Minutes of IND Committee meeting held on 25.07.2017 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

List of Participants:

1. Dr. Soumya Swaminathan, Secretary, Dept. of Health Research & Director General, Chairperson, IND Committee.
2. Dr. Y.K. Gupta, Prof. & Head, Dept. of Pharmacology, 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. C. D. Tripathi, Prof. & Head, Department of Pharmacology, VMMC, New Delhi.
6. Dr. Chandishwar Nath, Ex. Scientist-G & Scientist-in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
7. Dr. Bikash Medhi, Prof. Dept. of Pharmacology, PGIMER, Chandigarh.
8. Dr. S.K. Sharma, Ex-Prof. & Head, Dept. of Medicine, AIIMS, New Delhi.

ICMR Representative:

1. Dr. Vijay Kumar, Scientist G, Division of BMS-Co-ordinator, ICMR, New Delhi.
2. Dr. Monika Pahuja, Scientist C, ICMR, New Delhi.

CDSCO Representatives:

1. Dr. V. G. Somani, Joint Drugs Controller (India), CDSCO.
2. Mrs. Rubina Bose, Deputy Drugs Controller (India), CDSCO (HQ).
3. Mr. Sanjeev Kumar, Deputy Drugs Controller (India), CDSCO (HQ).
4. Mr. Sushant Sharma, Assistant Drugs Controller (India), CDSCO (HQ).

Following members could not attend the meeting:

1. Dr. Deepak Kaul, Prof. & Head, Deptt. Of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
2. Prof. Dinesh Puri, Head, Department of Medical Bio-Chemistry, GTB Hospital, Shahdara, New Delhi.

Dr. Soumya Swaminathan, Chairperson of the Committee welcomed the members to the meeting. She then apprised the Committee about the order of the Hon'ble Supreme Court of India, dated 21.10.2013 in the matter of W.P. (C) No. 33/2012 of Swasthya Adhikar Manch, Indore & Anr Vs. Ministry of Health and Family Welfare &Ors. with WP(C) No. 779/2012 regarding clinical trials wherein it was directed that the Technical Committee and the Apex Committee while evaluating the cases shall keep in view all relevant aspects of safety and efficacy particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic option and unmet medical need in the country.

In view of this the Chairperson requested the members for their critical evaluation of applications considering various scientific and ethical parameters of the proposals, specially all relevant aspects of safety and efficacy particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic option and unmet medical need in the country. The minutes of the last IND meeting held on 19.04.2017, which was already circulated to the members were taken as approved.

Sr. No. 01

Phase I clinical trial with PBL 1427 of M/s Panacea Biotec Limited.

This office has received an application from M/s Panacea Biotec Limited for grant of permission to conduct additional Phase I clinical trial with PBL 1427 entitled, "A randomized, double-blind, placebo-controlled Phase I study to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of single oral doses of different formulations of PBL1427 in healthy male volunteers".

PBL 1427 is a reversible competitive inhibitor of DPP IV, an enzyme responsible for degrading Incretin peptides like GLP-1 and GIP. By inhibiting DPP IV, PBL 1427 prolongs the half-life of incretins, potentiates GSIS and thus reduce glucose excursion without provoking hypoglycemia.

This is a single centric, randomized, double-blind, placebo-controlled, phase I study in which a total of 32 (8 x 4) healthy male subjects will be enrolled in 4 cohorts of eight subjects each in which six subjects will receive a single dose of active treatment and two subjects will receive placebo as a single dose. Subjects will be dosed in subsequent dose levels only after safety evaluation done by investigator and medical monitor of subjects recruited in the previous dose level. Interim Analysis will be done by DSMB for the safety evaluation of the subjects dosed in subsequent cohorts.

Cohort 1: A single oral dose of formulation A (240 mg) (n=6) or Placebo (n=2).

Cohort 2: A single oral dose of formulation B (220) mg (n=6) or Placebo (n=2).

Cohort 3: A single oral dose of C+ D (100 mg + 120mg tablets each) (n=6) or Placebo (n=2).

Cohort 4: A single oral dose of C+ D (100 mg + 120 mg tablets each) (n=6 under Fed condition) or Placebo (n=2 under Fed condition).

Formulation A:- PBL 1427 Extended release tablet 240mg:

Formulation B:- PBL 1427 Base tablet 220mg:

Formulation C:- PBL 1427 Base tablet 100mg:

Formulation D:- PBL 1427 Base Extended Release tablet 120mg:

The primary objective of the study is to determine safety and tolerability of different formulations of PBL 1427 and secondary objective is to evaluate the pharmacokinetics (PK) of PBL1427 and to determine exploratory Pharmacodynamic markers of PBL1427 in the study population.

Earlier, firm was granted permission to conduct Phase I clinical trial entitled, "A randomized, double-blind, placebo-controlled phase I study to determine the safety, tolerability, pharmacokinetics and Pharmacodynamics of single Ascending Doses of PBL1427 in healthy volunteers".

The primary objective of the study was to determine safety and tolerability of different formulations of PBL 1427 and to evaluate the pharmacokinetics (PK) of PBL1427. The secondary objective is to determine exploratory Pharmacodynamics markers of PBL1427 in the study population.

48 male subjects were enrolled in six cohorts at Sunflag Hospital & Research Centre, Fortis Clinical Research Limited, Sector 16 A, Faridabad-121002. Haryana, India.

Cohort 1: A single oral dose of 20 mg of PBL 1427 (n=6) or placebo (n=2).

Cohort 2: A single oral dose of 40 mg (20mg ×2) of PBL 1427 (n=6) or placebo (n=2).

Cohort 3: A single oral dose of 80 mg (20mg ×4) of PBL 1427 (n=6) or placebo (n=2).

Cohort 4: A single oral dose of 150 mg of PBL 1427 (n=6) or placebo (n=2).

Cohort 5: A single oral dose of 300 mg (150×2) of PBL 1427 (n=6) or placebo (n=2).

Cohort 6: A single oral dose of 600 mg (150×4) of PBL 1427 (n=6) or placebo (n=2).

The investigational drug products were found to be well tolerated and safe.

Recommendation of the Committee:- The firm presented the Phase I clinical trial protocol. After detailed deliberation the Committee recommended the conduct of Phase I clinical trial subject to the condition that sample size should be revised from 8 subjects to 12 subjects per cohort.

Accordingly, the firm shall submit revised clinical trial protocol to the office of DCG(I) and if above parameters are included, it may be approved.

Sr. No. 2

Phase II clinical trial with Arimoclomol of M/s Covance India Pharmaceutical Services Private Limited.

This office has received an application from M/s Covance India Pharmaceutical Services Pvt. Ltd. for grant of permission to conduct a Phase II clinical trial with Arimoclomol capsule entitled, "Multicenter Double-Blinded, Randomized Placebo-controlled study of Arimoclomol in patients diagnosed with Gaucher Disease Type 1 or 3".

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.

Arimoclomol act as a co-inducer of heat-shock protein 70 (HSP70), a major component under conditions of cellular stress. The HSP has been established as therapeutic target in lysosomal storage disorders (LSDs) in several preclinical studies. HSP70 proteins act as molecular chaperones, assisting in the folding of newly synthesized or damage protein for degradation. Furthermore, their cytoprotective effects include interactions with lysosomes where the lysosomal actions of the major stress-inducible member of the family, HSP70 reverse lysosomal aggregation, & prevent lysosomal membrane permeabilazation, the latter being hall marks of LSDs & stress induced cell death.

Lysosomal storage diseases are caused by mutations in lysosomal proteins. In Gaucher's Disease the symptoms are due to glucocerebrosidase enzyme (GBA) where malfunction induce lysosomal enlargement.

This is a placebo-controlled, randomized, double-blinded study evaluating the response of 3 dose levels of Arimoclomol on various pharmacodynamics biomarker in blood & cerebrospinal fluid as

indicator of enhanced glucocerebrosidase enzyme activity (GBA) in Gaucher disease Type 1 (GD1) & Gaucher disease Type 3 (GD3).

The purpose of this phase II, proof of concept study is to assess if Arimoclomol can increase the GBA enzyme activity in Gaucher disease patients in a dose related manner. The primary objective of the study is to evaluate the response of Gaucher's Disease biomarker versus placebo at 6 months and secondary objective is to evaluate the patient safety (after 6 months & long term) as well as long term effects on clinical endpoints & biomarkers in the open-label extension phase.

Approximately 40 eligible GD1 and GD3 patients will be randomized into 4 groups on a 1:1:1:1 basis to receive Arimoclomol 300mg/day, Arimoclomol 600mg/day, Arimoclomol 1200mg/day or placebo treatment 3 times daily.

Phase I studies with Arimoclomol include a single-dose study, a multiple-dose study, an ascending multiple-dose study, two food effect studies, a mass balance study to determine absorption, distribution, metabolism, and excretion (ADME), and a renal safety study. In addition, pharmacokinetic (PK) parameters have been assessed in a Phase II study in patients with amyotrophic lateral sclerosis (ALS). Phase I studies show that Arimoclomol is absorbed rapidly. In a double-blind, placebo-controlled, rising multiple-dose study of Arimoclomol following oral administration in healthy adult male subjects (AALS-005) with combined single dose and three times daily (t.i.d) treatment with Arimoclomol (100 mg to 600 mg) or placebo treatment during 7 days, Arimoclomol exposure (based on Cmax and AUC) increased in a dose proportional manner after single dose and t.i.d dosing. Steady state appeared to have been reached by 24 h after the start of t.i.d dosing for all dose levels. Across all Phase I clinical studies performed, including the Phase II study in ALS patients, an average t1/2 of 3.5 hours and a Tmax of 1 to 2 hours have been observed. There was approximately 40-50% accumulation of serum Arimoclomol following multiple dosing, which is insignificant given the half-life of 3.5 h. In addition, the exposure to Arimoclomol (AUC0-8 Day 7/ AUC0-inf Day 1) was not time dependent. However, a 12 week study (AALS-001) with 84 ALS patients, PK analysis of a subset of 44 patients showed no accumulation or auto-induction and demonstrated a dosage related increase in serum concentrations of Arimoclomol at all dosages, increasing proportionally with dosage.

No clinical studies with Arimoclomol have been conducted in the Gaucher disease indication, no corresponding efficacy data are available. Safety data reported originate from Phase I studies with Arimoclomol in healthy volunteers and from a Phase II study in Amyotrophic Lateral Sclerosis (ALS). Firm has not conducted Phase I trial in India and directly applied for Phase II clinical study.

Recommendation of the Committee:- The firm presented the Phase II clinical trial protocol. After detailed deliberation based on Phase I studies conducted outside India & based on fact that Gaucher disease is very rare disease & presently there are no therapeutic option available in the country. Further, since this drug is also under Phase II studies for other condition in other part of World, the Committee recommended the conduct of Phase II clinical trial.

Sr. No. 3

Phase II clinical trial with GRC 27864 of M/s Glenmark Pharmaceuticals Limited.

This office has received an application from M/s Glenmark Pharmaceuticals Limited for the grant of permission to conduct a Phase II clinical trial with GRC 27864 tablets entitled "A Phase 2 dose-

range finding 12-week, double-blind, randomized, parallel group study to evaluate safety and efficacy of GRC 27864 in patients with moderate to severe osteoarthritis pain".

GRC 27864 is a first in class, potent, selective, orally bioavailable inhibitor of microsomal prostaglandin E synthase-1 enzyme (mPGES-1) enzyme which is up-regulated under inflammatory conditions.

This is a four-arm, randomized, double-blind, double dummy, parallel group, placebo-controlled study. The study will comprise of three study periods: screening including wash out (2 weeks), double-blind treatment period (12 week) and a follow up (2 weeks). Firm has conducted three Phase I clinical studies outside India.

Primary objective of the study is to evaluate the efficacy of GRC 27864 given orally at daily doses of 10 mg, 25 mg and 75 mg for 12-weeks compared to placebo, in patients with moderate to severe osteoarthritis pain. Secondary objective is to evaluate safety and tolerability of GRC 27864 given orally at daily doses of 10 mg, 25 mg and 75 mg for 12-weeks compared to placebo, in patients with moderate to severe osteoarthritis pain. Exploratory objectives is to evaluate pharmacokinetics of GRC 27864 and metabolite, GRC 27884 at daily doses of 10 mg, 25 mg and 75 mg in patients with moderate to severe osteoarthritis pain and to evaluate the effect of GRC 27864 on ex-vivo lipopolysaccharide (LPS)-stimulated prostaglandin E2 (PGE2) release in whole blood and assess pharmacokinetic and pharmacodynamic relationship.

Male and female subjects of 40 to 70 years of age who have been diagnosed to have primary osteoarthritis (hip or knee) for at least 3 months based on American College of Rheumatology (ACR) clinical and radiologic criteria6, 7 and experiencing moderate to severe pain according to a WOMAC 3.1 Visual Analogue Scale 8 will be enrolled in the Phase II clinical study.

The sample size is calculated to detect a 10-mm difference in pain intensity on 0-100 VAS between GRC 27864 and placebo after 12 weeks of treatment, assuming a standard deviation of 25-mm. A sample size of 532 patients (133 patients per treatment group) is required to ensure 90% power at a significance level of 5% (two-sided) on the basis of these assumptions and with an assumed drop-out rate of 15%. A total of 624 (156 per arm) subjects will be enrolled in the study.

Eligible subjects will be randomly assigned to one of the following arms in double-dummy, double blind design with 1:1:1:1 ratio. Randomization across the treatment arms will be balanced for subjects having received previous NSAIDs as well as those who receive background treatment with chondroprotective agents.

Arm 1: GRC 27864, 10 mg, QD for 12 weeks.

Arm 2: GRC 27864, 25 mg, QD for 12 weeks.

Arm 3: GRC 27864, 75 mg, QD for 12 weeks.

Arm 4: Placebo, QD for 12 weeks.

Recommendation of the Committee:- The firm presented the Phase II clinical trial protocol. After detailed deliberation, based on the three Phase I clinical study outside India, the Committee recommended the conduct of Phase II clinical trial subject to the condition that:-

1. Patients with severe osteoarthritis pain should be excluded from the trial.
2. Firm shall submit the final toxicity study reports for Phase II clinical trial as per Appendix III of Schedule Y.

Accordingly, the firm shall submit revised clinical trial protocol to the office of DCG(I) and if above parameters are included, it may be approved.

Sr. No. 4

Phase II clinical trial with PMZ 1620 for treatment of Acute Ischemic Stroke of M/s Pharmazz India Private Limited.

This office has received an application from M/s PharmazzIndia Private Limited for the grant of permission to conduct a Phase II clinical trial with PMZ-1620 injection entitled "A prospective, multicentric, randomized, double blind, parallel, saline controlled Phase II clinical study to compare the safety and efficacy of PMZ-1620 therapy along with standard supportive care in subjects of Acute Ischemic Stroke".

PMZ 1620 is a highly selective Endothelin B (ETB) receptor agonist. It is a linear analogue of endothelin-1, with 120000 fold selectivity towards ETB receptors compared to ETA receptors.

Firm was granted Phase I clinical trial permission on 26.07.2016 and has conducted 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".

A total of seven (7) healthy male subjects were enrolled in three (3) cohorts. The study consisted of three different dose cohorts with three subjects in each cohort and all three subjects received multiple doses of PMZ-1620 (only one subject was enrolled in cohort III). Subjects were dosed in subsequent dose levels only after safety evaluation of subjects recruited in the previous dose level.

Cohort I - 0.3 µg/kg body weight.

Cohort II - 0.6 µg/kg body weight.

Cohort III - 0.9 µg/kg body weight.

PMZ-1620 was found to be well tolerated and safe when administered as multiple ascending doses in healthy male subjects. The dose of 0.9µg/kg was concluded as Minimum Intolerable Dose (MID). The MTD of PMZ-1620 determined was 0.6µg/kg (IV).

Now, firm has proposed to conduct a Phase II clinical trial entitled, "A prospective, multicentric, randomized, double blind, parallel, saline controlled Phase II clinical study to compare the safety and efficacy of PMZ-1620 therapy along with standard supportive care in subjects of Acute Ischemic Stroke". The dose of PMZ-1620 for the Phase II clinical study is 0.3µg/kg.

This is a prospective, multicentric, randomized, double- blind, parallel, saline controlled Phase II clinical study to compare the safety and efficacy of PMZ-1620 therapy along with standard supportive care in subjects with acute ischemic stroke. 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 determine the tolerability and safety of PMZ-1620 and secondary objective is to determine whether PMZ-1620 therapy over and above standard of care increases the proportion of ischemic stroke subjects with National Institute of Health Stroke Scale (NIHSS) score ≥ 6 score at 3 months.

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 subject, duration of the study will be 3 months (90 days), including 5 study visits: visit 1/Day 1 (screening/baseline/treatment visit), visit 2/Day 12, visit 3 (Day 30 ± 5), visit 4/telephonic visit (Day 60 ± 5), and visit 5/End of Study (Day 90 ± 5). At visit 1, approximately 40 subjects will be randomized 1:1 into 2 treatment groups after meeting the eligibility criteria:

Group 1: PMZ-1620+Standard of care.

Group 2: Normal Saline (Dose: Equal volume) + Standard of care

PMZ-1620 or Normal Saline will be administered as an IV bolus over 1 minute within the window of 24 hours after the onset of stroke. In PMZ group, 3 doses of PMZ-1620, at 0.3 µg/kg body weight will be administered as an intravenous bolus over 1 minute every 3 hours ± 1 hour on day 1, 3, and day 6 (total dose/day: 0.9 µg/kg body weight). In control group, 3 doses of equal volume of normal saline will be administered as an IV bolus over 1 minutes every 3 hours ± 1 hour on day 1, 3 and day 6 post randomization. In both treatment groups, subjects will be provided the best standard of care.

Recommendation of the Committee:- The firm presented the Phase I clinical trial report and Phase II clinical trial protocol. After detailed deliberation the Committee accepted the Phase I clinical trial report and recommended the conduct of Phase II clinical trial.

Sr. No. 5

Phase II clinical trial with PMZ 1620 for supportive care of Alzheimer's disease of M/s Pharmazz India Private Limited.

This office has received an application from M/s Pharmazz India Private Limited for the grant of permission to conduct a Phase II clinical trial with PMZ-1620 injection entitled “A Prospective, Multicentric, Randomized, Double Blind, Placebo Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 Therapy along with Standard Supportive Care in Subjects of mild to moderate Alzheimer's disease”.

PMZ 1620 is a highly selective Endothelin B (ETB) receptor agonist. It is a linear analogue of endothelin-1, with 120000 fold selectivity towards ETB receptors compared to ETA receptors.

Firm was granted Phase I clinical trial permission on 26.07.2016 and has conducted 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”.

A total of seven (7) healthy male subjects were enrolled in three (3) cohorts. The study consisted of three different dose cohorts with three subjects in each cohort and all three subjects received multiple doses of PMZ-1620 (only one subject was enrolled in cohort III). Subjects were dosed in

subsequent dose levels only after safety evaluation of subjects recruited in the previous dose level.

Cohort I - 0.3 µg/kg body weight.

Cohort II - 0.6 µg/kg body weight.

Cohort III - 0.9 µg/kg body weight.

PMZ-1620 was found to be well tolerated and safe when administered as multiple ascending doses in healthy male subjects. The dose of 0.9µg/kg was concluded as Minimum Intolerable Dose (MID). The MTD of PMZ-1620 determined was 0.6µg/kg (IV).

Now, firm has proposed to conduct a Phase II clinical trial entitled, "A Prospective, Multicentric, Randomized, Double Blind, Placebo Controlled Phase II Clinical Study to Compare the Safety and Efficacy of PMZ-1620 Therapy along with Standard Supportive Care in Subjects of mild to moderate Alzheimer's disease". The dose of PMZ-1620 for the Phase II clinical study is 0.3µg/kg.

This is a prospective, multicentric, randomized, double blind, placebo controlled Phase II clinical study to compare the safety and efficacy of PMZ-1620 therapy along with standard supportive care in subjects with mild to moderate AD. Assuming 80% power, 5% significance level with 95% confidence interval, standard deviation of 2.5 and considering 20% lost to follow-up, a total of 66 subjects (33 in each group) are required. To increase the power of the study, a total of 80 subjects (40 in each group) will be enrolled in this study.

The primary objective of the study is to evaluate the safety and tolerability of PMZ-1620.

Secondary objectives of the study are:

- To assess the effect of PMZ-1620 on clinical progression of Alzheimer's disease (AD) as measured by Mini-Mental State Examination (MMSE, a frequently used screening test for AD. It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two intersecting polygons).
- To assess the effect of PMZ-1620 on Neuropsychiatric Inventory (NPI) Score. The NPI uses a screening strategy to minimize administration time, examining and scoring only those behavioral domains with positive responses to screening questions. Both the frequency and the severity of each behavior are determined. Information for the NPI will be obtained from a caregiver familiar with the subject's behaviour.
- To assess the effect of PMZ-1620 on AD Assessment Scale-Cognitive Subscale (ADAS-Cog). It primarily measures language and memory.
- To assess the effect of PMZ-1620 on AD symptom progression of dementing process of hippocampal atrophy using magnetic resonance imaging (MRI) or computed tomography (CT) scan.

The enrolment period of the study will be approximately 12 months and total duration of the study will be approximately 18 months. For an individual subject, duration of the study will be 6 months (160 days), including 8 study visits: visit 1/Day 1 (screening/baseline visit), visit 2/Day 2-5 (treatment visit), visit 3/Day 30±3 (treatment visit), visit 4/Day 60±3 (treatment visit), visit 5/Day 90±3 (treatment and assessment visit),visit 6/Day 120±3 (treatment visit), visit 7/Day 150±3

(treatment visit)and final visit 8/End of study Day 157 to 160 (Follow-up visit). At visit 2, subjects will be randomized 1:1 into 2 treatment groups after meeting the eligibility criteria.

Group 1: PMZ-1620 + Standard of care.

Group 2: Placebo + Standard of care

After randomization, subjects will be administered with either PMZ-1620 or Placebo, once in a month for 6 months. Three doses of PMZ-1620/Placebo (each dose of 0.3 µg/kg body weight) will be administered as an IV bolus over one minute at an interval of 3±1 hours once in a month (total dose/day: 0.9 µg/kg body weight). Dose will be repeated every month for 6 months post randomization. In both treatment groups, subjects will be provided the best standard of care. Standard of care to be provided to the subjects shall be the one used in the particular hospital setup. Each subject will be monitored closely throughout his/her admission for the qualifying mild to moderate AD and will be followed for 6 months from randomization. Each subject will be assessed for efficacy and safety parameters over 6 months from randomization at a clinic visit.

Recommendation of the Committee: - The firm presented the Phase II clinical trial protocol. After detailed deliberation the Committee accepted the Phase I clinical trial report and recommended the conduct of Phase II clinical trial.

Sr. No. 6

Phase III clinical study report of FDC of Arterolane Maleate 37.5mg and Piperaquine Phosphate (PQP) 187.5mg Dispersible tablet for the treatment of acute uncomplicated *Plasmodium Vivax* malaria and *Plasmodium falciparum* of M/s Sun Pharmaceuticals Industries Limited.

This office has received an application from M/s Sun Pharmaceuticals Industries Limited India Private Limited for grant of manufacturing and marketing permission of permission FDC of Arterolane Maleate 37.5mg and Piperaquine Phosphate (PQP) 187.5mg dispersible tablets indicated for treatment of acute uncomplicated *Plasmodium falciparum* malaria and acute uncomplicated *Plasmodium vivax* malaria.

The FDC of Arterolane Maleate 150mg and Piperaquine Phosphate tablet 750mg was approved by CDSCO for the treatment of acute uncomplicated malaria infection due to *Plasmodium falciparum* in adult patients on 19.11.2011 and on for the treatment of acute uncomplicated malaria infection due to *Plasmodium vivax* in adult patients 14.10.2013.

Firm was granted permission to conduct Phase III clinical trial entitled, “A Phase III, open label, randomized, multicenter trial to assess the efficacy and safety of the dispersible Arterolane Maleate 37.5mg and Piperaquine Phosphate (PQP) 187.5mg tablet in comparison with Coartem dispersible in paediatrics patients with acute uncomplicated *Plasmodium falciparum* malaria” on 11.09.2013 and Phase III clinical trial entitled, “A Phase III, open label, randomized, multicenter, parallel group trial to assess the efficacy and safety of the Fixed Dose Combination of Arterolane Maleate 37.5mg and Piperaquine Phosphate (PQP) 187.5mg Dispersible tablet in comparison with Chloroquine Phosphate in paediatrics patients with acute uncomplicated *Plasmodium Vivax* malaria” on 08.05.2015.

Now, firm has submitted the reports of Phase III clinical trials.

Recommendation of the Committee:- The firm presented the Phase III clinical trial reports conducted on paediatric patients for the treatment of acute uncomplicated *Plasmodium Vivax* and *Plasmodium falciparum* malaria. After detailed deliberation the Committee recommended for manufacturing and marketing authorization subject to condition that the firm shall revise their prescribing information as per IND Committee suggestions like separate prescribing information for adults and paediatrics patients, disperse the tablets in two tea spoons drinking water, wait for complete dispersion and consume within defined minutes after dispersion. Further, being special product, patient information leaflet describing this process may also be provided by the firm. Adverse drug reaction and adverse events should be mentioned separately, results of post marketing surveillance should be mentioned on prescribing information.

Sr. No. 7

Phase IV clinical study report of FDC of Arterolane Maleate 150mg + Piperaquine Phosphate 750mg for treatment of acute uncomplicated malaria infection due to *Plasmodium vivax* of M/s Sun Pharmaceuticals Industries Limited.

M/s Ranbaxy Laboratories Limited (now Sun Pharma) was granted manufacturing and marketing permission of FDC of Arterolane Maleate 150mg + Piperaquine Phosphate 750mg for treatment of acute uncomplicated malaria infection due to *Plasmodium vivax* in adult on 14.10.2013 subject to condition that "Phase IV clinical trial with the drug is required to be conducted after getting protocol etc. approved by this office at study centres geographically distributed across the country".

Firm was granted permission to conduct Phase IV clinical trial entitled, "A Phase IV, non-comparative, open label, multicentric trial to evaluate the safety and efficacy of SYNRIAM® in the treatment of acute uncomplicated *Plasmodium vivax*" on 12.06.2015.

The primary objective of the study was to assess the safety and tolerability of SYNRIAM® in the treatment of acute uncomplicated *Plasmodium vivax* malaria. Secondary objective of the study was to assess the efficacy of SYNRIAM® in the treatment of acute uncomplicated *Plasmodium vivax* malaria.

This was a non-comparative, open label, multicentric, Phase IV study in subjects with acute uncomplicated *Plasmodium vivax* malaria. Primary objective of the study was to assess the safety and tolerability of SYNRIAM® in the treatment of acute uncomplicated *Plasmodium vivax* malaria and secondary objective of the study was to assess the efficacy of SYNRIAM® in the treatment of acute uncomplicated *Plasmodium vivax* malaria.

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

Recommendation of the Committee:- The firm presented the Phase IV clinical trial report. Firm conduct the Phase IV clinical trial on 399 patients. After detailed deliberation the Committee accepted the Phase IV clinical trial report & desired to reflect this in the prescribing information, as may be appropriate.

Sr. No. 8

Phase I clinical trial protocol amendment of K0706 of M/s Sun Pharma Advanced Research Company Limited.

This office received an application from M/s Sun Pharma Advanced Research Company Limited for the grant of permission to conduct Phase I clinical trial with K0706 entitled "A Phase I study to determine safety, tolerability, pharmacokinetics, and activity of K0706, a novel Tyrosine Kinase Inhibitor (TKI), in subjects with Chronic Myeloid Leukaemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)" and clinical trial permission was granted on 15.03.2017.

Now, has requested for protocol amendment and submitted revised clinical trial protocol entitled, "A Phase I study to determine safety, tolerability, pharmacokinetics, and activity of K0706, a novel Tyrosine Kinase Inhibitor (TKI), in subjects with Chronic Myeloid Leukaemia (CML) or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)" as per protocol no. CLR_15_03, version/Amendment – Version 07/ Amendment 09, Amendmet – 09 India specific dated 24.05.2017.

The primary objective is to determine the maximum tolerated dose (MTD; or recommended Phase 2 dose [RP2D]) of K0706 administered orally in subjects with the selected breakpoint cluster region-Abelson leukemia (BCR-ABL)-associated hematologic malignancies who have resistance or intolerance to the local Standard of Care CML therapy and to evaluate the safety of K0706 in subjects with BCR-ABL-associated hematologic malignancies listed in the entry criteria.

Secondary objective is to evaluate the therapeutic activity of K0706 and to evaluate the PK of K0706 after multiple oral doses in subjects with the selected BCR-ABL associated hematologic malignancies.

Exploratory objectives are to evaluate the pharmacodynamic (PD) activity of K0706 prior to and during exposure to K0706, including, but not limited to an analysis of phosphorylated CRKL, a downstream substrate of BCR-ABL, to evaluate the correlation of therapeutic activity of K0706 in the context of different BCR-ABL baseline ABL-kinase domain mutation profile and to evaluate the BCR-ABL mutation profile at disease progression for possible mechanisms of resistance.

Recommendation of the Committee:- The Committee deliberated the amended protocol with respect to increase in sample size, study design, eligibility criteria and decrease in cohort in details and recommended the conduct of Phase I clinical trial as per amended protocol.

Sr. No. 9

Phase I clinical trial protocol amendment of inactivated Zika virus vaccine of M/s Bharat Biotech International Limited.

M/s Bharat Biotech International Limited, Hyderabad was granted permission to conduct Phase I clinical trial entitled, "A phase I, multicenter, double-blind, placebo-controlled, randomize (Intra group) Clinical Trial to evaluate two doses of three sequentially escalating cohort of Inactivated Zika virus vaccine (BBV121) in healthy adult Dengue Sero-negative and Dengue Seropositive Volunteers" on 17.03.2017. [Protocol- BBIL/ZIKV/I/2016, version 1.0, dated 15.10.2016].

The objective of the said study is to evaluate the safety, tolerability and immunogenicity of two-doses of three-sequentially escalating cohort (2.5 µg, 5 µg and 10 µg) of BBV121 (purified inactivated Zika Virus Vaccine)compared with Placebo (Alum). The investigational product is administered intramuscularly on Day 0 and 28 with safety andimmunogenicity testing on Day 0, 28 and 56 and Month 6, 9 and 12.

Total 48 male and female volunteers aged between 19 and 65 years; 24 volunteers in Dengue Sero-Negative group and 24 volunteers in Dengue Sero-Positive group will be assigned to one of the three sequentially escalating cohorts in each group. Within each group, six volunteers will be randomized 3:1 to BBV121 and two volunteers will be randomized to receive Placebo for a specific dose.

Now, firm has requested for amendment in Phase I clinical trial protocol.

Recommendation of the Committee:- The Committee deliberated the amended protocol in details and recommended the conduct of Phase I clinical trial as per amended protocol.

Sr. No. 10

Phase I clinical trial protocol amendment of Chikungunya vaccine of M/s Bharat Biotech International Limited.

M/s Bharat Biotech International Limited, Hyderabad was granted permission to conduct Phase-I clinical trial entitled, “Phase I open Label Label, dose-escalation clinical trial to evaluate the safety, tolerability and immunogenicity of Chikungunya vaccine in healthy adults of 18 to 50 years age” on 13.07.2016.

The primary objective of the study is to assess the safety and tolerability of CHIKV vaccine in terms of adverse events (ex: fever, arthragia, myalgia) physical examination, vital signs and laboratory test including complete biochemical and haemoatological tests. Any serious adverse events will be recorded during the study period and secondary objective is to assess the immune response by the CHIKV vaccine in terms of CHIKV specific IgG or IgM antibodies, and CHIKV neutralizing antibodies by PRNT50.

Now, firm has requested for amendment in Phase I clinical trial protocol.

Recommendation of the Committee:- The Committee deliberated the amended protocol and recommended that since the firm has not submitted the amendments to Ethics Committee (EC) for relaxing the condition of stay of 48 hours in MICU, which is related more with patient safety, it shall first get its proposal (with justification) evaluated & approved from Ethics Committee.

The meeting ended with vote of thanks by the Chair

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