Minutes of IND Committee meeting held on 19.04.2017 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. A.K. Saxena, Ex. Scientist-G, Central Drug Research Institute, Lucknow.
4. Dr. C. D. Tripathi, Prof. & Head, Department of Pharmacology, VMMC, New Delhi.
5. Dr. Chandishwar Nath, Ex. Scientist-G & Scientist –in-charge, Division of Toxicology, Central Drug Research Institute, Lucknow.
6. Dr. Bikash Medhi, Prof. Dept. of Pharmacology, PGIMER, Chandigarh.
7. 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. Rajni Kaul, Scientist G, Division of BMS, ICMR, New Delhi.

CDSCO Representatives:

1. Dr. V. G. Somani, Joint Drugs Controller (India), CDSCO.
2. Mr. R. Chandrashekar, Deputy Drugs Controller (India), CDSCO (HQ).
3. Mrs. Rubina Bose, Deputy Drugs Controller (India), CDSCO (HQ).

Special Invitee (for S. No. 5):

1. Dr. Vinod Kumar, Associate Professor, VMMC and Safdarjung Hospital, New Delhi.

Following members could not attend the meeting:

1. Dr. Deepak Kaul, Prof. & Head, Deptt. Of Experimental Medicine & Biotechnology, PGIMER, Chandigarh.
2. Dr. Nilima Kshirsagar, Chair in Clinical Pharmacology, National Institute for Research in Reproductive Health, Mumbai.
3. 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 24.01.2017, which was already circulated to the members were taken as approved.

Sr. No. 01

Phase I/II clinical trial with Recombinant hCBβ-LTB vaccine of ICMR, New Delhi.

This office received an application from Dr. R. S. Sharma, Head, Scientist-G & Sr. DDG, Div. of RBMH, Indian Council of Medical Research (ICMR), Ansari Nagar, New Delhi-110029 for grant of permission to conduct a Phase I/II clinical trial entitled, "Phase I/II Clinical Trial on Safety, Immunogenicity and probing efficacy of the Revived Recombinant Vaccine against Human Chorionic Gonadotropin (hCG)".

The objective of the study is to determine the safety and immunogenicity of hCGβ-LTB Vaccine in sexually active healthy women and prove its ability to prevent pregnancy in sexually active women without impairment of ovulation and derangement of menstrual regularity and bleeding profiles. The duration of the study will be 42 months. Three doses i.e. 100, 300, 500µg of the proposed vaccine have been proposed for undertaking Phase-I clinical trial.

The proposal was deliberated in IND Committee meeting dated 08.11.2016. The applicant presented the Phase I/II clinical study protocol. After detailed deliberation, the Committee recommended for conduct of Phase-I study at present subject to following amendments in the protocol:-

The study shall be conducted in sequential manner starting from lower dose of 100 µg and evaluating safety for a predefined time period e.g. 7 days and then conducting at doses of 200 µg, 300 µg and 500 µg to finally establish the safety of the vaccine.

Accordingly, the applicant shall submit revised Phase I clinical trial protocol to the office of DCG (I).

However the applicant requested for re-deliberation of the proposed study with the following justifications:

The Safety, Reversibility of the Vaccine has already been tested in women in Finland, Sweden, Chile and Brazil under the International Committee on Contraception Research of the Population Council, besides India. Phase II efficacy studies were carried out in 3 major Institutions in India. Sexually active women of proven fertility did not become pregnant at and above titres of 50 ng/ml. They readily conceived below 20 ng titres. Immunisation did not derange ovulation, nor menstrual regularity.

Presently the Vaccine is same consisting of Beta subunit of hCG linked to a Carrier by the genetic engineering route instead of earlier tested synthetic vaccine. This Vaccine has received the approval of RCGM, who after extensive toxicology on an International Protocol conducted by a GLP Company have recommended to DCGI to approve Clinical trials.

It was claimed by the applicant that the protocol initially submitted conceived of a combined Phase I / Phase II trial, which was logical with the background of this Vaccine. Therefore, conducting only Phase I trial at this stage would be wastage of time. The r-DNA Vaccine will be manufactured by M/S Bharat Biotech, Hyderabad under GMP condition and is same as the synthetic vaccine.

Recommendation of the Committee:- As requested by the applicant, the proposal was re-deliberated and after detailed deliberation the committee recommended the conduct of proposed Phase I/II study in the present form with condition that the Phase I study should be conducted first and report should be submitted to the committee with the application and the clinical lots shall be manufactured & got tested as per GMP.

Sr. No. 2

Phase I clinical trial with ZYKR1 of M/s Cadila Healthcare Limited.

This office has received an application from M/s Cadila Healthcare Limited for the grant of permission to conduct a Phase I clinical trial with ZYKR1 intravenous injection entitled, "A prospective, randomized, double blind, placebo controlled study of intravenously infused ZYKR1 to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics in healthy volunteers".

ZYKR1 is a short-chain peptide based novel, potent, selective and peripherally restricted Kappa opioid receptors (KOR) agonist, identified by Zydus Research Centre. ZYKR1 has low permeability across the blood brain barrier. As ZYKR1 has low potential for CNS side effects, it represents an important therapeutic candidate for the treatment of visceral pain and post-operative pain.

This is a prospective, randomized, double blind, placebo controlled study.

Up to approximately 80 subjects will be enrolled at Zydus Research Centre, Village Moraiya, Ahmedabad. The study is divided in to two plans. Plan I is Single ascending dose (SAD) study, subjects will be enrolled in 8 cohorts and in each cohort 8 subjects will be enrolled (6 will receive study drug and 2 will receive placebo) and Plan II is single dose Gender effect study in female subjects. The gender effect study will be conducted based on PK results after the completion of suitable single dose panel for assessment of safety and tolerability. PD analysis may be carried out at the investigator's discretion. Eight female subjects will be enrolled in the study. Out of eight subjects, six will be administered a single intravenous dose of ZYKR1 and two will be administered a placebo in the overnight fasting condition to assess the effects of gender difference on safety, pharmacokinetics and Pharmacodynamic (if applicable) parameters.

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:-

1. The firm shall submit revised clinical trial protocol including (i) suggested changes in the inclusion and exclusion criteria with respect to range of BMI (with reference) specification of QT_c interval, pulse rate, (ii) the protocol shall include only non smokers as trial subject and (iii) the protocol shall include the marker test for autoimmune study & gas exchange measurement as the safety monitoring parameters.

2. The firm shall submit comparative data (calculated and actually obtained) of CHN analysis for six batches of proposed drug substance as the submitted data was found to be inconsistent with respect to CHN analysis.

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. 3

Phase I clinical trial with Tapentadol injection of M/s Torrent Pharmaceuticals Limited.

This office has received an application from M/s Torrent Pharmaceuticals Limited for grant of permission to conduct a Phase I clinical trial with Tapentadol Hemipamoate long acting injection entitled, "A mono centric, double blind, randomized, placebo controlled, sequential Phase-I study to evaluate safety, tolerability and pharmacokinetics of long acting injection of Tapentadol Hemipamoate (Torrent Pharmaceuticals Limited, India) following single ascending doses in healthy volunteers".

Tapentadol is a centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a μ-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Analgesia in animal model is derived from both of these properties. Tapentadol is 18 times less potent than morphine in binding to the human μ-opioid receptor and is 2-3 times less potent in producing analgesia. Tapentadol inhibits norepinephrine reuptake which results in increased norepinephrine concentrations. This dual mode of action may make tapentadol particularly useful in the treatment of acute pain.

This is a mono centric, double blind, randomized, placebo controlled, sequential, single dose, dose escalation Phase-I study. The objective of the study is to evaluate safety, tolerability and pharmacokinetics of Tapentadol Hemipamoate long acting injection following single ascending doses in healthy volunteers.

A total of 40 subjects will be enrolled at Bio-Evaluation Centre, Torrent Pharmaceuticals Limited, Gandhinagar – 382 428. Subjects will be enrolled in 5 cohorts and in each cohort 6 subjects will receive study drug and 2 will receive placebo.

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 condition that:-

1. The firm shall submit revised clinical trial protocol with suggested amendments in the inclusion/ exclusion criteria of healthy volunteers with respect to BMI, respiratory rate, viral marker test.
2. The protocol should include complete lipid profile, ABG test and pulseoxymetry with CO_2 analysis as safety monitoring parameters.
3. The firm is required to conduct and submit pharmacokinetic study data as per selected dose (50mg, 160mg, 260mg, 360mg and 500mg) of the formulation on minimum 6 non rodent animals (beagle dogs) per dose instead of presently submitted 3 animals data.

Accordingly, 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 III clinical trial with Endoxifen tablets of M/s Intas Pharmaceutical Limited.

This Directorate received an application from M/s. Intas Pharmaceuticals Limited for the grant of permission to conduct a Phase III clinical trial with Endoxifen Tablets entitled "A double-blind, oral, multiple-dose, parallel, randomized study to evaluate efficacy and safety of Endoxifen in bipolar I disorder patients."

The proposal to conduct Phase III clinical trial was deliberated in IND Committee meeting held on 27.04.2016. The firm presented the Phase II clinical study report and Phase III clinical study protocol. After detailed deliberation, the Committee accepted the Phase II clinical study report and recommended the following:-

1. Firm shall submit male fertility study and genotoxicity study reports for approval of Phase-III clinical protocol.
2. The firm shall submit revised Phase-III clinical trial protocol with placebo controlled arm being replaced by active controlled arm with suitable comparator

Now, firm has submitted revised clinical trial protocol, male fertility study and genotoxicity study reports as per recommendation of IND Committee.

Recommendation of the Committee:- The firm presented the revised Phase III clinical trial protocol as per recommendation of IND Committee dated 27.04.2016. After detailed deliberation the Committee recommended the conduct of Phase III clinical trial subject to condition that not less than 100 evaluable subjects will be enrolled in each arm with proper statistical calculation of power & non-inferiority margin of not more than 10% considering 10% dropout.

Accordingly, 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. 5

Phase III clinical trial with Remogliflozin Etabonate Tablets 100mg and 250mg tablets of M/s Glenmark Pharmaceuticals Limited.

This office received an application from M/s Glenmark Pharmaceuticals Limited for the grant of permission to manufacture and market Remogliflozin Etabonate bulk drug and Remogliflozin Etabonate Tablets 100mg/ 250mg and conduct a Phase III clinical trial with Remogliflozin Etabonate Tablets entitled, "A 24-week randomised, double-blind, double-dummy, parallel-group, multi-centre, active-controlled study to evaluate efficacy and safety of remogliflozin etabonate in subjects with type-2 diabetes mellitus". Remogliflozin Etabonate is a Novel SGLT2 inhibitor.

The proposal was deliberated in IND Committee meeting dated 24.01.2017. The Committee deliberated in detail the Phase III protocol presented by the firm and opined as follows:

1. Only diabetic patients who are on Metformin 1000 - 1500 mg doses and are not controlled should be included in the study and the investigational drug Remogliflozin should be given

as add-on drug only. Accordingly the committee suggested removing the treatment naïve arm of Remogliflozin.

2. The data presented by the firm suggested that 50 mg dose of Remogliflozin was more effective in reducing the Hb1Ac levels than the 100 mg dose. Further, there was a dose response relationship between 100 and 1000 mg dose at 12 weeks duration. The firm explained this by stating that in totality the efficacy of 100 mg was better than 50 mg in which they considered Hb1Ac, fasting blood glucose and body weight as efficacy parameters. However, the data of the latter two parameters was not presented.
3. Since the important safety concerns stated by the firm are Urinary Tract Infections/Genital Fungal Infections, atleast once in 4 weeks clinical and bacteriological analysis of the urine should be carried out to detect any such infections.
4. It was presented by the firm that three active metabolites have been detected [GSK189075, GSK189074, GSK279782] for Remogliflozin. However, no report of degradation pathway and the toxicity of the said metabolites were submitted by the firm.
5. Pre-clinical toxicological studies were conducted in dogs at a dose range of 60, 100, 250, 300, 650 and 1000 gm for different durations [2 weeks, 4 weeks, 13 weeks, 52 weeks]. The results shown that, at dose of ≥250 mg/Kg for 4 weeks duration, slight microscopic changes were observed in Kidneys in addition to atrophy of seminiferous tubules (in recovery group), whereas, no such findings were noted in higher doses and at higher duration studies. However, justification for the same was not furnished by the firm except for the statement that said changes were reversed on long duration of exposure.
6. The data presented of three trials of Phase II were not done in India, and although Asian populations represented at 7% of the sample size, none of these were of Indian origin. The firm stated that the metabolizing enzyme/metabolic pathway is unlikely to be different between the population studied in Phase II and the Indian subjects, however no supportive evidence for the same were presented. Further, it was stated that the mechanism of action of the drug is not through the route which is influenced by ethnic variation.
7. It was opined by the Committee that pharmacokinetics studies should be conducted in Indian populations, since the pharmacokinetics of the formulation of the investigational drug in Phase I/II is not available in Indian subjects and new API and formulation is going to be manufactured in India by M/s Glenmark Pharmaceuticals by way of technology transfer.
8. The committee also deliberated in detail the adequacy of sample size (204+204+204: Total 612) for the proposed study. The firm presented that the study isone sided non-inferiority trial with active comparator evaluating efficacy with a margin of 0.35 for reduction in HbA1c in 24 weeks assuming a SD = 1% with 90% power (assuming a dropout rate of 15%). Based on this, the committee opined that this number may be inadequate if the efficacy of the two doses show variability in the subjects having differential Hb1Ac. With this background it was suggested by the committee that the firm should submit the data in a stratified manner according to Hb1Ac ranges of 7-7.9, 8.8.9 and 9-10. Therefore, it was opined that as phase II studies are carried out upto 12 weeks only, the firm should submit data/report of 12 weeks with pharmacokinetics, initially for evaluation by the Committee, and then after 24 weeks with stratified analysis of data, for evaluation of adequacy of the sample size by the committee so that based on the report, decision on whether further trials are needed to grant marketing approval or will it be sufficient and the prescribing information shall also be submitted by the firm at the time of submission of Phase III results for examination of context in it vis-à-vis evidence.

9. The firm also stated that the API and formulation shall be manufactured in India with technology transfer from the innovator. Therefore, the firm should establish pharmaceutical equivalence and bioequivalence of the said formulation. Accordingly the firm should submit bioequivalence study protocol and conduct BE study of the formulation developed in India in comparison with the formulation used for Phase I/II study in a minimum of 24 normal healthy volunteers and similarly at least, repeat dose toxicity should be conducted for the drug developed in India (by technology transfer) as per Appendix III of Schedule Y of Drugs and Cosmetics Rules, 1945.

Considering these facts and that no concurrent Phase III trial is ongoing and similar class of drug is already in the market, the Committee recommended that the firm should submit study data/report of 12 weeks with pharmacokinetics initially and then after 24 weeks with stratified analysis of data, for evaluation of adequacy of the sample size by the committee so that based on the report, decision on whether further, non-inferiority phase III trial are needed shall be taken by the committee. The present permission of Phase III trial will not be construed as per only study for grant of marketing authorization after completion of trial and submission of report unless the above facts are examined to the satisfaction of the committee. Accordingly the firm should submit (i) revised clinical trial protocol with Pk study in Indian subjects by removing the treatment naïve patients & only including add on arm to Metformin (ii) BE study protocol for BE study of the formulation developed in India in comparison with formulation used for Phase I/II study outside India in a minimum of 20 normal healthy volunteers to CDSCO for re-deliberation in the next IND committee meeting.

Accordingly, firm has submitted the revised Phase III clinical trial protocol, justification for not conducting BE study and undertaking that they will conduct 4 week repeated dose toxicity study in rats and submit the report at the time of marketing authorization.

Recommendation of the Committee:- The firm presented the revised Phase III clinical trial protocol as per recommendations of IND Committee dated 24.01.2017 including all recommendation of earlier IND Committee. After detailed deliberation the Committee recommended the conduct of the Phase III clinical trial subject to condition that the firm shall initially conduct Pharmacokinetic study with the formulation manufactured in India on minimum 24 normal healthy human volunteers depending on intra subject variability and submit the report to office of DCG(I) in comparing with historical Pharmacokinetic data generated on the formulation manufactured and used in Phase I and II clinical study. This comparison of PK of formulation to be manufactured in India with historical data will be considered as accepted as firm has expressed that the earlier comparator formulations are not available for conducting head to head Bioequivalence study.

The Committee noted that pre-clinical toxicological studies, Phase-I and Phase-II have been conducted in overseas and therefore recommended that the applicant should conduct 28 days repeat dose toxicity study for the drug manufacture in the country. Further, the firm should continue to use the same manufacturing process for the batches intended to be used in Phase III clinical trial in the country.

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

Sr. No. 6

Phase III clinical trial with Levonadifloxacin (IV) and Levonadifloxacin (oral) of M/s Wockhardt Limited.

This Directorate received an application from M/s. Wockhardt Limited to conduct a Phase-III clinical trial entitled "A Phase III, Multi-centre, Randomized Study to Compare the Efficacy and Safety of Levonadifloxacin (IV and Oral) with Linezolid (IV and Oral) in Acute Bacterial Skin and Skin Structure Infections (ABSSSI)".

The proposal to conduct Phase III clinical study was deliberated in IND Committee meeting dated 15.12.2016, wherein the firm presented the revised Phase III clinical trial protocol. After detailed deliberation, the committee recommended the Phase III study with the amendment in the protocol that the firm shall provide separate inclusion and exclusion criteria for Intravenous (I.V.) and oral study arms to CDSCO, & if it is included with reference to MRSA patients, it may be approved.

Now, firm has submitted revised Phase III clinical trial protocol with separate inclusion and exclusion criteria for Intravenous (I.V.) and oral study arms. 500 adult subjects diagnosed with ABSSSI suspected to be caused by Gram-positive bacteria, including Methicillin-resistant Staphylococcus aureus (MRSA) will be enrolled in two groups.

- Sub Group 1 (oral): Approximately 250 subjects.
- Sub Group 2 (IV): Approximately 250 subjects.

This is a phase III, multi-center, randomized, active-comparator study in subjects with ABSSSI. The study has two subgroups for assessment of efficacy and safety - oral subgroup 1 and IV subgroup 2.

Primary objective of the study is to establish the non-inferiority of oral levonadifloxacin with oral linezolid in ABSSSI and to establish the non-inferiority of IV levonadifloxacin with IV linezolid in ABSSSI. Secondary objective is to evaluate the safety of oral and IV levonadifloxacin.

Recommendation of the Committee:- The firm presented the revised Phase III clinical trial as per recommendation of IND Committee dated 15.12.2016. After detailed deliberation the Committee recommended the conduct of Phase III clinical trial. However, it was opined by the Committee that IV administration shall be done only in cases of severe infections and when oral administration is not feasible. Firm shall revise the protocol accordingly, which may be considered for approval on revision.
Further, the firm presented the cleavage mechanism of WCK 2349 (oral) into Levonadifloxacin and L-alanine. The Committee agreed with the justification furnished by the firm that that the toxicity studies of WCK 771 (intravenous) are scientifically applicable to WCK 2349, as WCK 2349 is amino acid L-alanine prodrug of WCK 771 and it undergoes the biological transformation liberating the Levonadifloxacin which is an active drug corresponding to WCK 771 (L-arginine salt of Levonadifloxacin) in all preclinical species and human.

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

Sr. No. 7

Phase I/II clinical trial with Apaziquone of M/s Spectrum Oncology Limited.

This office received an application from M/s. Spectrum Oncology Private Limited for the grant of permission to conduct a Phase I/II clinical trial with Apaziquone "An Open-label, Phase I/II study of Topical Apaziquone for the treatment of Oral Leukoplakia" at Tata Memorial Hospital, Mumbai.

Apaziquone is a novel, fully synthetic bioreductive alkylating indoquinone synthesized at the University of Amsterdam in Netherlands in the mid – 1980s. Apaziquone is enzymatically reduced to generate cytotoxic species. It is a pro-drug that generates cytotoxic species after enzymatic activation.

Firm has conducted Phase I/II study with intravesical instillation of EOquin (Apaziquone) in early stage bladder cancer. No study has been conducted with Apaziquone oral topical application for Oral Leukoplakia.

The proposal to conduct Phase I/II clinical trial was deliberated in IND Committee meeting held on 08.11.2016. The firm presented the Phase I/II clinical study protocol. After detailed deliberation, the Committee made following observations:-

1. The proposed topical solution should be developed as a standard dosage form with concentration specified for application on the wound.
2. The method of application of the topical solution in cotton swab in the oral cavity and selection of dosage and basis of calculation are not convincing and justified.
3. The procedure of conversion of the pro-drug into drug in the local application in oral cavity is not clarified.
4. It is also not clear how efficacy shall be ascertained in biomarkers as stated in the presentation & protocol.

Therefore, the Committee opined that the protocol in its present form is not acceptable and cannot be considered at this stage. It was also opined that applicant shall come out with proposed/ final formulations, which will be used, otherwise appropriateness of different dose application by cotton swab & proportion of actual dose which will be available on specified mucosal topical site will need to be established or proven to correlate dose to response relationship, if further protocol is submitted for approval.

Now, firm has submitted revised clinical trial protocol alongwith firm's response in respect to IND Committee observation.

Recommendation of the Committee:- The firm presented the revised Phase I/II clinical trial protocol as per recommendation of IND Committee dated 08.11.2016. After detailed deliberation the Committee recommended the conduct of Phase I/II clinical study subject to condition that the protocol shall be amended to include the following:-

1. Procedure for measuring plasma concentration to monitor the systemic absorbtion (if any).
2. The absorbant pad shall be divided into quadrant for uniform distribution of the drug solution and physician shall be appropriately trained for the same.

The Committee also opined that as the formulation was already tested in human in bladder cancer, therefore there is no additional requirement of conduct of dermal and allergenicity/ hypersensitivity toxicity study in the present case.

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.

The meeting ended with vote of thanks by the Chair

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