

# Pharmacokinetics of THB001, an orally available, potent and highly selective small molecule inhibitor of wild type KIT receptor tyrosine kinase, in healthy volunteers

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## BACKGROUND

THB001 is a highly selective KIT inhibitor that depletes mast cells in tissues and therefore potentially effective in mast cell driven diseases. The PK features of THB001, both after dosing of a free base or as a HCl salt are presented.

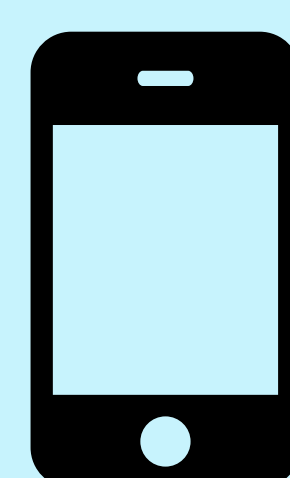
## METHODS

- ▶ Three Phase 1 studies in healthy volunteers
  - ♦ Single and multiple ascending dose study (study 1) with single doses of 10-600 mg and multiple doses of 200 and 500 mg QD and 200 and 400 mg BID
  - ♦ Bio-comparison and food effect study (study 2) with single doses of 200/400 mg (free base and HCl salt)
  - ♦ Drug interaction study (study 3) with 10 days of 400 mg QD with and without single doses of caffeine, omeprazole and midazolam

## RESULTS and CONCLUSIONS:

- ▶ At single doses of 10-600 mg: exposure increased approx. dose proportionally. The half-life in this study ranged from approx. 16-26h and at single doses in study 2, the half-life ranged from approx. 15-20h
- ▶ Upon BID dosing for 14 days, accumulation was 3 to 7 fold, whereas at QD dosing, there was no accumulation
- ▶ HCL salt resulted in higher  $C_{max}$  and AUC as compared to free base and food further increased the  $C_{max}$  and AUC following the HCL dosing
- ▶ Multiple doses of THB001 slightly induced CYP1A2 activity but not CYP3A4 and CYP2C19 activities
- ▶ PK features of THB001 justify the start of Phase 2 studies
- ▶ In all studies, THB001 was safe and well tolerated

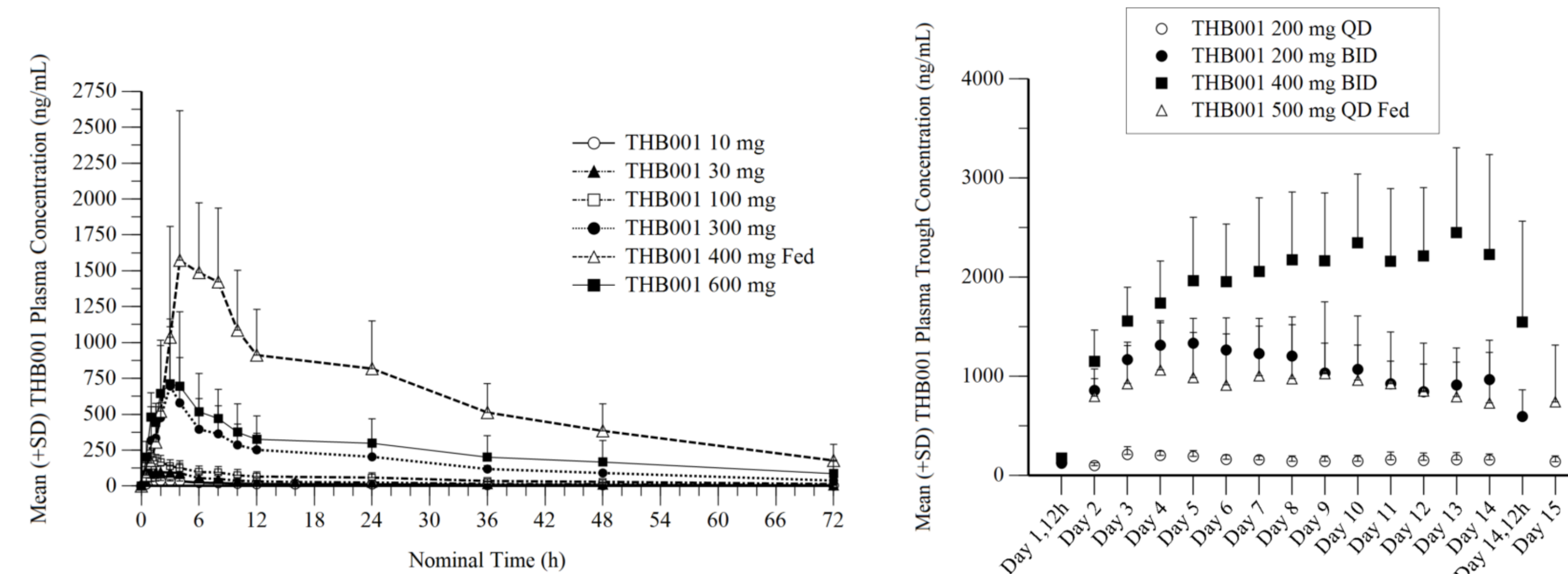
# Favorable pharmacokinetic and CYP450 inducing properties of orally dosed free base or HCl salt of THB001 in healthy volunteers



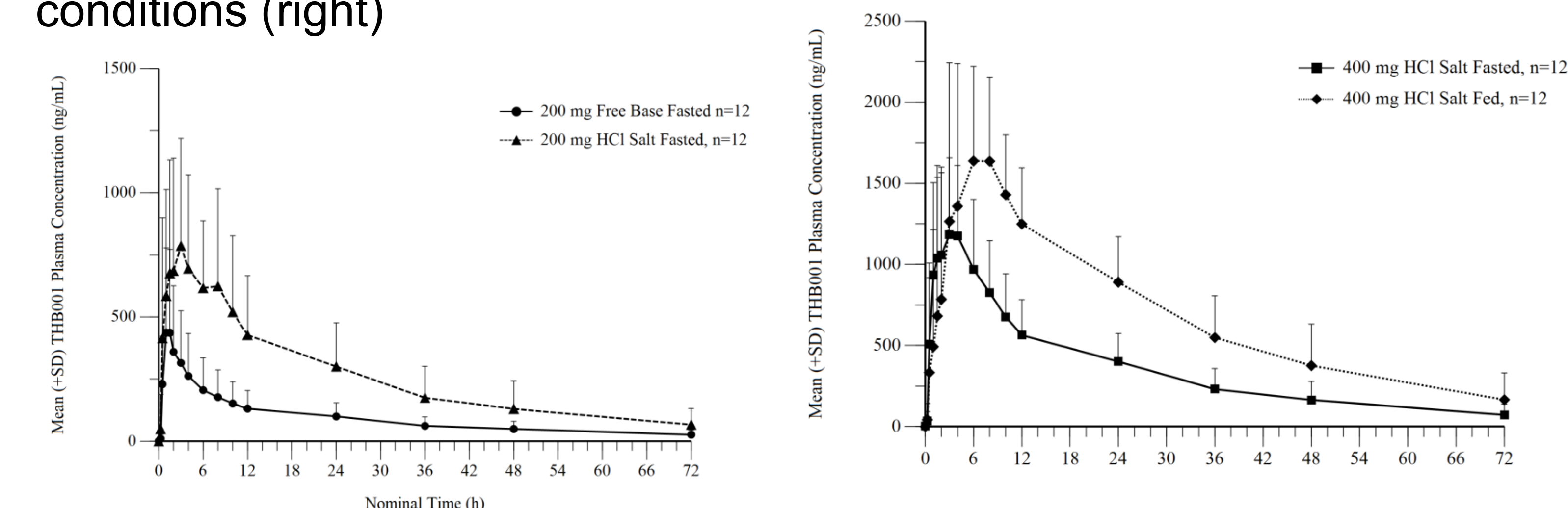
Scan the QR code to view the video



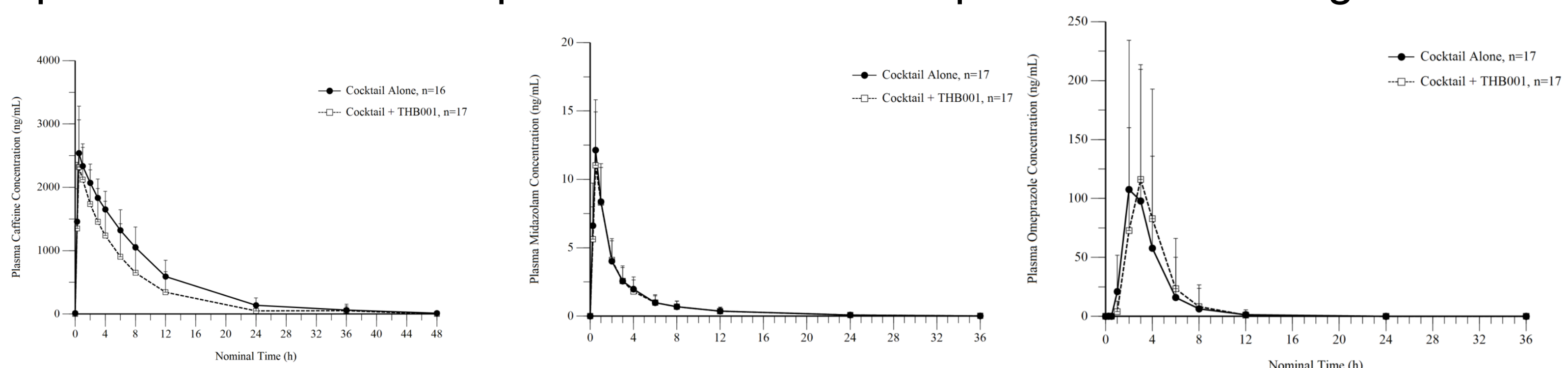
Arithmetic mean THB001 plasma concentrations after single doses (left) and as trough concentrations after multiple doses (right), in both studies as free base



Arithmetic mean THB001 plasma concentrations after single doses of the free base and HCl salt (left) and the HCl salt under fed and fasted conditions (right)



Arithmetic mean caffeine (left), midazolam (middle) and omeprazole (right) plasma concentration prior to and after multiple THB001 dosings



Summary of PK parameters of THB001

	$C_{max}$ (ng/mL)	$AUC_{0-24}$ (h*ng/mL)	$AUC_{0-12}$ (h*ng/mL)	$T_{1/2}$ (h)	Accumulation	Ratio (%)
	$C_{max}$	$AUC_{0-12}$	$C_{max}$	$AUC_{0-12}$		
<b>Study 1, all free base</b>						
10 mg SD (n=6)	53.2 (23.5)	433 (29.9)	743 (42.3)	25.6 (20.1)		
100 mg SD (n=5)	219 (19.1)	1930 (36.2)	3290 (36.8)	23.4 (20.5)		
300 mg SD (n=4)	728 (50.4)	6820 (46.9)	11500 (32.6)	19.3 (32.3)		
600 mg SD (n=5)	788 (53.2)	8760 (48.0)	15500 (60.1)	16.3 (81.2)		
200 mg QD, Day 1 (n=6)	361 (34.4)	3150 (27.4)				
200 mg QD, Day 14 (n=6)	472 (22.3)	4870 (39.6)	8010 (50.4)	22.4 (30.9)	1.31	1.54
200 mg BID, Day 1 (n=6)	362 (43.2)	2050 (51.6) <sup>1</sup>				
200 mg BID, Day 14 (n=6)	1180 (34.8)	9580 (48.0) <sup>1</sup>	22800 (65.0)	16.2 (24.5)	3.26	4.68
400 mg BID, Day 1 (n=6)	628 (34.7)	3150 (23.0) <sup>1</sup>				
400 mg BID, Day 14 (n=5)	2470 (34.4)	23000 (42.4) <sup>1</sup>	62900 (108.3)	11.5 (24.3)	4.14	7.11
<b>Study 2</b>						
200 mg SD free base (n=12)	402 (90.7)	3470 (65.7)	5670 (63.8)	19.4 (44.4)		
200 mg SD HCl (n=12)	887 (74.3)	9890 (72.4)	15600 (70.3)	16.6 (42.2)		221 285
400 mg SD HCl, fasted (n=12)	1300 (52.1)	15100 (43.1)	23100 (42.5)	16.7 (51.8)		
400 mg SD HCl, fed (n=12)	1960 (32.0)	26800 (31.5)	4500 (38.1)	15.0 (43.7)		150 178

<sup>1</sup>  $AUC_{0-12}$ . Values are presented as geometric mean and geometric CV%