1. PROTOCOL SUMMARY

Study Title	An Open-Label, Balanced, Randomized, Single Ascending Dose Study, To Evaluate The Pharmacokinetic Dose Linearity of Eicosapentaenoic Acid (EPA) and Calcium L-5-Methyltetrahydrofolate (L-5-MTHF) Following Oral Administration Of Different Dose Levels of Crenueros® CNS Fish Oil Plus Softgels Supplied By Sichuan Credit Pharmaceutical Co., Ltd, China in Healthy Subjects Under Fasting Conditions.
Investigational Medicinal Products	**Test Product (T):** CreNeuroS® CNS Fish Oil Plus Softgels Supplied by Sichuan Credit Pharmaceutical Co., Ltd, China. Each softgel contains, Eicosapentaenoic Acid (EPA) (as EE) 400 mg; Calcium L-5-Methyltetrahydrofolate 3.75 mg and other Vitamins and Minerals.
Objectives	**Primary Objective:** • To assess the Pharmacokinetic profile of single ascending doses of Eicosapentaenoic Acid (EPA) and Calcium L-5-Methyltetrahydrofolate (L-5-MTHF) after administration of CreNeuroS® CNS Fish Oil Plus Softgels in healthy subjects under fasting condition. • To demonstrate dose linearity of Eicosapentaenoic Acid (EPA) and Calcium L-5-Methyltetrahydrofolate (L-5-MTHF) following single dose administration (different doses) of CreNeuroS® CNS Fish Oil Plus Softgels in healthy subjects under fasting condition. **Secondary objective:** To evaluate the safety and tolerability of single ascending doses (different doses) of CreNeuroS® CNS Fish Oil Plus Softgels in healthy subjects under fasting condition.

Study Design	An Open-Label, Balanced, Randomized, Single ascending dose study to evaluate the Pharmacokinetic dose linearity in healthy subjects under fasting condition.
Regulatory Submission	NMPA (National Medical Products Administration) - Pivotal
Sample Size	At least 32 number of healthy, human subjects will be recruited to evaluate the Pharmacokinetic dose linearity in healthy subjects. Note: A total of 32 subjects (8 subjects in each groups) will be enrolled in this study. **SAD Cohort** / **Number of subjects** 1 / 08 Subjects 2 / 08 Subjects 3 / 08 Subjects 4 / 08 Subjects As per the discretion of the Investigator, a sufficient number of stand-by subjects will be included additionally to ensure successful dosing of 08 subjects in each cohorts during the study period.
Primary Enrollment criteria	Demographic data, medical and medication history, physical examination, 12-lead ECG, haematology, biochemistry, serology, urine routine analysis, additionally for females serum pregnancy test, hormone assay (FSH) will be done within 21 days and a chest X-ray within 06 months prior to check-in.
Housing	In study period, each group subjects will be housed in the clinical facility for at least -60.00 hours pre-dose to 72.00 hours post-dose. **Note:** **Dosing will be done individually for each cohort groups (Cohort 01, Cohort 02, Cohort 03, Cohort 04). The subsequent group's check-in will be at the check-out day of the previous group.**

Fasting condition	Standard meals will be provided starting -59.00, -48.00, -44.00, -40.00, -36.00, -24.00, -20.00, -16.00, -12.00 hours. Thereafter, subjects will be fasted for at least 08.00 hours prior to dosing. Standard meals will be provided starting at 04.00, 08.00, 12.00, 24.00, 28.00, 32.00, 36.00, 48.00, 52.00, 56.00 and 60.00 hours post-dose respectively.
Dose and Mode of Administration	In study period, after an overnight fasting of at least 08.00 hours, in the morning a single oral dose of the test product (T) will be administered (as per the randomization schedule) with 240 mL of drinking water at ambient temperature, to the subjects sitting in upright posture, under the supervision of the investigator or medical officer and/or trained study personnel, including the quality assurance auditor(s) or monitors. Investigational Medicinal products should not be chewed or crushed and should be swallowed whole. This activity will be followed by a mouth check with the help of a tongue depressor and a torch light to assess compliance to dosing. **Note:** Subjects in each SAD cohort will receive a single oral dose at the following planned dose levels:

SAD Cohort	Dose Level
1	02 capsules
2	04 capsules
3	06 capsules
4	08 capsules

Note:

- **Dosing will be done under yellow monochromatic light condition.**
- **Dosing will be done individually for each cohort groups (Cohort 01, Cohort 02, Cohort 03, Cohort 04). The subsequent group's check-in will**

	be at the check-out day of the previous group to ensure the subject's safety.
Restriction during the study	The subjects will fast for at least 08.00 hours prior to dosing and 04.00 hours post-dose. In study period, drinking water will be restricted from at least 01.00 hour prior to dosing until 01.00 hours post-dose except **240 mL of drinking water** during dosing. After 01.00 hours post dose, drinking water will be provided *ad libitum*. Subjects will remain in the sitting position for at least 04.00 hours of post-dose and only necessary movement will be allowed during this period. Thereafter, subjects will be allowed to move freely during the remaining part of the study. However, they will not be allowed to take part in any kind of strenuous exercise/activity. Note: Subjects' diet from at least 48.00 hours pre-dose and at least 72.00 hours post dose will be controlled. The meals during the diet control period should be eicosapentaenoic acid and folate limited.
Blood Sample Handling Procedure and Time Points	Blood sample will be drawn through an intravenous cannula inserted in a superficial forearm vein of the subject. The cannula will be kept in situ up to 24.00 hours post dose or as per subjects convenience. A total of 36 blood samples will be collected in study period (including pre-dose sample). The pre-dose (-24.00, -12.00, -01.00, -00.50 and 00.00 hour) blood sample 08 mL will be collected within 10 minutes prior to dosing. Post dose blood samples 08 mL will be collected at 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 06.50, 07.00, 07.50, 08.00, 08.50, 09.00, 10.00, 12.00, 16.00, 24.00, 48.00, 72.00 hours respectively (+02 minutes allowed for in house). (120.00, 168.00, 240.00, 312.00, 384.00 and 432.00 hours samples will be collected on ambulatory basis (±60 minutes)). All samples will be collected in pre-labeled K_2EDTA– vacutainers from a forearm vein using an indwelling cannula as per the discretion of the investigator. Heparin-lock technique will be used to

	prevent clotting of blood in the indwelling cannula. Before each blood sample is drawn via the indwelling cannula, 0.5 mL of blood will be discarded so as to prevent the saline diluted blood and heparin (10 IU/mL) from interfering with the analysis. Cannula will be removed after 24.00 hours sample is drawn or earlier if blocked. If required, sample may also be collected through a direct vein puncture for the 48.00 and 72.00 hours of in-house post dose blood samples and 120.00, 168.00, 240.00, 312.00, 384.00 and 432.00 hours of ambulatory samples (±60 minutes). Vacutainers will be placed upright in a rack kept in a wet ice bath until centrifugation and during separation. **Note: Sampling will be done under yellow monochromatic light condition.**
Blood Loss	Not exceeding **322 mL** (including Screening + in-house + Ambulatory + Post study) for the entire study. In house samples: 30 | Ambulatory samples: 06 | Total samples: 36
Sample Processing and Storage	After the collection of blood samples, the study personnel will place the collected samples in a thermo-insulated box containing wet ice and transfer the box to the sample processing room, where the blood samples will be centrifuged at 4000 ± 50 RPM for 10 minutes at 02°C to 08°C to separate the plasma. Centrifugation will start within 30 minutes of the collection of samples, at each collection time-point. The resulting plasma will be equally transferred into six aliquots, which contain 10 mg/mL solution of stabilizing agent (solution of 2-mercaptoethanol). Aliquot – 01 and 02 - Total Eicosapentaenoic Acid (EPA) lipids. Aliquot – 03 and 04 - Free (unesterified) Eicosapentaenoic acid (EPA) lipids Aliquot – 05 and 06 - L-5-methytetrahydrofolate (L-5-MTHF) **Preparation of stabilisation agent (10 mg/mL solution of 2-mercaptoethanol):** Measure 50 mL of water and transfer into 100 mL reagent bottle, and add

	approximately 1000 mg of 2-mercaptoethanol in water and add 50 mL of water mix well. Sonicate in ultrasonic bath for few minutes. Provide a suitable batch number and complete the 'Solution Preparation Form'. Use this solution for four days from the date of preparation. From the resulting plasma 1 mL will be transferred into pre-labeled polypropylene tubes which containing 10% w/v of Stabilizing agent (add 100 µL of stabilizing agent for 900 µL Plasma) as aliquot V and aliquot VI respectively. To ensure the complete mix up of contents in the RIA vial, vortex completely before storing. **All the activities performed under Yellow monochromatic light.** **Note:** • **As per the requirement, samples will be transferred from Clinical Facility to Bio-Analytical Facility even in between of clinical phase.** • **Sample processing and segregation will be done under yellow monochromatic light.**
Subject Safety Measures	• Blood pressure, radial pulse rate, body temperature, and wellbeing status will be enquired and recorded at pre-dose 00.00 hour (within 75 minutes of before dosing) and at 01.00, 03.00, 06.00, 12.00, 24.00, 48.00 and 60.00 hours (± 60 minutes) post dose. • Seated blood pressure, radial pulse rate, body temperature, and well-being status will be assessed and recorded prior to the collection of ambulatory blood samples at 120.00, 168.00, 240.00, 312.00, 384.00 and 432.00 hours from post-dose. • Physical examination and vitals will be recorded before check-in, check-out (72.00 hours) for study period and at any time if necessary. • ECG will be recorded before check out (72.00 hours) for study period and if any subject is withdrawn or dropped out during the study. • Monitoring for adverse events will be done throughout the study period

	in clinical phase.
Screening and Post Study Parameters	**For Screening:** • Haematology • Biochemistry • Serology • Urine routine analysis • 12 lead ECG and Chest X-ray • Serum Pregnancy Test (for females only) • Hormone assay (FSH) (for females only) **During Check-in:** • Urine drug of abuse test (Marijuana-THC, amphetamine-AMP, barbiturates-BAR, cocaine-COC, benzodiazepines-BZD and morphine-MOR) and alcohol test (urine sample) will be done prior to check-in of study period. • Urine pregnancy test (for females) will be done prior to check-in for study period. • Gynecological and breast examinations (for females) will be done before check in of study period only. **For Post Study Assessment:** • At the end of study period (72.00 hours) or after the subject has withdrawn or dropped-out from the study, blood samples will be collected for post study laboratory assessments include Haematology and Biochemistry. • ECG will be recorded before check out for study period or after any subject is withdrawn or dropped out from the study (72.00 hours). • Serum Pregnancy Test (For Female Only).
Bio-analytical Procedure	Total Eicosapentaenoic Acid (EPA) lipids, Free (unesterified) Eicosapentaenoic acid (EPA) lipids and L-5-methyltetrahydrofolate (L-5-MTHF) in plasma will be assayed using a validated LC-MS/MS method after completion of each SAD dose

	level. **For Eicosapentaenoic Acid (EPA):** Pre-dose blood samples will be drawn at -24.00, -12.00, 00.00 hours and post dose blood samples will be drawn at 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 06.50. 07.00, 07.50, 08.00, 08.50, 09.00, 10.00, 12.00, 24.00, 48.00, 72.00, 120.00, 168.00, 240.00, 312.00, 384.00 and 432.00 hours. **For L-5-Methyltetrahydrofolate (L-5-MTHF):** Pre-dose blood samples will be drawn at -01.00, -00.50, 00.00 hours and post dose blood samples will be drawn at 00.25, 00.50, 00.75, 1.00, 1.25, 1.50, 1.75, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00 and 16.00 hours. **Note:** • **Other vitamins and minerals will not be assayed.** • **Sample analysis will be done under yellow monochromatic light.**
Pharmacokinetic & Statistical Parameters	The following pharmacokinetic parameters for Eicosapentaenoic Acid (EPA) and Calcium L-5-Methyltetrahydrofolate (L-5-MTHF) will be calculated using non-compartmental model of Phoenix WinNonlin® version 8.3 or higher version of Pharsight Corporation, USA or SAS® software version 9.4 or R software or above (SAS Institute Inc., USA) or applicable software. 1) Total EPA lipids in plasma 2) Baseline-adjusted total EPA lipids in plasma 3) Free (unesterified) EPA lipids in plasma 4) Baseline-adjusted free (unesterified) EPA lipids in plasma 5) L-5-methytetrahydrofolate 6) Baseline-adjusted L-5-methytetrahydrofolate **For non-adjusted Total EPA lipids and Baseline-adjusted total EPA lipids:** Primary parameters: C_{max} and AUC_{0-72h} Secondary parameters: T_{max}, $t_{½}$, K_{el} and AUC_%Extrap_obs AUC_{0-t} and $AUC_{0-\infty}$

	For non-adjusted free (unesterified) EPA lipids and Baseline-adjusted free (unesterified) EPA lipids: Primary parameters: C_{max} and AUC_{0-72h} Secondary parameters: T_{max}, $t_{½}$, K_{el} and AUC_%Extrap_obs AUC_{0-t} and $AUC_{0-\infty}$ **For non-adjusted L-5-methytetrahydrofolate and Baseline-adjusted L-5-methytetrahydrofolate:** Primary parameters: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ Secondary parameters: T_{max}, $t_{½}$, K_{el} and AUC_%Extrap_obs **Note:** The mean of the pre-dose levels (period specific) should be used for the baseline adjustment of the post-dose levels of respective analyte. Baseline concentrations will be determined for dosing period, and baseline corrections will be period specific. Any negative values obtained from baseline correction should be designated as zero (0) prior to calculating the baseline-corrected pharmacokinetic parameter. Interim PK analyses will be performed after completion of each SAD dose level. Summary statistics will be used to describe the PK profile for each dose level.
Statistical Analysis for Dose linearity/ proportionality	Statistical analysis will be performed using SAS® (SAS Institute Inc., USA) Version 9.4 or higher for, • Baseline- adjusted total EPA lipids, • Baseline- adjusted free (unesterified) EPA lipids. • Baseline- adjusted L-5-MTHF **ANOVA Model:** The dose-normalized pharmacokinetic parameter AUC and C_{max} will be analyzed using ANOVA. The Rdnm will be the dose-normalized geometric means for highest dose relative to lowest dose. **Dose linearity:** Dose linearity will be tested by fitting the model:

	log(PK parameter) = a + b*log(dose) + Dose **Power Model:** Dose proportionality will be evaluated by assessing the slope from regression analysis of log (AUC or C_{max}) versus log (dose) from the power model.
Dose linearity/ proportionality criteria	**ANOVA model:** The 90% CI for the ratio of dose-normalized (highest to lowest), geometric mean values (Rdnm) for ln-transformed C_{max} and AUC for baseline-corrected total EPA lipids and baseline-corrected L-5-MTHF should be within 80.00% to 125.00%. **Linearity Model:** Dose linearity will be concluded if the p- value for the ln-transformed C_{max} and AUC for baseline-corrected total EPA lipids and baseline-corrected L-5-MTHF are not significant (p-value >0.05). **Dose Proportionality:** Dose proportionality will be concluded when the 90% CI for model-predicted Rdnm (highest to lowest) for Cmax and AUC is contained within 80.00% to 125.00%. **Note:** Baseline-corrected free (unesterified) EPA lipids data will be submitted as supportive evidence of comparable therapeutic outcome.
Ethical Issues	The study will commence only after written approval is obtained from the Ethics Committee. The study will be conducted as per the National Ethical Guidelines for Biomedical and Health Research involving Human participants ICMR (2017), ICH E6 (R3) (Step 4) 'Guidance on Good Clinical Practice', New Drugs and Clinical Trials Rules 2019 [Gazette notification G.S.R.227 (E), Dated 19.03.2019], India and its Amendment Rules [Dated 19th Sep, 2024], 'Good Laboratory Practice', 'Good Clinical Practices for Clinical Research in India' Guidelines, Good Clinical Laboratory Practice (GCLP), Declaration of Helsinki (Finland, October 2024) and NMPA (National Medical Products Administration) regulatory requirements.

2. INVESTIGATORS DECLARATION

We, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all the requirements regarding the obligations of investigators and all other pertinent requirements of the National Ethical Guidelines For Biomedical and Health Research Involving Human Participants ICMR (2017), ICH E6 (R3) (Step 4) 'Guidance on Good Clinical Practice', New Drugs and Clinical Trials Rules 2019 [Gazette notification G.S.R.227 (E), Dated 19.03.2019], India and its Amendment Rules [Dated 19th Sep, 2024], 'Good Laboratory Practice', 'Good Clinical Practices for Clinical Research in India' Guidelines, Good Clinical Laboratory Practice (GCLP), Declaration of Helsinki (Finland, October 2024) and NMPA (National Medical Products Administration) regulatory requirements.

We agree to comply with all relevant SOPs required for the conduct of this study. We further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

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Audit Trail

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Signer	Signature
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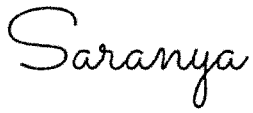
IP Address: 2401:4900:6753:f455:9c8d:5eff:fed5:a313	

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REC APPROVED

27 JAN 2026

3. SPONSOR DECLARATION

I, on behalf of Sichuan Credit Pharmaceutical Co., Ltd. China, have read, understood, and approved of this protocol.

I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of National Ethical Guidelines For Biomedical and Health Research Involving Human Participants ICMR (2017), ICH E6 (R3) (Step 4) 'Guidance on Good Clinical Practice', New Drugs and Clinical Trials Rules 2019 [Gazette notification G.S.R.227 (E), Dated 19.03.2019], India & its Amendment Rules [Dated 19th Sep, 2024], 'Good Laboratory Practice', 'Good Clinical Practices for Clinical Research in India' Guidelines, Good Clinical Laboratory Practice (GCLP), Declaration of Helsinki (Finland, October 2024) and NMPA (National Medical Products Administration) regulatory requirements.

Hitesh Shah 22 Jan'26

Signature and date

Mr. Hitesh Shah

Director – Operations

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