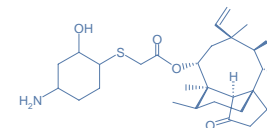


An Age and Gender Study Investigating the Safety, Tolerance and Pharmacokinetics of BC-3781

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BC-3781



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ABSTRACT

Background: BC-3781, a novel pleuromutilin, is being developed for the treatment of acute bacterial infections such as skin and skin structure infections and pneumonia. BC-3781 shows excellent antimicrobial activity against relevant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). Reported here are the results of an age gender study conducted to support transition of BC-3781 to a patient population.

Methods: This single-centre, double blind, randomized, placebo controlled, cross over study investigated the safety, tolerability and pharmacokinetics (PK) of BC-3781 administered to 12 healthy males and 12 healthy females aged 18–55 years and to 12 healthy elderly subjects ≥ 65 years. Subjects received 150 mg BC-3781 and placebo at separate study sessions as single intravenous infusions over 60-minutes. Vital signs, laboratory safety parameters, adverse events and ECG were recorded and samples taken for PK.

Results: No adverse events of clinical concern nor clinically significant changes in vital signs and safety laboratory parameters were reported in any subject. BC-3781 was well tolerated but some signs of local intolerance were observed after BC-3781 and placebo administration.

The plasma concentration curve showed a multi-phasic decline. Irrespective of age or gender of subjects, no significant differences in the pharmacokinetic parameters could be observed between the groups. BC-3781 is well distributed; the volume of distribution was large and tended to be slightly greater in the subjects aged ≥ 65 years. Covariate analysis indicated no effect of body weight, height and body mass index.

The urinary excretion of unchanged BC-3781 was low, <10%. No major effect of age or gender on the renal excretion of BC-3781 could be detected.

Conclusions: BC-3781 was well tolerated in all groups and showed comparable PK irrespective of age or gender. The results indicate that no dosing adjustment is needed for subjects of different age and gender.

INTRODUCTION

BC-3781 is a semi-synthetic pleuromutilin derivative and a novel representative of a new class of antibiotics for systemic use in humans which is being targeted for treating ABSSSI as well as bacterial pneumonia caused by MRSA and other drug-resistant bacteria. It is currently in a phase 2 in ABSSSI study.

BC-3781 interferes with bacterial protein synthesis by binding the peptidyl transferase center of the 50S subunit of ribosomes. The uniqueness of this mechanism implies the lack of cross-resistance with other antibacterial classes. BC-3781 can be dosed either orally or intravenously. Reported here is a study examining the pharmacokinetics of BC-3781 in three different populations: males, females and the elderly.

MATERIALS & METHODS

Primary objective:

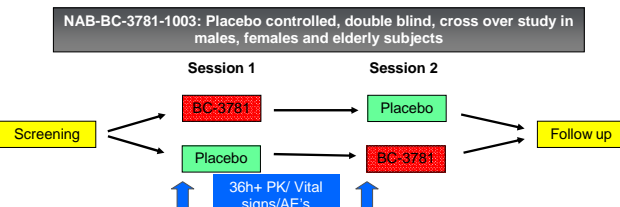
- To assess the safety and tolerability of a single dose of BC-3781 when administered as a single intravenous infusion in male and female subjects aged 18 to 55 years and in elderly subjects ≥ 65 years.

Secondary objectives:

- To delineate the pharmacokinetics of BC-3781 when administered as a single IV infusion in male and female subjects aged 18 to 55 years and in elderly subjects ≥ 65 years;
- To assess local tolerability at the site of infusion.

Study design:

- Single-center, double blind, randomized, placebo controlled, cross over
- Healthy male and female subjects aged 18 to 55 years and healthy elderly subjects ≥ 65 years
- All subjects participated in two study sessions
 - 150 mg BC-3781 or placebo (0.9% saline) administered as an intravenous infusion over 1 hour



Pharmacokinetics:

- Blood samples for PK: 13 over 36 hours
- Urine for PK: 0-6 h, 6-12 h, 12-24 h and 24-36 h post infusion start.
- BC-3781 concentrations in plasma and urine were determined using validated LC-MS/MS assays
- The limits of quantification (LOQ) were 1.00 and 10.0 ng/mL in plasma and urine, respectively
- For the pharmacokinetic evaluation, pre-dose values below the LOQ were set to zero
- Non-compartmental pharmacokinetic analysis was performed using Professional WinNonlin Version 5.2.1. [Pharsight Corporation, Mountain View, CA, USA]

Safety and tolerability:

- Vital signs
- ECG at 9 timepoints at each study session
- Clinical biochemistry and hematology
- Adverse events
- Local signs at site of infusion

RESULTS

Table 1. Demographics and Subject Disposition – Safety Population

Demographic/Characteristic Category/Statistic	Placebo (n = 39)	BC-3781 (n = 38)
Age at consent (years) +/- SD	47.5 +/- 16.96	46.9 +/- 16.82
Age category – n (%)		
18 to 55 yrs	26 (66.7)	26 (68.4)
≥ 65 yrs	13 (33.3)	12 (31.6)
Gender – n (%)		
Male	18 (46.2)	18 (47.4)
Female	21 (53.8)	20 (52.6)
Race, n (%)		
White	27 (69.2)	25 (65.8)
Black or African American	12 (30.8)	13 (34.2)
Ethnicity, n (%)		
Hispanic or Latino	0 (0.0)	0 (0.0)
Not Hispanic or Latino	38 (97.4)	37 (97.4)
Unknown	1 (2.6)	1 (2.6)
Weight at Screening (kg) +/- SD	77.86 +/- 14.459	77.99 +/- 13.91
BMI at Screening (kg/m ²) +/- SD	27.17 +/- 3.681	27.22 +/- 3.61

BMI = body mass index; SD = standard deviation

Pharmacokinetics:

- Descriptive statistics of BC-3781 plasma concentrations following intravenous infusion of 150 mg of BC-3781 by age and by gender are provided in Table 1 and the mean concentration-time curves are shown in Figure 1 and 2.

Effect of age:

- The mean plasma concentration-time profiles of BC-3781 were similar in subjects aged 18-55 years and ≥ 65 years.
- Following the end of infusion plasma concentrations decreased in a multi-phasic manner.
- Values for the main pharmacokinetic variables clearance (Cl) and volume of distribution (V_{ss}) were 19.6 l/h and 140 l in subjects aged 18-55 years and 20.0 l/h and 166 l in subjects aged ≥ 65 years.
- Cl varied little with age whereas there was a tendency for the volume of distribution (both V_d and V_{ss}) to be larger in the ≥ 65 years age group.
- The pharmacokinetic variables such as C_{max} and AUC were similar between the two age groups whereas the mean terminal $t_{1/2}$ was slightly longer in the ≥ 65 years age group compared to the subjects aged 18-55 years.
- No major effect of age on the renal excretion of BC-3781.

Effect of gender:

- The mean plasma concentration-time profiles of BC-3781 were similar in male and female subjects.
- Following the end of infusion, C_{max} plasma concentrations decreased in a multi-phasic manner.

- Values for the main pharmacokinetic variables Cl and V_{ss} were 19.6 l/h and 140 l in male subjects and 20.0 l/h and 166 l in female subjects.
- Cl and V_{ss} varied little with gender and all other pharmacokinetic parameters were similar in male and female subjects.
- No major effect of gender on the renal excretion of BC-3781.

Table 2. PK Parameters

Group	Statistic	C_{max} [$\mu\text{g/mL}$]	$t_{1/2}$ [h]	Cl [l/h]	AUC_{0-36h} [$\mu\text{g}\cdot\text{h/mL}$]	V_d [l]	V_{ss} [l]	Cl_r [l/h]
Young n=26	Mean	2.66	8.94	20.1	7.88	258	143	1.59
	SD	0.63	1.09	4.93	1.87	61.9	32.0	0.57
	Median	2.61	9.05	19.3	7.77	244	138	1.65
Elderly n=12	Mean	2.50	10.5	21.0	7.87	310	170	1.47
	SD	0.61	1.51	7.18	2.51	79.5	40.0	0.72
	Median	2.33	10.6	19.9	7.56	305	187	1.30
Female n=20	Mean	2.72	9.56	19.5	8.24	265	145	1.60
	SD	0.75	1.33	5.25	2.25	62.8	35.3	0.67
	Median	2.59	9.70	19.6	7.64	261	134	1.77
Male n=18	Mean	2.48	9.28	21.4	7.47	285	159	1.50
	SD	0.41	1.53	6.05	1.80	80.0	37.2	0.56
	Median	2.44	9.08	19.4	7.72	274	156	1.39

Figure 1. BC-3781 plasma concentration time curve in young and elderly subjects

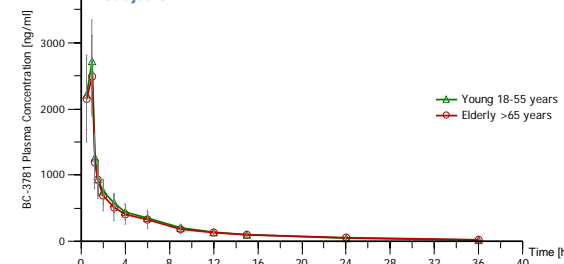
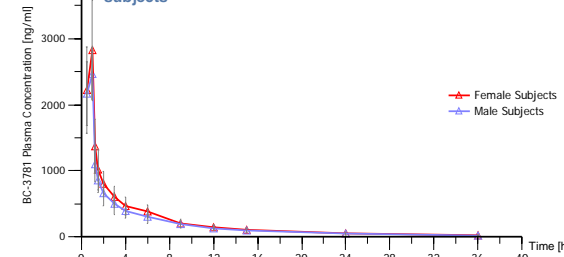


Figure 2. BC-3781 plasma concentration time curve in female and male subjects



Safety and tolerability:

BC 3781 was safe and well tolerated. There were no changes of clinical concern in vital signs (temperature, BP, heart and respiratory rate), ECGs, clinical biochemistry, hematology and adverse events. No subject withdrew from the study for investigational product related reasons and there were no serious adverse events. Adverse events are shown in table 3.

Table 3. All reported possibly or unlikely related Adverse Events

	Placebo	Male	Female	Elderly
Adverse events (n)	15 (10)	5 (5)	5 (3)	6 (4)
Pain at infusion site (n)	3 (3)	3 (3)	1 (1)	1 (1)
Erythema at infusion site (n)	3 (3)	1 (1)	2 (2)	1 (1)
Swelling at infusion site (n)	4 (4)		1 (1)	
Inflammation at infusion site (n)	2 (2)			
Itching at infusion site (n)	2 (2)			
Soreness at infusion site (n)			1 (1)	
Dermatitis right arm (n)		1(1)		
Transient Hypertension (n)				1 (1)
Sacral Pain (n)	1 (1)			1 (1)
Rash (n)				1 (1)
Nausea (n)				1 (1)

(n) = number of subjects reporting event

CONCLUSIONS

- No significant age or gender related differences in PK parameters were found in this study.
- The pharmacokinetic variables of BC-3781 were similar in male and female subjects and young and elderly.
- The renal excretion of BC-3781 was low (<8%) and without any major effect of age or gender.
- BC-3781 was well tolerated in all groups.
- The number of AE's were similar after placebo and BC-3781 infusion and were self limiting.
- There were no clinically meaningful treatment emergent abnormalities or changes from baseline in any safety parameter.
- No dose adjustment of BC-3781 is required because of age or gender.