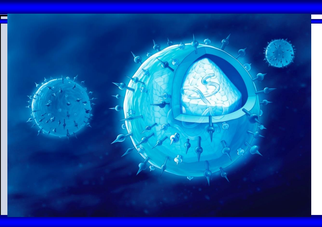

Pharmacokinetics, Safety and Antiviral Efficacy of BIT225 in Combination with Pegylated Interferon and Ribavirin in Genotype 3 HCV/HIV Co-infected Patients.

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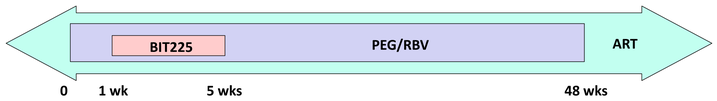
INTRODUCTION

BIT225 is the first in a new class of oral, direct-acting antiviral drugs for hepatitis C virus (HCV) targeting p7, a highly conserved viral protein essential for virus production and replication. BIT225 also has antiviral activity against HIV-1 Vpu.

STUDY DESIGN AND OBJECTIVES

The trial was a Phase 2, open-label pilot study of 300 mg BIT225 BID for 28 days with standard of care (PEG/RBV*) in patients with HCV G1 or G3 who are co-infected with HIV-1 and well controlled on ART.



Twelve treatment-naïve, HCV G1 or G3 subjects were enrolled from a single clinical site. PEG/RBV was given alone for 7 days before BIT225 treatment commenced. After the 28 day BIT255 dosing phase, subjects remained on PEG/RBV for up to an additional 44 weeks.

[* *PEG/RBV: Pegylated-interferon alfa-2b (PEG) at doses of 80, 100, or 120 mcg weekly and weight-based ribavirin (RBV)*]

Primary Objective :

• Evaluate the safety and tolerability of repeat dosing with BIT225 for 28 days with PEG/RBV in HIV-1/HCV G1 or G3 patients.

Secondary Objectives :

• Evaluate the pharmacokinetics of BIT225 with PEG/RBV in HIV-1/HCV G1 or G3 patients.

• Evaluate the antiviral activity of BIT225 + PEG/RBV in HCV G1 or G3 patients.

RESULTS

1. Baseline Characteristics

Table 1. Median data for Baseline Demographics

	Median
N	12
Age (yrs)	44
Sex (% male)	75%
Race (% Asian)	100%
Weight (kg)	57
Body Mass Index	22.7
Alcohol Use (%)	25%
Smoker (%)	17%

Median baseline demographics data are shown in **Table 1**. Twelve HIV-1/HCV co-infected patients were enrolled: 4 x HCV G1a; and 8 x G3 (7 were G3a) (**Table 2**). HIV-1 levels in all subjects remained below 40 copies/mL.

Table 2. Baseline Characteristics of G1a and G3/G3a Subjects

Subject No.	HCV Genotype	IL28B SNP	HCV RNA IU/ml	HIV-1 RNA copies/mL	ART Regimen
601	1a	CT GT	24,788,478	< 40	A
604	1a	CT GT	4,455,691	< 40	C
608	1a	CT GT	265,585	< 40	D
605	1a	CC TT	25,782	< 40	A
603	3a	CT GT	5,301,012	< 40	B
602	3a	CC TT	789,503	< 40	A
606	3a	CC TT	11,553,224	< 40	A
607	3a	CC TT	2,294,791	< 40	C
609	3a	CC TT	259,539	< 40	C
610	3a	CC TT	1,907,609	< 40	A
611	3a	CC TT	1,931,480	< 40	C
612	3	CC TT	3,682,819	< 40	C

A= Tenofovir, Lamivudine, Nevirapine; B= Zidovudine, Lamivudine , Nevirapine
C= Tenofovir, Lamivudine, Efavirenz; D= Stavudine, Lamivudine, Nevirapine
IL28B SNP: rs12979860 and rs8099917

2. HCV Viral Load Analysis

Of primary interest were the HCV G3/3a subjects - six of 6 subjects completing 28 days of BIT225 had undetectable HCV by week 12 (**Figure 1**). Two G3/3a subjects withdrew from the study. One HCV G3a subject with heterozygous IL28B SNPs had the slowest HCV RNA rate of decline, but achieved undetectable virus levels by week 12.

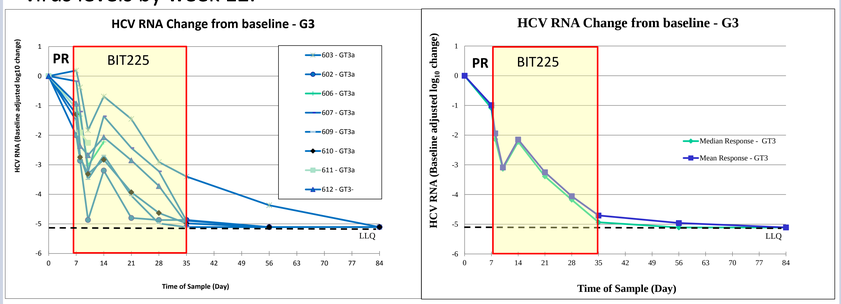


Figure 1. Effect of BIT225 plus PEG/RBV on HCV G3/G3a Viral Load to 12 Weeks
Log_{10} units are baseline adjusted and a change of -5.107 represents the maximum observable decline for all subjects.

Commencement of BIT225 was associated with a marked tri-phasic response in viral load kinetics, beginning with a significant acceleration of the rate of virus decay. This initial phase may reflect the synergistic antiviral activities of BIT225 and PEG/RBV previously reported.

Two of the G1a subjects were non-responders with heterozygous IL28B genotypes. The two other subjects had decreased viral load during treatment, one of these subjects (#605) had undetectable HCV RNA by day 14 and remained undetectable at Week 12, the second subject (#601) withdrew within the first fourteen days primarily due to PEG intolerance.

3. Pharmacokinetic data

All 12 subjects were included in the population for PK analysis. However, Subjects 601, 606, and 611 only had complete PK profiles on the first day of dosing (Day 7). PK parameters were derived using non-compartmental methods employing WinNonlin® Phoenix version 6.3 (Pharsight, St Louis, MO).

Plasma BIT225 concentration versus time data indicated that significant concentrations were achieved in all subjects on Day 7 (**Table 3, Figure 2**) and concentrations rose to achieve steady state by Day 10 (day 3 of BIT25 dosing) to Day 14, based on observed trough values between those and subsequent days. C_{max} and $AUC_{(0-4)}$ values increased between Days 7 and 35 (**Table 3**) due to both drug accumulation and to the transition to BID dosing on Day 8. Median BIT225 Tmax values were 3.0 hours on Day 7 and 4.0 hours on Day 35. BIT225 half-lives on Day 7 averaged 10. 8 hours. BIT225 could potentially be dosed once a day.

Table 3. Mean (%CV) Key Plasma BIT225 Pharmacokinetic Parameters by Day
(a, median and range; NC, not calculated)

Day	Cmax (ng/mL)	Tmax[a] (h)	AUC(0-4) (h•ng/mL)	t½ (h)	AUCinf (h•ng/mL)	CL/F (L/h)
7 (n=12)	3190 (29.7)	3.00 (1.5 – 6.0)	9363 (30.9)	10.8 (61.2)	57889 (84.3)	8.48 (75.4)
35 (n=(9)	5130 (69.0)	4.00 (1.0 – 4.0)	17452 (86.0)	NC	NC	NC

3. Pharmacokinetic data

Figure 2. Individual Subject BIT225 Concentration-Time Plots – Day 7

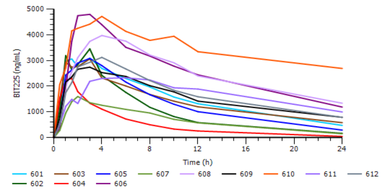
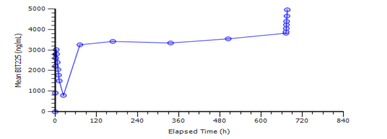


Figure 3. Mean Plasma BIT225 Concentration-Time Profile



4. Safety and Tolerability

As expected for this patient population, there were several AEs that were likely related to PEG/RBV. The most common of these were insomnia, headache, fever, and rash. The most common AEs reported related to BIT225 were nausea/vomiting and headache. Three participants withdrew from all treatment in the first 14 days due to drug intolerance. One further participant withdrew due to PEG-IFN/RBV intolerance after completing BIT225 treatment, with undetectable HCV. There was one SAE reported, with the participant receiving I.V. anti-emetic and fluids due to severe nausea and vomiting. This participant also had a Grade 3 (severe) neutropenia. All other AEs were mild to moderate in severity.

All subjects had HIV-1 viral load below 40 copies/mL during the 28 days of BIT225 therapy, and remained below this level throughout the first 12 weeks of HCV-related combination therapy with ART. At no time was HIV-1 detected above 40 copies/mL, indicating that BIT225 did not reduce the effectiveness of concomitant ART drugs.

CONCLUSIONS

Interim analysis of 12 week data demonstrated that BIT225 enhanced anti-HCV activity in co-infected HIV-1/HCV G3/3a patients treated with PEG/RBV.

- **Six of 6 HCV G3/3a per-protocol subjects had undetectable HCV RNA levels at 12 weeks of treatment.**
- **Commencement of BIT225 enhanced the kinetics of viral load decline in subjects with homozygous or heterozygous IL28B genotypes.**
- **BIT225 has a favorable PK profile in HCV/HIV co-infected patients**

This was a pilot study at a single site in Thailand. The sustained viral response (SVR) rate for PEG/RBV alone in HCV G3 subjects in Thailand is 68.8% (Vipatakul et al. 2010 Thai J Gastroenterology 11(1):13-21).

The addition of BIT225 to PEG/RBV may lead to an improvement in SVR rates in HIV-1/HCV G3 co-infected subjects, a difficult to treat genotype even with newer DAAs.

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