Pharmacokinetics, Safety, and Tolerability of GS-1427, a Prodrug of a Potent and Selective Small Molecule α4β7 Integrin Inhibitor, in Healthy Volunteers

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Poster #113

Conclusions

- Single (up to 1000 mg) and multiple (up to 500 mg QD) oral doses of GS-1427 were generally well tolerated in this study
- The pharmacokinetics, safety, and tolerability results support QD dosing and further therapeutic-dose identification of GS-1427 in the ongoing phase 2 UC trial (NCT06290934)

Plain Language Summary

- GS-1427 is a drug being studied as a possible treatment for ulcerative colitis
- In this study, participants took different amounts of GS-1427, either once only or every day for 2 weeks. Some took GS-1427 with food, others did not
- Participants' blood was analyzed to see how much of the drug was in it, and they were asked about any negative effects they experienced
- The study found that the drug did not build up much in the blood with repeated doses, although as doses increased from 20 mg to 500 mg, the increase in the amount in blood was higher than the increase in dose. The amount of the drug in the blood was lower when it was taken with food
- The participants had very few negative effects, and those they did have were mild. The most common were bloating, diarrhea, headache, and nausea
- With these supportive results, GS-1427 will be tested in people with ulcerative colitis to see if it can be used to treat this disease

Introduction

- Ulcerative colitis (UC) is a chronic, relapsing, and remitting inflammatory disease affecting the colonic mucosa[1]
- Remission rates for UC remain low despite the availability of multiple treatments[2]
- The efficacy and safety of α4β7 integrin inhibition, for example by the Food and Drug Administration approved drug vedolizumab, have been clinically validated in UC[3] and Crohn's disease[4]
- GS-1427 is an oral prodrug that is rapidly converted to the active species GS-1069518, a potent and selective α4β7 integrin inhibitor
- GS-1427 is being developed for the treatment of UC

Objectives

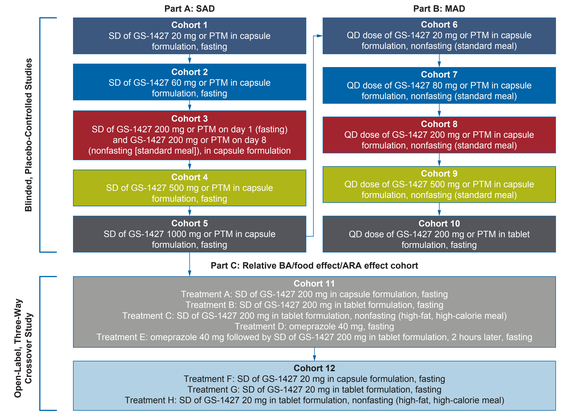
- To evaluate the pharmacokinetics, safety, and tolerability of single and multiple ascending doses of GS-1427
- To assess the effect of concomitant food intake on the pharmacokinetics of GS-1069518

Methods

Study Design

- This dual-center, first-in-human, phase 1 study comprised three parts (**Figure 1**)
  - Part A assessed the pharmacokinetics of GS-1427 and GS-1069518 with single doses of GS-1427 (20–1000 mg) in liquid-filled capsule formulation under fasting conditions
  - Part B assessed the pharmacokinetics of GS-1427 and GS-1069518 with multiple once-daily (QD) doses of GS-1427 (20–500 mg) in liquid-filled capsule formulation under nonfasting conditions or multiple QD doses of GS-1427 200 mg in tablet formulation under fasting conditions for 14 days
  - Part C assessed the relative bioavailability of tablet versus capsule formulations of GS-1427, and the effect of food and an acid-reducing agent on GS-1069518 pharmacokinetics (only bioavailability of tablet vs capsule and food effect data are reported here)
- Parts A (single ascending dose) and B (multiple ascending dose) were blinded (sponsor-unblinded), placebo-controlled studies, while part C used an open-label, three-way crossover design
- Intensive pharmacokinetic sampling followed a prespecified schedule (up to 120 hours post dose) depending on cohort and study day
- Safety and tolerability were assessed in all three study parts

Figure 1. Study Design



Parts B and C were run in parallel and initiated after evaluation of study data from part A. Doses of GS-1427 in part C were chosen based on data from part A. ARA, acid-reducing agent; BA, bioavailability; MAD, multiple ascending dose; PTM, placebo-to-match; QD, once-daily; SAD, single ascending dose; SD, single dose.

Analyses

- Plasma concentrations of GS-1427 and GS-1069518 were quantified using validated high-performance liquid chromatography-tandem mass spectrometry bioanalytical methods
- Pharmacokinetic parameters for GS-1427 and its metabolite, GS-1069518, were estimated with noncompartmental methods using Phoenix WinNonlin version 8.3.3.33 and summarized by cohort using descriptive statistics

Results

Participant Flow and Baseline Characteristics

- Overall, 148 healthy participants were enrolled in the study (part A: N = 50, part B: N = 62; part C: N = 36) and 144 completed the study drug
- The median (range) participant age was 31 (19–54) years
- The median (interquartile range) body mass index was 26.3 (24.3–28.2) kg/m^2
- The majority of participants were male at birth (64.9%); black/African American (42.6%) or white (49.3%); and not Hispanic or Latino (81.1%)

Pharmacokinetics of GS-1427 and GS-1069518

- GS-1427 was quickly converted to GS-1069518, as shown by the high parent-to-prodrug ratios in **Table 1**, with negligible plasma exposure of GS-1427
- Under fasting conditions following a single dose of the GS-1427 capsule formulation, GS-1069518 exposure was largely dose proportional between 20–60 mg and 200–500 mg, greater than dose proportional between 60 and 200 mg, and less than dose proportional between 500 and 1000 mg
- Steady-state exposure of GS-1069518 was reached by day 5 with limited accumulation upon repeated GS-1427 QD dosing (**Table 1**)
  - At steady-state, the median T_{max} of GS-1069518 was 1–3 hours; the median $t_{1/2}$ was 6.9–23.0 hours
- Under nonfasting conditions (after a standard meal) using the GS-1427 capsule formulation, the steady-state exposure of GS-1069518 increased in a slightly greater than dose-proportional manner in the GS-1427 20–500 mg range (**Table 1**, **Figure 2**)

Bioavailability of GS-1069518 With Tablet Versus Capsule Formulations of GS-1427

- Under fasting conditions, the geometric least-squares mean ratio (90% confidence interval) of AUC_{inf} for tablet relative to capsule was 57.0% (48.2–67.5) for the 20 mg dose and 92.9% (80.5–107) for the 200 mg dose

Results (cont.)

Table 1. Single and Multiple Dose Pharmacokinetic Parameters of GS-1069518

	Part A: SAD (capsule under fasting conditions)				
Parameter	**Cohort 1** GS-1427 20 mg (n = 8)	**Cohort 2** GS-1427 60 mg (n = 8)	**Cohort 3** GS-1427 200 mg (n = 8)	**Cohort 4** GS-1427 500 mg (n = 8)	**Cohort 5** GS-1427 1000 mg (n = 8)
AUC_{inf} (ng·h/mL)[a]	39.6 (37.1)	97.3 (40.3)	885 (61.6)	2400 (51.2)	4170 (62.5)
C_{max} (ng/mL)[a]	28.3 (44.3)	53.2 (48.9)	280 (57.4)	665 (64.3)	761 (49.4)
T_{max} (h)[b]	0.750 (0.500, 1.06)	1.00 (0.750, 1.04)	1.01 (1.00, 2.00)	2.53 (2.00, 3.00)	3.00 (2.00, 4.00)
$t_{1/2}$ (h)[b]	1.54 (1.44, 2.05)	4.72 (3.30, 6.71)	9.74 (7.82, 21.2)	15.4 (8.57, 19.7)	15.2 (9.43, 25.7)
MR AUC_{inf}[b]	761 (584, 1050)	141 (83.3, 220)	309 (244, 382)	277 (225, 355)	256 (173, 433)
	Part B: MAD				
	QD capsule under nonfasting conditions (standard meal)				**QD tablet under fasting conditions**
Parameter	**Cohort 6** GS-1427 20 mg (n = 9)	**Cohort 7** GS-1427 80 mg (n = 9)	**Cohort 8** GS-1427 200 mg (n = 9)	**Cohort 9** GS-1427 500 mg (n = 9)	**Cohort 10** GS-1427 200 mg (n = 10)
Day 1					
$AUC_{0\text{-}24}$ (ng·h/mL)[a]	20.2 (34.7)	112 (58.4)	249 (24.7)	670 (32.7)	552 (40.4)
C_{max} (ng/mL)[a]	6.63 (45.1)	31.6 (66.0)	68.4 (48.5)	165 (53.4)	130 (52.3)
T_{max} (h)[b]	2.00 (1.00, 3.00)	2.00 (2.00, 2.05)	3.50 (3.00, 4.00)	3.00 (2.00, 3.00)	2.00 (2.00, 2.00)
Day 14					
AUC_{tau} (ng·h/mL)[a]	24.5 (57.2)	142 (72.7)	315 (21.5)	936 (33.6)	728 (28.2)
C_{max} (ng/mL)[a]	5.69 (72.7)	37.7 (55.9)	78.3 (31.1)	249 (46.4)	154 (37.9)
C_{tau} (ng/mL)[a]	–[c]	0.689 (112)	1.76 (67.7)	6.05 (75.3)	7.57 (55.6)
T_{max} (h)[b]	2.00 (1.00, 4.00)	2.00 (2.00, 3.00)	3.00 (1.50, 3.50)	3.00 (3.00, 4.00)	1.00 (1.00, 3.00)
$t_{1/2}$ (h)[b]	6.90 (4.69, 8.47)	23.0 (18.1, 36.7)	12.1 (8.36, 18.8)	17.4 (13.3, 18.2)	20.6 (13.1, 23.9)
AUC_{tau}/D (ng·h/mL/mg)[d]	1.22 (57.2)	1.78 (72.7)	1.57 (21.5)	1.87 (33.6)	3.64 (28.2)
C_{max}/D (ng/mL/mg)[d]	0.285 (72.7)	0.471 (55.9)	0.391 (31.1)	0.497 (46.4)	0.770 (37.9)
AR AUC_{tau}	1.14 (25.2)	1.23 (24.5)	1.31 (23.1)	1.40 (12.7)	1.49 (32.5)

[a]Data are presented as unadjusted arithmetic mean (%CV).
[b]Data are presented as median (Q1, Q3).
[c]More than one-third of post-dose values were below the limit of quantification.
[d]Dose-normalized to GS-1427 dose.
MR AUC_{inf} is weight-normalized AUC_{inf} of metabolite GS-1069518 to AUC_{inf} of parent GS-1427 ratio.
AR AUC_{tau} was determined by comparing day 14 AUC_{tau} with day 1 $AUC_{0\text{-}tau}$.
%CV, percentage coefficient of variation; AR, accumulation ratio; $AUC_{0\text{-}24}$, area under the plasma concentration versus time curve from 0 to 24 h; AUC_{inf}, area under the concentration versus time curve from time zero to infinite time; AUC_{tau}, area under the concentration versus time curve from time zero to the last quantifiable concentration; $AUC_{0\text{-}tau}$, area under the concentration versus time curve over the dosing interval; C_{max}, maximum observed plasma concentration; C_{tau}, observed drug concentration at the end of the dosing interval; D, dose; h, hour; MAD, multiple ascending dose; MR, metabolite ratio; Q, quartile; QD, once-daily; SAD, single ascending dose; $t_{1/2}$, elimination half-life; T_{max}, time to maximum concentration.

Effect of Food on Pharmacokinetics of GS-1069518

- Following a high-fat, high-calorie meal using the tablet formulation for GS-1427, the AUC_{inf} of GS-1069518 was reduced by ~20% with the GS-1427 20 mg dose and 40% with the 200 mg dose compared with fasting conditions (**Table 2**)

Safety

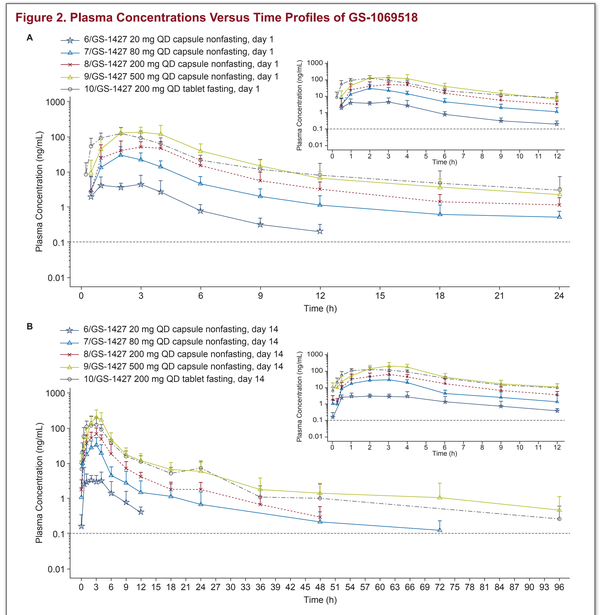
- Overall, 34/148 (23.0%) participants had at least one treatment-emergent adverse event (TEAE). Ten (6.8%) participants had at least one TEAE that was assessed to be related to the study drug
  - No serious adverse events were reported – all TEAEs were classified as grade 1 in severity
- Only 2/148 (1.4%) participants had a TEAE that led to discontinuation of the study (both COVID-19; one GS-1427, one placebo)
- TEAEs occurring in at least two participants who received GS-1427 in each study part are summarized below (**Supplementary Table 1**, available via the QR code)
  - In part A, nausea (4/8) and diarrhea (2/8) occurred only in the 1000 mg cohort, while abdominal distension (2/8) occurred only in the 20 mg cohort. Headache occurred in the 200 mg (1/8) and 1000 mg (1/8) cohorts. These events were not reported in patients receiving placebo in part A
  - In part B, nausea (2/9) occurred only in the 500 mg cohort and no instances were reported in patients receiving placebo. Headache occurred in the 20 mg (1/9) and 500 mg (1/9) cohorts and in one participant (1/16) in the pooled placebo group
  - In part C, no TEAEs were reported in at least two participants receiving GS-1427
- No dose-limiting toxicities, or clinically relevant electrocardiogram or vital sign abnormalities were reported

Table 2. Effect of Food on the Pharmacokinetics of GS-1069518

	Cohort 11 (SD GS-1427 200 mg tablet)			Cohort 12 (SD GS-1427 20 mg tablet)		
Parameter	Under nonfasting conditions (high-fat, high-calorie meal) (n = 17)	Under fasting conditions (n = 18)	**GLSMR, % (90% CI)** High-fat, high-calorie meal/fasting	Under nonfasting conditions (high-fat, high-calorie meal) (n = 18)	Under fasting conditions (n = 18)	**GLSMR, % (90% CI)** High-fat, high-calorie meal/fasting
AUC_{inf} (ng·h/mL)	420 (38.3)	771 (43.5)	58.8 (50.8–68.0)	24.9 (53.8)	30.1 (66.4)	82.0 (68.8–97.8)
C_{max} (ng/mL)	124 (65.5)	147 (43.5)	82.4 (64.1–106)	5.62 (63.1)	12.1 (70.0)	49.2 (39.0–62.1)

Data are presented as unadjusted arithmetic mean (%CV).
The GLSMR was calculated using a parametric (normal theory) analysis of variance model fitted to the natural log-transformed pharmacokinetic parameters.
%CV, percentage coefficient of variation; AUC_{inf}, area under the concentration versus time curve from time zero to infinite time; CI, confidence interval; C_{max}, maximum observed plasma concentration; GLSMR, geometric least-squares mean ratio; h, hour; SD, single dose.

Figure 2. Plasma Concentrations Versus Time Profiles of GS-1069518



Profiles following the administration of (A) the first QD dose of GS-1427 under nonfasting and fasting conditions on day 1 (cohorts 6–10) and (B) QD doses of GS-1427 under nonfasting or fasting conditions for 14 days (cohorts 6–10). Horizontal dashed lines represent the lower limit of quantification (0.1 ng/mL). Data points are mean values. Error bars show the standard deviation.
h, hour; QD, once daily.

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Disclosures: **JZ**, **NM**, **JM**, **YZ**, and **FH** are employees of, and may own stock in, Gilead Sciences, Inc. **AO** was employed by Gilead at the time the study was conducted, and may own stock in, Gilead Sciences, Inc.

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