A Phase 1, Randomized, Double-Blind, Placebo Controlled, First-in-Human Study to Assess Safety, Tolerability & Pharmacokinetics (PK) of Amilo-5MER in Healthy Volunteers

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PURPOSE

Amilo-5MER, is an investigational 5 amino acid synthetic peptide MTADV (Methionine, Threonine, Alanine, Aspartic acid, Valine) under clinical development for a potential therapy of acute and chronic inflammatory conditions like inflammatory bowel disease (IBD) [1]. Amilo-5MER has a high binding affinity to human serum amyloid A (SAA) protein, which in turn interferes with SAA polymerization and aggregation essential for its pro inflammatory activity and resulting in significant reduction of cytokine secretion e.g. IL-6, IL-1 & TNF. Amilo-5MER has shown strong disease-modifying effects in animal models of IBD and here we present first-in-human data of amilo-5MER.

METHODS

Objective

The primary objective was to assess and characterize the safety and tolerability of amilo-5MER in healthy young and elderly participants. The primary endpoints were measured by adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs) and physical examination findings.
The secondary objective was to investigate the pharmacokinetics (PK) of single and multiple doses of amilo-5MER..

Study Design

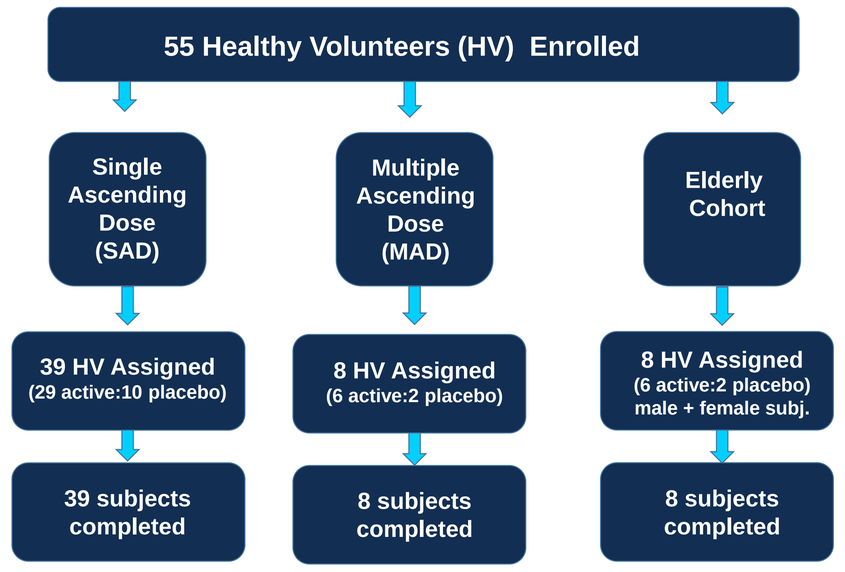
This was a 3-part, first-in-human (FIH) study including five single ascending dose cohorts (SAD, Part 1) and multiple dose cohort (MAD, Part 2) in healthy young adult volunteers, and a single dose assessment in a single cohort of healthy elderly subjects (Part 3). All study parts were conducted as double-blind, randomised, placebo-controlled investigations, targeting 8 subjects per cohort randomised 3:1 active to placebo.

Part 1 evaluated single ascending doses over the range 10-360 mg in cohorts of 8 subjects aged 18 to 45. Part 2 was a multiple dose assessment at 180mg in a single cohort of 8 subjects aged 18 to 45 years (randomised 3:1 active to placebo). Part 3 was a single dose assessment at 180mg in a single cohort of 8 older healthy cohort of male & female participants aged 65 to 80 years to allow comparison of the safety and PK with the Part 1 younger adult cohort aged 18 to 45.

Study participants in Parts 1 and 3 received a single subcutaneous (SC) administration on a single occasion, and participants in Part 2 received SC injections twice daily (12 hourly) for 5 days on 10 occasions approximately 2 h after receiving a light breakfast or after evening meal.

RESULTS

A total of 55 healthy participants were screened and enrolled in this three parts first-in-human study, and all the study participants enrolled completed the study per protocol. There were no major protocol deviations and no serious adverse events. All adverse events (AE) were mild in severity and clinically judged to be not related to amilo-5MER, except one subject who reported a mild headache at 30mg dose in Part 1. All AEs resolved within the clinical phase of the study (observation period) and no abnormal trend was seen in any system organ class.



Amilo-5MER's Time of maximum observed concentration (Tmax) occurred between 0.25 h and 1.02 h post-dose in all participants. Increases in area under the curve (AUC) exposures, based on AUC(0-t) and AUC(0-inf), were dose proportional over the 10 mg to 360 mg single dose range. Increases in Cmax, were also broadly consistent with dose proportionality. Amilo-5MER elimination half-life (T1/2) was approximately 0.5-0.7 hours. No accumulation was observed following BID dosing. Following a single 180 mg SC dose to elderly subjects, mean Cmax, AUC (0-t) and AUC (0-inf) appeared higher than in young adults, with exposures approximately 39%, 26% and 30% higher respectively, though the differences were not statistically significant.

The key geometric mean (geometric CV %), PK parameters for plasma amilo 5MER following single SC doses of Amilo-5MER solution in the fed state are summarised in Table 1 below.

Table 1: Part 1 (SAD) - Pharmacokinetic profile of Amilo-5MER

Dose level/ No. of Subjects	Young adult subjects					Elderly subjects
	10 mg (N=6)	30 mg (N=6)	90 mg (N=5)	180 mg (N=6)	360 mg (N=6)	180 mg (N=6)
Parameter						
T_{max} (h)	0.38 (0.25-0.75)	0.40 (0.25-1.01)	0.75 (0.50-0.76)	0.62 (0.50-1.02)	0.52 (0.50-0.75)	0.50 (0.50-0.75)
C_{max} (ng/mL)	96.2 (52.5%)	238 (62.8%)	545 (40.7%)	904 (33.0%)	2610 (23.5%)	1260 (45.5%)
$AUC_{(0-12)}$ (ng.h/mL)	102 (29.5%)	313 (29.4%)	852 (16.2%)	1690 (30.1%)	4270 (31.2%)	2120 (14.6%)
$AUC_{(0-24)}$ (ng.h/mL)	102 (29.5%)	313 (29.4%)	852 (16.2%)	1690 (30.1%)	4270 (31.2%)	2120 (14.5%)
$AUC_{(0-t)}$ (ng.h/mL)	98.6 (31.3%)	310 (29.7%)	845 (15.6%)	1680 (29.9%)	4270 (31.2%)	2110 (14.7%)
$AUC_{(0-inf)}$ (ng.h/mL)	102 (29.5%)	313 (29.4%)	852 (16.2%)	1690 (30.1%)	4270 (31.2%)	2190 (13.7%) [n=5]*
$T_{1/2}$ (h)	0.543 (51.7%)	0.497 (45.7%)	0.612 (55.0%)	0.717 (21.8%)	0.618 (24.9%)	0.634 (39.0%) [n = 5]*

*Abbreviations: Cmax: Maximum concentration; AUC: Area under the curve (= exposure); T1/2 : Plasma half-life; h: Hour; ng: Nanogram; mL: Millilitre; * The AUC(0-inf) profile for Subject 318 was flagged and excluded from the formal statistical analysis as the Adjusted rsq (the coefficient of determination) of regression was found to be <0.9*

The key geometric mean (geometric CV%) PK parameters for plasma amilo-5MER following multiple SC doses of 180 mg amilo-5MER for 5 days in the fed state are summarised in Table 2 below.

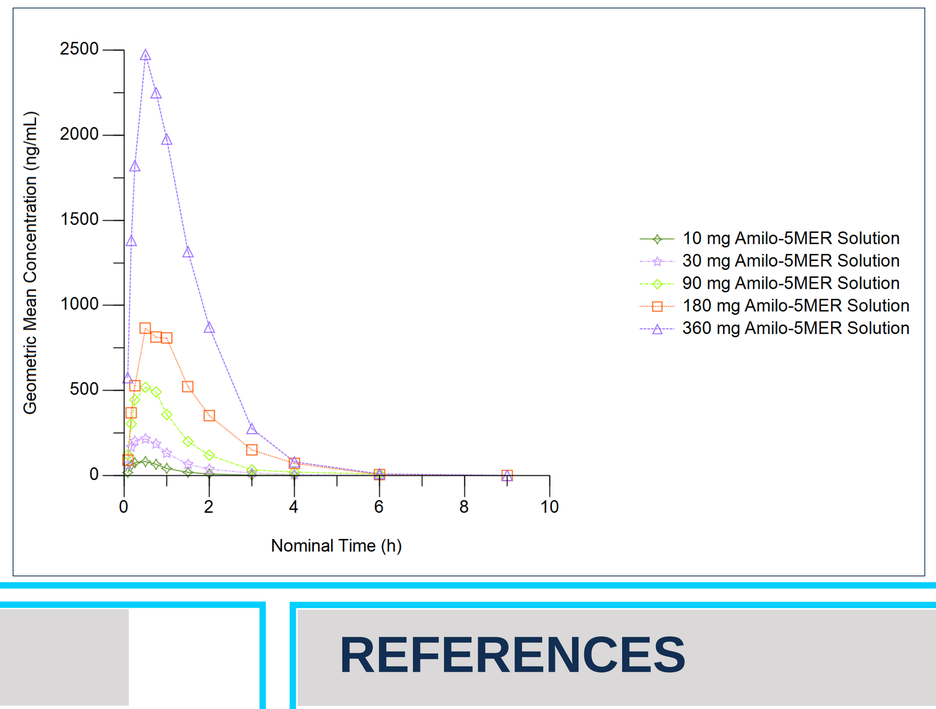
Table 2: Part 2 (MAD) - Pharmacokinetic profile of Amilo-5MER

Day	Day 1	Day 5
Dose Level / No. of Subjects	180 mg BID (N = 6)	180 mg BID (N = 6)
Parameter		
T_{max} (h)	0.63 (0.42-1.00)	0.51 (0.25-0.75)
C_{max} (ng/mL)	1040 (41.5%)	1030 (27.7%)
C_{tau} (ng/mL)	BLQ (NC)	0.72 (116.2%)
$AUC_{(0-tau)}$ ng.h/mL	2080 (29.1%)	1890 (16.1%)
$T_{1/2}$ (h)	NA	0.73 (47.8%)
AR C_{max}	NA	0.985 (23.8%)
AR AUC	NA	0.908 (16.0%)

For Tmax Median (range) is shown. Abbreviations: Tmax: Time to maximum concentration; Cmax: Maximum concentration; AUC: Area under the curve (= exposure); T1/2 : Plasma half-life; h: Hour; ng: Nanogram; mL: Millilitre; NA: Not applicable; BLQ: Below the limit of quantification; NC: Not calculable; BID: Twice daily dosing, tau: dosing interval (12h)

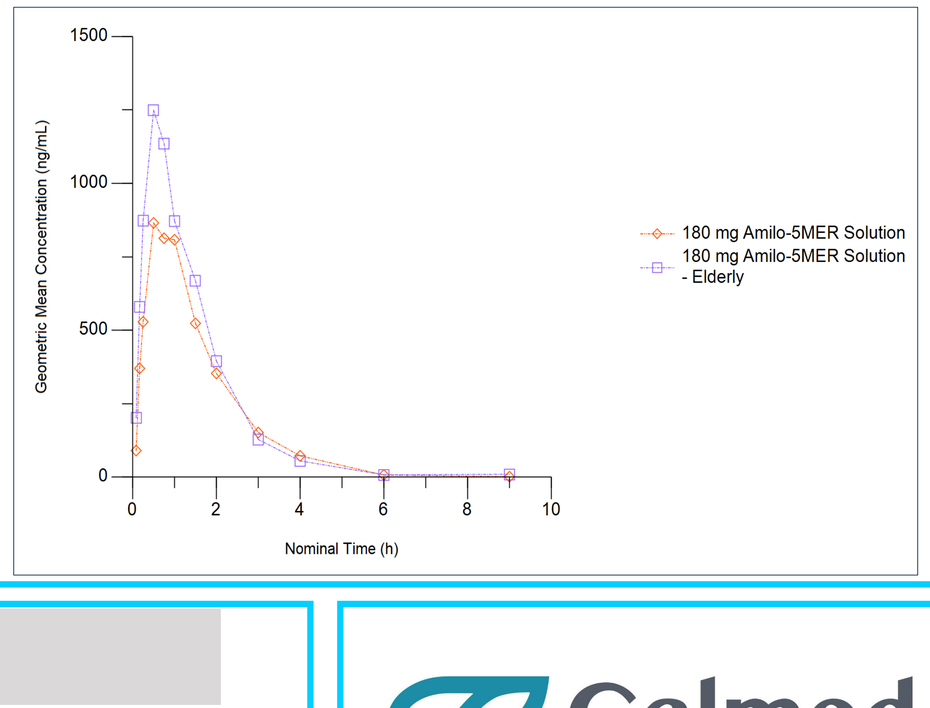
The geometric mean PK concentrations for plasma amilo-5MER following single SC doses of Amilo-5MER solution in the fed state to healthy young adult volunteers are summarised in Figure 1 on the right.

Figure 1



The geometric mean PK concentrations for plasma amilo-5MER following single SC 180 mg doses of Amilo-5MER solution in the fed state to healthy young adult and elderly volunteers are summarised in Figure 2 on the right.

Figure 2



CONCLUSIONS

The excellent safety & PK profile of Amilo-5MER with good tolerability in young and elderly healthy participants support further clinical development of the Amilo-5MER in a patient population.

REFERENCES

Bod1. Hemed-Shaked M, Cowman MK, Kim JR, et al. MTADV 5-MER peptide suppresses chronic inflammations as well as autoimmune pathologies and unveils a new potential target-Serum Amyloid A. J Autoimmun. 2021;124:102713. doi:10.1016/j.jaut.2021.102713

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