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A Study of the Safety and Pharmacokinetics of Single and Multiple-ascending Doses of BTA585, a Novel Fusion Inhibitor of Respiratory Syncytial Virus, in Healthy Volunteers

E DeNoia[1], R Campaneria[2], E Wenzel[2], L Reynolds[3], X Rivera[2], K Callicott[4], and A Novotney-Barry[2]

[1]ICON Early Phase Services, San Antonio, TX, [2]Aviragen Therapeutics Inc., Alpharetta, GA, [3]ICON Development Solutions, Gaithersburg, MD, [4]Callicott Consulting, Atlanta, GA

Aviragen Therapeutics
2500 Northwinds Parkway
Alpharetta, GA 30009
(678) 221-3343 – phone
(678) 221-3361 – fax
abarry@aviragentherapeutics.com

Background

Respiratory Syncytial Virus (RSV) is a major cause of acute upper and lower respiratory tract infection in infants, young children and adults. BTA585 is an oral, selective F-protein inhibitor of RSV A and B in development for the treatment of RSV infections.

Methods

A single ascending dose (SAD) study evaluated the safety and pharmacokinetics (PK) of single oral doses of BTA585. The starting dose was 50 mg with escalating dose level cohorts of 100 mg (both fed and fasted to assess food effect), 200 mg, 400 mg, 500 mg, and 800 mg. Following the SAD study, a multiple-ascending dose (MAD) study evaluated the safety and PK profile of 100 mg BID, 400 mg BID, and 600 mg BID over 7 consecutive days of fasted dosing. BTA585 was also measured in nasal wash fluid in the MAD study.

Results

BTA585 was well-tolerated in both single and multiple dose trials. The most common adverse events (≥ 2 subjects in both studies) were chromaturia (abnormal coloration of urine), headache, and nausea. There were no SAEs, or drug-related clinically-significant adverse changes in ECGs or clinical lab values in either the SAD or MAD studies. High precision, dose-response assessment of ECG data from all SAD cohorts was also conducted. There was no meaningful or statistically significant relationship between BTA585 exposure and placebo-controlled change from baseline in QTcF, and an effect of BTA585 on QTcF was not observed.

BTA585 was rapidly absorbed across all single doses, with median T_{max} of ~ 1 hour and $t_{1/2}$ ranging from 6 to 7 hours. A significant food effect on PK was not observed. In both SAD and MAD studies, C_{max} and AUC increased dose-proportionally with single and multiple doses. The predicted antiviral levels of BTA585 were rapidly achieved and maintained with no significant accumulation. In the MAD study, levels of BTA585 in nasal wash fluid increased with exposure, were present as early as 3 hours post first dose and still detectable 24 hours after last dose in all groups.

Conclusions

BTA585 demonstrated a favorable safety and pharmacokinetic profile across all dose cohorts in these Phase 1 studies. Antiviral levels of BTA585 in the plasma were reached rapidly and exceeded the EC_{50} for clinical isolates of RSV. These safety and pharmacokinetic results support further clinical evaluation of BTA585.

Figure 1 – Mean Plasma Concentration of BTA585 over Time Single-ascending Dose Study

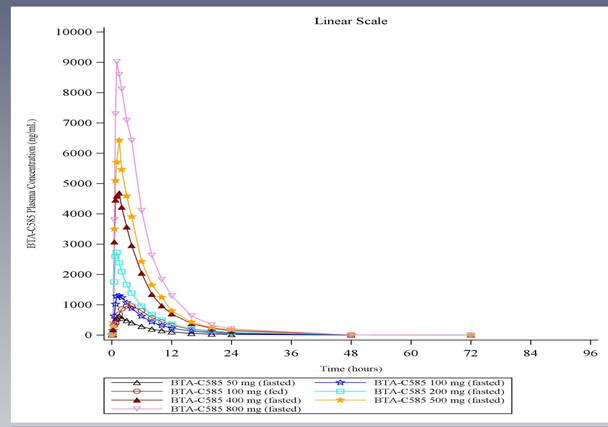

Table 1 – Summary of BTA585 PK Parameters in Healthy Subjects Following Single Oral Doses of BTA585 – SAD Study

Parameter (Unit)	Statistic	BTA585						
		50 mg N=7	100 mg N=7	100 mg (fed) N=6	200 mg N=7	400 mg N=7*	500 mg N=7*	800 mg N=7
C_{max} (ng/mL)	Mean (SD)	748 (245.2)	1510 (271.9)	1107 (185.5)	2820 (477.1)	5407 (1451.8)	7167 (1704.5)	9713 (1505.2)
	GM (GCV%)	718 (30.9)	1489 (18.6)	1095 (16.4)	2786 (17.0)	5253 (26.5)	6966 (28.0)	9610 (16.0)
$AUC_{0\text{-}24}$ (hr*ng/mL)	Mean (SD)	4217 (626.1)	9199 (2055.0)	9636 (2594.0)	15538 (2658.1)	30310 (3475.6)	37852 (7185.2)	58012 (6755.0)
	GM (GCV%)	4175 (15.5)	9013 (22.0)	9397 (23.8)	15372 (15.4)	30139 (11.8)	37305 (18.8)	57674 (11.7)
$AUC_{0\text{-}last}$ (hr*ng/mL)	Mean (SD)	4338 (726.0)	9523 (2315.3)	10101 (2995.6)	16381 (3455.8)	31603 (4126.7)	39329 (7784.0)	59531 (7489.0)
	GM (GCV%)	4284 (17.5)	9293 (24.1)	9799 (26.2)	16128 (18.3)	31375 (13.3)	38696 (19.9)	59133 (12.5)
T_{max} (hr)	Median	1.00	1.50	4.00	1.00	1.00	1.01	1.00
	Min, Max	0.50, 2.00	0.50, 3.00	1.0, 6.0	0.75, 1.00	0.50, 1.50	0.75, 1.50	0.75, 2.00
$t_{1/2}$ (hr)	Mean (SD)	5.40 (1.11)	5.12 (1.10)	5.20 (0.78)	5.99 (1.52)	5.82 (1.10)	5.29 (1.02)	5.27 (0.68)
	GM (GCV%)	5.29 (22.1)	5.02 (21.9)	5.15 (15.1)	5.83 (25.2)	5.74 (18.2)	5.22 (18.1)	5.23 (13.2)
T_{lag} (hr)	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Min, Max	0.0, 0.25	0.0, 0.25	0.0, 0.25	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0

* n=6
GCV%=geometric percent coefficient of variation; GM=geometric mean; hr=hour; L=liter; mL=milliliter; ng=nanogram; SD=standard deviation

Table 2 – Descriptive Summary of BTA585 Pharmacokinetic Parameters by Study Day – MAD Study

Parameter (Unit)	Statistic	BTA585					
		100 mg BID N=8		400 mg BID N=8		600 mg BID N=8	
		Day 0 n=8	Day 6 n=8	Day 0 n=8	Day 6 n=8	Day 0 n=8	Day 6 n=8
C_{max} (ng/mL)	Mean (SD)	1235 (320.5)	1568 (332)	5961 (1592)	6241 (1487)	7779 (1959)	9711 (2457)
	GM (GCV%)	1203 (23.8)	1536 (21.8)	5799 (24.8)	6097 (23.2)	7583 (24.0)	9487 (22.4)
C_{12} (ng/mL)	Mean (SD)	219 (72.0)	235 (73.9)	789 (184)	766 (173)	1474 (789)	1456 (905)
	GM (GCV%)	207 (41.3)	224 (34.6)	771 (23.0)	748 (23.0)	1314 (53.7)	1285 (53.4)
$AUC_{0\text{-}tau}$ (hr*ng/mL)	Mean (SD)	6536 (1105)	7720 (1314)	30745 (5748)	30990 (7229)	48087 (14221)	53911 (19659)
	GM (GCV%)	6446 (18.4)	7618 (17.8)	30248 (19.8)	30308 (22.5)	46529 (27.0)	51392 (32.5)
$AUC_{0\text{-}last}$ (hr*ng/mL)	Mean (SD)	8067 (1618)	ND	34647 (6589)	ND	56700 (20729)	ND
	GM (GCV%)	7903 (22.9)	ND	34081 (19.8)	ND	54011 (32.8)	ND
T_{max} (hr)	Median	1.00	0.76	0.75	1.00	1.00	1.00
	Min, Max	0.50, 4.00	0.75, 1.05	0.25, 2.00	0.50, 2.00	0.75, 3.00	0.75, 2.02
R_{acc}	Mean (SD)	ND	1.19 (0.115)	ND	1.01 (0.137)	ND	1.11 (0.116)
	GM (GCV%)	ND	1.18 (10.1)	ND	1.00 (14.6)	ND	1.10 (10.7)

GCV%=geometric percent coefficient of variation; GM=geometric mean; hr=hour; L=liter; mL=milliliter; ng=nanogram; ND=nor done; SD=standard deviation

Figure 2 – Mean Plasma BTA585 Concentration-time Profiles on Study Day 0 (0-12 hours) – Multiple-ascending Dose Study

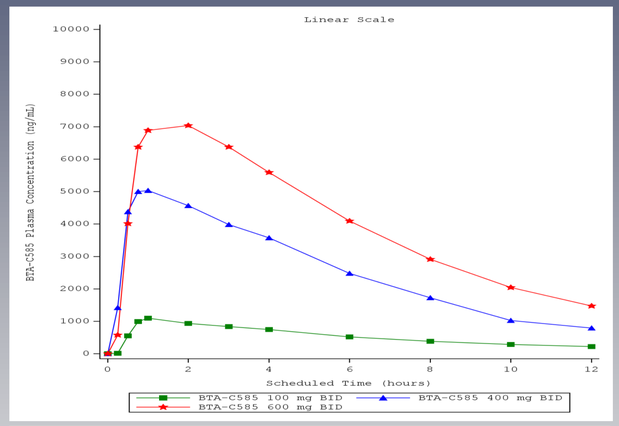

Figure 3 – Mean Plasma BTA585 Concentration-time Profiles on Study Day 6 (0-12 hours) – Multiple-ascending Dose Study

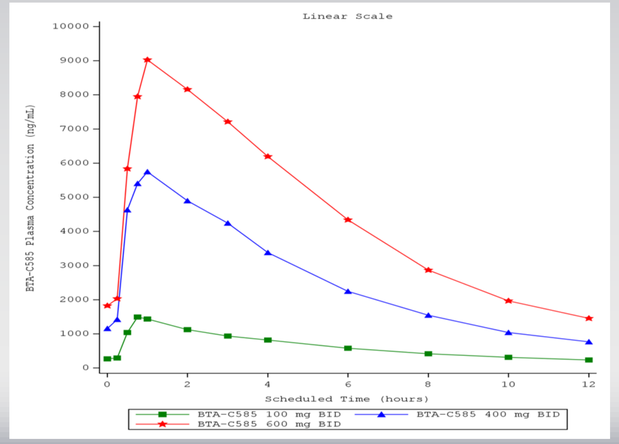

Table 3 – Overall Summary of TEAEs by Treatment – SAD Study

Category	BTA585							Placebo	Overall
	50 mg N=7 n (%)	100 mg N=7 n (%)	100 mg (fed) N=6 n (%)	200 mg N=7 n (%)	400 mg N=7 n (%)	500 mg N=7 n (%)	800 mg N=7 n (%)	N=18 n (%)	N=60 n (%)
Total number of TEAEs	1	4	1	2	7	11	4	5	35
Total number of subjects with:[a]									
At least one TEAE	1 (14.3)	2 (28.6)	1 (16.7)	2 (28.6)	3 (42.9)	5 (71.4)	4 (57.1)	4 (22.2)	22 (36.7)
At least one related TEAE[b]	0	2 (28.6)	1 (16.7)	2 (28.6)	2 (28.6)	5 (71.4)	4 (57.1)	2 (11.1)	18 (30.0)
At least one moderate TEAE	0	0	1 (16.7)	0	1 (14.3)	2 (28.6)	0	1 (5.6)	5 (8.3)
At least one severe TEAE	0	0	0	0	0	1 (14.3)	0	0	1 (1.7)
At least one PTAE	0	0	0	0	0	0	0	0	0
At least one SAE	0	0	0	0	0	0	0	0	0

SAE =serious adverse event; TEAE=treatment-emergent adverse event; PTAE=adverse event leading to permanent discontinuation of study drug
[a] Each event is only counted once, even if severity is unchanged between episodes.
[b] Includes events judged by the Investigator as possibly, probably, or definitely related to study drug.

Table 4 – Overall Summary of TEAEs by Treatment – MAD Study

Category	BTA585			Placebo	Overall
	100 mg BID N=8 n (%)	400 mg BID N=8 n (%)	600 mg BID N=8 n (%)	N=12 n (%)	N=36 n (%)
Total number of TEAEs	3	11	15	3	32
Total number of subjects with:[a]					
At least one TEAE	1 (12.5)	8 (100)	8 (100)	3 (25.0)	20 (55.6)
At least one related TEAE[b]	1 (12.5)	8 (100)	8 (100)	2 (16.7)	19 (52.8)
At least one moderate TEAE	1 (12.5)	0	2 (25.0)	0	3 (8.3)
At least one severe TEAE	0	1 (12.5)	0	0	1 (2.8)
At least one PTAE	0	0	0	0	0
At least one SAE	0	0	0	0	0

SAE =serious adverse event; TEAE=treatment-emergent adverse event; PTAE=adverse event leading to permanent discontinuation of study drug
[a] If a subject experiences the same event multiple times, only one occurrence will be included in the incidence.
[b] Includes events judged by the Investigator as possibly, probably, or definitely related to study drug.

Table 5 – TEAEs Occurring in ≥ 2 Subjects – SAD Study

System Organ Class Preferred Term	BTA585							Placebo	Overall
	50 mg N=7 n (%)	100 mg N=7 n (%)	100 mg (fed) N=6 n (%)	200 mg N=7 n (%)	400 mg N=7 n (%)	500 mg N=7 n (%)	800 mg N=7 n (%)	N=18 n (%)	N=60 n (%)
Renal and urinary disorders	**0**	**0**	**0**	**1 (14.3)**	**2 (28.6)**	**5 (71.4)**	**4 (57.1)**	**0**	**12 (20.0)**
Chromaturia	0	0	0	1 (14.3)	2 (28.6)	5 (71.4)	4 (57.1)	0	12 (20.0)
Gastrointestinal disorders	**1 (14.3)**	**1 (14.3)**	**0**	**0**	**1 (14.3)**	**1 (14.3)**	**0**	**1 (5.6)**	**5 (8.3)**
Nausea	1 (14.3)	1 (14.3)	0	0	0	1 (14.3)	0	0	3 (5.0)
Abdominal discomfort	0	1 (14.3)	0	0	1 (14.3)	0	0	0	2 (3.3)
Nervous system disorders	**0**	**0**	**1 (16.7)**	**1 (14.3)**	**1 (14.3)**	**1 (14.3)**	**0**	**1 (5.6)**	**5 (8.3)**
Headache	0	0	1 (16.7)	1 (14.3)	0	1 (14.3)	0	1 (5.6)	4 (6.7)

Table 6 – TEAEs Occurring in ≥ 2 Subjects – MAD Study

System Organ Class Preferred Term	BT585			Placebo	Overall
	100 mg BID N=8 n (%)	400 mg BID N=8 n (%)	600 mg BID N=8 n (%)	N=12 n (%)	N=36 n (%)
Renal and urinary disorders	**0**	**8 (100)**	**8 (100)**	**1 (8.3)**	**17 (47.2)**
Chromaturia	0	8 (100)	8 (100)	1 (8.3)	17 (47.2)
Nervous system disorders	**1 (12.5)**	**0**	**2 (25.0)**	**1 (8.3)**	**4 (11.1)**
Headache	1 (12.5)	0	2 (25.0)	0	3 (8.3)
Gastrointestinal disorders	**0**	**1 (12.5)**	**2 (25.0)**	**0**	**3 (8.3)**
Diarrhea	0	1 (12.5)	1 (12.5)	0	2 (5.6)
Nausea	0	0	2 (25.0)	0	2 (5.6)

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