The First-in-Human Clinical Trial of STP0404, a Novel Potent HIV-1 Allosteric Integrase Inhibitor

X. Meng[1], U.-I. Kim[1], Y. Donazzolo[2], B. Kim[3,4], K. Kim[1]

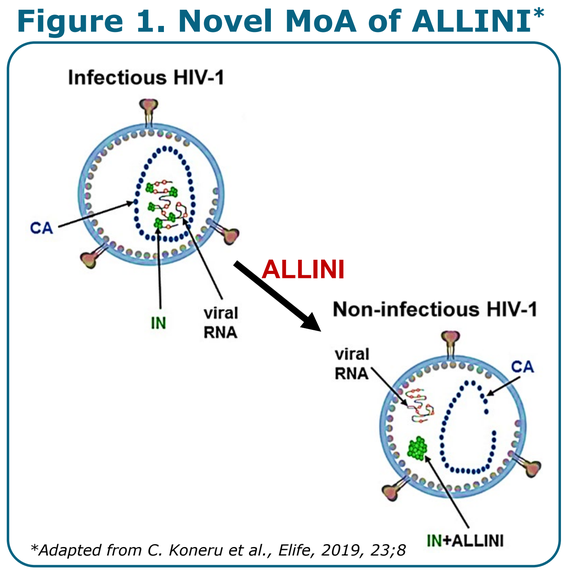
[1]ST Pharm Co., Ltd., Seoul, Korea, The Republic of; [2]Eurofins Optimed S.A.S, Grenoble, France;
[3]Emory University, School of Medicine, Department of Pediatrics, Atlanta, United States; [4]Children's Healthcare of Atlanta, Center for Drug Discovery, Atlanta, United States

BACKGROUND

STP0404 is a first-in-class HIV-1 allosteric integrase inhibitor (ALLINI) with a novel mechanism of action[1] (MoA, **Figure 1**). It binds to the LEDGF/p75 binding site of integrase (IN) and inhibits viral maturation.

STP0404 has shown potent *in vitro* anti-HIV-1 activities, an *in vitro* resistance profile different from those of other catalytic-site integrase inhibitors (CINIs), and favorable nonclinical safety and pharmacokinetics (PK) profiles[2].

Figure 1. Novel MoA of ALLINI*

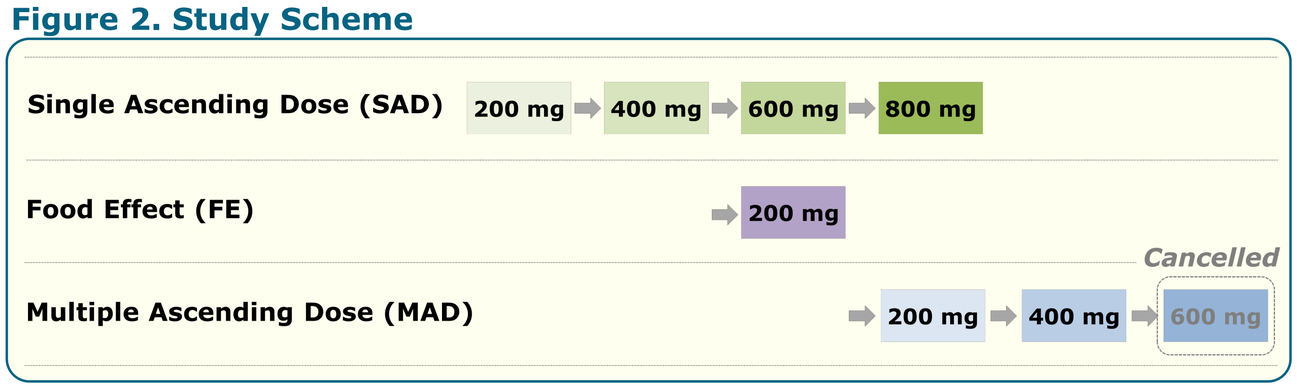


*Adapted from C. Koneru et al., Elife, 2019, 23;8

METHODS

The safety and PK of STP0404 was evaluated in a double-blinded, placebo-controlled, randomized phase 1 clinical trial in healthy male adult volunteers with once daily oral capsule regimen. This study is divided in 3 consecutive parts. See study scheme in **Figure 2**.

Figure 2. Study Scheme



RESULTS

- A total of 65 healthy male subjects aged 18 to 45 years old were enrolled in this study (SAD, 32; MAD, 21; FE, 12).
- Two subjects withdrew consents due to personal reason (MAD study).

Table 1. SAD Safety Data

Preferred Term	Placebo N=8		200 mg N=6		400 mg N=6		600 mg N=6		800 mg N=6	
	Case	n (%)	Case	n (%)	Case	n (%)	Case	n (%)	Case	n (%)
Subjects with any TEAEs	**1**	**1 (12.5)**	**2**	**1 (16.7)**	**1**	**1 (16.7)**	**3**	**3 (50.0)**	**5**	**3 (50.0)**
Diarrhoea	0		1	1 (16.7)	0		0		3	1 (16.7)
Regurgitation	0		0		0		0		1	1 (16.7)
Nasopharyngitis	0		0		0		1	1 (16.7)	0	
Rhinitis	0		1	1 (16.7)	0		0		0	
Back pain	0		0		0		1	1 (16.7)	0	
Musculoskeletal chest pain	1	1 (12.5)	0		0		0		0	
Headache	0		0		1	1 (16.7)	1	1 (16.7)	1	1 (16.7)

- A total of 28 cases AEs were reported. All TEAEs (26/28) were mild (19/26) to moderate (7/26) intensity. Mostly frequent AEs reported are headache (7/26) and diarrhea (5/26).
- No clinically significant trend/abnormalities observed in clinical examinations, laboratory biology tests, vital signs and 12-ECG evaluations. No SAEs or severe AEs.
- Maximum tolerated dose was not reached.

Table 2. MAD Safety Data

Preferred Term	Placebo N=5		200 mg N=8	
	Case	n (%)	Case	n (%)
Subjects with any TEAEs	**3**	**3 (60.0)**	**4**	**4 (50.0)**
Diarrhoea	1	1 (20.0)	0	
Hypoglycaemia	1	1 (20.0)	0	
Back pain	1	1 (20.0)	0	
Myalgia	0		2	2 (25.0)
Dizziness postural	0		1	1 (12.5)
Headache	0		1	1 (12.5)

Table 3. FE Safety Data

Preferred Term	Fasted N=12		Fed N=12	
	Case	n (%)	Case	n (%)
Subjects with any TEAEs	**5**	**2 (16.7)**	**2**	**2 (16.7)**
Abdominal pain	0	0	1	1 (8.3)
Vomiting	1	1 (8.3)	0	0
Headache	4	2 (16.7)	1	1 (8.3)

Figure 3. SAD Pharmacokinetics (~72h)

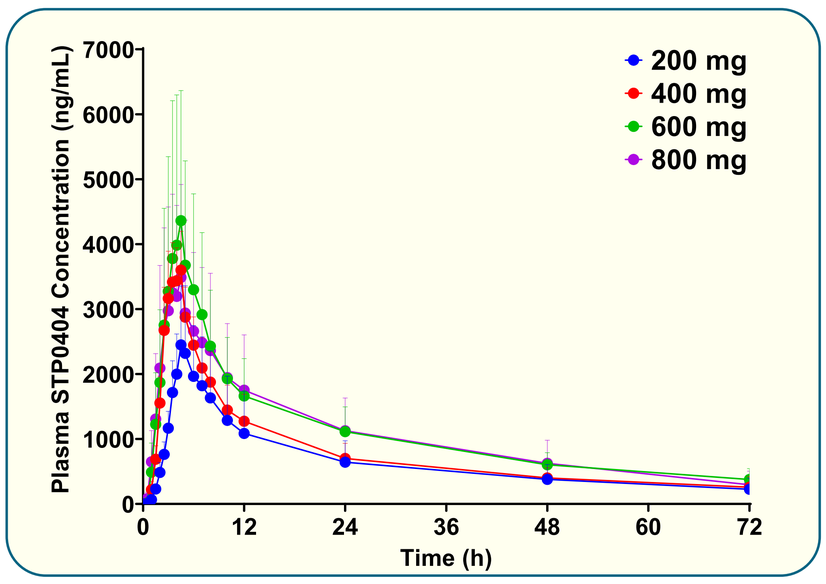


Figure 4. MAD Pharmacokinetics (~288h)

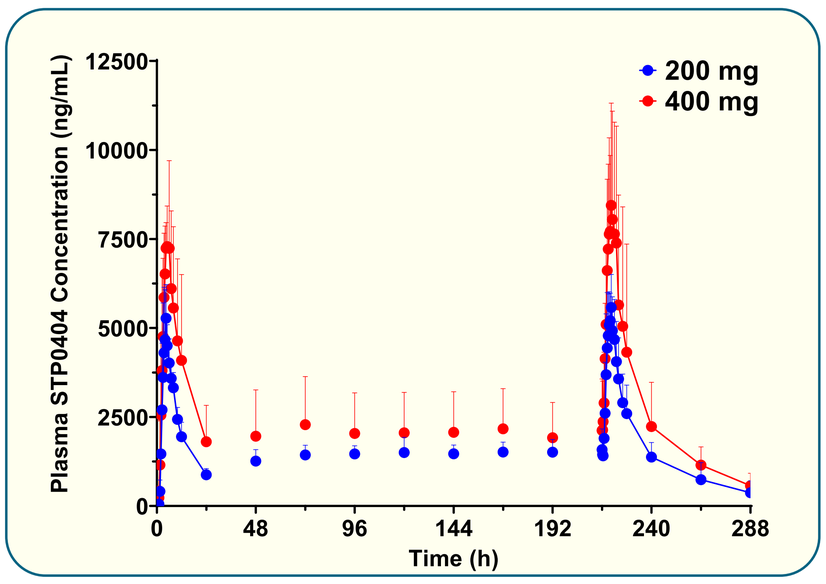


Figure 5. FE Pharmacokinetics (~72h)

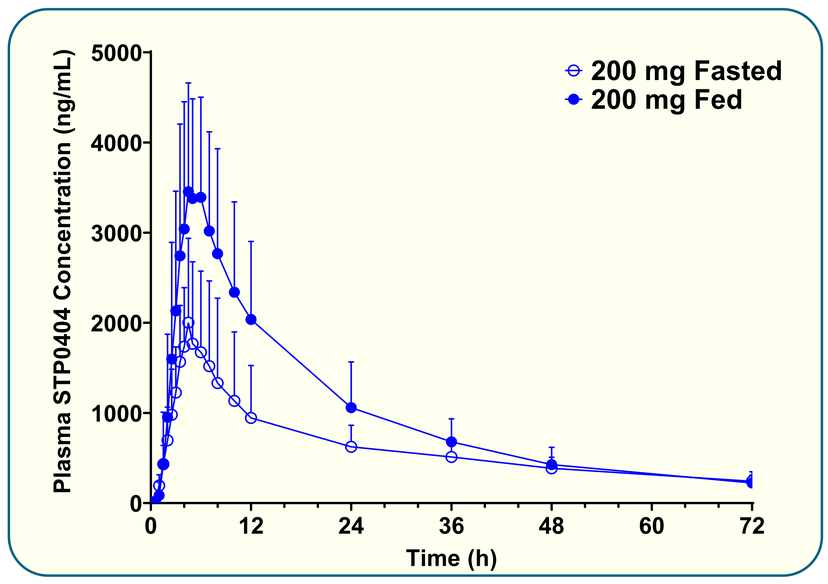


Table 4. SAD PK Parameters

Dose (mg)	C_{max} (ng/mL)	T_{max}* (h)	AUC_{0-24} (ng.h/mL)	AUC_t (ng.h/mL)	AUC_{inf} (ng.h/mL)	$t_{1/2}$ (h)
200	2,462.5 924.79	4.5 (4.5; 5)	26,438 12,320	45,932 22,549	59,323 32,284	20.04+ 3.64
400	3,723.7 578.98	4.5 (3.5; 4.5)	34,899 8,143	65,806 18,581	67,527 18,903	29.26 19.22
600	4,585.2 2,102.8	4.25 (3; 5)	45,653 15,911	91,971 27,842	93,943 28,692	24.78 10.78
800	3,760.5 1,682.9	4.5 (3; 4.5)	43,662 16,638	84,090 31,903	85,718 32,248	18.87 3.53

*T_{max}, median (min; max); other data, mean and standard deviation.
+Excluded data with $\%AUC_{extra}$ >15%.

Table 5. MAD PK Parameters (Day 10)

Dose (mg)	C_{max} (ng/mL)	T_{max}* (h)	AUC_{0-24} (ng.h/mL)	AUC_t (ng.h/mL)	AUC_{inf} (ng.h/mL)	$t_{1/2}$ (h)
200	6,161.4 809.23	4.5 (2; 6)	67,703 11,968	123,302 58,349	126,228 64,142	22.92 14.18
400	9,726.9 3131.7	4.5 (2.5; 7)	109,816 53,203	192,304 94,739	194,212 95,814	21.03 5.65

Table 6. FE PK Parameters

PK Parameters	Fasted State	Fed State	Ratio (Fed/Fasted)	90% CI
C_{max} (ng/mL)	2,049.8	4,180.2	2.18	[1.68, 2.82]
AUC_t (ng.h/mL)	52,278	79,820	1.57	[1.39, 1.76]
AUC_{inf} (ng.h/mL)	53,297	80,657	1.55	[1.38, 1.75]

- STP0404 exposure increased less-proportionally with dose. Long half-life supports once daily dosing. Steady-state achieved at 3~6 days post-dose. Slight accumulation (R_{AUC}, <2) after 10-day repeated dose. Food-intake notably increased exposure.
- Over **700-fold** therapeutic range (200 mg C_{trough} vs. *in vitro* PA-EC_{95}) achieved MAD study.

CONCLUSIONS

- STP0404 was well tolerated in healthy male subjects.
- STP0404 demonstrated consistent PK profile supporting once-daily dose regimen and will achieve target therapeutic concentration. Food-intake would strengthen STP0404 exposure without raising safety concern.
- A Phase 2a study of STP0404 is designed based on these results and planned in 4Q2022.

REFERENCES

1. C. Koneru et al., Elife, 2019, 23;8
2. T. Maehigashi et al., PLoS Pathogen, 2021, 17(7): e1009671

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