Welcome to the first newsletter of the CANTOS trial (protocol number CACZ885M2301): A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP.

**Enrollment Started**

The CANTOS trial is off to a great start. We achieved our First Patient First Visit on April 11, 2011! Congratulations to Dr. Reddi (US) and Dr. Dattani (Canada) for screening the first 3 patients in the trial! A special congratulations goes out to Dr. Reddi for randomizing the first patient on April 28, 2011!

As of 22 June 2011 we have more than 118 randomized patients in this study, and we look forward to building on this great start and carrying the momentum over the next 18 months as the rest of the countries become active. A special thank you to all of our Investigators for a job well done!!

**Country Start-up**

The enrollment target is to randomize 7302 patients. In order to achieve this we need to screen approximately 10500 patients, which means pre-screening potentially over 20,000 patients! We encourage you to screen as many patients as possible as enrollment is competitive, and please do not hesitate to contact your monitor with questions.

**Study timeline**

Last Patient First Visit (End of Screening) : 09 Oct 2012

Last Patient First Treatment (all pts randomized) : 06 Nov 2012

Last Patient last Visit: 26 Jan 2016

**High Enrollers**

Let’s give a big round of applause to our top 4 enrollers as of June 22, 2011!

- Dr. Pish - Site 1561: 8 pts
- Dr. Sabe-Affaki - Site 1012: 6 pts
- Dr. Srivastava - Site 1587: 6 pts
- Dr. Wu - Site 1585: 5 pts

Keep up the good work!

**Protocol Amendment**

Please note that the CANTOS protocol (CACZ885M2301 v03) was recently amended to allow for a specific reporting procedure in Japan only, as result of Japan Health Authority request. **CACZ885M2301 v04 is thus a country-specific global amendment that reflects revisions that will be implemented in Japan only.** For all countries other than Japan, there are no new revisions in v04. However v04 is a global amendment and will need to be filed.

For additional information, please contact your regional monitor.
Pre-identification of patients: Even though at the screening visit many assessments are performed to confirm the eligibility, the patients should be identified through pre-screening assessments to confirm initial eligibility.

Blood samples for CK-MB and troponin should not be sent to the central laboratory unless lab results for CK $\geq 2$

Remember to complete your Central Lab Center Information Sheet provided by your monitor and the Site Qualification Form via the eRT My Study Portal to receive study equipment

When searching for early MI patients, try reviewing the charts of patients that the PI sees on clinic rounds. If the patient meets I/E criteria then you can approach them at that visit or call them closer to the 28 day post MI date.

Keep local physicians informed about the study criteria and progress so referrals can be made.

Place brochures/posters in medical offices outside your area. You can also announce the trial at Grand Rounds

On behalf of the CANTOS staff in Boston and all of our research collaborators worldwide at Novartis, it is my honor to welcome you into the CANTOS community.

Working collaboratively with a network of investigators in 20 countries, we have the unique opportunity in CANTOS to address for the first time whether or not inhibiting inflammation can reduce cardiovascular event rates. Specifically, in a novel randomized trial that will enroll more than 7000 men and women, we will discover together whether interleukin-1B inhibition with canakinumab can significantly reduce the risk of myocardial infarction, stroke, or cardiovascular death in a group of patients who have previously suffered myocardial infarction and who remain at high risk for subsequent vascular events in part due to persistently elevated levels of hsCRP, an inflammatory biomarker known to predict risk of recurrent cardiovascular disease.

As the CANTOS Trial Chairman, I have had the pleasure of meeting many of you at the North American Investigators meetings that took place in April and May. Between June and September, I will have the opportunity to meet many more of you as the CANTOS trial launches worldwide.

The purpose of this newsletter is to provide you updated information about CANTOS that will make screening, enrollment, and follow-up as efficient as possible. For example, in this issue, my colleague Dr Brendan Everett describes “appropriate” and “inappropriate” patients who might be screened for CANTOS. As Dr Everett describes, it is crucial that you have clear clinical documentation of the qualifying myocardial infarction event so that few if any questions regarding protocol compliance will come up when your site is scheduled to be monitored.

I hope that you are as excited about the core inflammatory science behind CANTOS as we are. As the first major endpoint trial to directly address whether reducing inflammation can reduce cardiac risk, CANTOS has the potential to radically change how we treat cardiovascular disease.

Please feel free to contact me directly for any questions you may have.

~Paul M Ridker, MD
CANTOS Trial Chairman, Harvard Medical School, Boston, MA USA
What kind of patient is appropriate for CANTOS?

CANTOS is off to a superb start, with a large and growing number of investigators around the world screening, enrolling and randomizing patients into what we believe is a truly unique clinical research study. CANTOS represents a remarkable opportunity to better understand the role of vascular inflammation in heart and vascular disease, and it asks a ground breaking question: Can we prevent heart attacks, strokes, and cardiovascular death by giving patients an anti-inflammatory medication?

Of course, our ability to answer this question depends on enrolling the right kind of patients into the trial. Broadly speaking, the best patients to enroll are those who, in spite of aggressive preventive therapy, remain at an elevated risk of recurrent myocardial infarction, stroke, or cardiovascular death. The eligibility criteria in the protocol have been written to help us identify this type of patient, but as always, each individual investigator’s judgment is critical to selecting the right patients.

For example, an appropriate patient for CANTOS would be a patient who continues, in spite of aggressive preventive therapy, to have non-ST elevation myocardial infarctions. If cardiac biomarkers (troponin or CKMB), discharge summaries, and EKGS from the patient’s most recent heart attack are available, and the patient meets the other enrollment criteria for CANTOS, he or she would be an ideal candidate to enroll. By contrast, an example of a patient who would not be appropriate to enroll would be a man who suffered his first myocardial infarction several years ago, but has since not had any further cardiovascular complaints. Records from the index event are available, but are incomplete, and don’t include clear documentation of elevated cardiac biomarkers or Q waves on the EKG. This patient is not only ineligible for the trial (because of a lack of documentation for the index event), but is also not the kind of patient CANTOS seeks to enroll or study. CANTOS seeks patients who remain at elevated cardiovascular risk in spite of standard medical therapy; a patient whose coronary heart disease has been clinically silent for many years does not fit that profile.

On behalf of the CANTOS staff in Boston, and our colleagues at Novartis, we appreciate your extraordinary efforts to find and enroll patients for this unique trial. If you have any doubt about a patient’s qualifying event, or whether he or she might be an appropriate patient to enroll in the trial, please don’t hesitate to contact your CRA.

~By Brendan M. Everett, MD, MPH, Clinical Endpoints Committee Chair

Frequently asked questions

Q: When the CANTOS protocol specifies 'development of new pathological Q waves regardless of symptoms': do we have to refer to a baseline ECG prior to MI to compare the Q waves and meet Inclusion Criterion 4.1.4: Documented Spontaneous MI?

A: Yes. In CANTOS, in the absence of confirmative cardiac markers for all MI subcategories except Silent MI, comparative ECGs documenting new pathologic Q waves (in the absence of other ECG changes) are required to meet Inclusion Criterion 4.1.4, for 2 reasons. First, clear appearance of myocardial necrosis and altered conduction will be documented, and second, CANTOS stratifies patients by time from qualifying MI, into < or > 6 month categories. Only in the case of Silent MI does the presence of pathologic Q waves meet Inclusion Criterion 4.

Q: The CANTOS protocol does not clearly indicate that women with hysterectomy only are allowed, however it seems apparent that the uterus would be needed to be considered as WOCBP. Can you clarify this?

A: The Sponsor clearly understands the basis of the question. Accordingly, the Sponsor will now accept the following patients as well: “Female patients who have undergone vaginal or abdominal hysterectomy (complete removal of uterus) with or without oopherectomy”. This language will be reflected in an upcoming CANTOS Protocol Amendment.

Q: What are the live vaccines that patients should avoid in CANTOS? Allowed vaccines?

A: It has been recommended that the following list of live vaccines that should not be taken by patients participating in this study, including: live bacterial vaccines BCG (type of tuberculosis vaccine), Ty21a (a Salmonella typhi vaccine), and live viral vaccines including, Measles, Mumps, Rubella, Oral Polio LAIV: live attenuated Influenza, Yellow fever, Varicella, and Vaccinia.

Patients may safely receive other common vaccines such as pneumococcal vaccines and influenza TTV (an inactivated, or killed virus vaccine) as directed by their Primary Care Physician.
Tips for Drug Supply & IWR/IVR system

- Study drug will be shipped to the site within 5-7 days after the site registers their first screened patient.
- Upon receipt of the study drug, the site should immediately stop the temptale device that accompanied study drug shipment and check if there was any temperature excursion (Alarm bell sign).
- If there was a temperature excursion, study drug viability should be confirmed prior to registering the study drug in IVRS/IWRS.
- In case of temperature excursions, monitor should be notified immediately and the data from the temptale device should also be sent to the monitor. Instruction for obtaining the data from temptale device is available in the packing list.
- If there is no temperature excursion, the site should confirm receipt of study drug in IVRS/IWRS.
- Immediately upon arrival, study drug should be stored in a refrigerator between 2-8 degree Celsius (36-46 F) and protected from light.
- Study has automatic resupply of study drug.

Data management

1.) Data entry: When entering data, please use the attached discreet value groups (DVGs) for responses, which can be accessed by clicking on the magnifying glass to the right of the data entry field. When entering data for a time, date or numeric field, the DVG should only be used as needed.

2.) Responding to discrepancies: When responding to a discrepancy, please ensure that it is routed to the appropriate line function. For instance, if it is a manual discrepancy generated by a CRA, the response must be routed back to them. If it is a system generated discrepancy, meaning a validation has fired automatically in RDC, and a comment is entered and not an update to the data point, then the response should be routed back to Data Management. Incorrect routing will result in discrepancies being open longer than needed.

Tips for Completing the Dosage Administration Record

The "dose administered" section should be completed with a "1" or "0".

Tips for Completing concomitant Medications page in OCRDC

The "End Date" or "Ongoing at final examination" should be left blank unless the drug is stopped or if the study completion page has been completed.