CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	June 17, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	BLA 125319
Applicant Name	Novartis
Proprietary / Established (USAN) Names	Ilaris canakinumab
Dosage Forms / Strength	Subcutaneous Injection (sc) 180 mg/ml per single-use vial (reconstituted as 150 mg/ml)
Proposed Indication(s)	Cryopyrin-Associated Periodic Syndrome (CAPS)
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding canakinumab and the reader should refer to the reviews in the action package for a more detailed discussion. CAPS represents a spectrum of autosomal dominant rare disease, affecting approximately 200 to 300 people domestically, and is composed of three distinct autoinflammatory diseases that are characterized by mutations in the gene responsible for the production of the protein cryopyrin. The three autoinflammatory disorders comprising CAPS are:

-Familial Cold Autoinflammatory Syndrome (FCAS)
-Muckle-Wells Syndrome (MWS)
-Neonatal Onset Multisystem Inflammatory Disorder (NOMID)

Cryopyrin is a protein component of inflammasome, an intracellular complex of proteins that activate caspase-1 causing the release of interleukin-1 β (IL-1β), a cytokine which works with other host defenses to protect against microorganisms. CAPSis characterized by a single point mutation in the NALP3/CIAS1 gene on chromosome 1q44 which results in increased production of IL-1β. There are common features to all three syndromes that include chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and polymophonuclear leukocytosis with organ infiltration. Of the three, NOMID is the most serious form, presenting early in life with severe dermatologic, rheumatologic and neurologic manifestations, while MWS is associated with sensorineural deafness and an increased risk of anyloidosis and FCAS, considered the least severe form, is characterized by urticaria-like skin lesions, swollen and painful joints, conjunctivitis and fevers following exposure to cold. As Dr. Siegel points out, it is unclear why mutations in the same gene can give rise to different clinical syndromes, but there is overlap such that data in patients with MWS may be extrapolated to some extent to

those with FCAS. b(4)

Canakinumab is a recombinant human monoclonal anti-human interleukin-1β antibody. It selectively antagonizes the activity of cytokine IL-1 β by binding IL-1 β, interfering with its interaction with the IL-1 receptor. This is in contradistinction to another recently approved product for CAPS, rilonacept (approved for FCAS and MWS in patients 12 years of age and over, used sc once weekly) which, while being a IL-1 blocking agent, is a soluble IL-1 receptor fusion protein, a decoy receptor, that binds excess IL-1 β (but is permissive and also binds several other proteins that may interact with the cell surface receptor).

Efficacy

This has been thoroughly discussed in Drs. Yancey, Petullo, Siegel and Rappaport's reviews and I will only highlight there conclusions, all of which are in agreement. The applicant conducted a pivotal trial in 35 patients, age 9-75 years old, with MWS that had an initial open-label phase with a randomized, blinded withdrawal phase using disease flare as the primary endpoint. There were also two open-label trials providing supportive efficacy and safety evidence (down to the age of 4 years old). The results of the primary efficacy outcome analysis are demonstrated in the table below from Dr. Siegel's review.

Primary Efficacy Analyses - Study D2304							
Proportion of Patients with Disease Flare: Comparison between Treatment Groups at the End of Part 2 - (ITT population)							
	ACZ885		Placebo		Differences in Response rates		
	N = 15		N = 16		ACZ885 vs Placebo		
	n / N (%)	95% CI	n / N (%)	95% CI	Difference	95% CI	p-value*
Pts with disease flare	0 /15 (0.0)	(0, 0.22)	13/16 (81%)	(0.54, 0.96)	- 0.81	(-1.00, -0.62)	<0.001 **
n = total number of pts having disease flare; N = total number of pts in treatment group; * p-value from Fisher's exact test; ** statistical significance (two sided) at 5% level.							

This table demonstrates a very robust response in subjects receiving canakinumab that would fulfill previous agency guidance regarding using a single trial for drug approval. This trial was also supplemented by the two open-label studies mentioned previously where subjects exposed to canakinumab had complete responses of symptoms. The clinical reviewers concluded that canakinumab should be approved for MWS, the 'middle severity form' of CAPS and by extension, FCAS, the 'milder' form of CAPS.

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I agree with these conclusions.

Clearance of canakinumab varies according to body weight and, therefore, is dosed based on weight, with those over 40 kg receiving 150 mg and those between 15 and 40 kg receiving 2 mg/kg. The clinical pharmacology review team concluded that the proposed weight-based dosing for children was acceptable, but noted that children weighing less than 40 kg had lower exposure (37% less) than adults. This observation is supported clinically where children receiving weight-based dosing with 2 mg/kg had shorter median times to relapse compared to adults. As such, the clinical pharmacology team has recommended that those not clinically

responding to 2 mg/kg to have their dose increased to 3 mg/kg for exposures similar to the 150 mg in adults.

Safety

There is a limited amount of safety data available for the use of this drug in CAPS subjects (n=78), as would be expected for an orphan indication for a disease of this rarity. This is supplemented by safety information in subjects with other conditions such that approximately 700 individuals have had exposure to canakinumab. In the controlled clinical trials, all subjects received canakinumab at some point, so there is not any comparative safety data. The major safety signals identified were infections and vertigo. Infections are an expected event due to the mechanism of action of canakinumab. Vertigo is a complication of CAPS, and the cases of vertigo occurring during treatment resolved despite continuation of the drug, so it is unclear if these cases were due to treatment or to the underlying disease.

One safety issue to note (regarding CMC) is that canakinumab is currently obtained from a Master Cell Bank (MCB) and Working Cell Bank (WCB) ——— ——— which is not an approved source of HSA for domestic use. This becomes an issue in regard to the concern over the risk for transmissible spongiform encephalopathy (TSE) from the use of non-approved sources of HSA. Prior to administration to subjects, a thorough risk assessment by internal experts on TSE was conducted and it was felt that using the MCB ——— would have negligible risk for TSE transmission due to the fact that this step was very far 'upstream' with many purifications and dilutions of the ultimate product. This decision is consistent with that made for other products such as vaccines. The sponsor was required, for subsequent steps in the cell growth and fermentation process, to use HSA from approved sources. New WCB were introduced during clinical development and at that time it was believed that they were manufactured using HSA from US approved sources, as the sponsor was informed of this requirement during a pre-IND meeting with the FDA. Although the WCB ultimately used for manufacture of canakinumab material under IND was not generated using an approved source of HSA, the risk is identical to that initially determined for the original MCB. However, to further reduce the very low risk that currently exists and ensure compliance with our previous safety recommendation, a new WCB should be generated using approved HSA. Therefore, a PMR will be made of the sponsor to make this transition.

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Advisory Committee meeting

We did not convene an advisory committee meeting for this application as canakinumab is the third drug in this class and second in the class for CAPS and the data regarding risk/benefit relationships was favorable and in line with other approved products.

Conclusions and Recommendations

Canakinumab has demonstrated efficacy for ——— CAPS. The safety information, although limited, seems in line with other IL-1 antagonists. If appropriate

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labeling can be agreed to with the sponsor, I recommend that the action for this application should be approval.

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