A First-in-Human Single/Multiple Ascending Dose Study of ANPA-0073, a Novel Small Molecule G-protein Biased Apelin Receptor Agonist, in Healthy Volunteers

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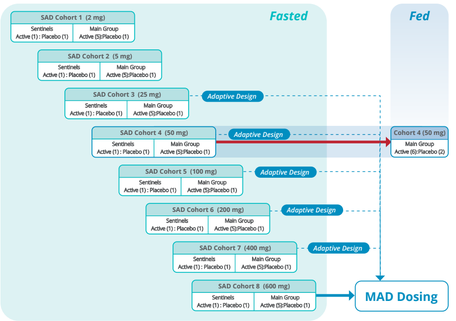
INTRODUCTION

- The apelin/G-protein-coupled apelin receptor (APJR) pathway represents an emerging therapeutic target. However, the clinical long-term administration of apelin and non-biased apelin agonists is limited by their short half-life and β-arrestin-related negative effects on blood pressure and APJR internalization
- Utilizing our unique structure-based drug discovery platform, we have discovered a novel small molecule APJ agonist, ANPA-0073, with favorable drug-like properties and biased signalling along the cAMP/G-protein pathway. With potentially fewer β-arrestin-related effects, ANPA-0073 demonstrated beneficial effects in animal models of pulmonary disease (Shi et al, ATS 2023 poster #6428)
- The objective of this first-in-human single ascending dose (SAD) and multiple ascending dose (MAD) study of orally-administered ANPA-0073 in healthy adult volunteers was to evaluate its safety, tolerability and pharmacokinetic (PK) profile for potential clinical use to treat apelin-related diseases

METHODS

- Medically healthy adult volunteers were enrolled and were randomized to ANPA-0073 or placebo groups
- Key inclusion criteria:
  - Healthy males and females aged ≥ 18 years to ≤ 55 years
  - Body mass index ≥ 18.0 to ≤ 30.0 kg/m², and body weight ≥ 50 kg
- Key exclusion criteria:
  - History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease
  - Any acute illness or surgery within the prior 3 months
  - Current infection requiring medication
  - History of malignant disease in the last 10 years
  - Presence of clinically relevant immunosuppression
- In the SAD, eligible participants were enrolled into eight cohorts of 8 participants each and randomized 6:2 to receive a single dose of ANPA-0073 at 2, 5, 25, 50, 100, 200, 400 and 600 mg or placebo **(Figure 1A)**. The food effect was investigated in one cohort (SAD Cohort 4) with a single dose of ANPA-0073 (50 mg) or placebo administered on Day 1 under fasted conditions and another dose administered on Day 4 under fed conditions (total of 2 doses)
- In the MAD, eligible participants were enrolled into four cohorts of 8 participants each and randomized 6:2 to receive ANPA-0073 at 75, 150, 300, and 500 mg or placebo once daily (QD) for 7 days **(Figure 1B)**
- The primary study endpoint was the safety and tolerability of single and 7-day repeat oral doses of ANPA-0073 to healthy adult volunteers
- The secondary study endpoints were:
  - PK analysis of ANPA-0073 in plasma following the administration of single and 7-day repeat oral doses
  - PK of ANPA-0073 in urine following the administration of a single oral dose (SAD Cohort 3 only)
  - Effect of food on the PK of ANPA-0073 following the administration of a single oral dose under fasted and fed conditions (SAD Cohort 4 only)

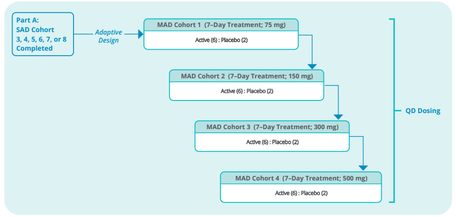
FIGURE 1A: SAD Study Design



N = 8 per Cohort, Active (6) : Placebo (2)

METHODS

Figure 1B: MAD Study Design



RESULTS

TABLE 1: SAD Participant Demographics

Demographic parameter	Sub-group	Placebo N = 16	ANPA-0073 (N = 6)								All Participants
			2 mg	5 mg	25 mg	50 mg	100 mg	200 mg	400 mg	600 mg	
Age, years Mean (SD)		28.9 (6.1)	35.5 (12.8)	32.7 (9.6)	27.5 (6.6)	31.0 (9.2)	26.5 (6.3)	33.7 (13.1)	25.3 (3.7)	31.7 (9.5)	30.1 (8.6)
Gender, n (%)	Female	9 (56.3%)	3 (50.0%)	—	1 (16.7%)	2 (33.3%)	2 (33.3%)	3 (50.0%)	6 (100%)	2 (33.3%)	28 (43.8%)
	Male	7 (43.8%)	3 (50.0%)	6 (100%)	5 (83.3%)	4 (66.7%)	4 (66.7%)	3 (50.0%)	—	4 (66.7%)	36 (56.3%)
Race, n (%)	White	9 (56.3%)	5 (83.3%)	2 (33.3%)	4 (66.7%)	1 (16.7%)	6 (100%)	4 (66.7%)	2 (33.3%)	4 (66.7%)	37 (57.8%)
	American Indian or Alaska Native	1 (6.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	—	—	—	—	6 (9.4%)
	Asian	5 (31.3%)	—	2 (33.3%)	—	4 (66.7%)	—	2 (33.3%)	—	2 (33.3%)	15 (23.4%)
	Black or African American	—	—	—	—	—	—	—	1 (16.7%)	—	1 (1.6%)
	Native South American	—	—	—	—	—	—	—	2 (33.3%)	—	2 (3.1%)
	Multiple	1 (6.3%)	—	—	1 (16.7%)	—	—	—	1 (16.7%)	—	3 (4.7%)
Ethnicity, n (%)	Hispanic or Latino	3 (18.8%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	—	—	3 (50.0%)	1 (16.7%)	15 (23.4%)
	Not Hispanic or Latino	12 (75.0%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	6 (100%)	6 (100%)	3 (50.0%)	4 (66.7%)	47 (73.4%)
	Not Reported	1 (6.3%)	—	—	—	—	—	—	—	1 (16.7%)	2 (3.1%)

TABLE 2: MAD Participant Demographics

Demographic parameter	Sub-group	Placebo N = 8	ANPA-0073 (N = 6)				ANPA-0073 (N = 24)	All Subjects (N=32)
			75 mg	150 mg	300 mg	500 mg	All Subjects	
Age, years Mean (SD)		34.4 (7.4)	25.5 (3.4)	28.8 (6.5)	31.7 (11.9)	29.0 (6.4)	28.8 (7.5)	30.2 (7.8)
Gender, n (%)	Female	2 (25.0%)	4 (66.7%)	1 (16.7%)	4 (66.7%)	3 (50.0%)	12 (50.0%)	14 (43.8%)
	Male	6 (75.0%)	2 (33.3%)	5 (83.3%)	2 (33.3%)	3 (50.0%)	12 (50.0%)	18 (56.3%)
Race, n (%)	White	8 (100%)	2 (33.3%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	14 (58.3%)	22 (68.8%)
	American Indian or Alaska Native	—	1 (16.7%)	1 (16.7%)	—	1 (16.7%)	3 (12.5%)	3 (9.4%)
	Asian	—	3 (50.0%)	1 (16.7%)	2 (33.3%)	—	6 (25.0%)	6 (18.8%)
	Black or African American	—	—	—	—	—	—	—
	Native South American	—	—	—	—	—	—	—
	Multiple	—	—	1 (16.7%)	—	—	1 (4.2%)	1 (3.1%)
Ethnicity, n (%)	Hispanic or Latino	2 (25.0%)	1 (16.7%)	2 (33.3%)	—	1 (16.7%)	4 (16.7%)	6 (18.8%)
	Not Hispanic or Latino	6 (75.0%)	5 (83.3%)	4 (66.7%)	6 (100%)	5 (83.3%)	20 (83.3%)	26 (81.3%)
	Not Reported	—	—	—	—	—	—	—

- The mean age (standard deviation [SD]) of participants in the SAD analysis was 30.1 (8.6) years with 43.8% females (28/64) and 56.3% males (36/64) **(Table 1)**
- The mean age (SD) of participants in the MAD analysis was 30.2 (7.8) years with 43.8% females (14/32) and 56.3% males (18/32) **(Table 2)**

RESULTS

FIGURE 2: SAD Mean Plasma Concentrations Over Time by Treatment (semi-log)

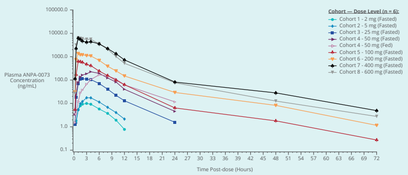
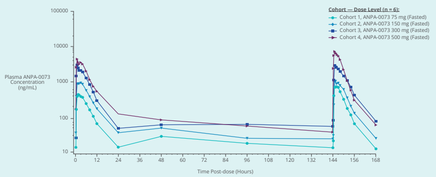
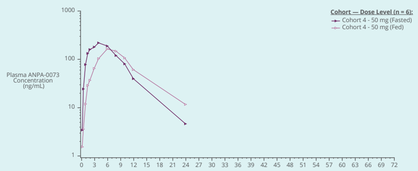


FIGURE 3: MAD Mean Plasma Concentrations Over Time by Treatment (semi-log)



- The median t_{max} range was 1.0 to 4.0 hours (h) under fasting conditions for all doses of ANPA-0073 **(Figure 2)**. The mean $t_{1/2}$ was variable across the dose range, with the mean $t_{1/2}$ by dose level ranging from 2.44 to 9.55 h. A longer $t_{1/2}$ was observed in cohorts receiving an ANPA-0073 dose greater than 100 mg. The AUC and C_{max} were proportional from 2 to 200 mg, super proportional for 200 to 400 mg, and less than dose proportional from 400 to 600 mg. Regarding the urine PK analysis, the renal excretion of unchanged drug was negligible and amounted to less than 0.10% of the dose
- The MAD plasma PK data are shown in **Figure 3**. Twenty-four hour plasma levels are depicted on days 1 and 7, with trough levels reflected at other timepoints. The median t_{max} range was 1.5 to 2.5 h across Day 1 and Day 7 for all doses of ANPA-0073. The mean $t_{1/2}$ was consistent across the dose range, with a mean $t_{1/2}$ ranging from 4.18–5.36 h on Day 1 and 3.75–4.89 h on Day 7. There was no significant accumulation across doses post QD dosing. The mean ratio by dose level of AUC over 24 hours post-dose on Day 7 compared with Day 1 ranged from 0.97 to 1.58, which was consistent with the observed $t_{1/2}$. The PK increased proportionally from 75 mg to 500 mg on Days 1 and 7

FIGURE 4: SAD Mean Plasma Concentrations Over Time by Treatment in Fasting and Fed Conditions (semi-log)



- When the single dose fed (high-fat meal) cohort was compared with the single dose fasted group, there was a delay in the median t_{max} of approximately 3 h (4:00 (fasted) vs 7:03 [fed]) and the C_{max} was decreased by approximately 30% **(Figure 4)**. In addition, the AUC_{0-t} and AUC_{0-inf} were similar between the fed and fasting groups

TABLE 3: Incidence of Treatment Emergent Adverse Events (TEAEs)

(A) SAD

	Number (%) of Participants with TEAEs [Number of TEAEs Reported]												
	ANPA-0073 (N = 6)										All Active (N = 48)	All Placebo (N = 16)	All Participants (N = 64)
	2 mg	5 mg	25 mg	50 mg Fasted	50 mg Fed	100 mg	200 mg	400 mg	600 mg				
Any TEAEs	2 (33.3%) [3]	—	3 (50.0%) [4]	2 (33.3%) [3]	2 (33.3%) [3]	—	—	1 (16.7%) [1]	3 (50.0%) [7]		12 (25.0%) [21]	5 (31.3%) [8]	17 (26.6%) [29]
Drug-Related TEAEs	—	—	1 (16.7%) [1]	1 (16.7%) [1]	—	—	—	—	3 (50.0%) [6]		5 (10.4%) [8]	3 (18.8%) [3]	8 (12.5%) [11]

(B) MAD

	Number (%) of Participants with TEAEs [Number of TEAEs Reported]						
	ANPA-0073 (N = 6)				All Active (N = 24)	All Placebo (N = 8)	All Participants (N = 32)
	75 mg	150 mg	300 mg	500 mg			
Any TEAEs	4 (66.7%) [4]	4 (66.7%) [9]	2 (33.3%) [4]	3 (50.0%) [5]	13 (54.2%) [22]	4 (50.0%) [13]	17 (53.1%) [35]
Drug-Related TEAEs	1 (16.7%) [1]	2 (33.3%) [2]	2 (33.3%) [4]	2 (33.3%) [2]	7 (29.2%) [9]	2 (25.0%) [5]	9 (28.1%) [14]

- No severe TEAEs, SAEs, or deaths were observed at any dose level of ANPA-0073 and no participants withdrew from the study due to TEAEs
- In the SAD analysis, a total of 64 participants (8 cohorts of n = 8) were randomized: 48 completed dosing with ANPA-0073 at 2, 5, 25, 50, 100, 200, 400, and 600 mg QD, and 16 received placebo
  - In the safety analysis set **(Table 3A)**, any TEAEs were reported for 12/48 participants (25.0%) receiving ANPA-0073 and 5/16 (31.3%) in the placebo group. The most common TEAE reported in participants who received ANPA-0073 was headache. Most TEAEs were classified as mild (24/29 of all TEAEs) in severity and 5 were classified as moderate in severity
- In the MAD analysis, a total of 32 participants (4 cohorts of n = 8) were randomized and 24 completed dosing at 75, 150, 300 and 500 mg QD for 7 days. There were no deaths or SAEs.
  - In the safety analysis **(Table 3B)**, TEAEs were reported for 13/24 participants (54.2%) receiving ANPA-0073 and for 4/8 participants (50%) in the placebo group

TABLE 4: Summary of Related TEAEs – SAD

	Number (%) of Participants with Related TEAEs [Number of Related TEAEs Reported]												
	ANPA-0073 (N = 6)										All Active (N = 48)	All Placebo (N = 16)	All Participants (N = 64)
	2 mg	5 mg	25 mg	50 mg Fasted	50 mg Fed	100 mg	200 mg	400 mg	600 mg				
Diarrhea	—	—	—	—	—	—	—	—	2 (33.3%) [2]		2 (4.2%) [2]	—	2 (3.1%) [2]
Headache	—	—	—	—	—	—	—	—	1 (16.7%) [1]		1 (2.1%) [1]	1 (6.3%) [1]	2 (3.1%) [2]
Blood creatine phosphokinase increased	—	—	1 (16.7%) [1]	—	—	—	—	—	—		1 (2.1%) [1]	—	1 (1.6%) [1]
Dizziness	—	—	—	—	—	—	—	—	—		—	1 (6.3%) [1]	1 (1.6%) [1]
Electrocardiogram T wave inversion	—	—	—	—	—	—	—	—	—		—	1 (6.3%) [1]	1 (1.6%) [1]
Lethargy	—	—	—	—	—	—	—	—	1 (16.7%) [1]		1 (2.1%) [1]	—	1 (1.6%) [1]
Nausea	—	—	—	—	—	—	—	—	1 (16.7%) [1]		1 (2.1%) [1]	—	1 (1.6%) [1]
Sinus tachycardia	—	—	—	1 (16.7%) [1]	—	—	—	—	—		1 (2.1%) [1]	—	1 (1.6%) [1]
Vomiting	—	—	—	—	—	—	—	—	1 (16.7%) [1]		1 (2.1%) [1]	—	1 (1.6%) [1]
Total	—	—	1 (16.7%) [1]	1 (16.7%) [1]	—	—	—	—	3 (50.0%) [6]		5 (10.4%) [8]	3 (18.8%) [3]	8 (12.5%) [11]

- In the SAD safety analysis set, drug-related TEAEs were reported in 5/48 subjects (10%) in the ANPA-0073 group vs. 3/16 (19%) in the placebo group
- Common drug-related TEAEs reported in participants following ANPA-0073 dosing were 2 events of diarrhea, and 1 each of headache, increased blood creatine phosphokinase, lethargy, nausea, sinus tachycardia, and vomiting **(Table 4)**. Most drug-related TEAEs in the ANPA-0073 treatment group were of mild severity, transient, and recovered without medical intervention

TABLE 5: Summary of Related TEAEs – MAD

	Number (%) of Participants with Related TEAEs [Number of Related TEAEs Reported]						
	ANPA-0073 (N = 6)				All Active (N = 24)	All Placebo (N = 8)	All Participants (N = 32)
	75 mg	150 mg	300 mg	500 mg			
Palpitations	1 (16.7%) [1]	—	—	—	1 (4.2%) [1]	—	1 (3.1%) [1]
Sinus tachycardia	—	—	1 (16.7%) [1]	—	1 (4.2%) [1]	—	1 (3.1%) [1]
Abdominal pain	—	—	—	—	—	1 (12.5%) [1]	1 (3.1%) [1]
Chills	—	—	2 (33.3%) [2]	—	2 (8.3%) [2]	—	2 (6.3%) [2]
Dizziness	—	—	—	—	—	1 (12.5%) [1]	1 (3.1%) [1]
Headache	—	2 (33.3%) [2]	1 (16.7%) [1]	2 (33.3%) [2]	5 (20.8%) [5]	1 (12.5%) [3]	6 (18.8%) [8]
Total	1 (16.7%) [1]	2 (33.3%) [2]	2 (33.3%) [4]	2 (33.3%) [2]	7 (29.2%) [9]	2 (25.0%) [5]	

- In the MAD **(Table 5)**, the most common TEAE reported was headache in participants who received ANPA-0073 (6/24 (25.0%): 2 with ANPA-0073 150 mg, 1 with ANPA-0073 300 mg and 2 with ANPA-0073 500 mg) and in 4 participants (4/8; 50%) in the placebo group. There was no apparent trend in the incidence of headache across the ANPA-0073 dose levels. Most TEAEs were classified as mild (23/35, 65.7% of all TEAEs) in severity, with 12 TEAEs classified as moderate in severity. No TEAEs were classified as severe
- Drug-related TEAEs were reported in 7/24 (29.2%) subjects in the ANPA-0073 group vs. 2/8 (25.0%) in the placebo group. Common drug-related TEAEs reported in participants receiving ANPA-0073 were headache, chills, palpitations, and sinus tachycardia. Most drug-related TEAEs were of mild severity, with 6 drug-related TEAEs of moderate severity in 4 participants (all headache: ANPA-0073 500 mg 2 events; ANPA-0073 150 mg 1 event, and placebo 3 events). Most drug-related TEAEs appeared transient and recovered with the use of paracetamol, with the exception of one participant (who received placebo) who experienced a moderate headache on Days 1 to 6 and was withdrawn from study drug prior to the Day 6 administration. There was 1 TEAE arising from electrocardiography in a participant who received ANPA-0073 300 mg (sinus tachycardia on Day 1, mild, likely related)

CONCLUSIONS

- In summary, ANPA-0073 was generally well-tolerated and demonstrated an adequate short-term safety profile with few TEAEs and no SAEs or deaths
- Furthermore, ANPA-0073 did not induce hypotension in contrast to the administration of apelin and its half-life of hours exceeds that of minutes for native apelin. The safety analysis indicated a maximal dose of 600 mg ANPA-0073 for use in humans because of the incidence of gastrointestinal-related AEs
- The PK increased proportionally from 75 mg to 500 mg and there was no significant accumulation of ANPA-0073 post dosing
- Animal and human studies have demonstrated the apelinergic pathway is involved in the pathogenicity of vascular diseases. Therefore, ANPA-0073, a small molecule G-protein biased APJR agonist with a good safety profile might be useful for the treatment of apelin-related diseases including atherosclerosis, sepsis, heart failure, idiopathic pulmonary fibrosis (IPF), and pulmonary arterial hypertension (PAH)

REFERENCES:

1. Shi S, et al. *Discovery of G-protein biased APJ agonist small molecule for pulmonary diseases.* ATS 2023, Poster #6428.