Efficacy and Safety of the PCSK9 Inhibitor Alirocumab 300 mg Every 4 Weeks in Individuals with Type 2 Diabetes on Maximally Tolerated Statin Therapy

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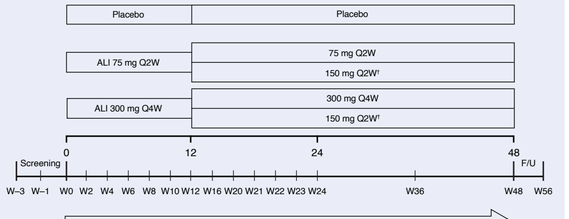
Background

- Individuals with diabetes and elevated low-density lipoprotein cholesterol (LDL-C) are at high to very-high risk for atherosclerotic cardiovascular disease (ASCVD).[1,2]
- Recently published statements, including the 2016 consensus statements from the American College of Cardiology and the European Society of Cardiology/European Atherosclerosis Society Task Force, state that it may be reasonable to consider therapy with proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors in patients with ASCVD or diabetes (with target organ damage or with a major cardiovascular risk factor) who are not adequately treated with statins and ezetimibe.[3–6]
- ODYSSEY CHOICE I (NCT01926782) assessed the efficacy and safety of the PCSK9 inhibitor alirocumab at a dose of 300 mg every 4 weeks (Q4W) in individuals with hypercholesterolemia who received either maximally tolerated statin or no statin.[7]
- This analysis evaluated the efficacy and safety of alirocumab in a participant subgroup with type 2 diabetes (T2DM) on maximally tolerated statins from CHOICE I.

Methods

- In the CHOICE I study, individuals received either alirocumab 300 mg Q4W (n=458), alirocumab 75 mg every 2 weeks (Q2W; calibrator arm) (n=115), or placebo (n=230) for 48 weeks (Figure 1).
- This analysis focused on individuals with T2DM (defined according to medical history) who received maximally tolerated statin with or without other lipid-lowering therapies.
- Efficacy endpoints included percentage change from baseline to Week 24 for LDL-C and time averaged LDL-C over Weeks 21–24, and percentage change from baseline to Week 24 for non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein (Apo) B, triglycerides (TGs), HDL-C, lipoprotein (a) [Lp(a)], and ApoA1.
- Additional efficacy endpoints included the impact of dose adjustment, and the percentage of subjects achieving LDL-C <70 mg/dL and non-HDL-C <100 mg/dL at Week 24.

Figure 1. CHOICE I study design



†The dose was adjusted to 150 mg Q2W at Week 12 if Week 8 LDL-C levels were ≥70/100 mg/dL, depending on cardiovascular risk, or if LDL-C reduction was <30% from baseline.
ALI, alirocumab; F/U, follow-up.

Results

- Individuals identified as having T2DM received either alirocumab 300 mg Q4W (n=96; with possible dose adjustment to 150 mg Q2W at Week 12, to be referred to as "300Q4W") or placebo (n=50) for 48 weeks.
- Baseline characteristics were similar in the alirocumab and placebo groups (Table 1).
  - The percentage of subjects on other lipid-lowering therapies in addition to statins was slightly higher in the alirocumab 300Q4W group, and slightly fewer subjects received glucose-lowering therapy versus the placebo group.

Efficacy

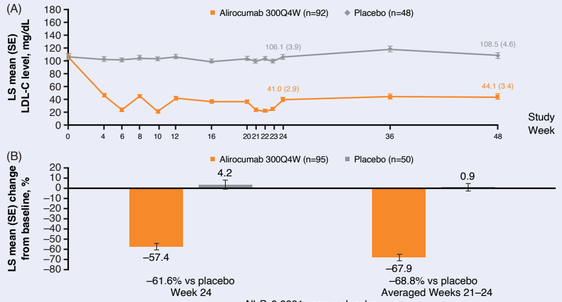
- LDL-C reductions with alirocumab 300Q4W were observed from Week 4 and maintained up to Week 48 (Figure 2A).
  - Reductions from baseline to Week 24 and average reductions from baseline to Weeks 21–24 were significantly greater with alirocumab 300Q4W versus placebo (Week 24 61.6%; averaged Weeks 21–24 68.8%; *P*<0.0001; Figure 2B).

Table 1. Baseline characteristics (randomized population)

	Individuals with T2DM on maximum tolerated statin (n=146)	
	Alirocumab 300Q4W (n=96)	**Placebo (n=50)**
Age, years, mean (SD)	62.8 (9.0)	62.6 (9.0)
BMI, kg/m², mean (SD)	33.6 (6.9)	34.5 (6.4)
ASCVD, n (%)	58 (60.4)	29 (58.0)
Hypertension, n (%)	85 (88.5)	44 (88.0)
LLT treatments other than statins, n (%)	33 (34.4)	13 (26.0)
Ezetimibe	12 (12.5)	5 (10.0)
Nutraceuticals	12 (12.5)	6 (12.0)
Fibrates	8 (8.3)	3 (6.0)
Bile acid sequestrants	0	0
Omega-3 fatty acids	10 (10.4)	5 (10.0)
Nicotinic acid and derivatives	3 (3.1)	1 (2.0)
Individuals with CKD, n (%)	5 (5.2)	5 (10.0)
Mild CKD/normal renal function	1 (1.0)	0
Moderate CKD	4 (4.2)	5 (10.0)
Fasting plasma glucose, mg/dL, mean (SD)	127.0 (39.3)	136.4 (46.9)
HbA1c, %, mean (SD)	6.9 (0.9)	6.9 (0.8)
eGFR, mL/min/1.73m², mean (SD)	74.9 (19.5)	74.8 (21.4)
Diastolic blood pressure, mmHg, mean (SD)	78.4 (8.5)	77.6 (9.5)
Systolic blood pressure, mmHg, mean (SD)	131.1 (12.2)	132.5 (13.6)
Individuals on insulin, n (%)	26 (27.1)	14 (28.0)
Individuals on glucose-lowering therapy, n (%)	72 (75.0)	44 (88.0)
Lipids, mg/dL, mean (SD)		
LDL-C	106.8 (29.4)	106.5 (35.7)
Non-HDL-C	139.2 (33.4)	136.0 (40.7)
HDL-C	46.2 (11.6)	44.9 (11.2)
TGs, median (Q1:Q3)	150.0 (106.5:196.0)	128.0 (103.0:185.0)
Lp(a), median (Q1:Q3)	20.0 (6.0:56.0)	20.5 (7.0:58.5)
ApoB	96.9 (20.9)	93.4 (24.7)
ApoA1	146.0 (23.6)	137.1 (26.0)

Mild CKD/normal renal function defined as eGFR 60–89/a90 mL/min/1.73m²; moderate CKD defined as eGFR 30–59 mL/min/1.73m²; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; LLT, lipid-lowering therapy; SD, standard deviation.

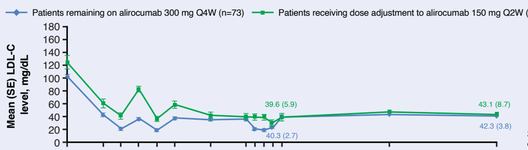
Figure 2. Mean calculated LDL-C levels (A) over time,† and (B) percentage change from baseline to Week 24‡ and averaged Weeks 21–24‡ in individuals with T2DM on maximally tolerated statin



For Weeks 24 and 48, absolute (SE) LDL-C values for the alirocumab and placebo groups are presented on the graphs.
†On-treatment population. ‡Intention-to-treat population.
LS, least squares.

- In the alirocumab group, 18% of patients received an adjusted dose of 150 mg Q2W at Week 12, which resulted in similar LDL-C reductions at Weeks 24 and 48 in these patients as well as those remaining on 300 mg Q4W (Figure 3).

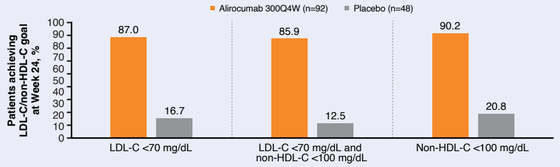
Figure 3. Impact of dosing/frequency adjustment (on-treatment population)



For Weeks 24 and 48, absolute (SE) LDL-C values for the alirocumab and placebo groups are presented on the graphs.

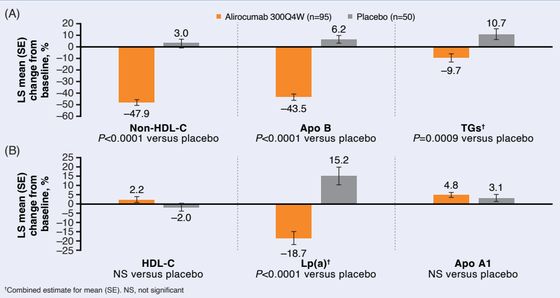
- At Week 24, most participants treated with alirocumab 300Q4W achieved LDL-C <70 mg/dL and non-HDL-C <100 mg/dL (85.9%; placebo 12.5%) (Figure 4).

Figure 4. Percent of individuals achieving LDL-C <70 mg/dL and non-HDL-C <100 mg/dL at Week 24 (on-treatment population)



- From baseline to Week 24, alirocumab 300Q4W significantly reduced levels of non-HDL-C, Apo B, TGs, and Lp(a) (Figure 5).

Figure 5. Percentage change from baseline to Week 24 in (A) non-HDL-C, ApoB, and TGs, and (B) HDL-C, Lp(a), and ApoA1 (intention-to-treat population)



†Combined estimate for mean (SE). NS, not significant

Safety

- In total, 84.4% (alirocumab 300Q4W) and 74.0% (placebo) of individuals with T2DM experienced treatment-emergent adverse events (TEAEs), with upper respiratory tract infection, diarrhea, injection site reaction, and urinary tract infection among the most common (Table 2).
- The mean (SD) absolute change in glycated hemoglobin (HbA1c) from baseline (alirocumab 300Q4W: 6.9% [0.9]; placebo: 6.9% [0.8]) to Week 24 was similar regardless of treatment allocation (alirocumab 300Q4W: 0.1% [0.7]; placebo: 0.1% [0.7]).
- For fasting plasma glucose (FPG), mean (SD) baseline levels were 127.0 (39.3) mg/dL for alirocumab and 136.4 (46.9) mg/dL for placebo. Mean (SD) change from baseline at Week 24 was 9.0 (50.5) mg/dL in the alirocumab 300Q4W group versus 0.8 (42.2) mg/dL in the placebo group (no significant difference between groups).

Table 2. Safety summary (safety population)

	Individuals with T2DM on maximum tolerated statin (n=146)	
n (%)	**Alirocumab 300Q4W (n=96)**	**Placebo (n=50)**
TEAEs	81 (84.4)	37 (74.0)
Treatment-emergent SAEs	12 (12.5)	7 (14.0)
TEAEs leading to discontinuation	6 (6.3)	2 (4.0)
TEAEs leading to death	0	0
Safety terms of interest		
Adjudicated CV events	3 (3.1)	0
General allergic TEAE	7 (7.3)	6 (12.0)
General allergic serious TEAE (CMQ)	0	1 (2.0)
Neurocognitive disorders	2 (2.1)	0
TEAEs occurring in ≥5% of individuals		
Upper respiratory tract infection	13 (13.5)	3 (6.0)
Diarrhea	3 (3.1)	5 (10.0)
Injection-site reaction	9 (9.4)	2 (4.0)
Urinary tract infection	9 (9.4)	2 (4.0)
Arthralgia	2 (2.1)	4 (8.0)
Back pain	4 (4.2)	4 (8.0)
Nausea	2 (2.1)	4 (8.0)
Nasopharyngitis	6 (6.3)	3 (6.0)
Sinusitis	6 (6.3)	0
Anemia	3 (3.1)	3 (6.0)
Gastroenteritis	2 (2.1)	3 (6.0)
Hypertension	1 (1.0)	3 (6.0)
Bronchitis	5 (5.2)	1 (2.0)

CMQ, custom Medical Dictionary of Regulatory Activities query; CV, cardiovascular; SAE, serious adverse event.

Conclusions

- In individuals with T2DM receiving maximally tolerated statin who required additional LDL-C-lowering, alirocumab 300Q4W significantly improved their lipid profiles.
- At Week 12, dose adjustment from alirocumab 300 mg Q4W to 150 mg Q2W in 18% of individuals resulted in a reduced variability in LDL-C levels from week to week (as observed between Weeks 21–24). Similar LDL-C reductions at Week 24 were seen versus patients remaining on 300 mg Q4W.
- Alirocumab was generally well tolerated; no significant differences were observed in HbA1c and FPG levels.
- The results of this analysis suggest that alirocumab 300Q4W dosing may provide an additional lipid treatment option in individuals with T2DM who receive maximally tolerated statin with/without other lipid-lowering therapies.

References

1. Jacobson TA et al. *J Clin Lipidol.* 2015;9:129–169.
2. Catapano AL et al. *Atherosclerosis.* 2016;253:281–344.
3. Lloyd-Jones DM et al. *J Am Coll Cardiol.* 2016;68:92–125.
4. Landmesser U et al. *Eur Heart J.* 2016 Oct 27 [Epub ahead of print].
5. Garber AJ et al. *Endocr Pract.* 2017;23:207–238.
6. American Diabetes Association. *Diabetes Care* 2017;40(Suppl. 1):S75–S87.
7. Roth EM et al. *Atherosclerosis.* 2016;254:254–262.

Acknowledgments

This analysis was funded by Regeneron Pharmaceuticals, Inc. and Sanofi. Medical writing support was provided by Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc. and Sanofi.

Disclosures

Dirk Müller-Wieland: Received consultant fees/honoraria from Amgen Inc., AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Merck & Co., Inc., Novartis Corporation, Novo Nordisk Inc., and Sanofi-Aventis; and participated in speaker's bureau for Amgen Inc., AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck & Co., Inc., Novartis Corporation, Novo Nordisk Inc., and Sanofi-Aventis. **Daniel J Rader:** Received consultant fees/honoraria from Aegerion Pharmaceuticals, Alnylam, Eli Lilly, MedImmune, Inc., Novartis, and Pfizer; and has ownership interest/partnership/principal in Staten Bio and Vascular Strategies. **Patrick M Moriarty:** Received consultant fees/honoraria from Aegerion, Duke University, Genzyme, Ionis Pharmaceuticals, Inc., Kowa Pharmaceuticals America Inc., Lilly USA, LLC, Regeneron Pharmaceuticals Inc., and Sanofi-Aventis; research/research grants from Amgen Inc., Genzyme, Ionis Pharmaceuticals, Inc., Kaneka, Novartis Corporation, Pfizer Inc., Regeneron Pharmaceuticals, Inc., and Sanofi-Aventis; and participated in speaker's bureau for the National Lipid Association. **Jean Bergeron:** Received consultant fees/honoraria from Aegerion, Amgen, and Sanofi; and research/research grants from Amgen Inc, Ionis, Medicines Company, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi-Aventis. **Gisle Langslet:** Received consultant fees/honoraria from Amgen, Boehringer Ingelheim Pharmaceuticals, Inc., Janssen Pharmaceuticals, and Sanofi. **Kausik K Ray:** Received consultant fees/honoraria from Aegerion, Algorithm, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Eli Lilly and Company, Ionis Pharma, Kowa, Medicines Company, MSD, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Resverlogix, Sanofi, and Takeda; was on the data safety monitoring board for AbbVie, Inc.; and received research/research grants from Kowa, Pfizer, and Regeneron Pharmaceuticals, Inc. **Garen Manvelian and Desmond Thompson:** Employees of and Stockholders in Regeneron Pharmaceuticals, Inc. **Maja Bujas-Bobanovic:** Employee of and Stockholder in Sanofi. **Eli M Roth:** Received consultant fees/honoraria from Regeneron Pharmaceuticals Inc. and Sanofi; and participated in speaker's bureau for Amarin, Amgen, AstraZeneca, and Merck & Co., Inc.

Poster presented at the American College of Cardiology 66th Annual Scientific Sessions, March 17–19, 2017, Washington, DC, USA.