferiority trial comparing Levonadifloxacin Injection(800 mg)every 12 hours with IV Linezolid (IV subgroup) and Levonadifloxacin Tablet (1000 mg) every 12 hours with oral Linezolid (oral subgroup). Aztreonam 1 g every 12 hours was given to all patients for at least 3 days to cover potential Gram-negative pathogens. Treatment duration was 7 to 14 days. For patients enrolled into the IV subgroup, a switch to the respective oral therapy was allowed after at least 2 days of IV therapy. The Modified Intent-to-Treat (mITT) population included all patients who received any amount of study drug according to their randomized treatment group and had at least one post baseline efficacy measurement. To evaluate the treatment effect of Levonadifloxacin Injection compared with IV Linezolid, a non-inferiority analysis was conducted in 250 patients with ABSSSI (including deep/extensive cellulitis, deep abscess, or wound infection). This analysis evaluated the overall clinical cure rates at the Test-of-cure (TOC) Visit. The clinical cure rates for Levonadifloxacin Injection were numerically higher compared to Linezolid at the TOC Visit (91.0% vs. 87.8%; treatment difference: 3.2% [95%CI, -4.5 to 10.9]). The primary objective of the study was met and Levonadifloxacin Injection was non-inferior to IV Linezolid.

Recommendation of the Committee:-The firm presented their Phase III clinical trial report before the committee. After detailed deliberation, the committee recommended that the firm should revise the claims in respect of indication, dosage and administration, etc. which should be in consonance with the clinical data generated and submit the same for review by the committee. Accordingly, the proposal should be deliberated in the next IND meeting along with one Medical Microbiologist as special invitee.

Agenda No. 5

Phase III clinical trial report of Risug

This is with reference to application on male contraceptive - Risug.

On 03.04.2006School of Medical Sciences and Technology, IIT, Kharagpur - 721302 was granted permission to conduct Phase III clinical trial of RISUG - An Injectable Intravasal Male Contraceptive

This was a straight, open labelled and non-randomize phase-III clinical trial carried out at five centers located in different hospitals in five States in the country.

The proposal was deliberated in IND Committee meeting dated 29.08.2018. Pre-clinical and clinical - Phase I, II, III data was presented before the committee. During the presentation, it was informed that formal application for marketing authorization has been submitted to CDSCO in the last week for review.

The Committee noted that the technique of contraception in male by injecting Risug has great potential and is of national importance. The committee observed that the results of non-clinical and clinical data are promising. However, certain issues like - scrotal swelling, psychological behavioural aspects, sexual activity, reversibility, and acceptability etc. needs to be addressed. After detailed deliberation the committee recommended that the proposal for marketing authorization may be deliberated in the next meeting of the committee for which two urologists mat be invited for participation in the deliberation.

The proposal was again deliberated in IND Committee meeting dated 08.10.2018. The applicant presented their view points/ proposed action on scrotal swelling, psychological behavioural aspects, sexual activity, reversibility, and acceptability etc. along with CMC data. After detailed deliberation the Committee recommended that the applicant should address following points before recommending for approval of the product:-

1. Claim for the product should be in consonance with the fact that:-
    a) Study for reversibility has not been carried out in human and hence not established. However, reversibility study has been conducted in monkey and has been found to be favourable.
    b) Azoospermia has been observed for 5 years in Phase III clinical trial.
    c) Need for scrotal support due to reported scrotal swelling after administration of the product,
2. Possibility/ feasibility of assessing reversibility through biopsy/FNAC evaluation or other evidences of tissue disruption in 30 subjects who were involved in the Phase III clinical trial should be explored specially in respect of ethical aspects including Informed Consent.
3. For CMC data, GMP status etc. For commercialization of the product the applicant should co-ordinate with CDSCO and submit the data as per the requirements.

Now, the applicant submitted the following clarifications:-

1. RISUG is at present being positioned as a single intervention long acting male contraceptive delivery which does not involve cutting and removal of any part of the vas deferens. Therefore, it is claimed that it is an improvement over Vasectomy and No Scalpel Vasectomy and is less traumatic to the user while retaining the single intervention long term effectiveness character.
2. Considering the overall clinical study (Phase-I, II, Restricted Phase III and Extended Phase III) data it is stated that long term "functional" azzospermia (that is Azzospermia as per definition given in STEDMAN Medical Dictionary) is obtained following a one-time injection of Risug. Unlike vasectomy and NSV which completely removes the path

of sperms from the testes to the ejaculatory duct Risug injection partially blocks the vas deferens. Study of Risug injected subjects indicate that Prostate and Accessory sex glands are protected.

3. Scrotal suspensory sling is routinely provided to Risug injected subjects for temporary use in weeks following Risug injection.
4. Studies on the rat and monkey have shown that RISUG injection has localized effect mainly on the vas deferens, Sperm production continues in the testes following RISUG injection into vas deferens. Detailed evaluation of Semen of randomly selected 25 subjects in the ICMR sponsored Restricted Phase-III clinical trial indicates that in human males injected with Risug spermatogenesis continues in the testes. Since Risug injection is partially obstructive, germ cells which are precursors of sperms are present in the semen. Further occasionally full sperms but with altered morphology are also present in the semen. Chemical secretions from the testes and epididymis are also present in the semen indicating that there is a patent pathway from the testes to the ejaculatory duct (Chaki, S. P.; Das, H. C. and Misro, M. M. 2003) "A short term evaluation of semen and accessory sex gland function in Phase III trial subjects receiving intravasal contraceptive Risug" Contraception 67(1): 73-78).

Further in few subjects who received less Risug into the vas deferens that the therapeutic dose either into the vas deferens than the therapeutic dose either as per study plan or on account of delivery problems mainly involving the Risug syringe it has been observed that after a period of azoospermis there is autonomous reversal with sperms appearing in the semen. This observation too implies that sperm production continues in the testes after Risug injection into the vas deferens.

Nevertheless, Risug injection subjects of the LNJP Hospital, New Delhi and Dyanand Medical College, Ludhiana are being contacted to ascertain they would agree to a testicular biopsy/ FNAC for detailed examination of the tissue and thereby get to know the exact status of spermatogenesis in the testes. If some volunteers agree then project application will be submitted for Ethical Clearance and thereafter with all permissions in hand, the procedure will be conducted.

Applicant has also informed that a comprehensive clinical reversibility study protocol of Risug injection in the human has been prepared by ICMR and will be submitted to DCGI for necessary permission to conduct the study.

Recommendation of the Committee:-In light of recommendations of the IND committee in its earlier meeting dated 08.10.2018, the firm presented the action taken to explore the feasibility of assessing reversibility through biopsy/FNAC evaluation and preparation for clinical reversibility study. The committee recommended that the applicant should submit the progress report on these points to consider the matter further.

Agenda No. 6

Phase III clinical trial with PMZ 2010 of M/s Pharmazz India Private Limited.

This office had received an application for grant of permission to conduct a Phase III clinical trial entitled, “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".

PMZ-2010(Centhaquin citrate) is targeted to be used as a “Regenerative agent for hypovolemic shock”. The proposed mechanism of action of centhaquin 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.

The proposal of the firm to conduct Phase III clinical trial was deliberated in IND Committee in its meeting held on 03.12.2018.

The firm presented their proposal for grant of marketing authorization and simultaneously permission to conduct Phase III clinical trial. The Committee after detailed deliberation opined that based on the data presented the proposal of marketing authorization cannot be considered at this stage.

However, the committee recommended for grant of permission to conduct Phase III clinical trial subject to following conditions:-

1. Before initiation of the Phase III trial, the blood gas analysis data from the Phase II trial as mentioned by the firm during the presentation should be submitted for review.
2. In the proposed Phase III clinical trial, the details of blood gas analysis should be included and the revised clinical trial protocol should be submitted.

The firm was granted permission to conduct Phase III clinical trial submitted to above mentioned conditions on 24.12.2018.

Now, firm has submitted the blood gases data of patients enrolled in Phase II clinical trial and informed that the blood gas analysis is already included in the submitted Phase III.

Recommendation of the Committee:-In light of recommendation of the IND committee in the meeting held on 03.12.2018, the firm presented the blood gas analysis data from the Phase II trial before the committee. After deliberation, the Committee recommended that the firm may now initiate the Phase III clinical trial for which permission has already been granted by CDSCO.

Agenda No. 7

Phase I clinical trial with K0706 of M/s Sun Pharma Advanced Research Company Limited

M/s Sun Pharma Advanced Research Company (SPARC) Limited was granted permission to conduct a Phase I clinical trial entitled, “A Phase I study to determine safety, tolerability, pharmacokinetics and activity of K0706, a novel Tyrosine Kinase Inhibitor (TKI), in subjects with Chronic Myeloid Leukaemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic leukemia (Ph+ ALL)" on 15.03.2017. Till date 5 subjects were enrolled at 2 sites.

Now, firm has submitted amended Phase I clinical trial protocol.

The clinical trial protocol has been amended to include clinical information available from the ongoing dose escalations, incorporate changes to inclusion and exclusion criteria, extend the duration of K0706 therapy based on the availability of 9 month repeat dose toxicity data and safety data from ongoing clinical trial, clarity on fasting requirement and provide additional guidance in operational conduct of the study.

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

Agenda No. 8

Phase III clinical trial with WCK4873 of M/s Wockhardt Limited

This office had received an application for grant of permission to conduct a Phase III clinical trial with WCK 4873 entitled, “A Phase III, Randomised, Multicentre, Double-Blind, Comparative Study to Determine the Efficacy and Safety of Oral Nafithromycin Versus Oral Levofloxacin in the Treatment of Community-Acquired Bacterial Pneumonia (CABP) in Adults."

WCK 4873 (INN: Nafithromycin) is Wockhardt‟s proprietary novel antibacterial agent belonging tolactone-ketolide class and being developed as safe and short duration empiric therapeutic option for the treatment of serious bacterial respiratory infections (RTI).

Earlier, the proposal was deliberated in IND Committee meeting dated 08.10.2018. The committee recommended that the firm should submit clarification on the following points to consider the matter further:-

1. Comparator drug should be Moxifloxacin instead of Levofloxacin as Phase II clinical trial data has been generated using Moxifloxacin as comparator. Accordingly the protocol should be revised with adequate checks and balance for monitoring safety.

2. Justification for proposing administration of the Investigational Product only for three days in the trial in light of the fact that the proposed study is going to be carried out in patients with CABP.

3. Exclusion criteria should be defined to exclude patients with TB infection.

Revised clinical trial protocol submitted by the firm along with justification for proposing administration of the investigational product only for three days in the trial, as per recommendation of IND Committee dated 08.10.2018 was deliberated in IND Committee meeting dated 03.12.2018.

The firm presented revised clinical trial protocol and justification for proposing administration of the investigational product only for three days in the trial. After detailed deliberation the Committee recommended for grant of permission to conduct the Phase III clinical trial as per the protocol presented subject to the condition that the relevant exclusion criteria should be modified to exclude TB patients by doing GeneXpert method. Revised clinical trial protocol should be submitted to CDSCO before initiation of the study.

Now, firm has submitted the revised clinical trial protocol.

As per revised clinical trial protocol, active and suspected pulmonary tuberculosis subjects will be excluded. Firm has mentioned that at India sites, the subjects not agreeing to diagnostic evaluation of tuberculosis by Xpert TB test (using GeneXpert). In the event that the results of Xpert TB test are not available promptly and all the other eligibility criteria are met, the subject can be randomized and given the first dose of study treatment for management of CABP. The subject will be discontinued from study therapy prior to the second dose if the results of Xpert TB test suggest "detection" of Mycobacterium tuberculosis complex (MTBC) and is indicative of active pulmonary tuberculosis.

Firm has also made some other changes viz:-

1. Changed the analysis set from ITT to MITT analysis set with justification that this modification allows the power of the study to be maintained in lieu of eligibility criteria amendment which excludes subjects with tuberculosis.

2. Sample size from 414 adult subjects to 488 subjects with justification that this modification allows the power of the study to be maintained in lieu of eligibility criteria amendment which excludes subjects with tuberculosis.

Recommendation of the Committee:- In light of recommendation of committee in its earlier meeting held on 03.12.2018, the firm presented the revised clinical trial protocol regarding exclusion of TB patients by doing GeneXpert test and certain other changes. After detailed deliberation the Committee recommended for grant of permission to conduct the proposed Phase III clinical trial as per the revised protocol submitted.

Agenda No. 9

Phase I clinical trial of International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi with PvDBPII (recombinant Plasmodium Falciparum malaria vaccine) formulated with adjuvant Alhydrogel.

This office is in receipt of an application from International Centre for Genetic Engineering and

Biotechnology (ICGEB), New Delhi for permission to conduct a "A Phase I, randomized, controlled, dose escalating, single blind, clinical trial to assess the safety, tolerability and immunogenicity of Bivalent (JAIVAC-2: PfMSPFu24 + PfF2 /Alhydrogel) and Monovalent (PfMSPFu24 / Alhydrogel) P. Falciparum malaria vaccines in malaria naïve healthy Indian adult males (total 60 subjects)"

Investigational vaccine: PvDBPII (recombinant Plasmodium falciparum malaria vaccine) formulated with adjuvant Alhydrogel.

Control vaccine: Hepatitis B vaccine (M/s Serum Institute of India Pvt. Ltd, Pune).

Name of the Investigational Vaccines:
The study involves administration of the following investigational vaccines:

- Bivalent P. falciparum malaria vaccine in three dose - escalating cohorts (Cohort 1, 2 and 3) corresponding to three doses of 30 µg,45µg and 75 µg (of each antigen, PfF2 and PfMSPFu24)
- Monovalent P. falciparum malaria vaccine (Cohort 4) with 75µg dose

Dose and immunization schedule:
Cohort 1: Dose 30 mcg of Bivalent P. falciparum malaria vaccine 30mcg 0.2mL
Cohort 2: Dose 45 mcg of Bivalent P. falciparum malaria vaccine 45mcg 0.3mL
Cohort 3: Dose 75 mcg of Bivalent P. falciparum malaria vaccine 75mcg 0.5mL
Cohort 4: Dose 75 mcg of Monovalent P. falciparum malaria vaccine 75mcg 0.5mL

Subjects in each cohort will be administered 3 immunizations of the investigational vaccine on Visit 1/ Day 0, Visit 5/ Day 28 and Visit 9/ Day 56.

Primary Objective(s): To evaluate the safety and tolerability of Bivalent and Monovalent P. falciparum malaria vaccines in malaria naïve healthy adult Indian male subjects, 18 to 45 years of age.

Secondary Objective(s):

- To assess the humoral response of Bivalent and Monovalent P. falciparum malaria vaccines by measuring the IgG antibody response to antigens PfMSP119, PfMSP311and PfF2 by Enzyme Linked Immunosorbent Assay (ELISA) in healthy Indian male subjects, 18 to 45 years of age.
- To assess the humoral response of Bivalent and Monovalent P. falciparum malaria vaccines by measuring antibody response by Immunofluorescence (IFA) in healthy Indian male subjects, 18 to 45 years of age

Clinical trial Site & Investigator: Dr. Anil K, MBBS, MD (Internal Medicine),Human Pharmacology Unit Syngene International Limited Tower 1,Ground Floor, Semicon Park Electronics City Phase 2, Bangalore -560100,India.

Inclusion Criteria:

1. Male subject 18 to 45 years of age at informed consent(both years inclusive). Willing and having the capacity to provide voluntary free informed consent for participation evidenced by signing of the IEC approved informed consent document.
2. Subject is in good general health and is free from clinically significant health problems as determined by medical history, physical examination including vital parameters and clinical laboratory evaluations that include hematology, chemistry, urinalysis and serology.
3. Willing to be available for the duration of the study with no plans to travel outside the study area, reachable by phone.
4. Capable and willing to complete and return diary cards.
5. Able to participate during the whole study period and to attend all follow-up visits.
6. Willing to undergo HIV test
7. Must agree to use one of the following medically-acceptable birth control measures throughout the duration of the study (birth control counselling and measures will be provided by clinical trial site as required
    - Double barrier method (e.g. condom with spermicidal jelly)
    - Subjects must be surgically sterile (undergone vasectomy)
8. Willing to take intramuscular injection

Exclusion Criteria:

1. Any past history of malaria
2. Simultaneous participation in any other intervention clinical Trial.
3. Subject with evidence of IgG antibodies against vaccine antigens, PfMSP119, PfMSP311and PfF2as measured by ELISA
4. Has prior history of immunisation with Hepatitis B vaccine.
5. Previous history of receipt of any other malaria vaccine.
6. HbA1c value reported > 6% at screening visit.
7. History of allergic reactions, hypersensitivity or anaphylaxis to immunizations, to any of the components of the study vaccines (including adjuvant or peptide) or of serious allergic reactions that required hospitalisation or emergency medical care.
8. Use of an investigational or non registered drug or vaccine within ninety (90) days prior to enrolment or expects to receive such an agent during the study period.
9. Clinical or laboratory evidence of significant systemic disease, including hepatic, renal, cardiac, immunologic or hematological disease, HIV positive or have any other known immunodeficiency Have a history of autoimmune disease (including inflammatory bowel disease, haemolytic anaemia, autoimmune hepatitis, rheumatoid arthritis, lupus, etc.) or connective tissue disease or have any other serious underlying medical condition. Includes the conditions and diagnoses defined as AESI (Adverse Events of Special Interest) in Section.
10. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune modifying drugs or cytotoxic therapies (chemotherapy or radiotherapy) within six months prior to the first Immunization. This includes any dose level of oral steroids or inhaled steroids, but not topical steroids.
11. Received a blood transfusion within the past 3 months.

12. History of splenectomy Subject has clinically significant laboratory abnormalities, which will include haematology, biochemistry, urinalysis, at the time of screening as determined by the Investigator.
13. Clinical or laboratory presence of Hepatitis B, C or HIV infection or Syphilis
14. Subject with an abnormal 12 lead ECG at screening associated with relevant clinical symptoms/signs suggestive of cardiac pathology.
15. Subject with an abnormal Chest X Ray associated with relevant clinical symptoms/signs of respiratory pathology at screening/ anytime in the past 6 months
16. Subject gives a history of social, occupational and/ or family problems due to illicit alcohol or drug abuse (to be determined by Urine Drug Screen) within the past 12 months.
17. Has any other condition that, in the opinion of the Principal Investigator, may jeopardise the safety and rights of the volunteer, may interfere with the capacity to provide free and willing informed consent or render the subject unable to comply with the requirements of the study protocol.

Primary Endpoints:

The safety and tolerability profile will be assessed on the basis of the following criteria:

1. Immediate reactogenicity (any event occurring within one (1) hour after each vaccination, with emphasis on allergic reactions)
2. Local and systemic solicited adverse events(any event occurring from one (1) hour post vaccination on Day 0 till Day 07 after each dose)
3. Any unsolicited adverse event upto 28 days after each vaccination
4. Any Serious Adverse Event (SAE) occurring post signing of ICD till the last follow-up visit.
5. Laboratory safety, 7days after each vaccination, in reference with the baseline before the first dose, and also at six months (Day 180) post first immunisation, by measuring the following :
6. Haematology: Complete Blood counts including Differential Blood counts and Platelet counts
7. Serum Chemistry: Potassium, Sodium, AST, ALT, direct, indirect and total bilirubin, alkaline phosphatase, Total serum protein with A/G ratio, creatinine and random blood glucose
8. Urinalysis: The Investigator will be responsible for causality assessment i.e. assessment of the relationship of the AE to either of the assigned study vaccines, using the following definitions: Related or Not related.

Secondary Endpoints:

1. The humoral response to the candidate vaccine antigens will be assessed (quantitative assessment) by measuring the level of IgG antibodies developed against PfMSP119, PfMSP11 and PfF2 by ELISA on Visit 1/ Day 0, Visit 9/Day 56, Visit 13/ Day 84 and Visit 14/Day 180.
2. The humoral response to the candidate vaccine antigen will be assessed qualitatively to verify the ability of the IgG antibodies developed against PfMSP119,

PfMSP311and PfF2 to recognise the native protein on late stage P. falciparum schizonts and merozoites in vitro by Immuno fluorescence Assay (IFA) on Visit 1/ Day 0, Visit 13/ Day 84, Visit 14/Day 180.

Exploratory Outcomes:

1. The quality of the humoral immune response will be assessed by measuring IgG1, IgG2, IgG3, IgG4 subclasses by ELISA on samples obtained at Visit 1/ Day 0 and Visit 13/ Day 84.
2. The ability of the IgG antibodies to block homologous and heterologous parasite growth in vitro by a P. falciparum blood-stage Growth Inhibition Assay (GIA) against falciparum parasite on samples obtained at Visit 1/ Day 0, and Visit 13/ Day 84.
3. Any Adverse Event of Special interest (AESI) occurring from the first dose of vaccine till the last follow-up visit.

Preclinical study: Preclinical Immunogenicity studies were performed in mice, rats and rabbits to assess immunogenic potential of Monovalent and Bivalent malaria vaccines. The immunogenicity data in the small animals had shown that combination of PfMSPFu24+PfF2 formulated with Freund's adjuvant as well as other human compatible adjuvants induced high titer antibodies compared to PfMSPFu24 alone. However, antibodies purified from immune rabbit sera of Bivalent vaccine (PfMSPFu24+PfF2) or the Monovalent malaria vaccine (PfMSP-Fu24) and tested in growth inhibition assays (GIA) did not shown any significant differences. Preclinical Immunogenicity studies were performed to down-select the adjuvant for further preclinical and clinical development. Various adjuvants tested in the pre-clinical immunogenicity studies were: Alhydrogel, GLA-AF (aqueous formulation), GLA-SE (stable emulsion formulation), and Alhydrogel + GLA-Aqueous formulation (Alhydrogel + GLA-Aq).Of the various adjuvants tested with Monovalent and Bivalent malaria vaccine candidates, Alhydrogel was down selected because of good in-vitro growth inhibition and availability of safety data in healthy Humans. Therefore, the final product of Bivalent malaria vaccine will consist of a physical mixture of PfMSPFu24+ PfF2/ Alhydrogel while Monovalent malaria vaccine will only contain PfMSPFu24/ Alhydrogel. When administered to humans, PfMSPFu24/ Alhydrogel alone or as combination of PfF2+PfMSPFu24/ Alhydrogel are expected to elicit antibodies that will block the erythrocyte invasion by P. falciparum. Taking lead from the Phase Ia clinical trial of JAIVAC-1 (PfMSP119+ PfF2 formulated with Montanide ISA720) in healthy adult male volunteers 30, 45and 75 µg of Bivalent and 75 µg of Monovalent P. falciparum malaria vaccines with Alhydrogel adjuvant have been chosen for this phase I clinical trial. The pre-clinical toxicology studies have been performed under GLP at Jai Research Foundation, Valsad, Gujarat in compliance with Schedule Y and WHO guidelines.

Monovalent (PfMSPFu24/Alhydrogel) and Bivalent (PfMSPFu24+PfF2/Alhydrogel) malaria vaccines were tested in acute toxicity studies conducted in CD1 Mice and Wistar rats. Intramuscular route of vaccine administration were evaluated in mice and rats whereas subcutaneous route of vaccine administration was evaluated in mice. In mice the dose level evaluated was more than 1000X of maximum proposed human dose (1.25µg/kg) on body weight basis, where as dose level equivalent to approximately 192X of intended

maximum dose in humans was evaluated in Wistar rats. Both the vaccines were well tolerated and no systemic toxicity was observed in either species by intramuscular route and in CD1 mice by subcutaneous administration. All animals were observed to be normal throughout the experimental period. There was treatment related nodule formation at the injection site observed in all acute toxicity studies. It was attributed to physiological response to Alhydrogel (adjuvant) administration and hence not considered as a toxic effect of vaccine administration.

Repeat dose intramuscular toxicity studies were conducted in Wistar rats and New Zealand White rabbits. Monovalent (PfMSPFu24/Alhydrogel) and Bivalent (PfMSPFu24+PfF2/Alhydrogel) malaria vaccines were administered repeatedly on days 1, 15, 29 and 43 with a recovery period of 14 days. Thus a total of four doses were administered in repeat dose studies as against maximum of three human doses proposed in this phase I clinical trial. The test vaccines were tested at two dose levels: low and high in NZW Rabbits equivalent to 30X and 60X of the intended maximum human dose (1.25 µg/kg) on body weight basis. Similarly in Wistar rats the low and high dose levels were equivalent to 96X and 192X of the intended maximum proposed human dose (1.25µg/kg) on body weight basis. Both Monovalent and Bivalent P. falciparum malaria vaccines were well tolerated with no mortality observed in rats and rabbits when administered through intramuscular route. Both vaccines did not reveal any indication of systemic toxicity up to the highest dose level on repeated administration in Wistar rats (equivalent to approximately 192X of the intended maximum proposed human dose (1.25 µg/kg) on body weight basis) and NZW Rabbits (equivalent to approximately 60X of the intended maximum proposed human dose (1.25 µ g/kg) on body weight basis).

There was a treatment related nodule formation at injection site that was attributed to physiological response to adjuvant and hence not a toxic effect of the vaccine. On microscopic examination the inflammatory changes were localised to injection site. They were reduced in intensity and severity in recovery groups in rabbits and thus, considered reversible. Significant PfMSPFu24 and PfF 2 specific antibody responses were induced by repeated immunizations as evaluated by ELISA in both rats and rabbits.

Recommendation of the Committee:-The firm presented their proposal along with Phase I clinical trial protocol for monovalent and bivalent malaria vaccines. After detailed deliberation the committee recommended that:

1. The applicant should submit two separate proposals for each of the monovalent and bivalent vaccines.
2. CDSCO should conduct inspection at the clinical trial site at M/s Syngene, Bangalore to verify the facilities available at the site for conduct of such clinical trial.
3. In the study, the IP should be administered one dose at a time and confirmed the safety before proceeding to the next higher dose.
4. The toxicity data generated is also required to be reviewed further by the committee members.

Agenda No. 10

Clinical trial with Rabimab of M/s Cadila Healthcare Limited.

This office had received an application for the grant of permission to conduct a clinical trial entitled "An open label, balanced, randomized, two-treatment, single period, single dose, parallel, non-inferiority pharmacodynamic study of Rabimab 40IU/KG intramuscular injection of M/s Cadila Healthare Ltd. India (treatment arm 01) and Imogam 20 IU/Kg intramuscular injection of Sanofi Pasteur Inc. (treatment arm) in healthy, adult, male, human Subjects under fasting condition".

Primary objective of the study is to compare the pharmacodynamics and secondary objective is to compare safety and tolerability of their indigenous developed Rabimab and Imogam 20 IU/Kg intramuscular injection of Sanofi Pasteur Inc.

This office has already granted the permission to conduct the Phase I/II clinical trial of their IND drug product which is undergoing. Firm had submitted the protocol to evaluate the impact on pharmacodymanic of their IND drug product when subject is already given the rabies vaccine.

The proposal was deliberated in IND Committee dated 29.08.2018.

The firm informed that the Phase III clinical trial in dog bite cases comparing their drug with Imogam is ongoing. The committee noted that the comparator drug (Imogam) is not approved in the country. The proposed study is to be conducted in healthy volunteers for comparing the study drug with Imogam for rabies virus neutralising activity (RVNA) at Day 1 and 2. After detailed deliberation the Committee recommended that the firm should submit report of Phase III clinical trial for review of the committee for consideration of the proposed study in healthy volunteers.

Accordingly, the firm has submitted the Phase III clinical trial report. The purpose of this study was to evaluate the 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.

A total of 308 subjects were randomized in this study in a ratio of 1:1. One-hundred and fifty-four subjects each in Rabimab and Imogam treatment arm. The safety population comprised 308 subjects. In total, 286 subjects qualified for the per protocol population analysis and 299 subjects for the mITT population analysis.
In total, 277 subjects completed the study, 137 (88.96%) subjects from Rabimab's 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 Rabimab group and 14 (9.09%) in the Imogam group. Similar percentages of subjects in both the treatment group completed the study.

Efficacy Conclusion:-Of 144, 130 (90.28%) participants in the Rabimab's group and 134 (94.37%) from 142 participants in Imogam group had REFIT ≥ 0.5 IU/ml on day 14 in PP population. Of 148, 133 (89.86) participants in the Rabimab's group and 137 (90.73%) from 151 participants in Imogam group had titre ≥ 0.5IU/ml on day 14 in mITT population.

Firm concluded that the results obtained for PP and mITT populations non-inferiority of Rabimab's compared to Imogam for responders with RFFIT titre ≥ 0.5 IU/ml on Day 14 is established.

Safety Conclusion:- After 28 days of treatment, the following can be concluded regarding the safety of Rabimab's 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 Rabimab's 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.

Sixty-eight subjects had AEs that were considered by Investigators to be related (Possibly related and related) to study medication: 42 (27.27%) subjects in the Rabimab's group and 26 (16.88%) subject s in the Imogam treatment group. Most of the AEs were mild in severity. 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.

Recommendation of the Committee:-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.

The meeting ended with vote of thanks to the Chair

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