



HIGH RAPID VIROLOGIC RESPONSE (RVR) WITH ACH-1625 DAILY DOSING PLUS PEGIFN- ALPHA 2A/RBV IN A 28-DAY PHASE 2A TRIAL

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ABSTRACT 1341

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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 reduce adverse events in patients with chronic hepatitis C when combined with peginterferon alfa-2a plus ribavirin (PR)
- 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 (eg, for genotype 1b [GT-1b])
 - It inhibits NS3 proteases of all genotypes with similar potency, except GT-3
- The mean EC₅₀ value in a cell line harboring the GT-1b/Con-1 subgenomic replicon is 11 nM (or 8.8 ng/mL no salt)
- ACH-1625 distributes rapidly and selectively to liver, partly due to transporter-mediated uptake³
- Subsequent analyses on individual PK curves and antiviral efficacy collected in a phase 1 trial in GT-1 patients yielded an EC₅₀ of 0.41 ng/mL
- Phase 1 trial data demonstrated the safety and tolerability of ACH-1625 monotherapy up to 1200 mg/day for 5 days in patients with HCV⁴
- Pharmacokinetic (PK) and viral kinetics profiles support QD dosing and the potential to combine ACH-1625 in an all direct-acting antiviral (DAA) combination^{4,5}
- This presentation describes Week 4 RVR data after administration of ACH-1625/placebo in combination with PR for 28 days

METHODS

- Phase 2a clinical study in treatment-naïve, HCV GT-1-infected adults who were randomized in a double-blind, placebo-controlled, dose-ranging study to receive either placebo or ACH-1625 plus PR for 28 days
 - Subjects received ACH-1625 200 mg (n=16), 400 mg (n=16), 800 mg (n=17), or placebo (n=15) plus PR for 28 days
 - After 28 days, study drug and placebo were discontinued and subjects received PR up to Week 48
 - Dose groups were stratified by IL28B status
 - Subject visits occurred at least weekly for the first 6 weeks followed by every other week through Week 12
- Assessments were performed for safety, rapid virologic response (RVR: HCV RNA <25 IU/mL at 4 weeks), PK, and HCV RNA collection for genotypic analysis
 - Baseline assessments included liver and kidney function tests, hematology tests, metabolic tests, physical examinations, vital signs, and electrocardiograms (ECG)
 - Safety was evaluated by assessment of clinical laboratory tests, physical examination findings, vital signs measurements, and 12-lead ECG recordings at baseline and at various time points during the study; adverse events monitoring; and documentation of treatment reductions, interruptions, and discontinuations
 - Changes in HCV RNA level between baseline and Weeks 4, 12, 24, 48, 60, 72, and at points in between were measured to assess the viral dynamics of HCV in the presence of, and following treatment with, ACH-1625
 - PK parameters were studied from baseline through Week 4 for ACH-1625 and Week 12 for PR, and relevant population PK/pharmacodynamic modeling was conducted
 - In Segment 1, trough PK samples were obtained from all subjects at pre-dose on Day 1 and at Weeks 1, 2, 3, and 4
 - For some subjects, full PK profiling samples (pre-dose through Hour 24 on Day 1 and Week 4) or limited PK profiling samples (pre-dose through Hour 9 on Day 1 and Week 4) were also obtained

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DISCLOSURES

HR, LR, and EO are employees of Achillion Pharmaceuticals

RESULTS

Patient Demographics

- 12 US sites enrolled 64 patients infected with HCV GT-1a (73%), GT-1b (25%), GT-1 (2%)
- Baseline demographics were similar across groups
- 47 (73%) were male; 38 (59%) Caucasian, 21 (33%) African American, 5 (8%) other
- Mean age: 50
- Mean BMI: 27.6
- 83% of patients enrolled were IL28B CT/TT and 17% were CC

Viral Response

- Administration of 800 mg QD dose for 28 days in combination with PR resulted in a 5 log₁₀ maximum reduction in HCV RNA (Figure 1 and Table 1)
- 400 mg QD dose with PR resulted in a 4.6 log₁₀ maximum reduction
- 200 mg QD dose with PR resulted in a 4.9 log₁₀ maximum reduction
- The results demonstrate similar response rates across dose groups

Figure 1. Viral Load Decay Through Week 4

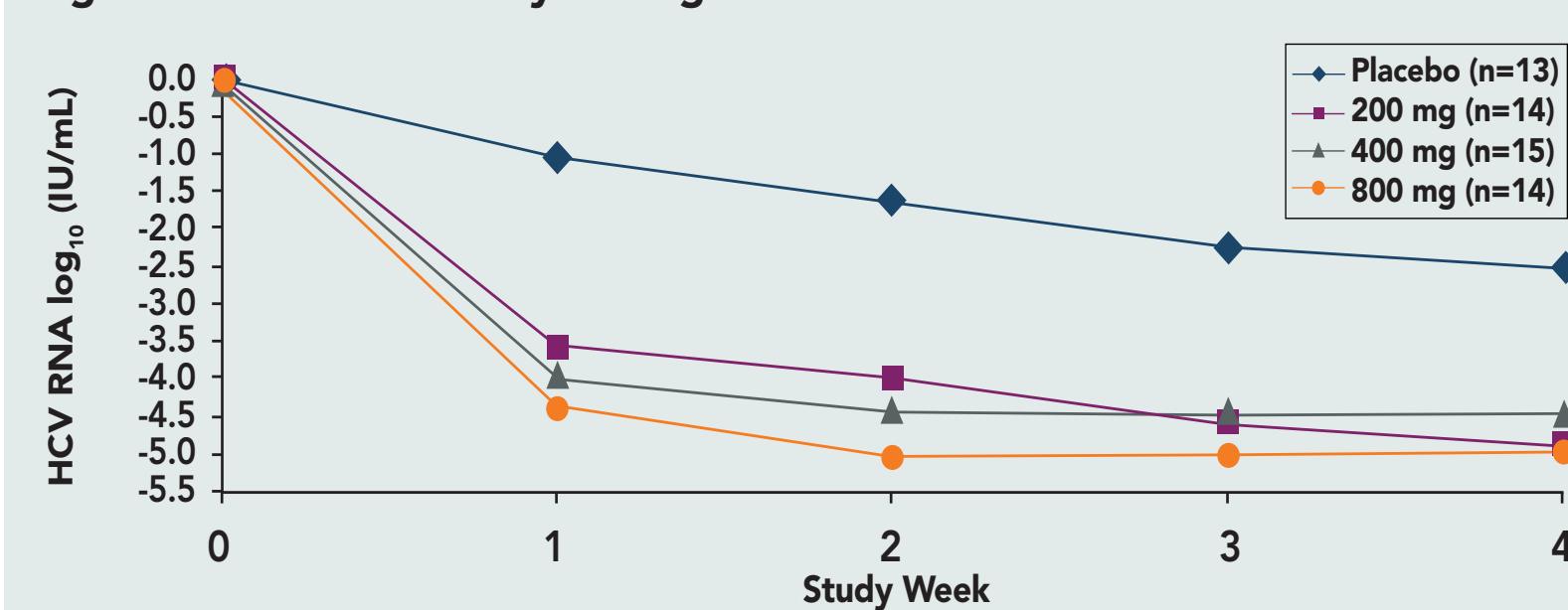


Table 1. Week 4 RVR Response

| Parameter | 200 mg QD (n=16) | 400 mg QD (n=16) | 800 mg QD (n=17) | Placebo QD (n=15) |
|--|------------------|------------------|------------------|-------------------|
| Week 4 RVR (HCV RNA <25 IU/mL) | 13/16 (81) | 12/16 (75) | 13/17 (76) | 3/15 (20) |
| VL <25 IU/mL, IL28B CT or TT | 10/13 (77) | 9/13 (69) | 10/14 (71) | 2/13 (15) |
| VL <25 IU/mL, IL28B CC | 3/3 (100) | 3/3 (100) | 3/3 (100) | 1/2 (50) |
| VL <25 IU/mL, GT-1a | 8/11 (73) | 9/13 (69) | 7/11 (64) | 2/12 (17) |
| VL <25 IU/mL, GT-1b | 4/4 (100) | 3/3 (100) | 6/6 (100) | 1/3 (33) |
| Baseline HCV RNA | | | | |
| <400,000 | 1/1 (100) | 2/2 (100) | 1/1 (100) | 2/2 (100) |
| ≥400,000 | 12/15 (80) | 10/14 (71) | 12/16 (75) | 1/13 (8) |
| Mean maximum HCV RNA decline through Week 4 (log ₁₀) | 4.90 | 4.63 | 4.96 | 2.25 |

Table 2. Segment 1 Week 4 Analysis of HCV RNA

| HCV RNA | 200 mg QD (n=16) | 400 mg QD (n=16) | 800 mg QD (n=17) | Placebo QD (n=15) |
|-------------------------------------|-------------------|------------------|------------------|-------------------|
| Mean (SD) log ₁₀ (IU/mL) | | | | |
| Baseline | 6.6 (0.6) | 6.2 (1.4) | 6.6 (0.9) | 6.5 (0.7) |
| Change from baseline | | | | |
| Week 1 | -3.5 (1.3) | -4.0 (1.2) | -4.4 (1.0) | -0.9 (0.8) |
| Week 2 | -4.0 (1.3) | -4.5 (1.3) | -4.7 (1.0) | -1.4 (1.2) |
| Week 3 | -4.6 (1.1) | -4.5 (1.4) | -4.8 (1.3) | -2.0 (1.4) |
| Week 4 | -4.9 (1.0) | -4.6 (1.4) | -4.8 (1.3) | -2.2 (1.4) |
| <25 IU/mL (n, %) | n=15 ^a | n=16 | n=17 | n=15 |
| Week 1 | 3 (19) | 3 (19) | 5 (29) | 0 |
| Week 2 | 5 (31) | 9 (56) | 11 (65) | 1 (7) |
| Week 3 | 10 (63) | 11 (69) | 13 (76) | 2 (13) |
| Week 4 | 13 (81) | 11 (69) | 13 (76) | 3 (20) |

^aExcludes subject 1088 whose VL <25 at baseline

Table 3. Parameter Estimates From Viral Kinetics Modeling

| | 200 mg QD (N=16) | 400 mg QD (N=16) | 800 mg QD (N=17) | Placebo QD (N=15) |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Efficiency (# of subjects for which HCV RNA was available at 48 hours post-dosing) | 0.9986 ± 0.0024 (n=7) | 0.9997 ± 0.0002 (n=5) | 0.9997 ± 0.0004 (n=8) | 0.9432 ± 0.0448 (n=3) |
| Efficiency, IL28B CT or TT | 0.9981 ± 0.0027 (n=5) | 0.9997 ± 0.0002 (n=5) | 0.9997 ± 0.0005 (n=7) | 0.9177 ± 0.0099 (n=2) |
| Efficiency, IL28B CC | 0.9999 (n=1) | n=0 | 0.9999 (n=1) | 0.9943 (n=1) |
| Efficiency, GT-1a | 0.9983 ± 0.0028 (n=5) | 0.9997 ± 0.0002 (n=5) | 0.9997 ± 0.0005 (n=7) | 0.9432 ± 0.0448 (n=3) |
| Efficiency, GT-1b | 0.9996 ± 0.0006 (n=2) | n=0 | 0.9999 (n=1) | n=0 |

- IL28B status and genotype (GT-1a or GT-1b) had no effect on the estimated efficiency of 800 mg QD plus PR in the first 48 hours of treatment
- Each of these factors affected the efficiency of 200 mg ACH-1625 plus PR in the first 48 hours
- Placebo plus PR had diminished estimated efficiency, and efficiency was affected by IL28B status

Safety and Tolerability

- Over the 4 weeks of coadministration of ACH-1625 and PR
 - No serious adverse events
 - No study discontinuations due to adverse events during the first 4 weeks
- Adverse events were generally consistent with PR; the most frequent events were headache, fatigue, nausea, diarrhea, flu-like illness, and pain (Table 5 shows the adverse events of special interest)
- Based on safety and tolerability, each dose level (200, 400, and 800 mg QD) achieved acceptable results
 - Grade 3 or 4 adverse events included nausea and migraine (200 mg QD; n=2), renal cell carcinoma and anemia (400 mg QD; n=2), and hemolytic anemia (800 mg QD; n=1)

Table 4. Safety Summary Through Week 4

| Number of Subjects Reporting | 200 mg QD (n=16) | 400 mg QD (n=16) | 800 mg QD (n=17) | Placebo QD (n=15) |
|------------------------------|------------------|------------------|------------------|-------------------|
| Grade 3 or 4 AEs, n (%) | 2 (13) | 2 (13) | 1 (6) | 0 |
| Grade 3 or 4 lab abnl, n (%) | 1 (6) | 1 (6) | 1 (6) | 3 (20) |
| D/C due to AE, n (%) | 0 | 0 | 0 | 0 |
| SAE, n (%) | 0 | 0 | 0 | 0 |
| Death, n (%) | 0 | 0 | 0 | 0 |

Table 5. Adverse Events of Special Interest

| Number of Subjects Reporting | 200 mg (n=16) | 400 mg (n=16) | 800 mg (n=17) | Placebo QD (n=15) | All Subjects (n=64) |
|------------------------------|---------------|---------------|---------------|-------------------|---------------------|
| Myalgia/arthritis, n (%) | 5 (31) | 1 (6) | 2 (12) | 3 (20) | 11 (17) |
| Rash, n (%) | 2 (13) | 2 (13) | 1 (6) | 2 (13) | 7 (11) |
| Pruritis, n (%) | 1 (6) | 2 (13) | 2 (12) | 1 (7) | 6 (9) |
| Dysgeusia, n (%) | 3 (19) | 2 (13) | | 1 (7) | 6 (9) |

Rash includes: rash, rash macular, rash papular, rash pruritic

Pruritis includes: pruritis, pruritis generalized

The difference between the proportions of 1625-treated subjects and placebo subjects reporting AEs was not significant at the p=0.05 level for any of the AE terms.

Laboratory Summary

- Observed laboratory abnormalities were generally grade 1 or 2 and included the following
 - Grade 1 indirect bilirubin changes occurred in 9/64 (14%) of patients in the first 4 weeks
 - Grade 2 indirect bilirubin changes occurred in 5/64 (8%) of patients in the first 4 weeks
- No accompanying liver enzyme changes were noted
- All treatment groups showed a mean ALT/AST decline over 4 weeks

Table 6. Grade 3 or 4 Laboratory Abnormalities in the First 4 Weeks

| Number of Subjects Reporting | 200 mg | 400 mg | 800 mg | Placebo |
|------------------------------|--------|--------|--------|---------|
| Hyperuricemia | 1 | 0 | 1 | 0 |
| Neutropenia | 0 | 1 | 1 | 2 |
| Anemia | 0 | 0 | 0 | 1 |

Pharmacokinetic Parameters

- A summary of the noncompartmental parameters is shown in Table 7
- ACH-1625 exposure, expressed as mean C_{max} and AUC_{last}, increased in a greater-than-proportional fashion from 200 mg to 800 mg, both at Day 1 and Week 4
- Mean exposure parameters were generally two-fold higher than the expected dose-proportional values at Week 1 and 4 for AUC_{last} and C_{max}
- Intersubject variability in ACH-1625 pharmacokinetics was high on all days, which may affect mean values
- Exposure was consistent from Week 1 through 4

Table 7. Segment 1 Pharmacokinetic Results of ACH-1625 After QD Dosing for 28 Days in HCV-Infected Subjects

| Time Point | PK Parameter | Statistic | 200 mg (n=16) | 400 mg (n=16) | 800 mg (n=17) | |
|------------------------------------|--------------|-----------|-----------------|---------------|-----------------|-------------|
| | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Day 1 | | | | | | |
| AUC _{last} (hr•ng/mL) | 10 | 295 (177) | 11 | 1322 (822) | 13 | 5406 (5321) |
| C _{max} (ng/mL) | 10 | 86 (56) | 9 ^b | 174 (77) | 12 ^a | 1097 (1067) |
| T _{1/2term} (hr) | 4 | 5 (4) | 8 | 5 (2) | 3 ^a | 4 (1) |
| T _{last} (hr) | 10 | 15 (8) | 11 | 16 (8) | 13 | 18 (8) |
| T _{max} (hr) | 10 | 3 (2) | 11 | 6 (6) | 13 | 6 (6) |
| Weeks 1, 2, and 3 | | | | | | |
| Week 1 C _{trough} (ng/mL) | 16 | 12 (10) | 14 ^a | 47 (103) | 14 ^a | 98 (165) |
| Week 2 C _{trough} (ng/mL) | 16 | 6 (4) | 16 | 31 (31) | 15 | 63 (102) |
| Week 3 C _{trough} (ng/mL) | 15 | 11 (11) | 16 | 22 (18) | 15 ^a | 52 (117) |
| Week 4 | | | | | | |
| AUC _{last} (hr•ng/mL) | 10 | 299 (464) | 9 | 1047 (1290) | 11 | 2757 (8513) |
| C _{max} (ng/mL) | 10 | 90 (196) | 9 | 240 (352) | 11 | 944 (3037) |
| C _{trough} (ng/mL) | 14 | 10 (5) | 15 | 26 (22) | 14 ^a | 40 (46) |
| T _{1/2term} (hr) | 6 | 10 (5) | 6 | 10 (5) | 6 | 9 (3) |
| T _{last} (hr) | 10 | 17 (8) | 9 | 16 (8) | 10 | 18 (8) |
| T _{max} (hr) | 10 | 2 (2) | 9 | 3 (2) | 10 | 2 (3) |

Note: ACH-1625/placebo administered QD in combination with PR for 28 days

Source: ACH-1625 Segment 1 Week 4 analysis

^a Excludes 1 outlier

^b Excludes 2 outliers

CONCLUSIONS

- ACH-1625 was safe and well-tolerated for 4 weeks in combination with PR
- ACH-1625 demonstrated robust antiviral activity
- RVR rates of 75%-81% were observed with ACH-1625 administered QD with PR in treatment-naïve, HCV GT-1 patients
- RVR rates with ACH-1625 were higher than the placebo RVR rate by 55%-61%
- The safety and efficacy data support further studies with both PR and DAA combinations
- A phase 2 trial with 12 weeks of ACH-1625 QD (200, 400, and 800 mg) with PR is ongoing