# Minutes of IND Committee meeting held on 14.05.2018 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

**List of Participants:**

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

**CDSCO Representatives:**

1. Mr. A. K. Pradhan, Deputy Drugs Controller (India), CDSCO (HQ).
2. Mr. Srinivasan K. M., Assistant 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.

Prof. Balram Bhargava, Secretary, DHR and DG ICMR, Chairman of the Committee welcomed the members. Before discussion of IND proposals, he stated that Indian Pharma industry has made phenomenal progress in manufacturing of generic drugs.There is an urgent need to shift the approach to put more focus on research and development of new drugs. He desired that to streamline the evaluation process of IND proposals by the committee a SOP should be prepared. For evaluation, it may be appropriate, that for each proposal one of the members may act as a primary reviewer who will brief with other members and make a summary of evaluation of the proposal. The member then places it in the IND committee for consideration. After this the applicant will make presentation on their proposal.

He also mentioned that, meeting should be held atleast once in two months and a calendar should be prepared and made available in the website.

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

## Agenda 01

**Phase I clinical trial with AXL1717 Capsules of M/s Cadila Pharmaceuticals Limited.**

The firm presented their proposal including **r**esults of earlier clinical trials conducted with oral solution of the drug and PK study data generated in animals with new formulation of oral capsule for the grant of permission to conduct a Phase I clinical trial entitled "Phase I trial of AXL1717, an orally bioavailable anti-cancer drug, in patients with solid tumors" with AXL1717 Capsules. During the presentation it was mentioned that due to bioavailability problem with earlier formulation, the oral capsule has been developed which has enhanced bioavailability.

AXL1717.H2O (Picropodophyllin Monohydrate) is a cyclolignan that inhibits the IGF-1R signaling pathway. Mechanistic studies have shown that treatment with AXL1717 reduces degradation of the IGF-1R and reduces the amount of phosphorylated (activated) IGF- 1R. Recent studies have shown that AXL1717 also has a rapid influence on microtubule dynamics and causes arrest of cell division in mitosis.

Pharmacodynamic studies of AXL1717 have been performed on a large number of cancer cell lines. The IC50 for inhibition of cell proliferation in cell culture ranges from 50 nM to more than 10 µM, and was found to be well below 1 µM with most cell lines.

Total 141 patients received AXL1717 by oral administration in a total of five completed trials, four Axelar-sponsored clinical trials and one investigator-initiated RUSH-001 study. Two of the completed trials (Studies AXL-003 and AXL-004) included only lung cancer patients and the other 2 studies (Studies AXL-001) included both lung cancer patients and patients with other tumors. The current recommended clinical dose of AXL1717 is 300 mg BID for repeated cycles of 2-4 weeks on treatment followed by in most cases, 1 week of treatment.

Primary objective of the study is to determination of maximum tolerated dose (MTD) by evaluating safety and tolerability of AXLI717.

**Recommendation: -** After detailed deliberations the committee recommended that Phase I single dose study with PK profile of the new formulation should be conducted and compared with the historical data of the earlier formulation. Accordingly detailed reports of earlier clinical trials and the revised clinical trial protocol should be submitted to CDSCO before approval of the study.

## Agenda 02

**Phase II clinical trial with ZYAN1 of M/s Cadila Healthcare Limited.**

The firm presented their proposal for the grant of permission to conduct a Phase II clinical trial entitled "A 6-week, Phase II, single arm, multi-center, open-label study to evaluate the safety and efficacy of ZYAN1 50mg in the treatment of anemia in pre-dialysis chronic kidney disease patients"

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.

Subsequently, the 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.

Now, firm has proposed to conduct a Phase II clinical trial with ZYAN1 50mg at Columbia Asia Hospital, Ahmedabad. A total of 21 subjects, including 20% dropout, will be enrolled in this study. ZYAN1 50 mg tablet will be orally administered on every alternate day to pre-dialysis CKD patients with anemia for a period of 06 weeks.

Primary objective of the study is to assess the efficacy and safety of ZYAN1 50 mg tablet on change of hemoglobin levels from the baseline (Duration: 6 weeks).

**Recommendation:-** The committee noted that the Phase II study with ZYAN1 100mg, 150mg and 200mg is already ongoing and no findings in respect of adverse effects or the data/evidence to suggest that the efficacy with 100mg may be similar with 50mg were available . After detailed deliberation the Committee recommended that the firm should submit appropriate justification for proposing the study with ZYAN1 50mg.

## Agenda 03

**Phase IA/IIB clinical trial with ZYAN1 (Desidustat) of M/s Cadila Healthcare Limited.**

The firm presented their proposal for the grant of permission to conduct a Phase IA/IIB clinical trial entitled "A Phase IB/IIA, multi-center, open-label clinical trial to evaluate the safety, tolerability and pharmacokinetic of Desidustat for the patients with Chronic Kidney Disease (CKD) on Dialysis".

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.

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Now, firm has proposed to conduct a Phase IA/IIB clinical trial with ZYAN1 (Desidustat) at 2 sites. A total of 24 subjects will be enrolled in this study. The study is divided into three panels - Panel I will receive single-dose of Desidustat 50 mg, Panel II will receive single-dose of Desidustat 100 mg and Panel III will receive single-dose of Desidustat 150 mg. An oral dose of ZYAN1 will be administered to each of the respective subjects with 240 ± 10 mL of water at ambient temperature. Primary objective of the study is to assess safety and tolerability

parameters including adverse events, clinical, laboratory, electrocardiogram, and vital signs assessments.

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

## Agenda 04

**Phase II clinical trial with PMZ 2010 injection of M/s Pharmazz India Private Limited.**

The firm presented their proposal for the grant of permission to conduct a Phase I clinical trial entitled "A Prospective, Multicentric, Randomized, Double Blind, Saline Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 Therapy along with Standard Supportive Care in Patients of Acute Spinal Cord Injury".

Earlier, based on the recommendation of the IND Committee firm was granted Phase I clinical trial permission for the drug. Report of Phase I study entitled, "An open label, Phase I study to determine the safety and tolerability and pharmacodunamics of multiple ascending doses of PMZ-1620 in healthy male volunteers" was deliberated in IND Committee dated 25.07.2017. Committee accepted the Phase I clinical study report. Based on the Phase I clinical study report, firm was granted two Phase II clinical trials with PMZ 1620.

Now, firm has proposed to conduct another Phase II clinical trial entitled, "A Prospective, Multicentric, Randomized, Double Blind, Saline Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 Therapy along with Standard Supportive Care in Patients of Acute Spinal Cord Injury".

This is a Prospective, Multicentric, Randomized, Double Blind, Saline Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 Therapy along with Standard Supportive Care in Patients of Acute Spinal Cord Injury. A minimum of 36 subjects (18 in each treatment arm) will be evaluated as per the protocol, taking into account a discontinuation rate of approximately 10 %, approximately 40 subjects will be enrolled in the study. The primary objective of the study is to evaluate the safety and tolerability of PMZ-1620 in patients of acute spinal cord injury.

The enrolment period of the study will be approximately 12 months and total duration of the study will be approximately 15 months. For an individual patient, duration of the study will be 3 months (85-95 days), including 4 study visits: visit 1/Day 1 to Day 6 (screening/baseline/treatment visit), visit 2/Day 30±5 (assessment visit), visit 3/Day 60±5 (assessment visit) and visit 4/End of Study/Day 90±5 (assessment and follow-up visit).

After randomization, patients will be administered with either PMZ-1620 or Normal Saline, on Day 1, 3 and 6. Three doses of PMZ-1620 (each dose of 0.3µg/kg body weight) or Normal Saline (equal volume) will be administered as an IV bolus over one minute at an interval of 3±1 hours on Day 1, 3 and 6. There will be total of 9 doses over 3 days (0.9µg/kg body weight/day). In both treatment groups, patients will be provided the standard of care. Standard of care to be provided to the patients shall be the one used in the particular hospital setup.

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

**Recommendation of the Committee:-** After detailed deliberation the Committee recommended for grant of permission to conduct the Phase II clinical trial as per the protocol presented with following conditions:-

1. First 8 patients should be evaluated at 15 days also.
2. To include those sites which have fairly common standard of care for patients of acute spinal cord injury.
3. The informed consenting through LAR should be discussed and decided by the respective Ethics Committee.

## Agenda 05

**Phase I clinical trial with TRC041266 of M/s Torrent Pharmaceuticals Limited.**

The firm presented their proposal for the grant of permission to conduct a Phase I clinical trial entitled "An Open Label, Randomized, Crossover Study to Compare the Pharmacokinetics of TRC041266 Powder with TRC4186 Tablet under Fasting Condition and to Evaluate the Effect of Food on the Pharmacokinetics of TRC041266 Powder in Healthy Human Subjects".

TRC041266 is a novel synthetic compound, chemically, 3-{[2-(methyl sulfonyl) hydrazinyl] carbonyl} -1 – [2-oxo-2-(thiophen-2- yl) ethyl] pyridinium decanoate-decanoic acid (1:1:1), which is co-crystal of TRC4186 freebase with decanoic acid. TRC4186 is currently in clinical development for the treatment of chronic heart failure associated with type-II diabetes.

Phase I study was conducted with TRC4186 tablet 500 & 1000 mg, which was further titrated to 125, 500, 1000 mg in Phase II study. Firm discontinued the Phase II clinical trial with TRC4186, a total of 298 patinents were randomized into 5 groups (2 on conventional treatment and placebo and 3 on different doses of TRC4186) out of which 140 completed 48 weeks treatment. A total of 54 SAEs were observed during the study out of which 24 were fatal and DSMB after review of data observed a trend of high all cause and cardiovascular fatalities in mid and high dose arms of IMP and therefore recommended for withdrawal of IMP in these dose arms.

To improve the bio-availability, drug substance (TRC 4186 Base) is conjugated with decanoic acid as TRC041266.

This study is monocentric, Open Label, randomised, single-dose, three-way crossover, comparative bioavailability study in healthy subjects. The study will be conducted at Bio-Evaluation Centre, Torrent Pharmaceuticals Ltd., Village Bhat, District-Gandhinagar-382428, Gujarat, India. Total of 36 (30 + 6 dropout) subjects will be enrolled in the study.

Planned study duration is approximately 9-10 weeks. Subjects will be randomized to one of the two treatment groups in a ratio of 1:1 i.e. TRC4186 750 mg Tablet or equivalent quantity of TRC041266 powder, in a ratio of 1:1. The randomization will be balanced and the code will be kept under controlled access.

**Recommendation of the Committee:-** After detailed deliberation, the committee recommended that the firm should conduct the PK study with the lower dose of TRC041266 equivalent to 500mg of TRC4186. Accordingly,the firm should submit the revised protocol to CDSCO before grant of permission to conduct the study.

## Agenda 06

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

M/s Sun Pharma Advanced Research Company (SPARC) Limited submitted an application for the grant of permission to conduct a Phase I/II clinical trial with K0706 entitled, "A Phase I/II Study to Determine Safety, Tolerability, Pharmacokinetics, and Activity of K0706, a Novel Tyrosine Kinase Inhibitor (TKI), in Subjects with Chronic Myeloid Leukaemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukaemia (Ph+ ALL)". K0706 is a novel BCR-ABL TKI developed by SPARC.

This is an open-label, dose-ranging, single-agent, multicenter, multidose, dose escalation study initiated in subjects with Ph+ CML (Ph + CML include CML-CP [with and without the BCR-ABL T315I mutation], CML-AP, and CML-BP) and Ph+ALL.

The proposal was deliberated in IND Committee dated 08.11.2016. The firm presented the Phase I/II clinical study protocol. After detailed deliberation, the Committee recommended that firm shall conduct Phase I clinical study sequentially at dose level of 12mg and 24mg and then at 48mg and established safety alongwith PK data and submit the report to the Committee. It was decided by the Committee that the Phase II clinical study protocol will be considered after review of the results of Phase I clinical study. Accordingly, the firm shall submit revised Phase-I protocol to the office of DCG (I).

As per the recommendation of IND Committee firm had submitted revised clinical trial protocol to this office and firm was granted permission to conduct Phase I clinical trial on 15.03.2017.

As per the condition, firm have conducted Phase I clinical study sequentially at dose levels of 12mg, 24mg and then at 48mg at four approved centers in India. K0706 was well tolerated by the oral route at doses of 12mg, 24mg and 48 mg once daily. As upon review of the safety data up to 48 mg cohort, iDMC (internal Data Monitoring Committee) recommended dose-escalation to 66 mg and patients are being enrolled globally in the cohort 4 at 66mg dose. Firm has submitted interim report of Phase I clinical trial conducted up to 48 mg dose.

**Recommendation of the Committee:-** After detailed deliberation the Committee recommended for grant of permission to conduct the Phase I clinical trial subject to submission of the following documents to CDSCO before the permission is granted.

1. The evidence that the protocol to coduct the study of K0706 with dose of more than 66 mg has been approved by USFDA.
2. Updated clinical data of the ongoing study.

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

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