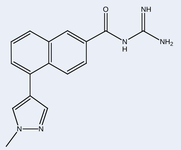

High sustained viral response with a HCV p7 inhibitor, BIT225: Antiviral activity and tolerability of BIT225 plus pegylated interferon alfa 2b and weight-based ribavirin for 28 days in HCV treatment-naïve patients.

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Introduction

The development of new classes of compounds with different modes of action will be essential for future therapy options to combat the disease and provide efficacy against the genetic diversity of hepatitis C virus (HCV). BIT225 is a novel, first in class, HCV p7 inhibitor. p7 is involved in the release of viral particles from the cell and is essential for viral replication. BIT225 is an investigational, orally-administered, novel antiviral compound in development by Biotron Limited (ASX: BIT). BIT225 was previously studied in a phase 1b trial for 7 days at doses up to 200 mg in HCV genotype 1, 2 and 3 subjects. BIIT225 was found to reduce viral load over 7 days and was well tolerated.

BIT225-005: A Phase IIa, Placebo-Controlled, Randomized Study of the Safety, Pharmacokinetics and Antiviral Activity of BIT225 in Combination with Pegylated Interferon and Ribavirin in Patients with Hepatitis C Virus Infection.

The trial design was to examine the safety and efficacy of two doses of BIT225 (200 and 400 mg) delivered orally twice a day for 28 days compared to placebo with standard of care (SOC). Twenty-four subjects were enrolled from a single clinical site. The subjects were genotype 1 that had not previously received antiviral therapy. After the 28 day treatment phase all subjects remained on SOC and were followed for an additional 44 weeks.

Study Objectives

Primary objective :

•to evaluate the safety and tolerability of 200 and 400 mg of BIT225 twice daily compared with placebo in combination with PEG-IFN and RBV in patients with chronic HCV infection that are treatment-naïve to antiviral treatment with ribavirin and/or interferon.

Secondary objectives :

•to evaluate the pharmacokinetics of 200 and 400 mg of BIT225 administered daily on Day 0 and Day 28 and twice daily on Days 1 - 27 for 28 consecutive days in combination with PEG-IFN and RBV in patients with chronic HCV infection.

•to evaluate the antiviral activity of BIT225 administered for 28 consecutive days in combination with PEG-IFN and RBV in patients with chronic HCV infection that are treatment-naïve to antiviral treatment with ribavirin and/or interferon.

Test formulation: BIT225 powder mixed with 25 mL OraSweetSF™

Placebo formulation: Lactose mixed with 25 mL OraSweetSF™

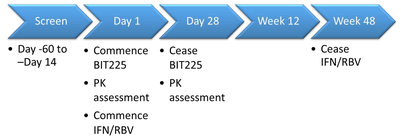
SOC: Peg-interferon alfa-2b (PEG-IFN) at doses of 80, 100, or 120 mcg weekly and ribavirin (RBV) 400 or 500 mg BID based on weight .

BIT225-005 Study Design

•Genotype 1, chronic HCV infection, treatment naïve patients between 18-55 yrs of age

•24 patients, randomized 8:8:8 (200mg BIT225: 400 mg BIT225: placebo) enrolled from a single clinical site, were administered BIT225 (200 and 400 mg) or placebo orally twice a day for 28 days in combination with pegylated interferon and ribavirin, remaining on SOC and monitored for an additional 44 weeks.

•Safety , pharmacokinetic, virologic response, IL28 SNP genotyping and genomic sequencing parameters were examined.



Results

Baseline Patient Characteristics

	400mg (SD)	200mg (SD)	Placebo (SD)
N	8	8	8
Age (yrs)	39 (5)	41 (8)	37 (7)
Sex (% male)	50	62.5	75
Race (% Asian)	100	100	100
Weight (kg)	68 (16)	66 (17)	63 (12)
Body Mass Index	25 (4)	25 (7)	23 (3)
Drug User (% current or previous)	12.5	12.5	37.5
Alcohol Use (%)	50	37.5	37.5
Smoker (%)	37.5	37.5	62.5

Baseline HCV Characteristics by Treatment Group

	400mg n= 8	200mg n= 8	Placebo n= 8
HCV Genotype 1a	75%	50%	25% (2 type "1")
HCV RNA (IU/mL), Median (Q1-Q3)	5,005,000 (863,125 - 9,262,500)	4,665,000 (1,785,000 – 6,112,500)	3,632,500 (2,410,000 - 4,997,500)
HCV RNA (Log10), Median (Q1-Q3)	6.687 (5.807 - 6.963)	6.609 (6.251- 6.783)	6.547 (6.382 - 6.698)

- 24 patients were enrolled into the study. 50% of patients were genotype 1a. 23 patients completed study therapy; 1 discontinued in the first week for intolerance (400 mg).
- Pharmacokinetic data suggested adequate BIT225 levels in the blood were detected for antiviral efficacy.

IL28 SNP genotyping

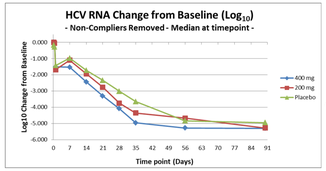
- The IL28B genotypes for 21 of 23 subjects were homozygous CC at rs12979860 and homozygous TT at rs8099917. One subject from each of the 400 mg BIT225 and placebo groups were heterozygous for both alleles.

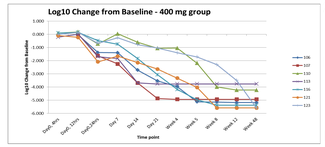
Viral Load

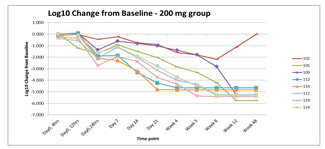
Cohort	RVR (week 4)	cEVR (week 12)	pEVR (week 12)	nonEVR (week 12)	SVR (week 48)	% SVR
Placebo	2/8	3/8	2/8	1/8	6/8	75
200mg	2/8	5/8	0	1/8	7/8	88
400mg	2/7	4/7	1/7	0	7/7	100

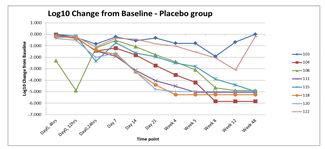
RVR = Rapid Virological Response: HCV RNA < LLQ at week 4
cEVR = complete Early Virological Response: HCV RNA < LLQ at week 12
pEVR = partial Early Virological Response: Change in HCV RNA > 2 log units at week 12
SVR = Sustained Virological Response: HCV RNA < LLQ at week 48

4 weeks of BIT225, IFN and RBV









- The week 48 sustained viral response (SVR) rates were 7/7, 7/8 and 6/8 subjects for 400 mg, 200 mg and placebo groups respectively.

Results to Week 4 – (RVR)

400mg cohort: Two out of seven (2/7) subjects had viral loads ≤ LLQ by week 4. 5/7 subjects experienced a viral load reduction > 2 logs. Median viral load reduction = -3.771 log units.

200mg cohort: 2/8 subjects achieved RVR by week 4. 6/8 subjects experienced a viral load reduction > 2 logs. Median viral load reduction = -3.871 log units.

Placebo cohort: 2/8 subjects achieved RVR by week 4. 6/8 subjects experienced a viral load reduction > 2 logs. Median viral load reduction = -3.013 log units

Regression analysis shows 400mg and 200mg cohorts have significantly faster median rates of decrease of HCV RNA than placebo over the first 35 Days (P<0.05).

Results to Week 48 – (SVR)

400mg cohort: All subjects in the 400mg cohort had viral loads ≤ LLQ by week 48 (this is defined as achieving "Sustained Virological Response" (SVR). This corresponds to a 100% rate of SVR. (Median viral load reduction = -5.189 log units.)

200mg cohort: 7/8 subjects achieved SVR by week 48. This corresponds to a 87.5% rate of SVR. (Median viral load reduction = -5.271 log units.)

Placebo cohort: 6/8 subjects achieved SVR by week 48. This corresponds to a 75% rate of SVR. (Median viral load reduction = --4.998 log units.)

E2-P7-NS2 Sequencing analysis

The day -14 (pretreatment) and day 28 plasma samples were analyzed by population sequencing and compared to the consensus sequences of HCV genotype 1a and 1b. The viral genes E2, P7 and NS2 were sequenced to determine if there were any alterations to the HCV population during antiviral therapy with IFN/RBV and BIT225 during the first 4 weeks of treatment. Several changes were identified but there were no unique mutations selected in the BIT225 treatment cohorts compared to placebo that would suggest the differences were significant over that of the usual HCV quasispecies.

Adverse Events

Most Frequent Adverse Events

	400mg n= 8	200mg n= 8	Placebo n= 8
Fever	6 (75%)	7 (87.5%)	7 (87.5%)
Vomiting	4 (50%)	3 (37.5%)	0 (0%)
Headache	4 (50%)	1 (12.5%)	0 (0%)
Anaemia	3 (37.5%)	1 (12.5%)	2 (25%)
Insomnia	3 (37.5%)	1 (12.5%)	0 (0%)
Myalgia	2 (25%)	1 (12.5%)	3 (37.5%)

Serious Adverse Events

	Dose BIT225	Day of BIT225 Dosing	Hospital	Treatment
Vertigo/ Vomiting	400mg	Day 2	3 days	I.V. Fluids, anti-emetics
Vomiting	200mg	Day 3	2 days	I.V Fluids
Syncope	400mg	2 days after final dose	2 days	
All SAEs fully resolved and participant completed trial				

•4 interrupted BIT225 dosing (2-5 Days)
- Vomiting/ Nausea (400mg, 400mg, 200mg); Vertigo (400mg)
- All recommenced dosing and completed trial

•5 Severe Adverse Events
- Vomiting (400mg, 200mg);
- Horizontal diplopia (400mg)- withdrew Day 10
- Vertigo (400mg)
- Syncope (200mg)

•All other AEs mild to moderate intensity

Conclusions

- First in class, novel p7 inhibitor BIT225 demonstrates clear antiviral activity in addition to IFN/RBV among treatment-naïve, genotype 1 patients. The week 48 sustained viral response (SVR) rates were 7/7, 7/8 and 6/8 subjects for 400 mg, 200 mg and placebo groups respectively.

•There were no detectable antiviral resistant variants generated during treatment (4 week analysis).

•The drug was well tolerated at the doses selected

•Potential to combine with current or next generation DAAs drugs

•Formulation development to optimize tolerability in progress

•Potential for use with HCV and HIV co-infected patients

•BIT225 is currently being evaluated in a phase 1b study in HIV infected subjects.

•BIT225 will be evaluated in a phase II study in HIV and HCV co-infected subjects in 4Q of 2012.

Acknowledgements

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For further information

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More information on this and related projects can be obtained at *www.biotron.com.au*

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Biotron