



PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF ACH-1625 (HCV NS3 PROTEASE INHIBITOR) IN HCV GENOTYPE 1 INFECTION

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Poster 458

ABSTRACT **A-343-0028-02852**
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BACKGROUND

- HCV NS3 serine protease is a prime target of new therapies that have the potential to improve SVR rates and/or lower adverse events in patients with chronic hepatitis C when combined with pegylated interferon alpha plus ribavirin.
- ACH-1625 is a potent, linear, noncovalent inhibitor of HCV NS3 protease.^{1,2}
 - It binds to NS3 protease slowly and tightly with an inhibition constant at steady state (K_i^{*}) of 0.06 nM (GT-1b).
 - It binds with similar potency to all genotypes, except genotype 3.
- The mean EC₅₀ value in a cell line harboring the GT-1b/Con-1 subgenomic replicon is 11 nM.
- Mutations causing resistance to ACH-1625 500 and 600 mg BID monotherapy have been identified at amino acid positions 155, 156, and 168 of NS3.¹
 - Some mutations associated with resistance to other NS3 protease inhibitors are not cross-resistant to ACH-1625.
- Despite the presence of resistant variants and drug plasma levels significantly below EC50, ACH-1625 suppressed viral replication through the end of follow-up.
- ACH-1625 distributes rapidly and selectively to liver, partly due to transporter-mediated uptake.³
- This report describes the final results of 400 mg and 600 mg QD fasted and 600 mg QD fed dosing regimens of ACH-1625 from a Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, 4-segment study evaluating plasma pharmacokinetic (PK) parameters, safety and tolerability, and effects on viral kinetics of the drug in patients with chronic, HCV genotype 1 infection.

METHODS

- Healthy, treatment-naïve or experienced HCV genotype 1 infected adults were randomized to placebo or ACH-1625 400 (n=6) or 600 (n=6) mg in the fasted state or 600 mg PO QD following a medium-fat meal (n=6) for 5 days.
- Subjects entered the inpatient facility on day 0 and received the first dose of ACH-1625 or placebo on day 1.
- Baseline assessments included liver and kidney function tests, hematology tests, metabolic tests, physical examinations, vital signs, and electrocardiograms.
- HCV RNA was obtained through Day 12 with Cobas AmpliPrep/Cobas TaqMan HCV test (LLOQ 45 IU/mL, LLD 15 IU/mL).
- The subjects were discharged on day 6 following the PK and HCV RNA blood draws 24 hours after the last dose.
- Subjects returned to the clinic that evening and on days 7, 8, 9, and 12 for additional PK and HCV RNA blood draws and safety assessments.

Pharmacokinetics

- A validated, non-compartmental PK analysis was performed on samples collected initially and at the time of each return visit (PK analysis performed by Kinesis).

Pharmacodynamics and Viral Kinetic Modeling

- HCV RNA data from subjects treated with ACH-1625 were analyzed by applying a single population viral dynamics model as described by Neumann et al.⁴
- Programming codes for viral kinetics modeling were developed in Matlab 7.9.0 (MathWorks, Natick, MA).
- An independent viral kinetic modeling analysis for ACH-1625 has also been conducted and will be presented at a future congress.⁵

Safety and Tolerability

- Safety and tolerability were assessed by standard chemistry, hematology, and metabolic tests plus physical examinations, vital signs, electrocardiograms, and adverse event (AE) reports.

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4. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science*. 1998;282:103-107.
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DISCLOSURES
HR, LR, AA, MD, and EO are employees of Achillion Pharmaceuticals.

RESULTS

Pharmacokinetics

- On Day 1, exposure expressed as mean C_{max} and mean AUC_{24hr} increased in a dose-proportional fashion for the 400 mg QD to 600 mg QD (Table 1).
- Two individuals in the 400 mg dose group had higher accumulation to steady-state levels compared to other subjects, thus affecting the mean values. Mean dose normalized C_{0h} values on Days 2, 3, 4 and 5 of treatment were comparable for the two dose groups when the two outliers were excluded.
- On Day 5, the dose normalized individual values of C_{max} and AUC_{24h} for 10/12 subjects were approximately the same range for both dose groups, suggesting dose proportionality.
- Inter-individual variability (%CV) for C_{0hr}, C_{minhr}, C_{max}, C_{55,8hr}, and AUC_{24h} was high for both dose groups on all days.
- The mean t_{1/2sterm} was similar for both QD doses fed and fasted and ranged between 19 and 31 hours.
- For most of the subjects in both dose groups, plasma concentrations of ACH-1625 were generally higher on Day 5 compared to Day 1 over the entire dosing interval (Figure 1).
- Both on Days 1 and 5 of treatment, drug exposure was considerably lower after intake under fasted conditions compared with intake under fed conditions.
 - On both days, median time to reach maximum plasma concentrations was about 3 hours after intake under fasted conditions and about 6 hours after intake under fed conditions.
 - For the 600 mg dose regimen, AUC was notably lower in fasted versus fed conditions.
- Individual values of C_{max} and AUC_{24h} were within the same range for the male and female subjects.

Pharmacodynamics and Viral Kinetic Modeling

- Viral load (Figures 2 and 3)
 - Mean baseline HCV RNA ranged from 6.05-6.36 log₁₀.
 - Reductions in viral load were substantial at 48 hours and were sustained up to 12 days.
 - In the 400 and 600 mg fasting and the 600 mg fed groups, the mean maximum drops in HCV RNA were 3.67, 3.40, and 3.81 log₁₀, respectively.
 - At Day 12, 7 days after the last dose, the HCV RNA remained suppressed, showing an observed mean range from -1.00 to -2.20 log₁₀ (Figure 2).
- Kinetic Modeling
 - All dose cohorts of ACH-1625 demonstrated a sharp phase-1 decline that is reflected in the high drug efficiency observed (Figures 4 and 5).
 - The three subjects (subject # 2121, 2091, and 2123) that demonstrated the highest efficiency among the patients treated with 400 mg QD in the fasted state had the largest viral load declines noted over the first 72 hours. This can be attributed to low viral load at baseline (< 4,000,000 IU/mL) and robust exposure (AUC_{24h} > 673 ng.h/mL).
 - The other three subjects in the 400 mg QD fasted treatment group (subject # 2112, 2136, and 2133) had intermediate efficiency and exposure observed. In addition, these subjects had baseline high viral load (> 4,000,000 IU/mL) and higher body mass index.

Safety and Tolerability

- ACH-1625 was safe and well tolerated at both doses for 5 days duration.
- There were no consequential changes in transaminases, bilirubin, or other clinical laboratory or hematological parameters (Table 2).
- There was a trend toward improvement of liver enzyme levels during treatment with ACH-1625 (Figure 6)
- AEs were transient, mild or moderate (Table 3)

RESULTS

Table 1: Summary of Plasma PK Profile of ACH-1625 400 mg and 600 mg (Fed/Fasted) QD

ACH-1625 Pharmacokinetics (Mean ± SD, t _{max} median [range])	400 mg QD for 5 Days (Fasted)	600 mg QD for 5 Days (Fasted)	600 mg QD for 5 Days (Fed)
n	6 ^a	6	6
DAY 1			
C _{max} , ng/mL	283.9 ± 232.1	515.8 ± 426.5	1406 ± 694.3
t _{max} , h	3.25 (1.5-5.0)	3.25 (3.0-4.0)	6.0 (5.0-9.0)
AUC _{24hr} , ng.h/mL	1322 ± 1442	2056 ± 1593	7134 ± 3873
DAY 2			
C _{0hr} , ng/mL	13.88 ± 18.46	14.18 ± 12.72	31.95 ± 19.33
DAY 3			
C _{0hr} , ng/mL	37.27 ± 60.25	19.85 ± 15.14	71.37 ± 84.57
DAY 4			
C _{0hr} , ng/mL	75.85 ± 121.1	31.14 ± 27.62	76.63 ± 70.19
DAY 5			
C _{0hr} , ng/mL	44.82 ± 64.84	37.41 ± 32.37	76.98 ± 87.36
C _{min} , ng/mL	43.76 ± 65.52	26.55 ± 23.66	42.52 ± 43.16
C _{max} , ng/mL	2559 ± 3149	1283 ± 1082	4304 ± 2560
t _{max} , h	4.0 (2.5-4.0)	3.0 (2.0-4.0)	6.0 (3.0-6.0)
AUC _{24hr} , ng.h/mL	13340 ± 18930	5046 ± 3920	21850 ± 13470
C _{55,8hr} , ng/mL	555.9 ± 788.8	210.2 ± 163.3	910.2 ± 561.2
FI, %	591.3 ± 404.9	573.9 ± 148.0	537.4 ± 228.8
t _{1/2sr} , h	2.613 ± 0.7729	1.396 ± 0.5380	2.419 ± 0.9906
t _{1/2sr} , h	31.06 ± 18.85	21.86 ± 3.304	18.76 ± 5.655
Acc. Ratio C _{max}	6.121 ± 6.022	2.600 ± 1.088	3.387 ± 1.598
Acc. Ratio AUC _{24h}	6.601 ± 6.709	2.921 ± 1.429	3.218 ± 1.737

^an = 4 for t_{1/2sr}

Table 2: Mean (SD) Baseline Values and Mean Change (SD) from Baseline in Selected Serum Chemistry and Hematology Parameters in HCV-infected Patients After Administration of ACH-1625 for 5-Days (Safety Population)

Laboratory Parameter (unit)	400 mg QD (n=6)	600 mg QD (n=6)
ALT (U/L)		
Baseline (Day 0)	57.3 (37.41)	69.0 (41.74)
Day 6	-18.0 (23.77)	-27.5 (25.59)
Day 12	-15.3 (20.18)	-45.2 (33.56)
AST (U/L)		
Baseline (Day 0)	46.3 (32.65)	59.8 (33.65)
Day 6	-18.2 (25.90)	-30.3 (24.97)
Day 12	-15.3 (22.03)	-35.0 (29.27)
Total Bilirubin (mg/dL)		
Baseline (Day 0)	0.74 (0.28)	0.71 (0.13)
Day 6	-0.24 (0.31)	-0.13 (0.16)
Day 12	-0.20 (0.21)	-0.18 (0.18)
Creatinine (mg/dL)		
Baseline (Day 0)	0.84 (0.15)	0.80 (0.16)
Day 6	-0.00 (0.07)	0.08 (0.24)
Day 12	-0.02 (0.08)	0.06 (0.09)
Hemoglobin (g/dL)		
Baseline (Day 0)	15.00 (0.94)	14.93 (1.55)
Day 6	0.55 (0.67)	-0.48 (0.27)
Day 12	0.02 (0.56)	-1.22 (0.53)
Absolute Neutrophils (10⁹/L)		
Baseline (Day 0)	2.84 (0.73)	3.50 (0.68)
Day 6	1.00 (1.63)	0.07 (1.04)
Day 12	0.49 (1.44)	-0.27 (0.99)

Notes: Segment 4: HCV-infected volunteers administered ACH-0141625 fasted QD (q24h for 5 days). SD=Standard Deviation

Table 3: Treatment Emergent Adverse Events in Fasting Groups

System Organ Class/ Preferred Term	400 mg QD (n=6) n (%)	600 mg QD (n=6) n (%)
Number of Subjects Reporting	4 (67)	3 (50)
Number of AEs	6	3
Cardiac Disorders	2 (33)	0
Atrial Fibrillation	1(17)	0
Ventricular Extrasystoles	1(17)	0
Gastrointestinal Disorders	1(17)	0
Constipation	1(17)	0
Nervous System Disorders	2 (33)	3 (50)
Headache	2 (33)	3 (50)
Vascular Disorders	1(17)	0
Hypotension	1(17)	0

FIGURES

FIGURE 1: MEAN LINEAR PLASMA CONCENTRATION vs TIME PROFILE

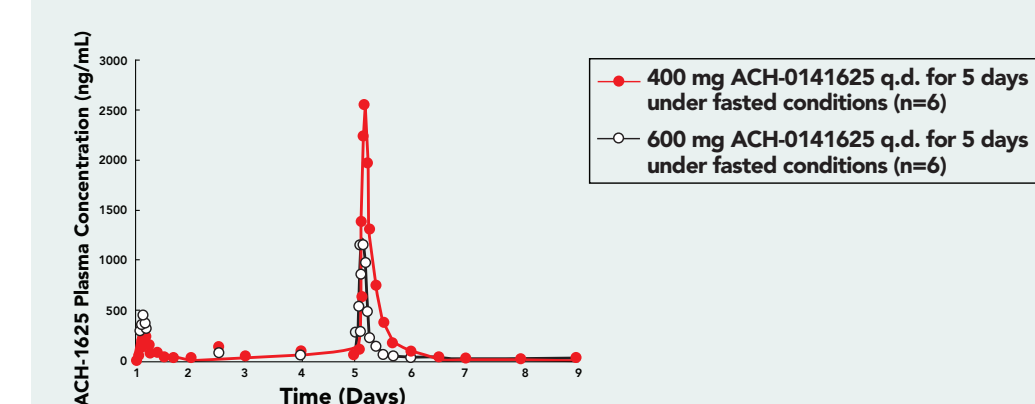


FIGURE 3: VIRAL LOAD DECAY FOR THE 400 mg QD FASTED DOSE GROUP

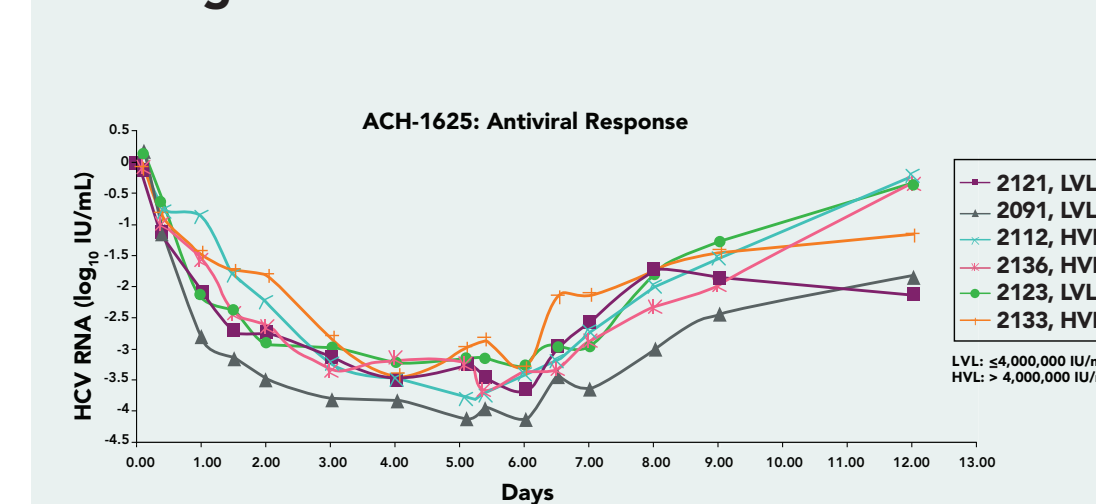


FIGURE 5: BEST FIT OF VIRAL KINETICS MODEL TO THE MEAN VIRAL LOAD DATA OF 400 mg QD FASTED DOSE SUBGROUPS

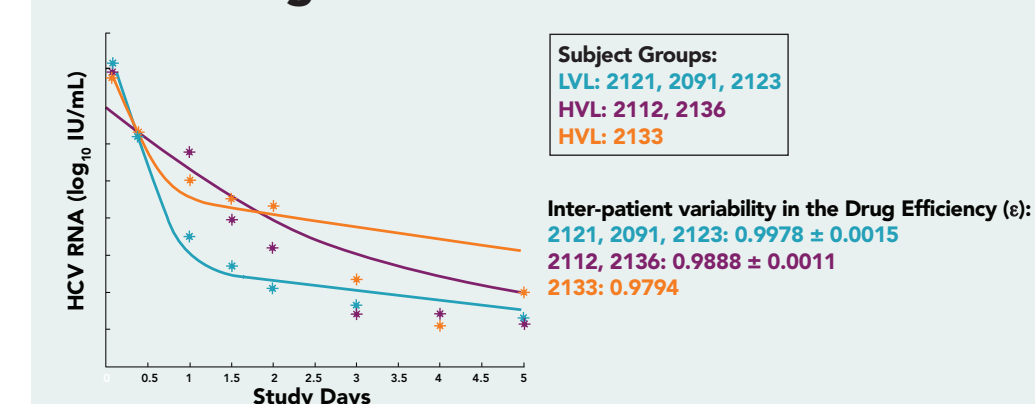


FIGURE 2: MEAN CHANGE FROM BASELINE HCV RNA THROUGH DAY 12

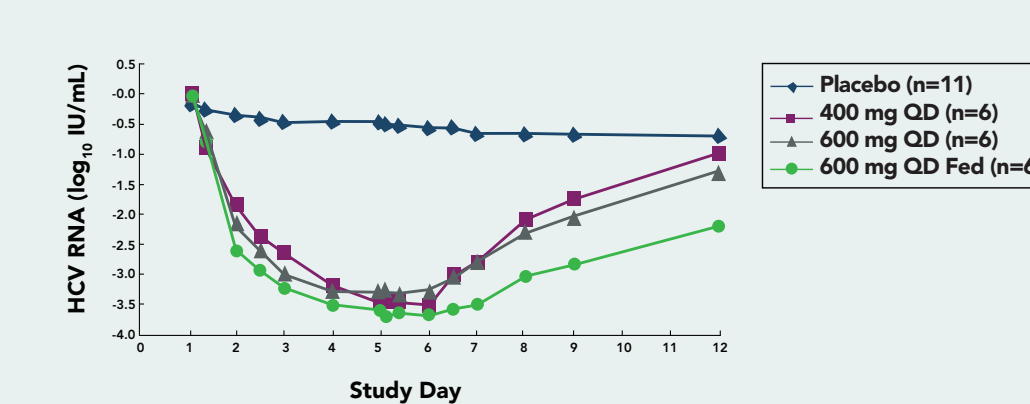


FIGURE 4: BEST FIT OF VIRAL KINETICS MODEL TO THE MEAN VIRAL LOAD DATA OF EACH DOSE GROUP

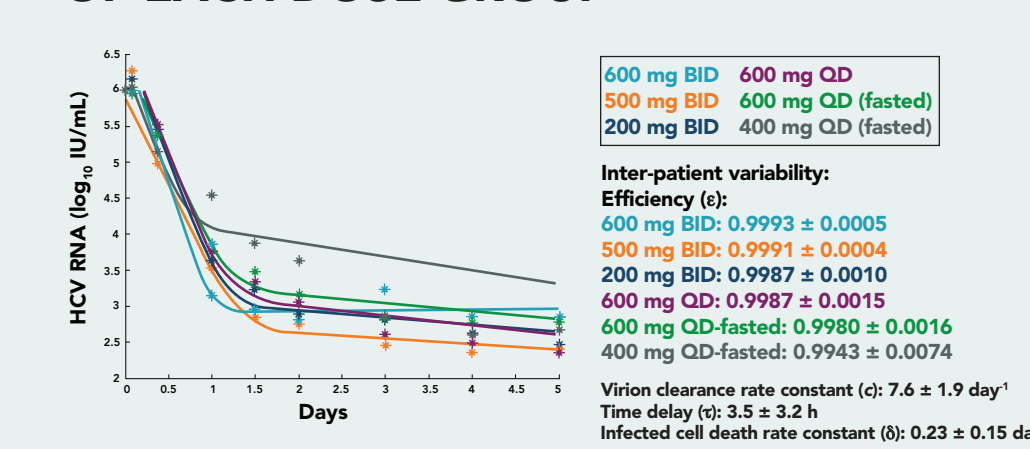
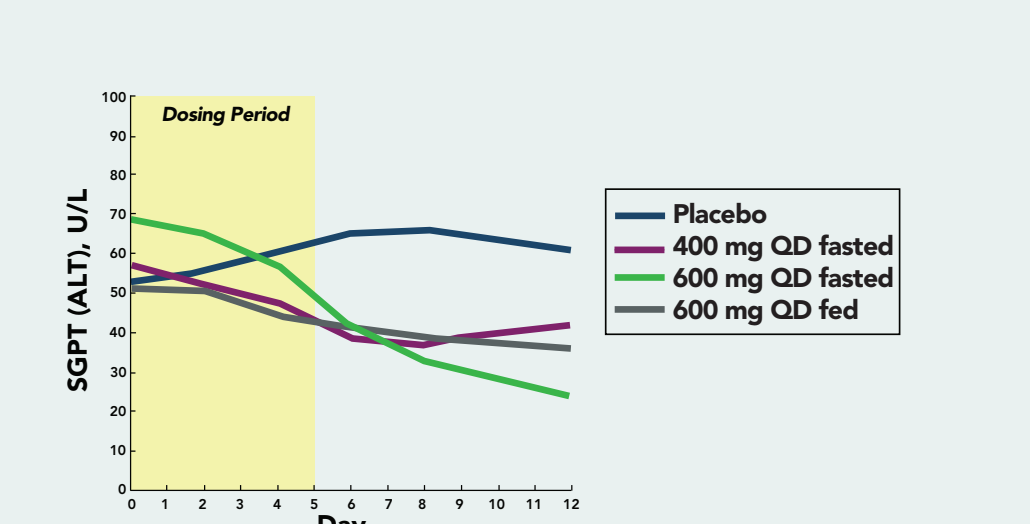


FIGURE 6: ALT OVER TIME



CONCLUSIONS

- Doses of 400 and 600 mg QD of ACH-1625 resulted in systemic ACH-1625 levels that produced robust antiviral effects.
- No virologic breakthrough occurred in any subject during monotherapy with ACH-1625.
- PK/PD modeling predicted that HCV RNA declines of >3 log₁₀ could be achieved with QD dosing, similar to that observed in previously described BID doses.
- The sustained viral load suppression observed among patients treated with the drug at Day 12 indicated that it may yield a potential advantage in longer duration combination treatment.
- ACH-1625 in combination with pegylated interferon alfa-2a and ribavirin is currently being studied in a phase 2 clinical trial, where 400 mg QD or 800 mg QD are predicted to increase RVR >3-fold compared with current standard of care.