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Safety, Tolerability, and Pharmacokinetics of SC1011 (Sufenidone), a Novel Antifibrotic Small Molecule, in Phase 1 Studies in Healthy Subjects

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ABSTRACT

SC1011 (sufenidone) is a novel pyridone derivative with therapeutic potential for idiopathic pulmonary fibrosis (IPF). Two Phase 1 studies evaluated the safety and pharmacokinetics of single (SAD) and multiple ascending doses (MAD) of SC1011 immediate-release (IR) and modified-release (MR) oral formulations in healthy adult subjects. In Phase 1a, subjects were randomized to receive oral SC1011 IR or placebo in SAD (50 mg-300 mg) or MAD (100 mg and 200 mg) twice daily for 7 days. The Phase 1b study consisted of three treatment groups that received 100, 150, or 200 mg SC1011 MR twice daily for 7 days. SC1011 IR was absorbed rapidly (mean time to maximum concentration, T_{max} ≤1 h) and eliminated rapidly (mean terminal half-life, $t_{1/2}$: 1.23–2.64 h) following 50–300 mg single-dose administrations. Reduced maximum plasma concentration (C_{max}), delayed T_{max}, and comparable total exposure were observed with the MR formulation compared with the IR formulation. Both formulations demonstrated dose-proportional pharmacokinetics at the applied dose ranges, and no obvious accumulation of systemic exposure was observed upon repeated administration. All treatment-emergent adverse events (TEAEs) with both formulations were mild or moderate in severity, and gastrointestinal reactions were the most frequently reported TEAEs. The tolerability of SC1011 was markedly improved with the MR formulation. Exposure–adverse event (AE) analysis with the most frequent AEs identified C_{max} rather than total exposure as a good predictor of AEs. Compared to the IR formulation, SC1011 MR demonstrated improved exposure and tolerability, supporting its further development in patients with IPF.

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Summary

- What is the current knowledge on the topic?
  - SC1011 is a novel pyridone derivative with therapeutic potential for idiopathic pulmonary fibrosis (IPF), a rare, devastating disease with a great unmet medical need.
- What question did this study address?
  - Two Phase 1 studies evaluated the safety and pharmacokinetics of both Immediate-release (IR) and modified-release (MR) formulations of SC1011.
- What does this study add to our knowledge?
  - Modified release formulation of SC1011 obtained similar total exposure as the immediate release formulation while reducing peak concentration, resulting in improved safety and tolerability. Peak plasma concentration rather than total exposure was identified as a good predictor of adverse events.
- How might this change clinical pharmacology or translational science?
  - By minimizing side effects, SC1011 MR has the potential to increase drug exposure, enhance medication adherence, and improve therapeutic effects in Phase 2 trials with IPF patients.

1 | Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic interstitial lung disease characterized by irreversible and progressive decline in lung function. The median survival is approximately 2–5 years after diagnosis [1]. The incidence of idiopathic pulmonary fibrosis has risen over time, and in Europe and North America, it is estimated to range between 2.8 and 18 cases per 100,000 people per year [2].

Pirfenidone and nintedanib are the only approved IPF therapies, and over 20 drugs have failed at different stages of development in the past decades [3–7]. Pirfenidone is a pyridone compound that has antifibrotic and anti-inflammatory properties. These anti-inflammatory effects may account for some of pirfenidone's antifibrotic effects [8]. Nintedanib is an indolinone derivative that potently inhibits receptor tyrosine kinases PDGFR, FGFR, and VEGFR [9]. Although both pirfenidone and nintedanib reduced the rate of FVC decline in IPF Phase 3 trials, neither molecule could stop or reverse disease progression [10]. Additionally, both treatments are associated with side effects that lead to dose reduction or discontinuation [11, 12]. For example, dosage reduction or interruption for gastrointestinal events (nausea, vomiting, etc.) was required in 18.5% of the patients in clinical studies of pirfenidone (ESBRIET label). Two real-world evidence studies from Spain and Japan recently reported that discontinuation rates due to adverse events (AEs) among patients with IPF using pirfenidone were 23.1% and 31.2%, respectively [11, 12]. Modified-release formulations are commonly applied to therapeutics to decrease patient burden, improve adherence, and enhance the overall patient experience [13, 14]. However, a modified release (MR) formulation of pirfenidone has not yet been developed in most countries. This may be partially due to the high daily dose of pirfenidone (2403 mg/day) and the challenges in achieving bioequivalence with the MR formulation [15]. Therefore, there is still a great unmet medical need for IPF, given the limitations of current therapies [2].

SC1011 (sufenidone) is a novel pyridone derivative designed to improve potency and safety over pirfenidone. In preclinical studies, SC1011 demonstrated superior anti-inflammatory and antifibrotic biological activities, favorable PK properties, and good safety profiles across multiple species (unpublished data). Currently, a Phase 2 clinical trial is ongoing to explore the therapeutic potential of SC1011 in IPF patients.

Here, we report the results of two Phase 1 clinical studies that assessed the safety, tolerability, and pharmacokinetic profile of SC1011 in healthy subjects. In the Phase 1a study, SC1011 was administered orally as an immediate-release (IR) formulation for single and multiple ascending doses. This study also provides a preliminary evaluation of the food effects on exposure. In addition to the IR formulation, a modified-release (MR) formulation of SC1011 was developed and evaluated in a Phase 1b study to assess which formulation will be developed further.

2 | Methods

2.1 | Study Design and Treatment

2.1.1 | Phase 1a: Immediate-Release Formulation (IR)

This Phase 1a study (NCT06160440) was conducted between June 3, 2021, and March 23, 2022, at The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou, China. The study adhered to the principles outlined in the Declaration of Helsinki and the Guidance on Good Clinical Practice. The independent ethics committee (IEC) of the hospital reviewed and approved the study (Approval No: ZYYEC [2020(031)]). Written informed consent was obtained from all participants prior to their enrollment in the study.

This single-center, randomized, double-blind, placebo-controlled trial investigated the effects of single and multiple ascending doses of immediate-release SC1011 in healthy subjects. A higher dose was initiated in the next group only once the preceding dose level was judged safe and well tolerated. In the single ascending-dose (SAD) phase (Figure 1A), the effect of food on the tolerability and PK of a single dose was assessed in a separate group of healthy participants.

In the SAD phase, 27 healthy participants were enrolled in a total of four groups, including 50, 150, 300, and 150 mg FE. A starting dose of 50 mg was selected according to the human equivalent dose (HED) of the most sensitive species NOAEL. A safety margin of approximately 10-fold was selected to ensure the safety of participants. The 50 mg group served as a pilot cohort, with all three participants receiving active treatment. The 150 and 300 mg groups each had eight participants who were randomized to receive active treatment ($n = 7$) or placebo ($n = 1$). The 150 mg FE group ($n = 8$) received active treatment after a standard (not high-fat) meal (250 mL milk,

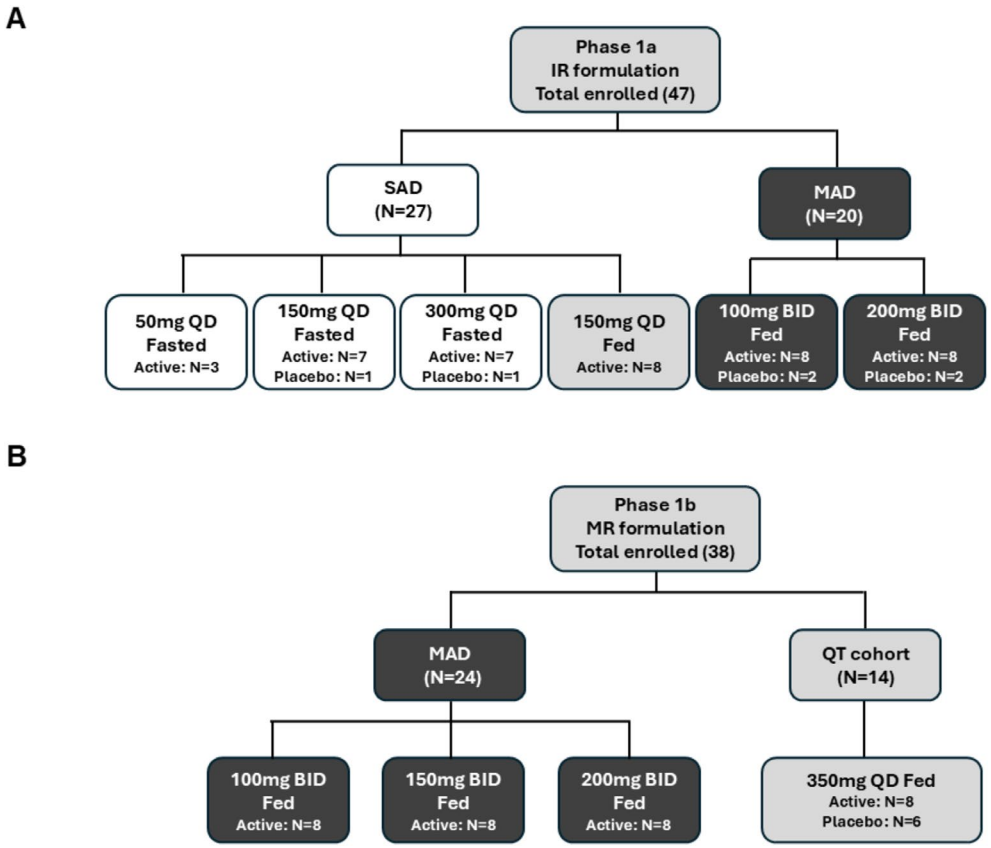


FIGURE 1 | Study design of Phase 1a (A) and Phase 1b (B). IR, immediate release; MR, modified release; BID, twice daily; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose; QT, QT study to assess cardiac risk.

one meat bun, and one vegetable bun). The doses for all other groups were administered under fasting conditions (overnight fasting of ≥ 10 h).

In the multiple ascending dose (MAD) phase (Figure 1A), 20 participants were divided into two groups (100 mg BID and 200 mg BID) after reviewing the safety, tolerability, and PK of the SAD phase. Within each group, 10 participants were randomized to receive either SC1011 IR ($n = 8$) or placebo ($n = 2$). One-hundred milligram or 200 mg SC1011 IR or placebo was administered after a standard meal twice daily (BID) from Day 2 to Day 6, or once daily (QD) on Day 1 and Day 7.

2.1.2 | Phase 1b: Modified-Release Formulation (IR)

This Phase 1b study (NCT06135363) was conducted between August 1, 2022, and January 16, 2023, at Shanghai Xuhui District Central Hospital, Shanghai, China. The study adhered to the principles outlined in the Declaration of Helsinki and the Guidance on Good Clinical Practice. Approval was obtained from the Institutional Review Board of Shanghai Xuhui Central Hospital (Approval No: [2022(022)]). Written informed consent was obtained from all participants prior to their enrollment in the study.

An open-label study assessed the effects of multiple doses of modified-release SC1011 in healthy subjects (Figure 1B). In this study, 24 participants were divided into three groups ($n = 8$/group): 100, 150, and 200 mg BID. For each group, 100, 150, or 200 mg of SC1011 MR was administered after a standard meal twice daily (BID) from Day 2 to Day 6 or once daily (QD) on Day 1 and Day 7. A higher dose was initiated in the next group only once the preceding dose level was judged safe and well tolerated. In a separate cohort of the Phase 1b study, an exploratory QT study with a randomized, double-blinded placebo control ($n = 6$) was conducted after a single supratherapeutic dose of 350 mg ($n = 8$) as the highest dose expected to be sufficiently tolerable to complete the QT study assessments (Figure 1B).

2.2 | Study Participants

Both the Phase 1a and Phase 1b studies enrolled healthy male and female participants aged 18–45 years with a body mass index (BMI) of 19–27 kg/m² (Phase 1a) or 19–26 kg/m² (Phase 1b). The Participants were assessed as healthy by physical examination, vital sign measurements, 12-lead electrocardiogram (ECG), chest X-ray imaging, abdominal ultrasonography, and clinical laboratory evaluations. Volunteers were excluded from the study if they had a QTcF of > 450 ms (men) or > 470 ms (women).

2.3 | Safety Assessments

The safety and tolerability of SC1011 were assessed by monitoring adverse events (AEs) throughout the studies. Additional safety assessments included physical examinations, vital signs,

clinical laboratory tests, and electrocardiogram (ECG). These analyses were performed during the initial screening, treatment, and exit assessments (within 2 days of the last PK blood sample collection) and at follow-up (within 7 days of the exit assessment).

In the QT cohort of Phase 1b, ambulatory ECG monitoring was performed from 1 h before to 24 h after single-dose administration. ECGs were acquired by the Dimao DMI-RH12 Holter Recorder (DM Information Co. Ltd., Guangzhou), which continuously recorded and digitized 12-lead ECGs. Data were transferred through Cardiovision software from the Holter to the computer. For replicate extraction at each time point, three 10-s windows on the nominal time point (± 10 min) were extracted using CarScan12 software, and all data were stored on the local server. PK samples were collected immediately after the ECG extraction at each time point. Predose data were collected 30, 20, and 10 min prior to dosing. Postdose data were collected at 1, 2, 4, 6, 8, 12, and 24 h (D2) postdosing. The QTcF values were calculated using Fridericia's correction based on the QT interval (QT) and heart rate (HR) values, which were obtained directly from the scanning or monitoring results.

2.4 | Pharmacokinetic Assessments

Blood samples were collected at several time points and analyzed to determine the concentration of SC1011. In the SAD Part of Phase 1a, blood samples were collected predose and at various time points up to 48 h postdose. In the MAD part of Phase 1a, blood samples were collected predose and up to 10 h postdose on Day 1, predose and 10 h on Day 6, and up to 48 h postdose on Day 7. Urine samples were obtained from the SAD 300 mg and food effect (150 mg) group at intervals 0–4, 4–8, 8–12, 12–24, 24–36, and 36–48 h postdose.

In the MAD Part of Phase 1b, blood samples were collected predose and up to 24 h postdose on Day 1, predose on Days 5 and 6, and up to 48 h postdose on Day 7. In the QT Part (350 mg) of Phase 1b, blood samples were collected predose and at various time points up to 24 h postdose.

Plasma and urine samples were analyzed using validated, sensitive, and specific liquid chromatography–tandem mass spectrometry at Wuhan Hongren Biopharmaceutical Inc. (Wuhan, China). The lower limits of quantification (LLOQ) for SC1011 in the plasma were 10 ng/mL (Phase 1a) and 5 ng/mL (Phase 1b). The LLOQ for SC1011 in urine was 2.5 ng/mL.

2.5 | Pharmacokinetic Analysis

PK calculations were performed using Phoenix WinNonlin 8.3.4 (Pharsight Corporation, Palo. Alto, California). The PK parameters determined for SC1011 included the maximum observed plasma concentration (C_{max}), the time of occurrence of C_{max} (T_{max}), the trough plasma concentration observed at the end of the dosing interval (C_τ), the area under the plasma drug concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the area under the plasma drug concentration-time curve over the dosing interval ($AUC_{0-\tau}$), the area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration, t (AUC_{0-t}), the area under the plasma drug concentration-time curve over 24 h (AUC_{0-24}), the first-order terminal half-life ($t_{1/2}$), apparent total plasma clearance (CL_z/F), apparent volume of distribution during the terminal elimination phase (V_z/F), renal clearance (CL_R), the amount excreted unchanged in urine over 48 h (Ae_{0-48}), fraction excreted unchanged in urine over 48 h (Fe_{0-48}), accumulation ratio based upon C_{max} or $AUC_{0-\tau}$ from Day 7 compared with Day 1 (Ra).

2.6 | Statistical Analyses

In both studies, all the subjects who received at least one dose of the study drug were included in the safety analysis. All subjects who received at least one dose of the study drug and had evaluable data excluding all major protocol violations were included in the PK analysis. Subjects who received placebo were combined into one cohort for statistical analysis, whereas those receiving active treatment were analyzed separately.

Dose proportionality was assessed using a power model of natural log-transformed C_{max} and AUC as follows: Ln (parameter) = $\alpha + \beta \times$ Ln (dose). The corresponding 95% CI of the regression slope β was also calculated. The results were considered dose-proportional if the 95% CI contained the value of 1.

The achievement of a steady state after multiple dosing was assessed using linear regression of three consecutive predose concentrations. A steady state was considered to be achieved if the 95% CI of the slope contained the value 0.

In Phase 1a, the effect of food (standard meal) was assessed by analyzing AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The PK parameters were naturally log-transformed prior to ANOVA with treatment as a fixed effect. If the 90% CI for the adjusted geometric mean ratio (fed/fasted) for the evaluated PK parameters fell within the 80%–125% equivalence interval, no significant difference between fed and fasted states was concluded for that parameter; that is, food had no effect on the pharmacokinetics of SC1011. A nonparametric test (Wilcoxon signed-rank test) was used to compare postprandial and fasting C_{max}, AUC, and T_{max}.

Data from subjects receiving active treatment in both Phase 1a ($N = 41$) and Phase 1b ($N = 32$) were pooled ($N = 73$) to assess the difference between subjects with and without TEAEs of interest using the Mann–Whitney test and explore the predictive value of two PK parameters (C_{max} and AUC_{0-t} on Day 1) for adverse events using receiver operating characteristic (ROC) curve analysis. The difference in PK parameters (C_{max} or AUC) between the groups of subjects with and without the TEAEs of interest was analyzed with the Mann–Whitney test. For ROC analysis, PK parameters (C_{max} or AUC) for subjects without the TEAEs of interest were entered as Control values, and subjects with the TEAEs of interest were entered as Patient values, and the Wilson/Brown method was selected for confidence level (95%) determination. Nausea and vomiting were included as GI AEs. Dizziness, headache, and somnolence were included as CNS AEs. ROC curves were plotted using GraphPad software (version 8.0). The cut-off values for the prediction of AEs

were determined as the point at which Youden's index (sensitivity + specificity −1) was maximized.

3 | Results

3.1 | Participant Disposition and Demographics

Phase 1a was the first-in-human study of SC1011 IR (Table S1). A total of 27 and 20 healthy participants were enrolled in the single ascending dose (SAD) and multiple ascending dose (MAD) groups, respectively. The mean age of the participants in Phase 1a ranged from 23 to 31 years for the different groups, and the majority were male Han Chinese.

In Phase 1b, 38 healthy Chinese participants were enrolled (Table S1). A total of 24 participants received multiple doses of SC1011 MR, and 14 participants received a single dose of 350 mg SC1011 MR or placebo for QT exploration. The participants enrolled in Phase 1b were mostly Han Chinese men with a mean age of 30–32 years for different groups.

There were no significant differences in the demographic characteristics between the placebo and active treatment groups in either the Phase 1a or Phase 1b studies.

3.2 | Safety and Tolerability

3.2.1 | Phase 1a: SAD and MAD of IR Formulation

After single oral doses of SC1011 IR in the fasted state, the incidence rates of Treatment-emergent adverse events (TEAEs) were 66.7%, 100%, 100%, and 50.0% in the 50, 150, 300 mg, and placebo groups, respectively (Table S2). These AEs were largely driven by nausea, vomiting, and dizziness. In the Phase 1a MAD study, the incidence of TEAE in the 100 mg BID (200 mg daily), 200 mg BID (400 mg daily), and placebo groups was 100%, 100%, and 75.0%, respectively. The most common AEs by organ class were gastrointestinal disorders, which were reported in 100% of participants receiving SC1011 IR and in 50% of participants treated with placebo. The second most common AEs by organ class were nervous system disorders, which were reported in 25%, 75%, and 100% of the participants receiving placebo, 100 and 200 mg BID, respectively.

All AEs in Phase 1a were mild or moderate in severity and were resolved before the end of the study (Table 1). No temporary discontinuations or dose reductions owing to AEs were reported in this study. Six subjects withdrew from the trial due to AEs. In the 100 mg BID group, one case experienced premature ventricular contraction and withdrew from the study before the second dose of D1. In the 200 mg BID group, five subjects withdrew from the study because of nausea, vomiting, dizziness, and other adverse events. Considering the high incidence of AEs and low adherence of subjects in the 200 mg BID group, a joint decision for early termination of the trial was made by the investigator and sponsor. No data were collected on D7 for the 200 mg BID group due to the early termination of the study. To mitigate adverse events, a modified release (MR) formulation of SC1011 was developed and evaluated in the following Phase 1b study.

3.2.2 | Phase 1b: MR Formulation

In the Phase 1b study, 35 participants out of the 38 participants completed the study, with three subjects from the 200 mg BID group withdrawing from the trial due to AEs (Table S3). One subject experienced moderate nausea and mild vomiting, one experienced mild vomiting, and one experienced a moderate headache.

All AEs in Phase 1b were mild or moderate in intensity. The incidence rates of TEAEs in the 100 mg BID (200 mg daily), 150 mg BID (300 mg daily), 200 mg BID (400 mg daily), 350 mg, and placebo groups were 25%, 75%, 87.5%, 75%, and 66.7%, respectively. The most frequently reported TEAEs following multiple doses of SC1011 MR were gastroesophageal reflux disease (33.3%), nausea (33.3%), headache (16.7%), abdominal distension (16.7%), and decreased appetite (16.7%) (Table 2).

All 14 volunteers in the QT cohort had QTc data for analysis. Categorical analyses of QTcF, PR, QRS, and heart rate are summarized in Table S4. No clinically relevant changes in heart rate, PR interval, or QRS interval were observed in either treatment group (Table S4). Categorical analyses of both the raw QTcF values and the change from baseline QTcF values provided evidence that SC1011 did not prolong the QTc interval. None of the participants in our study had a QTcF > 450 ms. None of the SC1011 or placebo QTcF values changed from the baseline to > 30 ms (Table S4).

3.3 | Pharmacokinetics

3.3.1 | Phase 1a: SAD and MAD of IR Formulation

Following oral administration of single doses of SC1011 IR from 50 to 300 mg. In the fasted state, SC1011 was absorbed rapidly with mean T_{max} values ranging from 0.79 to 1.00 h (Table 3A). After reaching T_{max}, the plasma concentrations declined quickly, and the mean terminal half-life ($t_{1/2}$) ranged from 1.23 to 2.64 h. AUC0−∞ and C_{max} increased proportionally for the IR formulation (Figure S1 and Table S5). Across all dosages, mean oral clearance values ranged from 35 to 48 L/h, and mean apparent oral volume of distribution values ranged from 74 to 124 L (Table 3A).

Administration of IR 150 mg after a standard meal slightly decreased the C_{max}, and the AUC was slightly reduced compared with fasted conditions. The ratios of geometric means between the fed and fasted states at 150 mg SC1011 were 69% (49% ~ 97%) and 86% (58% ~ 128%) for C_{max} and $AUC_{0-\infty}$, respectively. A significant delay in T_{max} was observed in the fed group (median T_{max}, 2.00 h) compared with that in the fasted state (median T_{max}, 1.00 h). Following a single oral administration of SC1011 IR, the 48-h cumulative urinary excretion rates (Fe_{0-48h}/F) were 0.20% ± 0.11% and 0.29% ± 0.18% for 150 mg (fed) and 300 mg (fasted), respectively (Table 3A).

The multiple-dose PK parameters of SC1011 IR are presented in Table 3B. On Day 7, following multiple-dose administration of SC1011 IR 100 mg BID (200 mg daily) after a standard meal,

TABLE 1 | Treatment-emergent adverse events (TEAEs) per treatment group in Phase 1a.

Phase 1a SAD					
SOC PT[a]	**Placebo (*n* = 2)**	**50 mg fasted (*n* = 3)**	**150 mg fasted (*n* = 7)**	**150 mg fed (*n* = 8)**	**300 mg fasted (*n* = 7)**
Overall total *n* (%)	1 (50.0)	2 (66.7)	7 (100.0)	7 (87.5)	7 (100.0)
Gastrointestinal disorders *n* (%)	0 (0)	1 (33.3)	7 (100.0)	6 (75.0)	7 (100.0)
Nausea *n* (%)	0 (0)	0 (0)	7 (100.0)	4 (50.0)	7 (100.0)
Vomiting *n* (%)	0 (0)	0 (0)	5 (71.4)	1 (12.5)	6 (85.7)
Nervous system disorders *n* (%)	0 (0)	0 (0)	7 (100.0)	5 (62.5)	7 (100.0)
Dizziness *n* (%)	0 (0)	0 (0)	7 (100.0)	5 (62.5)	7 (100.0)
Investigations *n* (%)	1 (50.0)	1 (33.3)	0 (0)	3 (37.5)	7 (100.0)
Prothrombin level increased *n* (%)	1 (50.0)	1 (33.3)	0 (0)	0 (0)	6 (85.7)
Occult blood positive *n* (%)	0 (0)	1 (33.3)	0 (0)	2 (25.0)	2 (28.6)
Skin and subcutaneous tissue disorders *n* (%)	0 (0)	1 (33.3)	2 (28.6)	1 (12.5)	6 (85.7)
Cold sweat *n* (%)	0 (0)	0 (0)	2 (28.6)	1 (12.5)	6 (85.7)

Phase 1a MAD			
SOC PT[a]	**Placebo (*n* = 4)**	**200 mg (*n* = 8)**	**400 mg (*n* = 8)**
Overall total *n* (%)	3 (75.0)	8 (100.0)	8 (100.0)
Gastrointestinal disorders *n* (%)	2 (50.0)	8 (100.0)	8 (100.0)
Nausea *n* (%)	1 (25.0)	6 (75.0)	8 (100.0)
Vomiting *n* (%)	0 (0)	2 (25.0)	7 (87.5)
Gastroesophageal reflux disease *n* (%)	0 (0)	3 (37.5)	0 (0)
Eructation *n* (%)	0 (0)	3 (37.5)	0 (0)
Abdominal pain *n* (%)	0 (0)	0 (0)	2 (25.0)
Abdominal distension *n* (%)	0 (0)	2 (25.0)	0 (0)
Dyspepsia *n* (%)	0 (0)	0 (0)	2 (25.0)
Nervous system disorders *n* (%)	1 (25.0)	6 (75.0)	8 (100.0)
Dizziness *n* (%)	1 (25.0)	6 (75.0)	8 (100.0)
Headache *n* (%)	1 (25.0)	0 (0)	3 (37.5)
Skin and subcutaneous tissue disorders *n* (%)	1 (25.0)	3 (37.5)	6 (75.0)
Hyperhidrosis *n* (%)	1 (25.0)	2 (25.0)	5 (62.5)
Cold sweat *n* (%)	0 (0)	1 (12.5)	2 (25.0)
Metabolism and nutrition disorders *n* (%)	1 (25.0)	1 (12.5)	3 (37.5)
Decreased appetite *n* (%)	0 (0)	1 (12.5)	3 (37.5)
Infections and infestations *n* (%)	2 (50.0)	1 (12.5)	0 (0)
Urinary tract infection *n* (%)	1 (25.0)	1 (12.5)	0 (0)

Note: Data are presented as the number of participants (percentage).
[a]For preferred term (PT), only TEAEs occurring in ≥ 2 subjects for either SAD or MAD are listed in the Table.

SC1011 was rapidly absorbed and eliminated with a mean T_{max} of 2.00 h and $t_{1/2}$ of 2.61 h (Table 3B). The accumulation ratio (Ra, Day 7/Day 1) was 1.47 ± 0.46 fold for $AUC_{0-\tau}$ and 1.34 ± 0.30 fold for C_{max} (Table 3B). On Day 6, a steady state was reached after BID dosing, based on a comparison of three predose trough concentrations on Day 6 and Day 7 (Table S6).

TABLE 2 | Treatment-emergent adverse events (TEAEs) per treatment group in Phase 1b.

SOC PT[a]	Placebo (*N* = 6)	100 mg BID (*N* = 8)	150 mg BID (*N* = 8)	200 mg BID (*N* = 8)	350 mg (*N* = 8)	Active total (*N* = 32)
Overall Total *n* (%)	4 (66.7)	2 (25.0)	6 (75.0)	7 (87.5)	6 (75.0)	21 (65.6)
Gastrointestinal disorders *n* (%)	1 (16.7)	1 (12.5)	4 (50.0)	7 (87.5)	4 (50.0)	16 (50.0)
Nausea *n*(%)	1 (16.7)	1 (12.5)	3 (37.5)	4 (50.0)	3 (37.5)	11 (34.4)
Gastroesophageal reflux disease *n* (%)	0 (0)	0 (0)	1 (12.5)	7 (87.5)	0 (0)	8 (25.0)
Abdominal distension *n* (%)	0 (0)	1 (12.5)	1 (12.5)	2 (25.0)	0 (0)	4 (12.5)
Vomiting *n* (%)	0 (0)	0 (0)	0 (0)	3 (37.5)	2 (25.0)	5 (15.6)
Diarrhea *n* (%)	1 (16.7)	0 (0)	0 (0)	2 (25.0)	1 (12.5)	3 (9.4)
Nervous system disorders *n* (%)	0 (0)	0 (0)	3 (37.5)	3 (37.5)	4 (50.0)	10 (31.3)
Dizziness *n* (%)	0 (0)	0 (0)	1 (12.5)	1 (12.5)	4 (50.0)	6 (18.8)
Headache *n* (%)	0 (0)	0 (0)	2 (25.0)	2 (25.0)	0 (0)	4 (12.5)
Somnolence *n* (%)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	2 (6.3)
Investigations *n* (%)	2 (33.3)	1 (12.5)	1 (12.5)	4 (50.0)	1 (12.5)	7 (21.9)
Electrocardiogram PR shortened *n* (%)	2 (33.3)	1 (12.5)	0 (0)	0 (0)	1 (12.5)	2 (6.3)
Blood triglycerides increased *n* (%)	0 (0)	0 (0)	1 (12.5)	2 (25.0)	0 (0)	3 (9.4)
Blood uric acid increased *n* (%)	0 (0)	0 (0)	0 (0)	2 (25.0)	0 (0)	2 (6.3)
Metabolism and nutrition disorders *n* (%)	0 (0)	0 (0)	1 (12.5)	3 (37.5)	0 (0)	4 (12.5)
Decreased appetite *n* (%)	0 (0)	0 (0)	1 (12.5)	3 (37.5)	0 (0)	4 (12.5)
Skin and subcutaneous tissue disorders *n* (%)	0 (0)	0 (0)	1 (12.5)	0 (0)	2 (25.0)	3 (9.4)
Hyperhidrosis *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25.0)	2 (6.3)
Psychiatric disorders *n* (%)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	2 (6.3)
Initial insomnia *n* (%)	0 (0)	0 (0)	2 (25.0)	0 (0)	0 (0)	2 (6.3)

Note: Data are presented as the number of participants (percentage).
[a]For preferred term (PT), only the TEAEs occurring in ≥2 subjects are listed in the table.

3.3.2 | Phase 1b: MR Formulation

In Phase 1b, multiple doses of SC1011 MR were administered (100, 150, or 200 mg BID) under fed (standard meal) conditions. The concentration–time profiles are illustrated in Figure 2 and the PK parameters on Day 1 (first dose) and Day 7 (last dose) are listed in Table 4. Compared with the rapid absorption of the IR formulation in the fed state (mean T_{max} < 2.5 h), SC1011 MR was absorbed gradually, with Day 1 median T_{max} ranging between 5.0 and 6.0 h across all dose groups (Table 4). Following the initial dose, the mean apparent terminal half-life of SC1011 MR on Day 1 was also longer for SC1011 MR (mean $t_{1/2}$ 3.35–3.51 h) than for IR formulations (mean $t_{1/2}$ 1.28–1.42 h) (Tables 3B and 4).

On Day 7, following multiple-dose administration of SC1011 MR, PK characteristics were similar to those observed with single-dose administration. The mean T_{max} was reached at 4.00 h on Day 7 across all dosages, and the mean terminal $t_{1/2}$ ranged from 4.95 to 5.73 h (Table 4). Day 7 $AUC_{0\text{-}\tau}$ was generally comparable for SC1011 MR versus IR formulation (2966 and 3726 ng*h/mL, respectively) while C_{max} was reduced (495 and 1035 ng/mL, respectively) following the last dose of the 100 mg BID group (Tables 3B and 4). Plasma SC1011 accumulation ratios were determined for 100, 150, and 200-mg BID MR treatments by calculating the ratio of Cmax and $AUC_{0\text{-}\tau}$ between D7 and D1 in the same subjects. The accumulation ratio (Ra, Day 7/Day 1) ranged from 1.06 to 1.38 fold for $AUC_{0\text{-}\tau}$ and from 1.01- to 1.47-fold for C_{max} (Table 4). Day 5 had reached a steady state after BID dosing, based on a comparison of predose trough concentrations across Days 5–7 (Table S7). The AUC and C_{max} increased in a proportional manner for the MR formulation at the steady state (Table S8).

3.4 | Exposure–Adverse Event Analysis

Day 1 PK parameters from 73 subjects receiving active treatment in both Phase 1a (*N* = 41) and Phase 1b (*N* = 32) were pooled to assess the predictive value of PK parameters for the occurrence of TEAEs of interest by SOC (System organ class, including GI and CNS disorders) and PT (Preferred term, including nausea, vomiting, and dizziness).

TABLE 3 | Summary of PK parameters in the first-in-human study for the (A) SAD and (B) MAD study populations with SC1011 IR.

A

Parameters	50 mg fasted ($n=3$)	150 mg fasted ($n=7$)	150 mg fed ($n=8$)	300 mg fasted ($n=7$)
C_{max}(ng/mL)	592 ± 49	1521 ± 768	956 ± 193	3239 ± 943
AUC_{0-t}(h*ng/mL)	1367 ± 554	3786 ± 2011	3081 ± 1013	9542 ± 3752
$AUC_{0-\infty}$(h*ng/mL)	1396 ± 557	3816 ± 2017	3136 ± 1034	9638 ± 3771
AUC_{0-24h}(h*ng/mL)	1396 ± 557	3815 ± 2016	3122 ± 1009	9575 ± 3726
T_{max}(h)	0.83 ± 0.29	0.79 ± 0.27	1.63 ± 0.52	1.00 ± 0.50
$t_{1/2}$ (h)	1.42 ± 0.57	1.23 ± 0.27	1.67 ± 1.33	2.64 ± 1.88
V_z/F(L)	74 ± 10	80 ± 31	114 ± 57	124 ± 99
CL_z/F(L/h)	39 ± 13	48 ± 20	54 ± 24	35 ± 12
Fe_{0-48h}/F(%)	NA	NA	0.20 ± 0.11	0.29 ± 0.18

B

Parameters	100 mg BID Day 1 ($n=8$)	200 mg BID Day 1 ($n=8$)	Parameters	100 mg BID Day 7 ($n=7$)
C_{max}(ng/mL)	804 ± 185	1584 ± 662	$C_{max,ss}$ (ng/mL)	1035 ± 292
	NA		$AUC_{0-\tau,ss}$ (h*ng/mL)	3726 ± 1279
AUC_{0-t}(h*ng/mL)	2930 ± 1230	5917 ± 2465	AUC_{0-t} (h*ng/mL)	3832 ± 1333
$AUC_{0-\infty}$(h*ng/mL)	3207 ± 1236	6070 ± 2609	$AUC_{0-\infty}$ (h*ng/mL)	3908 ± 1362
T_{max}(h)	1.81 ± 1.07	2.44 ± 1.40	$T_{max,ss}$ (h)	2.00 ± 1.00
$t_{1/2}$(h)	1.28 ± 0.21	1.42 ± 0.28	$t_{1/2}$ (h)	2.61 ± 2.03
NA			$Ra_{(Cmax)}$	1.34 ± 0.30
			$Ra_{(AUC)}$	1.47 ± 0.46

Abbreviation: NA, not applicable.

The distributions of C_{max} (Day 1) and AUC_{0-t} (Day 1) across subjects with and without TEAEs of interest (Day 1) are presented in boxplots, including GI AEs, CNS AEs, nausea, vomiting, and dizziness (Figure S2). For subjects with TEAEs of interest, the median SC1011 C_{max} levels were significantly higher than those of subjects without the TEAE of interest (725 vs. 1220 ng/mL for GI AEs, $p<0.001$; 731.5 vs. 1470 ng/mL for CNS AEs, $p<0.0001$; 762 vs. 1465 ng/mL for nausea, $p<0.0001$; 877 vs. 1670 ng/mL for vomiting, $p<0.0001$; and 731.5 vs. 1470 ng/mL for dizziness, $p<0.0001$). No statistically significant differences were found in AUC_{0-t} between the subjects with and without the indicated TEAEs.

ROC curve analysis was used to assess the predictive value of drug exposure (AUC_{0-t} and C_{max} on Day 1) for the occurrence of adverse events on Day 1. Our results showed that the areas under the ROC curves of SC1011 C_{max} were 0.7318 ($p<0.001$), 0.8049 ($p<0.0001$), 0.7617 ($p<0.001$), and 0.7948 ($p<0.001$) for the occurrence of GI AEs, CNS AEs, nausea, and vomiting, respectively (Figure 3). No statistical significance was found between the SC1011 AUC_{0-t} and any of the selected TEAEs. For the C_{max}–ROC curves, the cutoff values were 731.5 ng/mL (specificity 0.5152, sensitivity 0.9000), 872 ng/mL (specificity 0.6316, sensitivity 0.8571), 740 ng/mL (specificity 0.4872, sensitivity 0.9118), and 1525 ng/mL (specificity 0.8491 and sensitivity 0.65) for GI AEs, CNS AEs, nausea, and vomiting, respectively.

4 | Discussion

These Phase 1 studies evaluated the safety, tolerability, and PK of IR and MR formulations of SC1011, a potential antifibrotic treatment, in healthy adult participants. SC1011 has a favorable safety profile and is well tolerated in single oral doses of IR formulations of up to 300 mg, oral MR formulations of up to 350 mg, multiple oral IR doses of up to 100 mg BID, and MR doses of up to 200 mg BID.

For the IR formulation, all TEAEs were mild to moderate in severity, and the most common treatment-related TEAEs were gastrointestinal disorders, the incidence of which appeared to be dose-related. In Phase 1a, one patient in the IR 100 mg BID group and five patients in the IR 200 mg BID group withdrew from the study due to AEs. The AE profiles of SC1011 IR resembled those of the IPF drug pirfenidone, which is also a pyridone compound. In the pirfenidone CAPACITY Phase 3 trial, nausea, dyspepsia, vomiting, and dizziness were reported in 36%, 19%, 14%, and 18% of pirfenidone-treated patients versus 17%, 7%, 4%, and 10% of

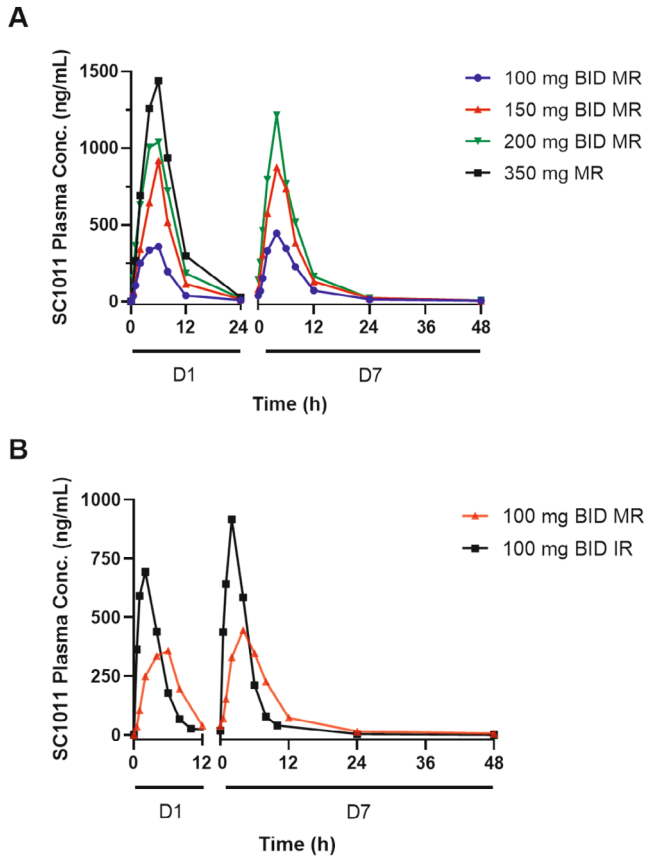


FIGURE 2 | SC1011 plasma concentration–time profiles. (A). Mean plasma concentrations of SC1011 following multiple-dose administration (MAD) of SC1011 MR (100, 150, 200 mg BID) and single-dose administration (350 mg). (B). Mean plasma concentrations of SC1011 in the standard-meal fed state on Day 1 and Day 7 following 7-day, repeat-BID dose administration of 100 mg SC1011 IR and MR. IR, immediate-release; MR, modified-release.

placebo-treated patients, respectively [16]. Two real-world evidence studies reported that discontinuation rates due to adverse events (AEs) among patients with IPF using pirfenidone were 23.1% and 31.2% [11, 12], respectively. Therefore, the TEAEs observed with SC1011 may reflect the limitations of drugs in the same class.

The development of modified formulation products may achieve therapeutic benefits, including improved efficacy, reduced adverse events, increased convenience, and patient compliance [17]. As anticipated, the MR formulation of SC1011 showed a markedly lower incidence of TEAEs than the IR formulation at the same dose level. For example, the incidence rates of GI TEAEs were 12.5% and 100% for the MR and IR 100 mg BID groups, respectively. Participants in the MR 100 mg BID group also experienced fewer neurologic TEAEs than those in the IR 100 mg BID group (0% vs. 75%). Improvement in safety by formulation optimization also leads to better participant adherence in the study. All subjects in the MR 100 mg BID group and MR 150 mg BID group completed the study. Only three subjects from the 200 mg BID group withdrew from the trial due to AEs. Therefore, the MR formulation leads to better compliance and tolerability at the same dosage. Evaluation of QT prolongation with new drugs is recommended by ICH to assess the potential risk of cardiac disorders [17]. A supratherapeutic dose of SC1011 (350 mg) did not prolong the QTcF interval or affect the other electrocardiogram parameters. Despite insufficient data for C-QTc modeling analysis, the supratherapeutic dose of SC1011 proved informative, since no hints of any potential cardiac safety issue were observed.

For single oral doses of IR SC1011 in the SAD study, the increase in exposure was dose-proportional over the 50–300 mg dose range. Consistent with its high permeability (data not shown), SC1011 IR was rapidly absorbed (mean $T_{max} \leq 1$ h) and eliminated (mean $t_{1/2}$ 1.23–2.64 h) in the fasted state. The minimal recovery of SC1011 in urine (< 0.3% within 48 h) indicates that urinary excretion is not a major route for the elimination of unchanged SC1011.

Preliminary food effect assessment in Phase 1a with IR formulation suggests a standard meal decreased the C_{max}, and the AUC was slightly reduced compared with fasted conditions. For 150 mg IR tablets fed versus fasted, the ratio (90% CI) of adjusted geometric means for C_{max} and AUC0–∞ was 69% (49% ~ 97%) and 86% (58% ~ 128%), respectively. Meanwhile, compared to the same dose level in the fasted state, participants in the fed state experienced a lower number of TEAEs, such as nausea (50% vs. 100%), vomiting (12.5% vs. 71.4%), and dizziness (62.5% vs. 100%). Considering the incidence of AEs was reduced when administered under fed conditions, BID dosing of SC1011 MR was designed to be after meals throughout the Phase 1b study.

The MR formulation demonstrated a delayed T_{max} and tapered C_{max} in the fed state. For example, at 100 mg BID (200 mg daily), the median T_{max} was 2.00 h and C_{max} was 1035 ng/mL for the IR formulation, while the median T_{max} was 4.0 h and C_{max} was 495 ng/mL with the MR formulation after the last dose of 100 mg on Day 7. The AUC of the MR formulation was generally comparable to that of the IR formulation at equivalent doses. Changes in the PK profile (reduced C_{max} and comparable AUC) of the MR formulation were consistent with the prolonged absorption of the MR formulation. Following multiple-dose administration of SC1011 MR, exposure to SC1011 increased dose proportionally between a total daily dose of 200 and 400 mg under fed conditions. Repeat dosing of SC1011 MR indicated that the elimination rate of SC1011 was dose-independent, and the mean apparent $t_{1/2}$ ranged from 3.39 to 3.51 h. A weak accumulation was noticed in the 100 mg BID group (IR, Phase Ia) and 200 mg BID MR group (MR, Phase 1b) with $Ra_{(AUC)}$ of 1.47 and 1.38, respectively. Considering the short half-life of SC1011, the weak accumulation may indicate the potential involvement of auto-inhibition of drug-metabolizing enzymes or transporters. The drug–drug interaction (DDI) studies, including clinical pharmacology and nonclinical ADME studies, will be conducted to elucidate the underlying mechanisms. Overall, the MR formulation lowered the peak-to-trough ratio and exhibited PK characteristics suitable for BID dosing in the fed state in future trials.

Comparison of the IR and MR formulations revealed similar total exposure, reduced C_{max}, and improved safety profile with the MR formulation. Decreased incidence of gastrointestinal AEs under fed condition may partially be explained by reduced gastrointestinal irritation. Yet the MR formulation exerted additional benefit on patient safety under the fed condition, indicating an association between drug concentration and occurrence of AEs. Exposure–AE analysis with the most frequent AEs by SOC (GI and neurologic disorders) and by PT (nausea and vomiting) identified peak

TABLE 4 | Pharmacokinetic parameters of SC1011 MR by treatment group in Phase 1b.

	Parameters	100 mg BID[a] ($n=8$)	150 mg BID[a] ($n=8$)	200 mg BID[a] ($n=8$)	350 mg ($n=8$)
D1	C_{max}(ng/mL)	420 ± 176	958 ± 354	1154 ± 534	1544 ± 680
	AUC_{0-t}(h*ng/mL)	2546 ± 1028	5892 ± 1699	8485 ± 4389	11,074 ± 6058
	$AUC_{0-\infty}$(h*ng/mL)	2615 ± 1116	5968 ± 1726	7471 ± 3313	11,211 ± 6087
	T_{max}(h)	5.00 (2.00,6.00)	6.00 (4.00, 6.00)	5.00 (4.00, 8.00)	6.00 (4.00, 6.00)
	$t_{1/2}$(h)	3.39 ± 1.00	3.35 ± 0.60	3.51 ± 0.82	3.42 ± 0.79
	Parameters	**100 mg BID[a] ($n=8$)**	**150 mg BID[a] ($n=8$)**	**200 mg BID[a] ($n=5$)**	
D7	$C_{max,ss}$(ng/mL)	495 ± 163	927 ± 286	1218 ± 450	
	$AUC_{0-\tau,ss}$(h*ng/mL)	2966 ± 1055	5676 ± 2035	7349 ± 2232	NA
	AUC_{0-t}(h*ng/mL)	3442 ± 1217	6578 ± 2428	8292 ± 2433	
	$AUC_{0-\infty}$(h*ng/mL)	3537 ± 1238	6677 ± 2421	8385 ± 2400	
	$T_{max,ss}$(h)	4.00 (2.00, 6.00)	4.00 (4.00, 6.00)	4.00 (2.00, 4.00)	
	$t_{1/2}$(h)	5.40 ± 2.63	5.73 ± 2.36	4.95 ± 2.02	
	$Ra_{(Cmax)}$	1.24 ± 0.26	1.01 ± 0.22	1.47 ± 0.50	
	$Ra_{(AUC)}$	1.26 ± 0.21	1.06 ± 0.14	1.38 ± 0.30	

Abbreviation: NA, not applicable.
[a]Daily doses were 200, 300, and 400 mg for 100 BID, 150 BID, and 200 mg BID groups, respectively.

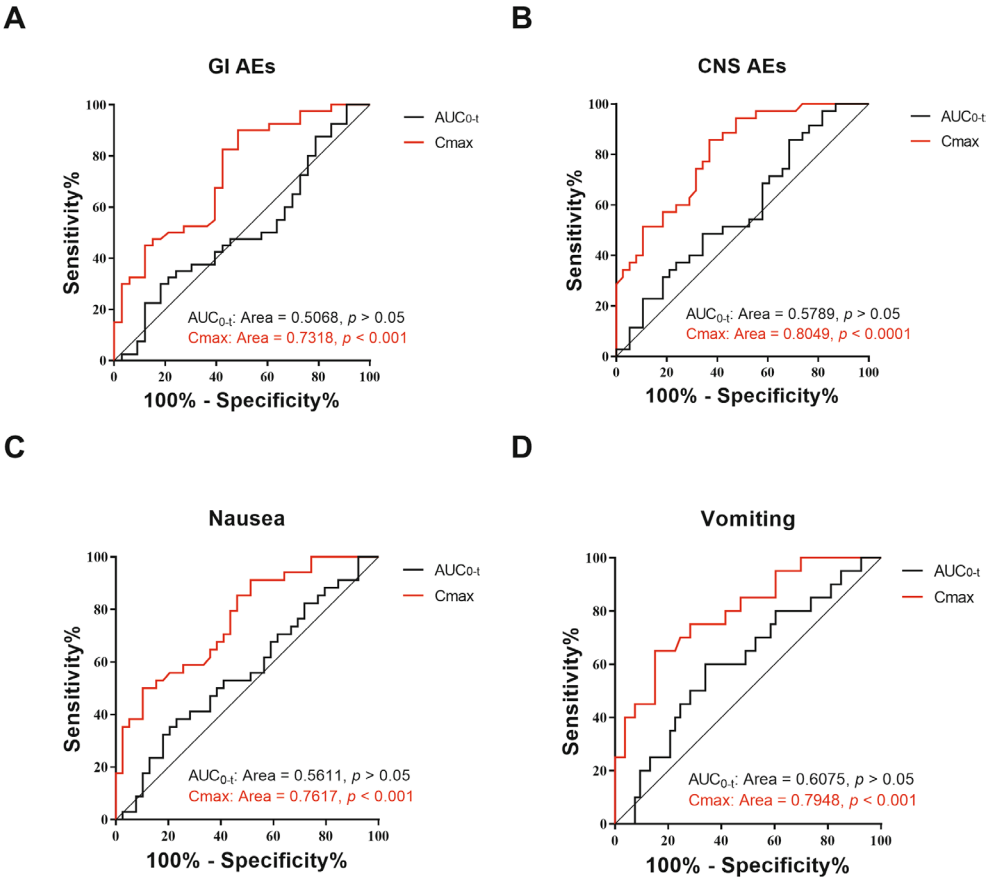


FIGURE 3 | ROC curve analysis for the prediction of adverse events on Day 1. ROC curves for SC1011 exposure (C_{max} and AUC_{0-t}) in predicting the occurrence of GI AEs (A), CNS AEs (B), nausea (C), and vomiting (D). ROC, receiver operating characteristic. GI AEs, SOC of gastrointestinal disorders, including nausea, vomiting, and diarrhea. CNS AEs, SOC of nervous system disorders, include dizziness, headache, and somnolence. $C_{max,}$ maximum observed plasma concentration. AUC_{0-t}, area under the concentration curve from 0 to the time of the last quantifiable concentration.

plasma concentration rather than total exposure as a good predictor of TEAE. Group comparisons of PK parameters between the subjects with and without the TEAEs of interest revealed C_{max} in subjects with the TEAEs of interest was significantly higher than the contrary group, while AUC in subjects with or without the TEAEs of interest showed no significant difference. Consistently, ROC analysis found statistical significance with C_{max} rather than total exposure for AE prediction. This finding is consistent with that of the marketed IPF drug pirfenidone, which reported a correlation between C_{max} exposure and GI side effects [18]. The current finding also explains the significantly lower incidence of AEs with the MR formulation (Phase 1b) than with the IR formulation (Phase 1a). For example, at the 100 mg BID dose level, C_{max} was reduced from 804 ng/mL (MR) to 420 ng/mL (IR) on Day 1, while the incidence rate of TEAEs was consequently lower for GI disorders (12.5% for MR vs. 100% for IR) and neurologic disorders (0% for MR vs. 75% for IR). The present data showed that, in line with its PK profile, SC1011 MR was associated with a significantly lower incidence of AEs in healthy subjects than in the IR formulation. By minimizing side effects, the formulation optimization of SC1011 could potentially lead to increased drug exposure, enhanced medication adherence, and improved therapeutic effects in Phase 2 trials with patients with IPF.

In conclusion, SC1011 demonstrated favorable safety and pharmacokinetic profiles in healthy volunteers. The MR formulation provided sustained exposure and improved tolerability compared with the IR formulation. Based on data from nonclinical studies and current Phase 1 studies, SC1011 MR tablets 100 and 150 mg BID are selected for Phase 2 dose exploration. The accumulated data support the continued evaluation of SC1011 MR in human clinical trials for the treatment of IPF.

Author Contributions

Y.L., Z.Y., Y.L., B.Z., X.S., Y.L., and X.C. wrote the manuscript. Y.L., Z.Y., and Y.L. designed the research. F.J., H.Z., H.Q., H.T., Y.T., Y.D., and S.L. performed the research. Z.G. contributed new reagents/analytical tools. Y.Z., B.Z., X.S., Y.L., and X.C. analyzed the data.

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Conflicts of Interest

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Supporting Information

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