A Phase 2 Open-Label Pilot Study of the Safety, Pharmacokinetics and Antiviral Activity of BIT225, an HCV p7 Inhibitor, in Combination with Pegylated Interferon and Ribavirin in Patients with HCV Genotypes 1 or 3 Co-infected with HIV-1.

Carolyn Luscombe[1], Gary Ewart[1], John Wilkinson[1], Michelle Miller[1], Winai Ratanasuwan[2], Marion G. Peters[3], Robert Murphy[4], Tawesak Tanwandee [2]

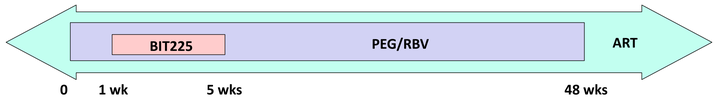
[1]Biotron Limited, North Ryde, NSW, Australia; [2]Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Department of Gastroenterology, University of California-San Francisco, San Francisco, CA, USA; [4]Medicine and Biomedical Engineering, NorthWestern University, Chicago, IL, USA.

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 ribavirin (RBV) 400 or 500 mg BID based on weight*.]

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

	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%

Table 1. Median data for Baseline Demographics

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**). All subjects enrolled had well controlled HIV-1 replication, below 40 copies of HIV-1 (**Table 2**).

The IL28B genotypes for 8 of 12 subjects were homozygous CC at rs12979860 and homozygous TT at rs8099917. Four subjects were heterozygous for both SNPs, CT GT respectively.

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

Subject No.	HCV Genotype	IL28B SNP	HCV RNA IU/ml Day 0	HIV-1 RNA copies/mL	ART Regimen
601	1a	CT GT	2,580, 288	< 40	A
604	1a	CT GT	5, 065,216	< 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	973,788*	< 40	C
612	3	CC TT	3,869, 862*	< 40	C

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

2. HCV Viral Load Analysis

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

Commencement of BIT225 was associated with a marked tri-phasic response in viral load kinetics, beginning with a significant acceleration of the rate virus decay (**Figure 2**). This initial phase may reflect the synergistic antiviral activities of BIT225 and PEG/RBV previously reported.

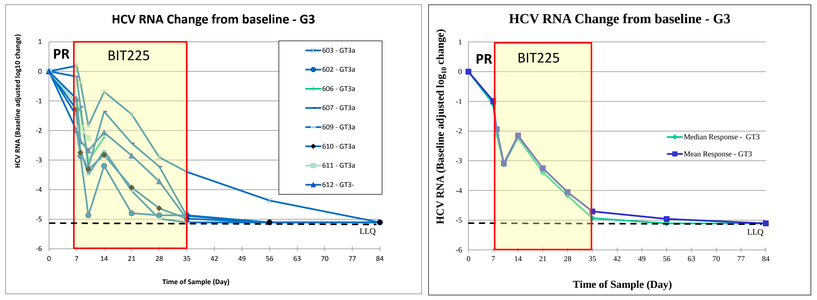


Fig 1. Effect of BIT225 plus PEG/RBV on HCV G3/G3a Viral Load to 12 Weeks
Log_{10} units are baseline adjusted and a change of -5.107 represents the maximum observable decline for all subjects.

Sub-analysis of the HCV G3/3a decline pre and post addition of BIT225 found that the greatest rate of decay occurred in the first few days after the addition of BIT225 to PEG/RBV therapy (**Figure 2**).

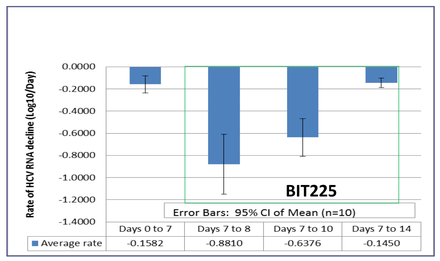


Fig 2. Rate of HCV G3/3a Viral Decay after PEG/RBV pre and post BIT225 treatment
Units are baseline- adjusted Log_{10}/day

One G1a subject was homozygous for IL28B; they rapidly responded to PEG/RBV treatment and had undetectable HCV by week 8. Three HCV G1a subjects had heterozygous IL28B genotypes at both SNPs; two were non-responders to treatment, so treatment was discontinued due to lack of efficacy. The other withdrew from the study due to treatment intolerance.

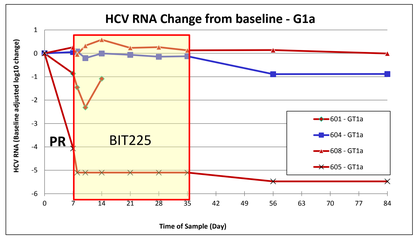


Fig 3. Effect of BIT225 plus PEG/RBV on HCV G1a Viral Load to 12 Weeks

3. Safety and Tolerability

This is an interim analysis of preliminary data out to 12 weeks. Safety and pharmacokinetic data analyses are in progress and will be presented at a later date.

As expected for this patient population, there were several AEs reported that were likely related to PEG/RBV. The most common AEs related to BIT225 were headache and nausea. Three subjects withdrew from all treatment during the first 14 days due to drug intolerance. One subject withdrew due to PEG/RBV intolerance after completing BIT225 treatment, with undetectable HCV.

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 had undetectable HCV RNA levels at 12 weeks of treatment.**
- **Commencement of BIT225 enhanced the kinetics of viral decline of PEG/RBV in subjects of homozygous and heterozygous IL28B genotypes.**

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.

Contact: mmiller@biotron.com.au

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FINANCIAL DISCLOSURES: CL, GE, JW & MM are employees of Biotron Ltd