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Safety, Pharmacokinetics and Target Engagement of a Novel Brain Penetrant RIPK1 Inhibitor (SIR9900) in Healthy Adults and Elderly Participants

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ABSTRACT

Receptor-interacting serine/threonine kinase 1 (RIPK1) regulates inflammatory signaling and induces apoptosis and necroptosis. Pharmacological inhibition of RIPK1 kinase activity has demonstrated efficacy in animal models of neurodegenerative, autoimmune and inflammatory diseases. SIR9900 is a potent and selective novel small molecule RIPK1 inhibitor. This first-in-human, phase I, randomized, double-blind, placebo-controlled study evaluated the safety, pharmacokinetics, and pharmacodynamics of single (3–200 mg) and multiple (3–60 mg daily for 10 days) ascending oral doses of SIR9900 in healthy adult (18–64 years, $n = 80$) and elderly participants (≥ 65 years, multiple doses 30 mg, $n = 8$). The study included a food effect component. Overall, SIR9900 was safe and well tolerated with no concerning dose-dependent trends in safety observed. SIR9900 was rapidly absorbed with a plasma maximum concentration time (T_{max}) of 3.0–4.0 h and plasma half-life ($t_{1/2}$) of 31.92–37.75 h following single doses. Similar T_{max} and $t_{1/2}$ results were observed following multiple doses. Systemic exposure to SIR9900 increased in a dose-proportional manner and was similar between adult and elderly participants. No appreciable food effect was observed. The cerebrospinal fluid to unbound plasma ratio was 1.15. A robust pharmacodynamic effect was demonstrated with approximately 90% peripheral target engagement at 3 h post-dose, and sustained RIPK1 inhibition over the 10-day treatment period. The promising safety, pharmacokinetic, and pharmacodynamic profile of SIR9900 with central nervous system penetrating potential in healthy adult and elderly participants supports its further clinical development in patients with inflammatory and degenerative diseases, particularly in the central nervous system.

1 | Introduction

Receptor-interacting serine/threonine kinase 1 (RIPK1) regulates inflammatory signaling and induces apoptosis and necroptosis [1, 2]. Activation of RIPK1 has been observed in human pathological samples from individuals with neurodegenerative, autoimmune and inflammatory diseases [3–5]. Pharmacological inhibition of RIPK1 activity has demonstrated efficacy in numerous animal models (i.e., systemic inflammatory response syndrome [6], aging-associated male reproductive system impairment [7], Alzheimer's disease [8], amyotrophic lateral sclerosis [4], chemotherapy-associated kidney disease [9], ischemia reperfusion induced organ injury [10], multiple sclerosis [11], rheumatoid arthritis [12], colitis [12], psoriasis [12]), which supports the development of RIPK1 inhibitors with therapeutic possibilities for a wide range of diseases [2, 13]. Furthermore,

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Summary

- What is the current knowledge on the topic?
  - RIPK1 regulates inflammatory signaling and induces apoptosis and necroptosis.
  - Pharmacological inhibition of RIPK1 has demonstrated efficacy in animal models of neurodegenerative, autoimmune and inflammatory diseases.
  - Most RIPK1 inhibitors are limited to the treatment of peripheral conditions. SIR9900 is a potent and selective CNS-penetrable inhibitor of RIPK1 activity.
- What question did this study address?
  - Safety and tolerability of single and multiple doses of SIR9900 in healthy adult and elderly participants were evaluated.
  - The pharmacokinetic profile of SIR9900 in plasma, urine and CSF was assessed, and target engagement was evaluated by inhibition of RIPK1 activity.
- What does this study add to our knowledge?
  - Oral administration of SIR9900 was safe and well tolerated.
  - SIR9900 demonstrated favorable pharmacokinetics and good blood–brain barrier permeability.
  - SIR9900 demonstrated 90% peripheral target engagement and sustained RIPK1 inhibition over the 10-day treatment period.
- How might this change clinical pharmacology or translational science?
  - Evidence of target engagement with relatively broad safety margin together with blood–brain barrier permeability support clinical development of SIR9900 as a potential treatment for RIPK1-related neurodegenerative conditions in the CNS.

development of a central nervous system (CNS) penetrating RIPK1 inhibitor has the potential to impact progression of neurodegenerative diseases [14].

Given the therapeutic benefit of inhibiting RIPK1, selective RIPK1 inhibitors have been reported. Small-molecule kinase inhibitors have been developed targeting the unique kinase-regulating allosteric pocket within RIPK1. These inhibitors only suppress the kinase activity of RIPK1, whilst sparing the essential scaffolding function that is required for postnatal survival [13]. Some RIPK1 inhibitors (e.g., GSK2982772, DNL747, DNL788, DNL104, DNL758, R552, ABBV-668) have progressed to early-stage human clinical trials [13] evaluating safety and pharmacokinetic profiles in healthy adults [15–19], and exploring preliminary efficacy in neurodegenerative (Alzheimer's disease and amyotrophic lateral sclerosis [16], multiple sclerosis [20]), autoimmune and inflammatory (psoriasis [21, 22], ulcerative colitis [23, 24], rheumatoid arthritis [25], Coronavirus disease 2019 [COVID-19] [26]) diseases. The reported safety profile appears favorable for continued clinical development of RIPK1 inhibitors with no specific target toxicity concerns identified. However, many RIPK1 inhibitors do not penetrate the CNS [13] (i.e., GSK2982772, DNL758, and R552) thereby limiting their clinical efficacy to peripheral disorders.

SIR9900 is a potent and selective CNS-penetrable inhibitor of RIPK1 kinase under clinical development by Sironax Ltd. In vitro assays demonstrate an antagonistic effect on RIPK1 kinase activity and a protective effect on cell necroptosis. Preclinical studies of SIR9900 conducted in Sprague–Dawley rats and Beagle dogs demonstrated appropriate oral bioavailability, unbound exposure in the CNS at similar levels to plasma in rats, and a favorable safety profile. SIR9900 has demonstrated good efficacy in several mice models. SIR9900 reduced hypothermia and systemic inflammation in a systemic inflammatory response syndrome model. SIR9900 delayed disease onset and reduced clinical score in an experimental autoimmune encephalomyelitis model, and reduced neuroinflammation in an Alzheimer's disease model. Together, these preclinical findings support the clinical development of SIR9900 for the treatment of inflammatory, autoimmune, and neurodegenerative diseases.

The primary objective of this Phase 1 first-in-human study was to evaluate the safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of oral SIR9900 in healthy adult and elderly participants. Secondary objectives included (1) establishing the pharmacokinetic profile of SIR9900 in plasma and urine, and detecting SIR9900 concentration in cerebrospinal fluid (CSF), (2) conducting a preliminary evaluation of the effect of food on the pharmacokinetic profile, (3) characterizing the pharmacodynamic profile.

2 | Materials and Methods

This study was undertaken in a clinical Phase 1 unit (Nucleus Network Pty Ltd. Melbourne, Australia) between June 2023 and January 2024 in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6(R2) (2016) (as adopted in Australia) and the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007, incorporating all updates). Ethical approval was obtained from the Alfred Hospital Ethics Committee (EC00315; June 1, 2023). Written informed consent was obtained from all volunteers prior to participation in the trial. This study has been reported using the CONSORT-DEFINE guidelines [27].

2.1 | Study Design and Population

This was a first-in-human, Phase 1, single-center, randomized, double-blind, placebo-controlled study in healthy adult (18–64 years; ACTRN12623000696695) and elderly (≥65 years of age) volunteers who were healthy or had managed, stable disease (ACTRN12623000790640). A full list of the inclusion and exclusion criteria is available in the Supporting Information. The study was conducted in two parts (Figure S1). *Part 1* sequentially enrolled participants into 5 cohorts, each consisting of approximately eight participants randomized to receive a single dose of SIR9900 or placebo at a ratio of 3:1. Five dose-level cohorts (SAD Cohorts 1–5; SIR9900 3, 10, 30, 100, and 200 mg, respectively) were assessed. Participants in SAD Cohort 3 also received

a second dose of study drug under fed conditions. *Part 2* sequentially enrolled participants into 4 cohorts, with an additional cohort of elderly participants, each consisting of approximately 10 participants randomized to receive multiple doses of SIR9900 or placebo at a ratio of 4:1. Four dose-level cohorts (MAD Cohorts 1–4; SIR9900 3, 10, 30, and 60 mg once per day [QD] for 10 days), and the elderly cohort (MAD Cohort 5; SIR9900 30 mg QD for 10 days), were assessed. After last dosing, all participants were observed for 5 days prior to discharge, with end of study visits conducted 1 week following discharge.

2.2 | Primary and Secondary Objectives

The primary objective of the study was to evaluate the safety and tolerability of single and multiple doses of SIR9900 in healthy participants. Secondary objectives included: determining SIR9900 concentration in plasma, urine and CSF; characterizing the pharmacokinetic profile of SIR9900 and evaluating the effect of food; and characterizing the pharmacodynamic profile of SIR9900 by measuring the level of phosphorylated-RIPK1 (p-RIPK1) protein (Table S1).

2.3 | Study Drugs and Administration

Tablets (SIR9900 and placebo of matching appearance; dosage strengths of 3, 10, and 50 mg) were manufactured by Shanghai STA Pharmaceutical Product Co. Ltd. (a subsidiary of WuXi App Tec [Shanghai] Co. Ltd). Study drugs were administered orally with water under fasted conditions (10 h). For SAD Cohort 3, a second dose was administered on Day 10 following a wash-out period > 5 terminal half-lives and within 30 min of consuming a standardized high-fat meal [28]. All study drugs were administered as per the Schedule of Assessments (Tables S2–S4).

2.4 | Starting Dose, Dose Escalation and Stopping Rules

Non-clinical studies were used to determine the initial 3 mg starting dose (Supporting Information). Dose escalation and commencement of Part 2 (MAD) were determined by the Safety Review Committee based on review of blinded cumulative safety and pharmacokinetic data (Supporting Information). In the event of a safety concern the Safety Review Committee was to determine if treatment discontinuation was warranted.

2.5 | Assessments and Procedures

All procedures/assessments were carried out at the clinical Phase 1 unit. Refer to Tables S2–S4 for the timing of all procedures/assessments.

2.6 | Demographic Characteristics

The following information was collected: age, sex, race, ethnicity, child-bearing potential for females, body height and weight, medical history, prior medication and eligibility (including serology, cotinine, alcohol, drug screen, COVID-19 testing; Supporting Information).

2.7 | Safety Assessments

Treatment-emergent AEs were defined as AEs that commenced on, or after, the first administration of study drug until the end of study visit. Blood and urine were collected for clinical safety tests (hematology, chemistry, coagulation, urinalysis; refer to Supporting Information). Full physical examination, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and tympanic temperature), and 12-lead electrocardiogram (ECG) parameters (HR, PR, QRS, QT, and QTcF) were conducted throughout the study. Women of child-bearing potential underwent pregnancy testing. Concomitant medications (medications continued or newly received after study drug administration) were recorded.

2.8 | Pharmacokinetic and Pharmacodynamic Evaluations

2.8.1 | Pharmacokinetic Tests

Plasma (all participants), urine (Part 1 SAD Cohort 3 [30 mg; fasted] and Cohort 4 [100 mg] only), and CSF (Part 2 MAD Cohort 3 [30 mg; adults] only) were collected at specified intervals (Tables S2–S4). SIR9900 concentrations were measured (360 Biolabs Burnet Institute, Melbourne, Australia) using a validated liquid chromatography with tandem mass spectrometry method (Supporting Information). SIR9900 concentrations in CSF and a matched plasma sample were determined on Day 8 (approximately 4 h post-dose), following daily doses of SIR9900 (30 mg). Concentrations of SIR9900 in urine, urine volume, and the amount excreted were determined.

2.8.2 | Pharmacodynamic Measurements

Blood samples (Part 1 SAD Cohorts 1–5; Part 2 MAD Cohorts 1 and 5) were collected (Tables S2–S4) for isolation of peripheral blood mononuclear cells (PBMCs) to evaluate target engagement. Isolated PBMCs were stimulated (i.e., with tumor necrosis factor (TNF)-α, Smac mimetic and zVAD-fmk (TSZ) using dimethyl sulfoxide (DMSO) as control) to undergo necroptosis, and total proteins were extracted. The level of phosphorylated-RIPK1 proteins were measured via Meso Scale Discovery electrochemiluminescence assay (method developed and established at Pharmaron, Method Number 015-NMQ-23052-SH-MO1). The lower limit of quantitation of the p-RIPK1 assay was 0.369 μg/mL.

2.9 | Randomization, Blinding, and Study Monitoring

Details regarding randomization, blinding and study monitoring are presented in the Supporting Information.

2.10 | Important Changes to Method After Study Commencement

The study protocol was amended three times, each amendment approved by the HREC (Supporting Information).

2.11 | Statistical Analyses

The number of participants in each cohort was deemed to be sufficient to allow for an initial assessment of the safety, pharmacokinetic and pharmacodynamic properties of SIR9900 following SAD and MAD dosing strategies, and to minimize exposure to the drug in healthy human participants. Details of the analysis populations are presented in the Supporting Information.

Categorical data were expressed as counts and percentages, and continuous data with descriptive statistics. SIR9900 results were reported for each dose cohort and pooled, placebo results were pooled within each study part. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Caroline, USA). Coding of AEs and medications was performed using MedDRA v26.0 and WHO-DD B3 March 1, 2023 dictionaries.

Plasma and urine pharmacokinetic parameters were calculated (Table S5). A non-compartmental analysis method consistent with the oral route of administration was used (Phoenix WinNonlin, version 8.3; supplier), and results summarized with descriptive statistics. Dose proportionality was assessed using the power model and the Hummel criteria for all dosed cohorts [29]. The food effect was evaluated using a general linear model via PROC GLM in SAS, and the 90% confidence interval for the geometric least-squares means ratio in pharmacokinetic parameters between fed and fasted periods was estimated. The concentration ratio of CSF and unbound plasma was calculated as CSF concentration/(plasma concentration × human plasma unbound fraction).

Pharmacodynamic parameters included calculation of percentage change from baseline of the p-RIPK1 protein levels from stimulated PBMCs (Supporting Information). Data were summarized using descriptive statistics.

3 | Results

3.1 | Participant Disposition

All 39 randomized participants in Part 1 were dosed and completed the study (Figure 1A). All 49 randomized participants in Part 2 received at least one dose, with 47 (95.9%) participants completing treatment and 46 (93.9%) participants completing the study (Figure 1B). Participant demographics at baseline were broadly similar across dose cohorts, with the exception of the elderly cohort having a higher median age (Table 1).

3.2 | Safety and Tolerability

Across the study, there were no deaths or serious TEAEs, no TEAEs leading to study drug withdrawal, or discontinuation from the study.

During Part 1 (SAD) of the study, TEAEs were reported for 15 (38.5%) of the 39 participants (total of 26 TEAEs), with the incidence of TEAE in higher dose cohorts (66.7% in both 100 mg and 200 mg cohorts) appearing greater than lower dose cohorts (16.7%–33.3%) (Table 2). The most common (> 10% participants) TEAEs by system organ class (SOC) were Gastrointestinal disorders (5 [12.8%] participants), Nervous system disorders (4 [10.3%] participants) and Musculoskeletal and connective tissue disorders (4 [10.3%] participants) (Table S6a). The majority of TEAEs were mild in severity, with 1 TEAE classified as moderate in severity (back pain) in one participant administered the highest dose of SIR9900 (200 mg). The TEAE was deemed not related to study drug and did not cause the participant to discontinue from the study treatment or the study. Few TEAEs (3 [7.7%] of 39 participants; three events) were deemed by the investigator to be related to study drug (Table S6b).

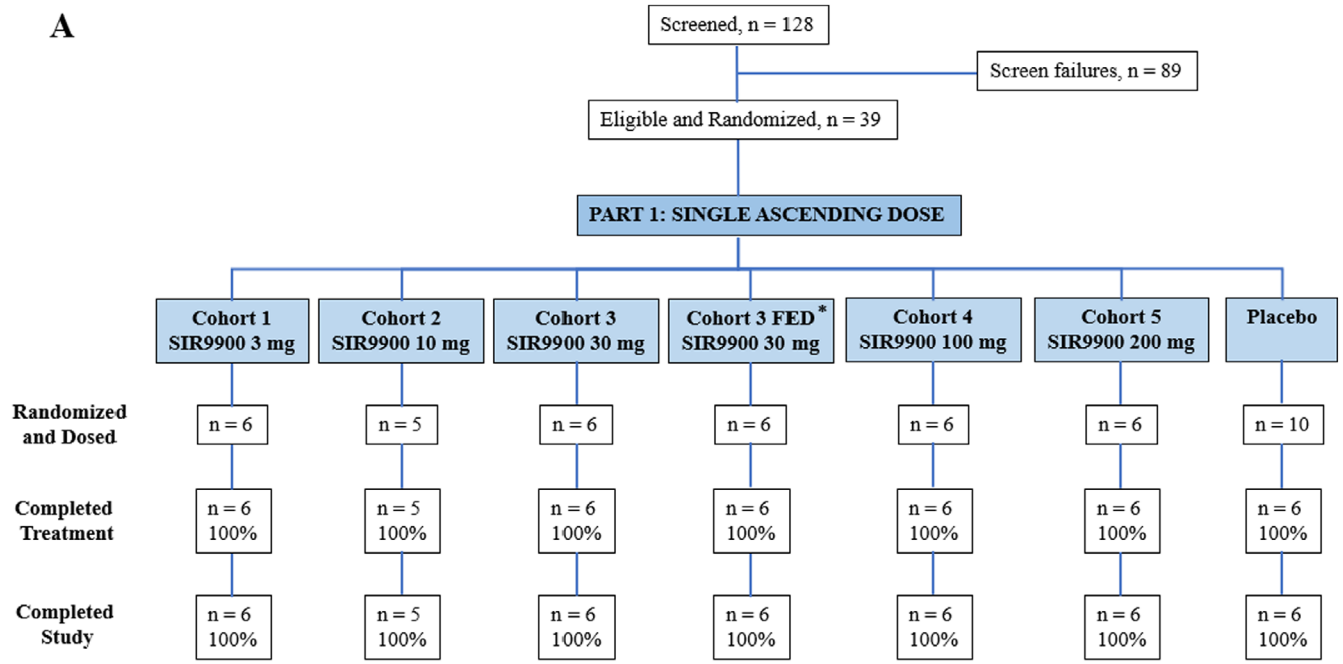
During Part 2 (MAD) of the study, TEAEs were reported for 27 (55.1%) of 49 participants (total of 43 TEAEs), with incidence in each SIR9900 group appearing less compared to that in the pooled placebo group (SIR9900 37.5%–66.7% vs. placebo 77.8%) (Table 2). The most common TEAEs by SOC were Nervous system disorders (10 [20.4%] participants), General disorders and administration disorders (9 [18.4%] participants), and Gastrointestinal disorders (7 [14.3%] participants) (Table S7a). The majority of TEAEs were mild in severity, with 3 TEAEs classified as moderate (2 [4.1%] of 49 participants) and 1 TEAE classified as severe (1 [2.0%] of 49 participants). Two adult participants (30 mg SIR9900; placebo) experienced moderate TEAEs of amylase increased, both were considered by the investigator as possibly related to study drug. One elderly participant (30 mg SIR9900) experienced a moderate TEAE of glaucoma traumatic (deemed not related to study drug) and 1 severe TEAE of syncope (deemed possibly related to study drug), these two TEAEs resulted in study treatment interruption on Days 7 and 8 in this elderly participant, however the treatment was continued later until Day 10, and the severe TEAE resolved quickly on the same day as it commenced. Most TEAEs were deemed by the investigator not related to study drug, with few TEAEs (10 TEAEs in 10 [20.4%] of 49 participants) deemed to be related to study drug (Table S7b).

In the elderly participants, the incidence of TEAEs was similar to adult participants (57.1% vs. 37.5%–66.7%). Of the four elderly participants with a TEAE (seven events), three participants experienced mild TEAEs (five events), and one participant reported both moderate (one event) and severe (one event) TEAEs (reported above).

Across the study, there were few other abnormal laboratory test results deemed as TEAEs, however, these were all single mild cases that resolved by the end of the study. Additional safety findings are presented in the Supporting Information, including a list of adverse events, per participant (Table S8). There were no apparent treatment or dose-related trends identified from clinical laboratory tests, ECG and vital signs results.

3.3 | Pharmacokinetic Evaluation of SIR9900 in Plasma

The mean SIR9900 plasma concentration-time profiles for each cohort in Part 1 (SAD) and Part 2 (MAD) are presented in Figures S2



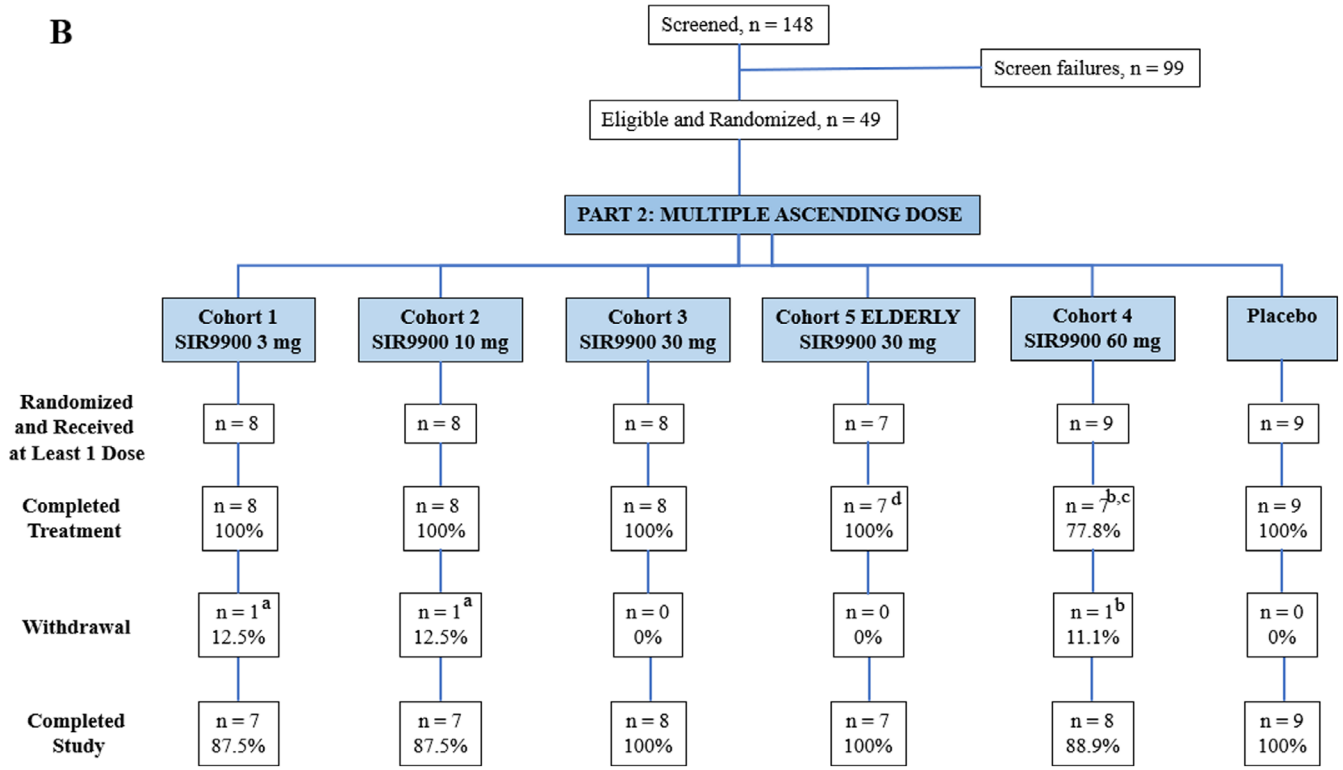


FIGURE 1 | Participant flow. CONSORT diagram depicting the participant flow through the study. (A) Part 1 (single ascending dose) and (B) Part 2 (multiple ascending dose). *Participants in Cohort 3 FED were the same as Cohort 3 dosed under fasted conditions; [a]one participant withdrew consent from study after receiving all doses; [b]one participant was withdrawn from the study before taking exclusionary concomitant medication; [c]one participant declined dosing and blood sampling on Day 10 but completed the study; [d]one participant was not dosed on Day 7 and 8 with dose interrupted due to an adverse event. This participant completed treatment (i.e., completed last dose on Day 10). Completed treatment: number of participants that completed dosing on Day 1 (Part 1) or completed last dose on Day 10 (Part 2). Completed study: number of participants that attended the final study visit.

TABLE 1 | Participant demographics at baseline.

	Part 1: Single ascending dose								Part 2: Multiple ascending dose[b]							
Variables statistics	**Cohort 1 SIR9900 3 mg**	**Cohort 2 SIR9900 10 mg**	**Cohort 3 SIR9900 30 mg (fasted/fed)**	**Cohort 4 SIR9900 100 mg**	**Cohort 5 SIR9900 200 mg**	**Pooled active**	**Pooled placebo**	**Overall**	**Cohort 1 SIR9900 3 mg**	**Cohort 2 SIR9900 10 mg**	**Cohort 3 SIR9900 30 mg**	**Cohort 5 SIR9900 30 mg (elderly[c])**	**Cohort 4 SIR9900 60 mg**	**Pooled active**	**Pooled placebo**	**Overall**
n	**6**	**5**	**6**	**6**	**6**	**29**	**10**	**39**	**8**	**8**	**8**	**7**	**9**	**40**	**9**	**49**
Age, years																
Mean (SD)	37.8 (14.77)	26.8 (4.82)	25.0 (4.60)	26.3 (3.27)	29.2 (7.22)	29.1 (8.93)	37.6 (14.22)	31.3 (10.99)	30.1 (9.75)	28.4 (7.67)	24.0 (4.38)	68.0 (1.83)	31.8 (10.38)	35.6 (17.03)	36.2 (14.30)	35.7 (16.42)
Sex, *n* (%)																
Male	4 (66.7%)	2 (40.0%)	3 (50.0%)	4 (66.7%)	1 (16.7%)	14 (48.3%)	4 (40.0%)	18 (46.2%)	6 (75.0%)	5 (62.5%)	6 (75.0%)	4 (57.1%)	5 (55.6%)	26 (65.0%)	4 (44.4%)	30 (61.2%)
Female	2 (33.3%)	3 (60.0%)	3 (50.0%)	2 (33.3%)	5 (83.3%)	15 (51.7%)	6 (60.0%)	21 (53.8%)	2 (25.0%)	3 (37.5%)	2 (25.0%)	3 (42.9%)	4 (44.4%)	14 (35.0%)	5 (55.6%)	19 (38.8%)
Race[a], *n* (%)																
White	6 (100%)	3 (60.0%)	5 (83.3%)	3 (50.0%)	3 (50.0%)	20 (69.0%)	7 (70.0%)	27 (69.2%)	5 (62.5%)	7 (87.5%)	4 (50.0%)	7 (100%)	6 (66.7%)	29 (72.5%)	7 (77.8%)	36 (73.5%)
Asian	—	2 (40.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	6 (20.7%)	3 (30.0%)	9 (23.1%)	2 (25.0%)	1 (12.5%)	3 (37.5%)	—	1 (11.1%)	7 (17.5%)	1 (11.1%)	8 (16.3%)
Black or African American	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (11.1%)	1 (2.0%)
White, South American	—	—	—	2 (33.3%)	—	2 (6.9%)	—	2 (5.1%)	—	—	—	—	—	—	—	—
White, Black or African American	—	—	—	—	—	—	—	—	—	—	1 (12.5%)	—	—	1 (2.5%)	—	1 (2.0%)
Australian-Chinese	—	—	—	—	—	—	—	—	1 (12.5%)	—	—	—	—	1 (2.5%)	—	1 (2.0%)
Brazil	—	—	—	—	—	—	—	—	—	—	—	—	1 (11.1%)	1 (2.5%)	—	1 (2.0%)
Chile	—	—	—	—	—	—	—	—	—	—	—	—	1 (11.1%)	1 (2.5%)	—	1 (2.0%)

(Continues)

TABLE 1 | (Continued)

	Part 1: Single ascending dose							Part 2: Multiple ascending dose[b]						
Variables statistics	**Cohort 1 SIR9900 3 mg**	**Cohort 2 SIR9900 10 mg**	**Cohort 3 SIR9900 30 mg (fasted/fed)**	**Cohort 4 SIR9900 100 mg**	**Cohort 5 SIR9900 200 mg**	**Pooled active**	**Pooled placebo**	**Overall**	**Cohort 1 SIR9900 3 mg**	**Cohort 2 SIR9900 10 mg**	**Cohort 3 SIR9900 30 mg**	**Cohort 5 SIR9900 30 mg (elderly[c])**	**Cohort 4 SIR9900 60 mg**	**Pooled active**	**Pooled placebo**	**Overall**
n	**6**	**5**	**6**	**6**	**6**	**29**	**10**	**39**	**8**	**8**	**8**	**7**	**9**	**40**	**9**	**49**
Not Reported	—	—	—	—	1 (16.7%)	1 (3.4%)	—	1 (2.6%)	—	—	—	—	—	—	—	—
BMI, (kg/m^2) at screening																
Mean (SD)	24.82 (1.932)	23.36 (2.330)	24.60 (3.915)	23.85 (2.193)	21.40 (2.281)	23.61 (2.750)	25.88 (2.849)	24.19 (2.915)	24.51 (2.832)	24.93 (2.834)	25.24 (2.308)	24.57 (2.894)	24.50 (2.857)	24.75 (2.624)	25.78 (2.462)	24.94 (2.602)

Abbreviations: BMI, body mass index; *n*, number of participants; SD, standard deviation.
[a]Race was collected via participant self-report at screening.
[b]Dose was administered once daily for 10 days.
[c]Current medical conditions present in the elderly cohort that were considered by the Investigator to be managed and stable included: angiomyolipoma, hematuria, anxiety, depression, sleep apnea syndrome, seasonal allergy, hypercholesterolemia, erectile dysfunction, symptoms of menopause, cat allergy, and hypertension.

and S3. Mean concentration over time profiles of SIR9900 were consistent with the oral route of administration in all cohorts, where an increase in mean concentrations up to approximately 1.5–4 h was observed in all profiles across dose levels and days, followed by a rapid decrease in concentration up to approximately 8 h post-dose, and finally gradually decreased to the end of the sampling period. Following once daily administration of SIR9900 for 10 days, concentrations reached a steady state on Days 6–8.

For Part 1 (SAD), the median time to maximum concentration (T_{max}) was similar across dose levels (3.00–4.00 h), except at the 3 mg dose (1.5 h). Mean terminal half-life ($t_{1/2}$), clearance (Cl/F), and apparent volume of distribution (V_z/F) were generally similar across all dose levels. Geometric mean $t_{1/2}$ was between 31.92 and 37.75 h, geometric mean Cl/F ranged from 2.739 to 4.651 L/h, and geometric mean V_z/F ranged from 142.5 to 232.6 L (Table 3).

For Part 2 (MAD), the median T_{max} was similar across dose levels (2.00–4.08 h). Following repeat dosing on Day 10, geometric mean $t_{1/2}$ was between 32.83 and 41.88 h, geometric mean Cl/F ranged from 2.877 to 3.667 L/h, and geometric mean Vz/F ranged from 148.0 to 207.1 L (Table 3), systemic exposure to SIR9900 was approximately 2–2.5 and 2–4-fold higher for maximum concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from time zero to end of dosing interval (AUC_{tau}) respectively, compared to the exposure on Day 1 (Table S9).

Following SIR9900 systemic exposure, the AUC and C_{max} increased proportionally as the dose level increased from 3 to 200 mg in SAD and from 3 to 60 mg following single and repeat dosing on Days 1 and 10 respectively in MAD (Table 4).

Repeat administration of SIR9900 (30 mg) in elderly participants resulted in similar systemic exposure to that of adult participants. Compared to healthy adult participants, on Day 1, geometric mean C_{max} was 12.1% higher and AUC_{tau} was 4.2% greater in elderly participants; on Day 10, geometric mean C_{max} was 1.5% higher and AUC_{tau} was 6.4% lower in elderly participants, with no obvious difference in geometric mean $t_{1/2}$ (Table 3).

Based on the preliminary food effect evaluation with a small sample size ($N=6$), food intake reduced C_{max} by 23.5% but did not appreciably affect total systemic exposure (AUC_{last} and AUC_{inf}) (Figure S4; Table S10).

3.4 | Pharmacokinetic Evaluation of SIR9900 in Cerebrospinal Fluid

Following repeat dosing (30 mg), unbound plasma SIR9900 concentrations were comparable to CSF concentrations in all participants, with a geometric mean CSF to unbound plasma ratio of 1.15. The CSF and matched plasma concentrations for each participant are presented (Table 5).

3.5 | Pharmacokinetic Evaluation of SIR9900 in Urine

The amount of SIR9900 excreted unchanged in urine was negligible (<0.1%) following a single dose of 30 and 100 mg (Table S11).

TABLE 2 | Treatment-emergent adverse events, severity and causality.

	Part 1: Single ascending dose									Part 2: Multiple ascending dose							
	Cohort 1 SIR9900 3 mg	Cohort 2 SIR9900 10 mg	Cohort 3 SIR9900 30 mg (Fasted)	Cohort 3 SIR9900 30 mg (Fed)	Cohort 4 SIR9900 100 mg	Cohort 5 SIR9900 200 mg	Pooled active[b]	Pooled placebo (fasted)[a,b]	Overall	Cohort 1 SIR9900 3 mg	Cohort 2 SIR9900 10 mg	Cohort 3 SIR9900 30 mg	Cohort 5 SIR9900 30 mg (Elderly)	Cohort 4 SIR9900 60 mg	Pooled active	Pooled placebo	Overall
n	**6**	**5**	**6**	**6**	**6**	**6**	**29**	**10**	**39**	**8**	**8**	**8**	**7**	**9**	**40**	**9**	**49**
TEAEs, *n* (%) *m*																	
Any TEAEs	2 (33.3) 5	1 (20.0) 8	—	1 (16.7) 1	4 (66.7) 4	4 (66.7) 5	11 (37.9) 22	3 (30.0) 3	15 (38.5) 26	3 (37.5) 4	4 (50.0) 4	3 (37.5) 5	4 (57.1) 7	6 (66.7) 11	20 (50.0) 31	7 (77.8) 12	27 (55.1) 43
Any treatment-related TEAEs[c]	1 (16.7) 1	1 (20.0) 1	—	—	—	1 (16.7) 1	3 (10.3) 3	—	3 (7.7) 3	—	1 (12.5) 1	1 (12.5) 1	4 (57.1) 4	2 (22.2) 2	8 (20.0) 8	2 (22.2) 2	10 (20.4) 10
Any serious TEAEs	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Any TEAEs leading to study discontinuation	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Any TEAEs leading to study drug withdrawal	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Any TEAEs leading to death	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Severity of TEAEs, *n* (%) *m*																	
Mild	2 (33.3) 5	1 (20.0) 8	—	1 (16.7) 1	4 (66.7) 4	3 (50.0) 4	10 (34.5) 21	3 (30.0) 3	14 (35.9) 25	3 (37.5) 4	4 (50.0) 4	2 (25.0) 4	3 (42.9) 5	6 (66.7) 11	18 (45.0) 28	6 (66.7) 11	24 (49.0) 39
Moderate	—	—	—	—	—	1 (16.7) 1	1 (3.4) 1	—	1 (2.6) 1	—	—	1 (12.5) 1	0, 1[d]	—	1 (2.5) 2	1 (11.1) 1	2 (4.1) 3
Severe	—	—	—	—	—	—	—	—	—	—	—	—	1 (14.3) 1	—	1 (2.5) 1	—	1 (2.0) 1
Causality of TEAEs, *n* (%) *m*																	
Not related	0, 1[d]	0, 6[d]	—	1 (16.7) 1	1 (16.7) 1	2 (33.3) 2	3 (10.3) 10	1 (10.0) 1	5 (12.8) 12	1 (12.5) 2	2 (25.0) 2	1 (12.5) 3	0, 1[d]	1 (11.1) 5	5 (12.5) 13	3 (33.3) 5	8 (16.3) 18
Unlikely related	1 (16.7) 3	0, 1[d]	—	—	3 (50.0) 3	1 (16.7) 2	5 (17.2) 9	2 (20.0) 2	7 (17.9) 11	2 (25.0) 2	1 (12.5) 1	1 (12.5) 1	0, 2[d]	3 (33.3) 4	7 (17.5) 10	2 (22.2) 5	9 (18.4) 15

(Continues)

TABLE 2 | (Continued)

	Part 1: Single ascending dose										Part 2: Multiple ascending dose									
	Cohort 1 SIR9900 3 mg	Cohort 2 SIR9900 10 mg	Cohort 3 SIR9900 30 mg (Fasted)	Cohort 3 SIR9900 30 mg (Fed)	Cohort 4 SIR9900 100 mg	Cohort 5 SIR9900 200 mg	Pooled active[b]	Pooled placebo (fasted)[a,b]	Overall	Cohort 1 SIR9900 3 mg	Cohort 2 SIR9900 10 mg	Cohort 3 SIR9900 30 mg	Cohort 5 SIR9900 30 mg (Elderly)	Cohort 4 SIR9900 60 mg	Pooled active	Pooled placebo	Overall
n	6	5	6	6	6	6	29	10	39	8	8	8	7	9	40	9	49
Possibly related	1 (16.7)	1 (20.0)	—	—	—	1 (16.7)	3 (10.3)	—	3 (7.7)	—	1 (12.5)	1 (12.5)	4 (57.1)	2 (22.2)	8 (20.0)	2 (22.2)	10 (20.4)
							3								8	2	10
Probably related	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Definitely related	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Abbreviations: *n*, number of events; *n*, number of participants; TEAEs, treatment-emergent adverse events.
[a]The placebo (fed) group contained two participants and had nil TEAEs reported (not presented).
[b]Data presented for fasted dose administration.
[c]Treatment-related TEAEs are defined as any TEAEs reported with the causality of 'Possibly Related', 'Probably Related', 'Definitely Related' to study treatment deemed by the investigator.
[d]Participants were counted at most once in the participant count (n) column, for the TEAE of maximum severity or maximum relationship to study drug.

3.6 | Pharmacodynamic Evaluations

For Part 1 (SAD), the median p-RIPK1 concentration in stimulated PBMCs was reduced after administration of a single oral dose of SIR9900 at all timepoints across all dose levels (3 mg—200 mg). The median p-RIPK1 concentration decreased rapidly at 3 h post-dose demonstrating a >90% target engagement of SIR9900 to inhibit RIPK1 activity (−90.7% to −97.5% change from baseline). This inhibition effect was relatively maintained over 96 h at high dose (−90.7% at 200 mg), but gradually reduced at low doses (ranging from −73.7% at 10 mg to −85.2% at 30 mg), exhibiting an approximately dose dependent manner of target engagement inhibiting RIPK1 activity (Figure 2A; Figure S5A).

In Part 2 (MAD), the median p-RIPK1 concentration in stimulated PBMCs was reduced after multiple doses of SIR9900 in adults (3 mg) and elderly (30 mg) participants. A median percentage change from baseline of −84.9% and −98.2% was achieved, respectively, on Day 1 (3 h post-dose). A similar reduction in p-RIPK1 was observed during the 10-day treatment period across all timepoints, including the trough level at predose on Day 7 (reduced by approximately 90%), demonstrating a sustained inhibitory effect. The inhibition of p-RIPK1 was also maintained at >90% up to Day 14 (i.e., 96 h post Day 10 dose) for 30 mg SIR9900, compared with a change from baseline on Day 14 of −73.6% for 3 mg SIR9900 (Figure 2B; Figure S5B).

In comparison, the median p-RIPK1 concentrations in stimulated PBMCs in participants who had been administered a single or multiple doses of placebo appeared to remain close to baseline across all timepoints.

4 | Discussion

Scientific literature and findings from preclinical studies provide a compelling rationale that support the development of RIPK1 inhibitors, such as SIR9900, for the potential treatment of a range of human inflammatory, autoimmune and degenerative diseases [13, 14] including but not limited to multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis, and rheumatoid arthritis.

In this first-in-human study, there were no concerning safety features for SIR9900 observed. There were some variations in TEAE incidence among SIR9900 cohorts, however, no consistent dose-dependent trends of any TEAEs by SOC or PT were observed across SAD and MAD parts. The most commonly reported TEAEs were headache and gastrointestinal disorders. The incidence of TEAEs did not show obvious differences between participants administered SIR9900 and placebo except for gastrointestinal disorders (approximately 17% higher in both SAD and MAD parts), however, these gastrointestinal disorders were mild and did not appear to be dose-dependent and therefore were not considered a major safety concern.

The majority of TEAEs were deemed by the investigator to be unrelated to SIR9900. Most TEAEs were mild or moderate in severity, except for one severe TEAE of syncope observed in an elderly participant who received SIR9900 (30 mg; possibly related to study drug). This event resolved quickly without the

TABLE 3 | Summary of plasma pharmacokinetic parameters.

	Median (range)		Geometric mean (geometric CV%)						
Dose level	***n***	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC0-24 (h×ng/mL)**	**AUClast (h×ng/mL)**	**AUCinf (h×ng/mL)**	**$t_{1/2}$ (h)**	**Cl/F (L/h)**	**Vz/F (L)**
Part 1: Single ascending dose									
Cohort 1: 3 mg	6	1.50 (1.00–3.00)	35.02 (10.4)	274.1 (8.6)	538.0 (12.4)	645.0[a]14.8)	34.66[a] (12.4)	4.651 (14.8)	232.6 (12.6)
Cohort 2: 10 mg	5	3.25 (2.00–6.00)	107.0 (22.7)	1330 (10.0)	2890 (15.9)	3230[b] (23.4)	31.92[b] (25.7)	3.094 (23.4)	142.5 (15.8)
Cohort 3: 30 mg Fasted (Day 1)	6	3.00 (1.00–4.00)	327.9 (20.1)	3710 (25.6)	7990 (25.5)	9240 (29.8)	34.50 (26.1)	3.248 (29.8)	161.7 (25.4)
Cohort 3: 30 mg Fed (Day 10)	6	4.025 (2.03–8.00)	251.0 (21.7)	3890 (22.1)	8910 (23.0)	11,000 (29.1)	37.75 (29.3)	2.739 (29.1)	149.2 (23.1)
Cohort 4: 100 mg	6	3.00 (2.00–4.00)	941.2 (18.9)	10,500 (17.6)	21,600 (11.1)	25,700 (19.0)	33.16 (38.3)	3.886 (19.0)	185.9 (25.3)
Cohort 5: 200 mg	6	3.50 (2.02–4.58)	1880 (8.1)	20,700 (7.6)	45,500 (16.8)	53000[a] (25.9)	33.27[a] (33.0)	3.772 (25.9)	181.0 (10.3)
		T_{max} (h)	**C_{max} (ng/mL)**	**AUC_{tau} (h×ng/mL)**		**$t_{1/2}$ (h)**	**Cl/F (L/h)**		**V_z/F (L)**
Part 2: Multiple ascending dose									
Cohort 1: 3 mg QD (Day 1)	8	2.50 (1.00–4.05)	28.11 (22.5)	273.2 (27.7)		NE	NE		NE
Cohort 1: 3 mg QD (Day 10)	8	2.00 (1.00–4.00)	71.82 (20.9)	1043 (27.8)		38.32[a] (23.2)	2.877 (27.8)		148.0[a] (23.6)
Cohort 2: 10 mg QD (Day 1)	8	3.00 (1.00–4.00)	93.35 (27.1)	1079 (26.1)		14.52[c] (5.05)	5.148[c] (21.8)		107.8[c] (16.6)
Cohort 2: 10 mg QD (Day 10)	8	4.08 (0.50–4.13)	218.7 (27.6)	3073 (27.8)		34.00[a] (25.2)	3.254 (27.8)		171.4[a] (21.4)
Cohort 3: 30 mg QD (Day 1)	8	3.00 (2.00–4.20)	296.5 (22.0)	3662 (18.9)		NE	NE		NE
Cohort 3: 30 mg QD (Day 10)	8	3.01 (2.00–4.00)	601.0 (16.8)	8746 (19.0)		37.95[e] (25.2)	3.430 (19.0)		192.9[e] (23.3)
Cohort 4: 60 mg QD (Day 1)	9	2.05 (1.02–4.00)	650.9 (18.6)	7676 (19.8)		NE	NE		NE
Cohort 4: 60 mg QD (Day 10)	7	3.00 (2.00–6.00)	1233 (15.3)	18,634 (9.75)		41.88[e] (39.4)	3.220 (9.75)		191.8[e] (37.0)
Cohort 5: 30 mg QD (Day 1 Elderly)	7	3.00 (2.00–4.00)	332.3 (15.9)	3815 (20.5)		9.550[d] (NE)	NE		NE
Cohort 5: 30 mg QD (Day 10 Elderly)	7	2.00 (1.00–3.00)	609.9 (28.3)	8182 (34.5)		32.83[b] (32.9)	3.667 (34.5)		207.1[b] (25.9)

Note: Number of evaluated samples indicated if less than the full cohort: [a]$n = 5$; [b]$n = 4$; [c]$n = 2$; [d]$n = 1$; [e]$n = 6$. Missing plasma samples in Part 1 and Part 2 did not have an obvious impact on the calculated PK parameters.
Abbreviations: $AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time 0 to 24 h; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the last quantifiable measurement; AUC_{tau}, area under the plasma concentration-time curve from time 0 to the end of dosing interval; C_{max}, maximum observed plasma concentration; Cl/F = SIR9900 clearance following oral route of administration; CV%, Coefficient of variation; NE, not estimable; QD, once daily; $t_{½}$, terminal elimination half-life; T_{max}, time to C_{max}; V_z/F, the apparent volume of distribution.

TABLE 4 | Assessment of dose proportionality.

Day	Pharmacokinetic parameter	No. of observations	Beta estimate	Lower CL	Upper CL	r^2	Criterion
Part 1: Single ascending dose							
1	Log (C_{max})	29	0.946	0.913	0.979	0.99	(0.8350, 1.1650)
1	Log ($AUC_{0\text{-}24}$)	29	1.007	0.965	1.048	0.98	
1	Log (AUC_{last})	29	1.024	0.977	1.071	0.98	
1	Log (AUC_{inf})	26	1.023	0.965	1.080	0.97	
Part 2: Multiple ascending dose							
1	Log (C_{max})	33	1.047	0.991	1.104	0.97	(0.7686, 1.2314)
1	Log (AUC_{tau})	33	1.114	1.057	1.172	0.97	
1	Log (AUC_{last})	33	1.114	1.056	1.171	0.97	
10	Log (C_{max})	31	0.942	0.888	0.997	0.97	
10	Log (AUC_{tau})	31	0.955	0.896	1.015	0.96	
10	Log (AUC_{last})	31	0.996	0.914	1.078	0.94	

Note: A power model assessed dose proportionality: Natural log-transformed (PK parameter result) = $\alpha + \beta \times$ Natural Log-transformed (Dose). Dose proportionality was declared if the 90% confidence interval for the estimated slope (β) is within the range of [1+ ln(0.5)/ln(r), 1+ ln(2.0)/ln(r)], where r is the dose range (r = the highest dose/the lowest dose).
Abbreviations: $AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time 0 to 24 h; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the last quantifiable measurement; AUC_{tau}, area under the plasma concentration-time curve from time 0 to the end of dosing interval; CL, confidence limit; C_{max}, maximum observed plasm concentration; NE, not estimable.

TABLE 5 | Summary of SIR9900 concentrations in cerebrospinal fluid and plasma following daily 30 mg doses in healthy adults.

Participant number	CSF concentration (ng/mL)	Plasma concentration (ng/mL)	The concentration ratio of CSF and unbound plasma[a]
1	7.43	532.76	1.28
2	5.72	419.45	1.25
3	4.33	434.34	0.915
4	5.82	401.67	1.33
5	7.44	607.21	1.12
6	4.26	307.65	1.27
7	5.16	523.70	0.904
8	5.54	428.20	1.19
Statistics			
n	8	8	8
Geometric mean	5.60	448	1.15
Geometric CV%	21.3	21.2	15.3

Abbreviations: CSF, cerebrospinal fluid; CV%, coefficient of variation.
[a]The concentration ratio of CSF and unbound plasma was calculated as: CSF concentration/(Plasma concentration × human plasma unbound fraction), on Day 8. The human unbound fraction was determined to be 0.0109.

need for additional treatment and did not result in study drug withdrawal or discontinuation from the study. Notably, no similar cases were reported even among participants who received higher doses of SIR9900. Furthermore, no other RIPK1 inhibitors have reported such risks. Therefore, this isolated case does not necessarily indicate a safety concern. No clinically meaningful trends were identified from ECG, vital signs or clinical laboratory results. Though few abnormalities were noted, most were considered not clinically significant.

Currently, the RIPK1 inhibitors under clinical development [13] and similar to SIR9900 have been found to be generally well tolerated [17, 18]. No mechanism-based adverse effects have been identified to date [13]. Commonly reported TEAEs in healthy

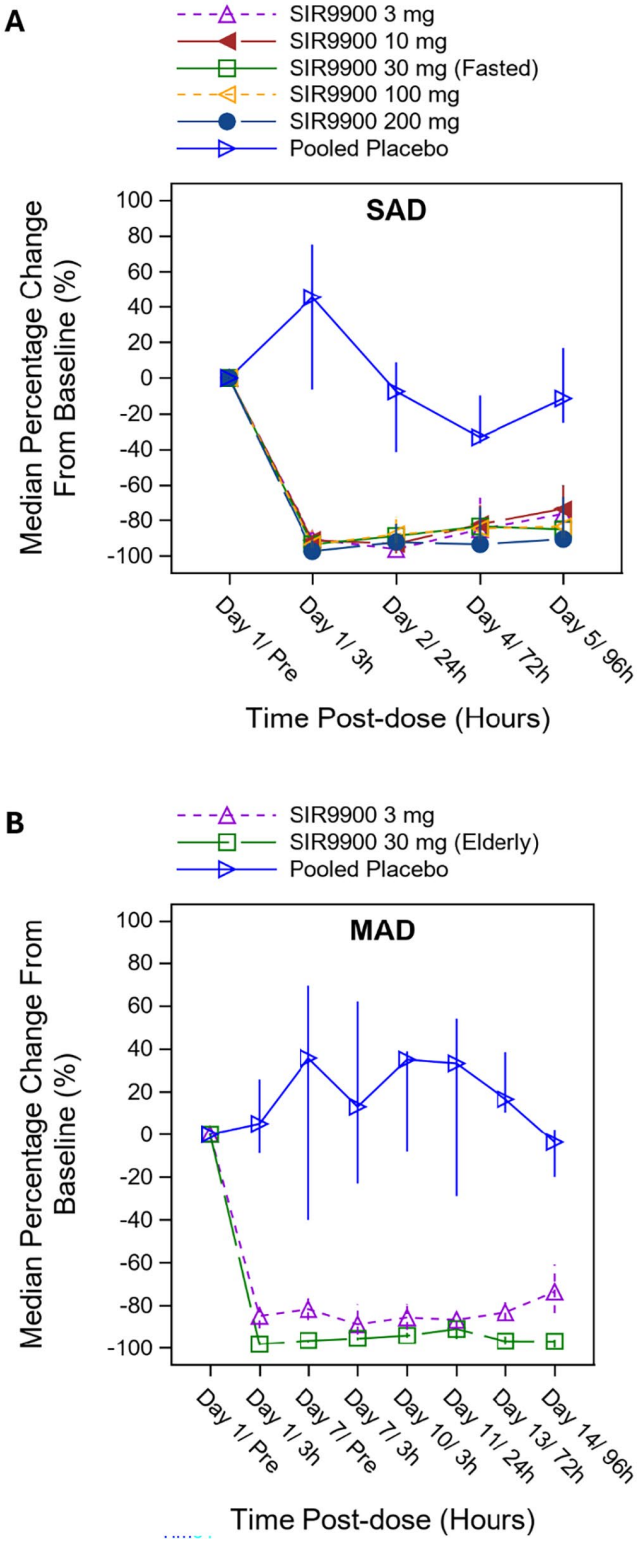


FIGURE 2 | Percentage change from baseline over time for p-RIPK1 concentrations. Percentage change from baseline of p-RIPK1 concentrations in PBMCs. (A) stimulated PBMCs following a single dose at 3, 10, 30, 100, and 200 mg SIR9900 or placebo; (B) stimulated PBMCs following repeated dose at 3 mg (adult), 30 mg (elderly) SIR9900 or placebo. h, hours; MAD, multiple ascending dose; PBMCs, peripheral blood mononuclear cells; PD, pharmacodynamic; p-RIPK1, phosphorylated receptor interacting protein kinase 1; SAD, single ascending dose.

volunteer studies (e.g., GSK2982772 [17, 18], DNL747 [16], DNL788 [19], DNL104 [15]) included contact dermatitis, headache, ventricular tachycardia, abnormal dreams, fatigue, dizziness, lethargy, and study procedure-related disorders. SIR9900 did not raise any significant safety concerns during dose escalation and demonstrated a favorable safety profile that is generally consistent with other RIPK1 inhibitors, including those capable of penetrating the blood brain barrier.

SIR9900 demonstrated favorable pharmacokinetic properties. The $t_{1/2}$ of over 30 h supports once-daily dosing. The dose proportionality observed ensures a predictable and linear relationship between dosage and systemic exposure, facilitating safe and effective dose adjustments without complex pharmacokinetic considerations. Food did not appreciably affect total systemic exposure of SIR9900. This enhances dosing flexibility and convenience for medication adherence. Meanwhile, the similar systemic exposure observed in elderly and adult participants suggests that no dose adjustment is needed for the elderly population. Additionally, one of the primary challenges in developing RIPK1 inhibitors for potential neurodegenerative disease therapies in the CNS is the drug's ability to cross the blood–brain barrier [13]. The unbound concentration of SIR9900 in plasma and CSF were similar (geometric mean CSF to unbound plasma ratio of 1.15; this is similar to that reported for DNL788 which ranged from 0.8 to 1.3 [19]). This suggests that SIR9900 effectively penetrates the blood–brain barrier and could, therefore, be a viable candidate for treating CNS conditions.

SIR9900 demonstrated a relatively broad safety margin from 3 to 60 mg, with approximately 90% peripheral target engagement at 3 h post-dose from the lowest dose level and also a sustained RIPK1 inhibition effect, even at trough levels over the 10-day multiple dose treatment period. Evidence of robust pharmacodynamic effect as demonstrated in peripherally-stimulated PBMCs, together with blood–brain barrier permeability, are important findings which support the clinical development of SIR9900 as a potential treatment for RIPK1-related neurodegenerative conditions in the CNS.

Considering neurodegenerative conditions primarily occur in older age populations, this study included evaluation of SIR9900 in a healthy elderly population. There was no obvious difference in the incidence of TEAEs between elderly and adult participants, and no specific concentrated TEAE was observed in the elderly group. Therefore, the overall safety profile of a relatively high and potential treatment level dose of SIR9900 in elderly participants is reassuring. Furthermore, systemic exposure to SIR9900 in healthy elderly participants was similar to healthy adults. Importantly, SIR9900 also demonstrated a robust target engagement effect in stimulated PBMCs from these elderly participants. Together, this data suggests that SIR9900 has a comparable response in adults and elderly people.

Limitations of the study include a short dosing duration with a small study population composed of healthy participants. The food-effect study is indicative only as it was not powered to provide definitive results. Therefore, the current findings may not fully reflect the impact of SIR9900 on long-term treatment of

patients with neurodegenerative conditions, many of whom may have other medical conditions or may use other medications that may affect the pharmacokinetic parameters of SIR9900. In addition, the pharmacodynamic effects are limited to the peripheral circulation instead of the target organ, especially in brain tissue due to technological barriers and ethical considerations.

5 | Conclusions

The favorable safety, pharmacokinetic, and pharmacodynamic profile in healthy adult and elderly participants, along with blood–brain barrier permeability suggest SIR9900 has development potential for the treatment of inflammatory, autoimmune, and neurodegenerative diseases by inhibiting RIPK1 activity. Further clinical trials are recommended in specific disease populations, especially those with CNS disorders.

Author Contributions

O.M.G., T.P., Y.S., B.W., F.X., Y.M., L.S., P.S., and W.F. wrote the manuscript. O.M.G., Y.S., B.W., Y.M., L.S., and P.S. designed the research. O.M.G., T.P., Y.S., and B.W. performed the research. O.M.G., Y.S., B.W., F.X., Y.M., L.S., and P.S. analyzed the data.

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Conflicts of Interest

Yang Shen, Buwei Wang, Fenchao Xue, Yongfen Ma, Linan Song, Pei Sun [3], and Weiliang Fan [3] are employees of Sironax Ltd. (Sironax). All other authors declared no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.