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Safety, Tolerability, and Efficacy of Single-dose AMG 890, a Novel siRNA Targeting Lp(a), in Healthy Subjects and Subjects With Elevated Lp(a)

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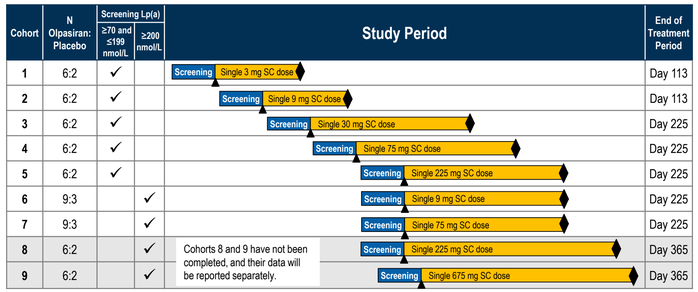
Background & Objective

- Lipoprotein(a) [Lp(a)] is a risk factor for myocardial infarction and other atherosclerotic events[1-3]
- No approved medicines selectively target Lp(a) and have demonstrated reduction in cardiovascular events
- Olpasiran (AMG 890) is a small interfering ribonucleic acid (siRNA) designed to reduce the production of Lp(a) by targeting messenger RNA transcribed from the *LPA* gene
- In this study (NCT 03626662), we evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of olpasiran

Methods

- Adults with plasma concentrations at screening of Lp(a) ≥70 to ≤199 nmol/L (cohorts 1–5) or ≥200 nmol/L (cohorts 6–7), were randomized 3:1 to receive a single subcutaneous dose of olpasiran or placebo (**Figure 1**)
- The primary endpoints were treatment-emergent adverse events, safety laboratory analytes, vital signs, and ECGs. Secondary endpoints included PK parameters and percent change from baseline in Lp(a)

Figure 1. Study Design



Screening was Day -28 to Day -1. ▲ = Dosing (Day 1). ◆ = End of treatment period. Subjects were to return for follow-up until Lp(a) was at least 80% of baseline (mean of screening and day 1 pre-dose values). Escalation to the next cohort occurred only after blinded assessment of safety and tolerability at each dose level after all subjects had been followed for 15 days. For cohorts 1-5 and 9, the first 2 subjects who received olpasiran and placebo (the sentinel pairs) were to be assessed for safety for at least 24 hours before completing the cohort. For cohorts 6–9, at least 6 subjects per cohort were to be on stable doses of statins for at least 6 weeks.

Disclosures & Acknowledgements

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- This study was funded by Amgen. Ellen Stoltzfus, PhD, (Amgen Inc.) provided medical writing assistance
- Olpasiran is an unlabeled/unapproved product

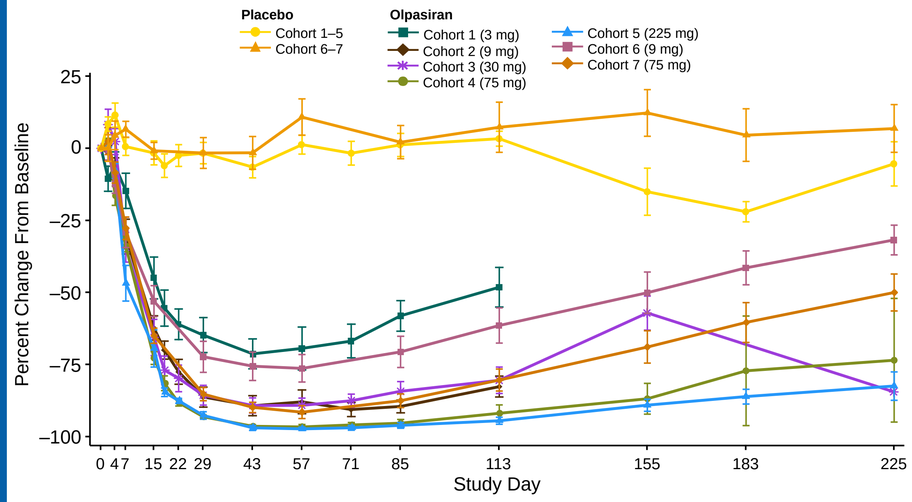
During the treatment period, one dose of olpasiran:

- **Was well tolerated**
- **Significantly reduced Lp(a) with observed approximate median percent reductions of >90% at doses ≥9 mg**
- **Led to reductions in Lp(a) persisting 3 to 6 months at doses ≥9 mg**

Table 1. Treatment-emergent Adverse Events

Adverse events, n (%)	Cohorts 1–5 Screening Lp(a) ≥70 and ≤199 nmol/L		Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L	
	Placebo (N=10)	Olpasiran (N=30)	Placebo (N=6)	Olpasiran (N=18)
Any AE	5 (50.0)	12 (40.0)	4 (66.7)	10 (55.6)
Serious AE	0	0	1 (16.7)	0
AEs occurring in more than one subject across cohorts				
Headache	1 (10.0)	0	3 (50.0)	5 (27.8)
Upper respiratory tract infection	1 (10.0)	4 (13.3)	1 (16.7)	3 (16.7)
Back pain	1 (10.0)	1 (3.3)	0	3 (16.7)
Non-cardiac chest pain	1 (10.0)	1 (3.3)	1 (16.7)	0
Viral upper respiratory tract infection	0	1 (3.3)	0	2 (11.1)
Blood creatine phosphokinase increased	1 (10.0)	1 (3.3)	0	0
Contusion	0	1 (3.3)	0	1 (5.6)
Skin abrasion	0	1 (3.3)	0	1 (5.6)
Fatigue	0	0	1 (16.7)	1 (5.6)
Arthralgia	0	1 (3.3)	0	1 (5.6)
Epistaxis	1 (10.0)	0	1 (16.7)	0
AEs of special interest				
Injection site reaction	0	1 (3.3)	0	0

Figure 2. Lp(a) Percent Change from Baseline After a Single Dose of Placebo or Olpasiran



Baseline values are the mean of screening and day 1 pre-dose values. If only 1 value was available, that value was used as the baseline value.
As-is data snapshot date: 21Oct2020

Results

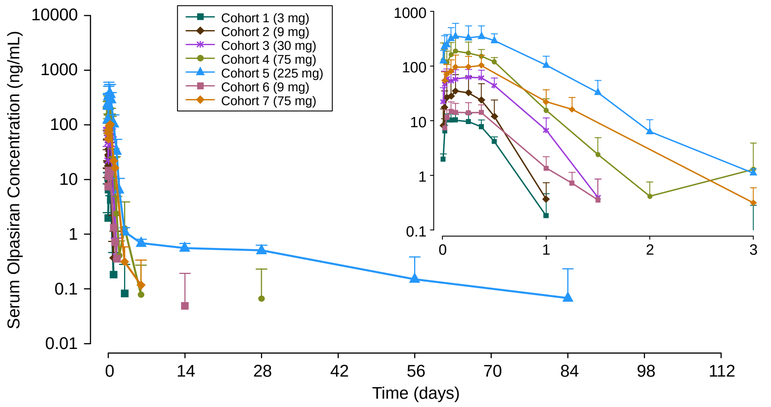
Table 2. Baseline Characteristics

Baseline Characteristic		Cohorts 1–5 Screening Lp(a) ≥70 to ≤199 nmol/L		Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L	
		Placebo (N=10)	Olpasiran (N=30)	Placebo (N=6)	Olpasiran (N=18)
Age (years), mean (SD)		46.3 (8.5)	43.9 (13.5)	57.8 (5.8)	52.7 (9.4)
Women, n (%)		3 (30.0)	9 (30.0)	4 (66.7)	6 (33.3)
Ethnicity, n (%)	Hispanic/Latino	5 (50.0)	19 (63.3)	2 (33.3)	5 (27.8)
	Not Hispanic/Latino	5 (50.0)	11 (36.7)	4 (66.7)	13 (72.2)
Race, n (%)	Black	3 (30.0)	9 (30.0)	0	1 (5.6)
	White	7 (70.0)	21 (70.0)	5 (83.3)	16 (88.9)
	Other	0	0	1 (16.7)	1 (5.6)
BMI, kg/m^2, mean (SD)		27.6 (3.5)	27.0 (3.6)	28.1 (2.1)	27.7 (3.3)
Lp(a) nmol/L, median (Q1, Q3)		124 (104, 137)	122 (97, 146)	272 (233, 307)	253 (224, 334)

Pharmacokinetic Results

- Olpasiran was rapidly absorbed with mean C_{max} occurring within 7.5 hours after dosing. Mean half-life ($t_{1/2}$) ranged from 3 to 8 hours with the vast majority eliminated from serum within 2 to 3 days
- Olpasiran AUC exposures in subjects with Lp(a) ≥200 nmol/L (Cohorts 6 and 7) were 18–33% lower than in subjects with Lp(a) ≥70 to ≤199 nmol/L (Cohorts 2 and 4)

Figure 3. Mean (SD) Serum Olpasiran Concentration-Time Profiles Following A Single SC Administration of 3, 9, 30, 75, or 225 mg



Conclusions

- No safety concerns were identified for olpasiran in this single dose study
  - No clinically relevant changes in liver tests, platelets or coagulation parameters, or renal function were observed
- Systemic exposures of olpasiran increased approximately dose-proportionally
- In adults with elevated Lp(a) (median Lp(a) = 122 nmol/L [cohorts 1 to 5] and 253 nmol/L [cohorts 6 and 7], a single dose of olpasiran significantly reduced Lp(a) with observed approximate median percent reductions of >90% at doses of ≥9 mg in a dose-dependent manner
  - Lp(a) reductions persisted for 3 to 6 months at doses of ≥9 mg
  - Per the protocol, follow-up is ongoing until patients return to 80% of baseline Lp(a)
- These results validate the approach of using hepatocyte-targeted siRNA to lower Lp(a) in people with elevated Lp(a)
- Olpasiran recently received a Fast Track Designation from the US Food and Drug Administration. A Phase 2 study to evaluate efficacy, safety, and tolerability of olpasiran in subjects with elevated Lp(a) is currently underway

References

1. Nordestgaard BG, et al. *Eur Heart J.* 2010;31:2844-2853.
2. Wilson DP, et al. *J Clin Lipidol.* 2019;13(3):374-392.
3. Mach F, et al. *Eur Heart J.* 2020;41(1):111-188.