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Nonclinical Profile and Phase I Results in Healthy Volunteers of the Novel and Potent HCV NS5A Inhibitor GS-5885

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Introduction

- NS5A has emerged as an important small molecule drug target for the treatment of chronic HCV
- GS-5885 is a potent and selective HCV NS5A inhibitor
  - GT1a EC_{50} = 41 pM; GT1b EC_{50} = 5 pM
  - *In vitro,* GS-5885 selected signature mutations of L31V and Y93H in NS5A
- An oral single-dose study of GS-5885 in healthy volunteers indicated:
  - GS-5885 was well tolerated at doses of 3, 10, 30, 60 and 100 mg
  - GS-5885 displayed dose proportional exposure
  - The mean terminal $T_{1/2}$ was 37-45 hours, consistent with once daily dosing

Objectives

- Identification of an NS5A inhibitor that is highly potent with a profile that is suitable for once daily dosing for the treatment of chronic HCV
- To establish the safety profile of GS-5885 in ascending doses in healthy volunteers
- To define the plasma pharmacokinetics of GS-5885 in healthy volunteers

Methods

- Potency and selectivity were studied using cell-based HCV replicon assays
- PK was assessed in rats, dogs and monkeys following intravenous and oral administration
- Safety pharmacology and repeat dose toxicology studies were conducted in rats and dogs
- Safety, tolerability and PK was studied in a phase I escalating single oral dose trial in healthy volunteers randomized to:
  - GS-5885 tablets or placebo (8:2), with dosing at 3, 10, 30, 60 and 100 mg under fasted conditions and 30 mg with food

Results

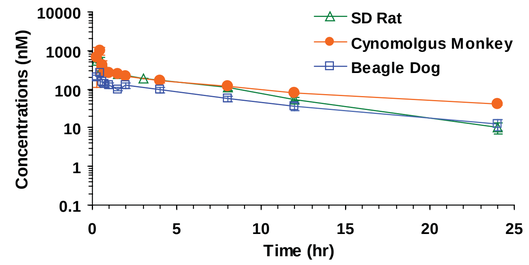
Table 1. GS-5885 EC_{50} for Genotypes 1-4

	GT1a	GT1b	GT2a	GT3a*	GT4a*
EC_{50}	0.041 nM	0.005 nM	20.8 nM	10.1 nM	0.007 nM

*Replicon constructs were GT3a and GT4a NS5A chimeric replicons that were based on a GT1b Rluc-neo backbone

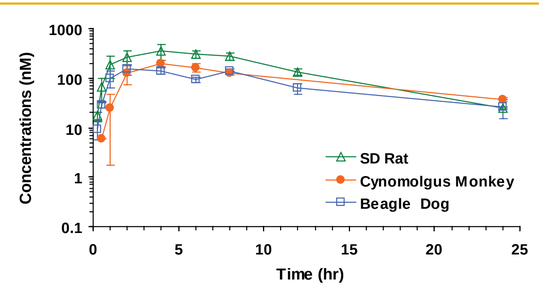
Results (cont'd)

Figure 1. Mean Plasma Concentration vs. Time Profile of GS-5885 Following IV Dosing of GS-5885



Data presented as mean ± SD, n = 3. GS-5885 was dosed to male SD rats at 1 mg/kg, male cynomolgus monkeys at 0.5 mg/kg, and male beagle dogs at 0.2 mg/kg

Figure 2. PK Profiles of GS-5885 Following Oral Administration to SD Rats, Beagle Dogs and Cynomolgus Monkeys



Data presented as mean ± SD, n = 3. GS-5885 was dosed in solution to male SD rats at 5 mg/kg, male cynomolgus monkeys at 1 mg/kg, and male beagle dogs at 0.5 mg/kg

Table 2. GS-5885 Pharmacokinetic Parameters in Rat, Dog and Monkey

	Rat	Dog	Monkey
CL (L/hr/kg)	0.43 ± 0.04	0.13 ± 0.02	0.17 ± 0.00
V_{ss} (L/kg)	2.66 ± 0.13	1.19 ± 0.13	2.15 ± 0.42
$t_{½}$ (hr)	4.67 ± 0.56	7.41 ± 0.80	10.3 ± 1.24
MRT (hr)	6.19 ± 0.28	9.20 ± 1.35	12.9 ± 2.10
%F	32.5 ± 6.7	53.0 ± 12.4	41.1 ± 3.6

Data presented as mean ± SD, n = 3

Nonclinical Safety

- No significant adverse findings in 14 day toxicity studies in rats and dogs or in the standard genotoxicity and safety pharmacology studies

Table 3. AEs by GS-5885 Dose in More Than One Subject in the Overall Study

	3 mg (n=8)	10 mg (n=8)	30 mg (n=8)	60 mg (n=9)	100 mg (n=8)	Placebo (n=10)
Subjects with at least 1 AE	3 (38%)	4 (50%)	4 (50%)	3 (33%)	4 (50%)	2 (20%)
Myalgia	0 (0%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Headache	1 (13%)	1 (13%)	2 (25%)	1 (11%)	0 (0%)	1 (10%)
Dizziness	0 (0%)	2 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dysmenorrhea	0 (0%)	1 (13%)	0 (0%)	0 (0%)	1 (13%)	1 (10%)
Dermatitis contact (ECG leads)	1 (13%)	0 (0%)	1 (13%)	0 (0%)	0 (0%)	0 (0%)

AEs in only 1 subject: abdominal pain, chapped lips, constipation, flatulence, nausea, toothache, oral herpes, URI, back pain, bursitis, extremity pain, palpitations, dysgeusia, somnolence, anxiety, hematuria, pityriasis rosea, hematoma

Safety Summary for Healthy Subjects

- No significant safety findings at any dose (3, 10, 30, 60, 100 mg fasted, 30 mg fed):
  - There were no SAEs, and adverse events were few, generally mild, and not dose limiting
  - All clinical chemistry and hematology abnormalities mild/moderate, no Grade 3/4 laboratory abnormalities through Day 7
  - No QTc prolongation
  - Well-tolerated

Figure 3. Mean Plasma Concentration vs. Time Profile of GS-5885 Following Oral Administration to Healthy Volunteers

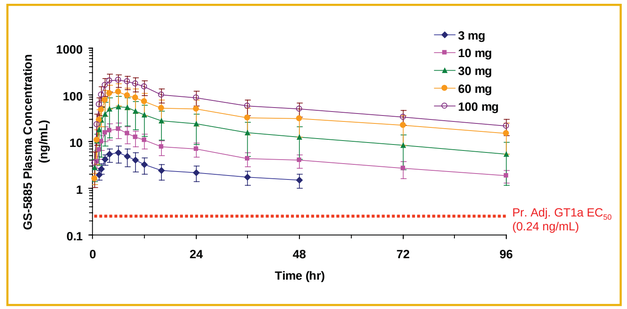


Table 4. Mean (CV%) GS-5885 Pharmacokinetic Parameters in Healthy Volunteers

	Cohort 1 (3 mg)	Cohort 2 (10mg)	Cohort 3 (30 mg)	Cohort 4 (60 mg)	Cohort 5 (100 mg)
C_{max} (ng/mL)	6 (37)	18.9 (36)	73.1 (51)	118 (50)	215 (35)
T_{max} (h)	5.25 (20)	5.0 (21)	5.75 (22)	5.5 (17)	5.5 (17)
$AUC_{0\text{-inf}}$ (ng•h/mL)	215 (54)	605 (31)	2402 (61)	4606 (58)	7558 (34)
$T_{½}$ (h)	45.2 (51)	42.4 (29)	37.2 (32)	44.2 (22)	39.5 (23)
C_{24} (ng/mL)	2.18 (37)	7.06 (34)	27.9 (60)	50.1 (57)	87.8 (35)

N=8 in each Cohort

Conclusions

- **GS-5885 is a potent picomolar HCV NS5A inhibitor that:**
  - **is well tolerated at all single oral dose levels (3-100 mg) with no grade 3-4 AEs**
  - **has dose proportional exposure in healthy volunteers and a $T_{1/2}$ of 37-45 hours, consistent with once daily dosing**
  - **produced mean 24 hour plasma concentrations that were multiple fold over the protein adjusted GT1a EC_{50} at all doses: 3 mg (9 fold); 10 mg (29 fold); 30 mg (116 fold) 60 mg (209 fold); 100 mg (366 fold)**
- **From these data, GS-5885 is expected to be well tolerated and to have substantial antiviral activity at low doses in GT1 HCV patients**
- **GS-5885 is being studied in a Phase 1, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of escalating multiple oral doses in treatment naïve subjects with chronic GT1 HCV Infection (GS US 256 0102)**
- **Based on its high potency, good oral exposure, long plasma half life, tolerability, and low projected dose, GS-5885 has potential utility in novel treatment regimens for HCV infection**

Acknowledgements

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