Properties	High	Intermediate 1	Intermediate 2	Low
Bioavailability (%) ±SD (CV%)	103±4 (4.4%)	57.1±12.2 (22.2%)	32±10 (30%)	15.5±4 (25.8%)
Plasma Clearance (L/h)	0.16	3.8	34-57	67
Renal clearance (L/h)	0.03	0.11	5.4	12
Distribution volume (L)	9	27	152-344	19.7
Blood to plasma ratio	0.7	0.62	0.93	1
MW (g/mol)	408.5	366.4	434.5	446.5
Solubility	Ranged from 0.02 mg/ml at pH 2.5 to 86 mg/ml at pH 7.2.	Solubility in water (pH=8), FaSSIF (pH=6.5), SGF (pH=1.7) and human intestinal fluids (pH=6.9), are 0.003, 0.006, 3.05 and 0.005 mg/mL respectively. Salt solubility in water is approx. 35 mg/mL.	3.1, 3.1 and 0.56 mg/mL at pH 9, 7 and 5, respectively	0.2, 9 and 50 mg/mL in water (pH=9.8), phosphate buffer (pH= 7.7) and 0.1M HCl (pH=7.2) respectively.
PKa	3.7 (Acid)	6.1 (Weak base)	9.9 (Base)	2.6, 9.7 (Base)
Partition Coefficient - log K_D	2.8	4.2	2.5	3

Table I: Compounds physicochemical properties and pharmacokinetic parameters based on non-compartmental analysis.

	Intravenous IV infusion	**Oral solution**	**Solid dosage form**
High	8 (1 mg)	9 (1 mg)	n/a
Age (years) Weight (kg)	42(30-50) 85(72-98)		
Intermediate 1	9 (20 mg)	58 (0.08-4 mg/kg)	14 (micronised base tablet) 65(mesylate salt tablet) 14 (micronised base tablet at elevated gastric Ph)
Age (years) Weight (kg)	25(20-50) 76.7(64-95)		14 (mesylate salt tablet at elevated gastric pH) (100 mg)
Intermediate 2	10 (70mg)	41 (fed and fasted) (10 - 500 mg)	32 (prolonged release tablet-fed and fasted) (125 mg)
Age (years) Weight (kg)	40(28-53) 79(66-93)		
Low	10 (100mg)	40 (50 – 600 mg)	96 prolonged-release tablet (250 mg)
Age (years) Weight (kg)	23(20-51) 71(51-90)		

Table II: The number of subjects (administered doses) used in the analysis of the clinical studies. Median age and mean weight (range) of the healthy male subjects for each compound are presented.

	Model Parameter	High	Intermediate 1	Intermediate 2	Low
Typical values (θ) (% RSE)	Intrinsic CL (L/h)	0.16 (10%)	3.99 (7%)	55.7 (9%)	282 (41%)
	Volume (L)	4.09 (9%)	8.59 (10%)	45.3 (26%)	19.7 (27%)
	Q1(L/h)	0.43 (36%)	28.9 (18%)	9.89 (26%)	132 (14%)
	V1 (L)	5.09 (13%)	9.35 (10%)	99.9 (11%)	123 (9%)
	Q2(L/h)	0.54 (25%)	0.43 (18%)	204 (11%)	19.3 (7%)
	V2 (L)	1.54 (27%)	9.65 (35%)	128 (5%)	236 (5%)
Inter-individual variability (Ω) (% RSE)	Intrinsic CL (L/h)	26.2% (27%)	21.4% (24%)	29.3% (24%)	102% (41%)
	Volume (L)	21.4% (22%)	27.3% (27%)	77.7% (33%)	56.4% (19%)
	Q1(L/h)	13.4% (33%)	37.7% (39%)	54.9% (33%)	37.7% (22%)
	V1 (L)	8.9% (25%)	26.2% (29%)	25% (33%)	22.3% (25%)
	Q2(L/h)	29.4% (26%)	45.1% (23%)	11% (55%)	0 FIXED
	V2 (L)	42.3% (6%)	71.1% (16%)	0 FIXED	0 FIXED
Residual error (Σ) (% RSE)	Variance	0.002 (24%)	0.006 (8%)	0.022 (6%)	0.018 (8%)
	Additive	0	105 (18%)	0	0

Table III: Disposition parameters of the final structural model. (Clint- intrinsic clearance Q1 – clearance of peripheral compartment; Q2– clearance of peripheral compartment 2; V1- volume of peripheral compartment 1; V2- volume of peripheral compartment 2)

Compound	Formulation	fa*fg (%)	CV (%) Based on simulations
High	Oral solution	99%	9%
Intermediate 1	Oral solution	61%	15%
Normal gastric pH	IR tablet in the base form	58%	14%
	IR tablet in the salt form	73%	13%
Elevated gastric pH	IR tablet in the base form	16%	38%
	IR tablet in the salt form	28%	25%
Intermediate 2	Oral solution fasted state	60%	33%
	Oral solution fed state	77%	28%
	PR fasted state	71%	30%
	PR fed state	71%	27%
Low	Oral solution	33%	39%
	PR tablet	57%	15%

Table IV: fa*fg estimations (%) and inter-subject variability based on simulations (CV%)