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Safety and Antiviral Activity of ANA598 in Combination with Pegylated Interferon α2A Plus Ribavirin in Treatment-Naïve Genotype-1 Chronic HCV Patients

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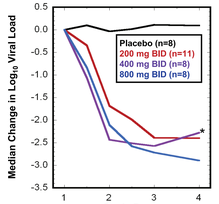
BACKGROUND

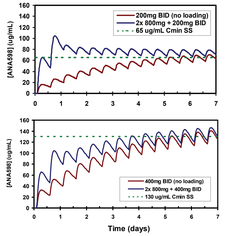
- ANA598 is a potent non-nucleoside inhibitor of the HCV genotype-1 (GT-1) NS5B polymerase.
- A Phase 1 study (ANA598-502) in treatment naïve HCV GT-1 patients demonstrated a rapid and sustained reduction in HCV RNA at 3 dose levels studied (**Figure 1A**).

Figure 1A. Median Antiviral Response



* D4 viral load data was missing for the single most responsive patient in the 400 mg BID dose (GT-1b), therefore n=7 (rather than 8) for D4 400 mg time point.

Figure 1B. Simulation of Loading-Dose Effect on ANA598 Concentrations



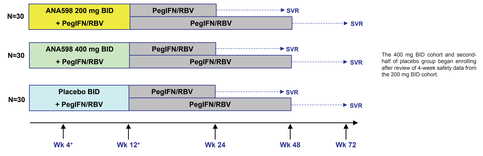
- The median viral load reduction was 2.4 $\log_{10}$ (range 0.4 to 3.4 $\log_{10}$) at 200 mg BID, 2.3 $\log_{10}$ (range 1.6 to 3.5 $\log_{10}$) at 400 mg BID, and 2.9 $\log_{10}$ (range 2.2 to 3.4 $\log_{10}$) at 800 mg BID on Day 4 (EOT). [EASL 2009, abstract LB 1055]
- Based on antiviral activity/kinetics seen in the 3-day monotherapy study, a loading dose was selected (**Fig. 1B**). Simulations predicted that a loading dose of 800 mg q12h would rapidly achieve ANA598 trough concentrations exceeding the minimum needed to prevent replication of wild-type virus and sustain C_{min} above the EC_{95} (24 μg/mL);
- We now describe preliminary results of an ongoing Phase 2 trial which evaluates safety and antiviral activity of ANA598 with PEG-IFN and ribavirin (SOC) for 12 weeks.

METHODS

Study Design

- A randomized, double-blind, placebo-controlled study in treatment-naïve GT-1 HCV patients (**Figure 2**);

Figure 2. Study Design



The 400 mg BID cohort and second-half of placebo group began enrolling after review of 4-week safety data from the 200 mg BID cohort.

- Patients received ANA598 200 mg BID or 400 mg BID, both with a loading dose of 800 mg q12h given on Day 1, or placebo, with SOC for 12 weeks;
- Patients who achieved undetectable virus at weeks 4 and 12 were randomized to SOC alone for 12 or 36 additional weeks; remaining patients were to receive SOC for additional 36 weeks;
- Approximately 90 patients were planned, 30 at each dose level of ANA598 and 30 on placebo, enrolled in two staggered cohorts each comprised of 30 patients on ANA598 and 15 on placebo.

OBJECTIVES

Primary

- To assess the proportion of patients achieving cEVR (defined as undetectable HCV RNA at Week 12).

Secondary

- To assess the proportion of patients achieving RVR (defined as undetectable HCV RNA at Week 4) and SVR (undetectable HCV RNA 24 weeks after end-of-treatment);
- To assess the comparative safety and tolerability of ANA598 administered with SOC compared to SOC alone during 12 weeks of treatment;
- To determine ANA598 plasma concentrations over 12 weeks of dosing.

Study Assessments

- Safety assessments included physical examination, vital signs, hematology, blood chemistry, urinalysis, ECG and adverse event reporting;
- Serum HCV RNA was determined at scheduled visits at weeks 1, 2, 3, 4, 6, 8, 10 & 12 by COBAS Amplicprep / COBAS Taqman Test (LLD = 15 IU/mL);
- Viral breakthrough was defined as a confirmed >1 $\log_{10}$ increase in HCV RNA from nadir;
- ANA598 plasma concentrations were measured during scheduled visits at weeks 1, 2, 3, 4, 6, 8, 10 & 12 in each cohort.

RESULTS

Note: The study is ongoing and the database has not been locked. Patients in the second cohort (400 mg BID) are still receiving ANA598 or placebo. Preliminary 8-week results for this cohort are reported here.

Baseline Demographics

Table 1. Demographics and Baseline Characteristics

Characteristic	200 BID (n = 29)	400 BID (n = 34)	Placebo (n = 32)
Age, mean (SD) yr	49 (12)	50 (8)	51 (10)
Male, n (%)	15 (52)	23 (68)	14 (44)
Race, %			
White	86%	85%	75%
Black	14%	12%	25%
Asian	0	3%	0
Ethnicity, % Latino/Hispanic	34%	18%	41%
BMI, mean (SD), kg/m²	28.4 (6)	28.3 (3.7)	27.4 (4.5)
HCV RNA $\log_{10}$ (IU/mL)			
Mean (SD)	6.26 (0.77)*	6.56 (0.59)	6.48 (0.53)
Range	4.67 - 7.53	5.01 - 7.46	5.02 - 7.40
Genotype, (1a/1b)	(20/7)*	(27/7)	(26/6)

* Total of 27 patients included in efficacy analysis.

- A total of 95 HCV GT-1 patients were dosed.
- Baseline characteristics were similar across all groups.
- The mean baseline HCV-RNA levels ranged from 6.26-$\log_{10}$ to 6.56-$\log_{10}$ IU/mL.

Study Patients

- In the 200 mg BID cohort, 44 patients received at least one dose of study drug (29 received ANA598 and 15 placebo):
  - 2 patients discontinued during the 1st week for personal reasons (unrelated to study drug).
  - 2 patients were lost to follow-up: 1 on ANA598 lost after week 4 (HCV RNA undetectable at week 4), and 1 on placebo lost after week 10 (HCV RNA 5.1 $\log_{10}$ at week 10).
  - 40 patients completed 12 weeks of treatment:
    - 1 patient discontinued ANA598 and 3 patients discontinued placebo due to failure to reach a 1 $\log_{10}$ decline in HCV RNA at week 4; they continued on SOC & are included in the 12-week data.
    - 1 patient on ANA598 discontinued all study drugs at week 8 due to Grade 3 rash, resumed SOC alone and is included in the 12-week data.

As of Data Cutoff:

- In the 400 mg BID cohort, 51 patients received at least one dose of study drug (34 received ANA598 and 17 placebo):
  - 1 patient (ANA598) voluntarily withdrew from the study between weeks 4 and 6, not related to AEs.
  - 1 patient discontinued ANA598 and SOC after 1 week due to mania (unrelated to ANA598).
  - 1 patient discontinued Placebo and SOC after 7 weeks due to colitis.
  - 3 patients discontinued placebo due to failure to reach a 1 $\log_{10}$ decline in HCV RNA at week 4, but continued to receive SOC and are included in the 8-week data.
  - 1 patient discontinued ANA598 due to Grade 1 rash at week 5; this patient continued SOC and is included in the 8-week data.
  - 1 patient discontinued ANA598 and SOC due to Grade 3 rash at week 6 and is included in the 8-week data.

Antiviral Activity

Table 2. Proportion of Patients (%) with Undetectable Virus (<15 IU/mL) by Week

Treatment	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
200 BID+SOC	11.1	22.2	44.4	55.6	65.4	69.2	73.1	73.1
400 BID+SOC	8.8	27.3	30.3	42.4	56.3	71.9		
Placebo+SOC	0.0	3.1	9.4	12.5	18.8	37.5		

Note: Placebo patients are combined from Cohorts 1 and 2.
Data not yet available for 400 mg BID and placebo groups at weeks 10 and 12 (in progress).

Figure 3. Time Course of HCV RNA for Individual Patients

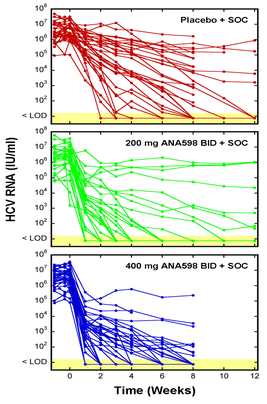
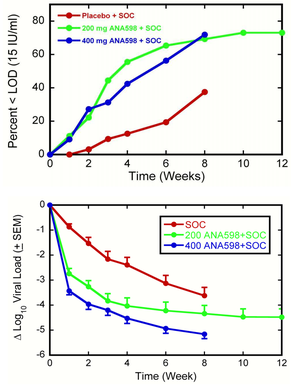


Figure 4. Undetectable (%) and Mean (±SEM) Change in Viral Load



Antiviral Activity Summary

- ANA598 in combination with SOC accelerated the rate of achieving undetectable levels of virus in genotype-1 patients. At week 4, the percentage of patients achieving undetectable levels of virus was 56%, 42% and 13%, respectively, for patients receiving ANA598 200 mg BID, ANA598 400 mg BID, or placebo, added to SOC. At week 8, the corresponding rates were 69%, 72% and 38%, respectively;
- ANA598 200 mg BID plus SOC resulted in a 73% cEVR;
- No patient receiving ANA598 experienced viral breakthrough;
- Six (6) patients receiving Placebo plus SOC failed to achieve at least a 1 log decline in viral load by week 4; in contrast, only one (1) patient receiving 200 mg BID ANA598 plus SOC and no patient on 400 mg BID ANA598 plus SOC failed to meet this protocol-defined benchmark. All 7 patients discontinued ANA598 or placebo at week 4 but continued on SOC;

Pharmacokinetics

- In the 200 mg cohort, ANA598 plasma concentrations achieved steady state by week 1 (the 1st time point measured);
- The observed mean concentrations of ANA598 were consistent with predicted trough values;
- There was no unexpected drug accumulation in the 200 mg BID cohort over time.

Safety Summary

Table 3. Summary of Reported AEs

Most Common Adverse Events (% Patients)*			
Adverse Event	**200 BID (n = 29)**	**400 BID (n = 34)**	**Placebo (n = 32)**
Headache	31	15	47
Fatigue	41	44	44
Nausea	21	24	38
Anemia	38	3	13
Influenza-like illness	28	35	28
Arthralgia	14	3	31
Rash (n)	41% (12)	32% (11)	25% (8)
Grade 1	38 (11)	27 (9)	25 (8)
Grade 2	0	3 (1)	0
Grade 3	3 (1)	3 (1)	0
Grade 4	0	0	0
Insomnia	3	29	22
Pruritus	24	21	19
Myalgia	0	21	22
Chills	10	9	19
Diarrhea	17	6	6
Irritability	10	6	16
Erythema at injection site	3	15	3
Pyrexia	14	6	9
Neutropenia	14	6	6
Dizziness	3	3	13
Cough	10	0	13
Pain	7	12	9
Anxiety	7	12	0
Back pain	10	3	3
Vomiting	0	3	3

*AE's listed are those reported in at least 10% of patients in any group.
400 mg bid cohort and approx. half of placebo patients reflect data available through 8 weeks

- ANA598 has been safe and well tolerated to date;
- The incidence of AEs has been similar between the active and placebo groups, with reported AEs being typical for patients treated with SOC alone;
- There have been no clinically significant changes in safety laboratory values.

CONCLUSIONS

- ANA598 plus SOC has been well tolerated to date with an AE profile comparable to the group receiving SOC alone.
- The combination of ANA598 with SOC accelerated the rate of achieving undetectable levels of virus in genotype-1 patients compared to patients receiving Placebo plus SOC.
- ANA598 200 mg BID plus SOC resulted in a 73% cEVR. At 8 weeks, ANA598 400 mg BID plus SOC resulted in 72% of patients achieving undetectable levels of virus.
- No patient receiving ANA598 has experienced viral breakthrough in this ongoing study.

DISCLOSURES

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.