Incremental Benefit of Atherogenic Cholesterol Reduction With Obicetrapib Administered With Moderate-Intensity Statins

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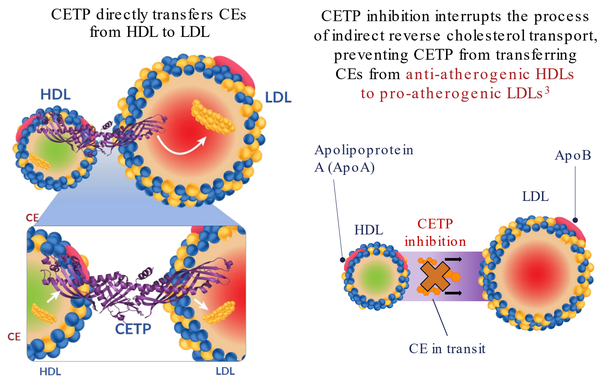
Background

- Robust evidence demonstrates that reducing the concentration of low-density lipoprotein cholesterol (LDL-C) results in a significant reduction in the risk of having a major cardiovascular (CV) event[1,2]
- Despite treatment with statins and other lipid-lowering therapies (LLTs), many patients remain at an unacceptably high residual risk of experiencing a future CV event[3,4]
- This finding has stimulated a major effort to develop drugs that provide additional lowering of LDL-C when administered with a statin[5-7]
- Several LDL-C-lowering strategies are being investigated, including cholesteryl ester transfer protein (CETP) inhibitors that interrupt the process of indirect reverse cholesterol transport, preventing CETP from transferring cholesterol esters (CEs) from anti-atherogenic high-density lipoproteins (HDLs) to pro-atherogenic low-density lipoproteins (LDLs)[8] (**Figure 1**)
- Obicetrapib is a novel, oral CETP inhibitor in phase 3 development for the treatment of patients at risk for CV disease with elevated LDL-C[7]

Figure 1. CETP inhibition reduces atherogenic apolipoprotein B (ApoB)-carrying lipoproteins



OBJECTIVE

- To investigate, in results from prior trials, the efficacy and safety of a potential fixed dose of obicetrapib with low-dose atorvastatin or rosuvastatin

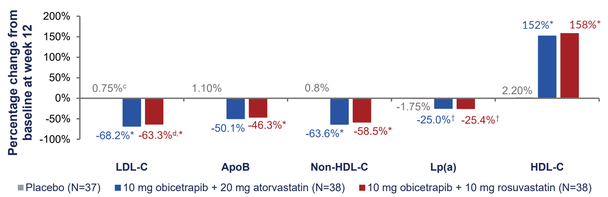
Methods

- Two multicenter, randomized, double-blind, placebo-controlled phase 2 trials were conducted in the Netherlands, Denmark (TULIP, NCT01970215), and Japan (NCT05421078)
- In TULIP, participants (n=364) were 18 to 75 years of age not taking LLT (or after washout) with LDL-C 96.7 to 174 mg/dL, high-density lipoprotein cholesterol (HDL-C) 30.9 to 69.6 mg/dL, and triglycerides <399 mg/dL
- Participants received 1, 2.5, 5, or 10 mg obicetrapib or matching placebo; or 10 mg obicetrapib + 20 mg atorvastatin, 10 mg obicetrapib + 10 mg rosuvastatin, or 20 mg atorvastatin or 10 mg rosuvastatin alone for 12 weeks. Percent change from baseline in LDL-C, ApoB, non-HDL-C, lipoprotein (a) (Lp[a]), and HDL-C and adverse events (AEs) were assessed at 12 weeks
- In the Japan trial, participants (n=102) included Japanese men and women 18 to 80 years of age with LDL-C >70 mg/dL or non-HDL-C >100 mg/dL and triglycerides <400 mg/dL within the past 3 months and were taking atorvastatin 10 or 20 mg per day or rosuvastatin 5 to 10 mg per day for ≥8 weeks prior to screening
- Participants received 2.5, 5, or 10 mg/day obicetrapib or matching placebo as an adjunct to stable statin for 8 weeks. Percent change from baseline in LDL-C, ApoB, non-HDL-C, and HDL-C and AEs were assessed at 8 weeks

Results

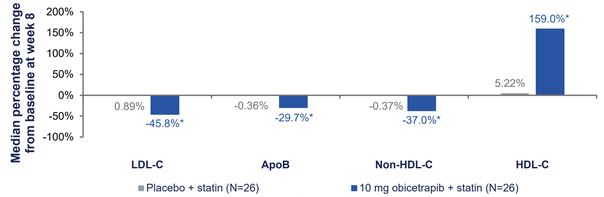
- In both trials, all atherogenic lipoproteins were significantly reduced and HDL-C was significantly increased from baseline in all obicetrapib monotherapy and combination therapy arms vs their respective controls (all *P*<0.01) (**Figures 2 and 3**)
- Across both trials, treatment with obicetrapib was generally safe and well tolerated when administered alone and in combination with statins (**Tables 1 and 2**)
  - In TULIP, rates of withdrawal due to AEs were low and similar between treatment groups and no effects on laboratory safety parameters, serum electrolyte concentrations, or blood pressure were noted
  - In the Japan trial, all treatment-emergent adverse events (TEAEs) were mild or moderate in severity and unrelated to the study drug; there were no TEAEs that led to study drug discontinuation or withdrawal from the study, and no deaths were reported during the study. There were also no clinically meaningful changes in biochemical safety measures or vital signs in any group

Figure 2. Percent change from baseline at week 12 in LDL-C and HDL-C (coprimary endpoints) and other lipoproteins in TULIP[a,b]



[a]Data are least-squares mean (95% CI); Lp(a) is presented as median (25-75th percentiles). [b]N includes all patients who received at least one dose of study drug and had both baseline and week 12 data. [c]N=36. [d]N=37. **P*<0.0001. †*P*<0.01.

Figure 3. Percent change from baseline at week 8 in LDL-C (primary endpoint) and other lipoproteins in the Japan trial[a]



[a]*P* values are from a mixed model for repeated measures with treatment, visit, and treatment-by-visit as factors and baseline value as a covariate. Missing at random was assumed for all missing data. **P*<0.0001.

Table 1. Rates of adverse events occurring in >5% of patients receiving 10 mg obicetrapib monotherapy in TULIP[a,b]

Adverse Events	Randomized Treatment Group			
	Placebo	10 mg obicetrapib	20 mg atorvastatin + 10 mg obicetrapib	10 mg rosuvastatin + 10 mg obicetrapib
N[c]	40	40	40	41
N with any AEs	32 (80%)	33 (83%)	28 (70%)	34 (83%)
N with severe AEs	2 (5%)	2 (5%)	2 (5%)	3 (7%)
N with serious AEs	0	2 (5%)	1 (3%)	1 (2%)
N with AE leading to interruption/withdrawal	4 (10%)	5 (13%)	4 (10%)	0
Nasopharyngitis	7 (18%)	8 (20%)	14 (35%)	6 (15%)
Headache	7 (18%)	8 (20%)	4 (10%)	6 (15%)
Abdominal pain upper	0	2 (5%)	0	0
Myalgia	2 (5%)	1 (3%)	0	2 (5%)
Influenza	1 (3%)	4 (10%)	0	3 (7%)
Back pain	3 (8%)	2 (5%)	1 (3%)	5 (12%)
Diarrhea	1 (3%)	2 (5%)	4 (10%)	2 (5%)
Dizziness	2 (5%)	1 (3%)	0	1 (2%)
Influenza like illness	1 (3%)	0	1 (3%)	1 (2%)
Cough	1 (3%)	0	0	1 (2%)

[a]Data are presented as number of patients (% of population per treatment group) unless otherwise indicated. [b]Data are presented in order of decreasing frequency (of AEs reported by patients receiving obicetrapib monotherapy) and then alphabetically. [c]N includes all patients who received at least one dose of study drug.

Table 2. TEAEs occurring in at least 1 subject overall across all treatment conditions in the safety population in the Japan trial

System organ class, preferred term[a]	Randomized Treatment Group	
	Placebo (N=26)	10 mg obicetrapib (N=26)
Any TEAE[b]	15 (57.7%)	15 (57.7%)
Infections and infestations	5 (19.2%)	4 (15.4%)
Nasopharyngitis	3 (11.5%)	2 (7.7%)
COVID-19	1 (3.8%)	1 (3.8%)
Metabolism and nutrition disorders	4 (15.4%)	3 (11.5%)
Diabetes mellitus	0	1 (3.8%)
Hypoglycemia	0	1 (3.8%)
Decreased appetite	1 (3.8%)	1 (3.8%)
Diabetes mellitus inadequate control	1 (3.8%)	1 (3.8%)
Hyperglycemia	2 (7.7%)	0
Musculoskeletal and connective tissue disorders	4 (15.4%)	3 (11.5%)
Back pain	3 (11.5%)	2 (7.7%)
Arthralgia	1 (3.8%)	1 (3.8%)
Investigations[c]	2 (7.7%)	3 (11.5%)
Blood pressure increased	0	1 (3.8%)
Gastrointestinal disorders	1 (3.8%)	0
Diarrhea	1 (3.8%)	0
Respiratory, thoracic, and mediastinal disorders	0	3 (11.5%)
Rhinitis allergic	0	2 (7.7%)
Vascular disorders	1 (3.8%)	0
Hypertension	1 (3.8%)	0

[a]Terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0.
[b]TEAEs were defined as AEs that started after the first dose of study drug.
[c]Investigations are the MedDRA system organ class defined as laboratory tests and other medical investigations that gave an unusual reading.

Conclusions

- **Obicetrapib, when used either as monotherapy or in combination with a statin, reduced LDL-C, ApoB, Lp(a), and non-HDL-C levels, while also significantly increasing HDL-C concentrations**
- **Obicetrapib was well tolerated across all treatment groups**
- **A fixed-dose combination of 10 mg obicetrapib with low-dose atorvastatin or rosuvastatin, which may be a more attractive treatment option to clinicians and patients than high-intensity statins, is expected to allow patients with dyslipidemia to substantially improve their lipid profile**

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