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Safety, Tolerability, and Pharmacokinetics of Orally Administered BC-3781, a Novel Antimicrobial

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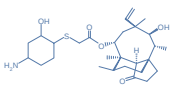
BC-3781



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ABSTRACT

Background: BC-3781, a novel pleuromutilin antibiotic for systemic use in humans, has antibacterial activity against pathogens causing acute bacterial skin and skin structure infections (ABSSSI) and respiratory tract infections and successfully treated patients in a Phase 2 study in patients with ABSSSI. This is the first time data is presented on the safety, tolerability and pharmacokinetics of the oral formulation.

Methods: This was a two part study. Part A was open label, crossover and randomized. Twelve healthy subjects received single oral doses of an immediate release (IR) tablet containing 600 mg BC-3781 on two study occasions, one in the fasted state and the other after a high fat high calorie breakfast.

Part B was randomized double-blind and placebo controlled: 8 subjects received repeat oral doses of 600 mg of BC−3781 and 4 subjects received placebo q12h for 6 days with a single dose on day 7. In both parts vital signs, laboratory safety parameters, adverse events, and ECG were recorded and samples were taken for PK.

Results: BC-3781 given orally was bioavailable and well tolerated. Following a single 600 mg IR-tablet administration to healthy subjects the mean $AUC_{0\text{-}12h}$ was 5.3 ± 1.7 µg/mL and t_{max} was 0.9 h. After multiple dosing the $AUC_{0\text{-}12h}$ at steady-state reached 10.8 ± 4.2 µg·h/mL. In contrast to the accumulation of 1.7-fold observed in mean $AUC_{0\text{-}12h}$ after repeat doses, the mean C_{max} was only increased by 1.3-fold at steady state. When a single oral dose of 600 mg BC-3781 (IR tablet) was given in the fed state the mean $AUC_{0\text{-}inf}$ and mean C_{max} showed a reduction of 10 % and 28 %, respectively. A few adverse events mainly related to the gastrointestinal tract were reported.

Conclusions: After administration as a 600 mg IR-tablet BC-3781 was rapidly absorbed and well tolerated. The exposure after a single oral dose in terms of AUC was similar to that observed after single doses of 150 mg i.v. BC-3781 in phase 1 studies and in patients with ABSSSI. Food caused a small reduction in $AUC_{0\text{-}inf}$. Based on the data obtained with the current IR-tablet, switch therapy using 150 mg i.v. followed by 600 mg oral would be possible.

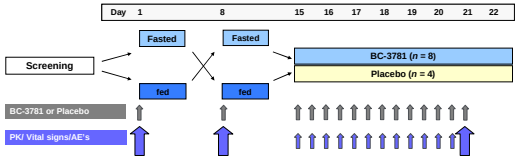
INTRODUCTION

BC-3781 is an investigational semi-synthetic pleuromutilin derivative. BC-3781 has demonstrated potent antimicrobial activity against Gram-positive and fastidious Gram-negative pathogens. Currently, BC-3781 is under development for treatment of acute bacterial skin and skin structure infections and hospital treated community-acquired pneumonia with both intravenous (i.v.) and oral treatment options. Proof of concept was demonstrated in a Phase 2 study in acute bacterial skin and skin structure infections where BC-3781 100 and 150 mg q12h i.v. produced clinical responses similar to vancomycin at the early time points and at test of cure.[1] The study presented here investigated the safety and pharmacokinetics of a new, immediate release tablet that will be used in future clinical studies to allow i.v. to oral switch with BC-3781.

METHODS

Study Design :

- Healthy male subjects aged 18 to 55 years (n = 12).
- Part A: single-center, open label, randomized, cross-over
  - 600 mg BC-3781 single dose with and without high fat high caloric breakfast
- Part B: single center, double-blind, randomized, placebo controlled
  - 600 mg BC-3781 q12h over 6.5 days



Pharmacokinetics:

- Part A: blood samples for pharmacokinetics: 16 samples over 36 hours
- Part B: blood samples pre-dose q12h daily and 16 samples over 36 hours on day 7
- BC-3781 concentrations in plasma determined using validated LC-MS/MS assays (LLOQ 1.00 ng/mL)
- Non-compartmental pharmacokinetic analysis was performed using WinNonlin Professional Version 5.2.1. [Pharsight Corporation, Mountain View, CA, USA]

Safety and tolerability:

- Vital signs
- Clinical biochemistry and hematology
- Adverse events

RESULTS

Pharmacokinetics

Descriptive statistics of the mean pharmacokinetic parameters for BC-3781 in plasma following oral administration (600 mg) and intravenous infusion (150 mg) are provided in Table 1.

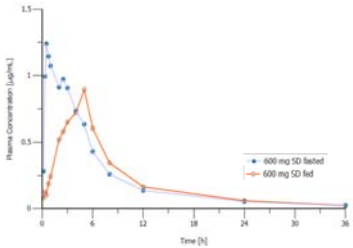
Table 1. Mean ±SD summary of the main PK parameters following intravenous and oral administration of BC-3781

Dose [mg]	Formulation	Population	t_{max} [h]	C_{max} [µg/mL]	C_{min} [µg/mL]	$AUC_{0\text{-}12h}$ [µg·h/mL]	$AUC_{0\text{-}inf}$ [µg·h/mL]
600 (n=12)	1x 600 mg IR tab fasted	Healthy volunteers	1.65	1.46 ± 0.44		6.35 ± 1.67	8.25 ± 2.31
600 (n=12)	1x 600 mg IR tab fed		4.50	1.06 ± 0.39		5.28 ± 1.74	7.46 ± 2.77
600 q12h (n=7)	1x 600 mg IR tab		1.64	1.85 ± 0.61	0.35 ± 0.17	10.8 ± 4.2	-
150 (n=8)	1x 150 mg i.v. 1 h		1	2.42 ± 0.52		5.75 ± 1.26	7.28 ± 1.62
150 q12h (n=8)	1x 150 mg i.v. 1 h		1	2.77 ± 0.52	0.24 ± 0.09	8.25 ± 2.00	12.8 ± 3.2
150 (n=65)	1x 150 mg i.v. 2 h	Patients	2	1.90 ± 0.71		6.59 ± 2.69	-
150 q12h (n=65)	1x 150 mg i.v. 2 h		2	2.06 ± 0.74		8.27 ± 3.11	-

RESULTS continued

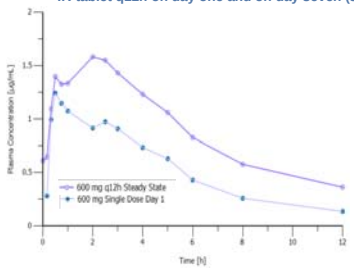
Plasma concentration time curves of BC-3781 following single oral administration of 600 mg IR-tablet under fasted and fed conditions (Figure 1), and following single and multiple dosing of q12h 600 mg IR-tablet (Figure 2) are depicted below.

Figure 1. Plasma-concentration time curves of BC-3781 following a single dose of 600 mg IR-tablet to healthy volunteers under fasted and fed conditions



- BC-3781 administered as a single oral dose of 600 mg IR-tablet was rapidly absorbed under fasted conditions
- The mean $AUC_{0\text{-}inf}$ and mean C_{max} showed under fed conditions a reduction of 10 % and 28 %, respectively
- The AUC on day one achieved therapeutic exposures. Efficacy of BC-3781 is driven by 24 h AUC/MIC[2]

Figure 2. Plasma-concentration time curves of BC-3781 following multiple doses of 600 mg IR-tablet q12h on day one and on day seven (steady state)



- The mean $AUC_{0\text{-}12h}$ increased 1.7-fold at steady state
- Mean C_{max} was only increased by 1.3-fold at steady state
- The $AUC_{0\text{-}inf}$ following a single oral dosing (600 mg) was with 8.25 ± 2.31 µg·h/mL equivalent to the exposure obtained after 150 mg i.v. dosing
- The $AUC_{0\text{-}12h}$ at steady state following 600 mg q12h dosing exceeded the exposures measured following multiple i.v. dosing (150 mg q12h)

Safety and tolerability:

- BC-3781 was safe and well tolerated (Table 2)
- • Nearly all reported adverse events (AEs), considered by the investigator to be drug-related, were of gastrointestinal origin (diarrhea, nausea, eructation and upper abdominal pain); AEs were generally of short duration and rated as mild to moderate in intensity
- A lower incidence of AEs was reported when BC-3781 was given in the fed state
- Mean laboratory parameters, vital signs and ECG parameters demonstrated no clinically relevant time- or dose-related changes

Table 2. All reported possibly related adverse events

	Part A		Part B	
	Single Dose fed	Single Dose fasted	Repeat Dose	Placebo
	n=12	n=12	n=8	n=4
Adverse events (n)	**3 (3)**	**13 (8)**	**23 (6)**	**4 (2)**
Abdominal discomfort (n)			1 (1)	
Abdominal pain upper (n)		1 (1)	4 (2)	
Diarrhea	3 (3)	2 (2)	5 (4)	
Dyspepsia (n)		1 (1)	3 (1)	
Eructation (n)		2 (2)	1 (1)	
Feces discolored (n)				1 (1)
Flatulence (n)			5 (2)	
Nausea (n)		5 (5)	3 (3)	
Vomiting (n)		1 (1)		1 (1)
Decreased appetite (n)			1 (1)	
Dysgeusia (n)		1 (1)		
Headache (n)				2 (1)

CONCLUSIONS

- Single and repeat oral doses of 600 mg BC-3781 were safe and well tolerated
- BC-3781 administered as a single oral dose of 600 mg in the fasted state was rapidly absorbed
- Administration of BC-3781 after a high fat high caloric breakfast led to a slightly but a statistically significantly lower exposure (AUC) of BC-3781
- After repeat dose administration of BC-3781 a 1.70-fold accumulation of AUC was observed for BC-3781, whereas Cmax increased at steady state compared to single dose Cmax only by a factor of 1.26
- The exposure after a single oral dose in terms of AUC was equivalent to that observed after single doses of 150 mg i.v. BC-3781 in Phase 1 studies and in patients with ABSSSI
- The BC-3781 IR-tablet is suitable to support intravenous to oral switch therapy

REFERENCES

1 Prince W.T. *et al.* AAC (2013) 57: 2087-2094

2 Craig W.A. *et al.* ICAAC (2010), Poster F1-2108

ACKNOWLEDGMENTS

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