Antiviral Activity of ANA598, a Potent Non-Nucleoside Polymerase Inhibitor, in Chronic Hepatitis C Patients

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ABSTRACT

Background: ANA598 is a non-nucleoside inhibitor of HCV polymerase with potent *in vitro* antiviral activity. ANA598 was well tolerated at single doses up to 3000 mg in healthy subjects. Plasma exposure generally increased with increasing doses and increased several fold after consumption of food. Plasma $t_{1/2}$ averaged ~24 hours. Results from a Phase 1b trial in HCV patients are reported here.

Methods: A Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose trial was conducted to evaluate safety, tolerability and antiviral activity of orally administered ANA598 in treatment-naïve patients with chronic HCV genotype 1 infection. Patients were treated with ANA598 capsules (or matching placebo) at doses of 200 mg, 400 mg or 800 mg, each given BID for 3 days. Viral load at Day 4 (12 hours after the last dose) was compared to baseline HCV RNA levels. Plasma drug levels were measured 12 hours following each dose for assessment of ANA598 trough concentrations. HCV RNA levels were measured using the COBAS AmpliPrep/COBAS TaqMan HCV test.

Results: ANA598 treatment resulted in rapid and sustained reductions in HCV RNA with median reductions at end of treatment (EOT, Day 4) exceeding 2 $\log_{10}$ at all dose levels. At 200 mg BID, the median viral load reduction was 2.4 $\log_{10}$ (range 0.4 to 3.4 log10), at 400 mg BID, 2.3 $\log_{10}$ (range 1.6 to 3.5 log10), and at 800 mg BID, 2.9 $\log_{10}$ (range 2.2 to 3.4 $\log_{10}$). Genotype 1a patients demonstrated median reductions of 1.4 $\log_{10}$, 1.8 $\log_{10}$, and 2.5 $\log_{10}$ at 200, 400 and 800 mg BID, respectively. Genotype 1b patients demonstrated median reductions of 2.6 $\log_{10}$, 2.5 $\log_{10}$ and, 3.2 $\log_{10}$, at 200, 400 and 800 mg BID, respectively. No patient showed evidence of viral rebound while on ANA598. ANA598 was well tolerated and no serious adverse events were reported.

Conclusion: ANA598 demonstrated rapid and potent dose-dependent antiviral activity after 3 days of monotherapy in treatment-naïve genotype 1 patients. Further studies are planned with ANA598 in combination with standard of care.

BACKGROUND

ANA598 is a novel non-nucleoside inhibitor of the HCV genotype 1 NS5B polymerase in development for the treatment of patients with chronic HCV infection. In *in vitro* studies, ANA598 has exhibited low nM potency against HCV genotype 1a and 1b replicon systems.

ANA598 was well tolerated at single doses up to 3000 mg in healthy subjects. The present study tested 3 days dosing in HCV genotype 1 patients.

OBJECTIVES

- To determine the safety and tolerability of ascending oral doses of ANA598 administered for 3 days to adult patients with chronic hepatitis C infection and compensated liver disease
- To assess the antiviral activity of ANA598, assessed by changes in serum HCV RNA

DESIGN & METHODS

- Randomized, double-blind, placebo-controlled, multiple ascending dose
- HCV patients with a baseline serum HCV RNA 75,000 IU/mL (375,000 copies/mL) were randomized into sequential cohorts of 200 mg BID, 400 mg BID, or 800 mg BID administered for 3 days
- Safety assessments included physical examination, vital signs, hematology, blood chemistry, urinalysis, ECG and adverse event reporting
- Antiviral activity (viral load) was determined by assessment of changes in serum HCV RNA levels (COBAS Ampliprep/COBAS Taqman)
- Plasma samples were collected for ANA598 concentrations at ~12h following each dose, except the 5th dose
- Patients who were appropriate candidates for and desired treatment were instructed to start SOC on Day 4
- Patients not starting SOC had an additional viral load assessment on Day 10

RESULTS

Note: The clinical portion of the study was recently completed but the database has not been locked. Final analysis is pending.

Study Patients

Table 1. Demographics

Dose (mg)	200 BID (n=11)	400 BID (n=8)	800 BID (n=8)	Placebo (n=8)
Gender				
M	7	7	6	4
F	4	1	2	4
Age (yr)				
18-30	1	1	0	0
31-40	0	1	3	1
41-50	6	3	2	3
51-60	3	3	3	4
61-65	1	0	0	0
Race				
Caucasian	2	0	1	1
Hispanic	8	8	5	6
Black	1	0	1	1
Asian	0	0	1	0
Weight (kg)				
Range	62.1 – 98.6	64.4 – 104.6	55.4 – 98.8	56.7 – 108.3
HCV RNA $\log_{10}$ (IU/mL)				
Mean (SD)	6.34 (0.64)	5.89 (0.40)	6.80 (0.48)	6.34 (0.38)
Median (range)	6.41 (5.28-7.17)	5.80 (5.31-6.62)	6.93 (5.82-7.26)	6.34 (5.72-6.94)

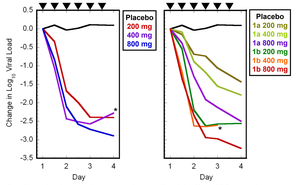
Table 2. Summary of Reported Adverse Events

Dose (mg)	Patient	Event	Severity
Placebo	002-010	Upper respiratory infection	Mod
	006-003	Intermittent nausea	Mild
200 BID	002-005	Back pain	Mild
400 BID	005-001	Painful urination	Mild
	005-001	Fatigue	Mild
800 BID	No AEs		

- Baseline characteristics were similar across cohorts
- All patients completed 3 days of dosing.
- Grade I (>ULN to 1.5x ULN) increase in total bilirubin was seen in one patient at 800 mg BID
- ANA598 was safe and well tolerated.

HCV RNA Reduction

Figure 1. Median Change in HCV RNA from Baseline Following BID Administration of ANA598 or Placebo



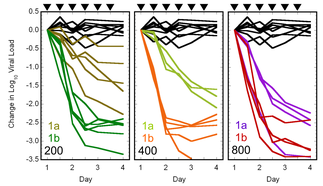
* D4 viral load data was missing for the single most responsive patient in the 400 mg dose group (infected with genotype 1b); therefore n = 7 (rather than 8) for D4 400 mg time point in the left panel and the D4 time point for genotype 1b was omitted from the right panel.

Table 3. Summary of HCV RNA Changes at the End of Treatment (Day 4)

Dose (mg)	Genotype	N	Median	Mean	SEM	Min	Max
Placebo	all	8	0.09	0.06	0.05	0.24	-0.15
200 BID	all	11	-2.40	-2.08	0.26	-0.44	-3.36
	1a	5	-1.43	-1.34	0.32	-0.44	-2.28
	1b	6	-2.55	-2.70	0.14	-2.40	-3.36
400 BID	all	8*	-2.27	-2.22	0.16	-1.60	-3.48*
	1a	3	-1.79	-1.83	0.15	-1.60	-2.10
	1b	5*	-2.50	-2.52	0.11	-2.28	-3.48*
800 BID	all	8	-2.89	-2.87	0.18	-2.24	-3.42
	1a	4	-2.50	-2.67	0.26	-2.24	-3.42
	1b	4	-3.23	-3.08	0.22	-2.42	-3.41

* D4 viral load data was missing for the most responsive genotype 1b-infected patient in the 400 mg dose group. The D3 value of -3.48 for this patient was included with the D4 values of other patients solely in calculation of *Max* viral load reduction but was excluded from the calculation of dose group medians and means. Therefore N = 7 and 4 for all and 1b median and mean results, respectively.

Figure 2. Individual Patient Changes in HCV RNA from Baseline Following BID Administration of ANA598 or Placebo

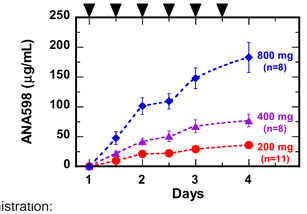


Summary: Robust Viral Load Reduction

- In the 200 mg BID dose group, 3/5 genotype 1a-infected patients and 6/6 genotype1b-infected patients had ≥1.4 $\log_{10}$ reduction in viral load at EOT (12h after the last ANA598 dose on Day 3)
- In the 400 and 800 mg BID dose groups, 14/16 patients achieved a viral load reduction >2 $\log_{10}$, and 6/16 patients achieved a viral load reduction >3 $\log_{10}$. The minimal EOT viral load reduction within the two higher dose groups was 1.6 $\log_{10}$
- In the 800 mg BID dose group, the median viral load reduction in genotype 1a-infected patients was 2.5 $\log_{10}$ (*2.7 ± 0.3; mean ± SEM*), similar to the median reduction of 2.6 $\log_{10}$ (*2.8 ± 0.1; mean ± SEM*) observed across all dose groups for genotype1b-infected patients
- For most genotype 1a-infected patients (10/12), viral load was still declining at EOT
- For the 17 patients that did not receive SOC after ANA598, the median viral load reduction on Day 10 (7 days after the last dose of ANA598) was 0.4 $\log_{10}$ (*maximum, 3.5; minimum, -0.3; mean ± SEM, 0.95 ± 0.29*)
- No rebound during the dosing period was observed for any patient

PK/PD Relationships

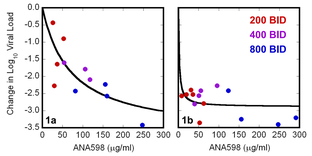
Figure 3. Mean (SEM) Plasma Trough Concentrations of ANA598 in HCV Patients



Following BID administration:

- Mean ANA598 trough values increased in a dose proportional manner over the 200 to 800 mg dose range
- The extent of ANA598 accumulation in plasma was moderate (~3-fold) over 3 days of BID dosing
- Steady-state PK was not achieved by the last dose, as expected based on elimination $t_{1/2}$ of ~24h
- Steady-state ANA598 concentrations are expected to be higher than those measured after the 6th dose

Figure 4. Individual Patient Changes from Baseline in HCV RNA vs. ANA598 Plasma Trough Concentrations on Day 4



* Data missing for 2 of 27 subjects: 200 mg, 1a (plasma [ANA598]), 400 mg, 1b (viral load)

- For genotype 1b patients, viral load change at Day 4 is essentially saturated across the exposures achieved in this study
- For genotype 1a patients, viral load change at Day 4 increases with increasing ANA598 exposure
- At higher exposures, response in genotype 1a patients approached the response seen in genotype 1b patients

CONCLUSIONS

- ANA598 was safe and well tolerated when administered as monotherapy for 3 days to patients with chronic HCV genotype 1 infection. There were no serious AEs or discontinuations from the study.
- ANA598 treatment resulted in rapid reductions in HCV RNA with median Day 4 reductions of 2.4 $\log_{10}$ in the 200 mg BID dose group, 2.3 $\log_{10}$ in the 400 mg BID group, and 2.9 $\log_{10}$ in the 800 mg BID group. No rebound was seen in any patient while receiving ANA598.
- The doses of ANA598 required for efficacy when used over longer duration in combination with other agents are expected to be lower than the doses required for antiviral activity in this study.
  - Plasma concentrations of ANA598 when dosed to steady-state are expected to be higher than those achieved with 6 doses
  - For genotype 1a patients, additional days of exposure are expected to lead to greater viral load reduction
  - Synergy demonstrated *in vitro* between ANA598 and IFNα or ANA598 and direct-acting antivirals (e.g. HCV protease inhibitors or nucleoside polymerase inhibitors) may have a corresponding benefit *in vivo*
- The robust antiviral activity and favorable safety observed following monotherapy support the continued clinical development of ANA598, including the initiation of studies designed to assess the safety and efficacy of ANA598 in combination with pegylated interferon and ribavirin

DISCLOSURES

James Appleman – Employee of Anadys Pharmaceuticals, Inc., Stock Holder of Anadys Pharmaceuticals, Inc., Mohamad Rahimy - Employee of Anadys Pharmaceuticals, Inc., Stock Holder of Anadys Pharmaceuticals, Inc., Constance Crowley - Employee of Anadys Pharmaceuticals, Inc., Stock Holder of: Anadys Pharmaceuticals, Inc.; James Freddo - Employee of Anadys Pharmaceuticals, Inc., Stock Holder of: Anadys Pharmaceuticals, Inc.

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