Committee meeting held on 10.10.2019 at ICMR (HQ), V. Ramalingaswami Bhawan, Ansari Nagar, New Delhi.

List of Participants:

1. Prof. Balram Bhargava, Secretary, Department of Health Research & Director General, Chairman, IND Committee.
2. Dr. Y. K. Gupta, Ex. Dean, AIIMS, New Delhi.
3. Dr. Nilima Kshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
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.
7. Dr. A. K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.

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, Drugs Controller General (India).
2. Dr. S. Eswara Reddy, Joint Drugs Controller (India).
3. Mr. A. K. Pradhan, Deputy Drugs Controller (India), CDSCO (HQ).
4. Mr. R. Chandrasekhar, 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.

Prof. Balram Bhargava, Secretary, DHR and DG ICMR, Chairman of the Committee welcomed the members and informed the committee that since he has to attend another important meeting, in his absence Dr. Y. K Gupta, and Dr. Nilima Kshirsagar would Chair the meeting. Thereafter, the agenda items were discussed one by one.

Sr. No. 01

Phase I clinical trial with Bivalent Malaria Vaccine

It is related to an application for permission to conduct a "A Phase- I, randomized, controlled, dose escalating, single blind, clinical trial to assess the safety, tolerability and immunogenicity of Bivalent (JAIVAC-2: PfMSPFu24 + PfF2 /Alhydrogel) and Monovalent (PfMSPFu24 / Alhydrogel) *P. Falciparum* malaria vaccines in malaria naïve healthy Indian adult males (total 60 subjects)" [Protocol No: MVDP/Falciparum/1/17/01, Version No. 01; Date: 07 Dec 2017].

The proposal was examined in IND Committee meeting held on 15.03.2019 at ICMR, New Delhi. The firm presented their proposal along with Phase I clinical trial protocol for Monovalent and Bivalent malaria vaccines. After detailed deliberation the committee recommended that:

1. The applicant should submit two separate proposals for each of the monovalent and bivalent vaccines.
2. CDSCO should conduct inspection at the clinical trial site at M/s Syngene, Bangalore to verify the facilities available at the site for conduct of such clinical trial.
3. In the study, the IP should be administered one dose at a time and confirmed the safety before proceeding to the next higher dose.
4. The toxicity data generated is also required to be reviewed further by the committee members.

As per the recommendation of IND Committee, CDSCO has conducted the GCP inspection on 17.07.2019 at the clinical trial site of Human Pharmacology Unit (HPU), Syngene International Limited, Clinical Development Tower 1, Semicon Park Electric City Phase II Bangalore. The inspection team opined that M/s Human Pharmacology Unit (HPU), Syngene International Limited, Bangalore has adequate facilities for the conduct of said Clinical trial.

Further, the firm has submitted the revised protocol for Bivalent *P. Falciparum* malaria vaccine titled "*A Phase I, randomized, controlled, dose escalating, single blind, clinical trial to assess the safety, tolerability and immunogenicity of Bivalent (JAIVAC-2: PfMSPFu24 + PfF2/Alhydrogel) P. falciparum malaria vaccine in malaria naïve healthy Indian adult males*" vide protocol no.: MVDP/Falciparum/1/17/01, Version No. 02; Dated 22.04.2019. and toxicity data for review of IND committee experts.

As per the proposal submitted by the applicant:

Investigational vaccine: Bivalent *P. falciparum* malaria vaccine: PfMSPFu24 (a chimera of PfMSP-119 and PfMSP-311) and PfF2 manufactured by M/s Cadila Healthcare, Ahmedabad.

Control vaccine: Hepatitis-B vaccine [20 µg/mL per dose will be administered on Visit 1/ Day 0, Visit 5/ Day 28 and Visit 9/ Day 56] (M/s Serum Institute of India Pvt. Ltd, Pune)

Dose and immunization schedule:

- Cohort 1: Dose 30 µg of Bivalent P. falciparum malaria vaccine
- Cohort 2: Dose 45 µg of Bivalent P. falciparum malaria vaccine
- Cohort 3: Dose 75 µg of Bivalent P. falciparum malaria vaccine.

Subjects in each cohort will be administered 3 immunizations of the investigational vaccine on Visit 1/ Day 0, Visit 5/ Day 28 and Visit 9/ Day 56.

Study Regimen: Each subject in the cohort will receive three immunizations of the pre-defined dose of the assigned investigational (Test) vaccine or the control vaccine by intramuscular route in deltoid muscle on Visit 1/ Day 0, Visit 5/ Day 28 and Visit 9/ Day 56.

- Follow up duration shall be about 180 days (06 months) after the administration of third immunization in each subject.

Primary Objective(s): To evaluate the safety and tolerability of Bivalent P. Falciparum malaria vaccines in malaria naïve healthy adult Indian male subjects, **18 to 45** years of age.

Secondary Objective(s):

- To assess the humoral response of Bivalent P. falciparum malaria vaccines by measuring the IgG antibody response to antigens $PfMSP1_{19}$, $PfMSP3_{11}$and PfF2 by Enzyme Linked Immunosorbent Assay (ELISA) in healthy Indian male subjects, 18 to 45 years of age.
- To assess the humoral response of Bivalent P. falciparummalaria vaccines by measuring antibody response by Immunofluorescence (IFA) in healthy Indian male subjects, 18 to 45 years of age

Clinical trial Site & Investigator: Dr. Anil K, MBBS, MD (Internal Medicine),Human Pharmacology Unit Syngene International Limited Tower 1,Ground Floor, Semicon Park Electronics City Phase 2, Bangalore -560100, India.

Inclusion Criteria:

1. Male subject 18 to 45 years of age at informed consent(both years inclusive).
2. Willing and having the capacity to provide voluntary free informed consent for participation evidenced by signing of the IEC approved informed consent document.
3. Subject is in good general health and is free from clinically significant health problems as determined by medical history, physical examination

including vital parameters and clinical laboratory evaluations that include hematology, chemistry, urinalysis and serology.

4. Willing to be available for the duration of the study with no plans to travel outside the study area, reachable by phone.
5. Capable and willing to complete and return diary cards.
6. Able to participate during the whole study period and to attend all follow-up visits.
7. Willing to undergo HIV test
8. Must agree to use one of the following medically-acceptable birth control measures throughout the duration of the study (birth control counselling and measures will be provided by clinical trial site as required

   -Double barrier method (e.g. condom with spermicidal jelly)

   -Subjects must be surgically sterile (undergone vasectomy)
9. Willing to take intramuscular injection

Exclusion Criteria:

1. Any past history of malaria
2. Simultaneous participation in any other intervention clinical Trial.
3. Subject with evidence of IgG antibodies against vaccine antigens, PfMSP119, PfMSP311and PfF2as measured by ELISA
4. Has prior history of immunisation with Hepatitis B vaccine.
5. Previous history of receipt of any other malaria vaccine.
6. HbA1c value reported > 6% at screening visit.
7. History of allergic reactions, hypersensitivity oranaphylaxis to immunizations, to any of the components of the study vaccines (including adjuvant or peptide) or of serious allergic reactions that required hospitalisation or emergency medical care.
8. Use of an investigational or non registered drug or vaccine within ninety (90) days prior to enrolment or expects to receive such an agent during the study period.
9. Clinical or laboratory evidence of significant systemic disease, including hepatic, renal, cardiac, immunologic or hematological disease, HIV positive

or have any other known immunodeficiency Have a history of autoimmune disease (including inflammatory bowel disease, haemolytic anaemia, autoimmune hepatitis, rheumatoid arthritis, lupus, etc.) or connective tissue disease or have any other serious underlying medical condition. Includes the conditions and diagnoses defined as AESI (Adverse Events of Special Interest) in Section.

10. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune modifying drugs or cytotoxic therapies (chemotherapy or radiotherapy) within six months prior to the first Immunization. This includes any dose level of oral steroids or inhaled steroids, but not topical steroids.
11. Received a blood transfusion within the past 3 months.
12. History of splenectomy
13. Subject has clinically significant laboratory abnormalities, which will include haematology, biochemistry, urinalysis, at the time of screening as determined by the Investigator.
14. Clinical or laboratory presence of Hepatitis B, C or HIV infection or Syphilis
15. Subject with an abnormal 12 lead ECG at screening associated with relevant clinical symptoms/signs suggestive of cardiac pathology.
16. Subject with an abnormal Chest X Ray associated with relevant clinical symptoms/signs of respiratory pathology at screening/ anytime in the past 6 months
17. Subject gives a history of social, occupational and/ or family problems due to illicit alcohol or drug abuse (to be determined by Urine Drug Screen) within the past 12 months.
18. Has any other condition that, in the opinion of the Principal Investigator, may jeopardise the safety and rights of the volunteer, may interfere with the capacity to provide free and willing informed consent or render the subject unable to comply with the requirements of the study protocol.

Primary Endpoints:

The safety and tolerability profile will be assessed on the basis of the following criteria:

1. Immediate reactogenicity (any event occurring within one (1) hour after each vaccination, with emphasis on allergic reactions)

2. Local and systemic solicited adverse events(any event occurring from one (1) hour post vaccination on Day 0 till Day 07 after each dose)
3. Any unsolicited adverse event upto 28 days after each vaccination
4. Any Serious Adverse Event (SAE) occurring post signing of ICD till the last follow-up visit.
5. Laboratory safety, 7days after each vaccination, in reference with the baseline before the first dose, and also at six months (Day 180) post first immunisation, by measuring the following :
6. Haematology: Complete Blood counts including Differential Blood counts and Platelet counts
7. Serum Chemistry: Potassium, Sodium, AST, ALT, direct, indirect and total bilirubin, alkaline phosphatase, Total serum protein with A/G ratio, creatinine and random blood glucose
8. Urinalysis: The Investigator will be responsible for causality assessment i.e. assessment of the relationship of the AE to either of the assigned study vaccines, using the following definitions: Related or Not related.

Secondary Endpoints:

1. The humoral response to the candidate vaccine antigens will be assessed (quantitative assessment) by measuring the level of IgG antibodies developed against PfMSP119, PfMSP11 and PfF2 by ELISA on Visit 1/ Day 0, Visit 9/Day 56, Visit 13/ Day 84 and Visit 14/Day 180.
2. The humoral response to the candidate vaccine antigen will be assessed qualitatively to verify the ability of the IgG antibodies developed against PfMSP119, PfMSP311and PfF2 to recognise the native protein on late stage P. Falciparum schizonts and merozoites in vitro by Immuno fluorescence Assay (IFA) on Visit 1/ Day 0, Visit 13/ Day 84, Visit 14/Day 180.

Exploratory Outcomes:

1. The quality of the humoral immune response will be assessed by measuring IgG1, IgG2, IgG3, IgG4 subclasses by ELISA on samples obtained at Visit 1/ Day 0 and Visit 13/ Day 84.

2. The ability of the IgG antibodies to block homologous and heterologous parasite growth in vitro by a *P. Falciparum* blood-stage Growth Inhibition Assay (GIA) against falciparum parasite on samples obtained at Visit 1/ Day 0, and Visit 13/ Day 84.

3. Any Adverse Event of Special interest (AESI) occurring from the first dose of vaccine till the last follow-up visit.

Applicant has submitted the following Animal Toxicity studies:-

Acute Toxicity Studies:

1. Single Dose Toxicity Study of Monovalent (PfMSPFu24/ Alhydrogel) and Bivalent (PfMSPFu24 PfF21 Alhydrogel) P. falciparum Malaria Vaccine through Intramuscular Administration in CD-I Mice.

2. Single Dose Toxicity Study of Monovalent (PfMSPFu241 Alhydrogel) and Bivalent (PfMSPFu24 + PfF21 Alhydrogel) P. falciparum Malaria Vaccine through Intramuscular Administration in Wistar Rats.

3. Single Dose Toxicity Study of Monovalent (PfMSPFu241 Alhydrogel) and Bivalent (PfMSPFu24 -I- PfF'2/ Alhydrogel) P. falciparum Malaria Vaccine through Subcutaneous Administration in CD-I Mice.

Repeat dose Intramuscular Toxicity Studies:

4. Repeated Dose Toxicity Study of Monovalent (PfMSPFu241 Alhydrogel) and Bivalent (PfMSPFu24 + PfF21 Alhydrogel) P. falciparum Malaria Vaccine through Intramuscular Administration in Wistar Rats with Two Weeks of Recovery Period

5. Repeated Dose Toxicity Study of Monovalent (PfMSPFu241 Alhydrogel)) and Bivalent (PfMSPFu24 + PfF21 /Alhydrogel) P. falciparum Malaria Vaccine through Intramuscular Administration in New Zealand White Rabbits with Two Weeks of Recovery Period.

Preclinical Immunogenicity studies were performed in mice, rats and rabbits to assess immunogenic potential of Monovalent and Bivalent malaria vaccines. The immunogenicity data in the small animals had shown that combination of PfMSPFu24+PfF2 formulated with Freund's adjuvant as well as other human compatible adjuvants induced high titer antibodies compared to PfMSPFu24 alone. However, antibodies purified from immune rabbit sera of Bivalent vaccine (PfMSPFu24+PfF2) or the Monovalent malaria vaccine (PfMSP-Fu24) and tested in growth inhibition assays (GIA) did not shown any significant differences. Preclinical Immunogenicity studies were performed to down-select the adjuvant for further preclinical and clinical development. Various adjuvants tested in the pre-clinical

immunogenicity studies were: Alhydrogel, GLA-AF (aqueous formulation), GLA-SE (stable emulsion formulation), and Alhydrogel + GLA-Aqueous formulation (Alhydrogel + GLA-Aq).Of the various adjuvants tested with Monovalent and Bivalent malaria vaccine candidates, Alhydrogel was down selected because of good in-vitro growth inhibition and availability of safety data in healthy Humans. Therefore, the final product of Bivalent malaria vaccine will consist of a physical mixture of PfMSPFu24+ PfF2/ Alhydrogel while Monovalent malaria vaccine will only contain PfMSPFu24/ Alhydrogel. When administered to humans, PfMSPFu24/ Alhydrogel alone or as combination of PfF2+PfMSPFu24/ Alhydrogel are expected to elicit antibodies that will block the erythrocyte invasion by P. falciparum. Taking lead from the Phase Ia clinical trial of JAIVAC-1 (PfMSP119+ PfF2 formulated with Montanide ISA720) in healthy adult male volunteers 30, 45and 75 µgof Bivalent and 75 µg of Monovalent P. falciparummalaria vaccines with Alhydrogel adjuvant have been chosen for this phase I clinical trial. •The pre-clinical toxicology studies have been performed under GLP at Jai Research Foundation, Valsad, Gujaratin compliance with Schedule Y and WHO guidelines.

Monovalent (PfMSPFu24/Alhydrogel) and Bivalent (PfMSPFu24+PfF2/Alhydrogel) malaria vaccines were tested in acute toxicity studies conducted in CD1 **Mice** and **Wistar rats**. Intramuscular route of vaccine administration were evaluated in mice and rats whereas subcutaneous route of vaccine administration was evaluated in mice. In mice the dose level evaluated was more than 1000X of maximum proposed human dose (1.25µg/kg) on body weight basis, where as dose level equivalent to approximately 192X of intended maximum dose in humans was evaluated in Wistar rats. Both the vaccines were well tolerated and no systemic toxicity was observed in either species by intramuscular route and in CD1 mice by subcutaneous administration. All animals were observed to be normal throughout the experimental period. There was treatment related nodule formation at the injection site observed in all acute toxicity studies. It was attributed to physiological response to Alhydrogel (adjuvant) administration and hence not considered as a toxic effect of vaccine administration.

Repeat dose intramuscular toxicity studies were conducted in **Wistar rats** and **New Zealand White rabbits**. Monovalent (PfMSPFu24/Alhydrogel) and Bivalent (PfMSPFu24+PfF2/Alhydrogel) malaria vaccines were administered repeatedly on days 1, 15, 29 and 43 with a recovery period of 14 days. Thus a total of four doses were administered in repeat dose studies as against maximum of three human doses proposed in this phase I clinical trial. The test vaccines were tested at two dose levels: low and high in NZW Rabbits equivalent to 30X and 60X of the intended maximum human dose (1.25 µg/kg) on body weight basis. Similarly in Wistar rats the low and high dose levels were equivalent to 96X and 192X of the intended maximum proposed human dose (1.25µg/kg) on body weight basis. Both Monovalent and Bivalent P.falciparum malaria vaccines were well tolerated with no mortality observed in rats and rabbits when administered through intramuscular route. Both vaccines did not reveal any indication of systemic toxicity upto thehighest dose level on repeated administration in Wistar rats (equivalent to approximately

192X of the intended maximum proposed human dose (1.25 µg/kg) on body weight basis) and NZW Rabbits (equivalent to approximately 60X of the intended maximum proposed human dose (1.25 µ g/kg) on body weight basis).

There was a treatment related nodule formation at injection site that was attributed to physiological response to adjuvant and hence not a toxic effect of the vaccine. On microscopic examination the inflammatory changes were localised to injection site. They were reduced in intensity and severity in recovery groups in rabbits and thus, considered reversible. Significant PfMSPFu24 and PfF 2 specific antibody responses were induced by repeated immunizations as evaluated by ELISA in both rats and rabbits.

The applicant has proposed for Phase I clinical trial with the bivalent vaccine only which will be conducted in 03 Cohort with Dose of 30 µg, 45 µg, 75 µg. It was presented that they have obtained *P. Falciparum* malaria strain from ATCC and used for development of the vaccine. Immunogenicity and toxicity studies have been carried out in 03 species namely mice, rats and rabbits along with the adjuvant toxicity studies. With regard to the animal challenge model for efficacy testing, the applicant presented that they have performed in-vitro Growth Inhibition Assay (GIA) test for efficacy evaluation and submitted various publications in its support.

Recommendation:- After detailed deliberation, the Committee recommended for grant of permission to conduct the Phase I clinical trial of the bivalent malaria vaccine subject to condition that the applicant should submit published documents/ guidelines as an evidence to indicate that Phase I clinical trial of such vaccine has been conducted based on consideration of efficacy from in-vitro Growth Inhibition Assay (GIA) study with no requirement of animal challenge test data.

Sr. No. 02

Manufacturing and marketing permission of Diperoxochloric Acid Concentrate Topical Solution 1.16mg/ml.

It is related to an application for grant of permission to import Diperoxochloric Acid Concentrate bulk drug substance & manufacture of 7.5 ml of the concentrate solution per bottle with 22.5 ml Saline (0.9 %w/v) indicated for wound healing in diabetic neuropathic ulcers of skin and subcutaneous tissues on 26.12.2013. Subsequently on 07.01.2017, firm applied in Form 44 for grant of permission to manufacture the DPOCL bulk drug in India at Plot 75, 76 & 76/1, Chikhloli MIDC, Ambernath, Thane (West), Mumbai – 421501, India which is WHO-GMP & US FDA approved facility.

The firm has already conducted Phase II and III clinical trial in India based on the recommendations of IND Committee.

The application of the firm for grant of New Drug permission alongwith the data submitted by the firm including Phase II and Phase III clinical reports generated in Indian patients was deliberated by the IND committee in its meeting held on 30.05.2014 and 06.08.2015.

IND Committee in its meeting dated 30.05.2014 recommended for the grant of permission for the import and marketing of Diperoxochloric acid (DPOCL) along with sterile sodium chloride solution BP 0.9% w/v (Cutaneous solution) in the country to be indicated for wound healing in diabetic neurophathic ulcers of skin and subsutaneous tissues subject to the condition that following was required to be submitted to the DCGI before the grant of approval.

- Long term stability data of drug substance and formulation as per Appendix IX of Schedule Y.
- Stability testing of formulation after constitution or dilution as per Appendix IX of Schedule Y.

Subsequently, the data / information submitted by the firm as per recommendation of IND Committee dated 30.05.2014 was deliberated by IND Committee in its meeting held on 06.08.2015. The Committee was already informed that the drug is not yet approved in the exporting country i.e. Germany.

After detailed deliberation, the Committee recommended for grant of permission to the Investigational New Drug DPOCL for import of bulk and filling of formulation in India on submission of revised package insert and details of stability studies of the bulk drug subject to submission of revised package insert with various correction in respect of contraindication, drug interaction, overdosage and storage condition etc., as recommended by the Committee.

Accordingly, the firm submitted various data / information as requested / recommended by the IND Committee alongwith revised prescribing information.

On 01.12.2016, the firm has informed that they are going to manufacture the DPOCL bulk drug in India at Plot 75, 76 & 76/1, Chikhloli MIDC, Ambernath, Thane (West), Mumbai – 421501, India which is WHO-GMP & US FDA approved facility. In this regard, they have obtained Test License in Form 29 from Food & Drugs Administration.

Firm informed that based upon Test license, they have taken couple of trials under the supervision of the patent holder - Dr. Dirk Kaiser & Dr. Pavlo Kos (Dermatools scientist) and confirm the feasibility of manufacturing commercial requirements of Diperoxochloric acid concentratein India itself than to import. They have also entered into an agreement with Dermatools for Technology transfer of manufacturing Diperoxochloric acid concentrate.

Firm have manufactured three commercial scale batches of Batch size (1.06 Kg, 1.274Kg and 1.028Kg) of Bulk Drug Diperoxochloric acid concentrate under the supervision of Dr.

Dirk Kaiser & Dr. Pavlo Kos (Dermatools scientist) at Ambernath manufacturing facility at Plot 75, 76 & 76/1, Chikhloli MIDC, Ambernath, Thane (West), Mumbai – 421501, India.

Firm informed that the route of synthesis at Ambernath facility followed for manufacturing Bulk Drug Diperoxochloric acid concentrate is identical to route of synthesis followed for manufacturing Bulk Drug Diperoxochloric acid concentrate at Dermatools. The quality of finished Bulk drug Diperoxochloric acid concentrate manufactured at Ambernath facility is equivalent to quality of Finished Bulk Drug Diperoxochloric acid concentrate manufactured at Dermatools.

Firm was asked to submit comparative evaluation of the formulation manufactured with indigenous bulk drug vis-a-vis the formulation with imported bulk drug used in clinical development of the drug vide letter dated 01.10.2018.

Firm submitted the comparative evaluation of formulation manufactured with indigenous bulk drug vis-a-vis the formulation with imported bulk drug used in clinical development of the drug on 26.10.2018 and IPC testing report of indigenous manufactured bulk drug and formulation manufactured with indigenous bulk drug on 14.02.2019. The referred sample was found to be of standard quality as per the manufacturer's specification.

Meeting was conducted with the firm at CDSCO (HQ), & further as per the decision inspection at manufacturing site of API & Finished Formulation & four Clinical Trials inspection sites for compliance of GMP & GCP as per the provisions of Drugs & Cosmetics Rules 1945 have been carried out.

Recommendation:- The firm presented their proposal with comparative evaluation data of their product with the imported product. The Committee, after detailed deliberation, recommended for grant of permission to manufacture and market Diperoxochloric Acid Concentrate bulk drug substance & Diperoxochloric Acid Concentrate topical solution indicated for wound healing in diabetic neuropathic ulcers of skin and subcutaneous tissue with the following conditions:

1. The firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.
2. Proposed Package Insert, Label, Carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.

Sr. No. 03

Marketing authorization of RISUG Injection - A male contraceptive.

This is with reference to application on male contraceptive - RISUG.

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.

The proposal was deliberated in IND Committee meeting dated 29.08.2018. 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 proposal was again deliberated in IND Committee meeting dated 08.10.2018. The applicant presented their view points/ proposed action on scrotal swelling, psychological behavioural aspects, sexual activity, reversibility, and acceptability etc. alongwith CMC data. After detailed deliberation the Committee recommended that the applicant should address following points before recommending for approval of the product:-

1. Claim for the product should be in consonance with the fact that:-
    a) Study for reversibility has not been carried out in human and hence not established. However, reversibility study has been conducted in monkey and has been found to be favourable.
    b) Azoospermia has been observed for 5 years in Phase III clinical trial.
    c) Need for scrotal support due to reported scrotal swelling after administration of the product,
2. Possibility/ feasibility of assessing reversibility through biopsy/FNAC evaluation or other evidences of tissue disruption in 30 subjects who were involved in the Phase III clinical trial should be explored specially in respect of ethical aspects including Informed Consent.
3. For CMC data, GMP status etc. for commercialization of the product the applicant should co-ordinate with CDSCO and submit the data as per the requirements.

The applicant had submitted the following clarifications:-

1. RISUG is at present being positioned as a single intervention long acting male contraceptive delivery which does not involve cutting and removal of any part of the vas deferens. Therefore, it is claimed that it is an improvement over Vasectomy and

No Scalpel Vasectomy and is less traumatic to the user while retaining the single intervention long term effectiveness character.

2. Considering the overall clinical study (Phase-I, II, Restricted Phase III and Extended Phase III) data it is stated that long term "functional" azzospermia (that is Azzospermia as per definition given in STEDMAN Medical Dictionary) is obtained following a one-time injection of Risug. Unlike vasectomy and NSV which completely removes the path of sperms from the testes to the ejaculatory duct Risug injection partially blocks the vas deferens. Study of Risug injected subjects indicate that Prostate and Accessory sex glands are protect.
3. Scrotal suspensory sling is routinely provided to Risug injected subjects for temporary use in weeks following Risug injection.
4. Studies on the rat and monkey have shown that RISUG injection has localized effect mainly on the vas deferens, Sperm production continues in the testes following RISUG injection into vas deferens. Detailed evaluation of Semen of randomly selected 25 subjects in the ICMR sponsored Restricted Phase-III clinical trial indicates that in human males injected with Risug spermatogenesis continues in the testes. Since Risug injection is partially obstructive, germ cells which are precursors of sperms are present in the semen. Further occasionally full sperms but with altered morphology are also present in the semen. Chemical secretions from the testes and epididymis are also present in the semen indicating that there is a patent pathway from the testes to the ejaculatory duct (Chaki, S. P.; Das, H. C. and Misro, M. M. 2003) "A short term evaluation of semen and accessory sex gland function in Phase III trial subjects receiving intravasal contraceptive Risug" Contraception 67(1): 73-78).

Further in few subjects who received less Risug into the vas deferens that the therapeutic dose either into the vas deferens than the therapeutic dose either as per study plan or on account of delivery problems mainly involving the Risug syringe it has been observed that after a period of azzospermis there is autonomous reversal with sperms appearing in the semen. This observation too implies that sperm production continues in the testes after Risug injection into the vas deferens.

Nevertheless, Risug injection subjects of the LNJP Hospital, New Delhi and Dyanand Medical College, Ludhiana are being contacted to ascertain they would agree to a testicular biopsy/ FNAC for detailed examination of the tissue and thereby get to know the exact status of spermatogenesis in the testes. If some volunteers agree then project application will be submitted for Ethical Clearance and thereafter with all permissions in hand the procedure will be conducted.

Applicant has also informed that a comprehensive clinical reversibility study protocol of Risug injection in the human has been prepared by ICMR and will be submitted to DCGI for necessary permission to conduct the study.

Subsequently, the matter was discussed in the IND committee held 15.03.2019 and the committee recommended that, the applicant should submit the progress report on feasibility of the assessing reversibility through Biopsy/ FNAC evaluation and preparation for clinical reversibility study.

In the meantime, the sample of the product was tested in IPC, Ghaziabad, However the sample did not comply with respect to the pH and impurities "free DSMO" . The firm has however , submitted detailed clarification in response to the test results of IPC that, the pH of a material like RISUG is undefined. There is no way to measure pH of RISUG in its native form. Until some new science defining pH for a material like RISUG comes there will remain doubts if pH is taken as a parameter. Therefore, the firm has suggested that pH be removed from the list of parameters considered in respect of RISUG.

Firm also submitted clarification regarding impurities that, "Free DMSO" cannot be quantified by any of known methods and free DMSO was not a parameter listed under impurities in earlier documentation submitted to the DCGI, the firm has requested that Free DMSO be removed from the listing of impurities.

Further, IPC has clarified that, they have analyzed the sample as per the test specification provided by the firm . As per IP 2018 (Vol. I) Chapter 5.4 for Residual solvent DMSO is class 3 solvent and concentration above 5000 ppm is toxic.

The Committee may deliberate the proposal and give its recommendations about safety & efficacy of the product and whether based on the data submitted permission to manufacture & market

The firm presented their proposal for marketing authorization of RISUG Injection clarifying various points in light of the recommendations made by the Committee in its earlier meetings along with clarification/ justification on the issue of presence of "Free DMSO" as impurity and "Ph" in light of the analytical test report of IPC, Ghaziabad.

Recommendation: - After detailed deliberation, the Committee recommended for grant of permission to manufacture and market the product subject to fulfillment of following conditions:-

1. The firm should conduct a Phase IV reversibility study for which protocol should be submitted before launching the product in the market.
2. While marketing the drug, post marketing reports on adverse effects specifically in respect of scrotal swelling should be captured and analysed considering need of scrotal support, time taken for its reversibility, need of anti-inflammatory agents, etc.
3. In light of the analytical test report of IPC, Ghaziabad, specification and detailed method of analysis of the drug with justification especially in respect of tests for "Free DMSO" and "pH" should be submitted

2. While marketing the drug, post marketing reports on adverse effects specifically in respect of scrotal swelling should be captured and analysed considering need of scrotal support, time taken for its reversibility, need of anti-inflammatory agents, etc.
3. In light of the analytical test report of IPC, Ghaziabad, specification and detailed method of analysis of the drug with justification especially in respect of tests for "Free DMSO" and "pH" should be submitted
4. Inspection should be carried out to verify GMP at the manufacturing facility of M/s IcubetG Ideas Pvt. Ltd. at IIT, Kharagpur.

Sr. No. 04

Marketing authorization of Saroglitazar tablets 2mg and 4mg.

It is related to an application for grant of permission to manufacture and market Saroglitazar tablets 2mg and 4mg (Additional indication).

Additional Indication: Type 2 Diabetes Mellitus -as an add-on therapy to Metformin.

CDSCO approval status:-

Drug Name	Strength	Indication	Date of approval
Saroglitazar 2mg/4mg Tablets	Each uncoated tablet contains; Saroglitazar 2mg, 4mg.	For the treatment of diabetic dyslipidemia and hypertriglyceridemia with type-2 diabetes mellitus not controlled by statin therapy.	25.02.13 to M/s Cadila healthcare Ltd.

CDSCO had granted permission dated January 09, 2015 (F. No. 12-05/05-DC (Pt-C) to conduct Phase III clinical trial entitled "A multi-centric, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2mg and 4mg as compared to Pioglitazone in Type 2 Diabetes Mellitus",

Protocol No.: SAR0.14.002.01.01. PROT, version No. 1.1, dated December 12, 2014.

Firm stated that they have completed the above mentioned Phase-III study as per approved protocol (Protocol No.: SAR0.14.002.0l.0l.PROT, version No. 1.1). This phase III study was planned to evaluate the efficacy and safety of Saroglitazar 2mg and 4mg as compared to Pioglitazone 30 mg in type 2 diabetes mellitus.

Results of the present study showed that statistically significant reduction from baseline in each treatment group (Saroglitazar 2mg group, Saroglitazar 4mg group and Pioglitazone 30 mg group) at Week 24 (p-value <0.016) when administered along with metformin. The within group mean(± SD) change in HbA1c (%)from baseline of the Saroglitazar (2mg and 4 mg)

and Pioglitazone 30mg treatment groups at week 24were: -1.38 ± 1.99 for Saroglitazar 2mg; 1.4 7 ± 1.92 for Saroglitazar 4mg and -1.41± 1.86 for Pioglitazone 30 mg, respectively

Overall, the treatment with Saroglitazar 2mg and 4mg improved glycemic control over 56 weeks in patients oftype II Diabetes mellitus receiving background Metformin therapy. Both the strengths of Saroglitazar met the primary objective of the study and led to a clinically meaningful reduction of HbA1c levels. This reduction which was evident by week 12 was consistently sustained through week 24 till week 56. Saroglitazar was well tolerated by the patients. Most of the adverse events were mild to moderate in severity and were resolved. There were no safety concerns with the laboratory evaluations.

Now, firm submitted application for approval of new indication as **Type 2 Diabetes Mellitus- as an add-on therapy to Metformin** by taking into consideration the results of Saroglitazar in this study wherein it has beneficial effects on the glycemic parameters and diabetic dyslipidemia, and without safety concerns.

Firm also submitted Therapeutic Rationale and Justification for the Proposed Additional Indication

Thiazolidinedione drugs are widely used to lower blood glucose levels in subjects with type 2 diabetes mellitus. In the United States, three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity; rosiglitazone (Avandia, GlaxoSmithKline), which recently received black-box warning from Food and Drug Administration (FDA) for its adverse effects on heart and the currently available Pioglitazone (Actos, Takeda).Thiazolidinediones act as agonists for PPAR-γ receptors, receptors which are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues. Similarly, fibric acid analogs, known to be PPAR-α agonists, are in clinical practice for lowering lipids in hyperlipidemic subjects albeit not very effectively. On the other hand, statin class of compounds is the most successful therapeutic agent for the management of dyslipidemia and hypercholesteremia. However, no single therapy is able to reach desirable clinical endpoint for Syndrome X.Several research groups have or are attempting to develop dual PPARα/γ agonist, some whichmay eventually reach desirable clinical efficacy and safety endpoint. But if the agonist has higher PPARγ binding properties then several of the side effects such as edema, weight gain, bone effect and cardiovascular complication may occur. Therefore, there has been an increasing interest to develop new molecular entities, which can treatinsulin resistance, lower plasma glucose in diabetic subject, improve lipid profile without weight gain and cardiovascular risk. New chemical entity having a superior PPAR-α agonist activity with a moderate PPAR-γ agonist activity is developed; it might have desirable clinical profile with having no edema or weight gain effects. Based on this assumption, Saroglitazar (LipaglynTM; Code:ZYH1) having a preferential PPARα agonist property with a moderate PPARγ agonist activity has been developed by Cadila Healthcare Limited (CHL).Thus, Saroglitazar belongs to a new class of NME having predominantly PPAR α agonist activity.

lower plasma glucose in diabetic subject, improve lipid profile without weight gain and cardiovascular risk.

New chemical entity having a superior PPAR-α agonist activity with a moderate PPAR-γ agonist activity is developed, it might have desirable clinical profile with having no edema or weight gain effects. Based on this assumption, Saroglitazar(LipaglynTM; Code:ZYH1) having a preferential PPAR α agonist property with a moderate PPARγ agonist activity has been developed by Cadila Healthcare Limited (CHL).Thus, Saroglitazar belongs to a new class of NME having predominantly PPAR α agonist activity.

Recommendation:- The firm presented their proposal along with Phase III clinical study report. The Committee noted that the drug is already approved for diabetic dyslipidemia and hence, this proposal should be deliberated in the next meeting in presence of Cardiologists and Diabetologists. The firm should also present details in respect of dosage, recommendation, precautions, warning etc for the drug.

Sr. No. 05

Marketing authorization of Recombinant Rabies G protein Vaccine

It is related to an application for grant of permission to manufacture and market "Recombinant Rabies G protein Vaccine". The proposal was examined in the IND committee meeting held on 10.06.2019 at ICMR, New Delhi. The firm presented their proposal along with Phase III clinical trial report for "Recombinant Rabies G protein Vaccine".

The committee observed that there are many discrepancies in the clinical trial and the results presented were not on accordance with GCP. Therefore, the committee recommended that the firm should submit actual results of the clinical trials with proper interpretation including details of number of subjects screened, randomized, drop out/lost to follow up, details of number of samples analyzed etc. along with the raw data of the Phase III clinical trial.

As per the recommendation of IND Committee, the firm has submitted the following data:

S. No.	IND recommendations	Response by Firm	Review by CDSCO
1	Details of number of subjects screened, randomized, dropped/lost to follow up	Firm has submitted the details as below: ❖ 1023 subjects were screened. ❖ 800 subjects were randomized (Test: 533 & R: 267 ❖ At Day 7: Sample :796 (T:531 &	1. In the subject disposition data, it has mentioned that 08 subjects were unsatisfactory; however, in the efficacy result, it has mentioned that, 07 subjects were unsatisfactory and as per raw data submitted by

		R:265) ❖ **At Day 14**: • Total sample analyzed (Test :526 & R: 263) • 8 sample unsatisfactory (T: 5 & R: 3) ❖ **At Day 42**: • Total sample analyzed (T: 387 & R: 189) • Samples unsatisfactory : (Test: 219 & Ref:144) • 1 missing visit	NIMHNS it is observed that 05 samples were unsatisfactory to analysis. 2. Further, the data regarding the unsatisfactory sample (08 samples) is not matched with the raw data given by National Institute of Mental Health & Neurosciences (05 samples). 3. In case of day 42, firm has mentioned that in the subject disposition data that total sample unsatisfactory were 219 in Test & 144 in Ref., however, in the efficacy result, it has mentioned that the sample unsatisfactory in Test were 144 & in reference were 75.
2	Details of number of samples analyzed by NIMHANS for the primary and secondary sampling points	1. At Day 14: (Primary endpoint) Sample analyzed: 789 (test: 526 & ref: 263) 2. At day 42: (secondary endpoint) Sample analyzed: 576 (test: 387 & Ref. 189)	As per the disposition of subjects, it has mentioned that 08 subjects were unsatisfactory at Day 14, However in efficacy result; firm has mentioned that 07 samples were unsatisfactory.
3	Raw data of Phase III CT	Firm has submitted the raw data regarding Phase III clinical trial along with CRF for all sites & reports of RFFIT Results by National Institute of Mental	Sample unsatisfactory at Day 14 & Day 42 has not matched with the submitted efficacy result.

		Health & Neurosciences. (samples received from M/s Cadila Pharmaceuticals)	

Earlier, CDSCO had conducted a GCP inspection at one of the site for Phase III CT and noted various observations which is under examined and action initiated.

Recommendation:- In light of recommendations of IND Committee dated 10.06.2019, the firm presented their proposal for grant of permission to manufacture and market Recombinant Rabies G Protein Vaccine. The committee noted that the primary end point of the study to demonstrate non-inferiority for seroprotection at Day 14 has been achieved. After detailed deliberation, the Committee recommended for grant of permission to manufacture and market Recombinant Rabies G protein Vaccine with the following conditions:

1. In clinical trial, seroprotection was observed at 14 days post 1st dose.
2. The firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.
3. Proposed Package Insert, Label, Carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.
4. However, issues regarding GCP inspection should be addressed by CDSCO .

Sr. No. 06

Phase IIa clinical trial with Zika Virus

It is related to an application for grant of permission to conduct phase IIa clinical trial of Zika Virus Vaccine (BVB121) in Dengue Sero-Negative & Dengue Sero-Positive healthy adults.

Earlier this office had granted phase I clinical trial titled "A Phase I, multicenter, double-blind,placebo-controlled, randomized (intra-group) clinical trial to evaluate two doses of three sequentially escalating cohort of inactivated (adsorbed) Zikavirus vaccine (BBV121) in healthy adult Dengue Sero-Negative and Dengue Sero-Positive volunteers" permission vide CT NOC no.: CT-07/2017, dated 17.03.2017 for zika Virus vaccine. A total 48 male and female volunteers aged between 18 (after completion of 18 years) and 65 years (before completion of 65 years); 24 volunteers in Dengue seronegative group and 24 volunteers in Dengue seropositive group were assigned to one of the three sequentially escalating cohorts in each group. Within each group, six volunteers were randomized 3:1 to BBV121 and two volunteers were randomized to receive placebo for a specific dose.

The study reports are placed below:

Safety Conclusions:

Among 79 participants, 48 were randomized into 6 different groups. 24 participants were randomized to Dengue seronegative group (Group 1) and 24 into Dengue seropositive group (Group 2). There was no significant difference for adverse events between vaccine and placebo groups.

Total 70 adverse events (64.81%) were observed in vaccine group in 27 participants and 38 adverse events (35.19%) were reported in the placebo group among 12 participants.

Immunogenicity conclusions:

- In Dengue seronegative group seroconversion results indicate that the after dose 1(day 28)there was 100% seroconversion (≥4 Foldseroconversion) in 5 µggroupin contrast to 2.5 µg, and 10 µg dose strengths whereasafterdose 2 (day 56), there was 100% seroconversion for all three dose strengths i.e. 2.5 µg, 5 µgand 10 µg.

- This was in contrast to the seroconversion in 2.5 µg, 5 µg and 10 µg dose strengths in Dengue seropositive group. In Dengue seropositive group, the ≥4 Fold seroconversion for 5µg dose strength was higher in comparison to 2.5 µg and10 µgdose strength. None of the dose strengths exhibited 100% seroconversion in Dengue seropositive group.
- The geometric mean titers for 2.5µg, 5µg and 10µg dose strengths in Dengue seropositive and Dengue seropositive groups showed a substantial increase in the GMT in all the groups after dose 1 and dose 2.
- The GMT was highest in the higher dose strength i.e. 10µg group after dose 1 and dose 2.
- We conclude that the 5µg and 10µg dose strengths in Dengue seronegative and Dengue seropositive groups indicated substantial seroconversion and GMT's. So, in future clinical studies 5µg and 10µg dose strengths will be tested in the participants.

Overall Conclusions:

- In the phase I Zika clinical study, total 70 adverse events (64.81%) were observed in vaccine group in 27 participants and 38 adverse events (35.19%) were reported in the placebo group among 12 participants.
- There was no significant difference for adverse events between vaccine and placebo groups.
- We conclude that Zika virus vaccine "BBV121" is safe for use in humans.
- The geometric mean titers for 2.5µg, 5µg and 10µg dose strengths in Dengue Seropositive and Dengue Seropositive groups showed a substantial increase in the GMT in all the groups after dose 1 and dose 2. The GMT was highest in the higher dose strength i.e. 10 µg group after dose 1 and dose 2.

- Hence, it is conclude that 5 µg and 10 µg dose strengthswillbe considered for future clinical studies.

As per the proposal submitted by the applicant:-

Protocol Title: A Phase IIa Double Blind, Placebo-controlled randomized clinical trial to evaluate immunogenicity and safety of a Zika Virus Vaccine (BBV121) in Dengue Sero-Negative & Dengue Sero-Positive healthy adults.

Study Objective: To evaluate the immunogenicity and safety (reactogenicity, adverse events and serious adverse events) of two-doses (dose strength 5 µg and 10 µg) of purified inactivated adsorbed Zika virus vaccine (BBV121) compared with placebo (Alum).

The investigational vaccine is administered intramuscularly on day 0 and day 28±2 with safety testing on screening, day 28±2, day 56+7, months 6 and 12 (±7 days) with immunogenicity testing on days 0, 28±2, 56+7, and months 6 and 12 (±7 days).

The safety and immunogenicity data obtained between day 0 and day 56+7 will be compiled and analyzed for each dose regimen and incorporated in the interim Clinical Study Report. The participants are followed long term for safety and immunogenicity tests up to the end of month 12 (months 6 and 12) after the last dose of administration of the investigational vaccine.

Study Design:

The proposed study will be conducted as a randomized, double-blind, placebo-controlled clinical trial to evaluate the immunogenicity and safety of two dose strengths (5µg and 10µg) of BBV121 (purified inactivated adsorbed Zika virus vaccine) compared with placebo (alum).

Study Arm:

- Group A (Dengue Seronegative), n=275: 110 volunteers will be randomized to receive 5 µg of BBV121, 110 to receive 10 µg of BBV121, and 55 to receive placebo
- Group B (Dengue Seropositive), n=275: 110 volunteers will be randomized to receive 5 µg of BBV121, 110 to receive 10 µg of BBV121,and 55 to receive Placebo

Blood Collection:

- 15 mL of blood will be collected at screening for DENV and ZIKV IgG assay by ELISA, and by Real Time PCR RT-PCR (CDC Trioplex Real Time RT

PCR/Altona Diagnostics for Zika and Simplexa™ Dengue, Focus Diagnostics for Dengue diagnosis will be used) and for laboratory investigations for safety.

- 5 mL of blood sample will be collected at day 0, 28±2 days, 56+7 days, and at the end of 6, months (±7days) and 12 months (±7days) for vaccine immunogenicity testing by $PRNT_{50}$. 10 mL blood will be collected for laboratory investigations for safety will be performed on days 28±2, 56+7 and at the end of 6 months (±7days) and 12 months (±7days).
- Additional 15 mL of blood will be collected in a subset of 20 subjects per vaccine group and the placebo group on days 0, 28±2 days, 56+7 days and 12 months (±7 days) for longitudinal study of cellular and humoral immune responses to the candidate vaccine.
- 5 mL blood sample will be collected only from persons reporting febrile illness anytime during the study period for differential diagnosis of Zika, Dengue and Chikungunya virus infections by PCR.

Investigational vaccine: Each 0.5mL vial of BBV121contains:

- Purified 5µg or 10µg inactivated Zika virus
- 0.25mg Al+++ as Aluminum hydroxide
- 2.5mg of 2-phenoxyethanol
- Phosphate buffered saline q.s.to 0.5mL

Composition of placebo: Each 0.5ml vial of placebo contains:

- 0.25 mg Al+++as Aluminum hydroxide
- 2.5 mg of 2-phenoxyethanol
- Phosphate buffered saline q.s.to 0.5mL.

The vaccine and placebo are stored between +2°C and +8°C, and administered intramuscularly in the deltoid region of the arm.

Study population:

Healthy volunteers, who are seronegative for Zika. Within each dose group, volunteers will be randomized in ratios of 2:2:1 to receive BBV121 (5µg), BBV121 (10µg), or placebo.

Group A (Dengue Seronegative), n=275	**Group B** (Dengue Seropositive), n=275
• 5 µg BBV121(n=110) • 10 µg BBV121 (n=110) • Placebo (n=55)	• 5 µg BBV121(n=110) • 10 µg BBV121 (n=110) • Placebo (n=55)

Inclusion Criteria: All the participants should meet the following eligibility criteria:

1. Normal healthy male and female volunteers aged between 18 (after completion of 18 years) and 49years (before completion of 49years) weighing at least 50 kg of body weight.
2. Ability to comprehend the full nature and purpose of the study, including possible risks and adverse events and meet with the requirements of the protocol; ability to co-operate with the Investigator to comply with the requirements throughout the entire study period.
3. Written informed consent prior to inclusion in the study.
4. Seronegative for Zika by IgG ELISA and RT PCR at screening.
5. Dengue seronegative at screening, confirmed negative for Dengue IgG by ELISA and RT PCR for Group A participants; Dengue seropositive at screening, confirmed positive for Dengue IgG by ELISA and RT PCR for Group B participants.
6. Married or sexually active females of child-bearing potential should agree to use adequate contraception (oral contraception, barrier methods, spermicide, etc.), from enrollment to 3 months following last vaccination.
7. Sexually active men must agree to use contraception during the study, and agree to continue the use for at least 3 months following last vaccination.
8. A negative serum pregnancy test at screening for married or sexually active females, and females >18 years of age.
9. No history of clinically significant immunosuppressive or autoimmune disorders.
10. No history of degenerative neurological disease for. e.g. Guillain-Barre Syndrome, multiple sclerosis.
11. Laboratory investigations at screening must be within normal limits. for e.g
12. Hemoglobin ≥10gm/dL
13. WBC (white blood cells) ≥4000/mm3
14. Platelets ≥100,000/mm3
15. Bilirubin and AST/ ALT <1.5 x ULN (upper limit of normal)e.Creatinine <1.5 x ULN for the clinical laboratory
16. Study participants should be healthy as determined by physical examination, medical history, with no significant abnormality in any of the clinical parameters including ECG and chest X-ray.
17. Willing to allow storage and future use of biological samples for Zika virus related research.

Exclusion Criteria: Any of the following criteria will preclude the participant from being enrolled in the study:

1. Participation in other investigational vaccine or drug trials either concurrently or within 30 days of first INV administration.
2. Previous receipt of an investigational vaccine or history of taking drug for the treatment or prevention of Zika virus infection.

3. Previous receipt of an investigational vaccine for prevention of Dengue virus infection
4. Administration of any vaccine in four weeks prior to first dose of investigational vaccine administration.
5. Administration of monoclonal antibody or immunoglobulin within 4 weeks of the first dose of vaccineadministration.
6. Pregnancy or breast feeding or planning for pregnancy throughout the study period.
7. Any chronic, unstable medical condition.
8. Positive serologic test for HIV, hepatitis B surface antigen (HBsAg); or any potentially communicable infectious disease as determined by the Principal Investigator or Medical Monitor.
9. Positive serologic test for hepatitis C.
10. Chronic liver disease or cirrhosis.
11. Current or anticipated concomitant therapy with immunosuppressive drugs.
12. Prior major surgery or any radiation therapy within 4 weeks of enrolment.
13. Presence of keloid scar formation or hypertrophic scar at the planned site(s) of injection.
14. Participants who fall in the category of vulnerable group who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness.
15. Any significant pre-existing co-morbidities, to be determined by the site Principal Investigator.
16. History of arthralgia and arthritis of any etiology.
17. An unusual or abnormal diet, for whatever reason.
18. Any illness or condition that in the opinion of the investigator may affect the safety of the participant or the evaluation of any study endpoint., such as active malignancy and tuberculosis, history of seizure, bleeding disorder and hypersensitivity or allergy to any component of the study vaccine.

Sample Size:

In the Dengue seronegative group, 275 healthy volunteers (males or females) aged between 18 to 49 years will receive the vaccine (BBV121 5 µg, BBV121 10 µg)or placebo, with assignment of 110 subjects to the 5 µg dosage, 110 subjects to the 10 µg dosage, and 55 subjects to placebo. This sample size was based on the following assumptions: assuming power of 84%, a two-sided alpha level of 2.5% for each comparison, to find a statistically significant difference in geometric mean titres (GMTs) at Day 56+7 between the groups receiving BBV121 (5 µg or 10 µg) and placebo, by a two sample t-test on log10 (titre), assuming log10 (titre) is normally distributed with standard deviation 0.2 in each group and the true GMT ratio (larger to smaller) is at least 1.236 and loss to follow-up of 10%. Similarly, in the Dengue seropositive group, a total of

275 subjects will receive the vaccine or placebo. The proposed allocation to dosages and the power considerations are the same as for seronegative subjects

Primary End-points:

The immune response to vaccine measured by neutralizing antibody titers to Zika virus will be considered as a surrogate for protection. Immunogenicity will be measured by 50% plaque reduction neutralization test ($PRNT_{50}$), Seroconversion is defined as $PRNT_{50}$ titerof ≥1:10 from a baseline titer of <1:10 post vaccination or a fourfold rise from baseline for a baseline titer ≥1:10. $PRNT_{50}$ titers will be expressed as Geometric Mean Titers (GMT).

($PRNT_{50}$ titers will be expressed as Geometric Mean Titers (GMT). GMT is defined as the antilog of the mean of individual log-transformed titers).

Secondary Endpoints:

The safety assessment will comprise local and systemic reactogenicity, laboratory (hematological and biochemical) parameters, solicited and unsolicited adverse events, and serious adverse events.

Exploratory research objectives:

The successful outcome of phase 2a clinical trials would be based on achieving the primary and secondary endpoints described in the preceding sections. The following research objectives that are included as part of the study are exploratory in nature, whose results will not be binding on the outcome of the phase 2aclinical trials.

The exploratory research objectives include:

a) To evaluate cellular and humoral responses of BBV121 among participants of vaccinated and Placebo group.
b) To determine Zika virus antigen specific cellular immune response by Interferon-gamma (IFN-γ) ELI Spot and/or Intracellular cytokine Staining (ICS) assays.
c) To understand the immunogenicity and longevity of BBV121 vaccination.
d) To identify the time to onset and longevity of humoral and cellular immune responses.

Clinical trial site & Investigators details:

1. Dr Vasudev, King George Hospital, Rajapantula, Vizag
2. Dr Madhav Balakrishna, KLE's Dr Prabhakar Kore Hospital & MRC, Belgaum
3. Dr Raman Sharma, SMS Medical College Hospital, Jaipur

Recommendation:- The firm presented the results of Phase-I trial alongwith protocol of Phase IIa clinical trial. After detailed deliberation, the Committee recommended for grant of permission to conduct the proposed Phase IIa clinical trial subject to condition that tubectomised women of child bearing age should be included in the study. However, analysis in respect of pregnancy reported, if any, should be carried out.

Dr. Bikash Medhi did not participate in the deliberation and decision making.

Sr. No. 07

Marketing authorization of Genopep@ (Peptide 0.05% cream)

It is related to an application for manufacturing and marketing of Genopep@ (Peptide 0.05%) cream in the country to be indicated for the treatment of wound, antimicrobial therapy, scar prevention/ reduction.

Genopep@ is a Peptide 0.05% cream which is applied gently on the wound area. It stimulates fibroblast and keratinocytes growth factors, reduces the scar formation and has a broad spectrum of antimicrobial activity. It inhibits the growth of the commonly occurring bacteria including the most resistant forms like *Staphylococci aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterobacter cloacae and Acinetobacter baumannii* on wound surface.

As per the proposal submitted by the firm:-

Genopep® is an Active Pharmaceutical Ingredient (API). Xylentra® is a topical cream, composed of 0.05% API. It is New Chemical Entity (NCE) and IND Novel, non-biological small molecule designed Antimicrobial Peptide (dAMP) lytic peptide For Second Degree Burn Treatment its empirical formula is C144H212N32O24. Molecular weight of 2775.42.

Mechanisms of Action: Drug acts through anti-bacterial activity (direct pore formation leading to cell lysis, gram +ve and -ve bacteria) (Staphylococcus aureus, Pseudomonas aeruginosa) Proven wound healing properties with no scar formation (stimulates fibroblast and keratinocytes cell growth).

Pre- Clinical Studies of *Genopep*® (Pharmacology):

Study type	Test System	Species/Strain	Method of administration	Dose/s	Noteworthy findings
Pharmacology	In- vitro screening	*Staphylococcus aureus* *Pseudomonas aeruginosa*	Drug substance and its cream formulations	Drug substance: 5 μM Cream :	Drug substance and cream formulations showed

				0.5 - 2% and 0.02-0.05%	potent anti-bacterial action at 5μM (21.5 μg/ml) concentration
Efficacy	Rodent	Male Wistar Rats (N=48) (with full thickness wound) Compared with controls, silver sulfadiazine (SSD) and Sulfamylon	Topical gel	Topical 2% D2A21 gel Control water based gel SSD 1% cream Sulfamylon cream	Promising antibacterial and wound healing efficacy by novel peptide
PK tissue distribution	Rodent	Rats (N=02) (with full thickness scald burn wound)	Topical gel	Radio labelled 2% D2A21 gel (^{3}H, ^{14}C)	No evidence of systemic absorption

Pre- Clinical Studies of Genopep® (Toxicology):

Study Type	**Species**	**Test Drug Dose**	**Formulation type (Type of End product used)**	**Treatment Duration**	**Total study Duration**	**Noteworthy findings**	**Study Type**
Toxicology studies through Topical Route							
01	**Sub Acute**		125mg/animal as low dose 250mg/animal as medium dose, 500mg/anima	Cream	Once daily for 28days	28days	No Mortality All the biochemical

			l as high dose.				parameters in treated were in the normal ranges and were comparable to those of control group.
	Toxicology studies through Subcutaneous Route						
02	Acute	10 Mice 10 Rats	10XTD = 8.950mg/kg	Liquid Injectable	Single exposure	14 days	No Mortality
	Sub Acute	40 rats	TD=0.895 mg/kg 5 TD=4.475 mg/kg 10TD = 8.950mg/kg	Liquid Injectable	Once daily for 5 consecutive days	28 days	No clinical significant abnormalities were observed. Animals have tolerated high dose in acute, sub acute and long term studies.
	Long Term	40 Rats	TD=0.895 mg/kg 5 TD=4.475 mg/kg 10TD = 8.950mg/kg	Liquid Injectable	5 times in week for 4 weeks	90 days	

Pre- Clinical Studies of *Genopep*® (Additional Studies):

Study type	Test System	Species/Strain	Method of administration	Dose/s	Noteworthy findings
Gene mutation assay	In-vitro	Thymidine Kinase (tk +/- tk-/-) in MOLY (L5178Y) cell, in absence and presence of rat S9 metabolic activation (N=2)	Serial dilutions were tested with without S9	2 to 12 µg/ml serial dilutions Pilot for 4 hrs, confirmatory for 24 hrs	No meaningfully significant difference noted
Hyper-sensitivity	Non-rodent	Guinea pig	Intradermal & topical D2A21 gel/cream	5% D2A21 50% D2A21	Elicit moderate dermal sensitization response at 5%, at 50% extreme reaction noted. Intradermal induction at lower than 5% did not elicit any sensitization
Primary dermal irritation study	Non-rodent	Rabbits (New Zealand), (N=06, M/F), compared with control gel, exposed for 4 hrs, observed for dermal irritation for 72 hrs post patch removal, graded	Topical gel	2% gel (0.5ml/site)	2% gel was found to be non-irritating
Vaginal Irritation study	Non-rodent	Rabbits (New Zealand), (N=40) five different drug concentrations, applied once a day for 10 days, compared with placebo, sham control, tissue evaluated gross and histopathologically	Topical gel	1, 2,3, 4, 5%	1% D2A21 gel formulation did not show any irritation. Other formulations caused a moderate vaginal irritation

Phase I Trial:

An open label, randomized, single center study (*n=24);* CT NOC received from CDSCO on 10-Nov-2005. Phase-I study was conducted in 24 healthy human volunteers to evaluate the safety of, Genopep®, topical cream. All the subjects completed and efficacy / tolerability results obtained with the intent-to-treat analysis. During the study Mild Adverse Events (Mild redness) occurred in about 4% of subjects treated with Genopep® and subsided without any medication (Symptomatic Rx). There were no clinically significant effects of any treatment on laboratory test results. No subject withdrawn from the study. Hence, conclude that the study drug is safe / tolerable.

Phase II:

Phase-II study was Double blind, randomized, multi center, placebo controlled study with Xylentra (0.02% vs 0.05% vs placebo) for efficacy and safety in patients with Partial Thickness Burns (n=120); CT NOC received from CDSCO on 04-Aug-2006. Phase-II study was conducted in 120 patients, who were above 18years of age with less than or equal to 20% partial thickness burns, to evaluate the efficacy and effective dose range of the product, with maximum period of 3 weeks. The trail results concluded the treatment compliance was good and there were no side effects or adverse reactions or toxic effects noted in laboratory parameters during the study.

Furthermore, the pharmacokinetic samples, at 0hr, 30mins and study termination day, showed that there was no availability of the drug in serum. Hence, it is clear that the Genopep® medication can be used as the long term medication to the patients without any side effects.

Conclusion: The results of this Phase II, placebo control clinical study, concluded that the *Genopep*® topical cream at 0.02 and 0.05 % was well tolerated and safe. The *Genopep*® 0.05% cream was efficacious and safe in wound healing, restricting the infections than placebo for the treatment of patients with partial thickness burn wounds.

Phase III:

Phase-III study design was Double blind, randomized, multi center study on Xylentra Vs. Silver Sulfadiazine (SSD) for efficacy and safety in patients with Partial Thickness Burns (n=160); CT NOC received from CDSCO on 21-Mar-2012.

Phase-III study was conducted in 160 patients (both groups) with main aim of to evaluate the efficacy and safety of Genopep® by compare with a standard drug of Silver Sulfadiazine 1% in partial thickness burn patients with the duration of 4 weeks or till the day of complete wound healing.

Clinical Evaluation was analysed by measuring the safety and efficacy parameters. The efficacy results demonstrate that overall percentage of completely healed patients is 94% in Genopep® group and 81% in Silver Sulfadiazine 1% group. The clinical and statistical significance was found (P=0.0168) between the groups.

Genopep® is potentially controlled the bacterial infection on most causative bacteria like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiela sps*, *Acinetobacter baumannii*, *Enterobacter cloacae,* etc. than that of Silver Sulfadiazine 1%.

The antibiotic consumption was recorded quite low in Genopep® group compared to Silver Sulfadiazine 1% group thus Genopep® showed potential broad spectrum Antibacterial activity .

Genopep® with very low concentration 0.05% showed potential wound healing, controlling infection and reducing the scar and contracture formation, where as Silver Sulfadiazine 1% concentration not reached this significant level of efficacy in any one these parameters.

The proposal of the firm for manufacturing and marketing of Genopep@ (Peptide 0.05%) cream was deliberated in IND Committee held on 30.05.2014, in which firm presented the proposal. The Committee noted that the firm had not submitted the following:

i Allergenicity/hypersensitivity and dermal toxicity data as per the Appendix III of Schedule Y of Drugs and Cosmetics Rules,1945.

ii Stability Data as per Appendix IX of Schedule Y of Drugs and Cosmetics Rules,1945.

After deliberation, the Committee recommended for the submission of the same before the Committee. Subsequently, the firm has submitted the following:

- Guinea pig Sensitization–Maximization test (Hypersensitivity Study). For the intradermal induction phase of this study, the vehicle control group (5 animals/sex), the test article group (10animals/sex) and positive control group (3animal/sex) where administered intradermal injections (0.1ml each) at six sites between the shoulders of each guinea pig according to the following table:

Sites	**Vehicle Control**	**Test Article**	**Positive Control**
1-2	Freund's Complete Adjuvant (1:1)	Freund's Complete Adjuvant (1:1)	Freund's Complete Adjuvant (1:1)
3-4	5% Placebo (in saline)	0.5% D2A21 (in saline)	0.1% DNCB
5-6	5% Placebo (in 1:1 FCA)	0.5% D2A21 (in 1:1 FCA)	0.1% DNCB (in 1:1 FCA)

It was reported that there were no clinical signs observed in the test article-treated animals throughout the course of the study. Thin body condition and/or flaccid body tone were observed in one vehicle control female on Days 10-14. No biologically relevant differences in final body weights occurred.

- Primary dermal irritation study in which test article, D2A21 (2.0%), and the placebo were applied to different sites on the clipped dorsal trunk of six New Zealand (3 males and 3 females) at (0.5 ml / site). The exposure period for the site was 4 hrs. Observations for dermal irritations were recorded 30-60 mins, 24, 48 and 72hrs (±1hr) after patch removal. Grading of irritation is according to the method of draize.

- Vaginal Irritation Study on 40 Rabbits with 1,2,3,4 & 5% dose for Once daily dose for 10 days. No rabbit was died or were sacrificed in moribund condition in any dose level. The vaginal tissues from rabbits that received 1,2,3,4 and 5% Genopep cream irritant more than 1%. Hence Genopep cream 1% showed as non irritant and safe.

- Long Term Stability Studies for 12 Months Conducted at -20±5°C & 06 Months Accelerated Stability Study at 5^0C ± 3^0C for Genopep API of three batches (B. No: ISI0716-01, ISI0716-02, ISI0716-03).

- Long Term Stability Studies for 12 Months Conducted at 25±2°C / 60±5% RH, 06 months Long Term Stability data at 30±2°C / 65±5% RH & Accelerated Stability Study for 06 months at 40±2°C / 75±5% RH for Finished Formulation 0.05% Genopep (cream) of three batches (B. No: XAAKP17-01, XAAKP17-02, XAAKP17-03).

The firm presented their proposal alongwith allergenicity/ hypersensitivity data, dermal toxicity study data and stability study data, etc.

Recommendation:- After detailed deliberation, the Committee recommended for grant of permission to manufacture and market the Genopep API & Genopep® (Peptide 0.05% cream) for treatment of wound, antimicrobial therapy, scar prevention/ reduction with the following condition-

1. The firm should submit protocol for active Post Marketing Surveillance of the drug to CDSCO before launching the product in the market.
2. Proposed Package Insert, Label, Carton to be adopted should be got approved from CDSCO as per the requirements of the Rules.

Meeting ended with thanks to the Chair.

****