15 November 2018
EMA/241276/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Canakinumab Novartis

International non-proprietary name: canakinumab

Procedure No. EMEA/H/C/004754/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Ab	antibody
ACE	angiotensin converting enzyme
ADA	anti-drug antibody
ADR	Adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
ACZ885	Canakinumab
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass grafting
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcomes Study
CEC	Cardiovascular clinical events adjudication committee
CHD	coronary heart disease
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMQ	Custom MedDRA query
CMV	cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CRF	case report form
CV	cardiovascular
DBP	diastolic blood pressure
DES	drug eluting stent
DMC	Data Monitoring Committee
ECG	electrocardiography
eDISH	evaluation of Drug Induced Serious Hepatotoxicity
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study
EQ-5D	EuroQol - 5 dimensions
ESRD	end-stage renal disease
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein-cholesterol
HF	heart failure
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
hsIL-6	high-sensitivity interleukin-6
IAC	infection adjudication committee
ICU	intensive care unit
IEC	Independent Ethics Committee
IG	immunogenicity
IL	interleukin

IL-1	RA interleukin-1 receptor antagonist
IQR	interquartile range
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAC	malignancy adjudication committee
MACE	major adverse cardiac events
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MFSI-SF	Multidimensional Fatigue Symptom Inventory-Short Form
MI	myocardial infarction
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	Modified Ranking Scale
MSD	Meso Scale Discovery
msDBP	mean sitting diastolic blood pressure
msSBP	mean sitting systolic blood pressure
NIH	National Institutes of Health
NLRP3	NOD-like receptor family pyrin domain containing 3
NMQ	Novartis MedDRA Query
NSTEMI	non-ST-Elevation Myocardial Infarction
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitor-1
PCI	percutaneous coronary intervention
PCS	Physical Component Score
PD	pharmacodynamic
PK	pharmacokinetic
PPS	Per Protocol Set
PRO	patient reported outcome
PT	preferred term
py	Patient years
QoL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
SA	surface area
SAA	serum Amyloid A
SAE	serious adverse event
SAF	Safety Analysis Set
SBP	systolic blood pressure
s.c.	subcutaneous
SD	standard deviation
SE	standard error
SF-36	Medical Outcomes Study 36-Item Short Form
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIS-16	Stroke Impact Scale 16
SMQ	Standardized MedDRA Query
SOC	system organ class
SoC	standard of care
SOP	Standard Operating Procedure
STEMI	ST-Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TBL	Total bilirubin
TG	triglycerides
TIA	transient ischemic attack
TNF	tumor necrosis factor

ULN	upper limit of normal
URL	upper reference limit
US(A)	United States (of America)
VAS	visual analogue scale
VLDL-C	very low density lipoprotein-cholesterol
WBC	white blood cell

1. CHMP Recommendation

Based on the review of the data and the applicant's response to the CHMP LoQ on quality, safety, efficacy, the application for canakinumab Novartis for the secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ≥ 2.0 mg/l prior to treatment initiation **is not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Benefit-risk balance

1. Concerns remain on the strength of evidence and the magnitude of the beneficial effect from the CANTOS study balanced against the increased risk of fatal/serious infections therefore a positive B/R in the claimed indication has not been demonstrated.

Efficacy

2. CANTOS did not demonstrate the relevance of pre-treatment and on-treatment hsCRP levels to identify patients with a positive benefit risk ratio and to monitor a treatment effect.

Questions to be posed to additional experts

A Cardiovascular SAG will be convened after the applicant's responses to the List of Outstanding Issues have been assessed, as the current MAA presents a new medicinal product with totally new mode of action and hence a totally new treatment paradigm for prevention of MACE in patients with previous MI. The CHMP LOQ to the SAG is provided as a separate document.

The Biostatistical Working Party has been consulted in relation to the appropriateness of using hsCRP as a surrogate to measure treatment effect. The BSWP report is provided as separate document.

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

N/A

New active substance status

Given that canakinumab is already registered in the European Union under the invented name Ilaris, no claim for a new active substance is made.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Canakinumab Novartis is indicated for the secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ≥ 2.0 mg/l prior to treatment initiation.

For study results with respect to populations/sub populations studied, see section 5.1.

2.1.2. Epidemiology and risk factors, screening tools / prevention

Cardiovascular disease is the leading cause of death in the EU. The Application aims at patients at a very high risk population (Piepoli et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice, Eur heart J 2016; 37:2 9) for CV morbidity and mortality, i.e. patients after a myocardial infarction with an estimated 10 year risk for a fatal cardiovascular event of > 10%.

The current European guidelines on prevention of CVD comprise a systematic risk assessment for individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, sedentary lifestyle, unhealthy diet, high BP, DM or raised lipid levels) or comorbidities increasing CV risk. Total CV risk estimation, using a risk estimation system such as SCORE, is recommended. Subjects who already have suffered a CV event, such as a MI should receive active secondary prevention addressing all of the above-mentioned risk factors, aggressively aiming to achieve defined target levels of weight, waist circumference, blood pressure, lipids, glycaemia, physical activity, and diet.

Routine measurement of other biomarkers than lipids and glycaemic measures, such as hsCRP, is not recommended in the European guidelines. Even though hsCRP is a risk factor integrating multiple metabolic and low-grade inflammatory factors, with RRs approaching those of classical CV risk factors, its contribution to the existing methods of CV risk assessment is deemed to be small. Hence, measurement of hsCRP is not part of the standard evaluation of CV risk in Europe.

2.1.3. Biologic features; Aetiology and pathogenesis

Since morbidity and mortality in patients after myocardial infarction is high despite of optimal therapy of the conventional risk factors listed in Section 2.1.2, there is a need for additional therapeutic options.

It has been known for years that atherosclerosis is linked with a low-grade inflammatory state of adipose tissue, elevated circulating inflammatory markers and local inflammatory reactions at vascular wall in several phases of evolution of the atherosclerotic plaque, plaque rupture, and thrombosis. It is not clear whether inflammation simply accompanies the atherosclerotic process or represents a major driver. Several studies have shown that inflammation is related to the metabolic syndrome (MetS), also called the insulin resistance syndrome. MetS per se poses an increased CV risk to the individual, as it is a cluster of known risk factors for CVD, encompassing some degree of glucose intolerance; abnormal uric acid metabolism; dyslipidaemia (elevated triglycerides, low and structurally small and dense HDL-cholesterol, small and dense LDL cholesterol); postprandial accumulation of TG-rich lipoproteins; haemodynamic changes (sympathetic nervous activity, renal sodium retention, high blood pressure); prothrombotic factors; elevated markers of inflammation, and endothelial dysfunction (AACE 2017 Guidelines. Endocrine Practice 2017;23 (Suppl 2):1-87).

It is noteworthy that the so-called “lipid hypothesis” and “inflammation hypothesis” are not alternative. Instead, dyslipidaemia and low-grade inflammation are linked by multiple metabolic pathways. To mention a few mechanisms, cholesterol crystals induce inflammation in the vessel wall (Grebe A, Latz E. Cholesterol crystals and inflammation. Curr Rheumatol Rep. 2013;15: 313-323). Oxidatively modified low-density lipoproteins (OxLDLs) that accumulate in the intima during the initiation and promotion of fatty streaks and fibrotic plaques mediate biological effects through multiple pathways, leading to the expression of genes involved in oxidative stress and the inflammatory response during generation of the atherosclerotic plaque (Leonarduzzi et al. Inflammation-related gene expression by lipid oxidation-derived products in the progression of atherosclerosis. Free Radical Biology & Medicine 2012; 52:19–34). Obesity, which predisposes to the metabolic syndrome and atherosclerosis, causes in itself inflammation, as the visceral adipose tissue is a source of numerous proinflammatory adipokines; whereas the secretion of the anti-inflammatory and vasculoprotective adiponectin by adipose tissue is reduced in obese subjects (Lovren F, Teo H, Verma S. Obesity and Atherosclerosis: Mechanistic Insights. Canadian Journal of Cardiology 2015; 31:177-183). Therefore, it is impossible to separate any part of the atherosclerosis to be predominantly “inflammatory” as opposed to “normal” atherosclerosis.

Although, according to the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), studies suggest that hsCRP may be of limited value as a broadly applied screening tool, it may be helpful in stratifying CV risk in individuals with a standard risk assessment that is borderline. The risk evaluation based on hsCRP is defined in the above cited guideline as follows: values <1, 1 to 3, and >3 mg/l indicate lower, average, or higher relative CV risk, respectively.

It is unclear if different treatment strategies should be used for prevention of CV events in patients with elevated hsCRP. If these patients are suffering from a more inflammatory form of atherosclerosis than those with a lower hsCRP remains still unresolved. Any secondary prevention of CVD should according to current guidelines be based on evaluation of the totality of the risk of the subject, not only on one laboratory marker.

Interestingly, a recent meta-analysis (Savarese et al. Reduction of C-reactive protein is not associated with reduced cardiovascular risk and mortality in patients treated with statins. A meta-analysis of 22 randomized trials. Int J Cardiol 2014; 177:152–160) concluded that statin-induced reduction in hsCRP levels, over a mean follow up of 1.97 years, was not correlated with the risk of stroke, CV and all-cause mortality and the composite of MI, stroke and CV death. However, statin-induced changes in hsCRP levels correlated significantly with the reduction of the risk of MI in patients at high CV risk. The importance of low-grade inflammation in the pathophysiology of these different CV events obviously varies. The importance of inflammation seems to be variable between patients, too, and in different phases of atherosclerosis. The specific role of IL-1β, or blockage of it, in the local inflammation at the vascular wall is not yet fully confirmed.

As the low-grade inflammation that promotes CVD is systemic, any anti-inflammatory treatment may exert pharmacological effects at different sites in the body. Importantly, adipose tissue inflammation is an organic part of MetS (Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation.J Endocrinol 2014; 222:R113-R127.). Low-grade inflammation is linearly correlated to the presence of insulin resistance and components of the metabolic syndrome (MetS) (Leinonen et al. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis. 2003 Feb;166(2):387-94). MetS includes known CV risk factors such as dyslipidaemia (high triglycerides, small dense LDL cholesterol, low HDL cholesterol, small dense HDL cholesterol etc.), hypertension, central obesity, and dysglycaemia (diabetes or prediabetes). Even though low-grade inflammation, reflected e.g. by elevated CRP levels, has been shown to be a predictor of CV risk (Li et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. Atherosclerosis 259 (2017) 75-82), some data indicate that the association is not independent, as controlling for conventional risk factors eliminates the association (Kuoppamäki et al. High sensitive C-reactive protein (hsCRP), cardiovascular events and mortality in the aged: A prospective 9-year follow-up study. Arch Gerontol Geriatr 2015;60:112-117).

It remains yet to be demonstrated when would be the most beneficial time point for anti-inflammatory medication for a patient with CV disease: during acute coronary syndrome, or later on as secondary prevention of CV events, as suggested by the applicant. Are there potentially patients with a quiet, non-progressive situation after CV events that can be controlled by conventional medications? Which are the best biomarkers or characteristics to distinguish patients with aggressively progressive cardiovascular disease and patients with a non-progressive course of the disease? In addition, how to distinguish potential responders to anti-inflammatory medication from non-responders?

Finally, the applicant has chosen to design the pivotal study so that many of these questions will remain unanswered, i.e. the pivotal study includes only patients with stable CV disease, after at least 30 days after the index MI. This assessment focuses only on the provided data in relation to the sought indication.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

As the MAA concerns canakinumab for secondary prevention of CV events in subjects with prior MI, the treatment and diagnosis of MI or other major adverse cardiovascular events (MACE) is not discussed here.

2.1.5. Management

The recommended strategy for secondary prevention of CVD is briefly explained in Section 2.1.2 of this AR. Despite best efforts to prevent subsequent CV events in individuals with prior MI by medical treatment of hyperglycaemia, dyslipidaemia, and hypertension, combined with lifestyle counselling and support for smoking cessation, exercise and healthy diet, these patients remain at higher risk than normal population. The applicant refers to this issue as “residual risk”.

The applicant has based the development strategy of canakinumab as a medicine for CV risk reduction on the overall concept of atherosclerosis being a chronic inflammatory disease. Interleukins (ILs), including interleukin 1β, belong to cytokines involved in the complex metabolic derangement leading to development of atherosclerosis. Prevention of CV risk by potent anti-inflammatory medical treatment is a new concept. However, some of the currently recommended preventive medications also exert anti-inflammatory effects. In addition to the lipid-lowering effects, statins have been shown to be anti-inflammatory (Antonopoulos et al. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des. 2012;18:1519-30. Review); and acetylsalicylic acid (ASA) has both anti-thrombotic and anti-inflammatory effects. However, a patient group with residual risk posed by inflammation and not controlled by established preventive measures remains to be defined.

2.2. About the product

Canakinumab, a highly specific, high affinity human anti-interleukin-1β (IL-1β) monoclonal antibody, has demonstrated clinical benefit in a number of IL-1β-driven inflammatory diseases and has an established safety profile in these indications. It is approved in more than 65 countries (approved indications may vary by country) under the Ilaris® tradename for the treatment of several rare heritable pediatric diseases, namely, periodic fever syndromes associated with IL-1β over-expression (cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor (TNF) receptor associated periodic syndrome, hyper-immunoglobulin D syndrome/Mevalonate Kinase Deficiency, and Familial Mediterranean Fever), as well as for the treatment of active Still's disease including Adult-Onset Still's Disease and systemic juvenile idiopathic arthritis, and gouty arthritis. The first approval for canakinumab was for CAPS in June 2009.

The MAH applies for a new indication in the secondary prevention of major cardiovascular events. The approach is based on the hypothesis that inflammatory components contribute to the pathogenesis of atherosclerosis. As an example, a meta-analysis of 54 prospective studies which evaluated lipid markers and inflammatory markers such as hsCRP (i.e. a high sensitivity assay for C-reactive protein) suggested that beyond blood lipid levels, inflammatory status also accounts for CV risk (The Emerging Risk Factors Collaboration Lancet. 2010 Jan 9; 375(9709): 132–140). However, despite of such data, markers of inflammation are not included in the key cardiovascular risk scores as proposed e.g. by the European Society of Cardiology. In addition, it is unclear, whether inflammatory markers may just indicate an increase in cardiovascular risk or whether a therapeutic intervention targeting inflammatory pathways may modify disease.

IL-1 is not only involved in inflammatory processes but has also been reported to be of relevance for lipid metabolism (e.g. Matsuki et al., IL-1 plays an important role in lipid metabolism by regulating insulin levels under physiological conditions. J Exp Med. 2003 Sep 15; 198(6): 877–888. Delgado-Lista et al. Interleukin 1B variant -1473G/C (rs1143623) influences triglyceride and interleukin 6 metabolism. J Clin Endocrinol Metab 2011; 96:E816–E820; Editorial by Netea MG and Dinarello CA, J Clin Endocrinol Metab. 2011 May; 96(5): 1279–1281.). Patients with specific gene variants of the IL1B promoter region had an altered lipid metabolism with higher triglyceride and cholesterols levels (older subjects) and higher post-prandial lipid levels (younger subjects) (Delgado-Lista et al., 2011). Individuals treated with monoclonal antibodies that block the IL-6 receptor (tocilizumab) have increased LDL levels (Kawashiri SY et al., Rheumatol Int. 2011 Apr;31(4):451-6). Thus, such data led to the concept that IL-1β-driven IL-6 modulates the regulation of serum lipids by the liver.

Taken together, there is evidence in support of IL-1 being a relevant factor in the pathophysiology of atherosclerotic diseases. Both, anti-inflammatory effects and a modulation of lipid metabolism may be relevant. hs-CRP has not been included in key CV guidelines as an independent factor for the assessment of the individual CV risk and there is no data showing that hs-CRP can be used as a PD parameter indicating efficacy in an interventional trial. In this regard the concept of using an anti IL-1 antibody for the prevention of CV endpoints is new and requires robust data to be acceptable.

2.3. The development programme/compliance with CHMP guidance/scientific advice

2 EMA Scientific Advices with 2 follow up requests were conducted.

a) Indication gout and pharmaceutical development

EMEA/CHMP/SA WP/629137/2009 PN EMEA/H/SA/677/2009/III

and FU EMA/CHMP/SAWP/287075/2010 PN EMEA/H/SA/677/3/FU/I/2010/III

The scientific advice concerned the comparability plans (PK/PD) between lyophilisate in vial and PFS

The FU addressed questions regarding autoinjector development and validation b) Indication cardiovascular prevention

EMA/CHMP/SAWP/686623/2010 PN EMEA/H/SA/677 /5/2010/II (November 2010)

and FU EMA/CHMP/SAWP/26135/2011 PN ENEA/H/SA/677/5/FU/1/2011/II (April 2011)

The advice concerned the following issues:

- On the Toxico-Pharmacological development the CHMP agree that no further animal testing is required.

- Clinical development:

- A thorough QT study, formal PK drug-drug interaction studies and studies in patients with renal and hepatic impairment were not considered necessary.

- Design of the pivotal study CACZ885I2302.

The CHMP stated that for a single pivotal trial with a new mechanism of action results have to be compelling, consistent across subgroups, and the trial is to be performed impeccably. Pre-defined subgroup analyses related to baseline CRP-levels were supported. The CHMP pointed out the all-cause mortality is preferred over CV-mortality as part of the composite endpoint.

Issues regarding event adjudication and reporting of cardiovascular events were addressed in the advice and inclusion of an interim-analysis in the trial was not supported.

Dose selection: Dose selection was to be based on hsCRP as a marker for biological activity of canakinumab. Initially the first dose selected was based on study CACZ885I2202 1st interim analysis data and secondly dosing interval based modeling and simulation of pharmacokinetics of canakinumab. In the first step canakinumab dose range selected for further development was 15 to 50 mg monthly based on hsCRP lowering used as surrogate for anti-inflammatory action of canakinumab. In the second step modeling and simulation data on tissue free IL-l~ used as surrogate for canakinumab pharmacokinetics. The modelling approach suggested that that canakinumab can be dosed quarterly with adequate suppression of tissue free IL-1~ and that 50 mg and 150 mg quarterly doses correspond to 15 mg and 50 mg month doses and cover the selected dose range. Therefore 50 mg and 150 mg quarterly doses of canakinumab were selected for the proposed study CACZ8852302. Based on calculations it was assumed that 150 mg quarterly was able to suppress hCRP near maximal. The CHMP commented that a drawback of the modelling approach was that patients with gout and type 2 DM were used but not patients with CV disease.

In the FU advice the company proposed to use a modified dose regime with a higher dose of 150 and 300 mg quarterly and by adding an induction dose based on data supporting safety of a higher dose and uncertainties regarding the dose needed for IL-1ß neutralization within a plaque or in atheroslerosis. An induction dose was proposed to provide early suppression of IL-1ß with shorter dosing intervals at randomization, after week2, ant month 3 and then at quarterly visits. During the discussion meeting a modification was proposed by the company using an induction dose only in the 300 mg arm. The CHMP expressed concerns regarding the safety of higher doses with respect to infection rates but was not in the position to give a clear advice on the dose selected.

- Significance of paediatric studies

Following the request for confirmation of the applicability of the Agency's decision on class waivers for the proposed cardiovascular indication, the EMA/PDCO confirmed that the proposed indication is covered within the condition of coronary atherosclerosis (CW/1/2011 and EMA/502643/2012). Although this class waiver was later revoked by the EMA/PDCO (July 2015), the requirement set out in Articles 7 and 8 shall not apply for 36 months from the date of the removal from the list of waivers as per Article 14.3 of the Paediatric regulation. Therefore, the class waiver remains applicable for the purpose of this submission. As such, there is no approved Paediatric Investigational Plan (PIP) for canakinumab in this condition. Novartis has completed all PIPs agreed with the EMA Paediatric Committee (PDCO) related to approved indications of Ilaris (CAPS- Cryopyrin-associated periodic syndromes; GA- Gouty arthritis; SJIA- Systemic juvenile idiopathic arthritis FMF- Familial Mediterranean Fever; HIDS- Hyperimmunoglobulin D syndrome; TRAPS- Tumour necrosis factor (TNF) receptor associated periodic syndrome.)

2.4. General comments on compliance with GMP, GLP, GCP

The MAH stated that Study No. ACZ885M2301 was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center.

After inspections in 18 sites two sites participating in the pivotal trial were closed due to GCP-related violations (8 patients total).

In 103 patients included in the pivotal trial, almost all in Brazil, it was noted that locally the blind was broken. According to the applicant the unblinding in these Brazilian centers was related to a single mistake related to a change in the local drug depot and not due to general mismanagement. It was unclear, whether treatment allocation was actually unblinded to the site personnel. Sensitivity analyses did not indicate an impact on the overall conclusions of the study. 2.2% (25 centers) reported a high rate of protocol deviations that were not considered to impact the overall results. There are remaining issues to be addressed concerning the inspections, the time point of exclusion of 3 patients from the efficacy analysis due to GCP issues and a clarification is requested on the number of patients that were included in disregard of exclusion criterion 5 (tuberculosis) **(OC)**.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application concerns a centralized procedure according to Regulation (EC) No 726/2004), Article 3(1).

- Accelerated procedure

N/A

- Conditional approval

N/A

- Exceptional circumstances

N/A

- Biosimilar application

N/A

- 1 year data exclusivity

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Name:	Canakinumab Novartis (canakinumab)
Dosage form and strength:	Solution for injection in prefilled syringe, 150 mg Solution for injection in prefilled pen, 150 mg
Procedure:	EMEA/H/C/4754
Therapeutic class or indication:	L04AC08 Immuno-suppressants, interleukin inhibitors
Proposed dosage range:	150 mg SC every 3 months

Canakinumab is currently registered in the European Union as Ilaris for the treatment of Cryopyrin-Associated Periodic Syndromes, Tumour necrosis factor receptor associated periodic syndrome, Hyperimmunoglobulin D syndrome / mevalonate kinase deficiency, Familial Mediterranean fever, Still's disease and Gouty arthritis. In the present marketing authorisation application (MAA) Novartis Europharm Limited is seeking approval for registration of canakinumab under a separate tradename (canakinumab Novartis) for the prevention of major cardiovascular events in patients with a prior myocardial infarction and high sensitivity C-Reactive Protein (hsCRP) >2 mg/l at treatment initiation.

The current commercially available dosage forms of Ilaris® include a lyophilized 150 mg of canakinumab powder for solution for injection and 150 mg/mL canakinumab solution for injection in vial. Canakinumab Novartis will have two new drug product (DP) presentations i.e. canakinumab 150 mg/ 1 mL solution for injection in prefilled syringe (PFS) assembled into safety device or fixed-dose disposable auto-injector (AI). The excipients of the PFS formulation are identical with the solution for injection in vial.

3.1.2. Active Substance

General Information

Canakinumab is a recombinant human monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1/κ isotype that was designed to bind selectively to and neutralize the activity of IL-1β for the treatment of IL-1β driven inflammatory diseases.

The applicant assures that the drug substance (DS) is the same as currently approved for Ilaris.

Manufacture, process controls and characterisation

The manufacture of canakinumab DS is performed by Novartis Pharma S.A.S, Huningue, France.

A cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) is used for the manufacture of the drug substance.

For initiation of the cell culture process, cells of the WCB are thawed and re-suspended in inoculum medium for propagation in T-flasks and roller bottles. Cells from the last set of roller bottles are then combined and further expanded in stainless steel bioreactors.

The purification process is adequately described. Information of the columns and process parameters are provided. Hold times of purification pools are presented which are further demonstrated in the validation studies. The purification process for DS was validated for adequate removal of process-related impurities host cell protein (HCP), DNA and leaching Protein A.

The manufacturing process and its development are described sufficiently in the dossier.

Regarding the control strategy, the applicant has provided a classification of all process controls critical and non-critical) of the canakinumab manufacturing process. Process parameters (in-put parameters) are described in section 3.2.S.2.2 "Description of manufacturing process and process controls". In-process controls (output parameters) are monitored during manufacturing and critical in-process controls are described separately in section 3.2.S.2.4 "Controls of critical steps and intermediates".

The canakinumab molecule is thoroughly characterised. The impurities and degradation products formed under different stressed conditions have been studied. Efficient removal of these impurities is demonstrated and clearance of the impurities is deemed sufficient.

Overall, drug substance specifications are adequately set and justified. The specification for the drug substance includes tests and limits for: appearance of the solution, colour of the solution, identification by peptide mapping, potency assay, pH, assay for protein, purity and impurity assays, determination of Sp2/0 host cell protein, bacterial endotoxins and microbiological quality.

Analytical procedures and reference standards

The analytical methods are considered capable to control the quality of the drug substance (DS) at release and stability testing. There is no international standard for canakinumab available and therefore an in-house reference standard material has been established. The reference standards are appropriately described and considered sufficient for the intended use.

Batch analysis

All clinical and commercial material is currently manufactured with the proposed commercial process. The provided results of DS batches met the release specification limits.

Container closure

The container for DS bulk is widely used for biological products. It fulfils the compendial requirements and is acceptable for storage of the bulk.

Stability

Stability studies follow ICH Q5C guideline. The proposed shelf life of 36 months when stored at ≤-60°C is supported by the results from three primary commercial validation batches and supportive results from three clinical batches. The photostability results show that DS is light-sensitive and should be protected from light.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Canakinumab Novartis 150 mg/ 1 ml of canakinumab solution for injection is supplied in prefilled syringe (PFS) assembled either into safety device (NSD) or fixed-dose disposable auto-injector (AI).

Pharmaceutical development

Formulation and process development

The DP formulation development studies are partly based on the studies of previous commercial presentations of canakinumab (Ilaris) i.e. powder for solution for injection and solution for injection in vial. The suitability of primary packaging i.e type 1 glass syringe for the canakinumab has been demonstrated in robustness studies. Stopper and needle adhesive as well as the effect of tungsten and silicone oil has been analysed by placing spiked DP samples on stability and further challenging some samples by shaking. The final formulation intended for marketing and used in phase III clinical trials consists of 150 mg/ml canakinumab in histidine buffer, mannitol and polysorbate 80. The formulation studies are generally considered adequate.

Manufacturing process development

The manufacturing processes of PFS, liquid in vial and powder form use comparable manufacturing steps and operating principles with the exception of the lyophilisation step and the need for controlling of the stopper position for the PFS, allowing an overfill. The process development of PFS has been described for the unit operations of DP manufacture. The process was validated. PFS presentation was confirmed to be robust for homogeneity of the production solution, mechanical stress during manufacturing and cumulative chemical standing time. The process development is appropriately described.

Container closure system

Canakinumab solution is packed in a Type I borosilicate glass syringe with staked needle, bromobutyl rubber stopper and rigid needle shield (BD Hypak syringe). The stability studies show that the PFS is able to keep the quality attributes within the specification limits and DP sterile. The pre-filled syringe is assembled either into NSD (CE marked 'UltraSafe Passive™' Needle Safety Device: NSD) or disposable Delta 01 auto-injector for fixed-dose administration. There is no contact of DP with any of the NSD or auto-injector components. The PFS has the same user-interface with other marketed products manufactured by the applicant and approved for self-administration. AI shares the same user-interface with another marketed product manufactured by Novartis. "Human factors" evaluation has been performed with no harmful events observed. The dose accuracy of AI is controlled by release and stability specifications. The primary and secondary packaging of all DP presentations have been properly described for their quality and testing. Stability studies for canakinumab solution in PFS and in AI have been conducted in line with ICH Q5C guideline and show that PFS is able to sustain DP sterile and the quality attributes within the specification limits.

Comparability of DP in un-assembled PFS and PFS assembled with NSD and AI has been demonstrated by batch release testing results, additional characterisation, and stability data showing no major differences. However some minor differences could be detected between PFS and PFS assembled in AI. The applicant has clarified that these differences result from differences in both the time of testing and assembly of PFS, auto-injector and NSD as well as method and batch related variability.

Risk management plan for the AI is provided for hazard analysis, risk evaluation and control. Commercial production and post-production surveillance are maintained for the AI device. Device-related complaints are recorded and tracked and are periodically assessed for impact on risk.

Compatibility

The suitability of the AI pen has been studied to identify potential risks for user. The AI components are biocompatible and free of phthalate (DEHP). The manufacturer (BD) has provided certificates for pharmacopoeial compliance of the container closure components and declaration of conformity with Council directive 93/42/EEC 14 June 1993. Compatibility of the PFS has been appropriately studied for tungsten, silicone oil and other leachates. The NSD (CE-marked, BD UltraSafe Passive™) constituents (polycarbonate and stainless steel) are biocompatible for skin contact. Solution for injection in prefilled syringe has been used in Phase III clinical trials and prefilled pen in bioavailability studies. Transportation compatibility has been demonstrated by a shipping study in cooling containers.

Manufacture of the product and process controls

Manufacture

The DP is manufactured by Novartis Pharma Stein AG in Switzerland. The manufacturing process of canakinumab solution for injection in PFS consists of multiple steps which are shown in flow-chart and described in the dossier.

Process controls

Critical steps have been identified and justified. The process parameters have been identified and designated as Operational (O), Performance (P), Critical (CPP) and Non-critical Process Parameters [Key Process Parameter (K) and Non-key Process Parameter (N). In-process controls have been established for PFS and AI pen to ensure a control of the manufacturing process. The holding times been listed. The manufacturing process is appropriately described and controlled.

Process validation / verification

Sufficient number of batches manufactured at Novartis Pharma Stein AG (Switzerland) has been used for validation of PFS (5 batches) and AI pen (3 batches) presentations. The analytical data of batches meet the specification limits at release. The provided in-process control testing data demonstrate that manufacturing processes are robust and consistently produce DP with determined quality characteristics. The provided data indicate that the manufacturing process is capable of consistently produce DP which meets the specifications.

Product specification, analytical procedures, batch analysis

Specification

The proposed specifications are based on the process capability, release and stability testing results and statistical data evaluation of solution in PFS and earlier solution for injection in vial. Where appropriate, acceptance criteria have been set according to the commercial canakinumab (Ilaris) 150 mg powder for solution for injection. This is further supported by the comparability studies of these presentations. No new impurities specific for PFS or vial have been detected compared to those previously observed in the powder formulation. For control of NSD and pen device additional specifications have been assigned for PFS assembled with NSD and AI.

The proposed DP specifications include tests and limits for: appearance of solution and container, color, identity, pH, extractable volume, osmolality, purity and impurities, assay of stabilizer, visible particles and subvisible particulate matter, potency, assay by protein, sterility and bacterial endotoxins, tightness of PFS, break out and sliding force.

The tests for Endotoxins, Sterility, Visible particles, Extractable volume, Particulate matter have been set according to Ph.Eur., USP and JP requirements. Release and stability specifications for canakinumab solution in PFS are sufficiently justified in general. A rapid sterility test is proposed as an alternative to the compendial sterility test.

Regarding “dose accuracy” for release of the pen, the acceptance limited has been aligned with the specification of extractable volume of the PFS.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D has been provided.

Analytical procedures and reference standards

The proposed control strategy and test methods are considered adequate to control the quality of the DP at release and stability testing. The analytical methods are considered capable to demonstrate and detect the degradation products of DP arising during manufacturing process and storage. The functional performance of the AI can be tested by automatic testing machines (SAMT1 and SAMT2), Instron method and fully manual testing, these methods have been cross validated. The analytical methods have been appropriately validated. Same reference standard is used for DS and DP release and stability testing of PFS and pre-filled pen.

Batch analysis

Batch analytical release data have been provided for representative clinical batches, supportive stability, registration stability, commitment stability, process validation and assembly validation batches of solution for injection in PFS and AI. The release results of all PFS and AI lots are within the specification limits and consistent.

Stability of the product

Stability studies for canakinumab solution in PFS and AI (six batches) have been conducted in line with ICH Q5C guideline. Generally acceptable stability testing programme is presented with stability data in tabular form with specification limits.

The stability results of 36 months are provided for three registration stability batches for solution for injection in PFS assembled with needle safety device stored at long term (5°C, 25°C and 30°C). The stress studies for photostability demonstrated that the DP should be protected from light. Additionally the impact of freeze-thaw cycles on the PFS formulation has been studied.

Similar testing programme have been performed for three AI batches. The functionality testing shows that the AI retains appropriate functionality for 36 months. Temperature excursion studies and a photo-stability study are ongoing for AI, not all results are yet available. However, post approval stability protocol and stability commitment is provided. The proposed shelf-life of 36 months at 2-8°C for canakinumab solution in PFS assembled into needle safety device or in AI is supported by the provided data.

Post approval change management protocol(s)

The applicant has provided a protocol for introduction of a future WCB. This protocol is acceptable.

Adventitious agents

The cell substrate is described and the cell banking system is established as required in ICHQ5A guideline. The specifications are regarded approvable. No identity test is set as a requirement in the specification for the WCB. Nevertheless, in the protocol for establishment of a new WCB identity test is requested as part of EOP and therefore the identity will be addressed indirectly.

The applicant applies a multi-tiered system to ensure microbial and viral safety of canakinumab DS solution which includes selection and control of the source and quality of raw materials, cell bank testing, testing of each pre-harvest cell culture fluid during routine manufacture and the canakinumab purification process with two orthogonal steps specific for virus inactivation/removal for which a virus validation study has been performed according to ICHQ5A.

For the virus validation studies, the canakinumab purification process was scaled down to appropriately reflect the full-scale purification process for the canakinumab production. There are two orthogonal clearance steps which exceeded the LRF 4 for all model viruses Q-Sepharose and nanofiltration. Low pH treatment is effective to inactivate the enveloped viruses. The probability of having retrovirus-like particles in a human dose of canakinumab was calculated using a model virus known to contaminate the Sp2/0 production cell line. Consequently, its reduction during the canakinumab purification process was evaluated with respect to potential retrovirus contamination present in the unprocessed bulk harvest.

Overall the virus inactivation/removal capacity of the canakinumab purification process (small scale) is considered to be capable to produce viral safe DS.

GMO

Not applicable

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The overall data in CTD dossier is considered appropriate for providing adequate description of the characterisation, manufacture and control of DS and DP. No major objections are identified, and all other concerns were adequately addressed by the applicant.

The canakinumab DS is manufactured according to a process which involves an up-stream SP2/0 cell culture process followed by down-stream purification using a series of chromatography and membrane filtration steps. Overall, the canakinumab DS manufacturing process is adequate. A criticality classification of all process controls (critical and non-critical) has been provided. The applicant is proposing a 36 month shelf life at ≤ -60°C for DS which is supported by the available stability data.

Canakinumab DP is manufactured according to a standard process of DP formulation, sterile filtration and filling of the syringe. The primary container is subsequently assembled with a safety device for the PFS presentation or an autoinjector for the pen presentation. Critical steps have been identified and justified, in-process controls have been established for PFS and auto-injector pen to ensure a control of the manufacturing process. Overall, the manufacturing process is considered adequate and is sufficiently controlled.

Sufficient number of DP batches manufactured at Novartis Pharma Stein AG (Switzerland) has been used for validation of PFS (5 batches) and AI pen (3 batches) presentations. The analytical data of batches meet the specification limits at release. Based on the provided release and stability data the process appears to be appropriately controlled.

The proposed DP specifications are based on the process capability, release and stability testing results and statistical data evaluation solution in PFS and earlier solution for injection in vial. The specifications are considered appropriate. For control of NSD and pen device additional specifications the have been assigned for PFS assembled with NSD and auto-injector.

Comparability of DP in un-assembled PFS and PFS assembled with NSD and AI has been demonstrated by batch release testing results, additional characterization, and stability data showing no major differences. Some minor differences could be detected between PFS and PFS assembled in AI. The applicant has clarified that these differences result from differences in both the time of testing and assembly of PFS, auto-injector and NSD as well as method and batch related variability.

Stability studies for canakinumab solution in PFS and PFS assembled with Pen (six batches) are conducted in line with ICH Q5C guideline. Acceptable stability testing programme is presented. The

stability results of 36 months provided for three PFS assembled with needle safety device or in pen stored at 5°C is supported by the provided data.

The application is considered approvable from the quality point of view.

3.2. Non clinical aspects

Introduction

Atherosclerosis is a chronic and progressive disease which affects the medium and large arteries and is the primary cause of coronary artery disease, stroke and peripheral vascular disease. During the past two decades, atherosclerosis has been defined as a chronic inflammatory disease. Indeed, increased circulating concentrations of C-reactive protein (CRP), an acute phase protein, were shown to be predictive of future cardiovascular events.

IL-1β is a key mediator involved in the progression of atherosclerosis. IL-1 is a pro-inflammatory cytokine and its expression is inducible by a variety of stimuli (e.g. microbial products, cytokines, stress factors). It was shown to be expressed in endothelial cells, vascular smooth muscle cells and macrophages and atherosclerotic plaques express significantly increased levels of IL-1β compared to control arteries. IL-1β induces adhesion molecule expression vascular permeability, leucocyte migration, macrophage activation and vascular smooth muscle cell proliferation leading to atherosclerosis and plaque instability.

Using animal models, IL-1β has been implicated the progression of atherosclerosis since reduced atherosclerosis was observed in IL-1β-deficient and IL-1R-deficient mice. Furthermore, in mouse models of atherosclerosis (e.g. ApoE- or LDL receptor-deficient mice on a high fat diet) the blockade of IL-1 signalling or genetic ablation of IL-1β or IL-1 receptor resulted in reduced deposition of fatty acids and plaque formation in coronary arteries by mechanisms targeting monocyte influx, the generation of artherogenic Th17 cells, and the expression of pro-inflammatory cytokines, chemokines and adhesion molecules.

Canakinumab is a fully human IgG1/κ mAb directed against human IL-1β and prevents the binding of human IL-1β to its cognate receptor on the surface of its target cells. By inhibition of IL-1β, canakinumab targets vascular inflammation in order to reduce the risk for major cardiovascular events.

3.2.1. Pharmacology

Primary Pharmacodynamics

In vitro

As shown by surface plasmon resonance, canakinumab binds specifically to human IL-1β with a KD of 30 to 60 pM. Canakinumab does not cross-react with IL-1α, IL-1Ra, or any other member of the IL-1 family, including IL-18 and IL-33. Using site-directed mutagenesis of recombinant human IL-1β the epitope of canakinumab was mapped precisely. By x-ray crystallography of IL-1β bound to the canakinumab Fab fragment it was found that the epitope partially overlaps with the binding site of IL-1β to the IL-1 receptor. Consequently, soluble IL-1 receptor (both type I and type II) dose-dependently inhibited binding to IL-1β to canakinumab in BIAcore analyses.

In a cell-based *in vitro* assay, canakinumab was found to inhibit the activity of natural and recombinant human IL-1β with IC50 of approximately 50 pM. Importantly, in this assay the inhibitory effect of canakinumab and IL-1Ra was found to be additive. Thus, canakinumab does not compromise the biological activity of IL-1Ra, an important endogenous inhibitor of IL-1 activity *in vivo*.

To provide evidence for the proposed role of IL-1β in the pathophysiology of atherosclerosis, the effect of blocking IL-1β was evaluated in ex vivo cultures of atheroma cells obtained from human carotid endarterectomies. The human atheroma cell population mainly consists of macrophages, smooth muscle cells and T lymphocytes and produces, cytokines, chemokines and MMPs in culture immediately after surgical resection without additional exogenous stimulation.
In cultures of cells that were freshly obtained from human atherosclerotic plaques blockade of IL-1β by canakinumab was associated with a reduction in pro-inflammatory cytokines (IL-6, IL-8, GROα, GM-CSF) and matrix metalloproteases (MMP1 and MMP10). Together with literature on the role of IL-1 in atherosclerosis, these data provide a sufficient pharmacological rationale for blocking IL-1β to reduce the risk of major cardiovascular events.

Species cross-reactivity

Canakinumab does not bind to IL-1β from mouse, rat, rabbit, or cynomolgus monkey. The only non-human species specifically recognized by canakinumab is the marmoset monkey. This limited species cross-reactivity can be explained with one amino acid in the IL-1β sequence that is crucial for canakinumab binding. At position 64, Glu is present in human and marmoset IL-1β but changed to Ala or Gly in all other species analysed.

With an equilibrium binding constant KD of ca. 23 pM the binding affinity of canakinumab for marmoset IL-1β was slightly higher than that for human IL-1β. In an i*n vitro* assay, canakinumab potently inhibited the expression of a reporter gene induced by marmoset IL-1β. the potency for marmoset IL-1β was found to be approximately two-fold lower than that for human IL-1β.

In vivo studies

Since canakinumab does not react with rodent IL-1β, the *in vivo* activity of canakinumab was demonstrated in models of inflammation induced by human IL-1β in rodents (i.e. mouse joint inflammation, neutrophil infiltration into mouse air pouch). In these models, canakinumab inhibited the IL-1β-induced effects.

Secondary Pharmacodynamics

With regard to secondary pharmacodynamics, it was shown that canakinumab does not block T cell proliferation in a human mixed leukocyte reaction *in vitro*, indicating that canakinumab is not acutely immunosuppressive *in vivo*.

Binding of canakinumab to Fcγ receptors was determined by surface plasmon resonance and was as expected for a human IgG1 antibody. Canakinumab did not bind to the surface of IL-1β-producing cells in an antigen-dependent manner and did not recruit the complement component C1q. Thus, canakinumab is not expected to mediate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To enable further toxicological studies a surrogate antibody (01BSUR) with a murine IgG2a/k isotype was developed. 01BSUR is specific for mouse IL-1β (KD 302 pM) and does not bind to IL-1α and IL-1Ra. *In vitro*, 01BSUR was able to inhibit IL-1-induced effects in a NIH3T3 fibroblast model with a potency comparable to that of canakinumab. *In vivo* bioactivity of 01BSUR was shown in mouse model of collagen-induced arthritis. When given in a semi-prophylactic treatment mode, 01BSUR almost completely inhibited the development of joint inflammation. Using this surrogate antibody in mice, it was further shown that neutralization of IL-1β does not inhibit the development of a T cell-dependent antibody response induced by immunization in the presence of aluminium hydroxide as adjuvant.

Safety pharmacology programme

Stand-alone safety pharmacology studies were not conducted with canakinumab. However, the cardiovascular system was analysed as part of the toxicology studies. No treatment-related effects on electrocardiography data were observed throughout treatment and recovery periods.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

Overall, the pharmacological studies have adequately characterized the specific binding of canakinumab to IL-1β and have demonstrated its capacity to inhibit IL-1-induced effects *in vitro* and *in vivo*.

3.2.2. Pharmacokinetics

The non-clinical PK studies submitted with the present application are the same as those reviewed at the time of the Ilaris marketing authorisation.

Pharmacokinetics of canakinumab was determined following single IV administration in marmosets, rhesus monkeys and mice and after single SC administrations in marmosets. Pharmacokinetics after multiple dosing was determined as part of the toxicology studies.

Levels of canakinumab in marmoset serum were detected by a competitive ELISA, which was initially developed for the human system and subsequently validated for marmoset matrix. For detection of the surrogate 01BSUR in murine system a comparable competitive ELISA was used. Antibodies against canakinumab and 01BSUR were measured with a BiaCore-based assay qualified to use in marmoset and murine matrix.

Taken together, the pharmacokinetics of canakinumab was as expected for a human IgG antibody characterized by a small volume of distribution, similar to the plasma volume, low systemic clearance and a long terminal half-life. Of note, with 4-7 days the elimination half-life of canakinumab in marmosets was shorter than in rhesus monkeys (17.4 days), mice (14.5 days) and humans (26 days). Shorter half-life for human IgG in marmosets has been observed previously.

Pharmacokinetic parameters were similar in male and female marmosets. A dose-proportional increase in Cmax was observed between 5 and 50 mg/kg and slightly less than dose-proportional between 50 and 150 mg/kg. On average, Cmax was reached 2-3 days after SC administration. After repeated dosing, a 2-3-fold accumulation occurred. Bioavailability after SC administration was determined to be 60 % based on a cross-study comparison to a single-dose IV study.

Two PK bridging studies were performed to support changes in the canakinumab manufacturing process. Using a cross-over design following single SC injection in marmosets, canakinumab from process A vs. B and from process B vs. C was found to be comparable with regard to its pharmacokinetic characteristics. In addition, the effect of glycosylation of canakinumab on the pharmacokinetics was investigated. These analyses were performed in mice with canakinumab containing primarily biantennary G0, G1 and G2 oligosaccharides vs. high mannose oligosaccharides. It was shown that the pharmacokinetics was not influenced by the type of oligosaccharides attached to the IgG heavy chain.

In addition, pharmacokinetics of 01BSUR was determined in mice after single and repeated SC administration. A dose-dependent increase in Cmax and AUC was observed. Tmax was approximately 24 h after dosing and the elimination half-life was ranged between 1 and 17 days.

3.2.3. Toxicology

An extensive programme of toxicology studies was performed. Toxicity of canakinumab was analysed in marmoset monkeys. Additional toxicity studies were conducted with the murine surrogate mAb 01BSUR in mice. Regarding toxicokinetics, exposure to canakinumab or 01BSUR was demonstrated in each study. With the analysis method used, no anti-drug antibodies were detected.

These studies had already been submitted and reviewed for the marketing authorisation of Ilaris. To support the present MAA, an up-dated carcinogenicity risk assessment was provided.

Single dose toxicity

No single-dose toxicity studies were performed with canakinumab, which is acceptable in view of the data provided by the repeated dose toxicity studies.

Repeat dose toxicity

In two IV repeat-dose studies canakinumab was given twice a week at doses of 0, 10, 30 and 100 mg/kg. In the first study, a 4-week treatment period was followed by 8 weeks of recovery. In the second study 26 weeks of treatment were followed by 6 weeks of recovery. In both studies, no deaths occurred. There were no test-item related changes with regard to clinical signs, body weight food consumption, ophthalmology, ECG, hematology, clinical biochemistry, urinalysis, organ weights and histopathology. In both studies, the NOEL was 100 mg/kg given IV twice weekly.

A total of three SC repeat-dose studies with canakinumab were performed.
In the first study female marmosets were treated with 0, 5, 50 and 150 mg/kg on day 1 and day 43, terminal necropsy was on day 44. In the second study, marmosets were treated at 0, 15, 50 and 150 mg/kg twice a week for a period of 13 weeks followed by a recovery period of 8 weeks. No test-item related deaths occurred during these studies. No test-item-related changes were observed with regard to clinical signs, body weight, food consumption, ophthalmology, ECG, macroscopic and microscopic evaluation and clinical chemistry. There were not alterations in hematology, immunophenotyping of blood and spleen. In both studies the NOEL was 150 mg/kg given SC.
A third SC repeat-dose study was performed. In this study, marmosets were treated twice weekly for 13 weeks with vehicle or with 150 mg/kg canakinumab from process A or from process C in a prefilled syringe. In this study, microscopic lesions and clinical pathology changes were observed in all groups, including controls. One male marmoset was sacrificed moribund due to septicemia. Fifteen days later, the cagemate was found dead without significant clinical signs. Other pathological changes included renal and intestinal lesions in both treated and control animals. Given the poor health already in the control animals, the study was not considered valid by the applicant.
In all other toxicity studies performed with canakinumab in marmosets, such changes have not been observed. Thus, the results of this SC repeat-dose study do not raise concerns regarding the toxicity of canakinumab.

Genotoxicity

No genotoxicity studies were performed with canakinumab, as it is a protein. This is acceptable according to guideline ICH S6.

Carcinogenicity

No carcinogenicity studies were performed with canakinumab. However, with the present application an up-dated carcinogenicity risk assessment was provided.

The update includes a review on literature data regarding the role of IL-1β in tumour development and immune surveillance. Literature indicates that IL-1β rather promotes tumour development. Thus, neutralization of IL-1β would be expected to be beneficial.

In addition, the MAH reviewed results from the non-clinical studies with canakinumab in marmosets and the surrogate antibody in mice. Of particular interest is the occurrence of a uterine adenocarcinoma in 1 female marmoset monkey treated with canakinumab in the 26-week repeat-dose toxicity study. Although uterine adenocarcinoma in marmoset monkeys are not described in the literature, this type of tumour was occasionally observed in marmosets by the CRO who conducted study. Given the lack of a mechanistic basis, the adenocarcinoma is considered a spontaneous event and not treatment-related.

Finally, the MAH discussed the potential of additional animal models, especially transgenic mice expressing human oncogenes to assess the carcinogenic potential of IL-1β blockade. Given their mechanistic basis such models are not considered relevant.

Based on the non-clinical carcinogenicity risk assessment blockade of IL-1β is not expected to result in an increased tumour growth promotion or occurrence. Furthermore, there was no evidence of an increased risk of malignancy in the pivotal phase 3 study (CANTOS). Consequently, additional non-clinical studies are not considered necessary. Instead malignancy events will be monitored in the clinic (refer to RMP). This is considered appropriate.

Reproductive and developmental toxicity

Reproductive toxicity studies in marmosets were limited to evaluation of male fertility (part of the 26 weeks repeat-dose toxicity study) and an embryo-fetal development study.
No canakinumab-related effects were observed on the male reproductive system.
In the embryo-fetal development study, pregnant marmosets were treated SC, twice a week, with 0, 15, 50 or 150 mg/kg from GD 25 to GD109. Caesarean section was performed on GD112-114. There were no signs for maternal toxicity. The only finding associated with canakinumab treatment was a slight reduction in the number of fetuses in the 150 mg/kg group, which correlated with a slight trend to decreased placental weight. Both findings were statistically not significant. There were no treatment-related effects regarding fetal development. At GD112-114, placental transfer of IgG was confirmed. However, given that transfer of IgG across the placenta starts late during gestation, it is unlikely that the fetus was exposed to canakinumab during the period of organogenesis.

In addition a full panel of reproductive toxicity studies was performed with the surrogate mAb 01BSUR in mice. In these studies, 01BSUR was administered once weekly by the SC route at doses of 0, 15, 50 or 150 mg/kg.
Male and female fertility was not affected by treatment with 01BSUR.
In the embryo-fetal development study, maternal functions were unaffected by treatment with 01BSUR. Regarding the fetus, 01BSUR had no effect on fetal weights and the overall incidence of fetal malformations or anomalies. However, in the high dose groups there was an increased incidence of litters and fetuses with incomplete ossification of the parietal and the frontal bone that was statistically significant. These findings were considered a transitory delay in ossification and to be of no teratological significance, as there were no changes on any other bones.
In the pre-/post-natal development study, mice were exposed to 01BSUR throughout gestation and lactation. Such treatment resulted in no evidence of maternal toxicity. Furthermore, there were no toxic effects on the development of the pubs, and their survival, physical development, behaviour and reproductive performance.

Taken together the reproductive toxicity studies in marmosets and in mice did not identify a signal for reproductive toxicity by neutralization of IL-1β.

A juvenile animal study was conducted with the surrogate mAb 01BSUR. Mice were treated once weekly with 01BSUR from day 7 to day 70 post partum. There were no treatment-related effects on the development pre- and post-weaning. In the 150 mg/kg group, the mean day to development of the vaginal opening was later than in controls. There was no effect of treatment on fertility.
Regarding the immune system, there were no differences in counts for total lymphocytes and lymphocyte subsets in blood, spleen and thymus. However, functional studies on the immune system were not included in this study. To exclude possible effects of neutralization of IL-1β on the developing immune system, the applicant committed to perform a juvenile immunotoxicity study, assessing the effect of the canakinumab surrogate on immune function in juvenile animals. Treatment of mouse pups with 01BSUR by once weekly SC injection for 9 weeks resulted in generally minimal, inflammatory reactions at the injection sites. These were reversible over a 4 week recovery period.

Local tolerance

The local tolerance to canakinumab at the SC and IV injection sites were assessed in the course of the repeat-dose toxicity studies in marmoset. Occasionally mild reactions were observed which were similar in the in the control animals and therefore not test article-related. In a dedicated local tolerance study, a single intra-articular injection of canakinumab (10 mg/kg) to marmosets was well tolerated.

Other toxicity studies

Three tissue-cross-reactivity studies were performed with canakinumab, each with canakinumab produced by a different process (A, B, C). Together the results indicate that canakinumab drug substance produced with the different manufacturing processes have similar tissue cross-reactivity profiles. In each study, full panels of human tissues (3 donors) and marmoset tissues (2 donors) were used. In general, the staining observed was consistent with the known expression of IL-1β in human tissues. Reactivity of canakinumab with marmoset tissue was qualitatively similar but quantitatively reduced compared with the reactivity for human tissues.

3.2.4. Ecotoxicity / environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, canakinumab is not expected to pose a risk to the environment.

3.2.5. Discussion on non-clinical aspects

An array of studies was performed which characterize the pharmacodynamic effects of canakinumab. The specific binding of canakinumab to human IL-1β was adequately shown. The selection of the marmoset as relevant species for toxicity studies was scientifically justified. The characterization of the surrogate mAb 01BSUR is considered adequate. The capacity of canakinumab and its surrogate to inhibit IL-1β-induced effects *in vitro* and *in vivo* was demonstrated adequately. Potential secondary pharmacodynamic effects have been addressed and ruled out.

In *ex vivo* cultures of human atheroma cells, blockade of IL-1β by canakinumab was associated with a reduction in pro-inflammatory cytokines (IL-6, IL-8, GROα, GM-CSF) and matrix metalloproteases (MMP1 and MMP10). Together with literature on the role of IL-1 in atherosclerosis, these data provide a sufficient pharmacological rationale for blocking IL-1β to reduce the risk of major cardiovascular events.

Overall, the pharmacological studies have adequately characterized the specific binding of canakinumab to IL-1β and have demonstrated its capacity to inhibit IL-1-induced effects *in vitro* and *in vivo*.

Pharmacokinetics of canakinumab was determined following single IV administration in marmosets, rhesus monkeys and mice and after single SC administrations in marmosets. Pharmacokinetics after multiple dosing was determined as part of the toxicology studies.

The pharmacokinetics of canakinumab was characterized by a small volume of distribution, similar to the plasma volume, low systemic clearance and a long terminal half-life. Of note, with 4-7 days the elimination half-life of canakinumab in marmosets was shorter than in rhesus monkeys (17.4 days), mice (14.5 days) and humans (26 days). A shorter half-life for human IgG in marmosets has been observed previously. Bioavailability after SC administration was 60 % based on a cross-study comparison to a single-dose IV. On average, Cmax was reached 2-3 days after SC administration. After repeated dosing, a 2-3-fold accumulation occurred.
Overall, canakinumab pharmacokinetics were as expected for a human IgG antibody.

A broad array of toxicity studies was performed with canakinumab and the surrogate mAb 01BSUR. In general, treatment of marmosets with canakinumab and of mice with the surrogate mAb 01BSUR was well tolerated. In all studies, the NOEL or NOAEL was the highest dose administered (100 mg/kg/dose IV or 150 mg/kg/dose SC). No signals were identified for general toxicity and for reproductive toxicity. Regarding the effects of IL-1β neutralization on the immune system, treatment of juvenile animals for 9 weeks and of adult animals for 4 weeks revealed no negative effects. There was no indication that susceptibility to infection is increased.

An updated carcinogenicity risk assessment was provided with the present application. Based on the assessment of literature data on the role of IL-1β in tumour development, results from the non-clinical studies and also clinical data with canakinumab, blockade of IL-1β is not expected to results in an increased tumour growth promotion or occurrence.

3.2.6. Conclusion on non-clinical aspects

The available non-clinical studies are considered adequate to support the marketing authorisation of canakinumab for secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ⩾ 2.0 mg/l prior to treatment initiation.

3.3. Clinical aspects

Tabular overview of clinical studies

Table 3.3.1. Overview of clinical studies supporting the MACE reduction indication

Study	Phase	Design and Objectives	Dose Regimen	Age in years (Range)	Enrolled number of subjects	Subjects received canakinumab
PK/PD studies in healthy subjects						
A2104#	I	R, OL, parallel group, bioequivalence, S&T and PD in healthy subjects	Single dose: 150 mg sc, comparing PFS with marketed lyophilized powder for solution	18 – 45	130	130
M2101	I	R, OL, parallel group, relative bioavailability, S&T in healthy subjects	Single dose: 150 mg via AI or SS administered by HCP	19– 62	80	80
Studies used in CANTOS dose selection						
A2213	II	R, DB, PC, dose escalation, S&T, and PK/PD in T2DM	Single dose iv; 0.3 mg/kg; 10 mg/kg; 0.1-, 0.3-,1.5- mg/kg; 0.03 mg/kg	52 – 57	231	147
I2202	II	DB, PC, efficacy, S&T, dose finding in T2DM	5/15/50/150 mg sc monthly	28 – 74	556	375
H2251#	II	DB, efficacy, S&T, in gouty arthritis patients	25-,50-,100-, 200-,300-mg sc D1, 50 mg sc	20 – 79	432	324
A2201#	II	R, DB, PC, efficacy, S&T, in patients with active rheumatoid arthritis	600 mg, 300 mg, 150 mg sc	23 – 87	274	204
Mechanistic and other vascular studies						
I2207	II	R, DB, PC, efficacy, S&T, in patients with T2DM or impaired glucose tolerance	150 mg sc single dose	27-74	246	154
X2201	II	R, DB, PC, efficacy, S&T, in patients with abdominal aortic aneurysms	150 mg sc monthly	53-86	65	31
M2201	II	R, DB, PC, efficacy, S&T, in patients with peripheral arterial disease	150 mg sc monthly	47 – 79	38	18
I2206	II	R, DB, PC, efficacy, S&T, in patients with atherosclerosis and T2DM or impaired glucose tolerance	150 mg sc monthly	40 – 74	189	95
Pivotal Phase 3 study (CANTOS trial)						
M2301	III	R, DB, placebo controlled, superiority study in post MI patients	50/150/300 mg sc q12w	54-92	10061	6717

PC=placebo controlled; OL=open label; R=Randomized; DB=Double blind; S&T=safety and tolerability; PK=pharmacokinetics; PD=pharmacodynamics; SS: Safety Syringe; AI: Auto-injector; HCP: Health care professional; PFS: pre-filled syringe; T2DM: Type 2 diabetes mellitus; #canakinumab studies submitted during previous submissions.

3.3.1. Pharmacokinetics

In patients with prior myocardial infarction and hsCRP levels ≥ 2.0 mg/L at treatment initiation, canakinumab is recommended to be dosed via pre-filled syringe or pre-filled pen at 150 mg subcutaneously every 3 months. The intended dosing regimen has been studied in 2284 patients in the pivotal phase 3 study M2301 (CANTOS). In total, 10 studies contributed to the clinical pharmacology program, among them 2 phase 1 biopharmaceutic studies, 4 phase 2 studies which were used for dose selection of the pivotal CANTOS study and 4 further phase 2 studies conducted in patients with cardiovascular diseases.

Non-compartmental PK analysis was conducted in biopharmaceutic studies investigating bioequivalence/relative bioavailability of different canakinumab formulations in healthy volunteers (studies M2101 and A2104) and in study A2213 investigating the safety and tolerability and PK/PD of multiple iv doses of canakinumab in type 2 diabetes mellitus patients. For the pivotal CANTOS study with only sparse PK sampling, a population PK model was developed to describe the pharmacokinetics of canakinumab in patients with prior myocardial infarction and elevated hsCRP.

Aside from the described studies, pharmacokinetics of canakinumab have been investigated in various other patient populations during the clinical development program of Ilaris®.

Analytical assays

Canakinumab concentration in human serum was analyzed by a competitive ELISA method which was already introduced in former applications of Ilaris®. The PK assay was accurately validated and all parameters investigated met the acceptance criteria of the relevant guidance. Several bioanalytical data reports refer to report BxSD RS710569 as the reference method validation report. Initially, this report could not be found in the dossier and was provided by the applicant in the MAA response submission. Validation was adequate and the method was shown to be suitable for the quantitative determination of ACZ885 in human serum. The applicant further provided an overview on which assay method was used for the detection of canakinumab in human serum in the studies that contributed to the clinical pharmacology program. In the pivotal study M2301, a total of 936 samples were outside of the validated stability window for canakinumab. Meanwhile, additional long-term stability experiments have been conducted. Referring to these results, less than 1% of samples are now considered out of established stability. Given the large number of samples from CANTOS and the minimal number of samples outside established stability, it is rather unlikely that the integrity of PK/PD results for CANTOS is impacted.

Total IL-1β was determined in human serum using a commercially available sandwich ELISA method. IL-1β concentration in early samples of study M2301 was analyzed using the same commercially available kit (Quantikine-HS, catalogue ref. HSL00C, R&D Systems) as used in former applications of Ilaris®. Afterwards, a new kit was used (Quantikine-HS, catalogue ref. HSL00D, R&D Systems), for which validation experiments revealed adequate performance with respect to intra-/inter-run precision and accuracy, dilution linearity, hook effect, selectivity and stability. Cross-validation experiments demonstrated the necessity of the application of a corrective factor of 0.6801 for reasons of comparability when the new kit was used.

Anti-canakinumab antibodies analysis followed a 3-tiered approach with screening, confirmatory and titration assays. The former ADA screening assay, a quasi-quantitative method that employed a bridging immunogenicity electrochemiluminescence immunoassay (ECLIA) was subsequently replaced by an improved assay employing an ECLIA with acid dissociation step and increased drug tolerance. The newly developed assay was already introduced in previous submissions of Ilaris®. Validation was accurate and parameters were in line with the acceptance criteria of the relevant guidance. The majority of ADA samples in CANTOS (97.4%) were analyzed with the improved assay. With regard to other studies contributing to ADA assessment, the applicant provided an overview on which immunogenicity methods have been applied in the respective studies. The method applied for determination of neutralizing antibodies was the same as used for Ilaris®. In response to the d120 LoQ, the applicant provided the method validation reports of the nADA assay. Method validation is considered adequate. Except for the inter-run precision determined during method transfer and validation at SGS Cephac Europe, all pre-defined acceptance criteria were met. Nevertheless, the applicant currently develops an optimized nADA assay which also aims at improving inter-assay precision. Final validation of this optimized assay will be shared in future applications or in following PSURs.

Population PK modelling

Pharmacokinetics of canakinumab in the CANTOS trial population was investigated with population PK analysis. PK sampling schedule was very sparse, only up to three samples per subject, and vast majority of samples were trough concentrations. A significant proportion (15.1%; 2462 of 16291) of post-dosing samples was below the limit of quantification (BLOQ). CANTOS PK model built upon the SJIA PK model [ACZ885 Japanese SJIA PPK Modeling Report] and was simplified due to the sparse PK sampling from a two-compartment to a one-compartment disposition model for canakinumab where absorption rate (Ka), bioavailability (F) and age effect on Ka were fixed at previously estimated values without random effects. For several reasons, the population PK modelling approach was initially considered inadequate:

a. The model built upon the Japanese SJIA PK model and absorption rate (ka) and bioavailability (F) were fixed to the values that derived from the SJIA population PK. Considering the expected differences in patient populations and the potential impact of different age, body weight and obesity on absorption, the use of fixed values for ka and F is deemed inappropriate. By inclusion of iv studies to the population PK model, ka and F should rather be estimated for the CANTOS population separately.

b. Owing to the sparse sampling performed in study M2301, the previous 2-compartment model (used in the SJIA PK model) was switched to a simplified 1-compartment model although it is not assumed that the PK profile in CANTOS suddenly changed as compared to other indications or patient populations, for which the 2-compartment model fitted quite well.

c. The goodness-of-fit plots for the CVRR population PK model reveal a considerable deviation of observed canakinumab concentrations from population predicted canakinumab concentrations. The plot of observed vs. population predicted concentrations indicated overprediction at low concentrations (less than ~2 µg/mL) and underprediction at high concentrations. Other goodness-of-fit plots, including observed vs. individual predicted concentrations, NPDE and CWRES plots generally indicated that the model provided adequate characterization of canakinumab kinetics in the population. However, ETA-shrinkages were high (36.5% for ETA-CL, 63.8% for ETA-Vc), thus individual predictions are considered of little value for assessing model adequacy, as they shrink back towards the observation.

The model was not considered adequate to thoroughly estimate PK parameters of the CANTOS population. Therefore, the applicant was requested to set up a population PK model which includes the

entire canakinumab PK data in adult subjects obtained so far. In response, the applicant provided the ACZ885 Japanese SJIA PPK Modelling report and clarified that the Japanese SJIA PPK analysis contained data from many populations, including gout and RA patients with age and body weight ranges that were close to the CANTOS population. The SJIA pooled analysis showed that the estimated population rate of absorption was similar across a wide age range of the adult population. Fixing of the rate of absorption and bioavailability in the CANTOS population to the estimated values in the SJIA pooled analysis might thus be deemed acceptable.

A comparison of the simulation results from the newly developed 2-compartment CANTOS pooled model with the original 1-compartment CANTOS model was provided and demonstrated that both models simulated very similar PK profiles. The use of the 1-compartment model is therefore considered acceptable.

The applicant further outlined that GOF diagnostic plots might be biased due to the inclusion of BLOQ samples (~15%) and in this case predictive checks are considered more informative with regard to model evaluation. The respective VPC plots revealed that the final model provided adequate prediction ability of the observed data.

In addition and as requested, the applicant developed an overall population PK analysis with the ACZ885 pooled dataset in the adult population. The population PK modelling report (CANTOS pooled analysis) was not provided. However, it might be agreed that the CANTOS pooled model provided a good description of the observed dataset and showed adequate prediction ability. Still, shrinkage for absorption rate and volume of distribution was quite high. The estimates for clearance, rate of absorption and bioavailability in the newly developed CANTOS pooled analysis were similar to those of the originally submitted CANTOS population PK model. Both the original and the newly developed CANTOS population PK analyses yield very similar estimates of PK parameters and exhibit similar predictive ability.

The published population PK models of canakinumab (Chakraborty et al. 2012) have described the kinetics of both canakinumab and IL-1β, whereas the presented model for CANTOS population at the time of MAA only described the PK of canakinumab. The applicant commented that the PK data collected in CANTOS (Study M2301) are insufficient to support estimation of all required parameters of the PK-binding model for canakinumab IL-1β. Since no reliable PKPD-model could be built, this issue is no longer pursued.

Absorption

Mean absolute bioavailability of canakinumab was demonstrated to be approx. 0.7 based on PK data from small number of healthy adult Japanese subjects. There are no reasons to expect that absolute bioavailability would be significantly different than 0.7 in other ethnic groups.

In the CVRR population PK absorption rate (ka) and absolute bioavailability (F) were fixed to the estimates deriving from SJIA population, therefore these parameters could not be estimated separately for the CANTOS patient population. The new population PK that is requested should allow for estimation of ka and F in CANTOS patients. In previous studies with Ilaris® the sc bioavailability estimate of canakinumab was approximately 60-70%.

Bioequivalence / Relative bioavailability

Two bioequivalence/relative bioavailability studies (A2104 and M2101) were conducted in healthy volunteers to confirm bioequivalence between i) a liquid formulation of canakinumab packaged as a pre-filled syringe (PFS) and a lyophilized formulation, and ii) a liquid formulation of canakinumab administered by self-injection via Delta AutoInjector (AI) compared with via a safety syringe (SS) administered by a healthcare professional. Both studies were parallel-group single dose (150 mg SC) studies and conventional primary PK endpoints (AUClast, AUCinf and Cmax) were determined using non-compartmental methods. Bioequivalence between the liquid and lyophilized formulations as well as between Delta AutoInjector and safety syringe devices was confirmed, as in both studies geometric mean ratios and associated 90% CIs for Cmax, AUClast and AUCinf fell within the bioequivalence margin of 0.8 – 1.25.

Distribution

The apparent volume of distribution for a typical patient in the CANTOS patient population (weight 86.5 kg) was estimated to 8.1 L and was comparable to the results obtained by non-compartmental PK analysis in healthy volunteers (7.9 – 10.5 L). Further comparison to previous submissions for Ilaris® revealed similar results for volume of distribution across various patient populations. As typical for monoclonal antibodies, volume of distribution of canakinumab was low, indicative of limited tissue penetration and distribution mainly in serum.

Elimination

Apparent clearance of canakinumab in CANTOS was estimated to be 0.225 L/day and the calculated elimination half-life was approximately 25 days. These values are in agreement with PK parameters determined in healthy volunteers and other patient populations investigated during the Ilaris® development program.

The main elimination pathway described for monoclonal antibodies is intracellular catabolism, followed by fluid-phase or receptor mediated endocytosis. Metabolic pathways and excretion of canakinumab have not been further studied, which is acceptable for an IgG antibody. Due to the large size of monoclonal antibodies, renal or hepatic elimination processes are expected to be negligible.

Linear pharmacokinetics

Canakinumab was studied over a dose range of 0.03 – 10 mg/kg intravenously and over a dose range of 25 – 300 mg subcutaneously. For both routes of administration, increasing doses led to dose-proportional increases in canakinumab exposure. There was no indication of accelerated clearance during the terminal elimination phase. As typical for monoclonal antibodies targeting a soluble antigen with low endogenous level, canakinumab mainly exhibits dose-independent linear clearance. Similarly, the CVRR population PK analysis suggested linear PK with 50 mg, 150 mg and 300 mg canakinumab quarterly sc dosing in CANTOS patients. The accumulation ratio, as assumed for quarterly dosing of canakinumab, was low (1.13), and no time-dependent changes in PK properties or accelerated clearance over time have been identified. Nevertheless, the estimated AUCtau at steady state after 150 mg quarterly dosing in CANTOS was lower compared to the AUCinf after sc administration of a single 150 mg dose canakinumab in healthy volunteers. In this regard, the applicant stated that the observed difference most likely results from a combined effect of differences in body weight (~20%) and the population differences in clearance (21%) between healthy volunteers and CANTOS patients, rather than from time-dependent differences in PK of the CANTOS population or model inadequacy.

Variability

Estimates of between subject variability in the final CVRR population PK model for both clearance and volume of distribution, if transformed to %CV, are quite high (> 60%). Since large shrinkage was determined for BSV on clearance (36.5%) and BSV on volume of distribution (63.8%), this might have led to misleading diagnostic plots of individual parameter estimates and covariates.

Special populations

As monoclonal antibodies are known to be primarily eliminated via intracellular proteolysis, no specific studies in patients with impaired renal or hepatic function are necessary. In the CVRR population PK analysis, a post-hoc estimation of canakinumab clearance across different stages of renal impairment suggested that canakinumab clearance was indeed independent from renal function. Therefore, dose adjustment is not required in patients with mild to moderate renal impairment (eGFR 30-90 mL/min). Pharmacokinetics of canakinumab has not been formally investigated in patients with severe renal or hepatic impairment.

The analysis of covariates (CVRR population PK analysis) only identified body weight as having a statistically significant and clinically relevant effect on canakinumab PK. Estimated clearance and volume of distribution increased with increasing body weight in an allometric relationship, with allometric exponents estimated to be 0.760 and 0.730 respectively, but elimination half-life was not significantly affected by body weight. For the intended canakinumab dose to be marketed (150 mg quarterly), median AUCtau ranged from 632 day*µg/mL (60 kg patient) to 362 day*µg/mL (124.96 kg patient), median Cmax ranged from 14.16 µg/mL (60 kg patient) to 8.25 µg/mL (124.96 kg patient) and median Cmin ranged from 1.8 µg/mL (60 kg patient) to 0.96 µg/mL (124.96 kg patient).

Age, albumin, gender and race were not considered leading to clinically relevant changes in canakinumab PK, as change in clearance for these covariates was generally no more than 10% from the typical value. Furthermore, the estimated clearance and volume of distribution of the CVRR population revealed no considerable difference compared to other patient populations that so far have been treated with canakinumab (healthy subjects, CAPS, gout, SJIA).

Interactions

No *in vitro* and *in vivo* metabolism or drug interaction studies have been conducted with canakinumab. Inflammatory cytokines, including IL-6 and IL-1β, down-regulate the expression and decrease the activity of hepatic cytochrome P450 (CYP) enzymes *in vitro* (Aitken and Morgan, 2007). In recent years, it has been demonstrated that biological medicinal products that inhibit inflammatory cytokine signalling significantly increase the activity of CYP enzymes. Restoration of CYP450 enzymes to normal levels could thus potentially reduce the exposure of certain co-administered CYP450-metabolized drugs. In CANTOS patients, this specifically applies to statins, which are commonly metabolized via the CYP450 system. Section 4.5 of the proposed SmPC is in line with that of Ilaris® and only CYP450 substrates with narrow therapeutic index are recommended to be monitored. It is not known if the systemic inflammatory cytokine concentrations in the applied target population are increased to such levels that significantly affect CYP activity and how much treatment with canakinumab alters their activities. This issue is clinically relevant because the target population is expected to have several concomitant medications (e.g. statins) that might be affected. In response, the applicant provided scientific literature supporting the conclusion that IL-1β and IL-6 levels observed in the target population are so much below the EC50 values that it is unlikely that CYP3A and other enzymes involved in drug metabolism are significantly suppressed by these cytokines. Thus, a further decrease in cytokine concentration is not expected to have a clinically relevant effect on the elimination of CYP-metabolized drugs, possible exception being drug with narrow therapeutic index, for which an adequate warning statement was included in section 4.5 of the SmPC.

3.3.2. Pharmacodynamics

Mechanism of action

Interleukin-1 (IL-1) may be relevant for the pathogenesis of CV diseases. It exists as IL-1α and IL-1β, with both forms exerting similar biological activities through the IL-1 type 1 receptor. IL-1 is activated upon tissue injury and plays an important role in several inflammatory conditions. The agonistic effects of the cytokine are balanced or fine-tuned by a naturally occurring competitive IL-1Ra. Therefore, any imbalance in this biological system has the potential to exacerbate inflammatory injury.

Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors. IL-1β is a potent inflammatory mediator and may play a role in atherogenesis. Canakinumab showed an effect on parameters related to atheroma formation and progression. An ex vivo atheroma culture was studied to evaluate a PD effect of canakinumab on IL-1ß activity, which showed that canakinumab significantly inhibited IL-6 production in atheroma cells, with a 40% reduction of IL-6 production compared to untreated cultures following 72 hours of treatment. CRP, a general inflammatory biomarker, lies downstream of IL-1β, and therefore suppression of IL-1β results in a decrease in hsCRP which was observed in canakinumab studies conducted in T2DM, rheumatoid arthritis, gouty arthritis patients and the pivotal trial CANTOS (see below). In addition, IL-1ß has been shown to ineract with pathways of lipid metabolism.

By binding to IL-1ß Canakinumab has the potential to interact with these pathophysiological pathways of atherogenesis. A wealth of data have, indeed, linked inflammatory processes with development of atherosclerosis and, more acutely, weakening of the fibrous cap, plaque rupture and thrombosis. However, the relevance of inflammation is variable between patients and different phases of atherosclerosis. Moreover, the specific role of IL-1β and blockage of IL-1β signalling pathway in the local inflammation at the vascular wall is not yet fully confirmed. It remains yet to be demonstrated when would be the most beneficial time point for anti-inflammatory medication for a patient with CV disease: during acute coronary syndrome, or later on as secondary prevention of CV events, as suggested by the applicant.

Primary pharmacology

- Effect on IL-1β

Canakinumab binds to human IL-1β and blocks the interaction of this cytokine with its receptors, thereby functionally neutralizing its bioactivity. The inactivation of IL-1β in the CVRR population aims at the reduction of downstream inflammatory mediators such as IL-6 and CRP, thus inhibiting inflammatory signals that are known to contribute to the development of atherosclerosis.

The resulting complex of canakinumab and IL-1β is supposed to be eliminated at a much slower rate than the free IL-1β, resulting in elevation of total IL-1β (free plus complex) following canakinumab administration. Thus, measurement of free plus complexed IL-1β, i.e. total IL-1β, is a relevant biomarker for canakinumab indicative of binding of IL-1β by the antibody.

An increase in total IL-1β was observed in all studies, in both healthy subjects as well as patient populations, after canakinumab dosing. The duration of increase in total IL-1β increased with canakinumab dose which is assumed to indicate binding of IL-1β by canakinumab. IL-1β concentrations at baseline were either not detectable or near zero and no meaningful difference was observed between healthy volunteers and differing patient populations analysed.

- Mechanistic and vascular studies addressing vascular PD parameters

The following Pharmacodynamic studies related to the proposed indication were submitted. The mechanistic and vascular studies investigating PD endpoints relevant for cardiovascular diseases and functional capacity of patients in a related state of disease are discussed in this section, the studies used in dose selection for the pivotal trials (CANTOS) are discussed below. In addition, in the CANTOS trial a PK/PD modelling study was included.

Table 2-1 Overview of individual clinical studies supporting the MACE reduction indication

Study	Phase	Design and Objectives	Dose Regimen	Age in years (Range)	Enrolled number of subjects	Subjects received canakinumab
PK/PD studies in healthy subjects						
A2104#	I	R, OL, parallel group, bioequivalence, S&T and PD in healthy subjects	Single dose: 150 mg sc, comparing PFS with marketed lyophilized powder for solution	18 – 45	130	130
M2101	I	R, OL, parallel group, relative bioavailability, S&T in healthy subjects	Single dose: 150 mg via AI or SS administered by HCP	19– 62	80	80
Studies used in CANTOS dose selection						
A2213	II	R, DB, PC, dose escalation, S&T, and PK/PD in T2DM	Single dose iv; 0.3 mg/kg; 10 mg/kg; 0.1-, 0.3-,1.5- mg/kg; 0.03 mg/kg	52 – 57	231	147
I2202	II	DB, PC, efficacy, S&T, dose finding in T2DM	5/15/50/150 mg sc monthly	28 – 74	556	375
H2251#	II	DB, efficacy, S&T, in gouty arthritis patients	25-,50-,100-, 200-,300-mg sc D1, 50 mg sc	20 – 79	432	324
A2201#	II	R, DB, PC, efficacy, S&T, in patients with active rheumatoid arthritis	600 mg, 300 mg, 150 mg sc	23 – 87	274	204
Mechanistic and other vascular studies						
I2207	II	R, DB, PC, efficacy, S&T, in patients with T2DM or impaired glucose tolerance	150 mg sc single dose	27-74	246	154
X2201	II	R, DB, PC, efficacy, S&T, in patients with abdominal aortic aneurysms	150 mg sc monthly	53-86	65	31
M2201	II	R, DB, PC, efficacy, S&T, in patients with peripheral arterial disease	150 mg sc monthly	47 – 79	38	18
I2206	II	R, DB, PC, efficacy, S&T, in patients with atherosclerosis and T2DM or impaired glucose tolerance	150 mg sc monthly	40 – 74	189	95

Study number: ACZ885I2206

Title of study: A multi center, randomized, double blind, placebo-controlled, study of the safety, tolerability, and the effects on arterial structure and function of ACZ885 in patients with clinically evident atherosclerosis and either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT)

It was a double-blind, randomized, placebo-controlled study in individuals who have clinically evident atherosclerotic vascular disease with T2DM (diagnosed ≤ 14 years ago) or IGT.

Eligible subjects were randomized in a 1:1 ratio to receive a monthly subcutaneous injection of 150 mg ACZ885 or placebo for twelve months (Figure 9-2). Following the first dose, subsequent doses were administered on each calendar month (i.e. the 14th of every month) with no subsequent changes when a date was shifted (i.e. due to a holiday or was a Sunday). The study consisted of a 28-day screening period, a 7-day baseline period, a 12 month treatment period, and a three month follow-up period following the last dose.

The results can be summarized as follows:

- There were no relevant changes in aortic distensibility assessed from images of all three segments of aorta at Months 3 and 12 compared to the baseline and the differences between ACZ885 and placebo treatment groups were not statistically significant.
- There was a significant attenuation in progression of atherosclerotic burden in the proximal ascending aorta at Months 3 and Month 12.

- There was a significant attenuation in progression of atherosclerotic burden in the proximal right carotid at Month 3 and the left carotid at Month 12 and a marginally significant attenuation in progression of atherosclerotic burden in the right carotid at Month 12.
- No change was observed in vascular stiffness as measured by aortic distensibility.
- More MACE events in more patients were observed in the Canakinumab group.

Imaging parameters for plaque burden can be used as an aspect for dose finding and as a contribution to proof of concept. They are not validated as a surrogate for clinical outcome.

The selected dose of 150 mg monthly is higher than the doses investigated in the pivotal trial. Whether the promising PD results on plaque burden can be transferred to the lower doses, is unclear.

No conclusions can be drawn based on the number of MACE events in this small sized study.

CACZ885X2201

A randomized, double-blind, placebo controlled multiple dose study of subcutaneous ACZ885 for the treatment of abdominal aortic aneurysm Purpose: To assess acute and chronic effects of canakinumab on abdominal aortic aneurysm (AAA)

This was a non-confirmatory, double-blind, randomized, placebo-controlled, two-arm parallel group study in patients diagnosed with abdominal aortic aneurysm (AAA). Eligible patients were randomized in a 1:1 ratio to receive a monthly subcutaneous injection of 150 mg ACZ885 or placebo for twelve months. The study consisted of a 30-day Screening period, a 12-month treatment period, and an end of study evaluation approximately one month after the last study drug administration. In addition, if the patients were tested positive for immunogenicity to ACZ885, they were followed up for three months after the last study treatment.

There was neither a positive nor a negative effect of Canakinumab 150 mg sc monthly on size and growth rate of abdominal aortic aneurisms. Canakinumab 150 mg sc monthly administration led to sustained reduction of hsCRP, IL-6 levels, and serum Amyloid A across 12 months of treatment period.

CACZ885M2201

A multicenter, randomized, double-blind, placebo-controlled study of the safety, tolerability and effects on arterial structure and function of ACZ885 in patients with intermittent claudication

This was a randomized, double-blinded, placebo-controlled study in patients who had peripheral arterial disease (PAD) and intermittent claudication. Eligible patients were randomized in a 1:1 ratio to receive 12 monthly sc doses of 150 mg of ACZ885 or placebo. Following the first dose, subsequent doses were given each calendar month.

- No significant changes in superficial femoral artery plaque burden was observed in either the placebo or canakinumab treatment groups.
- There was a statistically significant improvement in maximal walk distance and in pain free walking distance which was in the range of being clinically relevant. Also pain free walking distance was improved over a duration of 12 months. Since this was an exploratory study only, the observation requires confirmation in a controlled clinical trial. However, it can be considered as supportive with respect to possible beneficial effects in patients with CV disease.

According to the applicant the difference between an improvement in the functional capacity and the lack of an improvement in superficial artery plaque burden may be due to the fact that the rate of plaque deposition in the large proximal artery is too slow to be measured within 12 months of time and that possible changes in smaller vasculature/microvasculature were not assessed. This may well be but requires confirmation.

The results of the three studies can be summarized as follows:

In the patient population investigated in the three studies there was a consistent decrease in hsCRP and IL-6 levels, and inconsistent results with respect to a decrease of SAA.

- In patients with AAA there was neither a positive nor a negative effect of Canakinumab 150 mg sc monthly on size and growth rate of abdominal aortic aneurisms (CACZ885X2201)
- In patients with PAD no significant changes in superficial femoral artery plaque burden was observed in either the placebo or canakinumab treatment groups. (CACZ885M2201)
- In these patients there was a statistically significant improvement in maximal walk distance and in pain free walking distance which was in the range of being clinically relevant. Also pain free walking distance was improved over 12 months. (CACZ885M2201)
- In patients with atherosclerosis there was a significant attenuation in progression of atherosclerotic burden in the proximal ascending aorta at Months 3 and Month 12 and in the proximal right carotid at Month 3 and the left carotid at Month 12 and a marginally significant attenuation in progression of atherosclerotic burden in the right carotid at Month 12 (ACZ885I2206).
- No relevant changes in aortic vascular stiffness as assessed by distensibility assessed from images of three segments of aorta at Months 3 and 12 was observed in this population. (ACZ885I2206).

Secondary pharmacology

During the clinical pharmacology program, IL-6 and hsCRP as soluble serum biomarkers downstream of IL-1β were analysed. As assumed, the dose-dependent inhibition of IL-1β activity by canakinumab led to a corresponding dose-dependent reduction in downstream IL-6. Similar to IL-6, hsCRP was reduced in a dose-dependent and sustained manner after canakinumab treatment. hsCRP reductions were in the range of 30 – 60%. To further support the assumption of canakinumab reducing IL-1β downstream signalling, fibrinogen levels were determined in studies I2202 and M2301. In both studies, a significantly higher reduction of fibrinogen after treatment with canakinumab as compared to placebo was detected.

Immunogenicity

ADA development, as known from previous submission for Ilaris® appears negligible in canakinumab-treated subjects. As described in the integrated immunogenicity report, the incidence of ADAs was low in the overall patient population (<3%). Similarly, in the CVRR patient population, the incidence of treatment-emergent ADAs was determined to be only 0.4%. In addition, the incidence of treatment-emergent ADAs in CANTOS was comparable between the different canakinumab dose groups (50 mg, 150 mg and 300 mg quarterly) and placebo.

Exposure-response relationship

An exposure-response relationship was demonstrated for both efficacy measures (MACE and all-cause mortality).

The estimated hazard ratio for CEC confirmed MACE was determined to be reduced with increasing canakinumab trough concentrations: An increase of canakinumab trough concentrations by 1 µg/mL was predicted to decrease the log-hazard by 0.079. A large part of the change (57%) in the hazard upon treatment was explained by the time-dependent covariate “on treatment hsCRP”. In addition to hsCRP, IL-6 and fibrinogen are important downstream targets of IL-1β signaling in atherosclerosis. All of them demonstrate a dose-dependent response following treatment with canakinumab in the CANTOS trial and may therefore be involved in the canakinumab treatment effect.

Similar to CEC confirmed MACE, CEC confirmed all-cause mortality was improved with increasing canakinumab concentrations. For the efficacy measure all-cause mortality, the addition of on-treatment hsCRP as a time dependent covariate in addition to canakinumab concentration explained about 70% of the concentration-dependent treatment effect.

Exposure-response analysis of hsCRP revealed high canakinumab exposure was associated with decrease of hsCRP. Half-maximal hsCRP reduction as compared to baseline was achieved at canakinumab trough concentration of approx. 0.5µg/ml and then started to plateau at a canakinumab trough concentration of 1-2 µg/mL, which is consistent with the median exposure achieved in the 150 mg dose group. Nevertheless, the time-to-event analysis suggested a further hazard reduction (MACE and mortality) for the 2 -3 µg/mL bin in which the predicted median Ctrough of the 300 mg canakinumab dose is enclosed.

Predicted Ctrough concentrations of heavier patients (125 kg) to at least 50% fall into the 0.5 – 1 µg/mL bin (lower bound of Cmin is even lower: 0.15 µg/ml) and appear to be at higher risk of experiencing an event due to lower canakinumab exposure. Conclusively, based on the exposure-response model, a concern was raised that subjects in the higher body weight class may be underdosed. Referring to the time-to-event analysis for the first CEC confirmed MACE by baseline body weight quartile provided by the applicant in response; it appears that lower canakinumab exposure in heavier subjects does not systematically translate into an increase in MACE. The use of a fixed dose of 150 mg canakinumab for all body weight groups may therefore be considered acceptable.

No evidence of an exposure-safety relationship for both adjudicated confirmed malignancy AEs and confirmed serious infections was identified.

Analyses investigating the effect of canakinumab concentration on the incidence of neutropenia and thrombocytopenia revealed a numerical trend towards increased incidence of neutropenia and thrombocytopenia with increased canakinumab trough concentration. However, interpretation of the results is limited, given the very low incidence of those events.

Finally, as predicted trough concentrations were used as exposure measure, the exposure-response hsCRP analysis was updated with the predictions from the newly developed CANTOS pooled population PK analysis. The conclusions from this analysis were identical to the initial exposure-response hsCRP analysis.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

The submission includes two formulations: 1) 150 mg/1ml solution for injection in prefilled syringe and 2) 150 mg/1mL solution for injection in prefilled pen (autoinjector). Pharmacokinetic parameters of canakinumab are comparable for the two formulations.

The characterization of the PK properties of canakinumab refers to a large data package in healthy subjects and various patient populations. An extended knowledge of canakinumab PK already exists, which derives from former Ilaris® applications. Regardless of this, the applicant developed a population PK model which solely included highly sparse PK data from the pivotal CANTOS study. The model was built upon the previous SJIA population PK model which had to be in part adjusted owing the sparse PK data included. Various model deficiencies were identified, so that the applicant was requested to set up a new population PK model by inclusion of the whole PK data of canakinumab that has been gathered in the adult population so far. In response, the applicant developed an overall population PK analysis with the ACZ885 pooled dataset in the adult population. Although the population PK modelling report (CANTOS pooled analysis) was not provided, it might be agreed that the CANTOS pooled model showed adequate prediction ability. The estimates for clearance, rate of absorption and bioavailability in the newly developed CANTOS pooled analysis were similar to those of the originally submitted CANTOS population PK model. Both the original and the newly developed CANTOS population PK analyses yield very similar estimates of PK parameters and exhibit similar predictive ability.

The CVRR population PK model revealed that canakinumab displayed PK properties typical of monoclonal antibodies and PK in CANTOS patients was found comparable to healthy subjects and other patient populations. Canakinumab PK was dose-proportional with no time-dependent changes in the dose ranges studied.

Considering the elimination mechanisms of immunoglobulins, PK of canakinumab is not expected to be significantly affected by impaired renal or hepatic function or in elderly patients. Dose recommendations in section 4.2 of the SmPC in these special populations are generally appropriate. Still, section 5.2 of the SmPC is partly requested to be amended (**LoOI**).

The analysis of covariates only identified body weight as having a statistically significant and clinically relevant effect on canakinumab clearance. Respectively, canakinumab exposure was shown to be reduced with increased body weight. Age, albumin, gender and race were not considered leading to clinically relevant changes in canakinumab PK.

Formal drug-drug interaction studies were not performed. Inflammatory cytokines, such as IL-6 and IL-1β, can down-regulate the expression and decrease the activity of hepatic cytochrome P450 (CYP) enzymes. Biological medicinal products that inhibit inflammatory cytokine signalling significantly increase the activity of CYP enzymes e.g. in patients with rheumatoid arthritis. However, scientific literature was provided which supports the conclusion that IL-1β and IL-6 levels observed in the CANTOS population were much below the EC50 values of CYP inhibition, so that it is unlikely that CYP3A and other enzymes involved in drug metabolism are significantly suppressed by these cytokines.

The analytical methods used for the detection of canakinumab and (neutralizing) ADA in human serum have been appropriately validated and are considered adequate. Some reports were missing in the initial submission but were provided in response. All validations are considered to have been performed accurately.

Pharmacodynamics

- Primary and secondary pharmacology

Following canakinumab administration, a dose-dependent elevation of total IL-1β (free plus complex) is detected. The measurement of total IL-1β is a relevant biomarker for canakinumab indicating the binding of the antibody to IL-1β. In all primary PD studies described in this submission, an increase in total IL-1β was observed. As secondary PD parameters, IL-6, hsCRP and in part fibrinogen as soluble serum biomarkers downstream of IL-1β were analysed. As anticipated, the dose-dependent inhibition of IL-1β activity by canakinumab led to a corresponding dose-dependent reduction in respective downstream biomarkers.

- Mechanistic and vascular studies addressing vascular PD parameters

Overall, the concept of investigating Canakinumab in patients with atherosclerotic disease is reasonable. In patients with atherosclerotic diseases Canakinumab decreased hsCRP and IL-6 levels. Results on atherosclerotic burden were not consistent for different vascular areas and not conclusive and the doses selected were higher than the doses used in the pivotal CANTOS trial which raises questions about transferability. Whether there is a lack of an effect on atherosclerotic plaques or whether treatment duration was too short, numbers of patients were too low or specific patients groups like patients with aortic aneurism were not representative for a broader population with atherosclerotic disease, cannot be answered based on the PD studies.

There were preliminary indications of a possible positive effect on maximal walking distance and pain-free walking distance in patients with PAD. In case this finding can be established in additional studies this may contribute to the overall concept of inhibiting the effects o IL-1ß in patients with atherosclerotic disease.

There were preliminary indications for a beneficial PD.

- Exposure-response analysis

An exposure-response relationship was demonstrated for both efficacy measures (MACE and all-cause mortality). For CEC confirmed MACE, 57% of the change in the hazard upon canakinumab treatment was explained by on treatment hsCRP. However, other downstream targets of IL-1β (IL-6, fibrinogen) might similarly be involved in the canakinumab effect in the CVRR population.

The exposure-response analysis of hsCRP revealed that high canakinumab exposure was associated with a decrease of hsCRP. Half-maximal hsCRP reduction was achieved at canakinumab trough concentration of approx. 0.5 µg/mL and then started to plateau at a canakinumab trough concentration of 1-2 µg/mL, which is consistent with the median exposure achieved in the 150 mg dose group. Considering this observation, the choice of the 150 mg quarterly dosing regimen may appear reasonable. However, the time-to-event analysis suggested a further hazard reduction (MACE and mortality) for the 2 -3 µg/mL bin in which the predicted median Ctrough of the 300 mg canakinumab dose is enclosed.

Overall, there was a concern that subjects in the higher body weight class may be underdosed due to lower canakinumab exposure. The applicant responded that lower exposure in heavier subjects did not translate into a loss of efficacy with regard to the time to the first CEC confirmed MACE.

No evidence of an exposure-safety relationship for both adjudicated confirmed malignancy AEs and confirmed serious infections was identified. For neutropenia and thrombocytopenia, a numerical trend towards increased event proportion with increased canakinumab doses was observed, but no valid conclusions could be drawn due to the overall low number of incidences.

Immunogenicity

The incidence of ADAs after treatment with canakinumab was low: <3% ADAs in the overall patient population and 0.4% ADAs in CANTOS patients were detected. In CANTOS, the number of ADAs was comparable between all canakinumab doses investigated and placebo.

3.3.4. Conclusions on clinical pharmacology

Pharmacokinetics of the CANTOS patient population were described by two separate population PK models (SJIA pooled analysis [ACZ885 Japanese SJIA PPK Modeling Report] and CANTOS pooled analysis, provided by the applicant after the d120 LoQ). Both the original and the newly developed CANTOS population PK analyses yield very similar estimates of PK parameters and are considered to exhibit similar predictive ability. In conclusion, it may be considered that canakinumab PK in the CANTOS population has been accurately described.

As anticipated, canakinumab was proven to inhibit IL-1β activity, thereby reducing downstream inflammation mediators such as IL-6 and hsCRP in a dose-dependent manner. Exposure-efficacy analysis revealed a clear concentration-efficacy relationship, which was largely explained by the exposure-dependent reduction of on treatment hsCRP after canakinumab treatment. No relationship of canakinumab exposure to the incidence of adverse events was identified.

Overall the results in the vascular PD studies are sufficient to support the concept to investigate efficacy and safety of Canakinumab in patients at high risk for cardiovascular morbidity and mortality as the patients post myocardial infarction that were included in the pivotal trial.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

The dose in CANTOS was selected based on the following considerations:

In a dose finding study (CACZ885I2202) of patients with T2DM treated with 5, 15, 50 and 150 mg monthly doses, the largest observed reduction in hsCRP was observed at a dose of 50 mg monthly (-59.9% from baseline, placebo-subtracted), with no additional hsCRP reduction at 150 mg monthly (-54.0%). Pharmacokinetic/pharmacodynamic (PK/PD) modeling of this data predicted a dose-response profile of change from baseline in hsCRP that indicated a maximum hsCRP reduction at a dose between 75 and 100 mg canakinumab monthly, with persistent lowering across a wide range of higher doses. Therefore, based on modeling data, 50 mg monthly (or 150 mg quarterly) was considered as a potentially efficacious dose, 15 mg monthly (or 50 mg quarterly) as submaximal hsCRP-lowering dose, and 100 mg monthly (or 300mg quarterly) as the dose predicted to achieve maximal hsCRP reduction.

Dose selection finally was based on the results of the pivotal trial CANTOS. In the pivotal study cankinumab was administered quarterly at a dose of 50 mg, 150 mg and 300 mg respectively (with an additional loading dose after 2 weeks in the 300 mg arm) in each active treatment arm. A dose of 150 mg quarterly is proposed.

Main study

In support of the cardiovascular prevention indication the applicant has submitted the study report of one pivotal trial (study ACZ885M2301) that has included a total of10,061 patients. An extension phase of the study in 4,609 patients is ongoing. A report or results of the extension phase are not available, the anticipated report date is in Q2 2020.

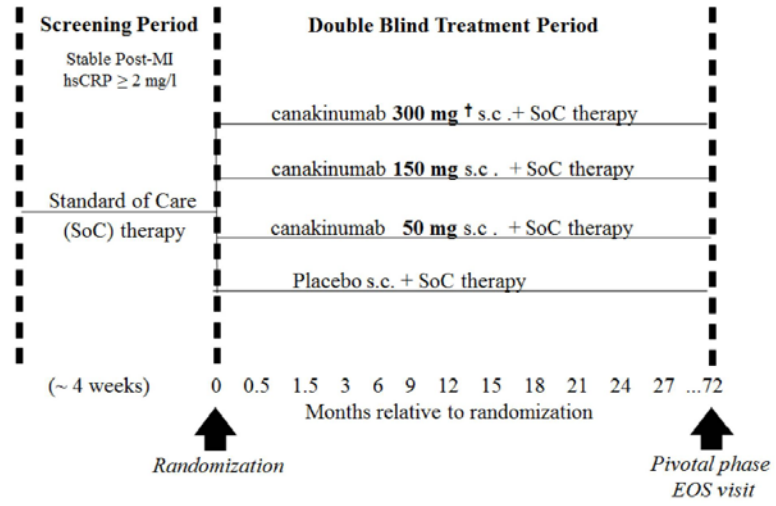
Pivotal study

ACZ885M2301 (CANTOS)

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

This was a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double blind event-driven global clinical study. It was designed to evaluate the effect of quarterly subcutaneous doses of 50 mg, 150 mg and 300 mg (300 mg included an induction dose) canakinumab compared to placebo in patients with a prior MI with an elevated inflammatory burden (hsCRP ≥ 2 mg/L) receiving standard of care therapy. Patients were randomized at least 30 days following their index-MI. The study design is depicted in Figure 9-1.

Figure 9-1 Study design



†- canakinumab 300 mg s.c. induction at randomization (month 0) and week 2 (month 0.5), and then 300 mg s.c. quarterly beginning at week 12.

Participants eligible for this study included male and non-child-bearing potential female patients age 18 years and older who (a) had a documented acute MI at least 30 days prior to randomization and (b) hsCRP ≥2 mg/L despite the use of standard of care post-MI medical therapies.

Treatments

Canakinumab (ACZ885) and matching placebo solution for injection were provided by Novartis as ready-to-use pre-filled syringes. Two strengths and respective corresponding matching placebos were supplied and administered s.c. at the time points indicated above:

- Canakinumab 50 mg in 0.5 mL solution for injection and one placebo formulation matching to this active drug formulation.

- Canakinumab 150 mg in 1 mL solution for injection and one placebo formulation matching to this active drug formulation.

The 50 mg dose was included later in the study protocol y amendment 6.

Primary endpoint

The primary endpoint was defined as the time to first CV clinical events adjudication committee (CEC) confirmed MACE occurring during the double-blind phase of the study, which was a composite of CV death, non-fatal MI, and non-fatal stroke.

An unknown death was presumed as a CV death.

Key secondary efficacy endpoints

- Time to the first occurrence of a CEC confirmed composite CV endpoint consisting of primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization

- Time to CEC confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (time to new onset type 2 diabetes) based on the following definition:

Definition of Pre-Diabetes at randomization:

- At visit 1 OR 2 HbA1c of 5.7-6.4% or fasting plasma glucose (FPG) 100-125 mg/dL (5.6- 6.9 mmol/L)

Other secondary efficacy assessments

- Time to first event of non-fatal MI, non-fatal stroke and all-cause mortality

- Time to all-cause mortality

Exploratory efficacy assessments

e.g. Different CV parameters, Biomarkers, Clrycemic control, PROs,

Safety objective

- To evaluate the long-term safety of canakinumab therapy in a placebo (standard of care) - controlled setting.

A total of 1,400 patients across all the three canakinumab treatment arms with an observed MACE provided ≥ 90% power for demonstrating the superiority of at least one dose of canakinumab over placebo using the closed testing procedure at the one-sided 2.45% level available for the final analysis if all doses had a true 20% net relative hazard reduction compared to placebo for MACEs after discounting for discontinuations of treatment. Additionally, in this case, both the 150 mg and 50 mg doses had ≥ 80% power to become significant.

Across trial part 1 (prior to the implementation of protocol Amendment 6), patients were randomized in a 1:1:1 ratio to canakinumab 300 mg, 150 mg, and placebo, respectively.

Across trial part 2 (following implementation of protocol Amendment 6 at each site), the approximate allocation was 1.3:1.3:1.4:2 to canakinumab 300 mg, 150 mg, 50 mg and placebo, respectively (Figure 9-2).

The overall study randomization ratio (taking into consideration Parts 1 and Part 2) was approximately 1:1:1:1.5 canakinumab 300 mg, 150 mg, 50 mg and placebo, respectively.

Statistical methods

Analysis of the primary variable(s)

The primary efficacy analysis and all analyses of secondary/exploratory efficacy variables used the FAS unless stated otherwise.

The time-to-event was computed as the number of days from randomization to the onset of the primary endpoint event. Data on patients who did not reach the primary endpoint by the study end date were censored at the latest date they were known to be at risk or their EOS visit or the study analysis cut off, whichever came first.

Unless otherwise specified, all time-to-event analyses were based on events occurring during the double-blind phase. The familywise type I error rate for this study was controlled at the one-sided 2.5% level. The primary efficacy variable was the time to first occurrence of CEC confirmed MACE, which was a composite endpoint consisting of CEC confirmed CV death, CEC confirmed MI, and CEC confirmed stroke.

The primary statistical null hypotheses were:

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis was tested against the one-sided alternative that the hazard rate was smaller for the respective active dose group than for the placebo group. . These hypotheses were tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (< 6 months and ≥ 6 months) and trial part on the FAS according to the intent-to-treat principle. Pre-specified analyses took into account the changes in randomization between trial part 1 and trial part 2 (e.g. by stratifying analyses by trial part) and that patients in trial part 2 were not recruited concurrently with those in trial part 1. The family-wise error rate was controlled at the two interim analyses and the final analysis using the closed testing procedure based on the graphical method of Bretz et al (Bretz et al 2009); however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses, these primary null hypotheses were tested using a weighted version of Dunnett's test (Dunnett 1955).

Two efficacy interim analyses, at which the trial could have been stopped for demonstrated efficacy, or one or more active arms could have been stopped for futility, were performed respectively after 50% and 75% of the target number of 1,400 patients had experienced a primary endpoint.

The study protocol was amended nine times. A key Amendment was Amendment 6 which introduced a lower 50 mg dose arm.

Results

A total of 17482 patients were screened, and 10102 (57.8%) patients completed the screening phase. A total of 10105 patients were randomized, and a total of 10061 patients were included in the FAS.

Patient characteristics were well balanced between the groups. Patients had a median age of 61 years, a median BMI of 29.8, and a median hsCRP level of 4.2 mg/L. The majority of patients were male (74.3%) and Caucasian (79.9%); most of the remaining patients were either Asian (11.6%) or Black (3.2%). A total of 49.3% of patients were prediabetic and 40.0% had type 2 diabetes. Patients had a mean DBP of 77.9 mmHg, a mean LDL-C of 2.3 mmol/L (88.9 mg/dL), and a mean eGFR of 79.4 mL/min/SA. The percentage of patients with LDL-C < 2.6 mmol/L (< 100.5 mg/dL) was 68.4% and the percentage of patients with eGFR ≥ 90 mL/min/SA was 29.5%.

Median time from MI to randomization was more than 2.5 years in all treatment groups; and the mean time in the 150 mg canakinumab group was 4.6 years. Median (range) time since index MI should be given in SPC section 5.1. Efficacy of canakinumab on prevention of MACE does not seem to depend on the time lapse since index MI.

A total of 93.9% of the patients were treated with platelet aggregation inhibitors (excluding heparin), 90.1% with HMG-CoA reductase inhibitors, 66.5% with beta-blocking agents, 54.0% with ACE inhibitors, 23.1% with angiotensin II antagonists, 11.1% with "other" lipid modifying agents, and 4.7% with fibrates.

There was a high incidence of comorbidities. Within the SOC of cardiac disorders, in addition to myocardial infarction, 21.6% of patients in the FAS had chronic cardiac failure, 20.6% had coronary artery disease, and 12.3% of patients had angina pectoris reported in their medical history. Comorbidity PTs reported in ≥ 10% of patients included hypertension (79.6%), dyslipidaemia (77.5%), glucose tolerance impaired (48.7%), type 2 diabetes mellitus (39.9%), osteoarthritis (13.6%), obesity (13.4%), and gastroesophageal reflux disease (11.1%).

Table 11-1 summarizes the analysis populations for this study.

Table 11-1 Analysis populations - n (%) of patients (Screened set)

Analysis Population	Screen failures n (%)	Can. 300 mg n (%)	Can. 150 mg n (%)	Can. 50 mg n (%)	Placebo n (%)	Total n (%)
Screened set	7386 (42.2)					17482
Randomized set		2271 (100)	2291 (100)	2180 (100)	3363 (100)	10105 (100)
Full analysis set (FAS)		2263 (99.6)	2284 (99.7)	2170 (99.5)	3344 (99.4)	10061 (99.6)
Per protocol set (PPS)		2134 (94.0)	2163 (94.4)	2030 (93.1)	3165 (94.1)	9492 (93.9)
Safety set (SAF)		2263 (99.6)	2285 (99.7)	2170 (99.5)	3348 (99.6)	10066 (99.6)

Percentages are computed using the number of patients in the Randomized set on each treatment as the denominator.
For screen failures the denominator is the total number screened. Screen failures are those who were screened, but failed to meet the inclusion or met the exclusion criteria.
Screened set includes those who signed informed consent. Randomized set includes those who received a randomization number, regardless of receiving study drug. Full analysis set includes all randomized patients (excluding those who failed to qualify for randomization and were inadvertently randomized). Per protocol set includes patients in the FAS who take at least one dose of study drug and have no major protocol deviations affecting the primary analyses. Safety set includes those who received at least one dose of study drug. Two patients included the SAF received double-blind study drug but were not randomized.
Can.: Canakinumab (all doses are measured in mg).
Source: Table 14.1-1.4a.

Primary efficacy results

The results for the primary efficacy endpoint and for the components of the primary composite endpoint in the FAS are summarized in table 11-8 and Figure 11-1 for the different strengths.

Canakinumab 150 mg was superior to placebo in reducing the risk of CEC confirmed MACE (a composite of CEC confirmed CV death, non-fatal MI, or non-fatal stroke). The adjusted p-value was statistically significant for the 150 mg strength but not for the other strengths. The primary outcome occurred in 322 (3.90/100 patient years), 320 (3.86/100 patient years) and 313 (4.11/100 patient years) patients in the 300, 150, and 50 mg groups, respectively, compared with 535 (4.50/100 patient years) patients in placebo. The HRs describing the relative risk of MACE for each canakinumab dose group (300, 150, and 50 mg) vs. placebo were 0.86 (95% CI, 0.75 to 0.99), 0.85 (0.74 to 0.98), and 0.93 (0.80 to 1.07), respectively.

Canakinumab 150 mg was superior to placebo in reducing the risk of CEC confirmed MACE (a composite of CEC confirmed CV death, non-fatal MI, or non-fatal stroke). The adjusted p-value was statistically significant for the 150 mg strength but not for the other strengths. The primary outcome occurred in 322 (3.90/100 patient years), 320 (3.86/100 patient years) and 313 (4.11/100 patient years) patients in the 300, 150, and 50 mg groups, respectively, compared with 535 (4.50/100 patient years) patients in placebo. The HRs describing the relative risk of MACE for each canakinumab dose group (300, 150, and 50 mg) vs. placebo were 0.86 (95% CI, 0.75 to 0.99), 0.85 (0.74 to 0.98), and 0.93 (0.80 to 1.07), respectively.

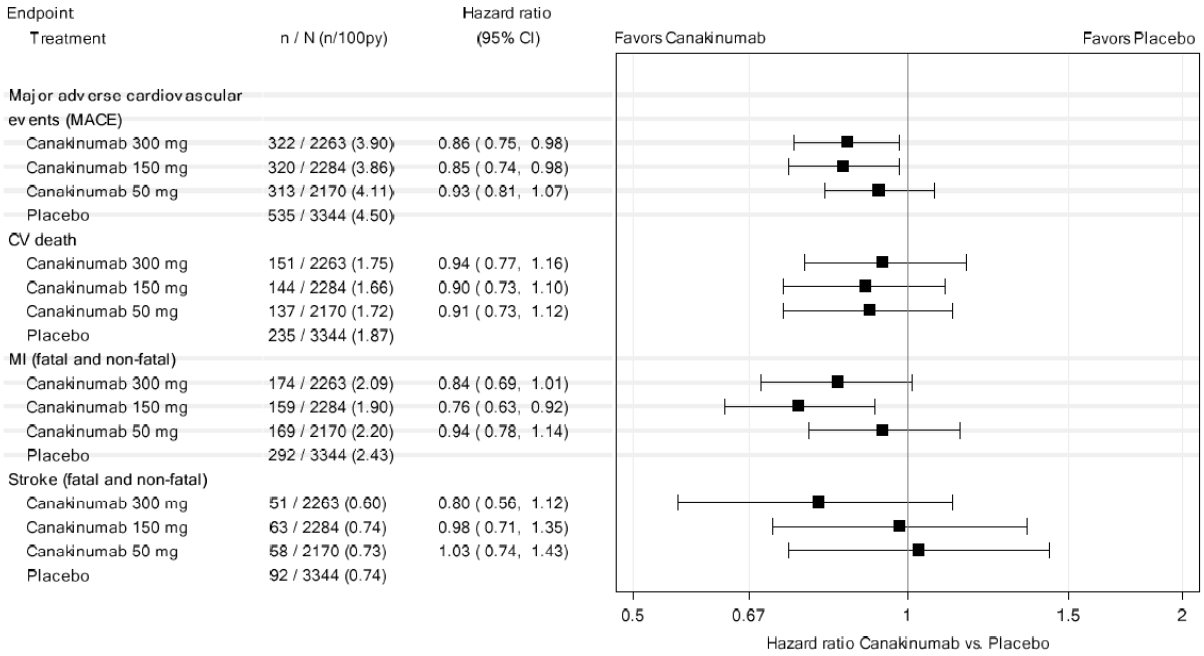
Table 11-8 Primary efficacy analysis of first CEC confirmed major adverse cardiovascular events (MACE) and its components (FAS)

Response variable	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)	Un-adjusted P-value	Adjusted P-value[1]
Major adverse cardiovascular events (MACE)	Can. 300 mg	2263	322 (3.90)	0.86 (0.75, 0.99)	0.0157	0.0648
	Can. 150 mg	2284	320 (3.86)	0.85 (0.74, 0.98)	0.0104	0.0241*
	Can. 50 mg	2170	313 (4.11)	0.93 (0.80, 1.07)	0.1473	0.1895
	Combined Can.	6717	955 (3.95)	0.88 (0.79, 0.97)	0.015	
	Placebo	3344	535 (4.50)			
CV death	Can. 300 mg	2263	151 (1.75)	0.94 (0.77, 1.16)	0.572	
	Can. 150 mg	2284	144 (1.66)	0.90 (0.73, 1.10)	0.296	
	Can. 50 mg	2170	137 (1.72)	0.91 (0.73, 1.12)	0.369	

Response variable	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)	Un-adjusted P-value	Adjusted P-value[1]
	Combined Can.	6717	432 (1.71)	0.92 (0.78, 1.07)	0.274	
	Placebo	3344	235 (1.87)			
MI (fatal and non-fatal)	Can. 300 mg	2263	174 (2.09)	0.84 (0.69, 1.01)	0.067	
	Can. 150 mg	2284	159 (1.90)	0.76 (0.63, 0.92)	0.006	
	Can. 50 mg	2170	169 (2.20)	0.94 (0.78, 1.14)	0.542	
	Combined Can.	6717	502 (2.06)	0.84 (0.73, 0.97)	0.020	
	Placebo	3344	292 (2.43)			
MI (non-fatal)	Can. 300 mg	2263	171 (2.06)	0.83 (0.68, 1.00)		
	Can. 150 mg	2284	158 (1.88)	0.76 (0.62, 0.92)		
	Can. 50 mg	2170	168 (2.19)	0.94 (0.78, 1.14)		
	Combined Can.	6717	497 (2.04)	0.84 (0.72, 0.97)		
	Placebo	3344	291 (2.43)			
Stroke (fatal and non-fatal)	Can. 300 mg	2263	51 (0.60)	0.80 (0.56, 1.12)	0.190	
	Can. 150 mg	2284	63 (0.74)	0.98 (0.71, 1.35)	0.912	
	Can. 50 mg	2170	58 (0.73)	1.03 (0.74, 1.43)	0.871	
	Combined Can.	6717	172 (0.69)	0.93 (0.72, 1.20)	0.581	
	Placebo	3344	92 (0.74)			
Stroke (non-fatal)	Can. 300 mg	2263	51 (0.60)	0.80 (0.57, 1.13)		
	Can. 150 mg	2284	63 (0.74)	0.99 (0.72, 1.37)		
	Can. 50 mg	2170	58 (0.73)	1.04 (0.75, 1.45)		
	Combined Can.	6717	172 (0.69)	0.94 (0.73, 1.21)		
	Placebo	3344	91 (0.73)			

N: Total number of patients on each treatment. n: Total number of patients with events included in the analysis. n/100py: Total number of patients with event per 100 patient years (randomization date to first event date or to censoring date used as denominator).The analysis is performed using Cox regression. The analysis model contains the treatment and is stratified by time since index MI and trial part. Can.: Canakinumab (all doses are measured in mg). A HR < 1 favors Canakinumab. P-values for the HR of the primary endpoint (excluding combined Canakinumab) are one sided and are based on a stratified log-rank test. P-values for the other HRs are two-sided and based on the Cox regression analysis. * Indicates p-value < 0.0245 (one-sided).
[1]Adjusted for multiplicity for both multiple treatment comparisons and interim analysis using weighted Dunnett's test.
MACE includes CV death, non-fatal MI and non-fatal stroke.
CEC = Clinical Endpoints Committee.
Patients were considered censored after the cut-off date.
Source: Table 14.2-1.1a, Table 14.2-1.1.c

Figure 11-1 **Forest plot of hazard ratios (canakinumab vs placebo) for the first CEC confirmed major adverse cardiovascular events (MACE) and its components by treatment (FAS)**



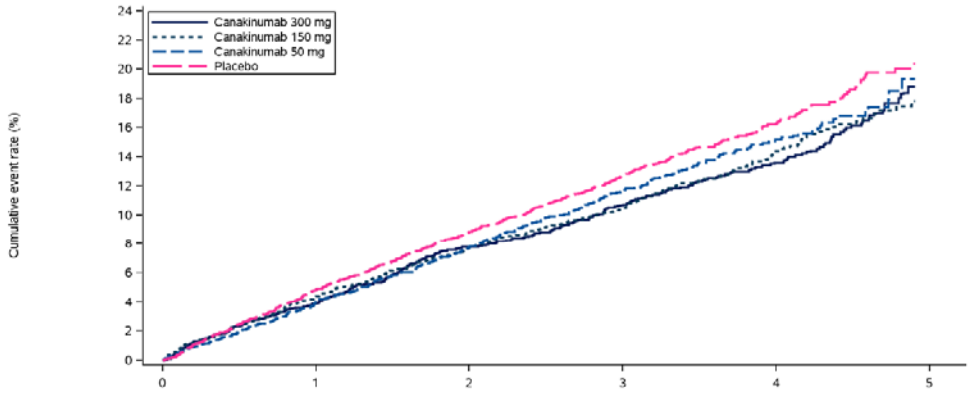
N: Total number of patients on each treatment. n: Total number of patients with events included in the analysis. n/100py: Total number of patients with event per 100 patient years (randomization date to first event date or to censoring date used as denominator).
MACE includes CV death, non-fatal MI and non-fatal stroke. CEC = Clinical Endpoints Committee.
Patients were considered censored after the cut-off date.
Source: Figure 14.2-1.1a

Results for the individual components

The first MACE event was non-fatal MI in 50.4% of patients and CV death in 34.0% of patients. The reduction in the risk of MACE with canakinumab 150 mg treatment was driven by a significant reduction in the risk of MI (fatal and non-fatal) (HR = 0.76 (95% CI, 0.63 to 0.92; unadjusted p-value = 0.006)) and a numerical reduction in the risk of CV death (HR = 0.90 (95% CI, 0.73 to 1.10)) relative to placebo (Table 11-8). There was no difference observed in the risk of stroke (fatal and non-fatal) between the 150 mg canakinumab treatment group and placebo. Taking some variability into account the results were numerically largely similar in the 300 mg group with a numerically lower HR for stroke and a HR close to 1 for CV death.

Figure 11-2 shows the cumulative event rate for the primary endpoint (median follow-up = 3.8 years).

Figure 11-2 Estimated cumulative event rate for the first CEC confirmed primary endpoint (cardiovascular death, non-fatal MI or non-fatal stroke) by treatment (FAS)



Canakinumab 300 mg	2263	2149	2038	1819	938
Canakinumab 150 mg	2284	2151	2057	1849	908
Canakinumab 50 mg	2170	2057	1950	1713	767
Placebo	3344	3141	2973	2632	1268

Source: Figure 14.2-1.6a

The results in part I and II were not consistent with no difference between the 150 mg strength and placebo in Part I and no difference between the 150 mg and the 300 mg arm in Part II. However, less than 10% of patients were included in part I. However, the interaction p-value comparing the results of the primary endpoint between Trial Part 1 and Trial Part 2 using a Cox regression model was non-significant for the primary outcome (p = 0.682) and for each of the components of CV death (p = 0.549), fatal or non-fatal MI (p = 0.483), or fatal or nonfatal stroke (p = 0.773).

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Subgroup analyses of the primary efficacy endpoint

Results for the 150 mg arm are summarized below (Figure 11-7, Table 11-9). Overall, the results for the primary endpoint were consistent irrespectively of the subgroup selected.

An interaction p-value <0.05 was noted for the

- Presence of an MI prior to index MI (no, yes, p 0.004 for MACE and p= 0.015 for stroke) and a p value between 0.05 and 0.1 for the MI (fatal and non-fatal) component

- Baseline DBP level (< 130 mmHg, ≥ 130 mmHg) for the composite MACE endpoint and the MI (fatal and non-fatal) component, and a p value between 0.05 and 0.1 for the CV death component

An interaction p value >0.05 < 0.10 was reported for

- Smoking status (never, current smoker, former smoker) for the component of CV death

- for baseline hsCRP level (≤ 4 mg/dL, > 4 mg/dL) for the component of MI (fatal and non-fatal)

- dyslipidemia (no, yes) for the composite MACE endpoint

- prior CABG (no, yes) for the composite MACE endpoint

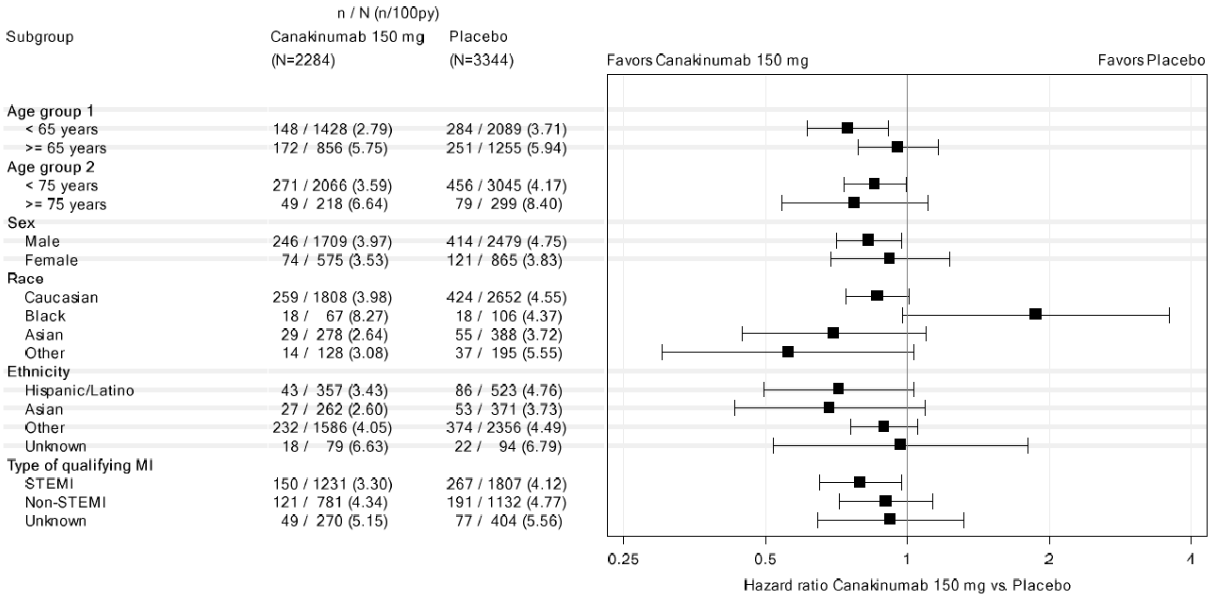
For the large group of patients on baseline statin therapy (irrespectively of dose, 88.4% of the patients included in this analysis) the HR for MACE (Canakinumab 150 mg vs. placebo: HR 0.91 (0.78; 1.05),Table 14.2-41) and for the components of the MACE endpoint was lower (Interaction P-value 0.1251).

Exp Table 14.2-4.1 (Page 1 of 4)
Time-to-event analysis for the first CEC confirmed major adverse cardiovascular event (MACE) and its components by baseline statin use
Full Analysis Set

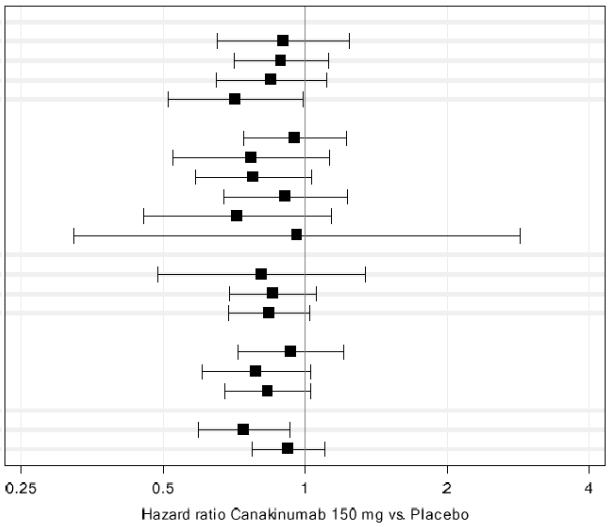
Response variabe: Major adverse cardiovascular events (MACE)

Subgroup	Subgroup level	Treatment	N	n(n/100py)	Hazard ratio vs. Placebo (95% CI)	Interaction P-value
Baseline statin use						0.1251
	Yes	Canakinumab 300 mg	1998	273 (3.75)	0.87(0.75, 1.02)	
		Canakinumab 150 mg	2011	284 (3.90)	0.91(0.78, 1.05)	
		Canakinumab 50 mg	1930	276 (4.06)	0.97(0.83, 1.13)	
		Combined Canakinum	5939	833 (3.90)	0.91(0.82, 1.03)	
		Placebo	2952	449 (4.26)		
	No	Canakinumab 300 mg	265	49 (4.97)	0.76(0.53, 1.07)	
		Canakinumab 150 mg	273	36 (3.60)	0.56(0.38, 0.82)	
		Canakinumab 50 mg	240	37 (4.57)	0.73(0.49, 1.07)	
		Combined Canakinum	778	122 (4.36)	0.68(0.51, 0.89)	
		Placebo	392	86 (6.42)		

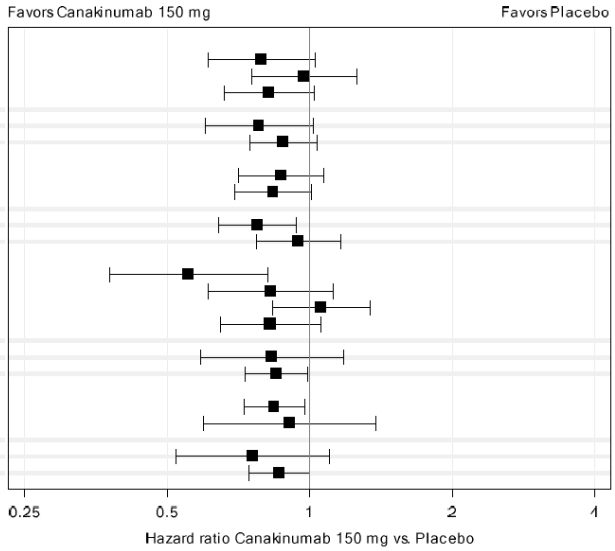
Figure 11-7 Forest plot of hazard ratios (canakinumab 150 mg vs. placebo) for CEC confirmed MACE in key subgroups (Full analysis set)

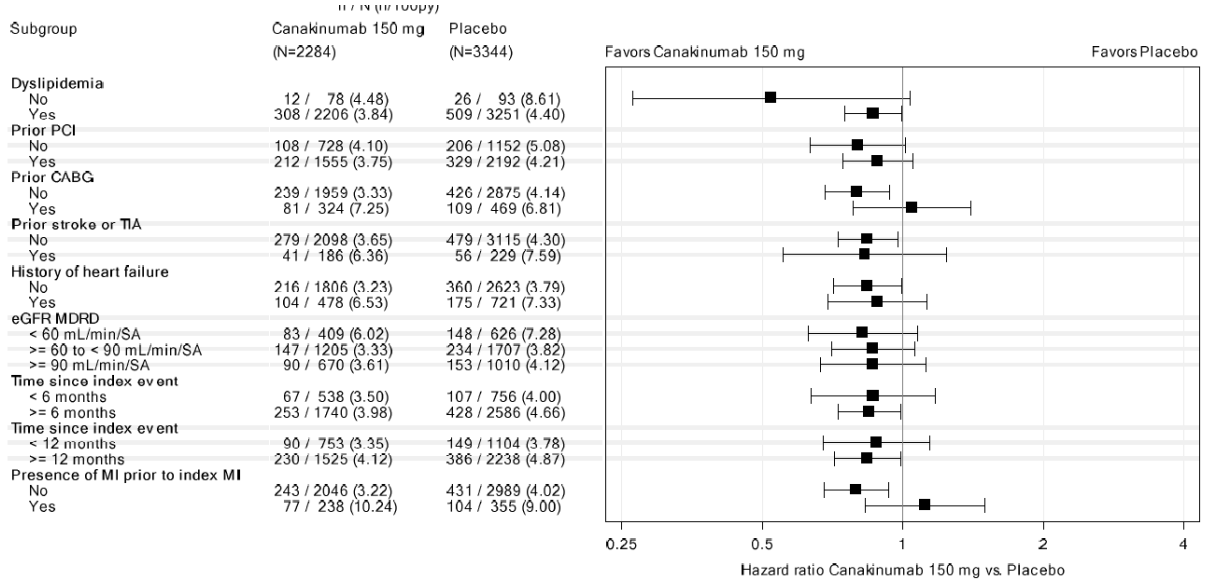


Subgroup	n / N (n/100py) Canakinumab 150 mg (N=2284)	Placebo (N=3344)
BMI		
< 25 kg/m²	61 / 356 (4.79)	95 / 522 (5.22)
>= 25 to < 30 kg/m²	117 / 814 (3.99)	194 / 1220 (4.47)
>= 30 to < 35 kg/m²	86 / 651 (3.65)	140 / 926 (4.27)
>= 35 kg/m²	54 / 459 (3.16)	106 / 673 (4.37)
Geographic region		
North America	106 / 587 (4.73)	145 / 796 (4.90)
Latin America	40 / 316 (3.65)	79 / 483 (4.75)
Western Europe	74 / 556 (3.74)	134 / 810 (4.81)
Central Europe	66 / 520 (3.69)	117 / 835 (4.08)
Asia	28 / 264 (2.69)	53 / 376 (3.69)
Others	6 / 41 (4.14)	7 / 44 (4.31)
Baseline glycemic status		
Normoglycemic	23 / 229 (2.78)	43 / 357 (3.43)
Prediabetic	136 / 1094 (3.38)	234 / 1645 (3.93)
Diabetic	161 / 961 (4.68)	258 / 1342 (5.53)
Baseline smoking status		
Never	97 / 689 (3.86)	141 / 960 (4.09)
Current smoker	85 / 534 (4.50)	150 / 765 (5.63)
Former smoker	138 / 1061 (3.55)	244 / 1619 (4.23)
Baseline hsCRP level		
<= 4 mg/L	116 / 1078 (2.93)	229 / 1635 (3.92)
> 4 mg/L	204 / 1205 (4.72)	306 / 1706 (5.08)



Subgroup	Canakinumab 150 mg (N=2284)	Placebo (N=3344)
Baseline LDL-C tertiles		
<= 1.81 mmol/L	91 / 773 (3.24)	155 / 1089 (4.05)
> 1.81 to <= 2.51 mmol/L	99 / 754 (3.56)	146 / 1113 (3.62)
> 2.51 mmol/L	126 / 740 (4.78)	226 / 1109 (5.79)
Baseline LDL-C level		
< 1.8 mmol/L	87 / 758 (3.16)	151 / 1075 (4.00)
>= 1.8 mmol/L	229 / 1509 (4.18)	376 / 2236 (4.71)
Baseline SBP level		
< 130 mmHg	145 / 1136 (3.47)	229 / 1602 (3.93)
>= 130 mmHg	175 / 1148 (4.26)	306 / 1742 (5.06)
Baseline DBP level		
< 80 mmHg	167 / 1241 (3.71)	300 / 1777 (4.73)
>= 80 mmHg	153 / 1043 (4.04)	235 / 1567 (4.24)
Baseline statin dose level		
No Dose	37 / 280 (3.62)	89 / 400 (6.50)
Low Dose	67 / 513 (3.49)	109 / 707 (4.21)
Medium Dose	116 / 768 (4.25)	163 / 1147 (3.97)
High Dose	100 / 723 (3.82)	174 / 1090 (4.57)
Aspirin usage		
No	51 / 271 (5.49)	85 / 386 (6.59)
Yes	268 / 2007 (3.65)	449 / 2953 (4.25)
Medical history of gout		
No	283 / 2109 (3.70)	480 / 3094 (4.36)
Yes	37 / 175 (5.87)	55 / 250 (6.41)
Hypertension		
No	42 / 470 (2.43)	82 / 700 (3.17)
Yes	278 / 1814 (4.24)	453 / 2644 (4.87)





N: Total number of patients on each treatment.
n: Total number of patients with events included in the analysis.
n/100py: Total number of patients with event per 100 patient years (randomization date to first event date or to censoring date used as denominator). Patients were considered censored after the cut-off date.
MACE includes CV death, non-fatal MI, and non-fatal stroke
CEC = Clinical Endpoints Committee.
Source: Figure 14.2-1.2b

Overall, the results for the 300 mg arm were similar. Some aspects are highlighted when comparing subgroups in the 150 mg arm and 300 mg arm.

Consistent results in subgroups:

- A HR >1 was consistently observed in Black patients for both strengths. While no significant interaction p-value by race was observed, the rate of recurrent MACE was numerically higher in the canakinumab treatment groups relative to placebo in Black patients. The HR was 1.17 (95% CI, 0.60 to 2.30) for the 300 mg group, 1.88 (95% CI, 0.98 to 3.61) for the 150 mg group, and 1.42 (95% CI, 0.68 to 2.94) for the 50 mg group.

- A HR close to 1 was observed for the region North America and Central Europe for the 300 mg arm with a similar pattern for the 150 mg arm.

- Results for dyslipidemia (yes/no) were consistent for the 150 mg arm and the 300 mg arm with a low HR in patients without dyslipidemia.

- For the 150 mg and 300 mg canakinumab groups, the HR in patients with a baseline DBP level < 80 mmHg or ≥ 80 mmHg numerically favoured canakinumab over placebo with an interaction p-value of p=0.016. For SBP that pattern was inconsistent with this result.

- Numerically efficacy was more pronounced in patients with hsCRP levels ≤ 4 mg/dL vs. > 4 mg/dL in the 150 mg arm whereas efficacy was similar in both groups in the 300 mg arm. However, results consistently did not show higher efficacy in patients with higher levels of hsCRP at baseline

Inconsistent results

- Numerically in the 150 mg arm there was a difference in the HR by age group < 65 years and ≥ years) for the 150 mg arm but not for the 300 mg arm.

- Numerically in the 150 mg arm there was a difference in the HR by gender indicating more favourable efficacy in male patients, whereas in the 300 mg arm numerically the HR numerically indicated more favourable efficacy in female patients.

- Numerically a HR close to 1 was seen in patients never having smoked for the 150 mg group but not for the 300 mg group.

- There were numerical differences in the HR related to LDL-C tertiles in the 150 mg arm but in the 300 mg arm and in the 50 mg arm the pattern was different.

- Presence of prior MI was associated with a HR >1 in the 150 mg arm but not in the 300 mg arm.

Secondary efficacy results

CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization.

The results in this secondary endpoint in the FAS were consistent with the result in the primary endpoint. A significant treatment effect was observed for the 150 mg group. The effect was sustained for the entire duration of the double blind phase (median follow up = 3.8 years). Numerically there was no relevant difference when comparing the cumulative event rate between the 150 mg group and the 300 mg group over time during the double blind phase. Overall, the secondary endpoint analyses performed on the PPS were consistent with the results from the FAS.

New onset of type 2 diabetes mellitus

No change in the incidence of new onset type 2 diabetes mellitus (T2DM) was observed among patients with pre-diabetes at randomization for any canakinumab treatment group.

CEC confirmed all-cause mortality and composite of all-cause mortality, non-fatal MI, or non-fatal stroke

The HR for the 150 mg canakinumab group was numerically in favor of canakinumab treatment relative to placebo in all of the treatment groups, without statistical significance over the whole duration of the double-blind phase or when examined by trial part. A total of 239 patients (2.76 per 100 patient years) in the 300 mg canakinumab group, 238 patients (2.73 per 100 patient years) in the 150 mg group, and 228 patients (2.85 per 100 patient years) in the 50 mg group died vs. 375 patients (2.97 per 100 patients years) in the placebo group (Table 14.2-3.1.a).

The results for the composite of all-cause mortality, non-fatal MI, or non-fatal stroke were consistent with the results for the primary composite endpoint that included CV mortality instead of all-cause mortality. The results for the subgroup analyses using this composite endpoint were overall consistent with the analyses for the primary composite endpoint.

CACZ885M2301 (cut-off date: 28MAR2017)

Table 14.2-3.1a (Page 1 of 1)
Time-to-event analysis for CEC confirmed secondary endpoints
Full Analysis Set

Response variable	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)	P-value
All-cause mortality	Canakinumab 300 mg	2263	239 (2.76)	0.93 (0.79, 1.10)	0.406
	Canakinumab 150 mg	2284	238 (2.73)	0.92 (0.78, 1.09)	0.329
	Canakinumab 50 mg	2170	228 (2.85)	0.96 (0.81, 1.13)	0.597
	Combined Canakinumab	6717	705 (2.78)	0.94 (0.83, 1.06)	0.307
	Placebo	3344	375 (2.97)		
All-cause mortality or MI or Stroke	Canakinumab 300 mg	2263	403 (4.88)	0.87 (0.77, 0.99)	0.028
	Canakinumab 150 mg	2284	395 (4.77)	0.85 (0.75, 0.96)	0.011
	Canakinumab 50 mg	2170	394 (5.17)	0.94 (0.83, 1.07)	0.377
	Combined Canakinumab	6717	1192 (4.93)	0.89 (0.81, 0.97)	0.013
	Placebo	3344	661 (5.56)		

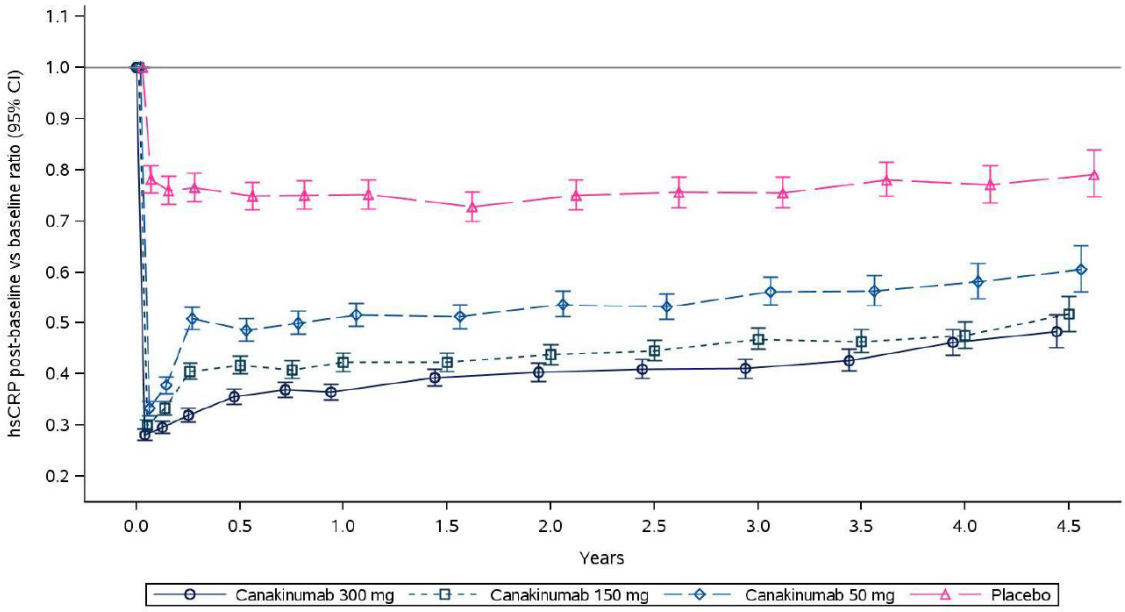
Relationship between canakinumab treatment, CV outcome, and hsCRP levels

(Further analyses concerning hsCRP in CANTOS are placed under section 3.3.6)

Mean and median baseline levels of hsCRP were similar in all treatment groups (mean values 6.4 – 6.7 mg/L, median 4.2 – 4.3 mg/L) and in the placebo group (mean value 6.4 mg/L, median 4.2 mg/L, for details see Table 11-4, above)

Canakinumab treatment induced a sustained reduction in mean hsCRP over the duration of the study. This reduction was observed with the first trough measurement for the 3 doses at 3 months (90 days). The geometric mean change from baseline in hsCRP was canakinumab dose-dependent; the geometric mean changes in hsCRP were larger in the higher canakinumab doses (Figure 11-16).

Figure 11-16 Geometric mean change from baseline in hsCRP with 95% confidence interval by treatment and visit (FAS)



Only visits where at least 15% of all patients had valid values in the variable under question were used in the analysis. Geometric means and CIs were derived by back-log transformation from mixed model repeated measures with treatment and visit as factors and baseline, trial part and time since index MI as covariates. The treatment*visit interaction term was also included. An unstructured covariance structure was used.

Effect of canakinumab treatment on CV disorders considered by the applicant as "with a known inflammatory component"

a) There was no relevant difference between the canakinumab 150 mg group relative to placebo in the time to first event analyses for the following endpoints:

- investigator reported other CV disorder considered by the applicant as "with a known inflammatory component" (for definition of the events see above, "Methods")

- supraventricular tachycardia/atrial fibrillation

- investigator reported hospitalization or prolongation of hospitalization for HF or CV death due to HF/cardiogenic shock

- investigator reported hospitalization or prolongation of hospitalization for heart failure

- CEC confirmed CV death due to HF/cardiogenic shock

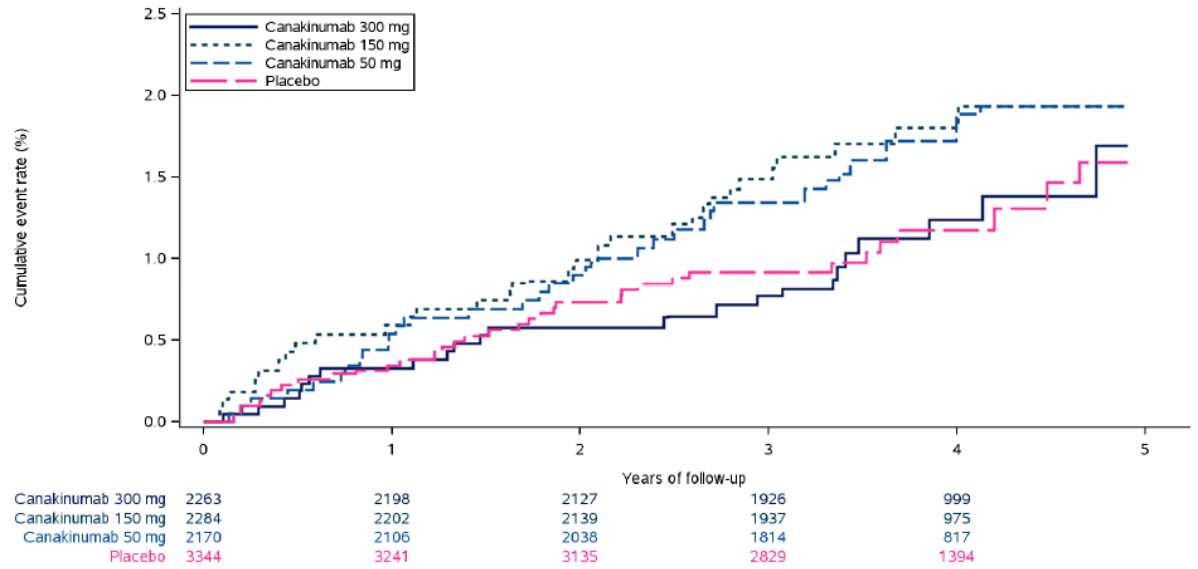
- CEC confirmed non-hemorrhagic cerebral infarction

- non-hemorrhagic infarction with hemorrhagic conversion

b) Numerically the event rate was lower in the placebo arm than in the 150 mg arm group for the following analyses:

- deep vein thrombosis/pulmonary embolism

Figure 14.2-3.1b (Page 1 of 1)
Estimated cumulative event rate for the first investigator reported deep vein thrombosis/pulmonary embolism by treatment
Full Analysis Set

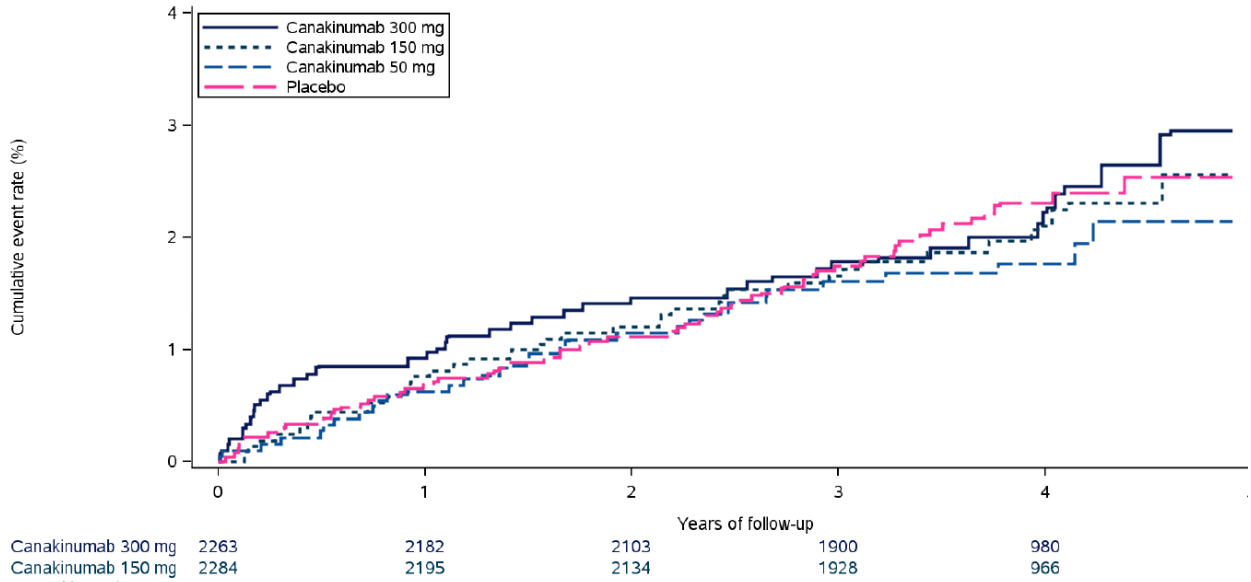


Canakinumab 300 mg	2263	2198	2127	1926	999
Canakinumab 150 mg	2284	2202	2139	1937	975
Canakinumab 50 mg	2170	2106	2038	1814	817
Placebo	3344	3241	3135	2829	1394

The estimated cumulative rate of subjects with an event is based on the Hakulinen method.
The curves are truncated at the point where less than 10% of subjects are still followed-up on all treatments.

- During the first year there was a slightly higher rate of stent thrombosis (definite or probable) in the 300 mg arm compared to the other treatment arms.

Figure 14.2-3.1d (Page 1 of 1)
Estimated cumulative event rate for the first investigator reported stent thrombosis by treatment
Full Analysis Set



Canakinumab 300 mg	2263	2182	2103	1900	980
Canakinumab 150 mg	2284	2195	2134	1928	966
Canakinumab 50 mg	2170	2103	2029	1803	821
Placebo	3344	3229	3123	2802	1375

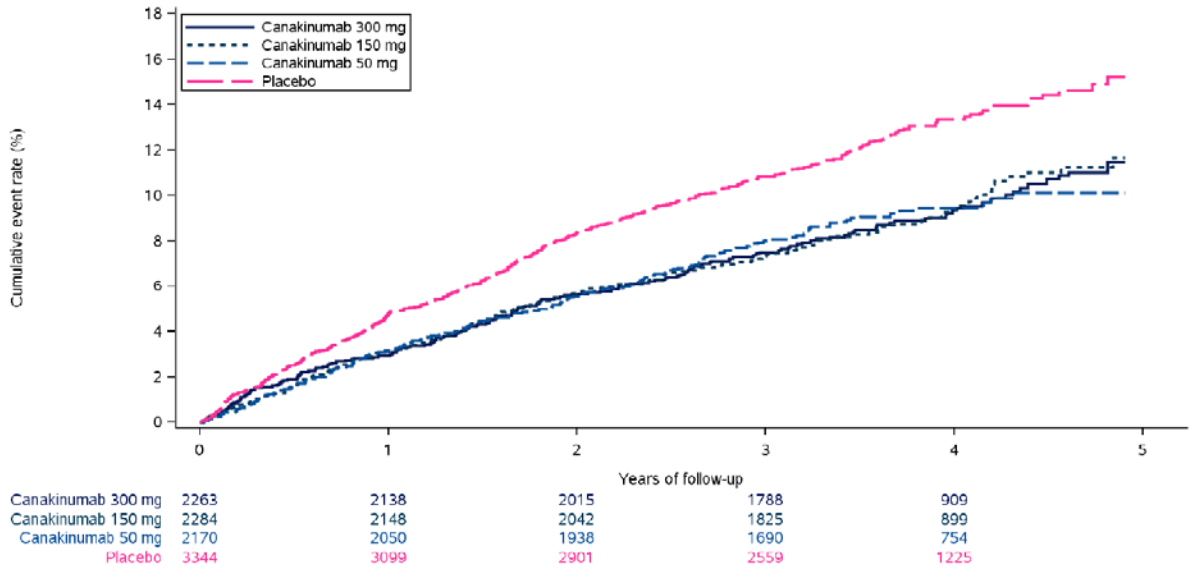
c) The event rate was numerically lower in the 150 mg arm as compared to placebo for the following analyses

- Major coronary event composite consisting of: CHD death or MI, where CHD death is defined as a death due to myocardial infarction, congenital heart failure/cardiogenic shock, directly related to revascularisation, due to arrhythmias, due to sudden death, death due to unknown cause or due to other vascular causes identified as Ischemic Heart Disease

- investigator reported vascular event

- first investigator reported coronary revascularization procedures (PCI or CABG)

Figure 14.2-3.1j (Page 1 of 1)
Estimated cumulative event rate for the first investigator reported coronary revascularization procedures (PCI or CABG) by treatment
Full Analysis Set



Patient reported outcomes

SF-36

No canakinumab treatment group showed a meaningful difference relative to placebo for any component score or domain score investigated over Months 1.5, 3, 6, 9 and 12.

Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)

No consistent differences in mean change from baseline in MFSI-SF total scores, general fatigue scores, physical fatigue scores, emotional fatigue scores, mental fatigue scores, or vigor scores were observed between any canakinumab treatment group and placebo over the time points at which the MFSI-SF was administered during the study (Months 1.5, 3, 6, 9, and 12).

EuroQol-5D (EQ-5D)

No canakinumab treatment group showed a statistical difference in score relative to placebo at Month 3, 6, 12, 36, or 48.

Stroke Functional Assessment Sub-Study

The modified Rankin Scale

No relevant difference was observed between Placebo and canakinumab dose groups.

MFSI-SF

Any patient who had a stroke at any time after enrollment in the study was targeted to complete the MFSI-SF instrument, where available, at 30 days and 90 days post their stroke event to assess tiredness. Analysis of MFSI-SF scores obtained 90 days after the first stroke similarly showed a lower LS mean score for the placebo group vs. the canakinumab treatment groups, with the difference from placebo (8.1 (SE 4.42)) to 300 mg canakinumab (19.0 (SE 4.62)) and the difference from placebo to 50 mg canakinumab (23.4 (SE 5.74)) being significant (p = 0.005).

Stroke Impact Scale 16 (SIS-16)

The repeated measures analysis of SIS-16 scores showed no statistically significant difference in the LS mean scores between any of the canakinumab treatment groups and placebo either 30 days or 90 days post-stroke.

Investigator reported hospitalizations

There was no positive or negative effect of Canakinumab treatment on factors related to hospital stays and admissions.

Table 4-1. Summary of efficacy for trial ACZ885M2301 (CANTOS)

	Title: CANTOS trial			
Study identifier		**ACZ885M2301**		
Design		This was a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double blind event-driven global clinical study. It was designed to evaluate the effect of quarterly subcutaneous doses of 50 mg, 150 mg and 300 mg (300 mg included an induction dose) canakinumab compared with placebo in patients with a prior MI with an elevated inflammatory burden (hsCRP ⩾ 2 mg/L) receiving standard of care therapy. Patients were randomized at least 30 days following their index-MI		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:			median follow-up = 3.8 years not applicable Ongoing, no data available
Hypothesis		Superiority		
Treatments groups	Placebo			Placebo n = 3344 (randomized)
	Canakinumab 50 mg Canakinumab 150 mg Canakinumab 300 mg			- Canakinumab s.c. 50 mg every three months n = 2170 - Canakinumab 150 mg every three months n = 2284 - Canakinumab 300 mg every three months and additional loadeing dose after 2 weeks n = 2263
Endpoints and definitions	Primary endpoint	primary MACE endpoint		composite of CV death, non-fatal MI, and non-fatal stroke

	Secondary	Secondary MACE + unstable angina Secondary MACE + all cause mortality Secondary All cause mortality		Primary MACE endpoint + hospitalization for unstable angina requiring unplanned revascularization Time to first event of non-fatal MI, non-fatal stroke and all-cause mortality Time to all-cause mortality
	Exploratory (among others)			- Primary MACE endpoint + hospitalization for unstable angina requiring unplanned revascularization or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary), coronary angiography and limb amputation -Other CV disorders • Time to first deep vein thrombosis/pulmonary embolism • Time to first supraventricular tachycardia/atrial fibrillation • Time to first stent thrombosis (definite or probable) • Time to first hospitalization or prolongation of hospitalization for heart failure • Time to first major coronary event (CHD death or MI) • Time to first event of coronary revascularization procedures (PCI or CABG) • Time to first stroke by etiology

Study initiation date: Study completion date		11-Apr-2011 (first patient first visit) 28-Mar-2017 (last patient last visit)			
	Results and Analysis				
Analysis description		**Primary Analysis**			
Analysis population and time point description		Intent to treat Patients at increased CV risk post myocardial infarction			
Descriptive statistics and estimate variability	Treatment group	Placebo	Canakinumab 50 mg	Canakinumab 150 mg	Canakinumab 300 mg
	Number of subject	3344	2170	2284	2263
	Primary MACE Events /n/100py)	535 (4.50)	313 (4.11)	320 (3.86)	322 (3.90)
	HR vs. Placebo (95% CI)		0.93 (0.80; 1.07)	0.85 (0.74; 0.98)	0.86 (0.75; 0.99)
	Adjusted P-value vs. placebo (*significant at p < 0.0245 one-sided)		0.1895	* 0.0241	0.0648
Analysis description		**Secondary analysis**			

	Secondary MACE + unstable angina	601 (5.13)	344 (4.56)	352 (4.29)	348 (4.25)
	HR vs. Placebo (95% CI)		0.90 (0.79; 1.03)	0.83 (0.73; 0.95)	0.82 (0.72; 0.94)
	Adjusted P-value vs. placebo		0.1895	* 0.0241	0.0648
	Secondary MACE + all-cause mortality	661 (5.56)	394 (5.17)	395 (4.77)	403 (4.88)
			0.94 (0.83; 1.07)	0.85 (0.75; 0.96)	0.87 (0.77; 0.99)
	Secondary All-cause mortality	375 (2.97)	228 (2.85)	238 (2.73)	239 (2.76)
			0.96 (0.81; 1.13)	0.92 (0.78; 1.09)	0.93 (0.79; 1.10)

Clinical studies in special populations

No specific studies were performed in elderly patients. However, a large number of patients included in the CANTOS trial were > 65 years.

Analysis performed across trials (pooled analyses AND meta-analysis)

This was an application based on one pivotal trial. No analyses across trials were submitted.

3.3.6. Assessment of surrogacy between hsCRP and primary endpoint with CANTOS study data

The applicant has provided an assessment of surrogacy between hsCRP and the primary endpoint utilizing CANTOS Data. (“*m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study”)*.

The explorative analysis plan was defined prior to unblinding the CANTOS study.

The objectives of the analysis were:

- To assess surrogacy between the measured level of hsCRP and the outcomes of the primary efficacy endpoint
- To evaluate the magnitude of the impact on the outcome of the primary efficacy endpoint derived from the measured level of the biomarker of interest, hsCRP.

The assessment relied on the method described by Prentice (1998). Prentice defines surrogate as a *response variable for which a test of the null hypothesis of no treatment relationship to treatment group under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.* This definition describes the surrogate for the given endpoint in a manner that depends on the treatment under comparison.

The method has four criteria; those are presented below with the CANTOS data.

Criterion 1: Treatment (Trt) has a significant impact on the true clinical endpoint (T)

This was demonstrated for the 150 mg dose using log-rank test. but not for the other strengths.

Table 14.2-1.1d (Page 1 of 2)
Time-to-event analysis for the first CEC confirmed major adverse cardiovascular events (MACE) and its components
Full Analysis Set

Response variable	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)	Unadjusted p-value	Adjusted p-value[1]
Major adverse cardiovascular events (MACE)	Cannkinumab 300mg	2263	322 (3.90)	0.86 (0.75, 0.99)	0.0157	0.0648
	Cannkinumab 150mg	2284	320 (3.86)	0.85 (0.74, 0.98)	0.0104	0.0241*
	Cannkinumab 50mg	2170	313 (4.11)	0.93 (0.80, 1.07)	0.1473	0.1895
	Canakinumab 300/150	4547	642 (3.88)	0.85 (0.76, 0.96)	0.007	
	Placebo	3344	535 (4.50)			

Criterion 2: Treatment (Trt) has a significant impact on surrogate (S)

The treatment effect on reduction from baseline in hsCRP over time was assessed by a mixed model for repeated measures (MMRM). To be precise, the dependent variable was the reduction from baseline of Ln-transformed hsCRP, i.e., Ln(post-baseline hsCRP) – Ln(baseline hsCRP), which is the ratio of geometric mean of post-baseline hsCRP vs. the geometric mean of baseline hsCRP. The MMRM included the following fixed effects: treatment and visit, treatment-by-visit interaction, Ln-transformed hsCRP at baseline as a continuous covariate, Trial part (Part I and II) and time since index MI (< 6 months and ≥ 6 months) as categorical variables. As the dose 50mg was not significant in the analysis related to Criterion 1, it was dropped from further analyses. Although the result for the 300 mg dose was also not significant, it was included based on the unadjusted p-value.

Table 14.2-1.2b below shows the post treatment vs. baseline ratio of hsCRP for placebo and the two higher dose treatment groups and the LS mean ration vs. placebo.

Table 14.2-1.2b (Page 1 of 4)
Mixed model with repeated measures for change from baseline in hsCRP
Full analysis set

		Descriptive statistics			Mixed model estimates		
Visit	Treatment	n	Baseline Geo. mean (SE)	Post-baseline Geo. mean (SE)	Ratio vs. baseline in Geo. LS Mean (SE)	Ratio vs. placebo Geo. LS Mean (95% CI)	p-value
Overall	Canakinumab 300 mg	2246	4.72 (1.016)		0.37 (1.016)	0.49 (0.47, 0.50)	< 0.001
	Canakinumab 150 mg	2267	4.72 (1.015)		0.41 (1.016)	0.54 (0.53, 0.56)	< 0.001
	Placebo	3318	4.64 (1.013)		0.76 (1.015)		

Criterion 3: Surrogate (S) has a significant impact on the true clinical endpoint (T)

The impact of hsCRP over time on time to first confirmed MACE was assessed by the Cox proportional hazards (PH) model with time-dependent covariate using exact method for handling ties in failure time. The model included: time-to-first confirmed MACE as the dependent variable, reduction from baseline in Ln-transformed hsCRP value over time as a time-dependent covariate, adjusting for Ln-transformed baseline hsCRP value as the covariate, and stratified by time since index MI (< 6 months, ≥ 6 months) and by trial part (trial part 1, trial part 2).

The key results of the analysis are presented below.

ACZ885M2301

Table 14.2-1.6 (Page 1 of 1)
Impact of change from baseline in hsCRP on the first confirmed major adverse cardiovascular event (MACE) and its components (cardiovascular death, non-fatal MI or non-fatal stroke) - using on-treatment hsCRP and event data only
Full analysis set

Response Variable	Explanatory Variable	Hazard ratio (95% CI)	p-Value
Major adverse cardiovascular events (MACE)	Time-dependent change from baseline in ln(hsCRP)	1.32 (1.24, 1.41)	< 0.001
	Baseline ln(hsCRP)	1.43 (1.31, 1.56)	< 0.001
CV death	Time-dependent change from baseline in ln(hsCRP)	1.55 (1.41, 1.71)	< 0.001
	Baseline ln(hsCRP)	1.86 (1.62, 2.14)	< 0.001
MI (fatal and non-fatal)	Time-dependent change from baseline in ln(hsCRP)	1.24 (1.13, 1.35)	< 0.001
	Baseline ln(hsCRP)	1.19 (1.05, 1.35)	0.006
Stroke (fatal and non-fatal)	Time-dependent change from baseline in ln(hsCRP)	1.19 (1.02, 1.39)	0.024
	Baseline ln(hsCRP)	1.33 (1.07, 1.64)	0.009

Criterion 4: The effect of the treatment upon the true clinical endpoint is capture/ or explained by the surrogate: f(T|S, Trt) =f (T|S)

The following two Cox PH models using the exact method for handling ties in failure times were performed to assess whether the effect of treatment on MACE is captured / explained by hsCRP as time-dependent reduction from baseline in Ln-transformed hsCRP measurements:

Model 1: This model is performed to assess the treatment effect on time to first confirmed MACE, which is identical to the model described above under Criterion 1 for the primary efficacy analysis to be presented in CSR, except that patients were excluded if they were in canakinumab treatment groups without an impact on the true endpoint, i.e. patients in 50 mg dose group

Model 2: This model was performed to assess the treatment effect on time to first confirmed MACE adjusting for reduction from baseline in Ln-transformed hsCRP value over time as a time-dependent covariate and the baseline Ln-transformed hsCRP value as the timeinvariant covariate.

As discussed, Model 2 = Model 1 + the effect of Ln -transformed hsCRP value at baseline + the time-dependent effect of reduction from baseline in Ln-transformed hsCRP value over time.

The following effects were included in the proportional-hazards model (Model 2): Treatment with placebo as the reference , Ln-transformed baseline hsCRP value as a time-invariant covariate, reduction from baseline in Ln-transformed hsCRP value over time as a time-dependent (i.e. time-varying) covariate, stratification by time since index MI (< 6 months, ≥ 6 months) and trial part (trial part 1, trial part 2).

The results are presented below:

Full analysis set

Response Variable Explanatory Variable	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	p-Value
Major adverse cardiovascular events (MACE)			
Canakinumab 300 mg	0.79 (0.68, 0.93)	0.96 (0.81, 1.13)	0.602
Canakinumab 150 mg	0.83 (0.71, 0.97)	0.98 (0.84, 1.15)	0.799
Time-dependent change from baseline in ln(hsCRP)		1.31 (1.23, 1.41)	<0.001
Baseline ln(hsCRP)		1.43 (1.30, 1.56)	<0.001

All these steps were repeated in a setting in which the time-dependent change from baseline in ln(hsCRP) was replaced with time-dependent absolute value of ln(hsCRP).

- Based on these calculations the applicant concluded that hsCRP can be used as surrogate for clinical responseWhereas the data indicate a correlation between baseline hsCRP levels/a reduction in hsCRP levels and MACE events on a group level, specificity and sensitivity of hsCRP levels or hsCRP response on treatment to predict MACE events on an individual patient level has neither been investigated nor been demonstrated.

Having established that hsCRP is prognostic of CV risk on a group level, the **causal analyses** were defined post Database Lock to estimate the effect of Canakinumab in those patients achieving an hsCRP value below a given target at 3 months. The subgroup of interest is defined by hsCRP value measured at the Month 3 visit under treatment with Canakinumab. The selected time point is appropriate as it corresponds to the first dosing interval after the initial administration. The early time point is practical from the point of view of granting approximately the same probability of observing the CRP response in the treatment groups.

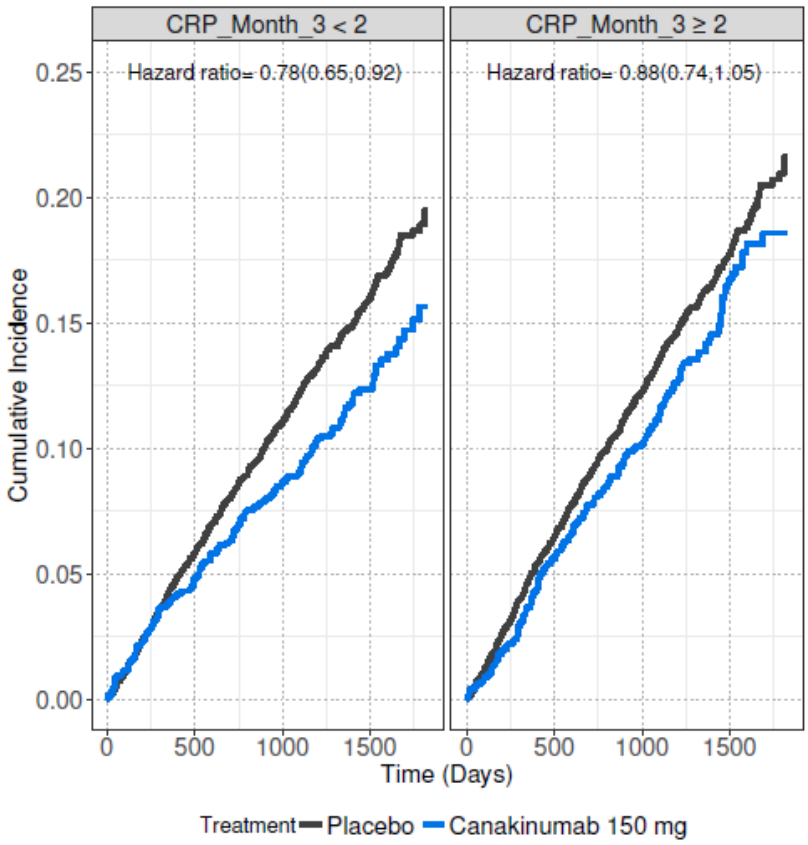
The causal estimands of interest are: (i) The difference between in the time -to-event survival curve at specified time points t and (ii) the ratio of the averaged hazard rates, over the maximum follow-up time observed in the study in patients reaching the target hsCRP at 3 months. In other words, in addition to actual observed survival curve measured on in patients treated with canakinumab and reaching the target hsCRP at 3 months, a theoretical survival curve of placebo effect for the same patients is needed for the estimation of the estimands.

The theoretical background and technical details how the estimation was conducted are presented in the submission material (*m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study SCE Appendix 2*). Shortly a set of baseline covariates with optimal capability to predict both hsCRP response at 3 months in patients treated with canakinumab, and outcome (MACE) in placebo treated patients were selected. Using these common covariates, placebo outcome was predicted for the canakinumab patients reaching the target hsCRP.

Figure below presents the survival curves as desrcribed above, when the cut-off for the hsCRP was set to 2mg/L; and the outcome variable was MACE.

Figure 14.2-16.1

Plot of cumulative incidence of CEC confirmed major adverse cardiovascular event (MACE) for Canakinumab 150 mg and placebo - by hsCRP < 2.0 and ≥ 2 mg/L at 3 months (Full Analysis Set)

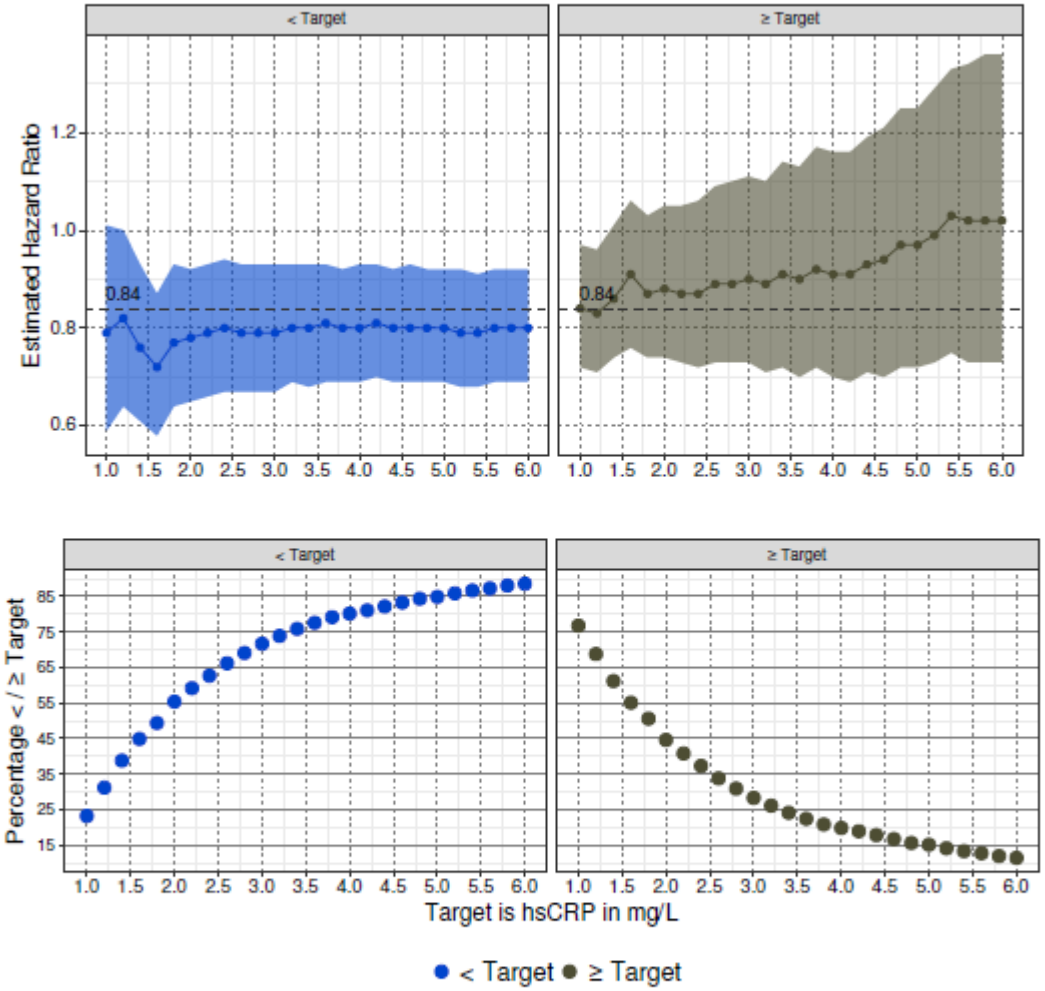


- Canakinumab survival is estimated based on observed data.
- Placebo survival obtained as mean adjusted by SMART risk score, BMI, log CRP, statin dose, recurrent MI LDL-C
corresponding to canakinumab hsCRP responders.
CACZ885M/sce/sce_usa_1/pgm/eff/ fig142_161.R Tue Dec 5 22:20:02 2017

In the next figure, a different target hsCRPs were applied, and HR was estimated for each.

Figure 14.2-20.1

Percentage and estimated hazard ratio (Canakinumab vs Placebo) of CEC confirmed major adverse cardiovascular event (MACE) for subjects reaching or not reaching hsCRP thresholds at 3 months when treated with canakinumab 150 mg (Full Analysis Set)



- Hazard rates derived using observed survival for canakinumab treated patients.
- Placebo placebo hazard rates derived adjusting for SMART risk score, BMI, log CRP, statin dose, recurrent MI, LDL-C corresponding to canakinumab hsCRP responders.
- Hazard ratios and confidence intervals are quantiles from 3,000 bootstrap samples.
- The hazard ratio of 0.84 is the treatment effect of canakinumab 150 mg vs placebo in patients alive at the Month 3 visit using the primary analysis model.

CACZ885M/sce/sce_usa_1/pgm/eff/ fig142_201.R Sun Dec 3 12:04:41 2017

The applicant has provided an alternative approach to look on the treatment effect using surrogate marker measured post baseline. Another approach would have been a subgroup analysis, where patients in both treatment arms with hsCRP response at 3 months are compared, however as the hsCRP response at 3 months depends on the randomized treatment, it is generally not a recommended approach. The results of these post hoc explorative analyses may help on the interpretation of the data, and give some grounds on discussion if and how hsCRP measurements could potentially be used in clinical practise.

From the analyses performed to demonstrate the value of hsCRP as a surrogate of response, and the exploratory causal analyses, it can be concluded that higher hsCRP predicts higher risk of event, irrespective of the treatment, but also that higher hsCRP post baseline, at 3 months may predict lower treatment effect for canakinumab. This finding is in line with the subgroup analysis with the baseline hsCRP values, where patients with higher baseline hsCRP (> 4 mg/L) had lower treatment effect than patients with lower baseline hsCRP (≤4 mg/L), though no statistically significant interaction was reported.

Thus, somewhat contrary to the hypothesis of relation of the mode of action of canakinumab in the anti-inflammatory atherosclerosis, the level of hsCRP at baseline may not be an appropriate marker to define the patients who would benefit most from canakinumab, as higher hsCRP at baseline may finally predict lower treatment effect for canakinumab. (part of **MO**)

On the other hand, if the post-baseline hsCRP remains high (≥2 at 3 months), canakinumab may not provide a beneficial effect for the patient, which could be a useful marker to recommend treatment discontinuation in clinical practice. It has to be emphasized, however, that the causal analyses to estimate the effect of canakinumab in patients who reached a certain hsCRP target at 3 months were performed as unplanned exploratory post-hoc analyses and hence their true value can be questioned. The issue requires further clarification. According to "sce appendix 1 page 80 Table 14.2-15-4" the number of patients (%) with hsCRP < 2mg/L at 3 months by treatment arm was: canakinumab 300mg 1392/2128 (65%), canakinumab 150mg 1185/2162 (54.8%), canakinumab 50mg 904/2058 (44%), and Placebo 699/3179 (22%). This indicates that about 40% of the responders in the Canakinumab arm would also have been categorised as responders without treatment just due to fluctuation of hsCRP not related to treatment. Whereas at entry an hsCRP > 2 mg/L is an inclusion criterion, the opposite is the case after 3 months for these patients, which appears to be contradictory (part of **MO**).

A statement from the biostatistical Working party has been submitted that can be summarized as follows:

A key issue with this analysis is that it is post hoc, and the cut-off value is not justified or validated. It may have been chosen to obtain optimal results. The applicant has not provided any data to describe whether the placebo predictor model actually worked at all at predicting response, and if it did work, how well it worked. Thus, the robustness of the "placebo predictor model" cannot be assessed. Furthermore, sensitivity analyses would be helpful to assess how robust the final estimates are.

The causal inference approach intended to explore a treatment effect in the stratum of patients with a specific biomarker response after 3 month of active treatment does not appear to be robust enough to be used as part of the registration process, due to unverifiable assumptions, unclear robustness and operational characteristics of the method used, lack of full pre-specification of the whole procedure and the lack of reliable confidence intervals.

Furthermore, in the context of the CANTOS trial results, the importance of the 3-months finding as compared to baseline finding can be questioned. The interaction with respect to the MACE HR in the subgroups defined at baseline (<4mg/L vs. > 4mg/L: HR = 0.74 vs 0.92) appears considerably larger than the corresponding interaction w.r.t. 3-months (<2 mg/L vs >2mg/L: HR = 0.78 vs 0.88). In relative terms, restricting the population by a baseline value of less than ≤4mg/L decreases the hazard ratio by approximately 20%, whereas selecting patients with respect to 3-months value below ≤ 2mg/L decreases the hazard ratio by only 11%.

Hence, the proposed 3-month selection based on a causal inference model appears even less convincing than a selection based on baseline hdsCRP, even when accepting the use of unverifiable assumptions in the causal inference analysis

Assessment of robustness of the estimates requires further sensitivity analyses, and a full assessment of operational characteristics of the selected methods which appears unrealistic considering the number of and uncertainty in the potential model deviations. Lack of pre-specification with respect to the method used (involving a number of complex steps) and the selected, unjustified cut-off value further invalidate a confirmatory conclusion. Furthermore, benefit risk assessment of the suggested treatment policy of treating all patients for three months and discontinuing those who do not reach the hsCRP target would have to consider that those patients that are not considered in the claimed efficacy results are to be treated with active treatment for three months.

The assessment of robustness of the causal inference analysis appears difficult, especially since the underlying assumption is unverifiable and a thorough discussion and justification was not provided. Investigations of robustness with respect to this and the other assumptions are lacking. Deviations from these assumptions would invalidate the results, i.e. lead to biased results. Due to the number of assumptions used it appears difficult to gauge to potential impact of such deviations.

Besides the issues related to robustness of the method and reliability of the results, the derived interaction between stratum and outcome (i.e. the difference in treatment effects between the selected population and the complementary group) does not appear statistically significant (even if a post-hoc test on this interaction were accepted) and the size of the interaction does not appear to be convincing.

In summary, the selected approach to estimate treatment effect in a subgroup defined by a post baseline finding using causal inference analysis does not appear to be acceptable to support licencing and the proposed algorithm to define a patient population eligible for a lifelong treatment is not considered appropriate.

Supportive study(ies)

Three controlled studies were submitted as report addressing the effect of Canakinumab in patients with intermittent claudication (CACZ885M2201) , with abdominal aortic aneurysm (CACZ885X2201) or with clinically evident atherosclerosis (ACZ885I2206) on imaging parameters, and functional capacity of patients. These studies are discussed in detail above (PD)

3.3.7. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose finding

No formal dose selection studies were performed. The multiple dose Phase II studies on pharmacodynamics used a different dosing (up to 150 mg sc. monthly) than the CANTOS study (up to 300 mg sc. every 3 months).

Dose selection was based on hsCRP as a marker for biological activity of canakinumab. A modelling approach was applied using results from phase 2 studies in other populations. Dose selection was finally based on the results of the pivotal study that also included PK/PD modelling part in the target population. The employed PK/PD modelling approach was considered acceptable by the CHMP during scientific advice, even though modelling based on data from gout and T2DM subjects for dose and posology selection, instead of CV patients, was considered less than optimal.

Efficacy

The application was mainly based on one pivotal trial (CANTOS, CACZ885M2301). A single pivotal study is usually not sufficient for demonstration of positive benefit-to-risk ratio. In cases where the confirmatory evidence is provided by one pivotal study only, this study should be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. Preferably the mode of action (MoA) of the medicinal product should be well defined. The anti-inflammatory MoA of canakinumab is known, but on the level of vasculature, the relevance of its effects is unclear. Further, when there is a new pharmacological principle, in this case using canakinumab for prevention of CVD, the results should be particularly convincing.

CANTOS was a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial, designed to evaluate the efficacy and safety of canakinumab compared to placebo in post-MI patients receiving standard of care therapy who were selected based on an hsCRP $\geq$ 2 mg/L. The qualifying MI had to occur at least 30 days prior to randomization. The trial was an event-driven global trial conducted in the outpatient setting. The study consisted of 3 periods: (1) screening period; (2) double-blind phase (event driven) and (3) follow up period. The trial was event driven and was designed to complete when a total of 1,400 patients had experienced one of the events comprising the primary CV endpoint. Thus, double blind treatment was continued until the target number of primary confirmed adjudicated CV events had been reached (ie, 1,400 patients with primary CV events). 1,109 sites randomized at least one patient each in 39 countries worldwide.

The primary objective of this study was to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular events (cardiovascular death, non-fatal MI and non-fatal stroke) in a population of clinically stable patients with prior MI with elevated hsCRP receiving standard of care. Key secondary objectives included additional cardiovascular endpoints and all-cause mortality as well as patient reported outcome and specific measures for the assessment of patients after stroke.

The study was completed as planned. The 50 mg arm was included in the protocol by an amendment after the start of the trial leading to an amendment of the randomisation scheme and two phases of randomisation. Amendment 8 revised the number of patients to be randomized into the study from 17,200 patients to approximately 10,000 patients.

Number of patients (planned and analyzed): A sample size of approximately 10,000 randomized patients was expected to be sufficient to accrue the planned number of 1,400 patients with a MACE. A total of 10105 patients were randomized, and a total of 10061 patients were included in the FAS. A total of 44 patients (8, 7, and 10 patients in the 300 mg, 150 mg and 50 mg arms, respectively, and 19 in the placebo arm) in the randomized set were excluded from the FAS because they did not qualify for randomization but were inadvertently randomized into the study via the IVRS/IWRS and did not receive double blind study medication (41 patients) or because they were randomized at sites that were closed due to serious GCP violations (3 patients).

Overall the CANTOS was well conducted as planned. In 103 patients included in the pivotal trial, almost all in Brazil, it was noted that locally the blind was broken. According to the applicant the unblinding in these Brazilian centers was related to a single mistake related to a change in the local drug depot and not due to general mismanagement. It was unclear, whether treatment allocation was actually unblinded to the site personnel. Sensitivity analyses did not indicate an impact on the overall conclusions of the study. 2.2% (25 centers) reported a high rate of protocol deviations that were not considered to impact the overall results. There are remaining issues to be addressed concerning the inspections, the time point of exclusion of 3 patients from the efficacy analysis due to GCP issues and a clarification is requested on the number of patients that were included in disregard of exclusion criterion 5 (tuberculosis) **(OC)**.

When developing the study plan for CANTOS, the applicant sought scientific advice from the CHMP. In general the CHMP stated that the anti-inflammatory concept and relation with hsCRP, in atherosclerosis is hardly supported by pharmacodynamic studies. The CHMP was of the opinion that it would be useful to study patients with cardiovascular disease in early phase to assess the effect of canakinumab on IL-1β, hsCRP levels and effect on cardiovascular pathology, before continuing to clinical trials. The Phase 2 studies tried to partly address these issues; however no definite link with canakinumab treatment and the structure and function of the vasculature could be confirmed in these studies.

Furthermore, the CHMP did not support the composite end-point which includes CV mortality, with the intention to present overall mortality as part of safety. All-cause mortality was preferred to CV mortality by the CHMP as part of the composite primary efficacy end-point. The overall rationale for testing the hypothesis on whether canakinumab is able to reduce cardiovascular risks in patients who remain stable following MI and who have persistently elevated CRP was supported in general by the CHMP. The CHMP understood that CRP level would be used as selection criterion, but not as a prognostic marker. Thus, the understanding was opposite to what was seen in CANTOS: hsCRP was a prognostic marker of subsequent risk, albeit not of subsequent response to canakinumab treatment.

The wording of the indication is in line with the patient population included in CANTOS. The proposed indication is

Canakinumab Novartis is indicated for the secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ≥ 2.0 mg/l prior to treatment initiation.

For study results with respect to populations/sub populations studied, see section 5.1.

Most patients were on baseline therapy for CV risk prevention and had several CV risk factors with a high rate of revascularisations/ PCIs/CABGs, section 4.2. refers to baseline therapy in CANTOS.

The patients who were at highest risk of death, e.g. patients with acute or recent (within 30 days) MI or multivessel CABG, were however excluded; the level of risk of the CANTOS-patients can be described by the cumulative rate of 20% of primary/secondary endpoints at 5 years in the placebo group. the revised study population was in line with the sought indication. Further modifications of the wording of the indication may be necessary depending on the final assessment of B/R in subgroups (e.g. patients with and without baseline statin therapy).

Further, it is notable that the great majority of the CANTOS cohort had either type 2 diabetes or prediabetes, were obese and dyslipidaemic and with hypertension; i.e. had metabolic syndrome. It is known that metabolic syndrome is associated with inflammation of adipose tissue; furthermore, adipose tissue is a source of inflammatory cytokines in these patients. Potentially also visceral fat, not only vessel wall, is a target of the MoA of canakinumab, which might explain why the results of Phase 2 studies on vessel wall structure were modest and discrepant and not entirely in line with the results of CANTOS.

Efficacy data and additional analyses

Dose finding

In the first step canakinumab dose range selected for further development was 15 to 50 mg monthly based on hsCRP lowering activity. In the second step modelling and simulation data on tissue free IL-lß was used as surrogate for canakinumab pharmacokinetics. The modelling approach suggested that canakinumab can be dosed quarterly with adequate suppression of tissue free IL-1ß and that 50 mg and 150 mg quarterly doses correspond to 15 mg and 50 mg monthly doses and cover the selected dose range. Therefore, 50 mg and 150 mg quarterly doses of canakinumab and 300 mg with an additional loading dose after 2 weeks were selected for the proposed study CACZ8852302. Based on calculations it was assumed that 150 mg quarterly was able to suppress hCRP near maximal.

Overall, when taking the effect on free IL-lß and hsCRP, modelling appears to be a reasonable approach to define a dose range to be investigated in the pivotal study. Quarterly dosing may be justified based on the long T ½ of Canakinumab of 26 days and on suppression of hsCRP over three months.

In summary, the rationale for the additional loading dose to be investigated in the pivotal trial is weak but the approach to define a dose range to be investigated in phase III appears to be appropriate. The final dose with the optimal B/R depends on the results of the pivotal trial.

Efficacy

Overall the patient characteristics were balanced between the 4 treatment groups. Patients had a median age of 61 years, a median BMI of 29.8, and a median hsCRP level of 4.2 mg/L. The majority of patients were male (74.3%) and Caucasian (79.9%); most of the remaining patients were either Asian (11.6%) or Black (3.2%). A total of 49.3% of patients were prediabetic and 40.0% had type 2 diabetes. Patients had a mean DBP of 77.9 mmHg, a mean LDL-C of 2.3 mmol/L (88.9 mg/dL), and a mean eGFR of 79.4 mL/min/SA. The percentage of patients with LDL-C < 2.6 mmol/L (< 100.5 mg/dL) was 68.4% and the percentage of patients with eGFR ≥ 90 mL/min/SA was 29.5%. There was a high incidence of comorbidities and associated co-medication. All patients had at least one documented CV risk factor in addition to prior MI. Prior to enrollment in the study, patients were treated with guideline recommended therapy. Of the SAF (10066 patients), a total of 93.9% were treated with platelet aggregation inhibitors (excluding heparin), 90.1% with HMG-CoA reductase inhibitors, 66.5% with beta-blocking agents, 54.0% with ACE inhibitors, 23.1% with angiotensin II antagonists, 11.1% with “other” lipid modifying agents, and 4.7% with fibrates. The rate of 90.1% provided for patients on HMG-CoA reductase inhibitors in the study report (based on 10066 patients, FAS, Table 14.3-1.4a) is not entirely consistent with the number in the analysis in Exp Table 14.2.-4.1 where 8891/10061 patients i.e. 88.4% were on statins. This should be clarified (OC).

Primary efficacy result

Canakinumab 150 mg was superior to placebo in reducing the risk of CEC confirmed MACE (a composite of CEC confirmed CV death, non-fatal MI, or non-fatal stroke). The adjusted p-value was statistically significant for the 150 mg strength but not for the other strengths. The primary outcome occurred in 322 (3.90/100 patient years), 320 (3.86/100 patient years) and 313 (4.11/100 patient years) patients in the 300, 150, and 50 mg groups, respectively, compared with 535 (4.50/100 patient years) patients in placebo. The HRs describing the relative risk of MACE for each canakinumab dose group (300, 150, and 50 mg) vs. placebo were 0.86 (95% CI, 0.75 to 0.99), 0.85 (0.74 to 0.98), and 0.93 (0.80 to 1.07), respectively.

Results for the individual components

The reduction in the risk of MACE with canakinumab 150 mg treatment was driven by a significant reduction in the risk of MI (fatal and non-fatal) (HR = 0.76 (95% CI, 0.63 to 0.92; unadjusted p-value = 0.006)) and a numerical reduction in the risk of CV death (HR = 0.90 (95% CI, 0.73 to 1.10)) relative to placebo (Table 11-8). There was no difference observed in the risk of stroke (fatal and non-fatal) between the 150 mg canakinumab treatment group and placebo. Taking some variability into account the results were numerically largely similar in the 300 mg group with a numerically lower HR for stroke and a HR close to 1 for CV death.

Subgroups

Overall, the results for the primary endpoint were consistent irrespectively of the subgroup selected with one relevant exception.

For the large group of patients on baseline statin therapy (irrespectively of dose, 88.4% of the patients included in this analysis) the risk reduction for MACE (Canakinumab 150 mg vs. placebo: HR 0.91 (0.78; 1.05), Table 14.2-41) and for the components of the MACE endpoint was lower (Interaction P-value 0.1251). This is relevant. Patients on baseline statin therapy are the key target group. There is biological plausibility of such a negative interaction since statins are known to decrease hsCRP and by their pleiotropic effects are considered to have an impact on inflammatory processes. A risk reduction by only 9% in the key target group of patients is of questionable clinical relevance and clearly not sufficient in the context of an application based on one pivotal trial investigating a medicinal product with a completely new mechanism of action.

An interaction p-value <0.05 was noted for the

- Presence of an MI prior to index MI (no, yes, p 0.004 for MACE and p= 0.015 for stroke) and a p value between 0.05 and 0.1 for the MI (fatal and non-fatal) component

- Baseline DBP level (< 130 mmHg, ≥ 130 mmHg) for the composite MACE endpoint and the MI (fatal and non-fatal) component, and a p value between 0.05 and 0.1 for the CV death component

- A HR >1 was consistently observed in Black patients for both strengths. While no significant interaction p-value by race was observed, the rate of recurrent MACE was numerically higher in the canakinumab treatment groups relative to placebo in Black patients. The HR was 1.17 (95% CI, 0.60 to 2.30) for the 300 mg group, 1.88 (95% CI, 0.98 to 3.61) for the 150 mg group, and 1.42 (95% CI, 0.68 to 2.94) for the 50 mg group.

- A HR close to 1 was observed for the region North America and Central Europe for the 300 mg arm with a similar pattern for the 150 mg arm.

- Results for dyslipidemia (yes/no) were consistent for the 150 mg arm and the 300 mg arm with a low HR in patients without dyslipidemia.

- For the 150 mg and 300 mg canakinumab groups, the HR in patients with a baseline DBP level < 80 mmHg or ≥ 80 mmHg numerically favoured canakinumab over placebo with an interaction p-value of p=0.016. For SBP that pattern was inconsistent with this result.

- Numerically efficacy was more pronounced in patients with hsCRP levels ≤ 4 mg/dL vs. > 4 mg/dL in the 150 mg arm whereas efficacy was similar in both groups in the 300 mg arm. However, results consistently did not show higher efficacy in patients with higher levels of hsCRP at baseline

Secondary efficacy results

CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization.

The results in the key secondary endpoint (CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization) in the FAS were consistent with the result in the primary endpoint. An overall significant treatment effect was observed for the 150 mg group. The effect was sustained for the entire duration of the double blind phase (median follow up = 3.8 years). Numerically there was no relevant difference when comparing the cumulative event rate between the 150 mg group and the 300 mg group over time during the double blind phase.

CEC confirmed all-cause mortality and composite of all-cause mortality, non-fatal MI, or non-fatal stroke The HR for the 150 mg canakinumab group was numerically in favor of canakinumab treatment relative to placebo in all of the treatment groups, without statistical significance over the whole the duration of the double-blind phase or when examined by trial part. A total of 239 patients (2.76 per 100 patient years) in the 300 mg canakinumab group, 238 patients (2.73 per 100 patient years) in the 150 mg group, and 228 patients (2.85 per 100 patient years) in the 50 mg group died vs. 375 patients (2.97 per 100 patients years) in the placebo group (Table 14.2-3.1.a).

The results for the composite of all-cause mortality, non-fatal MI, or non-fatal stroke were consistent with the results for the primary composite endpoint that included CV mortality instead of all-cause mortality. The results for the subgroup analyses using this composite endpoint were overall consistent with the analyses for the primary composite endpoint.

Exploratory efficacy results

Relationship between canakinumab treatment, CV outcome, and hsCRP levels

Canakinumab treatment induced a sustained reduction in mean hsCRP over the duration of the study. This reduction was observed with the first trough measurement for the 3 doses at 3 months (90 days). The geometric mean change from baseline in hsCRP was canakinumab dose-dependent; the geometric mean changes in hsCRP were larger in the higher canakinumab doses. Also in the placebo group a reduction in hsCRP levels by about 25 % (mean) was observed. Among the explanations for the rapid decrease in hsCRP are infections/status post infection or other acute events and regression to the mean. Since mean values in the screening/pre-screening period were used, it is conceivable that patients were included despite of decreasing hsCRP levels. Probably patients with hsCRP values < 2mg/L at randomisation were included in the study. Clarification on these issues is required. (part of MO)

There was no beneficial or negative effect of Canakinumab in any of the patient reported outcome measures investigated. When using measures for Stroke Functional Assessment higher fatigue scores were observed in the MFSI-SF in patients after stroke.

There are two major issues that require further discussion and analyses (MO).

1. Concerns remain on the **strength of evidence** and **the magnitude of the beneficial effect** from the CANTOS study balanced against the **increased risk of fatal/serious infections** therefore a **positive B/R in the claimed indication has not been demonstrated**:

a) In terms of the strength of evidence the **statistical significance is borderline** with a p value for efficacy of 0.0241 just below the predefined significance level of 0.0245 which is **not considered 'exceptionally compelling' in line with the principles** described in the *EMA Guideline on "Application with 1. Meta-analyses; 2. One pivotal study"* with respect to the strength of statistical evidence especially in a field with a new therapeutic approach. Whilst the company argues that this is not a new pharmacological principle, efficacy results related to inflammatory markers (see MO2) that were fully consistent with the a priori biological rationale would have strengthened the evidence for efficacy.

b) Most patients (88.4%) received baseline statin therapy. In this key group the estimated efficacy was considerably lower with **a risk reduction for MACE of only 9 %** (150 mg arm, HR = 0.91, 95% CI [0.78, 1.05]). There is biological plausibility this lower treatment effect. **Pleotropic effects of statins** on inflammatory processes associated with a decrease in hsCRP have been proposed to be relevant for efficacy of statins. Therefore, both the clinical relevance of efficacy in the key group of patients on baseline therapy with statins in terms of effect size and the overall risk-benefit balance is questionable.

2. **CANTOS did not demonstrate the relevance of pre-treatment and on-treatment hsCRP levels to identify patients with a positive benefit risk ratio and to monitor a treatment effect.**

a) A key issue of discussion is the role of hs-CRP for the characterisation of the patients to be included in the wording of the indication. hsCRP levels > 2 mg/dL were an inclusion criterion but the relevance of this value is not clear for the following reasons. Overall, it is conceivable that the hsCRP level is irrelevant for a treatment effect, baseline hsCRP did not predict the treatment effect. In the 150 mg arm efficacy of Canakinumab in patients with baseline hsCRP > 4mg/L was numerically lower than in those with baseline hsCRP between 2 mg/L and ≤4mg/L (HR for MACE 0.92 (0.77, 1.10) vs. 0.74 (0.59, 0.93)). No difference was observed in the 300 mg arm. Data in patients with hsCRP < 2 mg/L is not available.

Several issues have to be considered when analysing the data. There was a relevant decline by about 25% in hsCRP levels in the placebo group immediately after randomisation indicating that a relevant number of patients would not have met the inclusion criterion if hs-CRP levels had to be confirmed at randomisation or shortly thereafter. Acute illnesses like infections or status after acute illnesses not related to CV risk may have contributed to this observation. In this regard the protocol specified inclusion of patients based on mean hsCRP values during the pre-sreening/screening period may be an issue. Patients may have been included with hsCRP levels < 2 mg/L at randomisation based on pre-study mean values > 2 mg/L. Additional analyses on this issue are expected including efficacy analyses for those patients randomisation hsCRP values < 2 mg/L

It was noted that there was a correlation between hsCRP levels and AEs of infection. When patients with infection related instances during screening/pre-screening were eliminated, the initial fall in hsCRP in the overall placebo group by 25% was reduced to about 10%. Whether the population selected based on increased hsCRP levels was enriched by patients with subclinical or clinical infections, cannot be answered based on CANTOS.

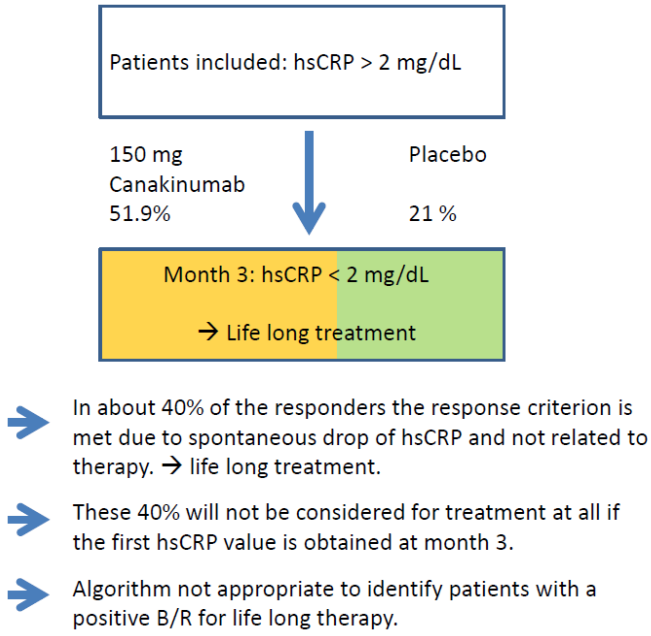
In summary, CANTOS failed to demonstrated that pre-study hsCRP values are relevant for a treatment effect of Canakinumab on MACE.

b) The proposed algorithm that includes patients with hsCRP > 2 mg/L and keeps patients on treatment with a 3 month hsCRP < 2 mg/L is not appropriate for the following reasons.

- The approach has not been prospectively confirmed.

- The algorithm predicts treatment effect less reliable than some of the baseline characteristics (e.g. baseline hsCRP level hsCRP > 4mg/L vs. ≤ 4mg/L).

- The algorithm does not identify a well-defined patient population. For 40% of the patients considered for life long therapy vs. no therapy the treatment decision is based on the time point of the hsCRP value taken (3 months earlier or later) and not on patient characteristics. The following figure summarizes the issue:



- In addition, more patients in the 300 mg arm were responders for the 3 month hsCRP < 2 mg/L criterion than in the 150 mg arm (61.1 % vs. 51.9%) but efficacy on MACE endpoints was not higher in the 300 mg group.

- The 3 month analysis in the 150 mg arm was influenced by the more pronounced treatment effect seen in patients with a lower baseline hsCRP.

Therefore, the proposed treatment algorithm is not appropriate to identify a patient population with a positive B/R (MO). Taking these concerns together clarification is expected on the following issues:

i) The applicant is asked to provide analyses for the key efficacy endpoints differentiating between 3 month hs-CRP responders and non-responders for the Canakinumab 300 mg arm and the Canakinumab 50 mg arm.

ii) It is understood that patients with a drop in hsCRP from a pre-screening/screening value > 2 mg/L to a randomisation value < 2 mg/L were included in the study. Since the mean of these values was used to calculate the baseline value such patients may have contributed to the apparent drop in hsCRP after inclusion. The applicant should explore this issue further and provide following data on the number of patients with more than one hsCRP value that had a drop in hsCRP from screening/prescreening to randomization and the number of patients included despite of the last measured hsCRP value at screening or randomisation being < 2mg/L. A sensitivity analysis for the key efficacy endpoints is expected differentiating between the patients with the last hsCRP value > 2 mg/L vs. < 2mg/L for all treatment arms in comparison to placebo. This may further elucidate the relevance of the 2 mg/L criterion. Such analyses may also be of relevance for the interpretion of the inverse correlation between pre-study hsCRP and efficacy in the 150 mg arm. In addition, the applicant should provide evidence that causal inference analysis is sufficiently robust against deviations from the claimed assumptions, e.g. the assumption that conditional on the selected baseline covariates, the event time under placebo is independent of the potential hsCRP response under treatment with canakinumab and the additional assumptions used in the estimation relating to proportional hazard, the exponential survival to estimate the hazard rates, the assumptions of the multiple imputation approach, as well the assumption that there is no treatment effect on survival during the first three months. Furthermore, the applicant should explain why the relative small insignificant interaction between the subgroup selection and treatment is large enough to justify 3 month selection.

In addition, there are cross-sectional data showing that inflammatory and endothelial markers, including CRP, are not related to the prevalent degree of atherosclerosis in T2DM subjects (Leinonen et al. Low-grade inflammation, endothelial activation and carotid intima-media thickness in type 2 diabetes. J Intern Med 256:119-27, 2004) - even though in the same study population, endothelial activation and acute-phase reaction (incl. hsCRP) correlated significantly with insulin resistance and obesity (Leinonen al. Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. Atherosclerosis 166: 387-394, 2003). Individual CV risk can be high also in subjects with hsCRP below 2 mg/L. Due to this limitation there are currently no data in patients who regardless of their low hsCRP value may be at risk of subsequent CV events e.g. due to uncontrolled other risk factors for CVD, or due to family history or other individual characteristics.

There are some other issues to be addressed (OC).

- Additional information is requested regarding including regions.

- There are some remaining issues on GCP regarding the time point of exclusion of 3 subjects for GCP issues, the number of patients excluded due to exclusion criterion 5 (tuberculosis) and the reasons for inspections performed in 18 centers that led to clusore of 2 centers.

Finally, the applicant performed Phase II studies in patients with T2DM, intermittent claudication and abdominal aortic aneurysm. These studies were partly designed to investigate if canakinumab treatment affects the distensibility and structure of vascular wall. Some improvement was seen in maximum walk distance and pain-free 6-min walk distance in patients with intermittent claudication and slight reduction in plaque burden was noted in T2DM and IGT patients in the aorta and the carotid arteries. However, no improvement was found in vascular stiffness in T2DM and IGT patients, vascular structure in patients with aortic aneurysm or plaque burden in the superficial femoral artery. The results supporting local vascular effects of canakinumab are very modest and contradictory. Furthermore, these studies were performed in different patient groups and with different posology of canakinumab than that used in CANTOS. Consequently, one should avoid over-interpretation of the results as supportive of prevention of CVD.

In summary, although canakinumab 150mg reduced both the primary and secondary composite endpoints, in the context of only single pivotal trial and totally new mode of action, and without compelling statistical significance, the clinical relevance of the relative risk reduction of 15% is only modest. Since in pateints taking statins (about 90% of the whole populatin) RR was only 9% the clinical relevance in the key group of patient sis questioned. The algorithm to start treatment with baseline hsCRP > 2 mg/L and to continue treatment in patients > hsCRP > 2 mg/L is not appropriate to idenfiy a patient group with positive B/R. When also considering the strength of statistical evidence the results of CANTOS are not sufficient to support an application based on one pivotal trial **(LoQ/MO).**

3.3.8. Conclusions on clinical efficacy

At present it is not possible to conclude on an established demonstration of a clinically relevant efficacy since the requirements for one pivotal trial are not met regarding strength of statistical evidence and compelling clinical results. Efficacy in the overall group of patients is modest, efficacy in the key group of patients (about 90%) on statin therapy is of questionable clinical relevance and the role of hs-CRP as a relevant inclusion criterion and a tool to monitor therapy is not known.

3.3.9. Clinical safety

Patient exposure

The primary source of safety data for canakinumab in the target population is the pivotal CANTOS study (M2301). The safety data in the CANTOS study encompassed a total of 32663 patient-years of treatment, including 6718 patients treated with canakinumab covering 21745 patient-years. The median follow-up was 3.8 years and median treatment duration was 3.5 years. The CANTOS study population was representative of a population of patients with prior myocardial infarction (MI) and elevated high sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L. Patients had a high incidence of comorbidities (hypertension, dyslipidemia and type 2 diabetes) at study entry which is characteristic of a population at high risk for cardiovascular (CV) events.

Additional safety data are provided by 6 completed Phase 2 studies with exposure up to 12 months and populations (atherosclerotic vascular disease and/or type 2 diabetes mellitus (T2DM)) considered relevant to the proposed indication (Table 1-1). Four of these studies had comparable treatment regimens (canakinumab 150 mg monthly and placebo) and included patients with atherosclerosis and diabetes (CACZ885I2206), abdominal aortic aneurysm (CACZ885X2201), atherosclerotic peripheral artery disease and intermittent claudication CACZ885M2201), and T2DM (CACZ885I2202).

The exposure in the pivotal trial and in the phase 2 trials is summarized in Table 1-7, 1-8, and 1-9.

Table 1-7 Duration of the double-blind phase in CANTOS (Safety set)

	Can 300 mg N=2263	Can 150 mg N=2285	Can 50 mg N=2170	Combined Can N=6718	Placebo N=3348	Total N=10066
Overall patient years	8716.2	8777.1	8043.6	25536.9	12680.9	38217.8
Number of patients by duration of double-blind phase (years) – n (%)						
< 1	51 (2.3)	59 (2.6)	46 (2.1)	156 (2.3)	82 (2.4)	238 (2.4)
>= 1 to <2	62 (2.7)	48 (2.1)	57 (2.6)	167 (2.5)	91 (2.7)	258 (2.6)
>= 2 to <3	185 (8.2)	190 (8.3)	209 (9.6)	584 (8.7)	289 (8.6)	873 (8.7)
>= 3 to <4	937 (41.4)	977 (42.8)	1009 (46.5)	2923 (43.5)	1451 (43.3)	4374 (43.5)
>= 4 to <5	789 (34.9)	762 (33.3)	791 (36.5)	2342 (34.9)	1172 (35.0)	3514 (34.9)
>= 5	239 (10.6)	249 (10.9)	58 (2.7)	546 (8.1)	263 (7.9)	809 (8.0)
Total	2263 (100)	2285 (100)	2170 (100)	6718 (100)	3348 (100)	10066 (100)
Duration of double-blind phase (years)						
n	2263	2285	2170	6718	3348	10066
Mean	3.85	3.84	3.71	3.80	3.79	3.80
SD	1.005	0.996	0.874	0.964	0.972	0.967
Median	3.89	3.85	3.74	3.82	3.83	3.83
Min, Max	0.06, 5.81	0.02, 5.79	0.01, 5.27	0.01, 5.81	0.05, 5.75	0.01, 5.81

Overall patient years are defined as the sum of all patient days [(end of double-blind phase – randomization date + 1) / 365.25].
The duration of double-blind phase is defined as ((latest of death date or date of last study assessment – date of randomization)+1).
Source: [Study M2301-Table 14.3-1.1e]

Table 1-8 Duration of treatment and exposure in CANTOS (Safety set)

	Can 300 mg N=2263	Can 150 mg N=2285	Can 50 mg N=2170	Combined Can N=6718	Placebo N=3348	Total N=10066
Overall patient years of treatment	7311.4	7454.7	6979.0	21745.1	10917.5	32662.6
Number of patients by duration of treatment (years) – n (%)						
< 1	278 (12.3)	273 (11.9)	232 (10.7)	783 (11.7)	380 (11.4)	1163 (11.6)
>= 1 to < 2	186 (8.2)	176 (7.7)	154 (7.1)	516 (7.7)	232 (6.9)	748 (7.4)
>= 2 to < 3	285 (12.6)	267 (11.7)	287 (13.2)	839 (12.5)	445 (13.3)	1284 (12.8)
>= 3 to < 4	799 (35.3)	837 (36.6)	874 (40.3)	2510 (37.4)	1237 (36.9)	3747 (37.2)
>= 4 to < 5	578 (25.5)	566 (24.8)	592 (27.3)	1736 (25.8)	893 (26.7)	2629 (26.1)
>= 5	137 (6.1)	166 (7.3)	31 (1.4)	334 (5.0)	161 (4.8)	495 (4.9)
Duration of treatment (years)						
n	2263	2285	2170	6718	3348	10066
Mean	3.23	3.26	3.22	3.24	3.26	3.24
SD	1.397	1.399	1.269	1.358	1.342	1.353
Median	3.47	3.47	3.46	3.47	3.49	3.47
Min, Max	0.06, 5.70	0.02, 5.79	0.01, 5.23	0.01, 5.79	0.05, 5.74	0.01, 5.79
Number of patients by duration of exposure (years) – n (%)						
< 1	288 (12.7)	282 (12.3)	239 (11.0)	809 (12.0)	395 (11.8)	1204 (12.0)
>= 1 to < 2	210 (9.3)	198 (8.7)	187 (8.6)	595 (8.9)	260 (7.8)	855 (8.5)
>= 2 to < 3	341 (15.1)	332 (14.5)	366 (16.9)	1039 (15.5)	537 (16.0)	1576 (15.7)
>= 3 to < 4	789 (34.9)	810 (35.4)	838 (38.6)	2437 (36.3)	1217 (36.4)	3654 (36.3)
>= 4 to < 5	531 (23.5)	536 (23.5)	520 (24.0)	1587 (23.6)	811 (24.2)	2398 (23.8)
>= 5	104 (4.6)	127 (5.6)	20 (0.9)	251 (3.7)	128 (3.8)	379 (3.8)
Duration of exposure (years)						
n	2263	2285	2170	6718	3348	10066
Mean	3.12	3.15	3.10	3.12	3.15	3.13
SD	1.382	1.381	1.259	1.343	1.328	1.338
Median	3.38	3.39	3.29	3.36	3.39	3.37
Min, Max	0.06, 5.70	0.02, 5.71	0.01, 5.23	0.01, 5.71	0.05, 5.69	0.01, 5.71

Overall patient-years of treatment is the sum of the patient days of treatment from first dose to last dose + 91 days including any temporary interruptions for all patients divided by 365.25.
The duration of treatment is defined as the time from 1st injection date to the first of (1) the last injection date plus 91 days, (2) the subject's death, (3) the subject's study completion visit during the study close-out period, or (4) the analysis cut-off.
The duration of exposure is defined as the time period in which the subject was under study drug (i.e. duration of treatment) minus number of days during which the period between doses of study drug exceeded 119 days.
Can.: Canakinumab (all doses are measured in mg).
Source: [Study M2301-Table 14.3-1.1a]

Table 1-9 Duration of treatment in multiple-dose Phase 2 studies (Safety set)

	I2206		X2201		M2201		I2202	
Duration	Can 150 mg N=95	Pbo N=94	Can 150 mg N=31	Pbo N=33	Can 150 mg N=18	Pbo N=20	Can 150 mg N=92	Pbo N=179
Duration (months)								
n	95	94	31	33	18	20	92	179
Mean	10.11	10.34	9.08	9.88	11.12	9.92	6.57	6.48
SD	3.794	3.554	4.321	3.453	2.802	3.738	1.986	2.311
Median	12.09	12.06	11.79	11.79	12.07	12.09	6.11	6.18
Min, Max	1.0, 13.7	1.0, 13.0	1.0, 12.0	1.9, 12.1	3.3, 13.8	3.0, 13.9	1.0, 14.9	0.6, 15.0
Duration categories - n (%)								
≥1 day - <1 mo	1 (1.1)	0	3 (9.7)	0	0	0	1 (1.1)	6 (3.4)
≥1 mo - <3 mo	10 (10.5)	7 (7.4)	3 (9.7)	2 (6.1)	0	0	1 (1.1)	3 (1.7)
≥3 mo - <6 mo	6 (6.3)	8 (8.5)	2 (6.5)	5 (15.2)	2 (11.1)	5 (25.0)	37 (40.2)	71 (39.7)
≥6 mo - <9 mo	5 (5.3)	3 (3.2)	2 (6.5)	1 (3.0)	1 (5.6)	1 (5.0)	47 (51.1)	81 (45.3)
≥9 mo - <12 mo	16 (16.8)	20 (21.3)	17 (54.8)	23 (69.7)	2 (11.1)	1 (5.0)	4 (4.3)	14 (7.8)
≥12 mo	57 (60.0)	56 (59.6)	4 (12.9)	2 (6.1)	13 (72.2)	13 (65.0)	2 (2.2)	4 (2.2)

Source: [SCS Appendix 1-Table 14.3.A-1.1]

Post-marketing exposure

Canakinumab was first approved in the US under the tradename Ilaris® for the treatment of CAPS and the International Birth Date (IBD) is 17-Jun-2009. The cumulative patient exposure from market experience (non-clinical trial) since the IBD up to 30-Jun-2017 is 15,260 patient-years.

Adverse events

Table 2-1 provides an overall summary of AEs in the CANTOS study. The rate of AEs, SAEs discontinuations of study treatment due to AEs and AEs leading to study treatment interruption was dose dependent with the highest rates in the Can 300 mg group, the lowest rate in the Can 50 mg group and a placebo rate that was overall in between the rate of the 50 mg and the 150 mg group.

Table 2-1 Overall summary of adverse events during the double-blind phase in CANTOS (Safety set)

	Can 300 mg N=2263 n (%)	Can 150 mg N=2285 n (%)	Can 50 mg N=2170 n (%)	Combined Can N=6718 n (%)	Placebo N=3348 n (%)	Total N=10066 n (%)
Patients with at least one AE [1]	1987 (87.8)	1970 (86.2)	1872 (86.3)	5829 (86.8)	2915 (87.1)	8744 (86.9)
AEs suspected to be related to study drug	355 (15.7)	350 (15.3)	267 (12.3)	972 (14.5)	474 (14.2)	1446 (14.4)
SAEs [1]	836 (36.9)	812 (35.5)	741 (34.1)	2389 (35.6)	1204 (36.0)	3593 (35.7)
Discontinued study treatment due to AEs [2]	175 (7.7)	164 (7.2)	143 (6.6)	482 (7.2)	245 (7.3)	727 (7.2)
Discontinued due to SAEs	135 (6.0)	130 (5.7)	117 (5.4)	382 (5.7)	198 (5.9)	580 (5.8)
Discontinued due to non-serious AEs	40 (1.8)	34 (1.5)	26 (1.2)	100 (1.5)	47 (1.4)	147 (1.5)
AEs leading to study treatment interruption [3]	268 (11.8)	270 (11.8)	228 (10.5)	766 (11.4)	399 (11.9)	1165 (11.6)

Clinical endpoints committee (CEC) confirmed and other pre-defined endpoints were not to be reported as AEs.
Can: Canakinumab
[1] AEs and SAEs include events with fatal outcomes.
[2] Includes permanent discontinuations due to an AE as identified on the AE page of the CRF.
[3] Includes temporary study drug interruptions due to an AE as identified on the AE pages of the CRF.
Source: [Study M2301-Table 14.3.1-1]

Infections and infestations was the most frequently affected primary SOC (Table 2-3). A higher rate of AEs on Canakinumab compared to Placebo was observed for the following SOC terms for the 150 mg and the 300 mg quarterly strength taken together (at both strengths increased or at on strength increased and at disorders, General disorders and administration site conditions, nervous system disorders, investigations, Injury, Poisoning and procedural conditions, renal and urinary disorders, skin and subcutaneous tissue disorders, psychiatric disorders, blood and lymphatic system disorders, hepatobiliary disorders, Immune system disorders.

A few of the common PTs (occurring in ≥ 5% in any group) showed numerical differences between the canakinumab and placebo groups (Table 2-4), including the following results:

- AEs with a higher rate in the canakinumab 150 mg group vs. placebo group included influenza (7.1% vs. 6.1%) and cellulitis (3.2% vs. 2.3%).

- Thrombocytopenia occurred at a higher rate for canakinumab 150 mg (1.5%) and canakinumab 300 mg group (2.2%) compared with placebo (1.3%). This corresponded to the higher rate of SOC “blood and lymphatic system disorders”.

- AEs with a higher rate in the placebo group vs. canakinumab 150 mg group included osteoarthritis (6.1% vs. 4.2%) and gout (3.0% vs. 1.3%).

Canakinumab 150 mg group had a higher incidence of viral upper respiratory tract infection than both 300 mg and placebo groups which were comparable (13.9% for 150 mg vs. 12.5% for 300 mg and 12.3% for placebo).

There was a higher rate of upper abdominal pain for canakinumab 150 mg (2.5% for 150 mg vs. 1.9% for placebo), but this was not seen for the related PT of abdominal pain which was less frequent on canakinumab 150 mg (2.9% vs. 3.8% for placebo). Canakinumab 150 mg group also had a higher incidence of acute kidney injury than both 300 mg and placebo groups (3.0% for 150 mg vs. 2.2% for 300 mg and 2.0% for placebo). Similarly, chronic kidney disease was observed more frequently in the 300 mg and in the 150 mg arm compared to placebo. This was not supported by other imbalances in renal AEs or by aggregate changes in laboratory measurements of eGFR though.

Relationship of adverse events to study treatment

The overall incidence of AEs suspected to be related to study drug in CANTOS were numerically higher in the Canackinumab 300 mg and 150 mg group as compared to the 50 mg group and Placebo. (15.7%, 15.3%, 12.3% and 14.2% for canakinumab 300 mg, 150 mg, 50 mg and placebo, respectively). The most frequently reported suspected drug-related AEs were in the SOC of infections and infestations (6.1%, 6.7%, 4.9% and 5.8%, respectively), followed by general disorders and administration site conditions (2.0%, 2.1%, 1.9% and 1.6%, respectively) and gastrointestinal disorders (1.1%, 1.6%, 1.1% and 1.6%, respectively). In the infections and infestations SOC, events of cellulitis, sepsis and pneumonia were more frequently suspected to be related to study drug in the canakinumab 300 mg and 150 groups than in the placebo group.

Severity of AEs.

The severity of AEs Severe in 24.1% of the patients, moderate in 40.5% and mild in 22.3%. Severe AEs were more frequently reported in the 300 mg arm (25.5%, 22.9%, 22.8% and 24.8% for canakinumab 300 mg, 150 mg, 50 mg and placebo, respectively). The most common SOC with severe AEs was infections and infestations, which showed a slightly higher rate in the canakinumab groups (7.8%, 7.5% and 7.3%, respectively) than in the placebo group (6.4%). This difference was driven in part by more severe AEs of cellulitis (1.0%, 0.9% and 0.6%, respectively, vs. 0.4% for placebo) and sepsis (1.2%, 1.2% and 1.0%, respectively, vs. 0.7%) in the canakinumab groups vs. the placebo group.

Serious adverse events and deaths

Deaths

All-cause mortality and CV death are pre-defined efficacy endpoints. All deaths were adjudicated by an independent CEC as mandated by the protocol. The most common cause of death was of cardiovascular origin (501 of 1081 deaths), followed by non-cardiovascular causes (414 total) and unknown causes but presumed cardiovascular (166 total) (Table 2-7). Overall mortality was numerically lower on canakinumab, with fewer CEC-confirmed deaths in the canakinumab groups compared with the placebo group (AER/100 patient-years: 2.76 and 2.73 for canakinumab 300 mg and 150 mg, respectively, vs. 2.98 for placebo). CV deaths were less frequent in the canakinumab groups vs. placebo group (AER/100 patientyears: 1.33 and 1.27 for canakinumab 300 mg and 150 mg, respectively, vs. 1.45 for placebo). The most common causes of CV deaths were congestive heart failure followed by MI. The incidence of unknown causes (presumed cardiovascular) was comparable across the treatment groups. Non-CV deaths were also less frequent in the canakinumab groups vs. placebo group (AER/100 patient-years: 1.02 and 1.08 for canakinumab 300 mg and 150 mg, respectively, vs. 1.12 for placebo). Malignancy was the most common cause of non-CV deaths and showed a lower rate for canakinumab, most notably the 300 mg group, compared with placebo (0.31 for 300 mg and 0.51 for 150 mg vs. 0.64 for placebo). The rate of deaths due to infection/sepsis was numerically higher for canakinumab vs. placebo, although the difference was small. The AER/100 patient-years of infection and sepsis deaths combined was 0.34, 0.28 and 0.18 in the canakinumab 300 mg, 150 mg, and placebo groups respectively, representing a difference of 0.10/100 patient-years between canakinumab 150 mg and placebo and 0.16/100 patient-years. The pattern of investigator-reported primary causes of death was similar to that from the CEC adjudication results between canakinumab 300 mg and placebo.

Table 2-7 CEC-confirmed primary causes of death during the double-blind phase in CANTOS (Safety set)

Primary cause of death	Can 300 mg N=2263 n (n/100py)	Can 150 mg N=2285 n (n/100py)	Can 50 mg N=2170 n (n/100py)	Combined Can N=6718 n (n/100py)	Placebo N=3348 n (n/100py)	Total N=10066 n (n/100py)
All-cause mortality	239 (2.76)	238 (2.73)	228 (2.85)	705 (2.78)	376 (2.98)	1081 (2.84)
CV death	115 (1.33)	110 (1.27)	94 (1.18)	319 (1.26)	182 (1.45)	501 (1.32)
Unknown (presumed cardiovascular)	36 (0.42)	34 (0.39)	43 (0.54)	113 (0.45)	53 (0.42)	166 (0.44)
Non-CV death	88 (1.02)	94 (1.08)	91 (1.14)	273 (1.08)	141 (1.12)	414 (1.09)
Malignancy	27 (0.31)	44 (0.51)	44 (0.55)	115 (0.45)	81 (0.64)	196 (0.52)
Infection/Sepsis	29 (0.34)	24 (0.28)	25 (0.31)	78 (0.31)	23 (0.18)	101 (0.27)
Respiratory failure	19 (0.22)	11 (0.13)	10 (0.13)	40 (0.16)	17 (0.14)	57 (0.15)
Other	13 (0.15)	15 (0.17)	12 (0.15)	40 (0.16)	20 (0.16)	60 (0.16)

CEC=Clinical Endpoints Committee; CV death, Non-CV death and Unknown death are presented based on adjudicated classification.
N=Total number of patients on each treatment; n=Total number of patients with events included in the analysis.
n/100 py=Total number of patients with event per 100 patient years (randomization date to first event date or to censoring dates used as denominator).
Source: [SCS Appendix 1-Table 14.3.2-7a]

Serious adverse events

Serious adverse events in CANTOS

For the overall incidence of SAEs there was numerically a dose relation over the dose range of Canakinumab investigated (Table 9-2). Overall the rate was comparable to placebo (36.9%, 35.5%, 34.1% and 36.0%, respectively, for canakinumab 300 mg, 150 mg, 50 mg and placebo.

- SAEs in the SOCs of infections and infestations and gastrointestinal disorders were numerically more frequent for canakinumab compared to placebo. Cardiac disorders were less frequent in the canakinumab groups than in the placebo group.

- Cardiac disorders: The lower incidence in canakinumab 150 mg group vs. placebo group was driven in part by lower rates of angina pectoris, angina unstable, coronary artery disease and cardiac arrest for canakinumab 150 mg. This is related to the efficacy of Canakinumab.

- Gastrointestinal disorders; Renal and urinary disorders; Reproductive system and breast disorders: There was a higher rate in the canakinumab 150 mg and 300 mg groups compared to the placebo group.

The most common SAEs are summarized in Table 2-10. Overall numerically higher rates of the most common AEs on treatment were observed for pneumonia, akute kidney injury, cellulitis and sepsis. The applicant states that the majority of these events occurred in the setting of other underlying causes of renal hypoperfusion.

Table 2-9 Serious adverse events by primary system organ class during the double-blind phase in CANTOS (Safety set)

System organ class	Can 300 mg N=2263 n (%)	Can 150 mg N=2285 n (%)	Can 50 mg N=2170 n (%)	Combined Can N=6718 n (%)	Placebo N=3348 n (%)	Total N=10066 n (%)
- Any SAE	836 (36.9)	812 (35.5)	741 (34.1)	2389 (35.6)	1204 (36.0)	3593 (35.7)
Infections and infestations	265 (11.7)	258 (11.3)	230 (10.6)	753 (11.2)	343 (10.2)	1096 (10.9)
Cardiac disorders	190 (8.4)	174 (7.6)	166 (7.6)	530 (7.9)	293 (8.8)	823 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	165 (7.3)	147 (6.4)	155 (7.1)	467 (7.0)	245 (7.3)	712 (7.1)
Gastrointestinal disorders	136 (6.0)	142 (6.2)	114 (5.3)	392 (5.8)	163 (4.9)	555 (5.5)
Respiratory, thoracic and mediastinal disorders	125 (5.5)	102 (4.5)	77 (3.5)	304 (4.5)	170 (5.1)	474 (4.7)
General disorders and administration site conditions	85 (3.8)	90 (3.9)	77 (3.5)	252 (3.8)	136 (4.1)	388 (3.9)
Injury, poisoning and procedural conditions	78 (3.4)	74 (3.2)	80 (3.7)	232 (3.5)	133 (4.0)	365 (3.6)
Musculoskeletal and connective tissue disorders	76 (3.4)	72 (3.2)	73 (3.4)	221 (3.3)	125 (3.7)	346 (3.4)
Renal and urinary disorders	70 (3.1)	87 (3.8)	58 (2.7)	215 (3.2)	98 (2.9)	313 (3.1)
Nervous system disorders	74 (3.3)	61 (2.7)	54 (2.5)	189 (2.8)	93 (2.8)	282 (2.8)
Vascular disorders	60 (2.7)	64 (2.8)	49 (2.3)	173 (2.6)	87 (2.6)	260 (2.6)
Metabolism and nutrition disorders	49 (2.2)	55 (2.4)	43 (2.0)	147 (2.2)	75 (2.2)	222 (2.2)
Hepatobiliary disorders	37 (1.6)	33 (1.4)	33 (1.5)	103 (1.5)	54 (1.6)	157 (1.6)
Blood and lymphatic system disorders	35 (1.5)	27 (1.2)	22 (1.0)	84 (1.3)	40 (1.2)	124 (1.2)
Psychiatric disorders	22 (1.0)	18 (0.8)	16 (0.7)	56 (0.8)	29 (0.9)	85 (0.8)
Eye disorders	14 (0.6)	22 (1.0)	9 (0.4)	45 (0.7)	25 (0.7)	70 (0.7)
Skin and subcutaneous tissue disorders	15 (0.7)	19 (0.8)	11 (0.5)	45 (0.7)	24 (0.7)	69 (0.7)
Reproductive system and breast disorders	16 (0.7)	15 (0.7)	13 (0.6)	44 (0.7)	18 (0.5)	62 (0.6)
Investigations	9 (0.4)	9 (0.4)	9 (0.4)	27 (0.4)	18 (0.5)	45 (0.4)
Ear and labyrinth disorders	7 (0.3)	10 (0.4)	9 (0.4)	26 (0.4)	12 (0.4)	38 (0.4)
Product issues	5 (0.2)	4 (0.2)	11 (0.5)	20 (0.3)	8 (0.2)	28 (0.3)
Endocrine disorders	4 (0.2)	5 (0.2)	2 (0.1)	11 (0.2)	8 (0.2)	19 (0.2)
Immune system disorders	2 (0.1)	3 (0.1)	6 (0.3)	11 (0.2)	3 (0.1)	14 (0.1)

Table 2-10 Most common SAEs (at least 1% in any group) by preferred term in CANTOS (Safety set)

Preferred term	Can 300 mg N=2262 n (%)	Can 150 mg N=2265 n (%)	Can 50 mg N=2175 n (%)	Combined Can N=6702 n (%)	Placebo N=3350 n (%)	Total N=10052 n (%)
- Any SAE	836 (36.9)	812 (35.5)	741 (34.1)	2389 (35.6)	1204 (36.0)	3593 (35.7)
Pneumonia	84 (3.7)	80 (3.5)	74 (3.4)	238 (3.5)	112 (3.3)	350 (3.5)
Non-cardiac chest pain	48 (2.1)	54 (2.4)	45 (2.1)	147 (2.2)	83 (2.5)	230 (2.3)
Angina pectoris	47 (2.1)	45 (2.0)	42 (1.9)	134 (2.0)	80 (2.4)	214 (2.1)
Angina unstable	43 (1.9)	38 (1.7)	38 (1.8)	119 (1.8)	68 (2.0)	187 (1.9)
Chronic obstructive pulmonary disease	32 (1.4)	33 (1.4)	19 (0.9)	84 (1.3)	48 (1.4)	132 (1.3)
Acute kidney injury	28 (1.2)	39 (1.7)	20 (0.9)	87 (1.3)	39 (1.2)	126 (1.3)
Cellulitis	35 (1.5)	32 (1.4)	19 (0.9)	86 (1.3)	30 (0.9)	116 (1.2)
Osteoarthritis	22 (1.0)	21 (0.9)	20 (0.9)	63 (0.9)	52 (1.6)	115 (1.1)
Sepsis	30 (1.3)	32 (1.4)	21 (1.0)	83 (1.2)	26 (0.8)	109 (1.1)

Clinical endpoints committee confirmed and other pre-defined endpoints were not to be reported as AEs.
Can.: Canakinumab
Preferred terms are presented in order of descending frequency of the total column
Source: [Study M2301-Table 14.3.1-8b]

Analysis of adverse events by organ system or syndrome

The majority of infection AEs consisted of non-serious upper respiratory tract infections. The incidence of investigator-reported infection SAEs and IAC-confirmed infections (which were mainly SAEs but also included medically important infections such as those treated with iv antibiotics) was 1-2% higher in the canakinumab 300 mg and 150 mg groups compared with the placebo group. The majority of infection AEs with an identified pathogen were viral infections. The proportion of patients with two or more IAC confirmed infections was higher for canakinumab 300 mg (n=58, 2.6%) and 150 mg (n=53, 2.3%) than for placebo (n=58, 1.7%).

Sepsis

Sepsis SAEs were higher across the canakinumab groups compared with the placebo group. The pattern of between-treatment differences was not influenced by age, diabetic status, or medical history of asthma or COPD.

Infectious pneumonia

Infectious Pneumonia SAEs were higher in the 150 mg and 300 mg canakinumab groups compared with the placebo group. The risk of infectious pneumonia (grouped term) was higher among patients with baseline asthma or COPD who are already at an elevated risk for pneumonia. There were no trends related to canakinumab dose, age, or diabetic status at baseline.

Post-procedural, wound and device related infections

There was almost a doubling in the incidence of post procedural, wound and device related infections for canakinumab 150 mg vs. placebo (1.1% and 0.6%, respectively). The most common PTs (≥ 0.1% total) were post-operative wound infection, wound infection, post procedural infection and device related infection. In addition, a few infections reported as ‘cellulitis’ and ‘staphylococcal infection/sepsis’ occurred in the setting of recent surgical procedures, devices and prostheses (including infections of pacemakers, implantable cardiac defibrillators, vascular grafts and joint prostheses).

Opportunistic infections

Overall, there were no clinically meaningful differences in potential opportunistic infections between the canakinumab and placebo groups.

Malignancies

Overall, the data do not indicate an increased risk for the development of malignancies or for the risk of death due to malignancies.

The applicant has provided a detailed discussion on malignancies and the finding of a lower rate of pulmonary neoplasms in the Canakinumab arms including an analysis in comparison to epidemiological data.

a) Comparison with epidemiologic data.

- The applicant has analysed the CANTOS data in comparison to the expected rates of malignancies using the US Surveillance, Epidemiology, and End Results (SEER) Program as the reference dataset. When comparing neoplasms in the Canakinumab and in the placebo group with epidemiological data the overall rate of neoplasm was higher in Canakinumab. The exploratory comparison by race raises the possibility that the neoplasm rate in the Asian population in the control group was higher than expected whereas in the canakinumab group it tended to be lower in Asians than in other race groups. The rate observed vs. expected malignancies was similar for Canakinumab and Placebo in the Caucasian population indicating that there was no obvious difference between placebo and Canakinumab treatment on the overall rate of malignancies. The rate of lung cancers was considerably higher in CANTOS than expected from the epidemiologic database. It was around three fold higher in the placebo group and roughly two fold higher than expected in the Canakinumab group than expected. The reason for this over-representation is unknown but indicates that the results on lung cancer have to be analysed with caution.

In summary, the analyses in comparison with epidemiological data have clear limitations but provide additional insight into the CANTOS results on malignancies and lung-cancer. The rate of malignancies was not increased by Canakinumab when compared with the expected rate from the epidemiological data.

b)Time course

The time to event analysis (first occurrence of lung cancer event) indicated a difference for lung cancers during the early phase of treatment. About 30% of first lung cancer AEs were observed during the first year in the placebo and in the low dose groups but not in the 300 mg group (less than 15%). Exclusion of 18 subjects with early onset of confirmed primary lung cancer events (defined as occurrence of primary lung cancer within 6 months of randomization) did not impact the imbalance favouring Canakinumab. Irrespectively, the low number of early events in the 300 mg arm may indicate baseline differences that were also relevant for the mortality analyses. Most of the difference in the mortality rate were seen immediately after initiation of the therapy which is a finding that is expected with baseline imbalances but not necessarily with a treatment effect. Considering the overall low number of events (first occurrence of lung cancer event) and of lung cancer associated mortality no reliable conclusions can be drawn regarding lung cancer.

Overall, the results do not indicate an increased risk for malignancies/death to malignancies of long term treatment with canakinumab in the CANTOS population.

Neutropenia

There were dose-dependent decreases in mean neutrophils early after initiation of treatment, which stabilized after two weeks. Most patients' neutrophil counts remained within the normal range. The majority of neutrophil decreases reported as laboratory findings were of CTC Grade 1 or 2. CTC Grade 3 or 4 decreases were transient (only occurred at one time point) and were not associated with an increased risk of infections

Thrombocytopenia

Overall, a dose-dependent increase in thrombocytopenia AEs and mild platelet count abnormalities (CTC Grade 1) were observed for canakinumab relative to placebo. Grade 2 abnormalities occurred at low and comparable rates between canakinumab 150 mg and placebo. More severe abnormalities in platelet counts (Grade 3 or 4) were rare and the rates were comparable across the treatment groups. None of the Grade 3 or 4 platelet count abnormalities was associated with clinically significant bleeding.

Hepatic safety

The incidence of mild hepatic transaminase elevations (mainly >3×upper limit of normal [ULN] but <5×ULN) and mild total bilirubin elevations (>1.5×ULN but <2×ULN) was numerically higher for canakinumab compared to placebo. Most elevations were transient, reversible and not dose-dependent. There were few combined elevations of transaminases and total bilirubin, and no confirmed cases of Hy's Law. The increased transaminases were not associated with clinically relevant AEs.

Interaction with vaccines

Overall, no interactions were observed between canakinumab and inactivated or live (attenuated) vaccines. Time to first infection by vaccination status within the 3 months prior to baseline for investigator reported infections, investigator reported serious infections and IAC-confirmed infections did not show any clinically meaningful differences between the treatment groups. Additionally, there was no evidence of herpes zoster infection related to receipt of Herpes Zoster live (attenuated) vaccine. as reflected in the proposed label, prior to initiation of canakinumab therapy, it is recommended by the applicant that patients complete all immunizations in accordance with current immunization guidelines. If a patient receives a live vaccine during treatment with canakinumab, the next dose of canakinumab should be administered no sooner than 3 months after the administration of the live vaccine. Data from CANTOS showed no interaction between canakinumab and inactivated vaccines.

Injection site reactions

Injection site reactions occurred at low and comparable rates across the treatment groups.

Disorders of lipoprotein metabolism

Overall, the incidence of dyslipidemia AEs was higher in the canakinumab groups compared with the placebo group (Table 2-37). The incidence of severe dyslipidemia AEs was very low, and there were no reported SAEs. There was an early increase of 2-5% in mean triglyceride levels which persisted throughout the study (geometric mean change from baseline range: 1.00-1.05 over Month 0.5-Month 54). The increases in triglycerides were modest and not dose dependent. Similar to the elevated triglyceride levels, there were small (2-4%) increases in total cholesterol as well as non-HDL cholesterol and VLDL-cholesterol but meaningful increase in LDL-cholesterol compared to placebo. The incidence of acute pancreatitis AEs was higher in the 300 mg arm only (0.8%, 0.5%, 0.5% and 0.5%, respectively, for canakinumab 300 mg, 150 mg, 50 mg and placebo).

Hypoglycemia

There was no consistently higher rate of hypoglycemic events on treatment.

Laboratory findings

Hematology

There was a greater incidence of notably abnormal decreases in platelets, leukocytes and neutrophils in canakinumab groups compared with the placebo group.

Clinical chemistry

There was a higher incidence of AST >100 U/L, ALT >110 U/L and urate >595 µmol/L in the canakinumab groups compared with the placebo group.

Safety in special populations

The majority (62.5%) of patients in CANTOS study were < 65 years of age, 37.5% were ≥ 65 years; 9.2% ≥ 75 years. The incidence of adverse events and selected safety topics of interest by age subgroups during the double-blind phase in CANTOS is summarized Table 2-46.

Infection AEs were more frequent in the older age groups (≥ 65 or ≥ 75 years) in all treatment groups but not particulary increased when comparing patients on treatment with the respective placebo groups. The profile of total SAEs and infection SAEs by age subgroups were similar to those in the overall population with some exceptions

Death due to respiratory failure

There was more than a doubling of the rate of death due to respiratory failure in in patients ≥ 65 and ≥ 75 years with the 300 mg dose of Canakinumab. However, up to a dose of 150 mg the rate was not increased. Therefore it is not an issue for the 150 mg dose.

Immunogenicity/Allergenicity

There was a clear dose relation in patients ≥ 65 and ≥ 75 years. In patients ≥ 65 years the event rate was (Placebo, 50 mg, 150 mg, 300 mg Canakinumab) 1.7, 1.8, 2.8, 3.7%, in the patients ≥ 75 years it was 0.7, 1.0, 3.2, and 3.4%. Overall there were 70 events in the Canakinumab arms and 21 in the placebo arm in patients ≥ 65 years of age. Since the pattern was preserved in the very elderly patients it appears to be a robust finding that should be reflected in the SmPC.

Acute kidney injury and chronic kidney disease

There was a clear dose relation in patients ≥ 65 and ≥ 75 years. In patients ≥ 65 the event rate was (Placebo, 50 mg, 150 mg, 300 mg Canakinumab) 13.8, 14.4, 17.3, 16.1%, in the patients ≥ 75 years it was 18.1, 16.3, 22.9, 23.7%. Further clarification is requested on this issue (OC)

The following AEs appear to be a particular issue in the elderly population > 65 years and/or > 75 years. Infections (infection/sepsis), long term effects on kidney function, increased uric acid, immunogenicity/allergenicity, respiratory failure and in particular thrombocytopenia.

Thrombocytopenia

The rate of thrombocytopenia was higher in patients ≥65 and ≥75 years in the placebo arm and in the canakinumab treatment arms. Despite of some variability there was a clear dose relation of this AE in all age groups. In patients < 65 years the event rate was (Placebo, 50 mg, 150 mg, 300 mg Canakinumab) 1.2, 1.3, 1.7, and 1.8%, in patients ≥ 65 years 2.1, 3.2, 2.5, and 4.2%, in patients ≥ 75 years it was 3.0, 4.0, 3.7, and 5.8%. It is concluded that thrombocytopenia is more frequently in elderly patients and the effect of Canakinumab on thrombocytopenia pronounced in the elderly population. The SmPC should be amended accordingly.

	Can 300 mg N=2263 n (%)	Can 150 mg N=2285 n (%)	Can 50 mg N=2170 n (%)	Placebo N=3348 n (%)
Injection site reactions	0	0	0	0

AE=adverse events; Can=canakinumab; N=; n=; SAE=serious adverse event; SOC=system organ class

Infection AEs are from the Infections and Infestations SOC which include secondary path terms.

Source: [EU Table 2.24-1]

Table 2-46 Incidence of events of specific safety concerns by extended age subgroups and treatment during the double-blind phase (Safety set)

	< 65 years		≥ 65 to < 75 years		≥ 75 to < 85 years		≥ 85 years	
	Can 150 mg N=1429 n (%)	Placebo N=2092 n (%)	Can 150 mg N=638 n (%)	Placebo N=957 n (%)	Can 150 mg N=200 n (%)	Placebo N=288 n (%)	Can 150 mg N=18 n (%)	Placebo N=11 n (%)
Total AEs	1200 (84.0)	1788 (85.5)	568 (89.0)	859 (89.8)	186 (93.0)	258 (89.6)	16 (88.9)	10 (90.9)
Total SAEs	426 (29.8)	612 (29.3)	272 (42.6)	419 (43.8)	102 (51.0)	164 (56.9)	12 (66.7)	9 (81.8)
Death	52 (3.6)	62 (3.0)	42 (6.6)	72 (7.5)	26 (13.0)	44 (15.3)	5 (27.8)	3 (27.3)
Investigator-reported hospitalization or prolongation of hospitalization for heart failure	53 (3.7)	106 (5.1)	52 (8.2)	64 (6.7)	30 (15.0)	32 (11.1)	0	1 (9.1)
AE leading to drop-out	76 (5.3)	107 (5.1)	65 (10.2)	95 (9.9)	22 (11.0)	40 (13.9)	1 (5.6)	3 (27.3)
Psychiatric disorders (SOC)	178 (12.5)	255 (12.2)	64 (10.0)	92 (9.6)	34 (17.0)	33 (11.5)	4 (22.2)	2 (18.2)
Nervous system disorders (SOC)	338 (23.7)	483 (23.1)	160 (25.1)	240 (25.1)	66 (33.0)	88 (30.6)	5 (27.8)	7 (63.6)
Accidents and injuries (SMQ)	225 (15.7)	313 (15.0)	116 (18.2)	166 (17.3)	42 (21.0)	68 (23.6)	8 (44.4)	4 (36.4)
Cardiac disorders (SOC)	333 (23.3)	459 (21.9)	136 (21.3)	246 (25.7)	50 (25.0)	91 (31.6)	5 (27.8)	5 (45.5)
Vascular disorders (SOC)	283 (19.8)	405 (19.4)	143 (22.4)	220 (23.0)	55 (27.5)	69 (24.0)	3 (16.7)	5 (45.5)
Cerebrovascular disorders (SOC)	0	0	0	0	0	0	0	0
Infections and infestations (SOC)	718 (50.2)	1002 (47.9)	360 (56.4)	516 (53.9)	114 (57.0)	163 (56.6)	11 (61.1)	6 (54.5)
Anticholinergic syndrome (PT)	0	0	0	0	0	0	0	0
Quality of life decreased (PT)	0	0	0	0	0	0	0	0
Postural hypotension (PT), fall (PT), black outs (Loss of consciousness PT), syncope (PT), dizziness (PT), ataxia (PT), fractures (HLGT)	102 (7.1)	142 (6.8)	55 (8.6)	84 (8.8)	33 (16.5)	47 (16.3)	3 (16.7)	3 (27.3)

AE=Adverse event; Can=Canakinumab; HLGT=High level group term; PT=Preferred term; SAE=Serious adverse event; SOC=System organ class
A patient with multiple AEs within a category is only counted once.
Source: [EU Table 2.24-2]

Immunological events

Immunogenicity, Allergenicity and Autoimmunity reactions

Overall, the incidence of immunogenicity/allergenicity AEs was higher in the Canakinumab groups. The risk of immunogenicity/allergenicity AEs relative to placebo was HR=1.47, 1.04 and 1.11 for Canakinumab 300 mg, 150 mg and 50 mg vs. Placebo. Treatment-emergent binding Anti-drug antibodies (ADA) were detected in low and comparable proportions of patients across all treatment groups (0.3% to 0.5%) and were not associated with any immunogenicity-related AE or altered hsCRP response. None of the ADA-positive samples that were tested showed neutralizing antibodies. There were no allergic events associated with positive ADA findings.

The incidence of autoimmunity AEs was higher in the Canakinumab groups with more events at higher doses e.g. for Psoriasis a doubling of the event rate was observed for the 300 mg arm and the 50 mg arm.

Safety related to drug-drug interactions and other interactions

PK interactions

Monoclonal antibodies are not metabolized by the cytochrome P450 (CYP) system, and their mechanism of elimination is via catabolism, different from metabolic or renal pathways of elimination for small molecules. Thus, no formal clinical drug interaction studies between canakinumab and other medicinal products were performed or required for the initial autoinflammatory indication approvals or the currently proposed CV risk reduction indication. Patients in CANTOS who were treated with canakinumab along with background therapies showed similar PK profiles compared to those collected from other studies, suggesting that canakinumab PK was unaffected by most common co-medications in patients with prior MI. There was no evidence of a drug interaction occurring with statins in CANTOS (most commonly used statins in all treatment groups were atorvastatin 51.1%, simvastatin 28.9%, rosuvastatin 24.1%, others less than 5.5%).

In vitro studies suggest that IL-1β does not have any meaningful suppression effect on CYP3A in patients with inflammation based diseases (Dickmann et al 2012). A recently published clinical drug interaction study using a potent monoclonal antihuman IL-6 antibody (Zhuang et al 2015) showed moderate changes in CYP probe substrates levels. Comparison of *in vitro* 3A suppression potency

between IL-6 and IL-1β indicated that IL-6 is 6-fold more potent than IL-1β (Dickmann et al 2012 and Dickmann et al 2011). Taken these theoretical considerations together, a risk associated with potential drug-drug interactions between canakinumab and concomitant drugs metabolized by the affected CYP enzymes may be relevant to narrow therapeutic index drugs.

Therefore, in the proposed labelling (consistent with the approved indications), it is recommended that upon initiation of canakinumab in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring of the effect or of the active substance concentration be performed and the individual dose of the medicinal product adjusted as necessary.

PD interactions

Data from anakinra (an IL-1 receptor antagonist that blocks both IL-1α and IL-1β), suggested a risk of a pharmacodynamics (PD) interaction with immunosuppressants, resulting in an increased risk of serious infections and neutropenia when administered with a TNF inhibitor. Concomitant use of immunosuppressant medications was not permitted in the CANTOS protocol. Consistent with the approach for other indications of canakinumab, concomitant use of canakinumab with TNF inhibitors or other agents that block IL-1 is not recommended.

Vaccination

There was no evidence of any interactions with inactivated or live (attenuated) vaccines in canakinumab-treated patients in CANTOS. The issue regarding vaccination has been addressed as part of the previous application for the approved indications.

The canakinumab label includes a warning that live vaccines should not be given concurrently with canakinumab. It is recommended that patients complete all immunizations in accordance with current immunization guidelines prior to initiating canakinumab therapy. If a patient receives a live vaccine during treatment with canakinumab, the next dose of canakinumab should be administered within 3 months after the administration of the live vaccine.

Discontinuation due to AES

Adverse events leading to study drug discontinuation

In Cantos the percentage of patients who had an AE leading to discontinuation during the double-blind phase was similar across the treatment groups (7.7%, 7.2%, 6.6% and 7.3% for 300 mg, 150 mg, 50 mg and placebo, respectively). The protocol mandated that study drug be discontinued on diagnosis of any malignancy except for excised basal cell carcinoma. In keeping with this and with the general pattern of malignancies in this population, the most common SOC of AEs leading to discontinuation was neoplasms, malignant and unspecified tumors which showed similar distribution across the treatment groups (4.6%, 3.7%, 4.1%, and 4.3%, respectively). The malignancies most frequently causing discontinuation were prostate cancer and malignant lung neoplasms. Infection SAEs led to discontinuation in more patients in the canakinumab groups than in the placebo group (0.8%, 0.9%, 0.5% and 0.3%, respectively, for canakinumab 300 mg, 150 mg, 50 mg and placebo). Pneumonia and sepsis were the most frequent reasons for premature study treatment discontinuations within the infections and infestations SOC.

Overall, a small number of patients discontinued due to an AE in the multiple-dose Phase studies. Consistent with CANTOS, the incidence of AEs leading to discontinuation in the multiple-dose studies was comparable between the canakinumab 150 mg monthly and placebo groups. The most common AEs leading to discontinuation were in the SOCs of cardiac disorders, neoplasms benign, malignant and unspecified and nervous system disorders. AEs in the SOC of infections and infestations led to discontinuation in a low and comparable percentage of patients between the two treatment groups.

In the single-dose studies, no patient discontinued due to an AE.

Adverse events leading to temporary dose interruption

The percentage of patients with an AE that led to temporary dose interruption (i.e., a missed dose) during the double-blind phase was similar across the treatment groups (11.8%, 11.8%, 10.5% and 11.9% for 300 mg, 150 mg, 50 mg and placebo, respectively). The most common SOC of AEs causing temporary dose interruption was infections and infestations which occurred at rates that were broadly comparable across the treatment groups (5.1%, 5.8%, 4.9% and 4.9%, respectively).

3.3.10. Discussion on clinical safety

Canakinumab has an established safety profile in previously approved indications not related to this application. The primary source of safety data for canakinumab in the target population for CV risk prevention is the pivotal CANTOS study (M2301) with 10,066 patients covering a total of 32662.6 patient-years of treatment. As opposed to the previously approved indications the CANTOS study population was representative of a population of patients with prior myocardial infarction (MI) and elevated high sensitivity C-reactive protein (hsCRP) $\geq$ 2 mg/L. Patients had a high incidence of comorbidities (hypertension, dyslipidemia and type 2 diabetes) at study entry which is characteristic of a population at high risk for cardiovascular (CV) events. Additional safety data are provided by 6 completed Phase 2 studies with exposure up to 12 months and populations (atherosclerotic vascular disease and/or type 2 diabetes mellitus (T2DM)) considered relevant to the proposed indication. Across all existing approved indications, the cumulative exposure to canakinumab up to 30-Jun-2017 is 4361 patient-years in Novartis-sponsored completed clinical trials, 7078 patient-years in all clinical trials including IIT and compassionate use programs, and 15,260 patient-years from market experience.

Adverse events

Infections and infestations was the most frequently affected primary SOC. A higher rate of AEs on Canakinumab compared to Placebo was observed for the following SOC terms for the 150 mg and the 300 mg quarterly strength taken together (at both strengths increased or at one strength increased and at the other strength similar to placebo): Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, nervous system disorders, investigations, Injury, Poisoning and procedural conditions, renal and urinary disorders, skin and subcutaneous tissue disorders, psychiatric disorders, blood and lymphatic system disorders, hepatobiliary disorders, Immune system disorders.

The severity of AEs was severe in 24.1% of the patients, moderate in 40.5% and mild in 22.3%. Severe AEs were more frequently reported in the 300 mg arm (25.5%, 22.9%, 22.8% and 24.8% for canakinumab 300 mg, 150 mg, 50 mg and placebo, respectively). The most common SOC with severe AEs was infections and infestations, which showed a slightly higher rate in the canakinumab groups (7.8%, 7.5% and 7.3%, respectively) than in the placebo group (6.4%). This difference was driven in part by more severe AEs of cellulitis (1.0%, 0.9% and 0.6%, respectively, vs. 0.4% for placebo) and sepsis (1.2%, 1.2% and 1.0%, respectively, vs. 0.7%) in the canakinumab groups vs. the placebo group.

A possible trend to higher rates with increasing dose was observed in

- Cellulitis AEs were more frequent in both canakinumab 300 mg and 150 mg groups than in the 50 mg group which was comparable to placebo. A similar pattern was also seen for influenza AEs (i.e., higher for canakinumab 300 mg and 150 mg vs. 50 mg and placebo).

- Thrombocytopenia AEs were more frequent in the canakinumab 300 mg group, while the rates for the canakinumab 150 mg and 50 mg groups were comparable to placebo.

- Additionally, abdominal pain upper was more frequent for canakinumab 300 mg than in the other dose groups, but this was not observed for the related PT of abdominal pain.

A dose-dependent increase with higher rates observed for canakinumab 300 mg compared with the other canakinumab dose groups was observed for sepsis and for safety topics of interest (per grouped MedDRA terms) of neutropenia , thrombocytopenia and elevated triglycerides.

Deaths

All-cause mortality and CV death are pre-defined efficacy endpoints. All deaths were adjudicated by an independent CEC as mandated by the protocol. The most common cause of death was of cardiovascular origin (501 of 1081 deaths), followed by non-cardiovascular causes (414 total) and unknown causes but presumed cardiovascular (166 total) (Table 2-7). Overall mortality was numerically lower on canakinumab, with fewer CEC-confirmed deaths in the canakinumab groups compared with the placebo group (AER/100 patient-years: 2.76 and 2.73 for canakinumab 300 mg and 150 mg, respectively, vs. 2.98 for placebo). CV deaths were less frequent in the canakinumab groups vs. placebo group (AER/100 patientyears: 1.33 and 1.27 for canakinumab 300 mg and 150 mg, respectively, vs. 1.45 for placebo).

Malignancy was the most common cause of non-CV deaths and showed a lower rate for canakinumab, most notably the 300 mg group, compared with placebo (0.31 for 300 mg and 0.51 for 150 mg vs. 0.64 for placebo). However, this finding showed large regional differences between Asian patients (numerically reduced rates of non fatal neoplasms) and Caucasian Patients (similar event rates in the Placebo group and the Canakinumab groups). The rate of deaths due to infection/sepsis was numerically higher for canakinumab vs. placebo, although the difference was small. The AER/100 patient-years of infection and sepsis deaths combined was 0.34, 0.28 and 0.18 in the canakinumab 300 mg, 150 mg, and placebo groups respectively, representing a difference of 0.10/100 patient-years between canakinumab 150 mg and placebo and 0.16/100 patient-years.

The incidence of infections AEs reported with a fatal outcome was numerically higher in the canakinumab groups than in the placebo group. The most frequent infection PTs with a reported fatal outcome overall were pneumonia, sepsis and septic shock. A clinical review of patients who died from an infection or sepsis (i.e., those with primary causes of death due to infection or sepsis per the CEC or the investigator) revealed that a number of the underlying infections were pneumonias, cellulitis/abscesses and related infections (particularly in patients with T2DM), and infections related to surgical procedures or devices.

The incidence of respiratory disorder AEs with a fatal outcome was higher in the Canakinumab 300 mg arm and similar in the other arms and placebo, with respiratory failure as the most frequently reported PT. There were no other notable imbalances in SOCs or safety topics of interest with a fatal outcome.

Serious adverse events

- SAEs in the SOCs of infections and infestations and gastrointestinal disorders were numerically more frequent for canakinumab compared to placebo. Cardiac disorders were less frequent in the canakinumab groups than in the placebo group.

- Cardiac disorders: The lower incidence in canakinumab 150 mg group vs. placebo group was driven in part by lower rates of angina pectoris, angina unstable, coronary artery disease and cardiac arrest for canakinumab 150 mg. This is related to the efficacy of Canakinumab.

- Gastrointestinal disorders; Renal and urinary disorders; Reproductive system and breast disorders: There was a higher rate in the canakinumab 150 mg and 300 mg groups compared to the placebo group.

Analysis of adverse events by organ system or syndrome

The majority of infection AEs consisted of non-serious upper respiratory tract infections. The incidence of investigator-reported infection SAEs and IAC-confirmed infections (which were mainly SAEs but also included medically important infections such as those treated with iv antibiotics) was 1-2% higher in the canakinumab 300 mg and 150 mg groups compared with the placebo group. The majority of infection AEs with an identified pathogen were viral infections. The proportion of patients with two or more IAC confirmed infections was higher for canakinumab 300 mg (n=58, 2.6%) and 150 mg (n=53, 2.3%) than for placebo (n=58, 1.7%).

Sepsis

Sepsis SAEs were higher across the canakinumab groups compared with the placebo group. The pattern of between-treatment differences was not influenced by age, diabetic status, or medical history of asthma or COPD.

Infectious pneumonia

Infectious Pneumonia SAEs were higher in the 150 mg an 300 mg canakinumab groups compared with the placebo group. The risk of infectious pneumonia (grouped term) was higher among patients with baseline asthma or COPD who are already at an elevated risk for pneumonia. There were no trends related to canakinumab dose, age, or diabetic status at baseline.

Post-procedural, wound and device related infections

There was almost a doubling in the incidence of post procedural, wound and device related infections for canakinumab 150 mg vs. placebo (1.1% and 0.6%, respectively). The most common PTs (≥ 0.1% total) were post-operative wound infection, wound infection, post procedural infection and device related infection. In addition, a few infections reported as ‘cellulitis’ and ‘staphylococcal infection/sepsis’ occurred in the setting of recent surgical procedures, devices and prostheses (including infections of pacemakers, implantable cardiac defibrillators, vascular grafts and joint prostheses).

Opportunistic infections

Overall, there were no clinically meaningful differences in potential opportunistic infections between the canakinumab and placebo groups.

Malignancies

Overall, the data do not indicate an increased risk for the development of malignancies or for the risk of death due to malignancies.

Neutropenia

There were dose-dependent decreases in mean neutrophils early after initiation of treatment, which stabilized after two weeks. Most patients' neutrophil counts remained within the normal range. The majority of neutrophil decreases reported as laboratory findings were of CTC Grade 1 or 2. CTC Grade 3 or 4 decreases were transient (only occurred at one time point) and were not associated with an increased risk of infections

Thrombocytopenia

Overall, a dose-dependent increase in thrombocytopenia AEs and mild platelet count abnormalities (CTC Grade 1) were observed for canakinumab relative to placebo. Grade 2 abnormalities occurred at low and comparable rates between canakinumab 150 mg and placebo. More severe abnormalities in platelet counts (Grade 3 or 4) were rare and the rates were comparable across the treatment groups. None of the Grade 3 or 4 platelet count abnormalities was associated with clinically significant bleeding.

Hepatic safety

The incidence of mild hepatic transaminase elevations (mainly >3×upper limit of normal [ULN] but <5×ULN) and mild total bilirubin elevations (>1.5×ULN but <2×ULN) was numerically higher for canakinumab compared to placebo. Most elevations were transient, reversible and not dose-dependent. There were few combined elevations of transaminases and total bilirubin, and no confirmed cases of Hy's Law. The increased transaminases were not associated with clinically relevant AEs.

Interaction with vaccines

Overall, no interactions were observed between canakinumab and inactivated or live (attenuated) vaccines. Time to first infection by vaccination status within the 3 months prior to baseline for investigator reported infections, investigator reported serious infections and IAC-confirmed infections did not show any clinically meaningful differences between the treatment groups. Additionally, there was no evidence of herpes zoster infection related to receipt of Herpes Zoster live (attenuated) vaccine. as reflected in the proposed label, prior to initiation of canakinumab therapy, it is recommended by the applicant that patients complete all immunizations in accordance with current immunization guidelines. If a patient receives a live vaccine during treatment with canakinumab, the next dose of canakinumab should be administered no sooner than 3 months after the administration of the live vaccine. Data from CANTOS showed no interaction between canakinumab and inactivated vaccines.

Injection site reactions

Injection site reactions occurred at low and comparable rates across the treatment groups.

Disorders of lipoprotein metabolism

Overall, the incidence of dyslipidemia AEs was higher in the canakinumab groups compared with the placebo group (Table 2-37). The incidence of severe dyslipidemia AEs was very low, and there were no reported SAEs. There was an early increase of 2-5% in mean triglyceride levels which persisted throughout the study (geometric mean change from baseline range: 1.00-1.05 over Month 0.5-Month 54). The increases in triglycerides were modest and not dose dependent. Similar to the elevated triglyceride levels, there were small (2-4%) increases in total cholesterol as well as non-HDL cholesterol and VLDL-cholesterol but meaningful increase in LDL-cholesterol compared to placebo. The incidence of acute pancreatitis AEs was higher in the 300 mg arm only (0.8%, 0.5%, 0.5% and 0.5%, respectively, for canakinumab 300 mg, 150 mg, 50 mg and placebo).

Hypoglycemia

There was no consistently higher rate of hypoglycemic events on treatment.

Laboratory findings

Hematology

There was a greater incidence of notably abnormal decreases in platelets, leukocytes and neutrophils in canakinumab groups compared with the placebo group.

Clinical chemistry

There was a higher incidence of AST >100 U/L, ALT >110 U/L and urate >595 µmol/L in the canakinumab groups compared with the placebo group.

Immunogenicity, Allergenicity and Autoimmunity reactions

Overall, the incidence of immunogenicity/allergenicity AEs was higher in the Canakinumab groups. The risk of immunogenicity/allergenicity AEs relative to placebo was HR=1.47, 1.04 and 1.11 for Canakinumab 300 mg, 150 mg and 50 mg vs. Placebo. Treatment-emergent binding Anti-drug antibodies (ADA) were detected in low and comparable proportions of patients across all treatment groups (0.3% to 0.5%) and were not associated with any immunogenicity-related AE or altered hsCRP response. None of the ADA-positive samples that were tested showed neutralizing antibodies. There were no allergic events associated with positive ADA findings.

The incidence of autoimmunity AEs was higher in the Canakinumab groups with more events at higher doses e.g. for Psoriasis a doubling of the event rate was observed for the 300 mg arm and the 50 mg arm.

Assessment of paediatric data on clinical safety

N/A

3.3.11. Conclusions on clinical safety

In summary, the safety profile of Canakinumab in patients at increased CV risk is in part consistent with the safety profile known from approved indications but specific safety concerns need to be addressed.

Overall, safety issues already identified in previous applications were also relevant in this group of patients but due to different patient characteristics some aspects not previously addressed were of relevance and some issues should be addressed by the applicant (OC).

- Some AEs are not included in section 4.8 of the SPC or require additional clarificaqtion i.e. akute kidney disease, chronic kidney disease, peripheral oedema, psoriasis and gastrointestinal disorders. In particular, some AEs that were of particular importance in elderly patients (acute kidney injury and chronic kidney disease(allergenicity and immunological reactions) should be included in the SmPC (**LoQ/OC)**
- A commitment to monitor for the following AEs with unclear relation to Canakinumab therapy should be provided:
    - o - hypoasthesia,
    - o - renal AEs including acute kidney injury and chronic kidney disease
    - o - GIT AEs including haemorrhage, gastritis and ulcer

- o - Allergic reactions including anaphylactic reaction, angiooedema, urticaria, eyelid oedema, swelling of face, serious immunogenicity/allergenicity events

- A statement regarding a lower rate of neoplasms on treatment should not be included in section 4.8 of the SmPC. There was almost a doubling in the incidence of post procedural, wound and device related infections for canakinumab 150 mg vs. placebo (1.1% and 0.6%, respectively). This is relevant in the target group of patients with CV disease. The applicant has included a warning in the SmPC but is asked to further discuss, whether specific advice should be given on the timing for implantation procedures and dosing of Canakinumab (**LoQ / OC)**
- The number of pneumonia deaths in the whole CANTOS should be given.
- A warning regarding de novo administration of Canakinumab in patients with grade 3 or 4 neutropenia and thrombocytopenia should be included in the SmPC

Transient increases in urate levels should be included in the SmPC (laboratory abnormalities) **The following issues should be included in the safety specification:**

- There was almost a doubling in the incidence of post procedural, wound and device related infections for canakinumab 150 mg vs. placebo (1.1% and 0.6%, respectively). This is relevant in the target group of patients with CV disease. A considerable number of these patients is subject to implantation of pacemakers, implantable defibrillators, stents, mitral clips or valves. Considering the long duration of action either device implantation may become necessary in some patients while on active treatment or procedures may be postponed which may be associated with a risk on its own. The risk may not be fully covered by a wording in the SmPC.

3.4. Risk management plan

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Infections
Important potential risks	Opportunistic infections Malignancy Pharmacodynamic interaction with live vaccines
Missing information	Use in pregnancy and lactation Long term safety data

3.4.1. Conclusions on the RMP

Treatment-emergent serious investigator-reported infections occurring within 3 months after the implant-related procedure were approximately doubled in patients receiving Canakinumab compared with the rate on placebo. With overall low numbers of events a clear dose response is usually not expected. Although a rare event, device related infection and endocarditis are severe and possibly life threatening conditions. Cases of deaths following device-related infections in patients with cardiac implantable devices and endocarditis have also been observed in patients treated with Canakinumab.

The applicant proposes to include the following warning in the SmPC:

“Infections related to surgical procedures, wounds and device implantations such as cardiac implantable electronic devices were reported in the CANTOS study.”

This is welcomed and endorsed. Considering the long T1/2 with a dosing every 3 months it is not possible just to discontinue treatment before surgery. On the other hand in many cases implantation of a pacemaker or an ICD cannot be postponed. The applicant is asked to comment whether additional advice should be given with respect to time point of surgery and dose of Canakinumab.

A dedicated Patient Alert Card is requested as an aRMM for all canakinumab products, including this application, in order to remember the patient and to remind the HCP taking care of an acute infection or planning vaccinations about canakinumab therapy. The RMP should be adjusted accordingly. **OC**

PRAC outcome

The PRAC noted that serious infections were more reported in the canakinumab arm in the clinical trial.

The PRAC endorsed the assessment of the RMP V1.0. The patient alert card to further minimise the risk for potentially serious consequences in case of infection or vaccination with live vaccines is supported and it will be important to make sure this card is easily made available.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Orphan medicinal products

Orphan designation

N/A

Similarity

N/A

Derogation(s) from market exclusivity

N/A

5. Benefit risk assessment

5.1.1. Disease or condition

Canakinumab Novartis is indicated for the secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ≥ 2.0 mg/l prior to treatment initiation. Cardiovascular disease is the leading cause of death in the EU. The application aims at patients at a very high risk population (Piepoli et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice, Eur Heart J 2016; 37:2 9) for CV morbidity and mortality, i.e. patients after a myocardial infarction with an estimated 10 year risk for a fatal cardiovascular event of > 10%.

Several risk factors contribute to the pathogenesis of atherosclerosis and of acute cardiovascular events. Risk factors included in risk assessment scores like the “SCORE” are systolic blood pressure, total cholesterol, smoking status, gender, age and region. For a thorough discussion of aetiology, pathogenesis, risk factors, clinical presentation, diagnostic workup and therapy of coronary artery disease and myocardial infarction it is referred e.g. to the above mentioned ESC guideline (Piepoli et al 2016).

Therapy in secondary prevention after myocardial infarction includes treatment of baseline risk factors, platelet aggregation inhibitors, specific therapy for comorbidities like cardiac arrhythmias or heart failure and invasive measures in case of a recurrent coronary event.

Since morbidity and mortality in patients after myocardial infarction is high despite of optimal therapy there is a need for additional therapeutic options.

5.1.2. Main clinical studies

The application was mainly based on one pivotal trial (CANTOS, CACZ885M2301).

It was a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial, designed to evaluate the efficacy and safety of canakinumab compared to placebo in post-MI patients receiving standard of care therapy who were selected based on an hsCRP ≥ 2 mg/L. The qualifying MI had to occur at least 30 days prior to randomization. The trial was an event-driven global trial conducted in the outpatient setting. The study consisted of 3 periods: (1) screening period; (2) double-blind phase (event driven) and (3) follow up period. The trial was event driven and was designed to complete when a total of 1,400 patients had experienced one of the events comprising the primary CV endpoint. Thus, double blind treatment was continued until the target number of primary confirmed adjudicated CV events had been reached (ie, 1,400 patients with primary CV events). 1,109 sites randomized at least one patient each in 39 countries worldwide.

The primary objective of this study was to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular events (cardiovascular death, non-fatal MI and non-fatal stroke) in a population of clinically stable patients with prior MI with elevated hsCRP receiving standard of care. Key secondary objectives included additional cardiovascular endpoints and all-cause mortality as well as patient reported outcome and specific measures for the assessment of patients after stroke.

The study was completed as planned. The 50 mg arm was included in the protocol by an amendment after the start of the trial leading to an amendment of the randomisation scheme and two phases of randomisation. Amendment 8 revised the number of patients to be randomized into the study from 17,200 patients to approximately 10,000 patients.

Number of patients (planned and analyzed): A sample size of approximately 10,000 randomized patients was expected to be sufficient to accrue the planned number of 1,400 patients with a MACE. A total of 10105 patients were randomized, and a total of 10061 patients were included in the FAS. A total of 44 patients (8, 7, and 10 patients in the 300 mg, 150 mg and 50 mg arms, respectively, and 19 in the placebo arm) in the randomized set were excluded from the FAS because they did not qualify for randomization but were inadvertently randomized into the study via the IVRS/IWRS and did not receive double blind study medication (41 patients) or because they were randomized at sites that were closed due to serious GCP violations (3 patients).

Overall the CANTOS was well conducted as planned. In 103 patients included in the pivotal trial, almost all in Brazil, it was noted that locally the blind was broken. According to the applicant the unblinding in these Brazilian centers was related to a single mistake related to a change in the local drug depot and not due to general mismanagement. It was unclear, whether treatment allocation was actually unblinded to the site personnel. Sensitivity analyses did not indicate an impact on the overall conclusions of the study. 2.2% (25 centers) reported a high rate of protocol deviations that were not considered to impact the overall results. There are remaining issues to be addressed concerning the inspections, the time point of exclusion of 3 patients from the efficacy analysis due to GCP issues and a clarification is requested on the number of patients that were included in disregard of exclusion criterion 5 (tuberculosis) **(OC)**.

5.2. Favourable effects

- Canakinumab 150 mg was superior to placebo in reducing the risk of CEC confirmed MACE (a composite of CEC confirmed CV death, non-fatal MI, or non-fatal stroke). The adjusted p-value was statistically significant for the 150 mg strength but not for the other strengths. The primary outcome occurred in 322 (3.90/100 patient years), 320 (3.86/100 patient years) and 313 (4.11/100 patient years) patients in the 300, 150, and 50 mg groups, respectively, compared with 535 (4.50/100 patient years) patients in placebo. The HRs describing the relative risk of MACE for each canakinumab dose group (300, 150, and 50 mg) vs. placebo were 0.86 (95% CI, 0.75 to 0.99), 0.85 (0.74 to 0.98), and 0.93 (0.80 to 1.07), respectively.
- The reduction in the risk of MACE with canakinumab 150 mg treatment was driven by a significant reduction in the risk of MI (fatal and non-fatal) (HR = 0.76 (95% CI, 0.63 to 0.92; unadjusted p-value = 0.006)) and a numerical reduction in the risk of CV death (HR = 0.90 (95% CI, 0.73 to 1.10)) relative to placebo (Table 11-8).
- The results in the key secondary endpoint (CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization in the FAS were consistent with the result in the primary endpoint. A significant treatment effect was observed for the 150 mg group.
- The results for the composite of all-cause mortality, non-fatal MI, or non-fatal stroke were consistent with the results for the primary composite endpoint that included CV mortality instead of all-cause mortality.
- Overall, the results for the primary endpoint were consistent in most subgroups.

5.3. Uncertainties and limitations about favourable effects

1. This application is based on one pivotal trial with the requirement to show strong statistical evidence with a low p-value. This is certainly not met. The only significant result obtained refers to the primary and key secondary endpoint in the 150 mg group. The obtained p-value of 0.0241 was just below the required significance level of 0.0245 (after adjustment for the interim analyses). Sensitivity analyses could not sufficiently strengthen the statistical evidence.

2. a) A reduction in MACE by 15% (150 mg arm) in the overall population is only modest and not compelling but might be sufficient in case of sufficient robustness of the data. However, most patients (88.4%/90.1%) received baseline statin therapy. In this key group efficacy was considerably lower with a RR for MACE of only 9 % (150 mg arm, overall interaction p value 0.1251). There is biological plausibility for such a negative interaction. Pleotropic effects of statins on inflammatory processes associated with a decrease in hsCRP have been proposed to be relevant for efficacy of statins. Therefore, the clinical relevance of efficacy in the key group of patients on baseline therapy with statins is questionable.3A key issue of uncertainty is the role of hs-CRP for the characterisation of the patients to be included in the wording of the indication. hsCRP levels > 2 mg/dL were an inclusion criterion but the relevance of this value is not clear. Overall, it is conceivable that the hsCRP level is irrelevant for a treatment effect, baseline hsCRP did not predict the treatment effect. In the 150 mg arm efficacy of Canakinumab in patients with baseline hsCRP > 4mg/L was numerically lower than in those with baseline hsCRP between 2 mg/L and ≤4mg/L (HR for MACE 0.92 (0.77, 1.10) vs. 0.74 (0.59, 0.93)). No difference was observed in the 300 mg arm. Data in patients with hsCRP < 2 mg/L is not available.

There are several issues that have to be considered when analysing the data. There was a relevant decline by about 25% in hsCRP levels in the placebo group immediately after randomisation indicating that a relevant number of patients would not have met the inclusion criterion if hs-CRP levels had to be confirmed at randomisation or shortly thereafter. Acute illnesses like infections or status shortly after acute illnesses not related to CV risk may have contributed to this observation. In this regard the protocol specified inclusion of patients based on mean hsCRP values during the pre-sreening/screening period may be an issue. Patients may have been included with hsCRP levels < 2 mg/L at randomisation based on pre-study mean values > 2 mg/L. Additional analyses on this issue are expected including efficacy analyses for those patients randomisation hsCRP values < 2 mg/L

It was noted that there was a correlation between hs-CRP levels and AEs of infection. When patients with infection related instances during screening/pre-screening were eliminated, the initial fall in hsCRP in the overall placebo group by 25% was reduced to about 10%. Whether the population selected based on increased hs-CRP levels was enriched by patients with subclinical or clinical infections, cannot be answered based on CANTOS.

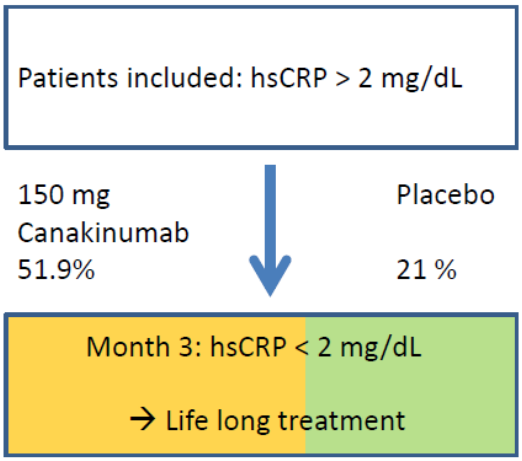
In summary, CANTOS failed to demonstrate that pre-study hsCRP values are relevant for a treatment effect of Canakinumab on MACE.

b) The proposed algorithm that includes patients with hsCRP > 2 mg/L and keeps patients on treatment with a 3 month hsCRP < 2 mg/L is not appropriate for the following reasons.

- The approach has not been prospectively confirmed.

- The algorithm predicts treatment effect less reliable than some of the baseline characteristics (e.g. baseline hsCRP level hsCRP > 4mg/L vs. ≤ 4mg/L).

- The algorithm does not identify a well-defined patient population. For 40% of the patients considered for life long therapy vs. no therapy the treatment decision is based on the time point of the hsCRP value taken (3 months earlier or later) and not on patient characteristics. This concern is depicted by the following figure:



- In about 40% of the responders the response criterion is met due to spontaneous drop of hsCRP and not related to therapy. → life long treatment.
- These 40% will not be considered for treatment at all if the first hsCRP value is obtained at month 3.
- Algorithm not appropriate to identify patients with a positive B/R for life long therapy.

- In addition, more patients in the 300 mg arm were responders for the 3 month hsCRP < 2 mg/L criterion than in the 150 mg arm (61.1 % vs. 51.9%) but efficacy on MACE endpoints was not higher in the 300 mg group.

- The 3 month analysis in the 150 mg arm was influenced by the more pronounced treatment effect seen in patients with a lower baseline hsCRP.

Therefore, the proposed treatment algorithm is not considered appropriate to identify a patient population with a positive B/R.

5.4. Unfavourable effects

Infections and infestations

This was the most frequently affected primary SOC.

The majority of infection AEs consisted of non-serious upper respiratory tract infections. The incidence of investigator-reported infection SAEs and IAC-confirmed infections (which were mainly SAEs but also included medically important infections such as those treated with iv antibiotics) was 1-2% higher in the canakinumab 300 mg and 150 mg groups compared with the placebo group. The majority of infection AEs with an identified pathogen were viral infections. The proportion of patients with two or more IAC confirmed infections was higher for canakinumab 300 mg (n=58, 2.6%) and 150 mg (n=53, 2.3%) than for placebo (n=58, 1.7%). In time-to-event analysis for the first event, the HR of IAC confirmed infections (SAEs and medically important AEs) was 1.27 (95% CI 1.06, 1.54) in canakinumab 150 mg treated patients compared to placebo. For cellulitis AEs this risk was 1.48 (95% CI 1.07, 2.05). The HR of cellulitis was even greater in patients with diabetes: HR 1.74 and 95% CI 1.12, 2.71 compared to placebo.

Sepsis and cellulitis SAEs

Sepsis SAEs were higher across the canakinumab groups compared with the placebo group. The pattern of between-treatment differences was not influenced by age, diabetic status, or medical history of asthma or COPD. The HR of treatment emergent sepsis SAEs was 1.55 (95% CI 1.00, 2.38) in canakinumab 150 mg group compared to placebo. For cellulitis SAEs this HR was 1.71 (95% CI 1.03, 2.83).

Infectious pneumonia

Infectious Pneumonia SAEs were higher in the 150 mg an 300 mg canakinumab groups compared with the placebo group. The risk of infectious pneumonia (grouped term) was higher among patients with baseline asthma or COPD who are already at an elevated risk for pneumonia. There were no trends related to canakinumab dose, age, or diabetic status at baseline.

Post-procedural, wound and device related infections

There was almost a doubling in the incidence of post procedural, wound and device related infections for canakinumab 150 mg vs. placebo (1.1% and 0.6%, respectively). The most common PTs (≥ 0.1% total) were post-operative wound infection, wound infection, post procedural infection and device related infection. In addition, a few infections reported as ‘cellulitis’ and ‘staphylococcal infection/sepsis’ occurred in the setting of recent surgical procedures, devices and prostheses (including infections of pacemakers, implantable cardiac defibrillators, vascular grafts and joint prostheses).

This is considered of particular relevance in the target population since these patients are likely to undergo invasive procedures and implantation of devices like pacemakers, defibrillators, artificial valves or stents.

Deaths

The most common cause of death was of cardiovascular origin (501 of 1081 deaths), followed by non-cardiovascular causes (414 total) and unknown causes but presumed cardiovascular (166 total). Of the non-CV deaths, the most common primary causes of deaths were malignancy (0.42% in canakinumab 150 mg group vs 0.52% in placebo group), respiratory failure (0.20% vs 0.16%), sepsis (0.23% vs 0.15%), and infection (0.09% vs 0.07%; 0.28/ 100 patient years vs 0.18/ 100 patient years).

Neutropenia

There were dose-dependent decreases in mean neutrophils early after initiation of treatment, which stabilized after two weeks. Most patients' neutrophil counts remained within the normal range. The majority of neutrophil decreases reported as laboratory findings were of CTC Grade 1 or 2. CTC Grade 3 or 4 decreases were transient (only occurred at one time point) and were not associated with an increased risk of infections

Thrombocytopenia

Overall, a dose-dependent increase in thrombocytopenia AEs and mild platelet count abnormalities (CTC Grade 1) were observed for canakinumab relative to placebo. Grade 2 abnormalities occurred at low and comparable rates between canakinumab 150 mg and placebo. More severe abnormalities in platelet counts (Grade 3 or 4) were rare and the rates were comparable across the treatment groups. None of the Grade 3 or 4 platelet count abnormalities was associated with clinically significant bleeding.

Hepatic safety

The incidence of mild hepatic transaminase elevations (mainly >3×upper limit of normal [ULN] but <5×ULN) and mild total bilirubin elevations (>1.5×ULN but <2×ULN) was numerically higher for canakinumab compared to placebo. Most elevations were transient, reversible and not dose-dependent. There were few combined elevations of transaminases and total bilirubin, and no confirmed cases of Hy's Law. The increased transaminases were not associated with clinically relevant AEs.

Disorders of lipoprotein metabolism

Overall, the incidence of dyslipidemia AEs was higher in the canakinumab groups compared with the placebo group. The incidence of severe dyslipidemia AEs was very low, and there were no reported SAEs. There was an early increase of 2-5% in mean triglyceride levels which persisted throughout the study (geometric mean change from baseline range: 1.00-1.05 over Month 0.5-Month 54). The increases in triglycerides were modest and not dose dependent. Similar to the elevated triglyceride levels, there were small (2-4%) increases in total cholesterol as well as non-HDL cholesterol and VLDL-cholesterol but meaningful increase in LDL-cholesterol compared to placebo. The incidence of acute pancreatitis AEs was higher in the 300 mg arm only (0.8%, 0.5%, 0.5% and 0.5%, respectively, for canakinumab 300 mg, 150 mg, 50 mg and placebo).

Immunogenicity, Allergenicity and Autoimmunity reactions

Overall, the incidence of immunogenicity/allergenicity AEs was higher in the Canakinumab groups. The risk of immunogenicity/allergenicity AEs relative to placebo was HR=1.47, 1.04 and 1.11 for Canakinumab 300 mg, 150 mg and 50 mg vs. Placebo. Treatment-emergent binding Anti-drug antibodies (ADA) were detected in low and comparable proportions of patients across all treatment groups (0.3% to 0.5%) and were not associated with any immunogenicity-related AE or altered hsCRP response. None of the ADA-positive samples that were tested showed neutralizing antibodies. There were no allergic events associated with positive ADA findings.

5.5. Uncertainties and limitations about unfavourable effects

-The study population was not very representative of the sought indication/ target population, as it excluded many types of patients that would be included in the applied indication and hence also in real-life clinical use. For example, patients with active or recurrent bacterial, fungal or viral infection, and patients with existing serious infections, as well as patients with abnormalities in eGFR, creatinine or ALT/AST were excluded, in addition to those with a multi-vessel CABG, patients with New York Heart Association Class IV heart failure, some of the patients with uncontrolled hypertension and uncontrolled diabetes – all belonging to the targeted population in the sought indication.

- Regarding neutropenia and thrombocytopenia grade 3 and 4 a warning should be included prior to initiation of therapy

- Some AEs are not included in section 4.8 of the SPC or require additional clarification i.e. acute kidney disease, chronic kidney disease, peripheral oedema, psoriasis and gastrointestinal disorders. In particular, some AEs that were of particular importance in elderly patients (acute kidney injury and chronic kidney disease (allergenicity and immunological reactions) should be included in the SmPC

- -The number of pneumonia deaths in the whole CANTOS should be given.

5.6. Effects Table

Table 4.6.1 Effects Table for Canakinumab Novartis (150 mg quarterly) in the following indication: Canakinumab Novartis is indicated for the secondary prevention of major cardiovascular events in adult patients at least 30 days after a myocardial infarction (MI) with high sensitivity C reactive protein (hsCRP) ≥ 2.0 mg/l prior to treatment initiation. For study results with respect to populations/sub populations studied, see section 5.1."

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
First events	CV Mortality + MI + Stroke First event	Events/100 py HR (95% CI)	3.86 HR 0.85 (0.74; 0.98)	4.50	p = 0.0241 p value very close to the predefined significance level of p < 0.0245 one-sided Robustness needs to be reassessed based on the possibility of GCP concerns in some centers. Effect on stroke did not contribute to the result.	CANTOS
	Secondary MACE + unstable angina		4.29 0.83 (0.73; 0.95)	5.13	p = 0.0241	

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Secondary MACE + all-cause mortality		4.77 0.85 (0.75; 0.96)	5.56		
	Secondary All-cause mortality		2.73	2.97		
	CV death		1.66 0.90 (0.73; 1.10)	1.87		
	MI (non-fatal)		1.88 0.76 (0.62; 0.92)	2.43		
	Stroke (non-fatal)		0.74 0.99 (0.72; 1.37)	0.73		
Unfavourable Effects						
	Deaths due to Infection/ Sepsis Sepsis Septic shock Respiratory failure	 n per 100 py % 	 0.28 0.6 0.4 0.4	 0.18 0.3 0.3 0.2		CANTOS (Table 2-7, 2-8

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Infections and infestations	%	52.6	50.4		CANTOS Table 2-3, 2-4
	Viral upper respiratory tract infection		13.9	12.3		
	Influenza		7.1	6.1		
	Pneumonia		6.7	6.2		
	Cellulitis		3.2	2.3		
	Sinusitis		3.6	3.0		
	Respiratory tract infection		2.7	2.1		
	Investigations		21.1	17.5		
	Renal and urinary disorders		16.4	15.9		
	Urinary tract infection		7.2	6.7		
	Acute kidney injury		3.0	2.0		
	Chronic kidney disease		2.1	1.5		
	Skin and subcutaneous tissue disorders		16.5	15.2		
	Psychiatric disorders		12.3	11.4		
	Insomnia		3.9	3.3		
	Anxiety		3.5	3.1		
	Blood and lymphatic system disorders		9.4	9.2		
	Diarrhea		7.4	7.0		
	Upper abdominal pain		2.5	1.9		
	Oedema peripheral		6.7	5.9		
	Weight increased		2.5	1.9		
	Thrombocytopenia		1.5	1.3		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Safety topics of interes	During double blind phase					CANTOS Table 2-12
	Opportunistic infections	%	25.8	24.0		
	Long term effect on kidney function		10.9	9.5		
	Disorders of Lipoprotein Metabolism		6.0	5.3		
	Hepatic Safety		6.4	5.9		
	Autoimmunity reactions		3.1	2.7		
	Immunogenicity/ Allergenicity		1.9	1.8		
	Thrombocytopenia		2.0	1.6		
	Hypoglycemia		1.8	1.5		
	Neutropenia		1.4	0.9		
	Injection site reaction		1.1	0.9		

Abbreviations:
Notes:

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Patients after a myocardial infarction are at a high risk for cardiovascular morbidity and mortality and there is an unmet medical need for therapeutic options in addition to standard of care. Canakinumab at a dose of 150 mg quarterly was beneficial in decreasing first events of a composite MACE endpoint (CV mortality, MI, stroke). The effect was mainly driven by a beneficial effect on myocardial infarction and to a lesser degree on CV mortality, whereas the effect on stroke was neutral. The numerical effect on CV mortality was preserved when assessing all-cause mortality and was supported by a decrease in the number of first investigator reported coronary revascularization procedures (PCI or CABG).

At present, there are several major concerns. The P value for the primary efficacy endpoint was just below the predefined margin which is not consistent with the requirements in a one pivotal trial application. In the context of one pivotal trial compelling results are expected. A risk reduction for MACE by 15% can be considered as being in the lower range of what can be considered clinically relevant in case the database is robust. However, in the key population included, patients on statin therapy (about 90% of the patients) the risk reduction on MACE in the Canakinumab arm was only 9%. Therefore, the clinical relevance of efficacy is questionable for the key population included in the wording of the indication. There is biological plausibility for such a negative interaction since statins are considered to influence inflammatory processes and also decrease hsCRP. The large difference in efficacy between 90% of patients on statins and 10% without statins is not consistent with the expectation of internal consistence in an application based on one pivotal trial. In addition, it is not clear from the data that the predefined criterion of increased hs-CRP levels is in fact relevant and appropriate for all patients. Efficacy did not depend on the baseline-hsCRP level and immediately after randomisation hsCRP levels decreased by about 25% in the placebo group. Therefore, a considerable number of patients would not have met the inclusion criterion of an hsCRP > 2 mg/dL in case the test would have repeated later on. Patients post infection or after other acute instances may have contributed to this observation. In fact, it is conceivable that a relevant number of patients with randomisation hsCRP values < 2mg/L were included in the study. Further clarification and analyses on this issue are expected. Therefore, the patient population as defined in the proposed wording of the indication requires additional consideration.

If importance, the proposed treatment algorithm that initiates therapy in patients with hsCRP > 2 mg/L and continues therapy with hsCRP < 2 mg/L is not appropriate to identify a patient population with positive B/R. The details have been discussed above.

Overall canakinumab was relatively safe and well tolerated in the large (10 000 patients) CANTOS-study, with no major differences between the treatment groups in the overall incidence of AEs, SAEs or AEs leading to study drug discontinuation. However, this needs to be placed into context with only modest beneficial effects of canakinumab in the overall group of patients and with an effect of questionable clinical relevance in the key group of patients on baseline statin therapy. There are, however some serious adverse events Despite of exclusion of patients with active or recurrent infection, patients with known immunosuppressive conditions and medications, infections – sepsis, cellulitis and pneumonia in particular – were the most common type of adverse events. Importantly, the relative risk was increased for fatal infections (0.28/100 patient years and 0.18/100 patient years in the canakinumab 150mg and placebo groups, respectively), as well as for IAC-confirmed infections (SAEs and medically important AEs), cellulitis SAEs, sepsis SAEs, and pneumonia SAEs (by 27%, 71%, 55%, 15%, respectively; statistically significant difference seen for the first two).

Infections were highlighted in patients with underlying diseases. T2DM patients, who represented 40 % of the study cohort, had a twofold risk for cellulitis and sepsis compared to non-diabetic subjects. As T2DM patients also have a higher risk of CV events, including deaths, even among patients with prior MI, the assessment of benefit/risk in diabetic subjects would be difficult in practice. Does the observed reduction in CV events outweigh increased risk for serious infections in diabetic patients? This is a clinically relevant issue as recent data indicate that similar reductions in incidence of CVD events can be achieved by choosing antihyperglycaemic agents that reduce CV risk. Infections seem to be also more common in patients with higher hsCRP and lower eGFR at baseline.

Finally, the numerical improvement in CV mortality was overall preserved in the numbers for all-cause mortality. This was in part due to an overall numerically lower rate of deaths due to malignancies. Based on analyses of the time course of malignancies and deaths due to malignancies and in comparison with epidemiological data a beneficial effect on malignancies is not considered a robust result. Data are reassuring though with respect to malignancy as a safety concern. Therefore, for patients with an increased risk of infections and for patients where infections are of particular concern, at present B/R cannot be considered positive. This may be relevant for immune-compromised patients and patients with implanted devices like pacemaker, implanted defibrillators or those with artificial valves. The risk of neutropenia/ thrombocytopenia has been identified during previous applications in other approved indications. There should be a warning in patients with grade 3 and 4 neutropenia/ thrombocytopenia prior to initiation of therapy.

5.7.2. Balance of benefits and risks

In conclusion, the benefit-risk balance is currently negative in the sought indication due to the following:

- This application concerns a completely new treatment concept/pharmacological principle. The data from the one pivotal study is not statistically compelling with regards to the strength of statistical evidence, precision of the results (upper confidence interval very close to 1) and the clinical relevance. A 15% risk reduction for MACE in the overall group of patients is modest but may be acceptable if based on robust results. However, since the risk reduction in the 150 mg arm was only 9% in the key subgroup of patients on baseline statin therapy, the clinical relevance of efficacy is questionable.

-The role of hsCRP for defining the target population and evaluating efficacy is questionable. The proposed treatment algorithm that initiates therapy in patients with hsCRP > 2 mg/L and continues therapy with hsCRP < 2 mg/L is not appropriate to identify a patient population with positive B/R.

- The relative risk was increased for fatal infections, IAC-confirmed infections (SAEs and medically important AEs), cellulitis SAEs, sepsis SAEs, and pneumonia SAEs, in addition to some other AEs in the canakinumab group, which questions the benefit/risk balance especially in patients at increased risk for infections.

Thus, the applicant should justify that the benefit/risk balance is positive in the sought indication.

5.8. Conclusions

The overall B/R of canakinumab Novartis in cardiovascular risk prevention is currently negative.

6. Biosimilarity assessment

N/A