ACZ885 media backgrounder

Quick facts

- ACZ885, also known as canakinumab, is being investigated in people who have survived a prior heart attack and have inflammatory atherosclerosis
- Inflammatory atherosclerosis is a thickening of the arterial wall due to the buildup of plaque, which is driven by inflammation, and which can increase risk of cardiovascular (CV) events such as heart attack or stroke
- Phase III CANTOS trial demonstrated that targeting inflammation with ACZ885 reduces major adverse cardiovascular events (MACE) by 15%
- New analysis from CANTOS shows a subgroup of patients whose inflammation levels dropped below 2mg/L at three months after the first dose of ACZ885 had an even higher reduction in MACE of 25%
- The analysis also showed the same subgroup of patients had a 31% reduction in cardiovascular death and a 31% reduction in all-cause mortality
- These data are significant because in the future physicians may be able to better identify patients who can achieve the greatest CV benefit from ACZ885 treatment

What is ACZ885?

- ACZ885 is **a selective, high-affinity, fully human** monoclonal **antibody** that inhibits IL-1β, a key cytokine (protein) in the inflammatory pathway known to drive the continued progression of inflammatory atherosclerosis (inflammation of the blood vessels)[1-5]
- ACZ885 works by blocking the action of IL-1β for a sustained period of time, therefore inhibiting inflammation that is caused by its over-production[6,7]
- ACZ885 has shown that selectively **targeting inflammation reduces CV risk** in patients who have had a prior heart attack and have inflammatory atherosclerosis
- ACZ885 is administered via subcutaneous injection every three months (quarterly)

CANTOS study: Global Phase III trial[8]

- CANTOS (NCT01327846) is a randomized, double-blind, placebo-controlled, event-driven Phase III study designed to evaluate the **efficacy, safety and tolerability** of quarterly subcutaneous injections of ACZ885 in combination with standard of care in the **prevention of recurrent CV events**
- The study included 39 countries and 10,061 people with a prior heart attack and with a high-sensitivity C-reactive protein (hsCRP) level of ≥2mg/L
- hsCRP is a clinical indicator of elevated CV inflammation in the body
- The median follow-up time is 3.8 years

CANTOS primary analysis

Primary data from the study presented at the European Society of Cardiology (ESC) Congress in August 2017, and simultaneously published in *The New England Journal of Medicine,* showed that treatment with ACZ885 led to:

- A significant **15%** reduction in the risk of MACE, a composite of non-fatal heart attack, non-fatal stroke and CV death, compared to SOC alone.
    - This was driven by a 24% relative reduction in risk of heart attack
    - Benefit was sustained throughout the duration of the study and generally consistent across key pre-specified sub groups.
- **17**% reduction in the relative risk of a composite of MACE and hospitalization for unstable angina requiring unplanned revascularizations.
- **36**% reduction in the relative risk of hospitalization for unstable angina requiring unplanned revascularization, as a component of this composite.

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The safety profile for ACZ885 was generally comparable to placebo, with overall incidence of AEs serious AEs, and discontinuations due to AEs similar to placebo across all doses.

CANTOS subgroup analysis

- A new analysis, presented at the American Heart Association Scientific Sessions in November 2017 and published simultaneously in *The Lancet,* showed that for a subgroup of patients with lower hsCRP levels, treatment with 150mg of ACZ885 led to:
    - **25% reduction** in MACE
    - **31% reduction** in each of CV death and all-cause mortality
- The subgroup consisted of patients whose inflammation levels dropped below 2mg/L at three months after the first dose of ACZ885, as measured by hsCRP
- These data indicate that on-treatment **hsCRP testing may offer a quick and reliable way** to identify patients most likely to achieve the highest benefit from treatment with ACZ885
- The analysis included patients whose inflammation level at three months was equal to or greater than 2mg/L. 2mg/L is a commonly used clinical cut point for hsCRP measuring residual inflammatory risk

CANTOS subgroup analysis: safety

- The safety profile of ACZ885 in the subgroup of patients whose inflammation levels **dropped below 2mg/L** was consistent with the overall study population
- The safety profile of ACZ885 in the subgroup of patients whose inflammation levels **did not drop below 2mg/L** was consistent with the overall study population
- The overall rates of adverse events (AEs), serious AEs, and discontinuations due to AEs in CANTOS were similar to placebo across all ACZ885 doses for both groups
- There was no relationship between on-treatment hsCRP levels and AEs
- The safety results from the new analysis indicate that patients whose **levels of inflammation dropped below 2mg/L** had a **greater positive response without an increase in side effects**

What are the endpoints of the CANTOS study?

- The **primary endpoint** is time to first occurrence of MACE which is a composite of CV death, non-fatal heart attack, and non-fatal stroke.
- **Secondary endpoints** include time to first occurrence of the composite CV endpoint consisting of CV death, non-fatal heart attack, non-fatal stroke and hospitalization for unstable angina requiring unplanned revascularization; time to new onset type 2 diabetes among people with pre-diabetes at randomization; time to first occurrence of non-fatal heart attack, non-fatal stroke and all-cause mortality composite; and time to all-cause mortality.

ACZ885 indications

ACZ885 is currently approved and marketed as Ilaris® for the treatment of systemic juvenile idiopathic arthritis (SJIA) in the US and EU, for the treatment of adult-onset Still's disease (AOSD) and the symptomatic treatment of refractory acute gouty arthritis in the EU. Ilaris is also approved in more than 70 countries, including in the EU, Switzerland, Canada, and Japan for the treatment of the periodic fever syndrome cryopyrin-associated periodic syndromes (CAPS). In the US, Ilaris is approved for two subtypes of CAPS: Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS).

The future of ACZ885

There is an extension study of CANTOS currently ongoing, intended to collect additional long-term safety data on continued ACZ885 exposure in patients who participated in the main CANTOS study.

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References

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