Minutes of IND Committee meeting held on 03.12.2018 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. 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. 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. 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.

CDSCO Representatives:

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

Following members could not attend the meeting:

1. Dr.Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
2. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
3. Dr. Deepak Kaul, Prof. & Head, Department of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
4. 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 and Dr. Nilima Kshirsagar would Chair the meeting. Thereafter, the agenda items were discussed one by one:

Agenda No. 1

Phase II clinical trial with NRC-2694 of M/s Natco Pharma

The firm presented their proposal for grant of permission to conduct a Phase II clinical trial with NRC-2694-A entitled, "A Phase II Clinical Study to evaluate the efficacy and

safety of NRC-2694-A in patients with recurrent Head and Neck Squamous Cell Carcinoma".

The investigational agent, NRC-2694 belongs to the quinazoline class of EGFR tyrosine kinase inhibitor and showed superior activity in in-vitro and in-vivo cancer models than an approved drug Erlotinib. It has demonstrated good anti cancer activity in animal models of lung (NSCLC), pancreatic and Her-2 positive breast cancer.

Firm was granted permission to conduct a Phase I Clinical Study to evaluate the safety, pharmacokinetics and anti-tumor activity of NRC-2694-A in patients with advanced Solid Malignancies on 22.03.2011.

As per the proposal submitted by the firm:-

The Phase I clinical trial was an open label, prospective, non-randomized, multicenter, dose escalation study. The starting dose selected for this study was 100 mg and the maximum dose received was 500 mg/day. The dose escalation was done as per Modified Fibonacci Number Series. As per this method the dose escalation was done in cohorts of three patients. If no Dose Limiting Toxicity (DLT) was observed in any of these patients, next dose as per protocol was administered. If two or more of the six patients treated at a dose level experience DLT, then the MTD was considered to have exceeded, and dose escalation was stopped. All eligible patients were housed in Phase-I unit of the hospital for 12 days and patients who tolerated the drug were administered the drug on out-patient basis.

The primary objective of the study was to determine the maximum tolerated dose (MTD) and Dose Limiting Toxicity (DLT) of NRC-2694-A given orally once daily and to characterize the safety and tolerability of NRC-2694-A. Secondary objective of the study was to evaluate the single and multiple dose pharmacokinetics and anti-tumor activity of NRC-2694-A.

A total of 26 subjects were enrolled in the study, out of 26 subjects 23 completed the study and 3 withdrawn.

Once daily administration of NRC-2694-A showed tolerable safety profile. Objective response in terms of tumour size was observed in 5 patients with recurrent and metastatic head and neck cancer. Dose proportional relationship with respect to pharmacokinetics was also seen. Dose limiting toxicity was observed in 3 subjects at 500 mg dose level. The MTD defined as per protocol was achieved at 400 mg dose level. The dose level of 300 mg/day was concluded to be the safe dose for proceeding to the Phase-II study.

The proposed Phase II study is an open-label, prospective, randomized, active controlled, multicentric Phase-II study.

The primary objective of the study is to evaluate the efficacy of NRC-2694-A containing platinum regimen compared to platinum regimen alone in terms of Progression Free

Survival (PFS). Secondary Objective of the study is to compare the objective response rate in patients with recurrent or metastatic squamous cell cancer of the head and neck treated with NRC-2694-A and cisplatin regimen, to compare the stable disease rates, duration of response, time to response, median survival, and overall survival of patients treated with this regimen and to compare the safety and tolerability of this regimen in these patients.

Recommendation of the Committee:- The firm presented their proposal alongwith Phase I clinical trial report 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. DSMB should be constituted to review the safety aspects in the clinical trial.
2. Standard of care in all the sites should be uniform.
3. In case the any patient benefits from the study drug, the drug may be continued beyond 126 days at Investigator's discretion.
4. In vitro data on elimination of the drug should be generated.

Agenda No. 2

Proposal for marketing authorization cum Phase III clinical trial with PMZ 2010 of M/s Pharmazz India Pvt. Ltd

The presented their proposal for grant of marketing authorization and simultaneous permission for Phase III clinical trial with PMZ-2010 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".

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

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

As per the proposal submitted by the firm:-

PMZ-2010 (Centhaquin citrate) is targeted to be used as an 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 Phase II clinical trial was a prospective, multicentric, randomized, double- blind, parallel, saline controlled, safety and efficacy clinical study of PMZ-2010 therapy in patients with Hypovolemic shock due to blood loss with systolic arterial blood pressure ≤ 90 mmHg at presentation and continues to receive standard Shock Treatment.

50 patients were randomized 1:1 into 2 treatment groups after meeting the eligibility criteria. An Interactive Web Response System (IWRS) was used to randomize the eligible patient to the treatment groups:-

- Group 1: PMZ-2010 (Dose: 0.01 mg/kg) + Standard of care
- Group 2: Normal Saline (Dose: Equal volume) + Standard of care

In control group total 26 patients were randomized. Out of 26, 22 patients completed the study, 2 patients were withdrawn by the investigator because of terminal illness, and 2 patients withdrew their consent. In PMZ-2010 group total 24 patients were enrolled. Out of 24, 23 patients completed the study and 1 patient was withdrawn by the investigator because the patient was suffering with systemic disease before having trauma.

In patients of hypovolemic shock due to blood loss, PMZ-2010 demonstrated highly significant efficacy in improving systolic blood pressure, diastolic blood pressure, lactate levels, base-deficit, time on ventilator, reduction in use of vasopressors and reduced mortality compared to control. PMZ-2010 was found safe and was well tolerated in patients of hypovolemic shock.

Now, firm has submitted 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" at 6 sites on 105 subjects. Total 70 patients will be enrolled in PMZ-2010 group (Group 1) and in Normal Saline group (Group 2) total 35 patients will be enrolled.

- Group 1: PMZ-2010 (Dose: 0.01 mg/kg) + Standard of care
- Group 2: Normal Saline (Dose: Equal volume) + Standard of care

This is a prospective, multi-centric, randomized, double-blind, parallel, controlled phase-III efficacy clinical study of PMZ-2010 therapy in patients with Hypovolemic shock with systolic arterial blood pressure ≤ 90 mmHg at presentation and continue to receive standard Shock Treatment.

The primary objectives of the study are to determine-

- Change in systolic and diastolic blood pressure, Mean through 48 hours [Time frame: first 48 hours].

- Change in blood lactate, Mean through 48 hours [Time frame: first 48 hours].
- Change in Base-deficit, Mean through 48 hours [Time frame: first 48 hours].

Firm has also requested for marketing authorization alongwith Phase III clinical trial with following justification:-

- PMZ-2010 has shown unprecedented safety and efficacy in a serious and life-threatening condition of hypovolemic shock.
- All the key surrogate clinical endpoints of blood pressure, blood lactate and base-deficit significantly (P<0.001) improved with PMZ-2010 compared to standard of care.
- Safety and efficacy established in Indian population (Phase I and Phase II clinical studies conducted in India).
- There are limited therapeutic options for this life-threatening condition and these options are associated with many adverse effects.
- PMZ-2010 fulfills the unmet need for serious and life-threatening condition.

Recommendation of the Committee:- 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 the 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.

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 by the firm:-

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 nafithromycin is 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 nafithromycin in the safety analysis set.

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.

The proposal was deliberated in IND Committee meeting dated 08.10.2018. 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.

Now, firm has submitted the revised clinical trial protocol entitled, "A Phase III, Randomised, Multicentre, Double-Blind, Comparative Study to Determine the Efficacy and Safety of Oral Nafithromycin Versus Oral Moxifloxacin in the Treatment of Community-Acquired Bacterial Pneumonia (CABP) in Adults" alongwith 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.

Recommendation of the Committee: - In light of recommendation of the committee in its earlier meeting held on 08.10.2018, 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 test. Revised clinical trial protocol should be submitted to CDSCO before initiation of the study.

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 by the firm:-

> 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 also 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.

60 patients were enrolled in the Phase II study. Out of 60, 02 patients withdrawn their consent and fifty eight patients completed the study. Statistical analysis was done for data available from 58 patients. The primary objective of the study was to evaluate HbA1c levels between oral CPL-2009-0031 (70mg and 140mg) as compared to oral sitagliptin 50mg [Time frame: Baseline and 12 weeks from onset of therapy].

This study was prospective, randomized, double blinded, parallel group, three arm, multicentric, comparative, dose finding study of oral CPL-2009-0031 (70 & 140mg) as compared to Sitagliptin 50mg among.

Efficacy was evaluated based on HbA1c and fasting plasma glucose and post-prandial plasma glucose. Safety was evaluated based on - frequency of SAEs, frequency and severity of hypoglycemic events, frequency and severity of AEs, Laboratory safety variables.

No serious adverse event was observed during the conduct of this study. Three adverse events were reported in three patients, all were mild in nature and unrelated to study medication.

Firm concluded that that the investigational product has been found safe and well tolerated, effective in reducing HbA1c, observed glycemic control was maintained throughout the treatment duration in all the three arms.

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].

Earlier, the proposal was deliberated in IND Committee meeting dated 08.10.2018. 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.

Now, Firm has replied and submitted the Phase II clinical study report, cleavage mechanism and Protocol to study the effect of food on the Pharmacokinetic of the drug in Humans.

Firm has submitted the study protocol entitled, "A randomized, open-label, two-treatment, four period, two-sequence, single dose, balanced, crossover comparative pharmacokinetic study of CPL-2009-0031 tablets 140mg of Cadila Pharmaceuticals Ltd., India with Januvia (Sitagliptin) Tablets 100mg of MSD Pharmaceuticals Limited, India in healthy, adult human subjects under fasting and fed condition" to conduct the study in 16 subjects.

Recommendation of the Committee:- In light of recommendation of committee in its earlier meeting held on 08.10.2018, the firm presented their proposal alongwith protocol for food interaction study. Phase III clinical trial protocol was presented in the last IND Committee meeting held on 08.10.2018.

After detailed deliberation the Committee recommended for grant of permission to conduct the proposed Phase III clinical trial and the food interaction study as per protocol presented.

Agenda No. 5

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

The firm applied 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."

As per the proposal submitted by the firm:-

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.

Subsequently, the proposal was again deliberation in IND Committee meeting dated 08.10.2018. 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.

The firm has submitted their justification on the above mentioned points.

Recommendation of the Committee:- In light of recommendation of committee in its earlier meeting held on 08.10.2018, the firm presented their justification/ clarification on points raised.

After detailed deliberation, the Committee recommended for grant of permission to conduct the proposed Phase I clinical trial as per protocol presented.

Agenda No. 6

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

The applied 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 by the firm:-

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).

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% in mice and 37% in rats. The half-life of HRF-4467 ranges from a low of ~4.8 hours in rats up to ~49 hours in mice. Definitive excretion studies have not yet been completed but preclinical 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 associated with HRF-4467 at doses up to 100 mg/kg/day for up to 28 days in mice. The no observed-adverse-effect level (NOAEL) for both sexes was 100 mg/kg/day, the highest dose level administered. Based on the decreases in circulating platelets and increases in reticulocytes correlating with increased splenic weights and microscopic evidence for increased extramedullary haematopoiesis in the spleen at doses >30 mg/kg/day, the no observed-effect level (NOEL) was determined to be 10 mg/kg/day for both sexes.

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

Non adverse HRF-4467-related clinical observations consisted of an increased incidence of emesis at ≥10 mg/kg for both sexes and an increased incidence of liquid feces at ≥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. Exposure in 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 was considered to be 100 mg/kg. Based on a non adverse 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 of dogs. There were no test article-related clinical observations and no test article-related changes in the body weight. There were no changes in blood pressure parameters (mean arterial, systolic, diastolic), heart rate, body temperature, and

echocardiogram (ECG) parameters (QT, QTcV, QRS, PR interval) that were considered test article related. No arrhythmias 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. It was shown to be non-clastogenic and non-aneugenic in the in vivo mouse micronucleus study.

Earlier, the proposal was deliberated in IND Committee meeting dated 08.10.2018. 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 especially in respect of $T_{1/2}$ 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.

The firm has submitted their justification/clarification on the above points.

Recommendation of the Committee:- In light of recommendation of committee in its earlier meeting held on 08.10.2018, the firm presented their justification/ clarification on points raised.

After detailed deliberation, the Committee recommended for grant of permission to conduct the proposed Phase I clinical trial as per protocol presented.

Agenda No. 7

Phase III clinical trial with Remogliflozin of M/s Glenmark Pharmaceuticals.

The firm presented the details of the revision made in the Phase III clinical trial protocol for grant of permission to conduct Phase III clinical trial entitled, "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", as per the amended clinical trial protocol submitted.

Remogliflozin Etabonate is a Novel SGLT2 inhibitor.

As per recommendation of IND Committee dated 19.04.2017 and Apex Committee dated 02.06.2017, the firm was granted permission to conduct a PK study and Phase III clinical trial on 09.06.2017 with conditions that the firm shall initially conduct Pharmacokinetic study with the formulation and submit the report to DCG(I) office before initiation of the Phase-III clinical trial.

Now, the firm has revised the Phase III clinical trial protocol with certain protocol amendments.

These amendments are related to the statistical analysis of safety and efficacy and reconsideration of sample size for doing PK analysis in the subpopulation as under:-

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 the clinical trial.
2. Revise PK sample size from 48 subjects to 30 subjects, considering the challenged 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.

Recommendation of the Committee:- The firm presented their proposal for protocol amendment in the Phase III clinical trial protocol. After detailed deliberation the Committee recommended for approval of the Phase III clinical trial protocol amendment.

Agenda No. 8

Phase IV clinical trial report of Saroglitazar of M/s Cadila Healthcare Limited.

M/s Cadila Healthcare Limited was granted manufacturing and marketing permission of Saroglitazar Tablets 2mg/4mg for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type-2 diabetes mellitus not controlled by statin therapy on 25.02.2013.

Subsequently, firm was granted permission to conduct Phase IV clinical trial entitled, "A multi-centric, prospective, randomized, double-blind, study to evaluate the safety and efficacy of Saroglitazar (LipaglynTM) 2 and 4 mg as Compared to Fenofibrate 160 mg in Patients with Dyslipidemia" on 01.09.2014.

Now, firm has submitted the reports of Phase IV clinical trial.

This was a prospective, randomized, multicentric, Double-blind, clinical study to evaluate the safety and efficacy of Saroglitazar (LipaglynTM) 2 and 4 mg as compared to Fenofibrate 160 mg in patients with dyslipidemia.

A total of 997 subjects were randomized and enrolled in the study. Of which, 395 subjects were enrolled in the Saroglitazar 2 mg arm, 404 subjects were enrolled in the Saroglitazar 4 mg arm and 198 subjects were enrolled in the Fenofibrate 160 mg arm in a ratio of 2:2:1.

It is reported that Saroglitazar 2 mg and 4 mg were safe and well tolerated. Saroglitazar appeared to be an effective and safe therapeutic option for improving hypertriglyceridemia in patients with dyslipidemia.

The number of subject experiencing AEs was comparable between the Saroglitazar and Fenofibrate treatment groups. All AEs reported by subjects from Saroglitazar 2 and 4 mg treatment arms were either mild or moderate in severity and most of them were not related to the study drug. None of the subjects were discontinued from the study due to AEs in any of the treatment group.

The most frequently reported AEs were: pyrexia 5 (1.27%), headache 6 (1.52%) and increased blood creatine phosphokinase 4 (1.01%) in Saroglitazar 2 mg; nausea 7 (1.73%), pyrexia 7 (1.73%), vomiting 10 (2.48%), headache 9 (2.23%) in Saroglitazar 4 mg and diarrhoea 2 (1.01%), nausea 2 (1.01%), vomiting 2 (1.01%), pain and pyrexia 3 (1.52%), increased blood creatine phosphokinase 2 (1.01%), and headache 3 (1.52%) in Fenofibrate 160 mg etc. The proportions of subjects with adverse events in these SOCs were similar between all the groups. No statistically significant difference ($p > 0.05$) was observed between the treatment arms in respect to subjects experiencing AE during the study.

No serious adverse events and deaths were reported in Saroglitazar treatment arm and no persistent change in laboratory parameters. Overall efficacy by global tolerability assessment was good or excellent for all patients as recorded by investigators.

Saroglitazar (2 mg, 4 mg) treatment showed statistically significant reduction in TG from baseline at both weeks 12 and 24 in the PP and mITT population. Saroglitazar 2 mg was found to be non-inferior in reducing TG as compared to Fenofibrate 160 mg. Saroglitazar 4 mg was found to be superior in reducing TG as compared to Fenofibrate 160 mg post-treatment for 24 weeks.

Saroglitazar (2 mg and 4 mg) treatment showed significant percentage reduction from baseline in VLDL cholesterol, non-HDL cholesterol, total cholesterol and Apo B in both the populations (mITT and PP) at week 12 and 24. However, the percent change from baseline of LDL cholesterol in Saroglitazar 4 mg arm was found to be significant in mITT population at week 12 and 24. Additionally, significant increase from baseline in HDL was observed at week 12 and 24 in both Saroglitazar 2 mg and 4 mg treatment groups. Overall efficacy by global tolerability assessment was good for all patients as recorded by investigators.

Recommendation of the Committee:-

The Committee noted that the company has not carried out / reported the phase 4 study as recommended for example : objectives have not been clearly stated, company did not mention safety assessment as primary objective, there was no sample size calculation. Company should submit the report corrected considering above comments..

The meeting ended with vote of thanks to the Chair

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