LEGACY

Phase 2a Trial to Evaluate the Safety, Pharmacokinetics and Pharmacodynamic Effects of the Anti-Endothelial Lipase Antibody MEDI5884 in Subjects with Stable CAD

Christian T. Ruff[1], Joseph Grimsby[2], Anton Rosenbaum[2], Chao Yu Jin[2], Lan-Feng Tsai[2], Sotirios Karathanasis[2], Judith Falloon[2], Tim Hummer[2], Xiao Tu[2], Judith Hsia[2], Boaz Hirshberg[2], Michael J. Koren[3], Marc S. Sabatine[1]

[1]TIMI Study Group, Brigham and Women's Hospital, Boston, MA; [2]MedImmune, LLC, Gaithersburg, MD; [3]JCCR, Jacksonville, FL

Background

- Even with marked lowering of LDL-C, patients with CAD remain at significant risk of CV events.
- Elevated HDL-C is one of the strongest epidemiologic surrogates for protection against CHD but functional HDL particles that facilitate cholesterol efflux may be the main driver of cardioprotection.
- Endothelial lipase (EL) hydrolyzes HDL phospholipids resulting in catabolism of HDL and renal excretion. Loss-of-function EL gene mutations are associated with higher HDL-C, increased cholesterol efflux and lower CV risk.
- MEDI5884 is a selective, humanized, monoclonal EL neutralizing antibody.

Methods

- LEGACY was a phase 2a, double-blind, placebo-controlled, parallel-designed trial (NCT03351738) that randomized 132 subjects 45-80 years of age with stable CAD receiving high-intensity statin therapy with an LDL-C ≤ 100 mg/dL to 3 monthly doses of one of 5 dose levels of the EL inhibitor MEDI5884 (50, 100, 200, 350, or 500 mg SC) or matching placebo.
- The primary EP was the safety and tolerability of MEDI5884 through the end of the study (Day 151). Additional EPs included change in HDL-C and cholesterol efflux from baseline to Day 91 compared to placebo as well as various other lipids, lipoproteins, and apolipoproteins (ANCOVA adjusted by baseline value and treatment group).

Results

- 132 subjects underwent randomization to one of the 5 MEDI5884 treatment groups (109 subjects) or placebo (23 subjects).
- The baseline characteristics across treatment groups were similar: mean age 66 years, 87% were men and 44% of the subjects had a history of MI. All subjects were taking high-intensity statin therapy and 6% were also taking ezetimibe.

Baseline Characteristics

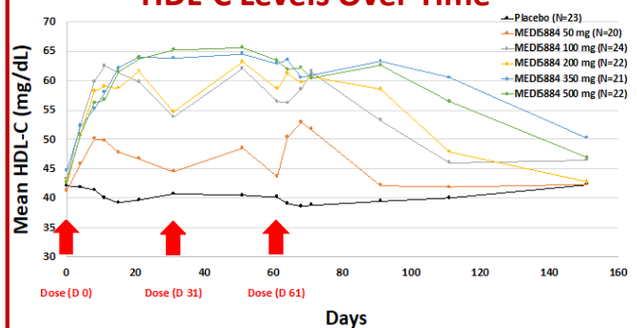
	MEDI5884					Placebo	Total
	50 mg (N=20)	100 mg (N=24)	200 mg (N=22)	350 mg (N=21)	500 mg (N=22)	(N=23)	(N=132)
Age, mean	64	67	65	67	68	66	66
Male sex (%)	85	96	82	95	82	83	87
CV risk factors (%)							
Hypertension	85	88	91	86	91	87	88
Diabetes	65	50	41	48	41	52	49
MI (%)	30	50	45	43	45	48	44
Statin use (%)							
Atorva 40-80 mg	95	96	82	90	77	87	88
Rosuva 20-40 mg	5	4	18	10	23	13	12
Ezetimibe	5	4	9	5	5	9	6
Mean lipids, mg/dL							
Total cholesterol	137	130	137	129	126	129	131
LDL cholesterol	71	70	75	66	64	68	69
HDL cholesterol	41	43	43	45	43	42	43
Triglycerides	173	109	133	130	123	121	131

- AEs were balanced between placebo and MEDI5884 groups. There were few SAEs and none were thought to be related to study drug.
- Antidrug antibodies were uncommon, low titer and similar between placebo & MEDI5884 groups.

	MEDI5884					Placebo
	50 mg (N=20)	100 mg (N=24)	200 mg (N=22)	350 mg (N=21)	500 mg (N=22)	(N=23)
Adverse event - n (%)						
AE	10 (50)	11 (46)	12 (55)	13 (62)	13 (59)	17 (74)
SAE	2 (10)	1 (4)	0	4 (19)	0	2 (9)
related to study agent	0	0	0	0	0	0
Injection site reactions - n (%)						
Mild	0	1 (4)	3 (14)	4 (19)	1 (5)	3 (13)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Antidrug Antibodies - n (%)						
Baseline	0	1 (4)	1 (5)	0	1 (5)	1 (4)
Median titer	NA	320	10	NA	40	10
Post-baseline	1 (5)	2 (8)	4 (18)	3 (14)	4 (18)	2 (9)
Median of maximum titer	10	120	10	20	40	10

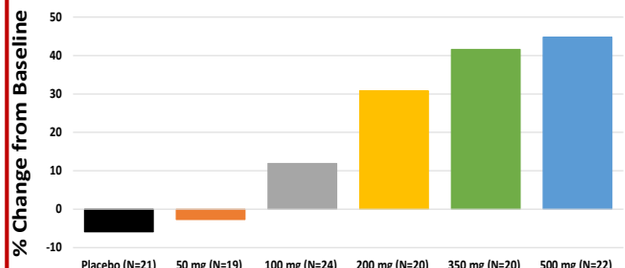
- MEDI5884 increased HDL-C up to 51% (p<0.0001) compared to placebo.

HDL-C Levels Over Time



- Compared to placebo, MEDI5884 also increased:
  - ApoA1: up to 36% (p<0.0001)
  - HDL particle number: up to 14% (p<0.0001)
  - HDL size: up to 6% (p<0.0001)
- MEDI5884 increased non-ABCA1 cholesterol efflux up to 51% (p<0.0001) compared to placebo.

Mean Non-ABCA1 Cholesterol Efflux Capacity



- An increase in LDL-C up to 29% (p<0.0001) and apoB up to 13% (p=0.04) was observed with MEDI5884 compared to placebo but with a decrease in small dense LDL-C by up to 34% (p=0.0006).

Conclusions

- Inhibition of EL by MEDI5884 increases the quantity of functional HDL in subjects with stable CAD on high-intensity statin therapy.
- MEDI5884 warrants further clinical investigation to determine if it prevents progression of atherosclerosis.

Disclosures – CTR and MSS are members of the TIMI Study Group which has received institutional research grant support through Brigham and Women's Hospital from: Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, Zora Biosciences. CTR has received honoraria for advisory boards and consulting from: Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Janssen, MedImmune, Pfizer, Portola, Anthos. JG, AR, CYJ, LFT, SK, JF, TH, XT, JH and BH are employees of MedImmune/AstraZeneca. MJK an employee of a company that has received research study grants and modest consulting fees from MedImmune and AstraZeneca. MSS reports significant research grant support from Abbott Laboratories, Amgen, AstraZeneca, Bayer, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, Gilead, GlaxoSmithKline, Intarcia, Janssen Research and Development, The Medicines Company, MedImmune, Merck, Novartis, Poxel, Pfizer, Quark Pharmaceuticals, Roche Diagnostics, and Takeda; has received modest consulting feest from Alnylam, AstraZeneca, Bristol-Myers Squibb, CVS Caremark, Dyrnamix, Esperion, IFM Pharmaceuticals, Intarcia, Ionis, Janssen Research and Development, The Medicines Company, MedImmune, Merck, MyoKardia, and Novartis; and has received significant consulting fees from Amgen.