Clinical Trial Summary Document

Study Title

A Randomized, Double-Blind, Placebo-Controlled, First-in-Human, Phase I Study to Assess the Safety, Tolerability, and Pharmacokinetics of ZS98987 and DM68831 Following Subcutaneous Administration in Healthy Volunteers

Study Summary

This Phase I clinical trial was designed as a two-part, randomized, double-blind, placebo-controlled study in healthy adult volunteers. The objective was to assess the safety, tolerability, and pharmacokinetics of two investigational drugs, ZS98987 and DM68831, compared to saline or sterile water placebo. The study population included healthy men and women aged 18 to 55 years, with body mass index (BMI) ranging from 18 to 30 kg/m². Women of childbearing potential were required to use highly effective contraception, and subjects with significant medical history, abnormal laboratory values, or recent exposure to investigational agents were excluded.

A planned total enrollment of 64 participants was distributed across both parts of the trial. Dose escalation proceeded in cohorts of 8 participants, randomized in a 3:1 ratio so that 6 received active drug and 2 received placebo. The study was conducted at a single site under controlled inpatient and outpatient conditions. Each participant remained in the trial for approximately 28 days, including screening, treatment, and follow-up.

Part 1: ZS98987 (Single Ascending Dose)

ZS98987 was evaluated under a single ascending dose (SAD) design. Doses were escalated across sequential cohorts beginning at 0.2 mg, with further groups exposed to higher levels until a maximum of 0.8 mg was reached. Each dose was administered once by subcutaneous injection. The comparator consisted of sterile 0.9% sodium chloride solution, provided as placebo. To maintain administration safety, the maximum injection volume per subject was capped at 2 mL and withdrawn from a single vial. The ZS98987 drug product was prepared as a sterile aqueous solution containing hydroxypropyl-β-cyclodextrin at 5% w/v as solubilizer, sodium chloride at 0.9% w/v as tonicity agent, sodium phosphate buffer at 10 mM adjusted to pH 7.4 as buffering system, polysorbate 80 at 0.01% w/v as surfactant, and water for injection to final volume. The solution was prepared to meet an osmolality range of 280 to 320 mOsm/kg.

Part 2: DM68831 (Multiple Ascending Dose)

DM68831 was studied under a multiple ascending dose (MAD) design. Dosing began at 0.2 mg administered once daily and escalated stepwise to a maximum of 1.4 mg daily over sequential cohorts, with each cycle lasting 14 days of active treatment. Comparator injections consisted of sterile water for injection. Each dose required a subcutaneous injection volume not exceeding 2 mL. The DM68831 solution was formulated with mannitol at 2% w/v as a stabilizer and tonicity agent, sodium citrate buffer at 10 mM with pH adjusted to 6.5, hydroxypropyl methylcellulose at 0.1% w/v to slightly increase viscosity, polysorbate 20 at 0.01% w/v as surfactant, and water for injection as solvent. The formulation was designed for stability and physiological tolerability.

Drug Supply, Packaging, and Storage

The investigational products ZS98987 and DM68831 were supplied in sterile, single-use 2 mL Type I clear glass vials, each filled with 1.5 mL of solution. Each vial was sealed with bromobutyl rubber stoppers and capped with aluminum seals. Placebo controls were supplied in larger 20 mL Type I glass vials filled with either sterile saline solution (for Part 1) or sterile water for injection (for Part 2). To preserve blinding, the unblinded pharmacy staff withdrew doses from each vial and placed them into identical disposable syringes, preventing investigators or participants from ever observing differences in vial size. Both active and placebo vials were identically labeled using randomized identifiers and protocol-specific codes, without indication of treatment identity. All drug products and placebos were shipped under controlled conditions and stored at 2–8 °C, protected from light. Vial accountability was strictly recorded with 100% reconciliation requirements.

Randomization and Blinding

Participants were randomized in blocks using a centralized computer-generated system with stratification for sex to maintain balanced representation. A 3:1 allocation ratio was applied within each cohort. Blinding was ensured through matched presentation of active and placebo syringes, with preparation restricted to unblinded pharmacy staff who had no role in participant evaluation. Clinical staff and outcome assessors remained fully blinded to treatment allocation. Emergency code-break capability was maintained via sealed envelopes and electronic systems accessible only for medical necessity. Periodic audits confirmed that blinding procedures were strictly followed with no breaches.

Endpoints and Assessments

The primary endpoint was the incidence of treatment-emergent adverse events from baseline through the follow-up visit. Safety assessments included repeated physical

examinations, monitoring of vital signs, 12-lead ECGs, and laboratory evaluations of hematology, clinical chemistry, and urinalysis. Secondary endpoints included pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to maximum concentration (Tmax), area under the concentration-time curve (AUC), terminal elimination half-life (t½), and in Part 2, accumulation ratio across multiple doses. Exploratory endpoints included pharmacodynamic biomarkers and exploratory tolerability questionnaires.

Safety Monitoring and Oversight

All cohorts in both parts included a sentinel dosing strategy, with two participants (one active, one placebo) dosed at least 24 hours prior to dosing the remainder of the cohort. Dose escalation required review and approval by an independent Safety Review Committee, which evaluated adverse events, clinical laboratory results, ECG changes, and injection-site assessments. Participants were followed for safety through Day 28, which included a final follow-up visit after completion of dosing.

Compliance and Conduct

The trial was conducted under Good Clinical Practice and in alignment with the Declaration of Helsinki and applicable regulatory guidelines. Fully informed consent was obtained from all participants. Study oversight included on-site monitoring, source data verification, and pharmacovigilance reporting procedures. The integrity of the study was maintained through strict adherence to protocol procedures, compliance checks, robust accountability for investigational products, and quality assurance audits.