Minutes of IND Committee meeting held on 29.08.2018 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. Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
5. Dr. S. K. Sharma, Ex-Prof. & Head, Department of Medicine, AIIMS, New Delhi.
6. Dr. C. D. Tripathi, Prof. & Head, Department of Pharmacology, VMMC, New Delhi.

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).

Following members could not attend the meeting:

1. Dr. Deepak Kaul, Prof. & Head, Department of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
2. Prof. Dinesh Puri, Head, Department of Medical Bio-Chemistry, GTB Hospital, Shahdara, New Delhi.
3. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
4. Dr. Bikash Medhi, Prof., Department of Pharmacology, PGIMER, Chandigarh.

Prof. Balram Bhargava, Secretary, DHR and DG ICMR, Chairman of the Committee welcomed the members. He mentioned that the meeting of the committee should be held every month so as to evaluate the proposals in expedited manner.

The Chairman also informed the committee that since he has to attend another important meeting after some time, in his absence Dr. Nilima Kshirsagar will Chair the meeting. Therefore, the agenda items were discussed one by one as under:

Agenda No. 01

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

The firm presented their proposal for the 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,

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. Results of in-vitro studies show 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.

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 not approved in any country and it is under primary stage of clinical development. The proposed study will be First in Men study i.e. phase I study. Preclinical studies with PNB-028 have been carried out and the data are captured in the Investigator's Brochure appended herewith the application in relevant section.

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.

Recommendation of the Committee:- 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.

Agenda No. 2

Phase I clinical trial with Bioplatin of M/s Rasayani Biologics Pvt. Ltd.

The firm presented the details of the revision made in the Phase I clinical trial protocol.

As per the proposal submitted,

Bioplatin is a nano metallic complex based on platinum prepared by a unique patented procedure. It is prepared by exposure of metal platinum to thermal gradient and subsequent treatment with naturakl enzymes. It is hypothesized that due to its nano size, Bioplatin has an inherent property to attach itself to the mucus membarnes of the mouth and gastro intestinal lining leading to longer retention time in the human body as compared to Platinum metal powder. Such particles are transferred by phagocytosis to blood through the gastointestinal tract.

As per recommendation of IND Committee, Technical Committee and Apex Committee, the firm was granted permission to conduct Phase I clinical trial on 20.12.2013.

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

This is an open-label, single arm sequential dose escalation study to determaine the maximum tolerated dose (MTD) of Bioplatin when administered once daily over a period of 21 consecutive days in a 28 day cycle.

The objective of the trial is to detemine the MTD and Dose Limiting Toxicity (DLT) of Bioplatin administered orally in patients with advanced solid tumors, establish the recommended dose of Bioplatin to be used in Phase II studies, determine the pharmacokinetics of Bioplatin, investigate the safety profile of Bioplatin and quality of life of patients taking Bioplatin.

Recommendation of the Committee:- The committee deliberated on the proposed amendments to protocol regarding inclusion criteria and assessment of patients administered with the investigational product, beyond 21 days. The committee recommended approval of the amended protocol with the condition that the DSMB should be informed about the amended protocol and study report as per amended protocol.

Agenda No. 3

Clinical study with ZYAN1 50mg and 100mg of M/s Cadila Healthcare Limited.

The firm presented has presented their proposal for the grant of permission to conduct a clinical study entitled “An open label, randomized, single-treatment, two-period, two-conditions (fed vs. fasting), two-sequence, crossover, single dose oral food effect bio-

availability study of Desidustat (ZYAN1) 50 mg and 100 mg tablet in healthy adult male and female subjects".

As per the proposal submitted,

earlier, firm was granted permission to conduct Phase II clinical study entitled, “A randomized, double-blind, placebo controlled, parallel group, Phase II multi-centric trial to assess safety, tolerability and efficacy of PHD-inhibitor, ZYAN1 in the treatment of anemia in pre-dialysis chronic kidney disease patients” on 15.03.2017. This study included the four treatment arms – Placebo, ZYAN1 100mg, ZYAN1 150mg and ZYAN1 200mg tablets.

Firm had conducted Phase I clinical study in India and Australia. Based on the study reports of Australia ZYAN1 150mg single dose was selected for conducting Phase I study in India. Out of 8 healthy male volunteers, 6 were administered ZYAN1 and 6 volunteers were administered placebo in the overnight fasting condition. Single dose of ZYAN1 150mg were well tolerated by healthy subjects. No serious adverse event and adverse event was reported. Firm conducted Phase I in Australia at ZYAN1 10mg, 25mg, 50mg, 100mg, 150mg, 200mg and 300mg. Phase I clinical study report was deliberated in IND Committee dated 08.11.2016.

Now, firm proposed to conduct a clinical study entitled “An open label, randomized, single-treatment, two-period, two- conditions (fed vs. fasting), two-sequence, crossover, single dose oral food effect bio-availability study of Desidustat (ZYAN1) 50 mg and 100 mg tablet in healthy adult male and female subjects".

Recommendation of the Committee:- After detailed deliberation the Committee recommended for grant of permission to conduct the clinical trial as per the protocol presented.

Agenda No. 4

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

The firm presented has presented their proposal for 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 Cadial 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".

As per the proposal submitted,

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.

It may be noted that, this office has already granted the permission to conduct the Phase I/II clinical trial of their IND drug product which is undergoing. Now firm has submitted the protocol to evaluate the impact on pharmackodymanic of their IND drug product when subject is already given the rabies vaccine.

Recommendation of the Committee:- 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.

Agenda No. 5

Phase II clinical trial with Arimoclomol of M/s Covance India Pharmaceuticals Services Pvt. Ltd.

The firm presented the details of the revision made in the Phase II clinical trial protocol.

As per the proposal submitted,

Arimoclomol Citrate is a hydroximic acid derivative, which is currently under development for the treatment of Gaucher's Diseasae & Niemann pick disease, type C (NP-C). Arimoclomol is available as hard gelatin capsules for oral administration either in whole or dispersed in water or food stuff.

As per recommendation of IND Committee meeting dated 25.07.2017, the firm was granted permission to conduct Phase II clinical trial on 03.11.2017.

Now, firm has submitted revised Phase II clinical trial protocol.

This is a multicentre, double-blinded, randomised, placebo-controlled trial of arimoclomol in patients diagnosed with Gaucher Disease Type 1 or 3.

The primary objective of the trial is to evaluate the effect of 6 months of treatment with arimoclomol on GD biomarkers compared to 6 months of treatment with placebo. Secondary objectives are:-

- To evaluate the safety and tolerability of arimoclomol in patients with GD.
- To evaluate the long-term effects of arimoclomol on clinical endpoints and biomarkers.
- To determine the plasma area under the curve [AUC] from time 0 to 8 hours [AUC_{0-8}] of arimoclomol following administration of the first dose, and to assess appropriateness of dose with respect to target AUC_{0-8}.

Recommendation of the Committee:- After detailed deliberation the Committee recommended for grant of permission to conduct the Phase II clinical trial as per the amended protocol.

Agenda No. 6

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 centers 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 centers. 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.

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.

The meeting ended with vote of thanks to the Chair

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