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Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BI 685509, a Soluble Guanylate Cyclase Activator, in Healthy Chinese and Japanese Males: a Randomised, Single-Blind, Placebo-Controlled Multiple Rising Dose Trial

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Objectives : BI 685509 is a novel, potent, soluble guanylate cyclase activator in development for diabetic nephropathy. This trial investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 685509 in healthy Chinese and Japanese males following administration of multiple rising doses (MRDs).
Methods : This was a randomised, placebo-controlled, single-blind, Phase I trial. Healthy Chinese or Japanese males aged 20–45 years were randomised 3:1 within each ethnicity to one of three BI 685509 dose groups (DGs; DG1, daily dose 0.5/1.0 mg; DG2, 2.5/5.0 mg; DG3, 1.0/3.0/6.0/9.0 mg) or placebo. Treatment was administered orally for 15 days: a single dose on Day 1 followed by multiple doses on Days 4–17. The primary endpoint was the number of participants with of treatment-emergent adverse events (TEAEs). Secondary endpoints were pharmacokinetic parameters: AUC_{0-24}, C_{max}, $AUC_{\tau,steady\ state\ (SS)}$, $C_{max,SS}$.
Results : In total, 72 participants received trial medication across all DGs (n=36, Chinese; n=36, Japanese). Baseline characteristics were generally similar between ethnicities. Overall, 70.8% of participants had a TEAE (BI 685509, 38/54 [70.4%]; placebo, 13/18 [72.2%]). The most common TEAE across ethnicities and treatment groups was orthostatic hypotension (Tables 1 and 2). There were no TEAEs leading to discontinuation of trial medication, severe AEs, protocol-specified AEs of special interest, serious AEs or deaths. Investigator-defined treatment-related AEs (TRAEs) occurred in 21/27 (77.8%) Chinese participants and 15/27 (55.6%) Japanese participants. All TRAEs were mild and resolved by the end of the trial. BI 685509 exposure (AUC and C_{max}) increased in a dose-proportional manner. BI 685509 plasma concentrations reached SS during the multiple dosing periods. No dose-dependent effect on plasma and urine cGMP levels was observed. These results were consistent across both ethnicities.
Conclusions : MRDs of BI 685509 were well tolerated in healthy Chinese and Japanese males. These results support further clinical investigation of BI 685509.

Table 1_AEs in Chinese Subjects.png

System organ class/ Preferred term	Placebo	BI 685509			
		Dose group 1	Dose group 2	Dose group 3	Total on BI Treatment
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	9 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	27 (100.0)
Total with AEs	8 (88.9)	6 (66.7)	8 (88.9)	8 (88.9)	22 (81.5)
Vascular disorders	5 (55.6)	3 (33.3)	6 (66.7)	7 (77.8)	16 (59.3)
Orthostatic hypotension	5 (55.6)	2 (22.2)	6 (66.7)	7 (77.8)	15 (55.6)
Hypotension	0	1 (11.1)	0	0	1 (3.7)
Nervous system disorders	4 (44.4)	2 (22.2)	3 (33.3)	5 (55.6)	10 (37.0)
Dizziness	3 (33.3)	2 (22.2)	2 (22.2)	4 (44.4)	8 (29.6)
Headache	1 (11.1)	0	1 (11.1)	1 (11.1)	2 (7.4)
Syncope	0	0	0	1 (11.1)	1 (3.7)
Respiratory, thoracic and mediastinal disorders	1 (11.1)	2 (22.2)	2 (22.2)	2 (22.2)	6 (22.2)
Cough	0	1 (11.1)	0	2 (22.2)	3 (11.1)
Nasal congestion	1 (11.1)	2 (22.2)	0	0	2 (7.4)
Rhinorrhoea	0	1 (11.1)	2 (22.2)	1 (11.1)	4 (14.8)
Gastrointestinal disorders	1 (11.1)	2 (22.2)	1 (11.1)	2 (22.2)	5 (18.5)
Diarrhoea	0	2 (22.2)	0	0	2 (7.4)
Constipation	1 (11.1)	1 (11.1)	0	0	1 (3.7)
Gingival hypertrophy	0	0	0	1 (11.1)	1 (3.7)
Nausea	0	0	1 (11.1)	1 (11.1)	2 (7.4)
Cardiac disorders	0	0	2 (22.2)	1 (11.1)	3 (11.1)
Palpitations	0	0	2 (22.2)	1 (11.1)	3 (11.1)
Eye disorders	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	3 (11.1)
Eye pruritus	0	1 (11.1)	0	0	1 (3.7)
Eyelid oedema	0	1 (11.1)	0	0	1 (3.7)
Conjunctival hyperaemia	1 (11.1)	0	0	0	0
Eye irritation	1 (11.1)	0	0	0	0
Vision blurred	0	0	0	1 (11.1)	1 (3.7)
Visual impairment	0	0	1 (11.1)	0	1 (3.7)
Skin and subcutaneous tissue disorders	2 (22.2)	2 (22.2)	0	1 (11.1)	3 (11.1)
Pruritus	1 (11.1)	2 (22.2)	0	0	2 (7.4)
Alopecia	1 (11.1)	0	0	0	0
Cold sweat	0	0	0	1 (11.1)	1 (3.7)
Erythema	1 (11.1)	0	0	0	0
General disorders and administration site conditions	0	0	1 (11.1)	0	1 (3.7)
Chest discomfort	0	0	1 (11.1)	0	1 (3.7)

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Number of subjects	9 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	27 (100.0)
Total with AEs	5 (55.6)	3 (33.3)	9 (100.0)	4 (44.4)	16 (59.3)
Vascular disorders	3 (33.3)	3 (33.3)	9 (100.0)	4 (44.4)	16 (59.3)
Orthostatic hypotension	3 (33.3)	3 (33.3)	9 (100.0)	4 (44.4)	16 (59.3)
Gastrointestinal disorders	1 (11.1)	0	0	0	0
Diarrhoea	1 (11.1)	0	0	0	0
Infections and infestations	1 (11.1)	0	1 (11.1)	0	1 (3.7)
Influenza	0	0	1 (11.1)	0	1 (3.7)
Nasopharyngitis	1 (11.1)	0	0	0	0
Metabolism and nutrition disorders	1 (11.1)	0	0	0	0
Hyperamylasaemia	1 (11.1)	0	0	0	0
Skin and subcutaneous tissue disorders	1 (11.1)	0	0	0	0
Hyperhidrosis	1 (11.1)	0	0	0	0