EudraCT No.	**2017-001502-15**
Swissmedic No.	**2017DR3042**
Trial Name:	**PACMAN-AMI**
Trial Title:	**Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in PatieNts with Acute Myocardial Infarction. A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study**

FINAL REPORT SYNPOSIS

According to ICH Guideline E3

Investigational product:	Alirocumab (PCSK9 Antibody)
Indication:	Coronary Atherosclerosis in patients with acute Myocardial Infarction
Trial description:	International, multicentre, double-blind, randomised, placebo controlled study with 12 month of IMP/Placebo intake and final coronary atherosclerosis evaluation after 12 month
Study period:	FPFV: 09/05/2017/ LPLV: 13/10/2021
Sponsor:	Insel Gruppe AG, Bern University Hospital, Inselspital Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland Phone +41 31 632 50 00; Email: kardio.studien@insel.ch
Date of report:	12.09.2022
Identification Code:	PACMAN-AMI
Phase:	Phase III
Coordinating Investigator & Sponsor-Investigator and Contact Person:	Prof. Lorenz Räber, MD, PhD, Insel Gruppe AG, Bern University Hospital, Inselspital Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland Phone +41 31 632 50 00; Email: kardio.studien@insel.ch and lorenz.raeber@insel.ch

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

Synoposis

Name of Sponsor: Insel Gruppe AG	*(For National Authority Use only)*
Name of Finished Product: Alirocumab/ Placebo	
Name of active Ingredient: Human IgG1 monoclonal antibody that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9)	

Title of Study:

Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in PatieNts with Acute Myocardial Infarction. A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study

Investigators:

See study center listing below

Study centre(s) and Investigators (local PI):

- Insel Gruppe AG, University Hospital Berne, Inselspital Berne, Berne, Switzerland
  Prof. Lorenz Räber, MD, PhD (Sponsor-Investigator and local PI Inselspital Bern)

- Hôpitaux Universitaires de Genève, Genève, Switzerland
  Dr. Juan F. Iglesias, MD
- University Hospital Basel, Basel, Switzerland
  Dr. Gregor Fahrni, MD
- University Hospital Zurich, Zurich, Switzerland
  Prof Dr. Dr. Christian Templin
- Stadtspital Triemli, Zurich Switzerland
  Prof. Dr. med. Matthias Meyer
- Vienna General Hospital, AKH Wien, Wien, Austria
  Prof. Irene M. Lang, MD
- Rigshospitalet, Copenhagen, Denmark
  Prof. Thomas Engstrøm, MD
- Radboud UMC, Nijmegen, Netherlands
  Dr. Joost Daemen, MD
- Erasmus MC, Rotterdam, Netherlands
  Prof. Robert-Jan van Geuns, MD

Main Publications (Appendice 16.1.11):

- JAMA. 2022 May 10;327(18):1771-1781. doi: 10.1001/jama.2022.5218. PMID: 35368058
- Am Heart J. 2021 Aug;238:33-44. doi: 10.1016/j.ahj.2021.04.006. Epub 2021 May 2. PMID: 33951415

Studied period (years):	**Phase of development:**
FPFV: 09/05/2017 LPLV: 13/10/2021	**Phase III**

Objectives:

To determine the effects of alirocumab on coronary atherosclerosis using serial multimodality intracoronary imaging in patients with acute myocardial infarction.
Methodology: Intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography were serially performed in the 2 non–infarct-related coronary arteries at baseline and after 52 weeks. The primary efficacy end point was the change in IVUS-derived percent atheroma volume from baseline to week 52. Two powered secondary end points were changes in near-infrared spectroscopy–derived maximum lipid core burden index within 4mm (higher values indicating greater lipid content) and optical coherence tomography–derived minimal fibrous cap thickness (smaller values indicating thin-capped, vulnerable plaques) from baseline to week 52.
Number of patients: 300
Diagnosis and main criteria for inclusion: Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
Test product, dose and mode of administration: Patients were randomized to receive biweekly subcutaneous alirocumab (150mg; n = 148) or placebo (n = 152), initiated less than 24 hours after urgent percutaneous coronary intervention of the culprit lesion, for 52 weeks in addition to high-intensity statin therapy (rosuvastatin, 20mg).
Duration of treatment: 52 weeks
Reference therapy, dose and mode of administration: see description above
Criteria for evaluation: **Efficacy:** Efficacy endpoints were assessed using 2-vessel IVUS, NIRS and OCT of the proximal segments (≥50mm length) of two non-infarct-related coronary arteries after successful PCI of the culprit lesion at baseline (week 0) and after 52 weeks of treatment **Safety** Safety endpoints considered Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), product complaints and laboratory data.
Statistical analysis: For the primary end point, powered secondary end points, and other secondary imaging end points, the statistical comparisons between groups were performed using mixed-effect models by fitting the interaction between group (alirocumab or placebo) and time point (baseline or follow-up) as fixed effects and patient identity as the random effect. These models account for repeated measures for a given vessel (baseline and followup) and for the multiple vessels imaged per patient. For biomarker secondary end points, statistical comparisons between groups were performed using mixed-effect repeated models at the patient level. The difference between treatments is reported as the marginal difference (with 95% CIs) computed from the mixed-effect models. The primary analysis was performed on the full analysis set, which included all patients with available serial IVUS data. Patients were analyzed according to their randomization group. Patients with missing data were excluded from the primary analysis. The stratification variables used in the stratified randomization were not included in the model for the primary analysis; stratification variables were included in a post hoc sensitivity analysis, with type of myocardial infarction (STEMI vs NSTEMI) and use of stable (≥4 weeks) statin treatment at presentation (yes vs no) fitted as fixed effects and site identity as a random intercept. Analyses for the secondary end points were performed in the full analysis set excluding patients with missing

serial data for the considered end point (imaging or biomarker). For binary outcomes, treatment groups were compared using logistic regression. Analyses of adverse events included patients who received at least 1 administration of the study drug. Adverse events were summarized per treatment group by keeping only the first event of each type per patient. Statistical tests were 2-sided and the significance level was set at .05. For the primary and powered secondary outcomes, a gatekeeping procedure was applied, where by the primary end point was first tested at an α level = .05. If the *P*-value was ≥.05, *P* values for the powered secondary end points were not interpreted; if the *P* value was <.05, the significance level was equally split between the 2 powered secondary end points using Bonferroni correction (ie, significance level set to .025).
Because of the potential for type I error due to multiple comparisons, findings for analyses of the other secondary end points should be interpreted as exploratory. Statistical analyses were Performed using Stata, version 17 (StataCorpLLC),and R software, version 3.6.2 (R Core Team).

Summary - Conclusions

Results:

Among 300 randomized patients (mean [SD] age, 58.5 [9.7] years; 56 [18.7%] women; mean [SD] low-density lipoprotein cholesterol level, 152.4 [33.8]mg/dL), 265 (88.3%) underwent serial IVUS imaging in 537 arteries. At 52 weeks, mean change in percent atheroma volume was −2.13%with alirocumab vs −0.92%with placebo (difference, −1.21% [95%CI, −1.78%to −0.65%], P < .001). Mean change in maximum lipid core burden index within 4mmwas −79.42 with alirocumab vs −37.60 with placebo (difference, −41.24 [95%CI, −70.71 to −11.77]; P = .006). Mean change in minimal fibrous cap thickness was 62.67 μm with alirocumab vs 33.19 μmwith placebo (difference, 29.65 μm [95%CI, 11.75-47.55]; P = .001).

Adverse events occurred in 70.7%of patients treated with alirocumab vs 72.8%of patients receiving placebo.

Conclusion
Among patients with acute myocardial infarction, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non–infarct-related arteries after 52 weeks. Further research is needed to understand whether alirocumab improves clinical outcomes in this population.

Date of report

12SEP2022