A Phase I Clinical Trial Assessing the Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of *NTP42:KVA4*, a Novel Thromboxane Receptor Antagonist, in Healthy Subjects

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BACKGROUND

- **Pulmonary arterial hypertension** (**PAH**) is a rare, yet devastating disease with high morbidity, mortality, and significant **unmet clinical needs**.
- Recent studies by us reported that the **thromboxane A_2 receptor (TP) antagonist** ***NTP42*** attenuates several multifactorial hallmarks of the disease in preclinical models of PAH and of right ventricular (RV) overload & dysfunction (**1**,**2**,**3**).
- ***NTP42*** addresses PAH pathophysiology by not only reducing pulmonary vasoconstriction, **but also by alleviating other pulmonary pathologies** (**1**,**2**,**3**).
- Uniquely, ***NTP42*** also has **direct cardioprotective benefits**, reducing RV remodeling, promoting beneficial RV adaptation resulting in improved cardiac function (**3**) – a **key unmet need in PAH therapy**, as well as in other pulmonary hypertension groups and related conditions involving RV dysfunction (**4**).

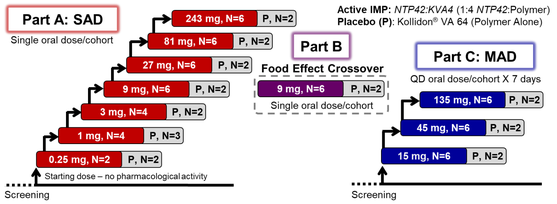
OBJECTIVE

- The objective of this first-in-human (FIH) Phase I clinical trial was to evaluate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) properties of ***NTP42***, delivered orally as the formulated investigational medicinal product (IMP) ***NTP42:KVA4***.

METHODS

- This was a randomized, placebo controlled, FIH Phase I clinical trial conducted in healthy adult male volunteers involving three parts (**Figure 1**).
- The API ***NTP42*** was formulated with the excipient Kollidon® VA 64 at a ratio of 1:4 (drug substance: polymer), where the IMP is referred to as ***NTP42:KVA4***.
- Matching placebo was prepared as a fill of the corresponding weight of the excipient Kollidon® VA 64 only.

Figure 1. Clinical Study Design



SAD Study (Parts A & B)

- The SAD study included 7 cohorts (up to 8 participants, randomized to ***NTP42:KVA4*** [n = 6] or placebo [n = 2]) who were administered 0.25, 1, 3, 9, 27, 81, or 243 mg single oral doses of ***NTP42:KVA4*** or placebo (Part A, **Figure 1**).
- In a cross-over study, one SAD group (9 mg dose) received an additional dose of ***NTP42:KVA4*** or placebo following a high-fat breakfast (Part B, **Figure 1**).

MAD Study (Part C)

- The MAD study included 3 cohorts who were administered 15, 45, or 135 mg oral doses of ***NTP42:KVA4*** or placebo once daily (QD) for 7 days (Part C, **Figure 1**).

RESULTS

Study Participants

- A total of 79 healthy male volunteers (SAD, n = 55; MAD, n = 24) participated in the study. The demographic characteristics of subjects are summarized in **Table 1**.

Table 1. Trial Participant Demographic Summary		Part A* Placebo (Fasted)	Part A* *NTP42:KVA4*# 0.25 - 243 mg (Fasted)	Part B Placebo (Fed)	Part B *NTP42:KVA4*# 9 mg (Fed)	Part C* Placebo QD	Part C* *NTP42:KVA4*# 15 - 135 mg QD (Fasted)
Age (y) (Mean ± SD)		31.9 ± 8.8	32.0 ± 10.6	32.5 ± 14.9	41.2 ± 8.0	32.8 ± 9.1	36.2 ± 10.4
Gender (Male; N)		16	39	2	6	6	18
Race	White (n)	15	31	2	5	5	14
	Asian (n)	1	3	0	0	0	0
	Black/African American (n)	0	3	0	0	1	3
	Other (n)	0	2	0	1	0	1
Height (cm) (Mean ± SD)		178.5 ± 7.7	178.0 ± 7.5	180.0 ± 2.8	170.9 ± 7.4	177.5 ± 5.3	177.9 ± 8.4
Weight (kg) (Mean ± SD)		78.5 ± 14.1	77.1 ± 12.0	90.8 ± 6.2	76.0 ± 16.1	80.5 ± 10.0	78.9 ± 14.1
BMI (kg/m²) (Mean ± SD)		24.5 ± 2.9	24.1 ± 3.0	28.0 ± 1.0	23.5 ± 3.0	25.5 ± 2.7	24.8 ± 2.5

*All subjects in Parts A & C were given *NTP42:KVA4* or Placebo under fasted conditions. #*NTP42:KVA4* or placebo delivered as oral suspensions or solutions, respectively, in water. ***Abbreviations***: BMI, body mass index; N, total subjects; n, applicable subjects; QD, once daily; SD, standard deviation.

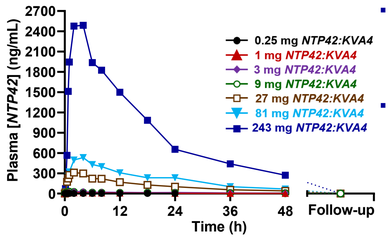
SAD Pharmacokinetics

- ***NTP42*** was rapidly absorbed, with plasma concentrations detected from 10 min after single doses ≥ 1 mg, with peak concentrations observed 2 – 4 h after dosing (**Figure 2** & **Table 2**).
- Generally, dose proportional increases in exposure (C_{max}/AUC) were observed, and favorable clearance rates (mean T½, 18.7 h) indicate that ***NTP42:KVA4*** is suited for once daily dosing.
- While ***NTP42*** absorption was slower after food (Part B), there was no overall difference in exposure (AUC_{inf}) between the fed and fasted state (**Table 2**, 9 mg ***NTP42:KVA4*** dose).

Table 2. *NTP42* SAD PK Parameters		*NTP42:KVA4* SAD (Parts A & B) 0.25 mg (Fasted) (N = 2)	1 mg (Fasted) (N = 4)	3 mg (Fasted) (N = 4)	9 mg (Fasted) (N = 11)	9 mg (Fed) (N = 6)	27 mg (Fasted) (N = 6)	81 mg (Fasted) (N = 6)	243 mg (Fasted) (N = 6)
C_{max} (ng/mL)	Geo Mean	2.74	12.5	27.7	87.5	64.5	325	528	2,459
	95% CI	(0.2 - 39.6)	(9.2 - 17.1)	(18.0 - 42.7)	(73.2 - 105)	(49.2 - 84.6)	(226 - 468)	(360-774)	(1,488 - 4,065)
T_{max} (h)	Median	2.5	2.0	3.1	2.0	7.0	2.0	3.0	2.0
AUC_{inf} (h·ng/mL)	Geo Mean	134	323	823	1,801	1,818	6,695	11,705	50,279
	95% CI	(0.7 - 24,151)	(244 - 429)	(426 - 1,588)	(1,367 - 2,373)	(943 - 3,505)	(5,124 - 8,749)	(8,729 - 15,696)	(31,426 - 80,444)
$T_{½}$ (h)	Geo Mean	43.2	21.8	23.1	17.6	22.1	17.3	15.4	17.0
	SD	16.0	3.2	5.7	8.4	13.1	6.1	5.5	6.9

Abbreviations: AUC_{inf}, Area under curve *versus* time from dosing to infinity; CI: Confidence interval; C_{max}, Peak plasma concentration after dosing; Geo, Geometric; N, number of subjects; PK, Pharmacokinetic; SD, standard deviation; $T_{½}$, Apparent terminal elimination half-life.; T_{max}, Time to reach C_{max} or peak plasma concentration after dosing.

Figure 2. Concentration-Time Profiles Following SAD of *NTP42:KVA4* (Part A)



- Blood samples collected pre-dose, up to 48 h post-dose and at follow-up (7-10 days after dose) from subjects given single doses of placebo or ***NTP42:KVA4*** (0.25 - 243 mg).
- Data presented as mean change in concentration of plasma ***NTP42*** at pre-dose and up to 48 h post-dose as determined by liquid chromatography tandem mass spectrometry (LC-MS/MS) using a validated method for quantification of ***NTP42*** in plasma.

MAD Pharmacokinetics

- C_{max} for ***NTP42*** was observed at 2 h (Day 1) and 4 h (Day 7). $T_{1/2}$ values ranged from 14.9 - 26.1 h (Day 1) and 19.6 - 23.1 h (Day 7) (**Table 3**).
- C_{max} increased close to dose proportionally on Day 1 and slightly less than dose proportionally on Day 7. Exposure (AUC) after single/repeat dosing increased slightly less than dose proportionally (**Table 3**). Steady-state exposure was attained between Days 3 - 6.
- Day 1 - 7 ratios of exposure ($AUC_τ$ & C_{max}) suggest little to no accumulation of ***NTP42*** at the highest dose level tested (**Table 3**, 135 mg ***NTP42:KVA4*** dose).

Table 3. *NTP42* MAD PK Parameters		*NTP42:KVA4* MAD (Part C) 15 mg QD (N=6) Day 1	15 mg QD (N=6) Day 7	45 mg QD (N=6) Day 1	45 mg QD (N=6) Day 7	135 mg QD (N=6) Day 1	135 mg QD (N=6) Day 7
C_{max} (ng/mL)	Geo Mean	160	249	524	640	1,293	1,124
	95% CI	(113 - 228)	(166 - 372)	(423 - 650)	(447 - 915)	(739 - 2,262)	(671 - 1,883)
T_{max} (h)	Median	2.0	3.0	2.0	3.0	2.0	1.0
$AUC_τ$ (h·ng/mL)	Geo Mean	2,249	3,868	6,414	8,667	15,676	16,407
	95% CI	(1,632 - 3,099)	(2,420 - 6,182)	(5,138 - 8,007)	(6,011 - 12,496)	(9,911 - 24,793)	(10,449 - 25,762)
$T_{½}$ (h)	Mean	26.1	23.1	14.9	19.6	16.6	21.5
	SD	8.3	6.3	2.9	3.8	6.8	4.7
$R_{ac(AUC)}$	Mean Ratio	1.75		1.38		1.15	
	95% CI	(1.41 - 2.08)		(1.06 - 1.70)		(0.626 - 1.67)	
$R_{ac(Cmax)}$	Mean Ratio	1.57		1.25		1.00	
	95% CI	(1.27 - 1.88)		(0.942 - 1.55)		(0.449 - 1.56)	

Abbreviations: $AUC_τ$: Area under curve across a dosing time (τ) interval (0-24 h); CI: Confidence interval; C_{max}, Peak plasma concentration after dosing; Geo, Geometric; N, number of subjects; PK, Pharmacokinetic; QD, once daily; $R_{ac(AUC)}$, Accumulation ratio for AUC (calculated from $AUC_τ$ at steady state and $AUC_τ$ after single dose); $R_{ac(Cmax)}$: Accumulation ratio for C_{max} (calculated from C_{max} at steady state and C_{max} after single dose); SD, standard deviation; $T_{½}$, Apparent terminal elimination half-life.; T_{max}, Time to reach C_{max} or peak plasma concentration after dosing.

Safety & Tolerability

- There were no significant AEs or SAEs that stopped dose escalation or resulted in withdrawal.
- Drug- or placebo-related TEAEs were considered as mild/moderate in severity, with no correlation in incidence/severity of TEAEs to ***NTP42:KVA4*** dose.
- The most common TEAEs were dizziness, orthostatic hypotension, and headache (**Table 4**).
- There were no clinically relevant changes in physical examination findings, ECG, or laboratory parameters (hematology, coagulation, clinical chemistry, and urinalysis).

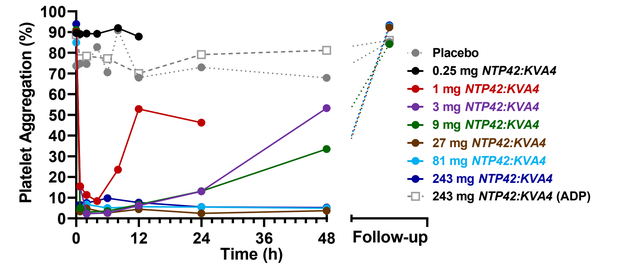
Table 4. Drug- or Placebo-related TEAEs		Number of subjects with ≥ 1 TEAE [Total number of TEAEs] Part A* Placebo (Fasted) (N=16)	Part A* *NTP42:KVA4*# 0.25 – 243 mg (Fasted) (N=39)	Part B Placebo (Fed) (N=2)	Part B *NTP42:KVA4*# 9 mg (Fed) (N=6)	Part C* Placebo QD (N=6)	Part C* *NTP42:KVA4*# 15 – 135 mg QD (Fasted) (N=18)
Any TEAE§		4 [6]	11 [16]	0	0	3 [3]	5 [5]
Drug or Placebo Related TEAE†	Total	3 [5]	6 [9]	0	0	0	2 [2]
	Dizziness	2 [2]	2 [2]	0	0	0	0
	Postural Dizziness	0	2 [2]	0	0	0	0
	Headache	0	1 [1]	0	0	0	2 [2]
	Orthostatic Hypotension	2 [2]	1 [1]	0	0	0	0
	Orthostatic Tachycardia	0	2 [2]	0	0	0	0
	Nausea	1 [1]	0	0	0	0	0
	Decreased Appetite	0	1 [1]	0	0	0	0
Any SAE		0					
TEAE Leading to Withdrawal		0					
Mild TEAE‡		3	6	0	0	3	3
Moderate TEAE‡		1	5	0	0	0	2
Severe TEAE‡		0					

*All subjects in Parts A & C were given *NTP42:KVA4* or Placebo under fasted conditions. #*NTP42:KVA4* or placebo delivered as oral suspensions or solutions, respectively, in water. †TEAE defined as adverse event (AE) occurring after *NTP42:KVA4* or Placebo that was not present prior to dosing or an event that worsens in intensity or in frequency after dosing. †Drug- or placebo related AEs were determined by the Principal Investigator to be related to either study drug or placebo. ‡ Level of TEAE noted as the worst severity. ***Abbreviations:*** N, total subjects; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Pharmacodynamic Assessments

- Following single dosing of ≥ 1 mg ***NTP42:KVA4***, significant dose-dependent inhibition of TP agonist (U46619)-induced platelet aggregation was observed. Complete inhibition (≥ 90 %) was observed after dosing of ≥ 3 mg ***NTP42:KVA4*** that was sustained for up to 24 h (**Figure 3**).
- U46619-induced platelet aggregation returned to baseline in a dose- and time-dependent manner, with all ***NTP42:KVA4*** doses (1 – 243 mg) back at pre-dose baseline levels at the follow-up assessment, some 7 to 10 days after dosing.
- No inhibition of ADP-induced aggregation was observed, confirming target engagement and specificity of ***NTP42*** for TXA_2/TP-, and not ADP/(P2Y1/P2Y12)-, receptor responses.

Figure 3. Platelet Aggregation Profiles Following SAD of *NTP42:KVA4* (Part A)



- Aggregation profiles following single oral doses of placebo or 0.25 - 243 mg ***NTP42:KVA4*** following stimulation with 1.5 µM U46619 (TP agonist) or 10 µM ADP (243 mg group only).
- Data presented as mean change in maximal platelet aggregation (Platelet Aggregation; %) at pre-dose, up to 48 h post-dose and at follow-up (7 – 10 days after dose).

CONCLUSIONS

- **First clinical evaluation** of ***NTP42***, a novel TP antagonist in development as a treatment for PAH and other cardiopulmonary diseases.
- ***NTP42***, administered as the oral formulation ***NTP42:KVA4***, was found to be **safe and well-tolerated in all subjects** after all single doses up to 243 mg and all repeat once-daily dosing up to 135 mg.
- ***NTP42*** was **rapidly absorbed** after single/repeat dosing, with favorable clearance rates indicating that ***NTP42:KVA4*** suited for use as a **convenient once-a-day oral medication**. ***NTP42:KVA4*** may be taken with or without food, another key benefit for patient compliance.
- Excellent **PK/PD correlation** between ***NTP42*** levels and inhibition of TP-mediated platelet aggregation, with no effect on ADP-induced aggregation.
- With **compelling preclinical efficacy** in the lung **AND** heart (1,2,3), this study supports the **continued development** of ***NTP42:KVA4*** for the treatment of PAH, as well as for related cardiopulmonary diseases.

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PAHHOPE

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Disclosure of Commercial Support and Relevant Financial Interests:
BTK (Founder/Director, ATXA Therapeutics), **HMR** & **EPM** (Employees, ATXA Therapeutics), **MB** & **TY** (Employees, Hammersmith Medicines Research), **MM** & **CMP** (Paid Advisors/Consultants, ATXA Therapeutics) The clinical trial, performed at Hammersmith Medicines Research, was sponsored by **ATXA Therapeutics Limited**.