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Safety, Tolerance and Pharmacokinetics of Single and Repeat Doses of BC-3781, a Novel Antimicrobial

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Amended Abstract

Background: BC-3781 is a new pleuromutilin which is in clinical development for the treatment of 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 the first two studies investigating the safety, tolerance and pharmacokinetics (PK) of BC-3781.

Methods: NAB-BC-3781-1001, a double-blind, placebo randomized, single intravenous (i.v.) dose escalation study in which BC-3781 was given to 2 cohorts of 8 healthy subjects each. Each subject in Cohort 1 received 25, 50 and 100 mg BC-3781 and placebo and in cohort 2, 200, 300 and 400 mg BC-3781 and placebo. NAB-BC-3781-1002, a second double-blind, placebo-controlled, randomized study in which 3 cohorts of 12 subjects were given single and repeat doses of BC-3781 or placebo. Cohort 1 received 75 mg BC-3781 or placebo: Day 1 single dose, days 3 - 14 twice daily (q12 h) and day 15 single dose. Cohort 2 received 150 mg BC-3781 or placebo infused over 1 h and cohort 3 150 mg or placebo infused over 2 h. In both studies vital signs, laboratory safety parameters, adverse events and ECGs were recorded and samples taken for PK.

Results: No adverse events of clinical concern were reported. Also, there were no clinically significant changes in vital signs or safety laboratory parameters in any subject at any session. At expected therapeutic doses BC-3781 was well tolerated but at the highest single doses tested (300 and 400 mg) some subjects showed signs of local intolerance. The plasma concentration of BC-3781 after i.v. administration shows a multi-phasic decline. After single doses the terminal half life is 8.6–11.7 h and AUC increases linearly with dose supporting q12 h dosing. After repeat dosing of BC-3781 to steady state the AUC increased and no significant increase of C_{max} was seen. The large volume of distribution indicates BC-3781 is well distributed.

Conclusions: BC-3781 was safe and well tolerated up to the maximum doses tested, 400 mg single dose and 150 mg q12 h. The PK of BC-3781 show that it behaves in a predictable manner in humans and the plasma levels indicate it has therapeutic potential for the treatment of Gram-positive infections. BC-3781 is being progressed into phase 2 studies.

Introduction

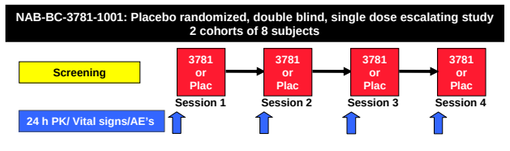
BC-3781 is a semi-synthetic pleuromutilin derivative and a novel representative of a new class of antibiotics for systemic use in humans for the treatment of Gram-positive infections especially MRSA.

BC-3781 is a prokaryotic protein synthesis inhibitor. Its novel mode of action is mediated by a unique interaction with the central part of domain V of 23S rRNA, subsequently preventing the correct positioning of the CCA-ends of tRNAs for peptide transfer. The uniqueness of this mechanism implies the lack of cross-resistance with other antibacterial classes. Also, multiple interaction sites with the ribosomal target are the most likely explanation for the observed low mutation frequency of below 10^{-11}. The first single and repeat dose studies where BC-3781 was given by the intravenous route are reported. BC-3781 was dissolved in saline (0.9 % NaCl) for intravenous administration.

Methods

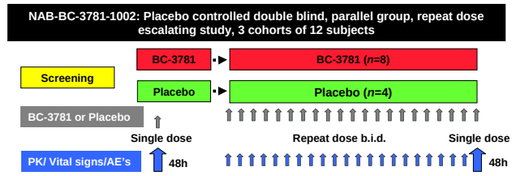
NAB-BC-3781-1001

- First Time in Human (FTIH) study with BC-3781 administered by intravenous infusion
- Single dose, cross over, placebo randomized, double blind, dose escalating
- 2 cohorts of 8 healthy male subjects aged 18-45 years
  - Cohort 1 received placebo and 25, 50 and 100 mg BC-3781
  - Cohort 2 received placebo and 200, 300 and 400 mg BC-3781
- Endpoints: Safety and tolerability (vital signs, clinical biochemistry, hematology and adverse events), plasma and urine concentrations of BC-3781, identification of metabolites, and local tolerability at the site of infusion.



NAB-BC-3781-1002

- Single center, placebo controlled, parallel group, double blind, repeat escalating dose
- 3 cohorts of 12 (placebo (*n*=4) or BC-3781 (*n*=8)) healthy male subjects aged 18-45
  - Cohort 1: 75 mg BC-3781 or placebo, 1 h infusion
  - Cohort 2: 150 mg or placebo 1 h infusion
  - Cohort 3: 150 mg BC-3781 or placebo 2 h infusion
- Endpoints as FTIH plus 6β-OH cortisol/cortisol ratio predose and on the final day



Primary objective

- To assess the safety and tolerance of BC-3781 when administered intravenously as single and repeat doses

Secondary objectives

- To assess the plasma and urine pharmacokinetics of BC-3781
- Where possible, to identify major metabolites of BC-3781 in plasma and urine
- To assess local tolerability at the site of injection
- Study NAB-BC-3781-1002 only: To measure the urine 6β-OH cortisol/cortisol ratio before and after repeat doses of BC-3781

Results

Pharmacokinetics

- Descriptive statistics of single and multiple dose BC-3781 plasma pharmacokinetic parameters are summarized in Table 1 and depicted in Figure 1 and Figure 2.
- Plasma concentration-time curves of intravenously administered BC-3781 shows a multi-phasic decline.
- The pharmacokinetics of BC-3781 are time independent
- $AUC_{0\text{-}inf}$ values showed a dose proportional increase at doses between 100 mg to 400 mg
- Clearance being constant across doses
- The volume of distribution is large and is 2- to 5-fold greater than total body water indicating a low affinity to plasma proteins and good distribution into tissues and organs (cf. rat Whole Body Autoradiography – ECCMID 2010 Poster 909)
- Steady state was reached within 2-3 days
- Extending the infusion time from 1 h to 2 h had little effect on AUC
- BC-3781 metabolism was evaluated for study NAB-BC-3781-1001 in 14 subjects administered single doses of 100 mg and 400 mg, respectively
- Overall amount of identified metabolites in any subject did not exceed 6.5 % of total drug related systemic exposure measured as AUC (individual metabolites ranged from <0.1 % to 3.8 %)
- No unique metabolites not seen previously in animal studies were found
- <15 % of the given dose of 400 mg were excreted in the urine as BC-3781 and metabolites within the first 24 hours
- The ratio of urinary 6β-hydroxycortisol:cortisol (a marker for CYP 3A4 activity) was not changed comparing pre-dose and after multiple doses

Figure 1. Mean plasma concentration time curves after single i.v. infusion of BC-3781

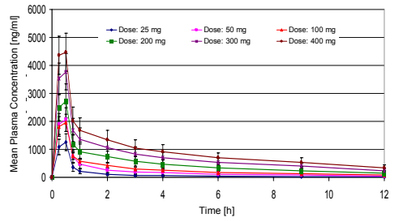


Figure 2. Mean plasma concentration time curves after multiple i.v. infusion of 150 mg BC-3781

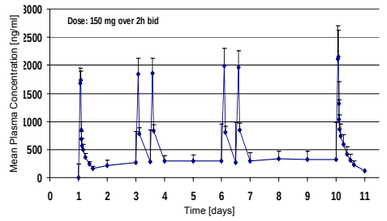
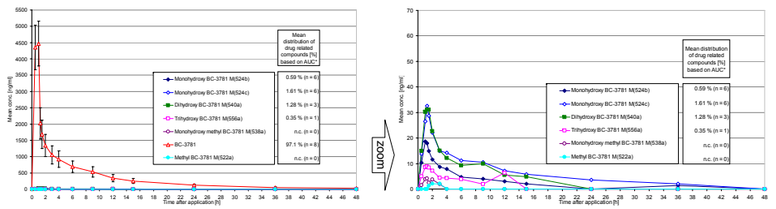


Figure 3: Mean pharmacokinetic profile of BC-3781 and identified metabolites in plasma of 8 subjects after i.v. administration of 400 mg BC-3781 (right figure without BC-3781)



***** Distribution of drug related compounds was calculated on the basis of $AUC_{0\text{-}inf}$. "n" indicates the number of valid and reliable $AUC_{0\text{-}inf}$ values used for mean calculation. The graphs are displaying mean curves of 8 subjects

Table 1. Overview of mean BC-3781 pharmacokinetic parameters after single or multiple doses of intravenous BC-3781

Dose	*n*	Single or Multiple Dose	Infusion Duration	C_{max} [µg/ml]	C_{min} [µg/ml]	Terminal $t_{1/2}$ [h]	$AUC_{0\text{-}12h}$ [µg·h/ml]	$AUC_{0\text{-}inf}$ [µg·h/ml]	V_{SS} [l]	Cl [l/h]
				Arithmetic Mean±SD						
25 mg	8	single	30 min	1.26±0.30	-	8.6±0.82	1.28±0.37	1.48±0.45	84±16.9	18±4.6
50 mg	10	single	30 min	2.08±0.43	-	8.6±0.87	2.71±0.78	3.21±0.93	95±40.6	17±5.3
75 mg	8	single	60 min	1.56±0.22	-	10.7±1.62	3.21±0.52	3.92±0.59	129±29.6	19.5±2.99
75 mg		multiple	60 min	1.79±0.21	0.12±0.02	13.6±1.81	4.55±0.68	6.47 ±0.93	129± 26.4	11.8±1.51
100 mg	6	single	60 min	1.95±0.31	-	9.1±0.46	3.96±0.75	4.90±1.00	117±40.8	21±5.0
150 mg	38	single	60 min	2.61±0.62	-	9.43±1.42	6.11±1.52	7.87±2.06	152±36.4	20.4±5.65
150 mg	8	single	60 min	2.42±0.52	-	10.7±0.74	5.75±1.27	7.28±1.63	160±44.2	21.7±5.44
150 mg		multiple	60 min	2.77±0.52	0.23±0.07	14.6±1.12	8.25±1.06	12.8±3.23	161±45.5	12.5±3.62
150 mg	8	single	120 min	1.74±0.27		-	5.34±0.89	6.14±1.17	117± 17.0	25.1 ±4.41
150 mg		multiple	120 min	2.03±0.37	0.24±0.09	9.76±1.16	7.56±2.13	10.8±3.68	138±30.4	15.1±4.0
200 mg	8	single	60 min	2.73±0.62	-	10.9±1.15	6.55±1.75	8.51±2.33	200±75.6	25±6.8
300 mg	8	single	60 min	3.78±0.65	-	11.7±0.98	9.70±2.29	13.0±3.12	213±64.1	24±5.7
400 mg	8	single	60 min	4.48±0.69	-	11.3±0.79	12.3±2.73	16.9±3.40	250±53.5	25±5.4

Safety

BC-3781 was safe and well tolerated up to the highest doses tested: Single doses up to 400 mg and repeat doses up to 150 mg q12 h. 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 events. Adverse events are shown in table 2 and 3.

Table 2: NAB-BC-3781-1001: All reported Adverse Events

Doses given [mg]	Placebo	25 mg	50 mg	100 mg	200 mg	300 mg	400 mg
Total AE (*n*)			1 (1)		2 (2)	6 (4)	10 (5)
Heat rash			1[1] (1)				
Headache					1 (1)		1 (1)
Pain at infusion site						4 (4)	5 (5)
Erythema at infusion site						1 (1)	1 (1)
Paraesthesia							2 (2)
Thrombosis at infusion site						1 (1)	
Musculoskeletal pain							1 (1)
Abdominal discomfort					1[2] (1)		

[1] rated as unrelated to study medication [2] rated as unlikely related *n* = number of subjects

Table 3: NAB-BC-3781-1002: All reported systemic Adverse Events (possibly and probably related to study drug)

Cohort	Placebo *n*=12	Cohort 1 75 mg 1 h infusion *n*=8	Cohort 2 150 mg 1 h infusion *n*=8	Cohort 3 150 mg 2 h infusion *n*=8
Number of AEs (*n*)	1 (1)	1 (1)	11[1] (5)	4 (3)
Headache (*n*)	1 (1)	1 (1)	9 (3)	4 (3)
Arthralgia (*n*)			1[1] (1)	
Muscle twitching (*n*)			1 (1)	

Superscript = moderate AE

Conclusions

- BC-3781 was safe and well tolerated when infused intravenously to the highest doses tested – single dose 400 mg and repeat dose of 150 mg q12 h
- There were no SAEs; no subject discontinued the studies due to drug related adverse events
- There were no clinically relevant changes in clinical biochemistry, hematology or vital signs
- Plasma PK showed a multi-phasic decline
  - a rapid distribution phase over 0.5 h
  - extended elimination phase with mean half-lives of 8.6 h to 11.7 h
- $AUC_{0\text{-}inf}$ showed a dose-proportional increase over the range of 100 mg to 400 mg
- C_{max} was not dose-proportional but showed a linear increase
- Steady state was achieved after 2-3 days and was as predicted from the single dose pharmacokinetics. There was little increase in C_{max} and there was ~50 % increase in AUC at steady state
- Sum of metabolites did not exceed 6.5 % (measured as AUC) of total drug related systemic exposure in any subject
- BC-3781 is being progressed into studies in patients