Joana Gomes da Costa | joana.gomes_da_costa@novartis.com

Poster# **CO55**

Estimation of the effect of inclisiran in LDL-C reduction in a regional Portuguese population

F. Araujo[1] , C. Gavina[2] , M. Afonso-Silva[3] , C. Ferreira[3] , AS. Freitas[3] , D. Seabra[2] , R. Lopes[4] , I. Costa[3] , J. Gomes-da-Costa[3]

[1] Hospital dos Lusiadas, Lisbon, Portugal; [2] Hospital Pedro Hispano, Matosinhos, Portugal; 3 Novartis Farma - Produtos Farmacêuticos SA, Porto Salvo, Portugal; [4] MTG Research and Development Lab, Porto, Portugal

KEY FINDINGS & CONCLUSIONS

- We found sizable number of patients fulfilling criteria for ORION-10/11 in a population in Northern Portugal.
- Inclisiran could potentially translate into substantial LDL-C reductions and LDL-c target achievement, as observed in pivotal RCT, in this population.

Poster presented at ISPOR Europe, held on 17–20 November 2024

INTRODUCTION

- Cardiovascular (CV) disease is considered to be the leading cause of morbidity and mortality globally, with dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), recognized as a major modifiable risk factor.[1,2]
- LDL-C has emerged as a primary target for lipid control in the prevention of atherosclerotic cardiovascular disease (ASCVD), proving to be crucial for effectively manage ASCVD and its risk equivalents.[3] It is of major importance to ensure optimal LDL-C levels, considering the findings from the Lipid mAnagemenT IN pOrtugal (LATINO) study.[4]
- Inclisiran, a first in class siRNA for effective and consistent LDL-C reduction, provided sustained and clinically meaningful reductions of LDL-C in ORION 10/11 trials in patients with ASCVD and ASCVD risk equivalent.[2]

OBJECTIVES

- This study aims to assess the potential effects of inclisiran on LDL-C reduction and LDL-C target level achievement as well as its effects on CV risk reduction (cardiac death or cardiac arrest or non-fatal MI or stroke), by extrapolating ORION-10/11 trials to a Portuguese adult patient population.

METHODS

- We scanned relevant eligibility criteria for ORION-10/11 in the complete electronic health record database (EHRD) of Local Health Unit of Matosinhos (ULSM).
  - ULSM includes 14 primary care centers and 1 public hospital in northern Portugal.
- Patients with the following criteria were included in the analysis:
  - ≥1 general practitioner (GP) visit in the 3 years before index date (31/12/2021);
  - ORION-10 eligibility criteria[5]: ≥18 years-old patients with ASCVD AND LDL-C levels ≥70 mg/dL (1.8 mmol/L) at index date ;
  - ORION-11 eligibility criteria[5]: ≥18 years-old patients with ASCVD or ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a CV event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent) AND LDL-C level ≥100 mg/dL (2.6 mmol/L) at index date.
- No matching method was performed; every patient that met the inclusion criteria for ORION-10/11 was included in the respective cohorts.
- Relative reductions in LDL-C found in the ORION-10/11 were estimated to the population of interest (LDL-C reductions of 52.3% and 49.9% were reported, at day 510, for ORION-10 and 11, respectively[5]) using a Gaussian distribution (point estimates as means and standard deviations, derived from the reported 95% CI).
- This model was applied to the baseline LDL-C of the EHRD population to estimate the potential LDL-C reduction and LDL-C target achievement according to the ESC/EAS'19 guidelines, at day 510, of continued therapy with inclisiran.
- ORION-10/11 considered a composite CV endpoint including cardiac death, any signs or symptoms of cardiac arrest, non-fatal MI or stroke as prespecified safety endpoint.[5]
  - The risk ratios of the composite CV endpoint in the ORION-10/11 at 540 days were 0.7 (95% CI, 0.5-1.0) in ORION-10 and 0.8 (95% CI, 0.6-1.0) in ORION-11.[5]
  - The potential effects of 510 days of treatment with inclisiran within the ULSM were transposed based on these ORION-10/11 results.

RESULTS

- From 189 720 adult patients followed at ULSM (total population, irrespective of disease), we identified 4 643 (2.5%) similar patients for ORION-10 and 13 628 (7.2%) for ORION-11. Their characteristics are presented in **Table 1**.
- Estimated reductions of ORION-10/11 would translate into a median LDL-C (P25-P75) of 49 (41-60) mg/dL and 66 (57-80) mg/dL, for the ULSM ORION-10 and ULSM ORION-11 cohorts, respectively (**Figure 1**).
- A total of 65% and 39% of patients reaching LDL-C targets, at day 510, is also estimated for ORION-10 and 11 cohorts from ULSM, respectively.

Table 1. Baseline characteristics: ORION-10/11 (randomized controlled trial [RCT]) population versus eligible ULSM population

	ORION-10		ORION-11	
	RCT (n=1 561)	ULSM (n=4 643)	RCT (n=1 617)	ULSM (n=13 628)
Age, mean (SD)	66.1 (8.9)	69.0 (16)	64.8 (8.5)	68.0 (16)
Male, n (%)	1 083 (69.4)	2 566 (55.3)	1 160 (71.7)	5 759 (42.3)
Baseline LDL-C (mg/dL), P50 (IQR)	104.7 (38.3)	102.0 (40.0)	105.5 (39.1)	132.0 (45.0)
Patients on LDL-C target (%)	0	0	0	0
Diabetes, n (%)	702 (44.97)	2 719 (58.56)	568 (35.13)	7 707 (56.55)
Hypertension, n (%)	1 415 (90.65)	3 809 (82.04)	1 301 (77.86)	10 301 (75.59)
Familial Hypercholesterolemia, n (%)	20 (1.28)	115 (2.48)	28 (1.73)	334 (2.45)
Statin Therapy - high-intensity dose (%)	68.03	26.38	78.6	10.73
Ezetimibe (%)	14.49	9.86	9.99	7.05

IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; P50: median; RCT: randomized controlled trial; SD: standard deviation; ULSM: Local Health Unit of Matosinhos.

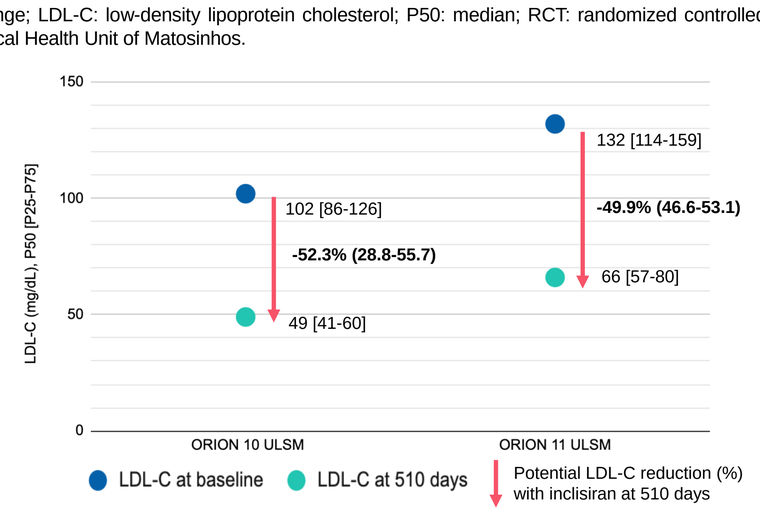

Figure 1. Estimated effect of inclisiran in LDL-C at day 510 for ULSM cohorts based on ORION-10/11 results

LDL-C: low-density lipoprotein cholesterol; P25: 25th percentile; P50: median; P75: 75th percentile; RCT: randomized controlled trial; ULSM: Local Health Unit of Matosinhos.

Risk of cardiovascular events

- The results of transposing the potential effects of treatment with inclisiran on cardiovascular adverse events within the ULSM cohorts are presented in **Table 2**:
  - In the current scenario with no inclisiran treatment, 250 and 127 cardiovascular adverse events were identified;
  - Transposing the potential effects of 510 days of treatment with inclisiran, we estimate that we would have 175 and 102 events contributing to this composite CV outcome on the ULSM ORION-10 and ORION-11 cohorts, respectively.

Table 2. Potential effect of inclisiran on cardiovascular adverse events in ULSM cohorts at 510 days

	ULSM ORION-10 (n=4 643)		ULSM ORION-11 (n=13 628)	
	Without inclisiran	With inclisiran*	Without inclisiran	With inclisiran*
Composite cardiovascular endpoint (cardiac death or cardiac arrest or non-fatal MI or stroke), n (Ev/100PY)	250 (6.17)	175 (4.32)	127 (0.88)	102 (0.7)

Ev/100PY: number of events per 100 person-year; MI: Myocardial infarction; ULSM: Local Health Unit of Matosinhos.
* Estimated with the possibility of use of inclisiran in ULSM.

Limitations

- Our study focused on a specific regional population in Northern Portugal, caution should be exercised when transposing the results of a trial to broader populations, considering diverse geographic and ethnic groups, potential variations in genetic predispositions and lifestyle factors.
- Demographic differences between the studied population from ULSM and the ORION trials populations, is one of the challenges associated with transposing trial populations to real-world settings.
- Adjustment for baseline covariates was not straightforward because that level of detail was not available from ORION 10 and 11.
- The long-term effect of inclisiran on cardiovascular events is currently under further investigation in large, placebo-controlled trials, ORION-4 (NCT03705234), VICTORION-1 Prevent (NCT05739383), and VICTORION-2 Prevent (NCT05030428).

References

1. Du Z, Qin Y. Dyslipidemia and Cardiovascular Disease: Current Knowledge, Existing Challenges, and New Opportunities for Management Strategies. J Clin Med Res. 2023;12

2. Liu Y, Liu F, Zhang L, Li J, Kang W, Cao M, et al. Association between low density lipoprotein cholesterol and all-cause mortality: results from the NHANES 1999-2014. Sci Rep. 2021;11:22111

3. Wilkinson MJ, Lepor NE, Michos ED. Evolving Management of Low-Density Lipoprotein Cholesterol: A Personalized Approach to Preventing Atherosclerotic Cardiovascular Disease Across the Risk Continuum. J Am Heart Assoc. 2023;12:e028892.

4. Gavina C, Carvalho DS, Pardal M, Afonso-Silva M, Grangeia D, Dinis-Oliveira RJ et al. Cardiovascular Risk Profile and Lipid Management in the Population-Based Cohort Study LATINO: 20 Years of Real-World Data. J Clin Med Res. 2022;11(22).

5. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med. 2020;382:1507–19.

Disclosures

This study was funded by Novartis Farma, Produtos Farmacêuticos SA.