VIROLOGICAL RESPONSE, SAFETY, AND PHARMACOKINETIC PROFILE FOLLOWING SINGLE – AND MULTIPLE-DOSE ADMINISTRATION OF ACH-1625 PROTEASE INHIBITOR TO HEALTHY VOLUNTEERS AND HCV GENOTYPE-1 PATIENTS

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Abstract

Background and Aims: ACH-1625 is a highly potent and specific HCV NS3/4A protease inhibitor (PI). A phase 1 study was conducted to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity following single- and multiple-dose administration of ACH-1625 to male and female healthy volunteers and HCV genotype-1 patients.

Methods: In the single-dose segment 18 healthy subjects received doses of 50–2000 mg ACH-1625 or placebo in an alternating panel, multiple period, dose escalation scheme. In the multiple dose segment, 18 healthy subjects received doses of 600 mg BID or 1000 mg BID of ACH-1625 or placebo for 5 days in a double-blind serial-panel study. In addition, 18 HCV patients randomized in a 2:1 ratio received 500 mg BID or 600 mg BID of ACH-1625 or placebo for 5 days in a double-blind serial panel segment. All patients were followed for 12 days. Clinical safety evaluations (adverse events, clinical chemistry, hematology, urinalysis, vital signs and ECG) were performed throughout each segment. Plasma samples for ACH-1625 pharmacokinetic data were collected. Viral load measurements were taken for the HCV patients.

Results: Mean age among patients was 41, BMI 25.9 +/–3.79 SD, and mean $\log_{10}$ VL at baseline was 5.9. A > 3 $\log_{10}$ maximal drop in HCV RNA was observed in all subjects treated with 500 and 600 mg ACH-1625. No response was seen with placebo. No breakthrough was observed during treatment. Maximal VL decline achieved was 4.25 and 3.94 $\log_{10}$ for 500 mg BID and 600 mg BID, respectively. Two patients in the 600 mg BID dose group achieved HCV RNA BLQ (15 IU/mL). In patients receiving ACH-1625 a sustained mean 2.53 $\log_{10}$ decline was observed at Day 12. ACH-1625 showed supra-dose proportional plasma exposure at doses below 1000 mg. There were no serious AEs reported, nor were there any discontinuations due to AEs. AEs were mild or moderate and transient.

Conclusions: ACH-1625 is generally safe and well-tolerated, and exhibits plasma pharmacokinetics and viral load reduction that support once or twice daily dosing. The sustained viral load suppression observed among patients treated with ACH-1625 at Day 12 suggests a potential advantage that warrants continued investigation.

Background

- ACH-1625 is an open chain noncovalently bound peptidomimetic NS3/4A PI.
- Internally discovered by Achillion Pharmaceuticals, Inc.
- EC_{50} 11 nM / EC_{90} 31 nM (EASL Poster 492 Huang M., et al).
- Rat and dog studies showed rapid and substantial partitioning into the liver (EASL Poster 172, Stauber K., et al).
- Preclinical studies indicated an acceptable safety and PK profile for ACH-1625 to advance into the clinic.

Methods

- *36 HV and 18 HCV infected genotype 1 patients were enrolled in 3 segments.*
- *HV (healthy volunteers) aged 18–45.*
- *HCV infected genotype 1 patients aged 18–69 with > 10^5 HCV RNA at baseline, ALT < 5X ULN, and either Naïve to prior IFN / RBV therapy or have been a relapser, breakthrough, or an incomplete responder during prior IFN / RBV therapy.*
- *HCV RNA (Segment 3) was obtained through Day 12.*
- *Safety assessments for each segment included:*
  Vital signs, ECG, Laboratory: biochemistry, hematology, and biomarkers, adverse events, pharmacokinetic data.
- *Stopping criteria were applied prior to dose escalation.*
- *Cobas AmpliPrep/Cobas TaqMan HCV test LLOQ 45 IU/mL, LLD 15 IU/mL.*

FIGURE 1.

Segment 1 HV SAD	
Group 1 Period 1: 50 mg	Group 2 Period 1: 350 mg
Group 1 Period 2: 1000 mg	Group 2 Period 2: 1400 mg
Group 1 Period 3: Fasted 1000 mg	Group 2 Period 3: 2000 mg

Segment 2 HV MAD 4.5 DAYS	
Group 3: 600 mg BID	Group 4: 1000 mg BID

Segment 3 HCV MAD 4.5 DAYS	
Group 5: 600 mg BID	Group 6: 500 mg BID

Results

1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

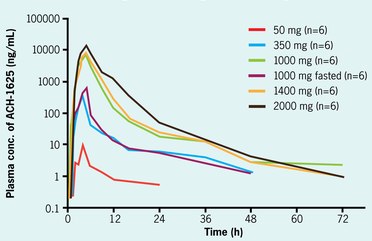
TABLE 1.

Enzyme	Group 1 (n=9)	Group 2 (n=9)	Group 3 (n=9)	Group 4 (n=9)	Group 5 (n=9)	Group 6 (n=9)
Male	4 (44%)	9 (100%)	6 (67%)	8 (89%)	5 (56%)	7 (78%)
White	9 (100%)	8 (89%)	9 (100%)	9 (100%)	7 (78%)	9 (100%)
HCV type 1a vs.1b					1 (11%) vs.8 (89%)	0 vs. 9 (100%)
HCV RNA mean (SD) $\log_{10}$					5.68 (0.43)	6.11 (0.54)
Age mean (SD) yrs	42 (11)		45 (8)		41 (12)	
BMI mean (SD) kg/m2	25 (2)		25 (3)		26 (4)	

2 PK SUMMARY: SINGLE DOSE IN HEALTHY VOLUNTEERS AND HCV INFECTED PATIENTS

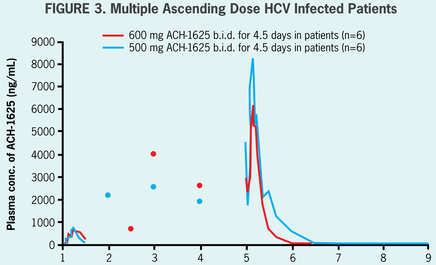
- *After intake of a single dose of ACH-1625, C_{max}, AUC_{last}, and AUC_{inf} increased more than dose proportionally in the 50 mg to 1000 mg dose range.*
- *In the 1000 mg to 2000 mg dose range dose proportionality was observed for these parameters.*
- *The mean $t_{1/2term}$ was comparable between the 350 mg to 2000 mg single dose groups and ranged 11 to 14 hours; $t_{1/2term}$ could not be determined for the 50 mg dose group.*

FIGURE 2. Single Ascending Dose Healthy Volunteers



- *In healthy volunteers, accumulation after multiple doses was more than expected based on single dose PK and was higher after 4.5 days of treatment for the 1000 mg BID dose group compared to the 600 mg BID dose group.*
- *The PK profiles observed in healthy volunteers and HCV infected patients administered 600 mg BID for 4.5 days were similar for C_{max}, $C_{ss,av}$, and AUC_{12h}.*

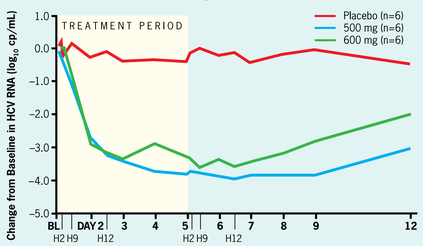
FIGURE 3. Multiple Ascending Dose HCV Infected Patients



3 ANTIVIRAL RESPONSE

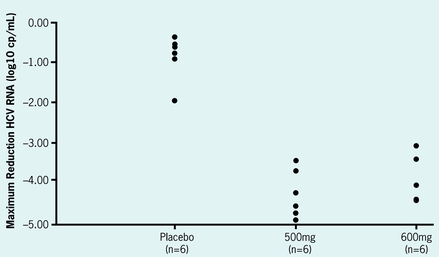
- *Administration of ACH-1625 at 500 mg BID for 4.5 days resulted in a maximal mean HCV RNA decrease of 4.25 $\log_{10}$, and at 600 mg BID for 4.5 days a 3.94 $\log_{10}$ decrease.*
- *Substantial viral load suppression was observed out to day 12, 7 days after the completion of study drug administration, reflected by a pooled mean HCV RNA decrease of 2.53 $\log_{10}$*
- *No virologic breakthrough was observed for any subject receiving ACH-1625 during treatment.*

FIGURE 4. Mean Change from Baseline in HCV RNA



Note: Observations recorded as "not detected" were assigned the limit of detection value of 15 IU/mL.

FIGURE 5. Maximum Reduction in HCV RNA Over All Visits



Notes: Observations recorded as "not detected" were assigned the limit of detection value of 15 IU/mL. In the 600 mg group, 2 subjects had maximum reduction = – 4.36; thus their markers overlap.

TABLE 2. Virologic response to ACH-1625

	500 mg BID (n=6)	600 mg BID (n=6)
Maximum VL reduction from baseline to Day 12, mean $\log_{10}$ (range)	– 4.25 (– 4.9, – 3.4)	– 3.94 (– 4.4, – 3.1)
VL < 35 IU/mL	4 (67%)	0
HCV type 1a vs. 1b	0	2 (33%)
Day 12 VL reduction from baseline, mean $\log_{10}$ (range)	– 3.0 (– 4.2, – 1.7)	– 2.0 (–.9, – 0.9)

4 SAFETY AND TOLERABILITY

- *Safety and tolerability was good in healthy volunteers and in HCV infected patients.*
- *All adverse events in healthy volunteers were graded mild, and there were no clinically significant changes in vitals signs, ECGs, or laboratory values during treatment.*
- *There were no serious AEs (SAEs) reported nor were there any discontinuations due to adverse events in either healthy volunteers nor in HCV infected patients.*

TABLE 3. Treatment Emergent Adverse Events (TEAEs) occurring in more than one patient in Segment 3, Groups 5 and 6

	Placebo (n=6)	500 mg BID (n=6)	600 mg BID (n=6)	All Patients
Patients with TEAEs	5	6	4	15
Number of TEAEs	17	20	6	43
Dry Mouth	0	2	0	2
Nausea	1	1	1	3
Oral Herpes	1	1	0	2
Pruritis	1	3	0	4
Dysgeusia	1	3	0	4
Headache	4	1	1	6

- *All treatment emergent adverse events were graded either mild or moderate.*
- *Events graded moderate included: upper abdominal pain, flatulence, dyspepsia, nausea, pruritis, back pain, and headache.*

TABLE 4. Treatment Emergent Adverse Events (TEAEs) by grade in Segment 3, Groups 5 and 6

	Placebo (n=6)	500 mg BID (n=6)	600 mg BID (n=6)	All Patients
Patients with TEAEs	5	6	4	15
Mild TEAEs	4	4	2	10
Moderate TEAEs	1	2	2	5

- *Mean aspartate aminotransferase (AST) (FIGURE 6) and mean alanine aminotransferase (ALT) (FIGURE 7) decreased over the treatment period and continued to show decline at day 12.*

TABLE 5. Mean safety laboratory values from baseline, Day 6 and Day 12

	Placebo (n=6)			500 mg BID (n=6)			600 mg BID (n=6)		
	D 0 Mean	D 6 Mean	D 12 Mean	D 0 Mean	D 6 Mean	D 12 Mean	D0 Mean	D 6 Mean	D 12 Mean
AST (U/L)	51.8	53.8	41.3	41.5	26.7	18.3	20.2	15.5	15.5
ALT (U/L)	43.5	62.7	62.5	61.3	38.0	23.7	32.2	19.8	17.0
Total Bilirubin (mg/dL)	0.54	0.50	0.27	0.34	0.77	0.37	0.59	0.70	0.70
WBC (10^9 cells/L)	5.6	6.7	6.3	6.0	6.1	6.5	5.7	6.9	6.3
PLT (10^9 cells/L)	174	169	198	195	192	200	237	223	253
Hgb (10^9 cells/L)	14.2	14.2	13.5	14.8	14.6	13.9	14.6	14.6	13.8
Crs (mg/dL)	0.78	0.80	0.78	0.77	0.82	0.74	0.80	0.82	0.85
ANC (10^9 cells/L)	3.1	3.8	3.4	3.1	3.2	3.3	3.1	4.0	3.5

FIGURE 6. Mean Aspartate aminotransferase (AST)

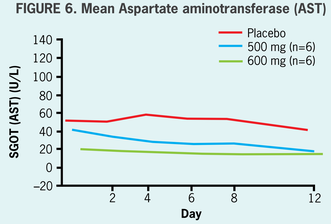
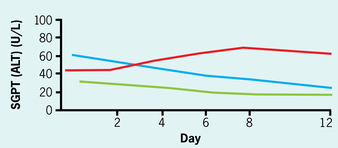


FIGURE 7. Mean Alanine aminotransferase (ALT)



Conclusions

- ACH-1625 shows a rapid and robust antiviral effect in genotype 1 naïve and treatment experienced HCV infected patients within the first 48 hours of treatment.
- All patients had a more than 3 $\log_{10}$ decrease in plasma HCV RNA with a maximum decrease of 4.25 and 3.94 $\log_{10}$ drop in the 500 mg BID and 600 mg BID dosing groups, respectively.
- The sustained viral load suppression observed among patients treated with ACH-1625 at day 12 may yield a potential advantage in longer duration combination treatment.
- The plasma pharmacokinetic profile shows a dose related increase in C_{max} and AUC that is supra-dose proportional at doses below 1000 mg.
- ACH-1625 is safe and tolerable at doses up to 2000 mg / day for 4.5 days duration.
- Initial results from dosing at 500 mg BID and 600 mg BID indicate that the investigation of additional doses at the QD interval are warranted.

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