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Three-Day, Dose-Ranging Study Of The HCV NS3 Protease Inhibitor GS-9451

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Introduction

- GS-9451 is a potent and selective, non-covalent HCV NS3 protease inhibitor
- *In vitro* EC_{50} ranging from 7-10 nM in HCV 1a or 1b replicon assays
- *In vitro*, GS-9451 selected resistance mutations at positions 168 and 156 in NS3 protease
- A single-dose study of GS-9451 in healthy subjects indicated:
  - GS-9451 was generally well-tolerated at all tested doses (10 – 1000 mg)
  - C_{24} > protein-binding adjusted EC_{50} at GS-9451 doses >/= 300mg.
  - Median terminal half-lives ranged from 12-14 hours, supporting QD dosing
  - Food increased GS-9451 exposure ~ 2-fold

Objectives

Primary:

- To evaluate the safety and tolerability of escalating, multiple, oral doses of GS-9451 in subjects with chronic genotype 1 Hepatitis C Virus (HCV) infection
- To evaluate the antiviral activity of GS-9451 against genotype 1 HCV following administration of multiple oral doses

Secondary:

- To characterize the plasma pharmacokinetics of GS-9451 following administration of escalating, multiple, oral doses in genotype 1 HCV-infected subjects
- To assess the PK/PD relationship between HCV viral load change and GS-9451 plasma concentrations following multiple dose administration
- To compare GS-9451 antiviral activity in genotype 1a versus 1b infections
- To evaluate genotypic changes from baseline in the NS3/4A coding region of HCV following multiple dose administration of GS-9451 and for up to 48 weeks thereafter

Methods

- Randomized, double-blind, placebo-controlled, dose-escalation study conducted in treatment naïve subjects with genotype 1 chronic HCV infection
- Three days of GS-9451 monotherapy (tablets dosed with food)
- Cohorts:
  - 60 mg GS-9451 or placebo QD (N=10, genotype 1a)
  - 200 mg GS-9451 or placebo QD (N=10, genotype 1a)
  - 400 mg GS-9451 or placebo QD (N=11, genotype 1a)
  - 200 mg GS-9451 or placebo QD (N=10, genotype 1b)
- Serial PK (Days 1 & 3)
- Resistance testing
  - population sequencing of the entire NS3/4A coding region
  - at Baseline, Day 4 and Day 14 (and Weeks 12, 24, and 48)

Results

Table 1. Subject Demography and Baseline Characteristics

	GS-9451 Regimen				
	60 mg QD (N = 8)	200 mg QD (N = 8)	400 mg QD[a] (N = 9)	200 mg QD (N = 8)	Placebo (N=8)
HCV Genotype (1a/1b)	8/0	8/0	9/0	1/7[b]	7/1[b]
Mean Age (yrs)	52	49	48	55	48
Sex (Male/Female)	6/2	5/3	7/2	7/1	7/1
Ethnicity (Non-Hispanic/Hispanic)	5/3	4/4	6/3	6/2	5/3
Caucasian African American	7 1	8 0	7 2	3 5	6 2
Median HCV RNA (log_{10} IU/mL)	6.17	6.76	6.79	6.56	6.67
Mean Body Mass Index (kg/m^2)	29	28	27	30	25
Mean Weight (kg)	86	80	77	92	78

[a] One subject randomized to GS-9451 400 mg QD was misdosed and removed from virologic/PK analyses
[b] Two subjects who were identified as genotype 1b at screening were subsequently demonstrated to be genotype 1a

Results (cont'd)

Results - Safety

- All Laboratory abnormalities were all Grade 1/2 except:
  - Grade 4 total bilirubin in 1 subject (GS-9451 200 mg)
  - Grade 3 amylase in 1 subject (GS-9451 200 mg)
  - Grade 3 PT in 1 subject (GS-9451 200 mg)
    - Total bilirubin and other labs were normal for this subject
  - Grade 3 urine glucose (GS-9451 60 mg)
- Five subjects with total bilirubin > upper limit of normal (ULN)
  - One Grade 1 at GS-9451 60 mg
  - One Grade 4 at GS-9451 200 mg
    - No graded ALT values for this subject until the bilirubin resolved on Day 14, when there was a Grade 1 ALT (74 U/L); direct bilirubin elevated as well
  - Two Grade 1 and one Grade 2 at GS-9451 400 mg
- Frequency of serum bile acids > ULN similar across all groups, including placebo (38-67% of subjects)

Table 2. Adverse Event (AE) Summary by GS-9451 Regimen

AEs Occurring in > 1 Subject[a,b]	GS-9451 Regimen			
	60 mg QD (N = 8)	200 mg QD (N = 16)	400 mg QD (N = 9)	Placebo (N = 9)
# Subjects with at least 1 AE[c]	3 (38%)	11 (69%)	2 (22%)	1 (13%)
Headache	2 (25%)	4 (25%)	1 (11%)	1 (13%)
Dyspepsia	0	2 (13%)	0	0

[a] number of subjects experiencing AEs are counted only once for each AE
[b] all AEs were mild or moderate in severity except one serious AE - one subject died of an unrelated heroin overdose 5 days after last dose
[c] The following AEs occurred in only 1 subject receiving active drug: ear pain, constipation, diarrhea, dry mouth, dry lip, nausea, enlarged parotid gland, toothache, hyperbilirubinemia, sinusitis, narcotic intoxication, prolonged PT, back pain, somnolence, nightmare, dysuria, cough, nasal congestion, pharyngolaryngeal pain, contact dermatitis, hot flush, hypertension

Figure 1. Median (Q1, Q3) HCV RNA Change from Baseline By Treatment & Subtype

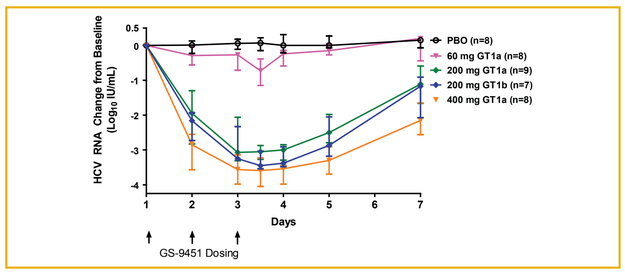


Table 3. Median (Range) Maximum Changes from Baseline in HCV RNA (log_{10} IU/mL)

GS-9451 60 mg QD (GT1a) (N=8)	GS-9451 200 mg QD (GT1a) (N=9)	GS-9451 400 mg QD (GT1a) (N=8)	GS-9451 200 mg QD (GT1b) (N=7)
-0.88 (-1.5, -0.3)	-3.2 (-4.2, -2.5)	-3.6 (-4.7, -3.0)	-3.5 (-3.6, -2.3)

Figure 2. Mean (± SD) GS-9451 Plasma Concentration-Time Profiles at Day 3

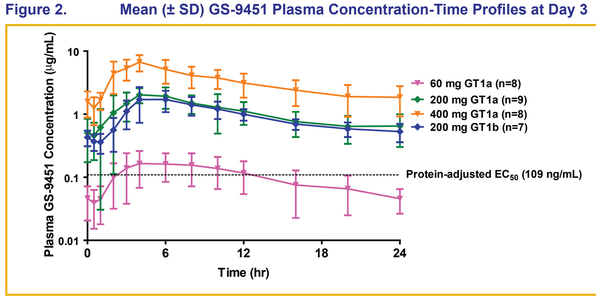


Table 4. Mean (CV%) GS-9451 Pharmacokinetic Parameters at Day 1

GS-9451 Pharmacokinetic Parameter	GS-9451 Regimen/Genotype			
	60 mg QD GT1a (N = 8)	200 mg QD GT1a (N = 9)	200 mg QD GT1b (N = 7)	400 mg QD GT1a (N = 8)
C_{max} (µg/mL)	0.2 (43)	1.6 (51)	1.5 (41)	5.4 (35)
T_{max} (h)[a]	4 (2,8)	4 (3,6)	4 (3,8)	4 (2,6)
C_{24} (µg/mL)	0.04 (46)	0.29 (65)	0.28 (16)	0.85 (32)
$AUC_{0\text{-last}}$ (µg•h/mL)	1.8 (32)	14.2 (40)	13.4 (22)	44.5 (21)

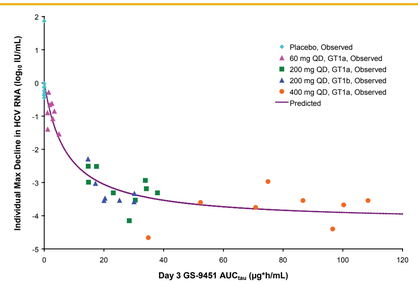
[a] Median (min, max)

Table 5. Mean (CV%) GS-9451 Pharmacokinetic Parameters at Day 3

GS-9451 Pharmacokinetic Parameter	GS-9451 Regimen/Genotype			
	60 mg QD GT1a (N = 8)	200 mg QD GT1a (N = 9)	200 mg QD GT1b (N = 7)	400 mg QD GT1a (N = 8)
C_{max} (µg/mL)	0.2 (51)	2.4 (29)	2.0 (39)	7.2 (24)
T_{max} (h)[a]	7 (3,8)	4 (2,8)	4 (3,10)	4 (2,4)
C_{tau} (µg/mL)	0.05 (42)	0.65 (54)	0.53 (32)	1.86 (51)
AUC_{tau} (µg•h/mL)	2.4 (54)	26.1 (34)	22.5 (27)	78.1 (32)
$T_{1/2}$ (h)[a]	17.0 (9.1, 31.1)	16.0 (14.2, 19.7)	15.7 (13.4, 29.5)	14.1 (7.6, 19.8)

[a] Median (min, max)

Figure 3. Individual Maximum Decline in HCV RNA vs. Day 3 AUC_{tau}

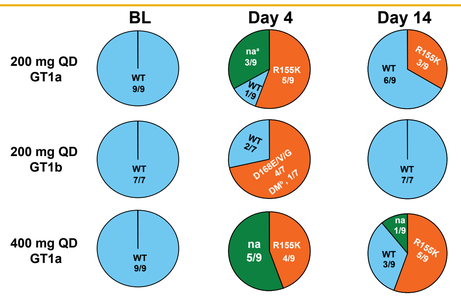


Exposure-response relationship was determined with a pharmacologically simple E_{max} model (WinNonlin Professional, v.5.2) in which:

Antiviral Activity (E) = $E_0 + E_{max} \times AUC_{tau} \div (EC_{50} + AUC_{tau})$

Model predicted parameters include: E_0 = 0.02 log_{10} IU/mL, E_{max} = -4.19 log_{10} IU/mL, EC_{50} = 7.4 µg*h/mL, R = 0.946

Figure 4. Resistance Mutations Identified by Population Sequencing



No mutations were detected in subjects in the 60 mg dose group
[a] na, sample failed to amplify due to low viral load (<1000IU/ml in 5/8)
[b] DM, double mutant (D168E/G+A156T)

Table 6. Susceptibility of GS-9451 Resistance Mutations to Other HCV Agents

Compound	Fold Change in EC_{50} from WT[a]				
	R155K	D168G	D168E	D168V	A156T
GS-9451 (PI)	122[b]	41	109	8321	3051
GS-9256 (PI)	566	88	32	628	819
TMC-435350 (PI)	93	4.6	11	>182	>256
Telaprevir (PI)	7.6	0.4	0.6	0.4	97

[a] Mutations were generated by site-directed mutagenesis,
[b] values in red >4-fold

Results Summary

- GS-9451 200 mg QD resulted in a median maximal change from baseline of -3.6 IU/mL (range -4.7 to -3.0)
- GS-9451 was well-tolerated
- GS-9451 plasma exposure > dose proportional within 60-400 mg QD
- GS-9451 had a median half-life of 14-17 hours
- Day 3 mean C_{tau} were ~ 6- and ~17-fold > protein-binding adjusted mean EC_{50} for GT1 for GS-9451 at 200 and 400 mg QD, respectively
- A strong correlation was observed between maximum HCV RNA change from baseline and GS-9451 plasma exposure
- NS3 protease mutations R155K/R and/or D168E/V/G occurred among subjects receiving GS-9451 200 mg or 400 mg QD only

Conclusions

- **GS-9451 is a novel NS3 protease inhibitor with potent (>3 log) antiviral activity in patients**
  - **Well-tolerated at all tested doses**
  - **Similar activity in genotype 1a & 1b patients**
  - **QD dosing (14-17 hour $T_{1/2}$ in HCV patients)**
- **Phase 2B evaluation of GS-9451 is currently underway**

Acknowledgements

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