Minutes of IND Committee meeting held on08.10.2018 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

List of Participants:

1. Prof. Balram Bhargava, Secretary, Department of Health Research & Director General, Chairperman, IND Committee.
2. Dr. Y.K. Gupta, Ex. Dean, AIIMS, New Delhi.
3. Dr.Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
4. Dr. S.K. Sharma, Ex-Prof. & Head, Department of Medicine, AIIMS, New Delhi.
5. Dr. C. D. Tripathi, Prof. & Head, Department of Pharmacology, VMMC, New Delhi.
6. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
7. Dr. Bikash Medhi, Prof., Department of Pharmacology, PGIMER, Chandigarh.

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.

Special Invitee for Agenda No. 5:-

1. Dr. Rajeev Sood, Prof. and Head, Department of Urology, Dr. RML Hospital & PGIMER, New Delhi.

CDSCO Representatives:

1. Mr. A. K. Pradhan, Deputy Drugs Controller (India), CDSCO (HQ).

Following members could not attend the meeting:

1. Dr. Nilima Kshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
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. Y. K. Gupta will Chair the meeting. Thereafter, the agenda items were discussed one by one:

Agenda No. 1

Phase I clinical trial with PNB 028 of M/s Lambda Therapeutics Limited.

The firm presented their proposal for grant of permission to conduct a Phase I clinical trial entitled, "A Single arm, Open label, Multiple Ascending Dose, Prospective, multicentre study to assess Safety, Tolerability and Pharmacokinetics and Pharmacodynamic of PNB-028 in Colon or Pancreatic Cancer Patients." Sponsor has developed PNB 028 capsules of different strengths i.e. 25 mg, 50 mg, 100 mg & 200 mg Capsules.

As per the proposal submitted :-

Results of in-vitro studies are reported to have shown that PNB-028 inhibits the proliferation of colon and pancreatic cancer cell lines. In preclinical studies PNB-028 inhibited the growth of colon and pancreatic cancer xenografts in NOD SCID Gamma (NSG) mice.

It is reported that in preclinical model it bound potently and selectively to CCK-A at 12 nM and with 60 fold selectivity towards CCK-A, than CCK-B. PNB-028 also inhibited CCK-A activity in low nanomolar concentration.

It is claimed that in preclinical safety studies PNB-028 demonstrated lack of adverse effects. It had excellent efficacy in various colon and pancreatic cancer xenografts, it was advanced to toxicology and safety pharmacology studies conducted in accordance with ICH guidelines. PNB-028 tested for up to 28 days exhibited impeccable safety with no adverse events. PNB-028 at doses as high as 400 mg/kg was safe and had no adverse events of any kind. Genotoxic studies also demonstrated a lack of any adverse effects.

PNB-028 is under primary stage of clinical development. The proposed study will be First in Men study i.e. phase I study.

The study will be conducted in four cohorts (cohort I to cohort IV) consisting of 6 patients of colon cancer and 3 patients of pancreatic cancer. Maximum 45 patients will be enrolled in the study. 30 patients of colon cancer and 15 patients of pancreatic cancer will be enrolled in the study at 04 sites.

The primary objective is to assess safety and tolerability of PNB-028 in patients of colon or pancreatic cancer. The secondary objective is to assess pharmacokinetic of PNB028 in patients of colon or pancreatic cancer & to assess pharmacodynamic effect of the study drug in patients of colon or pancreatic cancer.

The proposal was deliberated in IND Committee dated 29.08.2018. During presentation, while clarifying certain points raised by the committee members, the firm informed that their concerned technical person could not come for the presentation due to some reasons and requested to give them opportunity to present their proposal in next meeting.

Accordingly. the committee agreed to their request for presentation in the next meeting.

Recommendation of the Committee:- The firm presented the pre-clinical alongwith Phase I clinical trial protocol. After detailed deliberation the committee recommended that the firm should submit clarification on the following points to consider the matter further:-

1. In PK data in rats, it was not clear as to how the C_{max} of 1mg I.V. was same to that of 10mg oral administration. Further, AUC with 10mg oral administration was apparently more than that with 1mg I.V., although 10mg oral dose is not comparable to 1mg IV dose, it was claimed that there is 100% bioavailability with oral dose.
2. Justification for administration of 200mg and 400mg dose for upto 56days is not clear considering the fact that repeated dose toxicity data has been generated for 28 days and biomarkers can be assessed at 28 days in the study.

Agenda No. 2

Phase I clinical trial with HRF 4467 of M/s Lambda Therapeutics Limited.

The firm presented their proposal for grant of permission to conduct a Phase I clinical trial with HRF-4467 solution entitled, "A Randomized, Phase-I, Double-Blind, Placebo-Controlled, Dose-Escalation (Single Ascending Dose) Study To Evaluate Safety, Tolerability & Pharmacokinetics Of HRF-4467 Solution of Hetero Labs Limited, India In Normal, Healthy, Adult, Human Male Subjects Under Fasting Condition And Evaluation Of Food Effect With Any One Cohort Of Single Ascending Dose".

As per the proposal submitted:-

HRF-4467 works by blocking the viral maturation by a distinctly different mechanism of action in HIV virus life cycle. HRF-4467 prevent the HIV virus maturation due to interaction with gag to block a specific step in gag processing, last cycle of virus life cycle and thus results in a non-infective viral strains.

Primary objective of the study is to assess safety, tolerability & pharmacokinetics of HRF-4467, a HIV maturation inhibitor, in Solution formulation in Healthy Adult Male Human subjects under Fasting Condition & evaluation of food effect with one cohort in Single Ascending Dose (SAD).

Secondary objective of the study is to assess safety, tolerability & pharmacokinetics of HRF-4467, a HIV maturation inhibitor, in Solution formulation in Healthy Adult Male Human subjects under Fasting Condition & evaluation of food effect with one cohort in Single Ascending Dose (SAD).

Firm has proposed to conduct the Phase-I study on 48 male subjects in India.

Pharmacokinetic studies have been performed in animals- mice, rats, dogs and monkeys.The absolute oral bioavailability of HRF-4467 ranges from ~26% in dogs, to 30% inmice and 37% in rats. The half-life of HRF-4467 ranges from a low of ~4.8 hours in ratsup to ~49 hours in mice. Definitive excretion studies have not yet been completed butpreclinical studies have evidenced that HRF-4467 is eliminated primarily as ahydroxylated metabolite.

It is claimed by the firm that in toxicology studies completed to date, there have been no adverse effects associatedwith HRF-4467 at doses up to 100 mg/kg/day for up to 28 days in mice. The noobserved-adverse-effect level (NOAEL) for both sexes was 100 mg/kg/day, the highestdose level administered. Based on the decreases in circulating platelets and increases inreticulocytes correlating with increased splenic weights and microscopic evidence forincreased extramedullary haematopoiesis in the spleen at doses >30 mg/kg/day, the noobserved-effect level (NOEL) was determined to be 10 mg/kg/day for both sexes.

In dogs, once daily oral gavage administration of HRF-4467 to male and female beagledogs at dose levels of 0, 10, 30, and 100 mg/kg/day was well tolerated with no effects onsurvival, body weight, food consumption, ophthalmology, electrocardiography, clinicalpathology, organ weights, macroscopic necropsy observations, or microscopic findings.

Nonadverse HRF-4467-related clinical observations consisted of an increased incidenceof emesis at ≥10 mg/kg for both sexes and an increased incidence of liquid fecesat ≥30 mg/kg for females.

Maximum plasma concentration (C_{max}) and area under the curve time 0-24 hours (AUC)0-24 values were similar in males and females, suggesting no gender differences. Exposurein animals on day 28 was similar to exposure on day 1, indicating no accumulation ofHRF-4467 with multiple dosing.

Based on the lack of any adverse effects, the NOAEL for both male and female dogs wasconsidered to be 100 mg/kg. Based on a nonadverse increase in the incidence of emesis at10 mg/kg for both sexes, a NOEL was not determined for either sex.

HRF-4467 is reported to have no adverse pharmacologic effect on the cardiovascular system ofdogs. There were no test article-related clinical observations and no test article-relatedchanges in the body weight. There were no changes in blood pressure parameters (meanarterial, systolic, diastolic), heart rate, body temperature, and echocardiogram (ECG)parameters (QT, QTcV, QRS, PR interval) that were considered test article related. Noarrhythmias were reported that were considered related to test article administration.

HRF-4467 was shown to be non-mutagenic in the Ames and mouse lymphoma studies. Itwas shown to be non-clastogenic and non-aneugenic in the in vivo mouse micronucleusstudy.

Recommendation of the Committee:- The firm presented the pre-clinical alongwith Phase I clinical trial protocol. After detailed deliberation the committee recommended that the firm should submit clarification on the following points to consider the matter further:-

1. There are vast difference in PK parameters specially in respect of T1/2 and AUC observed in rats and mice.
2. Justification for proposing the study in healthy volunteers instead of patients in light of the safety aspects and the fact that the Investigational Product is a HIV maturation inhibitor.

Agenda No. 3

Phase III clinical trial with WCK 4873 of M/s Wockhardt

The firm presented their proposal 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."

As per the proposal submitted:-

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

This is a Phase III, prospective, multicentre, randomised, double-blind, comparative efficacy and safety study of oral nafithromycin versus oral levofloxacin for the treatment of male and female adults with CABP.

Primary objective of the study is to demonstrate that oral nafithromycinis non-inferior to oral levofloxacin in the clinical response at Day 4 in the Intent-to-Treat (ITT) analysis set and to assess overall safety of oral nafithromycinin the safety analysis set.

Firm claimed that approximately 414 adult subjects diagnosed with CABP and meeting all study eligibility criteria will be enrolled in the study and randomised in a 1:1 ratio to either of the following 2 treatment arms:

- Nafithromycin800 mg (two 400-mg tablets) orally (PO)every 24hours (q24h)for 3days; subjects will receive matching placebo PO q24h on Day4 through EOT(2 tablets)and matching levofloxacin placebo PO q24h, on Day1 through EOT(2tablets), to maintain the blind(4tablets total).
- Levofloxacin500mg (two 250-mg tablets) PO q24h for 7days; subjects will receive matching nafithromycin placebo PO q24h on Day 1 through EOT(2tablets), to maintain the blind(4tablets total). Levofloxacin and matching placebo may be presented as over-encapsulated tablets.

It is claimed by the firm that, single dose acute oral Maximum Tolerated Doses of WCK 4873 in Wistar Rats and Swiss Albino mice were 5000 and 2000 mg/kg, respectively. Median Lethal Doses (LD50) of WCK 4873 in Wistar Rats and Swiss mice for acute oral toxicity were estimated to be >5000 mg/kg and 8681.28 mg/kg, respectively. The exposures in terms of AUC at single dose oral MTD in Wistar Rats and Swiss mice were 216.75 (male), 219.97 (female) and 315.55 (male), 175.38 (female), respectively.

Single dose acute intravenous Maximum Tolerated Doses of WCK 4873 in Wistar Rats and Swiss mice were 66.66 and 53.33 mg/kg respectively. LD50 values of WCK 4873 in Wistar Rats and Swiss mice for acute intravenous toxicity were estimated to be 114.55 and 112.58 mg/kg, respectively. The exposures in terms AUC at single dose intravenous MTD in Wistar Rats and Swiss mice were 52.66 (male), 40.60 (female) and 21.36 (male), 32.14 (female), respectively.

The safety and tolerability of WCK 4873 has been established through 28-day repeat-dose GLP toxicity studies in Rat and Dog as well as through a battery of safety pharmacological studies. In 28-day repeat dose toxicity studies conducted in Rat and Dog, WCK 4873 was administered at 50, 100 and 200 mg/kg and 25, 50 and 75 mg/kg respectively. Exposures attained were significantly high, serum AUCs at highest dose in Rat and Dog were 219 and 103 µg.h/mL respectively. In both the species, WCK 4873 even at higher exposures did not bring about elevation of hepatic enzymes or bilirubin to pathologically relevant levels. However a mild pulmonary phopholipidos was observed in Dogs at the highest dose studied. Phospholipidosis is reported in most agents of this class such as clarithromycin and azithromycin as well. However for telithromycin, significant elevation of hepatic enzymes (4–15x) along with the histopathological changes in liver was reported at 150 and 300 mg/kg dose in Rat. The AUC at 150 and 300 mg/kg in Rat was in the range of 46–82 and 108–130 µg.h/mL respectively. Similarly, azithromycin and clarithromycin are also reported to cause significant elevation of rat hepatic enzymes accompanied with histopathological changes in liver at 100 and 50 mg/kg respectively.

For WCK 4873, mild to moderate reversible vacuolation in lymphoid organs was noticed at highest dose in rat and dog indicating the milder nature phospholipidosis, which is considered to be a class specific effect. These changes observed were

completely or partially reversed at the end of 28- day recovery period. Hence, this minimal nature of change observed was not considered as an adverse effect. Such changes are not expected to have any functional or physiological consequences as evidenced by the absence of changes in clinical chemistry. Other vital organs/tissues were not involved in drug induced toxic effects. In case of telithromycin, azithromycin and clarithromycin, the severity of phospholipidosis was high and it was observed in various vital organs such as liver including bile duct, lung, kidney, intestine and lymphoid organs. The prevailing theory is that the phospholipidosis is a primary adaptive response to this class of compounds rather than the toxic response. In this case, cell adapts to the drug exposure by sequestering it in the lamellar bodies thus reducing toxicity to intracellular structure.

WCK 4873 was evaluated through battery of reproductive studies. WCK 4873 was found to be potential to cause fetal toxicity in rats, however WCK 4873 did not elicit any effects on male and female fertility parameters in rats.

Firm has conducted Phase I and II clinical trials outside India.WCK 4873 has been administered to 117 healthy volunteers in two Phase 1 studies (55 subjects in the single ascending dose and food effect study and 24 subjects in the multiple ascending dose study and 38 subjects in intra-pulmonary PK study). In Phase II clinical trial a total of 147 adult subjects who met criteria for Community Acquired Bacterial Pneumonia (CABP) were enrolled at 36 study sites in Bulgaria (6 sites), Georgia (4), Latvia (4), Romania (6), Serbia (3), South Africa (7), and the United States (6) to assess the safety, tolerability and pharmacokinetics. Firm claimed that Phase II study outcome indicates that Nafithromycin (WCK 4873) is well-tolerated and effective in treating subjects with CABP.

Recommendation of the Committee:- The firm presented the pre-clinical, clinical data generated outside India alongwith Phase III clinical trial protocol. After detailed deliberation 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.

Agenda No. 4

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

The firm presented their proposal for grant of permission to conduct a Phase III clinical trial with CPL-2009-0031tablets 140mg entitled, "Prospective, Randomized, Double Blind, Parallel Group, Two arm, Comparative, Multicenter, Clinical study to compare efficacy and safety of oral CPL-2009-0031 140 mg of Cadila Pharmaceutical Limited, India against innovator Sitagliptin 100 mg in patients with Uncontrolled Type-2 Diabetes Mellitus (T2DM)".

As per the proposal submitted :-

The investigational agent, CPL-2009-0031 phosphate is a novel DPP-IV inhibitor. Its activity profile in mice is similar to that of clinically used DPP-IV inhibitors i.e. sitagliptin and saxagliptin. While saxagliptin and sitagliptin are L-amino acid and B-amino acid derivatives, respectively, CPL 2009-0031 incorporates between an L-amino acid and a B-amino acid in its structure.

The anti-diabetic effect of CPL-2009-0031 was evaluated by oral glucose tolerance test in normal animals, nSTZ induced diabetic animal models and HFD+STZ induced diabetic mice model. Sitagliptin was administered as a reference product.

As a part of safety pharmacology, CPL-2009-0031 was administered orally at 14, 35, 70 and 140mg/kg dose in Wistar rats (for cardiovascular system, respiratory studies & oxygen saturation studies) and at 28, 70, 140 & 280 mg/kg dose in swiss albino mice (for central nervous system studies). Safety pharmacology studies showed no adverse, consistent or sustained effect on these parameters.

Pharmacokinetic profile and tissue distribution study of CPL-2009-0031 was conducted in male Wistar rats. Oral dose of 12mg/kg was administered to sixty animals, divided in ten groups. Concentration of the drug and its metabolite (sitagliptin) were measured in plasma, duodenum, liver, pancreas, kidney and heart. Concentration of CPL-2009-0031 was observed only in the duodenum. No other tissue or plasma samples have shown the concentration of CPL-2009-0031.

Maximum concentration of metabolite was observed in duodenum (422.451 ±172.465 ng/ml) followed by liver (370.500 ±151.256 ng/ml), plasma (239.773 ±97.887 ng/ml), kidneys (179.202 ±73.159 ng/ml), pancreas (191.232 ±78.070 ng/ml) and heart (68.995 ±28.167 ng/ml).

The T_{max} and plasma elimination half-life were observed as 1.167 hrs and 1.351 hrs, respectively. In contrast of these results, the concentration of CPL-2009-0031 (parent compound) was observed only in duodenum (406.043 ±165.766 ng/ml). Similar concentrations of parent compound, CPL-2009-0031 (406.043 ±165.766 ng/ml) and its metabolite (422.451 ±172.465 ng/ml) were indicative of the fact that duodenum might be the site of metabolism for parent compound.

Firm claimed that two oral and one intra-peritoneal acute toxicity studies of CPL-2009-0031 were conducted in Swiss albino mice and Wistar rats. The LD_{50} for CPL-2009-0031 given orally to Swiss albino mice and Wistar rats was found to be 2000mg/kg (maximum dose tested) while LD_{50} of CPL- 2009-0031 given intra-peritoneally was 400mg/kg (maximum dose tested).

Sub-acute (28-day) oral toxicity studies was conducted in Swiss albino mice and Wistar rats at doses of 65/195/585 mg per kg and 35/140/560mg per kg, respectively. NOAEL was found to be 585mg/kg among mice where as it was 560mg/kg in rats.

CPL-2009-0031 did not reveal any adverse effect on sex organs and fertility of male rats when it was administered for 28 days at dose levels of 135, 67.50 and 33.75 mg/kg/day prior to and throughout mating.

CPL-2009-0031 was found to be non-mutagenic or non-clastogenic in the following genetic toxicology studies: Ames test with salmonella typhimurium, chromosomal aberration assay in mouse bone marrow cells, in-vitro chromosomal aberration assay in human peripheral lymphocytes and micronucleus assay in mouse bone marrow cells.

Firm was granted permission to conduct a Phase I, dose-blocked-randomized, double-blind, placebo-controlled, first-in-human (FIH), ascending single-dose to evaluate the safety, pharmacokinetics and pharmacodynamics for three dose levels i.e. 35 mg, 70 mg and 140 mg of CPL-2009-0031 in 36 healthy volunteers on 14.12.2015. Results of the study showed that CPL-2009-0031 was found to be safe and well tolerated up to dose level 140 mg, without any major safety concerns in healthy volunteers under fasting condition.

Firm was granted permission to conduct Phase II clinical trial entitled, " Prospective, randomized, double blinded, parallel group, multicentric, comparative clinical study to compare efficacy and safety of oral CPL-2009-0031 of Cadila Pharmaceutical Limited, India against innovator Sitagliptin in patients with Uncontrolled Type-2 diabetes mellitus (T2DM)" on 60patients at 8 sites on 29.06.2017 subject to condition that "firm shall conduct repeat dose toxicity study in non-rodent species equivalent to exposure time of the Phase II clinical trial and female reproduction and developmental toxicity studies as per Appendix-III of Schedule Y and submit report to DCG(I) office before initiation of Phase-II clinical trial".

Firm submitted justification for waiver of repeat dose toxicity study in non-rodent species equivalent to exposure time of the Phase II clinical trial and the same was deliberated in IND Committee meeting dated 24.10.2017. M/s Cadila Pharmaceuticals Limited made a detailed presentation on their proposal and presented, comparative rat pharmacokinetics of Sitagliptin Vs CPL-2009-0031 in plasma, comparative tissue distribution – duodenum wall (rats) of Sitagliptin Vs CPL-2009-0031, Phase – I

pharmacokinetic data of 35mg, 70mg and 140 mg alongwith justification for waiver of toxicity study for CPL-2009-0031 being a prodrug of Sitagliptin.

It was presented the non-clinical as well as human Phase-I studies have shown that when CPL-2209-0031 is administered through oral route, it gets metabolized to Sitagliptin before reaching blood stream. During pre-clinical studies it was also observed that only Sitagliptin is detected in plasma, liver, heart, kidney and pancreas after oral administration of CPL-2009-0031. Phase I clinical trial data have shown Sitagliptin concentration in human plasma but no parent compound.

The firm also presented that US FDA has a provisions under the 505(b)(2) new drug application which allows sponsor to rely on the US FDA's findings of safety and effectiveness for a previously approved drug. A pro-drug is covered under this provision which is considered as new molecular entity by US FDA when the studies conducted by other sponsors and published information is pertinent to the application of a pro-drug.

The firm gave following examples of approval of pro-drugs:-

1. Valganciclovir – Pro-drug of ganciclovir.
2. Gabapentin enacarbil – Pro-drug of gabapentin.
3. Lisdexamfetamine dimesylate – Pro-drug of dextroamphetamine.

After detailed deliberation, the Committee recommended for allowing the firm to conduct the Phase II clinical trial based on the data generated so far.

Phase II clinical trial is going on.

Now, firm has submitted an application for grant of permission to conduct a Phase III clinical trial with CPL-2009-0031entitled, "Prospective, Randomized, Double Blind, Parallel Group, Two arm, Comparative, Multicenter, Clinical study to compare efficacy and safety of oral CPL-2009-0031 140 mg of Cadila Pharmaceutical Limited, India against innovator Sitagliptin 100 mg in patients with Uncontrolled Type-2 Diabetes Mellitus (T2DM)".

This study is a Prospective, Randomized, Double Blind, Parallel Group, Two arm, Comparative, Multicenter, controlled study to determine the efficacy, safety, and tolerability of oral CPL-2009-0031 140 mg compared to Sitagliptin 100 mg among patients with Uncontrolled Type-2 Diabetes Mellitus (T2DM).

Total 356 patients with Uncontrolled Type-2 Diabetes Mellitus will be randomized in 1:1 ratio among two arms of CPL-2009-0031 140 mg or Sitagliptin 100 mg.

Primary objective of the study is to evaluate HbA1c levels between oral CPL-2009-0031 140 mg and oral Sitagliptin 100 mg [Time frame: Baseline, 12 weeks, 24 weeks and 36 weeks from onset of therapy].

Secondary objective of the study is to compare:-

- Fasting Blood Sugar and Postprandial Blood Sugar. [At visit 1, 3 and 5-16].
- Determination of safety and tolerability of CPL-2009-0031 140 mg versus Sitagliptin 100 mg based on:
- Frequency of serious adverse events. [Time frame: randomization to end of 12, 24 & 36-weeks therapy].
- Number and severity of hypoglycemic events. [Time frame: randomization to end of 12, 24 & 36-weeks therapy].
- Frequency and severity of adverse events. [Time frame: randomization to end of 12, 24 & 36-weeks therapy].

Recommendation of the Committee:- The firm presented the Phase III clinical trial protocol. After detailed deliberation the committee recommended that the firm should submit report of Phase II clinical trial to CDSCO alongwith action taken in respect of earlier IND Committee recommendations that mechanism of cleavage of the drug CPL 2009-0031 to Sitagliptin in animal models and effect of food on the Pharmacokinetics of the drug in humans should be conducted, for further consideration by the committee.

Agenda No. 5

Phase III clinical trial report of clinical trial with Risug.

The applicant presented the clinical study report of clinical trial entitled, "Phase III clinical trial with an intravasal injectable male contraceptive - RISUG".

As per the proposal submitted :-

On 3.04.2006 School 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 labeled and non-randomize phase-III clinical trial carried out at five centres located in different hospitals in five States in the country.

Phase I clinical trial permission was issued on 01.03.1989 and was undertaken at the L.N.J.P. Hospital, New Delhi during the period 1990-93. Two males each were treated with different doses of styrene maleic anhydride (SMA); the dose level ranged from 0 (control administered solvent dimethyl sulphoxide alone) up to 140 mg into each vas deferens. A total of 16 subjects were treated in this series. Later the study was extended to cover 47 male subjects. In order to delink safety from efficacy, subjects inducted were those whose wives were tubectomized. Indirect information on efficacy was obtained from semenology data.

Phase II clinical trial permission was issued on 13.08.1993 and was undertaken at the L.N.J.P. Hospital, Safdarjung Hospital and Deen Dayal Upadyaya Hospital, New Delhi during the period 1993-97. During the study the subjects were followed for one year after the injection in respect of general physical parameters, semenology and pregnancy in the female. It is reported that recovery from the Injection procedure was uneventful in all cases. As was also observed during the Phase I clinical trial, mild scrotal enlargement on account of diffuse scrotal tissue edema occurred in four subjects beginning two to three days after the injection. There was no pain but tenderness in the spermatic cord and inguinal canal was bilaterally present. The enlargement and tenderness resolved spontaneously over a period of one to two weeks. All subjects maintained the same pattern in their sex life as prior to Injection. Regular monthly semen examination beginning three weeks after the Injection was planned but the protocol could not be implemented strictly. The outcome in all subjects was sustained azoospermia. Wives of the male subjects retained good health throughout the study. There were eight incidences of delayed menses, which tested, negative for pregnancy. No pregnancy occurred during the period of the study, which was at least one year beyond the two months recommended, for condom use after Injection.

Phase III clinical trial permission was issued on 03.04.2006. The objective of the trial was to obtain sufficient evidence about the efficacy and safety of the Risug® in a large number of healthy subjects. ICMR has conducted the trial and submitted the report to CDSCO.

As per the report of the Phase III clinical trial, a total of 315 subjects received RISUG injection at all five participating centres. Out of 315 subjects, 5 subjects did not come after receiving the RISUG injection and were considered as lost to follow up. Out of 310 subjects, in 7 subjects protocol violations were observed. It is reported that overall 92.7% subjects achieved azoospermia at 2.5 month post injection and it reached to highest level (97.2%) at 6th month post RISUG injection. 1.2% method failure was observed. Over all failure of the drug RISUG was 1.5% Contraceptive were reported out of that 0.3% pregnancies were due to method failure, 0.98% pregnancies were due to drug failure and 1.3% pregnancies were due to social reasons. The overall efficacy of the drug RISUG, as per achievement of pregnancies is concerned, is 99.02%.

No adverse side effect was reported and observed on clinical evaluation of these subjects on their scheduled follow up visit up to 7 years post RISUG injection. No adverse trend were observed in any parameter related to haemogram, liver function test (LFT), kidney function test (KFT), blood sugar, urine examination of the subjects on their scheduled follow up visit up to 7 years post RISUG injection.

The proposal was deliberated in IND Committee meeting dated 29.08.2018. **Recommendation of the Committee:-** 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.

Recommendation of the Committee:- The applicant presented their view points/ proposed action on scrotal swelling, psychological behavioural aspects, sexual activity, reversibility, and acceptability etc. alongwith 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 submits the data as per the requirements.

The meeting ended with vote of thanks to the Chair

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