Table 1. The Effect of Ambrisentan, Darusentan, Bosentan and Sitaxsentan on the MRP2 Mediated Biliary Excretion of DPDPE in Human Hepatocytes (Average ± Standard Deviation, n=3).

	Dose (μM)	Accumulation in Cell Lysate With Calcium (pmol/mg)	Accumulation in Cell Lysate Without Calcium (pmol/mg)	BEI (%)	SD	% Control	SD
Control	0	1.57	1.12	33.7	10.72	100.0	0.0
Positive Control (Probenecid)	1000	0.80	0.31	20.8	2.0	62.0	2.62
Ambrisentan	2	1.69	1.19	36.6	15.9	106	18.2
	20	0.87	0.53	39.7	31.4	102	73.2
	100	0.55	0.32	43.6	12.3	149	96.2
Darusentan	2	0.89	0.43	50.7	5.71	168	84.3
	20	0.52	0.31	44.4	9.9	154	28
	100	0.69	0.33	52.5	5.8	190	103
Bosentan	2	0.89	0.48	47.8	13.5	143	8.89
	20	0.67	0.48	28.6	-*	69	-
	100	0.33	0.25	33.0	19.2	111	76.0
Sitaxsentan	2**	0.82	0.62	30.6	24.3	79.4	54.4
	20	0.35	0.53	-56.4	67.2	-228	295
	100	0.35	0.55	54.8	167	88.2	505

* BEI values were negative for donors 2 and 3

** High degree of variability at all concentrations, donor #1 appeared to be the most consistent.

The BEI of DPDPE in the absence of the test compounds was on average 33.7(10.7) % which the sponsor postulated to be consistent with previous studies. Probenecid serving as positive control reduced BEI to 62% of the control. The data obtained with the 4 endothelin antagonists exhibited large variability hampering their interpretation.

Comments

1. The criteria for determining the viability of the hepatocytes and the functionality/expression of MRP2 used should be stated.

2. The report should indicate whether the metabolic capacity of the cultured hepatocytes is maintained and controlled.

3. The biliary clearance is normalized for body weight. The body weight of the donors was not indicated in the report.

4. The full name of DPDPE should have been provided and a literature reference given in support of this compound's probe status as a substrate of MRP2.

5. Data acceptance criteria were not provided.

6. The typographical error on p. 2, second bullet: .... plate should read probenecid plate as positive control...."

Study Report: MG-1005: The Effect of Probe-Inhibitors on the Hepatobiliary Disposition of Ambrisentan, Darusentan, Bosentan and Sitaxsentan in Sandwich-Cultured Human Hepatocytes

Study Investigator and Study Site:

Objective

To characterize the hepatobiliary disposition of ambrisentan, darusentan, sitaxsentan (potential competitor A-receptor selective antagonist), and of the marketed mixed A/B receptor antagonist bosentan

1 Page(s) Withheld

0 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Table 1. Uptake, Biliary Excretion Index (BEI) and Biliary Clearance (Mean ± Standard Deviation, n=3) for Taurocholate (TC) and E217BG in Sandwich-cultured Human Hepatocytes.

	Uptake (pmol/mg protein)		BEI %		Cl biliary (ml/min/Kg)	
	Avg.	Std. Dev.	Avg.	Std. Dev.	Avg.	Std. Dev.
TC	73.0	58.8	62.0	24.4	81.9	24.7
E217BG	28.1	4.63	17.2	14.0	5.4	4.64
E217BG + BSP	9.89	0.57	2.89	3.12	0.26	0.29
% Control	35.6	3.85	17.7	7.57	5.20	3.53

Hepatic uptake, biliary excretion index and biliary excretion are much higher for taurocholate than for the other probe substrate, E2-17β-glucuronide. The respective values for taurocholate and E2-17β-glucuronide (in the absence of the OATP uptake inhibitor bromsulfalein) are postulated to be in the range of historical values of the laboratory. The uptake of E2-17β-glucuronide in the presence of bromsulfalein is decreased to 35.6%.

The impact of transport probe inhibitors on the hepatic uptake of the endothelin receptor blockers is shown in Table 2:

Table 2. The Effect of Various Transport Probe Inhibitors on the Uptal (Intracellular Accumulation) of Ambrisentan, Darusentan, Bosentan and S in Sandwich-Cultured Human Hepatocytes (Mean ± Standard Deviation,

		Uptake (pmol/mg protein)		% Control	
		Mean	Std. Dev.	Mean	Std. Dev.
Ambrisentan	Control	37.2	21.8	100	-
	Ritonavir	22.7	5.52	70.5	25.0
	BSP	15.8	7.70	44.6	5.88
	Erythromycin	29.4	8.90	89.4	27.9
	Probenecid	22.5	5.45	69.9	24.1
Darusentan	Control	60.4	19.8	100	-
	Ritonavir	48.9	9.82	83.7	13.3
	BSP	51.0	12.3	92.1	21.6
	Erythromycin	53.3	9.44	106	21.4
	Probenecid	56.7	9.04	106	19.6
Bosentan	Control	325	134	100	-
	Ritonavir	153	31.1	55.1	31.2
	BSP	181	56.9	57.9	11.6
	Erythromycin	290	74.3	94.1	21.6
	Probenecid	90.3	12.5	32.0	16.1
Sitaxsentan	Control	1104	540	100	-
	Ritonavir	820	300	77.2	9.03
	BSP	820	334	76.0	10.1
	Erythromycin	846	151	86.4	31.1
	Probenecid	614	88.3	64.1	26.3

The extent of hepatic uptake of the 4 tested endothelin receptor antagonists increased in the order sitaxsentan, bosentan, darusentan and ambrisentan.

The impact of the probe inhibitors on the hepatic uptake of the 4 endothelin receptor antagonist's varied individually. Ritonavir appeared to inhibit the hepatic uptake of all 4 endothelin receptor blockers. Bromsulfalein and probenecid appeared to inhibit the uptake of ambrisentan, bosentan and sitaxsentan, whereas the impact on darusentan was not overt. Erythromycin appeared not to

interfer with the hepatic uptake of the endothelin receptor antagonists. Overall darusentan appeared to be least impacted by the presence of the uptake probe inhibitors.

The impact of transport probe inhibitors on the biliary excretion index is shown in Table 3:

Table 3. The Effect of Various Transport Probe Inhibitors on the Biliary Excretion Index (BEI) of Ambrisentan, Darusentan, Bosentan and Sitaxsentan in Sandwich-Cultured Human Hepatocytes (Mean ± Standard Deviation, n=3).

		BEI		% Control	
		Mean	Std. Dev.	Mean	Std. Dev.
Ambrisentan	Control	9.98	0.82	100	
	Ritonavir	8.59	5.33	84	48
	BSP	10.2	4.61	102	45
	Erythromycin	8.93	2.77	90	30
	Probenecid	30.5	8.70	303	72
Darusentan	Control	3.91	0.40	100	
	Ritonavir	14.1	9.0	370	220
	BSP	5.39	3.02	173	102
	Erythromycin	1.62	1.55	64	22
	Probenecid	28.1	6.36	830	193
Bosentan	Control	9.17	7.53	100	
	Ritonavir	13.8	1.63	251	221
	BSP	5.96	9.40	184	263
	Erythromycin	2.25	1.98	72.3	48.4
	Probenecid	39.4	15.6	688	836
Sitaxsentan	Control	0.69	0.76	100	
	Ritonavir	2.26	2.31	193.8	274
	BSP	0.00	0.00	0	0
	Erythromycin	4.38	2.65	301	21
	Probenecid	9.69	7.62	862	464

The results show significant variability limiting their interpretability. Among the 4 probe-inhibitors only probencid impacted BEI of ambrisentan (increase). Bromsulfalein and probenecid increased and erythromycin decreased the BEI of darusentan. A comparative evaluation of the effect of the 4 probe inhibitors on BEI of bosentan and sitaxsentan is hampered by the large variability of the data.

The impact of transport probe inhibitors on the biliary clearance is shown in Table 4:

Table 4. The Effect of Various Transport Probe Inhibitors on the Biliary Clearance ($Cl_{biliary}$) of Ambrisentan, Darusentan, Bosentan and Sitaxsentan in Sandwich-Cultured Human Hepatocytes (Mean ± Standard Deviation, n=3).

		Cl biliary (ml/min/Kg)		% Control	
		Mean	Std. Dev.	Mean	Std. Dev.
Ambrisentan	Control	1.90	0.30	100	
	Ritonavir	0.78	0.47	39.2	19.3
	BSP	0.66	0.16	34.5	3.89
	Erythromycin	1.11	0.26	60.8	23.2
	Probenecid	3.63	0.78	190	14.6
Darusentan	Control	1.10	0.08	100	
	Ritonavir	2.56	1.36	239	116
	BSP	1.27	0.94	120	98
	Erythromycin	0.32	0.28	30.3	26.5
	Probenecid	8.34	3.08	778	348
Bosentan	Control	8.05	6.12	100	
	Ritonavir	6.76	1.92	93.2	55.8
	BSP	4.36	7.14	106	176
	Erythromycin	1.99	1.84	34.8	47.5
	Probenecid	17.0	7.76	301	267
Sitaxsentan	Control	2.61	3.1	100	
	Ritonavir	5.38	5.56	160.5	227
	BSP	0.0	0.0	0	0
	Erythromycin	12.9	9.13	260	128
	Probenecid	17.6	10.4	448	19.7

All four endothelin-receptor blockers are excreted into bile to varying extents and the efficiency of this process as measured by biliary clearance varies also from compound to compound. Ritonavir, bromsulfalein and erythromycin decreased the biliary clearance of ambrisentan, whereas probenecid increased the biliary clearance of ambrisentan. Ritonavir increased and erythromycin decreased the biliary clearance of darusentan. Erythromycin appeared to increase and probenecid to decrease the biliary clearance of bosentan. Erythromycin and probenecid appeared both to increase the biliary clearance of sitaxsentan.

The role of NTCP on the uptake of the endothelin receptor blockers is shown in Table 5:

Table 5. The Role of NTCP on the Uptake of Ambrisentan, Darusentan, Bosentan and Sitaxsentan in Sandwich-Cultured Human Hepatocytes (Mean ± Standard Deviation, n=3).

		Average		Std. Dev.		Average Difference	Std. Dev.	Average % Difference	Std. Dev.
		Na	Chol	Na	Chol				
Ambrisentan	Na/Chol buffer	34.8	34.0	11.9	10.4	0.78	3.01	0.63	9.45
	Cyclosporin A	29.8	28.5	10.4	7.31	1.36	3.34	1.63	13.2
Darusentan	Na/Chol buffer	86.4	69.1	25.6	18.7	17.2	14.4	18.9	11.6
	Cyclosporin A	74.8	68.0	33.3	23.4	6.91	11.2	6.71	9.77
Bosentan	Na/Chol buffer	413	296	98.7	92.4	117	7.55	29.0	4.82
	Cyclosporin A	298	286	121	49.7	34.5	35.7	9.15	8.9
Sitaxsentan	Na/Chol buffer	1005	881	210	165	129	117	12.1	11.6
	Cyclosporin A	919	804	474	469	115	90.5	14.1	8.75

The results indicate that only bosentan and sitaxsentan are significantly taken-up by NTCP. However, only the uptake of bosentan is importantly impaired by cyclosporine A.

Conclusion

The paucity of information on the validation of the method and the variability of some of the data must be considered. It can be concluded that the four endothelin-receptor antagonists including ambrisentan are substrates of OATP. Bosentan and sitaxsentan may also be substrates of NTCP. All four endothelin receptor antagonist are excreted into bile and the extent and the efficiency of the process varies among the compounds. However, the data do not allow a definitive identification of the possibly involved biliary canalicular transporters for the endothelin-receptor antagonists.

Comments

1. Some of the results show significant variability which makes the interpretability of the findings difficult.

2. A rationale for the selected concentrations of the transport inhibitors was not provided

3. The criteria for determining the viability of the hepatocytes and the functionality/expression of the different transporters used should be stated.

4. The report should indicate whether the metabolic capacity of the cultured hepatocytes is maintained and controlled.

5. The biliary clearance is normalized for body weight. The body weight of the donors was not indicated in the report.

Study Report: EE-001 "A Randomized, Double-Blind, Placebo Controlled, Single Ascending Dose Trial to Investigate the Tolerability, Pharmacodynamics, Pharmacokinetics and Possible Food Effect of the Endothelin Receptor Antagonist BSF 20875 in Healthy Male Volunteers"

Study Site and Investigator: [redacted]

Objectives

Primary

To investigate safety and tolerability of single ascending doses of BSF 208075 in healthy young subjects

Secondary

To evaluate the PD effect of BSF 208075 on cardiovascular parameters
To screen for potential effects of BSF 208075 on endogenous endothelin-1 plasma concentrations
To assess the single dose PK of 208075 in plasma and urine
To obtain information on the relationship between BSF 208075 dose and PD response
To assess a possible food effect on the PK and PD of BSF 208075

Formulations

1 mg BSF 208075 tablets (Batch No. L0003021,P270/2), 5 mg BSF 208075 tablets (Batch No. L0003020,P2771/2), 10 mg BSF 208075 tablets (Batch No. L0003024,P272/2), 100 mg 2BSF 08075 tablets (Batch No. L0003023,P262/5), matching 5 and 10 mg Placebo tablets (Batch No. L0003022,P269/2)

Design

The subjects to be enrolled in the study were healthy males in the age between 18 and 50 years. A placebo controlled parallel group single ascending dose design was used. A food interaction arm, carried out according to a placebo-controlled, single dose repeated measurement design with a washout of at least 5 days, was to be included at the 50 mg dose level. Ascending dose levels of 1 mg, 5 mg, 10 mg, 20 mg, 50 mg, 100 mg, 200 mg and 300 mg were to be administered in the fasted state together with 240 mL of water. The subjects of the 50 mg group were to be treated first in the fasted and then in the fed state (high fat content breakfast). At each dose level 7 subjects received the drug and 2 subjects were administered placebo as shown in the below diagram:

Table 1 Experimental plan

	Part of the study								
	1	2	3	4	5	6	7	8	9
BSF 208075 dose [mg]	1	5	10	20	50	100	60[a]	200	300
N_{BSF}	7	7	7	7	7	7	7	7	7
$N_{placebo}$	2	2	2	2	2	2	2	2	2

[a] To be administered under fed conditions to the subject group participating in Part 5

The study activities are shown in the below flow chart:

Table 2 Study flow chart

Day time	Regulations	Blood pressure, ECG, pulse	Vital signs	Cardiac impedance	Adverse events (investigators' rating)	Blood sampling	Urine collection
Day -1 20:00	Start of in-house period						
Day 1 06:30	Get up						X (blank urine sample)
08:00	Administration of study medication	X	X			X_1 X_2 X_3 X_4	
08:30		X				X_1	
09:00		X				X_1	
09:30						X_1	
10:00		X	X	X		X_1 X_2 X_4	
10:30	Breakfast*						
11:00						X_1	0–12 h period
12:00		X	X			X_1	
13:00						X_1 X_4	
14:00	Lunch	X	X			X_1	
16:00		X				X_1	
18:00		X				X_2	
19:00	Dinner						
20:00		X	X			X_1	
24:00						X_1	12–24 h period
Day 2 08:00		X	X			X_1 X_2 X_3 X_4	
20:00	End of in-house period					X_1	24–48 h period
Day 3 08:00	End of study			X		X_1 X_3 X_4	

* prior to BSF 208075 administration under fed conditions (50 mg group), a standardized high-fat breakfast was to be served at around 07:30 am (meal composition is described in Appendix A6 to the protocol)

X_1: blood sampling for determination of BSF 208075 concentrations

X_2: blood sampling for determination of endothelin concentrations

X_3: blood sampling for determination of hematology and clinical chemistry parameters

X_4: blood sampling for determination of coagulation parameters

Pharmacokinetic Profiling

Blood samples for the determination of BSF 208075 were collected pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h after drug administration. Total volumes of urine for the determination of BSF 208075 were collected during the intervals from 0-12 h, 12-24 h and 24 to 48 h after drug administration.

Bioassay

The plasma and urine concentrations of BSF 208075 were to be measured by [redacted] using a validated HPLC-MS/MS method with [redacted] in plasma and urine of [redacted] respectively..

PK Data Analysis

The parameters Cmax, tmax, AUC0-t, λz, t1/2, AUC0-00, CLR and Ae and Ae0-48 were to be determined using compartment model independent methods. CLR was to be obtained from Ae0-48/AUC.
Dose linearity was determined by performing least square linear regressions of log transformed Cmax and AUC vs log transformed doses. The slope of the regression lines was to be tested for a significant difference from 1.

The effect of food on the PK of BSF 208075 was to be examined with Cmax and AUC using an analysis of variance with subject and condition effects (fasting or fed). Point estimates and 90% CI were also computed.

PD Profiling

Blood pressure, pulse rate, ECG and stroke volume, cardiac output, ejection time and pre-ejection period (derived from cardiac impedance and ECG measurements) were recorded at defined time points. Blood samples for the determination of the plasma concentrations of endothelin-1 were collected at the following times: Predose, 2, 10 and 24 h post administration.

Bioassay for Endothelin-1

The assay method used a solid extraction and measured endothelin-1 by enzyme immunoassay [redacted] performed the assay.

Results

A total of 63 instead of the planned 72 male subjects were enrolled in the study. At the 100 mg dose level adverse events occurred in 2 subjects and the remainder 5 subjects of the group were not administered 100 mg BSF 208075. No subject received the 200 mg and 300 mg dose levels. One subject was withdrawn after receiving the 50 mg dose in the fasted state. The subject experienced multiple adverse events including flush, shivering, headache, vertigo, nausea, and vomiting. This subject was replaced. The untreated subjects from the 100 mg, 200 mg and 300 mg dose groups were reassigned to receive doses of 15 mg or 20 mg of BSF 208075.

Linear plots of the plasma concentration profiles of BSF 208075 are shown in Figure 2:

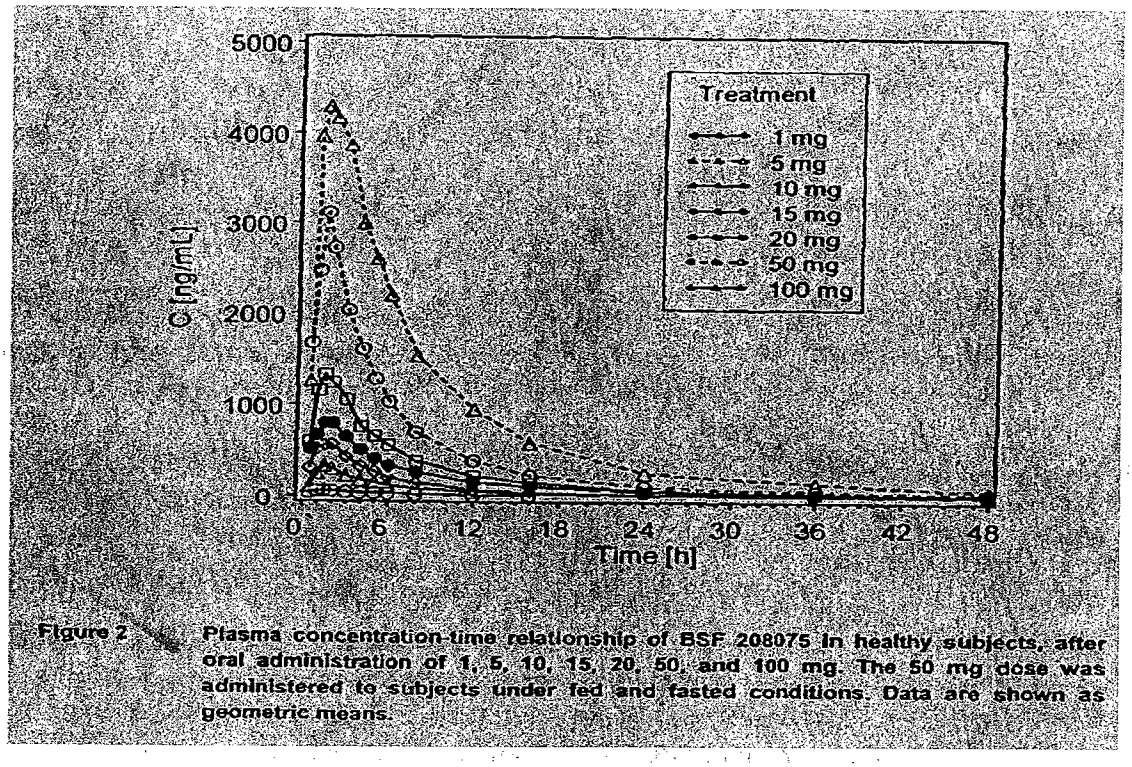

Figure 2 Plasma concentration-time relationship of BSF 208075 in healthy subjects, after oral administration of 1, 5, 10, 15, 20, 50, and 100 mg. The 50 mg dose was administered to subjects under fed and fasted conditions. Data are shown as geometric means.

The PK parameters of BSF 208075 are listed in Table 4:

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Table 4 Pharmacokinetic parameters of BSF 208075, given as geometric means and geometric standard deviations (t_{max} is given as median and minimum-maximum range)

Parameter [unit]	Treatment (number of subjects)							
	1 mg (N = 7)	5 mg (N = 7)	10 mg (N = 7)	15 mg (N = 5)	20 mg (N = 14)	50 mg (N = 8)	50 mg, fed (N = 7)	100 mg (N = 2)
C_{max} [ng/ml] (geom. SD)	56.96 (1.22)	344.94 (1.24)	669.82 (1.18)	904.60 (1.49)	1402.31 (1.20)	3229.84 (1.19)	2803.70 (1.46)	4520.69 (1.33)
t_{max} [h], median (range)	1.0 (1.0–2.0)	1.5 (1.5–2.0)	1.0 (1.0–3.0)	1.5 (1.0–2.0)	1.5 (0.5–3.0)	1.5 (1.0–2.0)	1.5 (1.5–2.0)	2.0 (1.0–3.0)
AUC_{24} [ng·h/ml] (geom. SD)	335.85 (1.15)	2037.30 (1.36)	3815.59 (1.26)	6523.94 (1.45)	9720.18 (1.23)	19223.07 (1.35)	20336.64 (1.03)	37144.90 (1.29)
AUC [ng·h/ml] (geom. SD)	382.60 (1.16)	2137.28 (1.41)	3692.88 (1.27)	6741.12 (1.45)	10055.70 (1.24)	19856.70 (1.36)	21081.31 (1.02)	38065.65 (1.31)
λ_z [1/h] (geom. SD)	0.12 (1.23)	0.08 (1.72)	0.07 (1.50)	0.06 (1.20)	0.06 (1.31)	0.05 (1.32)	0.05 (1.01)	0.06 (1.35)
$t_{1/2}$ [h] (geom. SD)	5.75 (1.23)	8.66 (1.72)	9.41 (1.50)	12.02 (1.20)	11.11 (1.31)	12.71 (1.32)	13.40 (1.01)	10.68 (1.35)
A_e [µg] (geom. SD)	n.d. (n.d.)	95.94 (1.40)	181.80 (1.37)	317.85 (1.91)	554.30 (1.58)	1172.96 (1.69)	1018.65 (1.15)	2363.15 (1.71)
A_e [% dose] (geom. SD)	n.d. (n.d.)	1.92 (1.40)	1.82 (1.37)	2.12 (1.91)	2.77 (1.58)	2.35 (1.69)	2.04 (1.15)	2.36 (1.71)
CL_R [L/h] (geom. SD)	n.d. (n.d.)	0.04 (1.15)	0.05 (1.43)	0.05 (1.38)	0.06 (1.51)	0.06 (1.41)	0.05 (1.13)	0.06 (1.74)

n.d.: not determined
Data source: Table 9.2.1

The data indicate that the PK of BSF 208075 in the range between 5 mg and 100 mg are dose proportional. This is also confirmed by the regressions of Cmax and AUC on dose shown in Figure 4:

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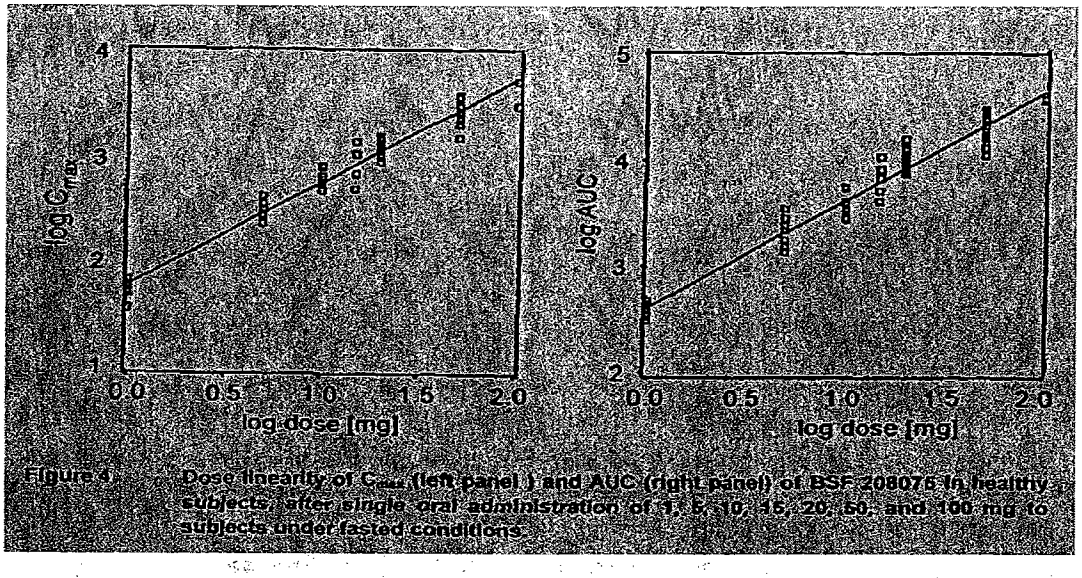

Figure 4 Dose linearity of C_{max} (left panel) and AUC (right panel) of BSF 208075 in healthy subjects after single oral administration of 1, 5, 10, 15, 20, 50, and 100 mg to subjects under fasted conditions.

The median tmax ranges between 1.0 h and 2.0 h indicating rapid absorption. The terminal disposition half life of BSF 208075 is about 11 h. The recovery of the drug in urine is about 2% indicating that BSF 208075 is mainly eliminated by non-renal routes. The renal clearance is about 1 mL/min suggesting high plasma protein binding and/or intensive tubular re-absorption.

The impact of food on the plasma concentration profile of BSF 208075 is shown in Figure 3:

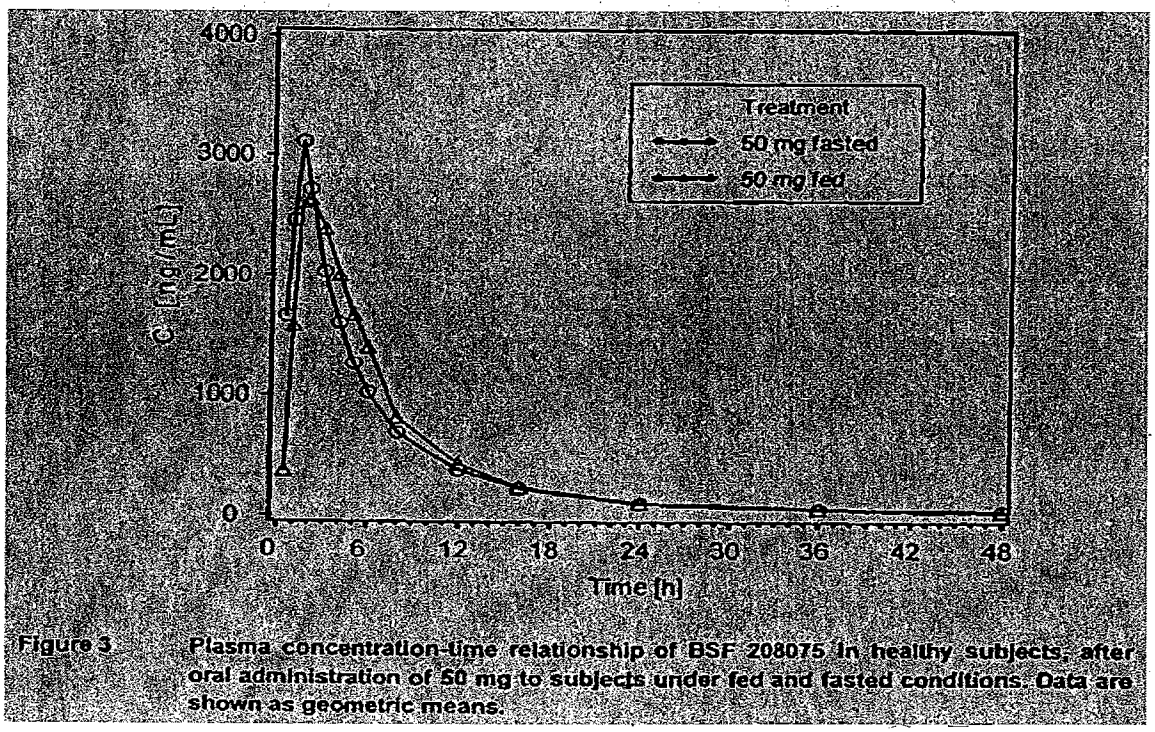

Figure 3 Plasma concentration-time relationship of BSF 208075 in healthy subjects after oral administration of 50 mg to subjects under fed and fasted conditions. Data are shown as geometric means.

The impact of food on the respective ratios of Cmax and AUC in the fed to the fasted state is listed in Table 7:

Table 7 C_{max} and AUC values after 50 mg BSF 208075 under fasted and fed conditions, and their fed/fasted ratios

Parameter	Subject	Fasted	Fed	Ratio (Fed/Fasted)
C_{max}	37			1.11
	38			M.v.
	39			0.90
	40			0.94
	42			0.74
	43			0.76
	45			0.74
	138			1.04
AUC	37			1.43
	38			M.v.
	39			1.08
	40			1.16
	42			0.85
	43			1.11
	45			1.17
	138			0.94

M.v. = missing value (due to withdrawal of Subject 38 following adverse events in the fasted state)

Data source: Table 10 in Appendix 2.5.3

Food appears to impact the disposition of BSF 208075 only marginally: Cmax is slightly decreased and AUC slightly increased in the fed state.

Placebo subtracted median endothelin-1 plasma (pg/mL) concentrations in the subjects in the fasted state after administration of ambrisentan in single doses of 1 mg to 100 mg are listed in the table below (calculated by Reviewer):

Dose, mg	Baseline	2 h	10 h	24 h
1	0.30	1.20	0.50	-0.40
5	0.10	1.60	0.30	0.80
10	- 0.10	1.10	0.50	0.30
15	0	1.60	0.70	0.20
20	0.05	2.25	1.05	0.55
50	0.15	4.65	1.75	1.50
100	-0.95	4.65	3.45	0

The data show that the administration of BSF 208075 increases the endothelin-1 concentrations in dose dependent manner. Significant increases are observed at 2 h after administration, the only time point considered in the early phase after administration. At the higher dose levels some

effect appears to be present at 10 h post-dose. At 24 h the levels approach the pre-dose concentrations.

There was no consistent effect of BSF-108075 on blood pressure, heart rate and the other cardiovascular parameters.

Tolerability

Headache was the predominant type among the severe adverse events and the incidence increased with increasing dose above 15 mg as shown in Table 12:

Table 12 Summary of severe adverse events (N = 13)

Adverse event, preferred term	Treatment	Serious adverse event	Subject(s) afflicted (all mentions)
Nausea	20mg	No	56
Headache	20mg	No	60
Headache nos*	50mg	No	38, 38, 38
Vertigo	50mg	No	38
Dizziness	50mg	No	38
Headache nos*	50mg (fed)	No	39
Headache	100mg	No	46, 46, 48, 48
Nasal congestion	100mg	No	46

* nos = not otherwise specified

Elevations of SGPT and SGOT were found in 4 subjects receiving placebo and 5 subjects receiving BSF 208075 as shown in the below table:

Appears This Way
On Original

Subject No	Treatment	Description of event	Pre-dose values	Maximum intensity	Relation-ship
13	Placebo	Elevated SGOT [a] 27.3 U/L (48 h).	17.2 U/L	Moderate	Possible
13	Placebo	Elevated SGPT [b] 34.2 U/L (0 h) 39.2 U/L (24 h). 57.0 U/L (48 h)	34.2 U/L	Moderate	Possible
41	Placebo	Elevated SGPT. 31.4 U/L (0 h) 29.0 U/L (24 h). 34.0 U/L (48 h)	31.4 U/L	Moderate	Possible
41	Placebo, fed	Elevated SGPT. 28.9 U/L (0 h). 27.2 U/L (24 h). 27.7 U/L (48 h)	28.9 U/L	Mild	Possible
64	Placebo	Elevated SGPT. 25.9 U/L (48 h)	21.2 U/L	Mild	Possible
12	5 mg	Elevated SGPT. 43.2 U/L (0 h). 37.6 U/L (24 h). 32.3 U/L (48 h)	43.2 U/L	Moderate	Possible
19	10 mg	Elevated SGPT. 28.2 U/L (0 h). 25.5 U/L (24 h). 24.2 U/L (48 h)	28.2 U/L	Mild	Possible
35	20 mg	Elevated SGOT. 23.2 U/L (24 h)	15.6 U/L	Mild	Possible
35	20 mg	Elevated SGPT. 29.0 U/L (24 h). 30.2 U/L (48 h)	11.4 U/L	Moderate	Possible
38	50 mg	Elevated SGPT. 49.6 U/L (0 h). 53.6 U/L (24 h). 56.5 U/L (48 h)	49.6 U/L	Moderate	Possible

[a] SGOT: normal range 0-20 U/L
[b] SGPT: normal range 0-24 U/L

The elevated LFT values were < 2 •ULN and returned spontaneously within the normal range.

Conclusions

The PK of BSF 802075 after administration of doses ranging between 1 mg and 100 mg BSF 208075 are dose proportional. The drug is readily absorbed with a mean tmax of between 1.0 h and 2.0 h and eliminated with a terminal disposition t1/2 of about 11 h. The elimination from the body is mainly by non-renal routes. Renal recovery of the unchanged drug and renal clearance are small. Food has a small impact on drug exposure.
Pharmacological activity of BSF-208075 is demonstrated by dose dependent elevations of the plasma concentrations of endothelin-1 2 h post-dose. At dose levels in excess of 10 mg significant elevations of endothelin last until 10 h post-dose.
The maximum dose level tested was 100 mg. The sponsor did not state what they consider the maximum tolerated dose and the dose limiting toxicity. The tolerability limiting adverse event appears to be headache. The incidence of headache increased with doses in excess of 15 mg.

Comments