

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Drug Risk Evaluation

Date: Oct 29, 2008

To: Susan Walker, M.D.,
Director,
Division of Dermatological and Dental Products

From: Solomon Iyasu, M.D., M.P.H. 
Director,
Division of Epidemiology Drug Risk Evaluation
Office of Surveillance and Epidemiology (OSE)

Subject: Covering memorandum for Syed Rizwanuddin Ahmad, M.D.,
M.P.H., F.I.S.P.E memorandum on Ustekinumab dated October 20,
2008

Drug Name(s): Ustekinumab (CNTO 1275)

Submission Number: 0030

Application Type/Number: BLA/STN 12--5261

Applicant/sponsor: Centocor, Inc.

OSE RCM #: 2008-225

Background

This is written as a covering memorandum to the memorandum by Syed Rizwanuddin Ahmad M.D, M.P.H., F.I.S.P. on ustekinumab dated October 20, 2008. Dr. Ahmad's memorandum contains his specific opinions and recommendations on approvability of the product and the sponsor's postmarketing risk assessment proposals. The epidemiology review was reassigned after Dr. Ahmad missed two internal deadlines and it became obvious that it was impossible to complete an OSE team leader and Division Director review and sign-off and still provide OND the

needed review in a timely manner. Dr. Ahmad submitted the attached memorandum after it was reassigned. Therefore, this is being sent to you for your information and separately from the integrated OSE review of the risk assessment and mitigation program for ustekinumab forwarded to you on October 23, 2008.

Dr. Ahmad's memorandum represents his own opinions and not those of OSE. Dr. Ahmad has provided an opinion that states that approval of ustekinumab, "amounts to post-approval human experimentation" and offers editorial commentary. Dr. Ahmad's opinions on approvability are inconsistent with the OSE review and recommendations contained in the October 23, 2008 OSE memorandum,¹

Dr. Ahmad's memorandum does not include a description of the efficacy and safety data from the clinical development program, an evaluation of the pre-clinical and clinical data pertaining to the safety concerns and an assessment of the risks and benefits of ustekinumab. While the DODAC voted that the pre-market safety database for ustekinumab was inadequate, it nevertheless voted unanimously for marketing approval, essentially believing that the benefits outweigh the potential risks of the drug. Foremost among the DODAC's safety concerns was the potential for malignancy risk with long term use of ustekinumab. The DODAC voted that the sponsor's proposed risk assessment proposals were inadequate to evaluate the long-term safety of ustekinumab after discussing the challenges and limitations of each of the proposed approaches. It is important to note that, despite the concerns about the proposed post marketing risk assessment approaches, DODAC unanimously voted for marketing approval.

Below, I offer specific comments on Dr. Ahmad's memorandum, specifically with regards to his comments on the sponsor's risk assessment proposals and the regulatory options he has offered in his memorandum.

Sponsor's postmarketing risk assessment proposals:

Dr. Ahmad commented on the following sponsor's postmarketing risk assessment proposals: Large managed care and population-based datasets; PSOLAR (PSoriasis Longitudinal Assessment and Registry) and Nordic Database Initiative; Long-term extensions of pivotal phase 3 trials; and pharmacovigilance. He did not provide any assessment or comments regarding the ongoing phase 3 multicenter, randomized Etanercept Comparator Study (C0743T12) and the Pregnancy Research Initiative (C0I68T71).

In general, I share the concerns he raised regarding the limitations of each of the sponsor's postmarketing risk assessment proposals to evaluate long term outcomes such as malignancies. Some of these limitations arise from the voluntary nature of enrollment in registries, slow market uptake of drug after approval, limited sample size, loss to follow-up, incomplete ascertainment of outcomes and lack of a comparison group to enable quantification of risk. At best, such registry-based studies without a comparison group can potentially provide a loose upper bound for the incidence rate of malignancies relative to background rates in a demographically comparable US

¹ OSE memorandum of 23 October 2008 from Kathryn O'Connell, Suzanne Berkman, and Allen Brinker, M.D., M.S, to Susan Walker, Evaluation of risk assessment and mitigation needs for ustekinumab.

population. Therefore, the choice of comparison background rates and assumptions of attrition rates (loss to follow-up) must be justified in sample size calculations.

At the present time, similar postmarketing observational studies are in place for many of the biologic agents approved for marketing. It must be noted that, the same limitations cited above generally apply to these postmarketing registry-based observational studies. However, an evaluation of data from such observational studies has not been done by the Agency to date to determine their usefulness in quantifying the risk of rare and serious safety issues such as malignancies and serious infections associated with biologic agents.

Dr. Ahmad proposes four regulatory options for consideration in his memorandum and I will provide my comments on each below.

1. Additional randomized controlled trials pre-approval in serious non-dermatological indications such as multiple sclerosis, Crohn's disease, and rheumatoid arthritis:

Comment: It is unclear what authorities would enable FDA to ask sponsors that they should pursue other indications and perform randomized clinical trials. Dr. Ahmad states that requiring the sponsor to pursue other indications is in line with the FDA Amendments Act (FDAAA) but does not provide the specific authority in FDAAA.

2. Allow ustekinumab to be available under treatment IND while the sponsor conducts additional randomized controlled trials.

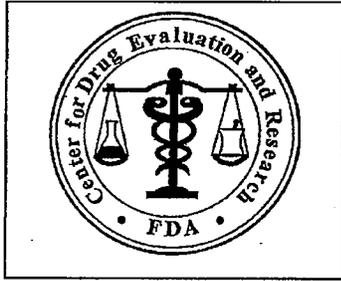
Comment: This option may not be viable because the regulatory threshold for treatment IND is unlikely to be met for psoriasis of "moderate to severe" clinical severity. Treatment Investigational New Drugs (21CFR312.34) are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. In addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished. FDA has approved products with moderate to severe psoriasis as the indication for therapy.

3. Formation of single-disease-based Psoriasis Registry.

Comment: In general, a disease-based registry is an option that is worth exploring for not only psoriasis but for any number of other indications for which anti-TNF agents are currently approved for. PSOLAR is a voluntary disease-based registry and is already being used for infliximab. NORDIC is also deemed to be a disease-based registry. Disease-based registries are still voluntary and may suffer from the same constraints as exposure registries. Therefore, their potential to assess the long term safety of biologic agents is yet to be determined. In fact, such an effort, including convening a public workshop of experts is being planned for pediatric rheumatic diseases and anti-TNF agents.

4. Mandatory Registry:

Comment: Requiring patients to participate in a mandatory registry for the purposes of conducting a study may be unethical and contrary to the federal regulations governing the protection of human subjects. Participation in a study should always be voluntary and with informed consent of the patient. However, a mandatory registry to protect patient safety or mitigate known serious drug risks is an option if the safety issue justifies deployment of such a restricted program. Dr. Ahmad's memorandum does not provide a benefit risk analysis and risk mitigation elements that will justify a mandatory registry with restricted distribution.



Department of Health and Human Services
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Office of Surveillance and Epidemiology
Division of Epidemiology

Date: October 20, 2008

To: Susan Walker, M.D., Director
Division of Dermatologic & Dental Products (DDDP)

Through: Solomon Iyasu, M.D., M.P.H., Director
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Syed Rizwanuddin Ahmad, M.D., M.P.H., F.I.S.P.E.
Medical Epidemiologist

Subject: Review of Sponsor's Post Advisory Committee Enhanced Risk
Management Submissions

Drug Name(s): Drug: Ustekinumab

Submission Number: BLA 125261

Applicant/sponsor: Centocor, Inc.

OSE RCM #: 2008-225

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EXECUTIVE SUMMARY

Ustekinumab is a novel biologic, with a novel mechanism of action, which is being considered for approval of mild to moderate psoriasis. This product has not been approved for any indication anywhere in the world.

The approval of ustekinumab was discussed at the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) meeting held on June 17, 2008. At the time of the DODAC meeting, the sponsor had presented data on clinical trials involving about 2000 patients with a maximum duration of human exposure of ustekinumab of about 18 months in 373 patients. Although the DODAC recommended approval of ustekinumab for moderate to severe psoriasis there was unanimous agreement that this biologic has not been studied in sufficient number of patients for sufficient length of time. In addition, the DODAC members were in unanimous agreement about the safety concerns of ustekinumab such as the potential malignancy demonstrated by this class of compounds, including the findings from animal studies that indicated an increased carcinogenic risk with inhibition of IL-12/IL-23. In addition, the DODAC members unanimously agreed that the sponsor's risk assessment proposal (PSOLAR and 5 year extension of pivotal trials) was not adequate. The Agency has to make a regulatory decision with all these factors in consideration. We must start somewhere, and have to deal with already approved drugs later and there is precedence for this. The safety profile for ustekinumab is far from established. Approving this biologic for psoriasis at this time would amount to post-approval human experimentation. There is no way to state with any confidence that the potential benefits of ustekinumab exceed its risks, or its superior efficacy exceeds the unknown risks, which could be substantial. We simply do not know because the safety database is too scant and inadequate in the case of ustekinumab. The Agency is on record to require additional pre-approval safety studies in cases of products considered for the treatment of both life-threatening and non life-threatening diseases when there have been safety concerns before approval. In the past, the Agency has held up approval of drugs because of potential safety concerns and has required pre-approval additional safety studies to be done by sponsors in the case of diseases for which alternative therapies exist (newer coxibs some of whom were approved in other countries, antidiabetic muraglitazar, the antibiotic telithromycin) and also in

the case of investigational drug tacrine, which was being evaluated for Alzheimer's disease, a life threatening disease for which no therapy existed.

The postmarketing risk assessment plan as currently proposed by the sponsor may be inadequate and insufficient in providing us the much needed safety data in a timely fashion. In addition, the sponsor's plan may not have the power to detect outcomes of serious concerns namely malignancy and serious opportunistic infections and hence give us a false reassurance on the safety of ustekinumab.

The statistician who reviewed the sponsor's post-advisory committee submission is of the opinion that the power calculations proposed by the sponsor are not adequate unless the sponsor can justify the choices of background rates and also take into account the loss to follow-up in the study cohorts.

Given the uncertain and potential safety concerns with ustekinumab, it may be prudent to request the sponsor to pursue other serious non-dermatologic indications such as rheumatoid arthritis and multiple sclerosis and Crohn's disease and build the safety database before this biologic is approved for psoriasis. This requirement will be certainly not an extra-ordinary measure by any regard and in fact will be in line to meet the mandates of last year's FDA Amendments Act (FDAAA) which gave the Agency much needed power to perform its job.

INTRODUCTION

This memorandum is in response to a request from the Division of Dermatologic & Dental Products (DDDP) to the Office of Surveillance and Epidemiology (OSE) to review and comment on what appears to be a multipronged postmarketing risk assessment proposal submitted by Centocor, Inc., - the makers of ustekinumab. Ustekinumab is a human monoclonal antibody with an apparently novel mechanism of action that targets the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23). These naturally occurring proteins regulate immune responses and are reported to be associated with some immune-mediated inflammatory disorders, including psoriasis.

The approval of ustekinumab was discussed at the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) meeting held on June 17, 2008. At the time of the DODAC meeting, the sponsor had presented data on clinical trials involving about 2000 patients with a maximum duration of human exposure of ustekinumab of about 18 months in 373 patients. Although the DODAC recommended approval of ustekinumab for moderate to severe psoriasis there was unanimous agreement that this biologic has not been studied in sufficient number of patients for sufficient length of time. In addition, the DODAC members were in unanimous agreement about the safety concerns of ustekinumab such as the potential malignancy demonstrated by this class of compounds, including the findings from animal studies that indicated an increased carcinogenic risk with inhibition of IL-12/IL-23. In addition, the DODAC members unanimously agreed that the sponsor's risk assessment proposal (PSOLAR and 5 year extension of pivotal trials) was not adequate. The Agency has to make a regulatory decision with all these factors in consideration. We must start somewhere, and have to deal with already approved drugs later and there is precedence for this. The safety profile for ustekinumab is far from established. Approving this biologic for psoriasis at this time would amount to post-approval human experimentation. There is no way to state with any confidence that the potential benefits of ustekinumab exceed its risks, or its superior efficacy exceeds the unknown risks, which could be substantial. We simply do not know because the safety database is too scant and inadequate in the case of ustekinumab. The Agency is on record to require additional pre-approval safety studies in cases of products considered for the treatment of both life-threatening and non life-threatening diseases when there have been safety concerns before approval. In the past, the Agency has held up approval of drugs because of potential safety concerns and has required pre-approval additional safety studies to be done by sponsors in the case of diseases for which alternative therapies exist (newer coxibs, antidiabetic muraglitazar, the antibiotic telithromycin) and also in the case of investigational drug tacrine, which was being evaluated for Alzheimer's disease, a life threatening disease for which no therapy existed.

In her reply to a question if the Agency has become more "conservative" in its approval decisions, Dr. Janet Woodcock, Director, CDER, recently stated "probably not". Dr. Woodcock continued as reported in FDA Webview that "indeed, the regulatory process now

involves more technical hurdles than previously, this is solely due to advances in science. Agency reviews have always relied upon "all tests applicable," she said. As the science advances, more tests become available – and more are applicable..... CDER has issued 21 letters directing drugs/biologics sponsors to conduct clinical studies addressing safety issues." (Safety hasn't made us more conservative: Woodcock. FDA Webview. October 16, 2008)

The postmarketing risk assessment plan as currently proposed by the sponsor may be inadequate and insufficient in providing us the much needed safety data in a timely fashion. In addition, the sponsor's plan may not have the power to detect what we are looking for and hence may give us a false reassurance on the safety of ustekinumab.

Given the uncertain and potential safety concerns with ustekinumab, it may be prudent to request the sponsor to pursue other serious non-dermatologic indications such as rheumatoid arthritis and multiple sclerosis and Crohn's disease and build the safety database before this biologic is approved for psoriasis. This requirement will be certainly not an extra-ordinary measure by any regard and in fact will be in line to meet the mandates of last year's FDA Amendments Act (FDAAA) which gave the Agency much needed power to perform its job.

OSE consulted Quantitative Safety and Pharmacoepidemiology Group in the Office of Biostatistics to comment on the adequacy of sample size and power calculations used in the enhanced risk management plan proposed by the sponsor. Office of Biostatistics' review is attached as an appendix to this memorandum. The bottom line comments of the Yu-te Wu, Ph.D., M.P.H., Mathematical Statistician, is that "the power calculations proposed by the sponsor are not adequate unless the sponsor can justify the choices of background rates and also take into account the loss to follow-up" in the study cohorts. The sponsor will compare the malignancy risk in ustekinumab-exposed patients with that in the control group. However, the sponsor chose the incidence rates in patients taking ustekinumab rather than control group as the background rate. "Sponsor needs to justify the adequacy of background rate used in the calculation".

MATERIALS REVIEWED

1. Centocor's 8/21/08 submission to address the "Response to Clinical Information Request on August 15, 2008."
2. Centocor's 07/17/2008 Enhanced Risk Management Plan and Malignancy Position Paper, submitted in response to the DODAC June 17, 2008 meeting.
3. Transcript of the Ustekinumab DODAC meeting 06/17/2008.
4. FDA's Briefing Document for the Ustekinumab DODAC meeting 06/17/2008.
5. Centocor's Briefing Document for the Ustekinumab DODAC meeting 06/17/2008.
6. Statement of Andrew C. von Eschenbach, M.D., Commissioner of the Food and Drug Administration before Subcommittee on Oversight and Investigations Committee on Energy and Commerce, March 22, 2007 (<http://www.fda.gov/ola/2007/drugsafety032207.html>)
7. Guidance for Industry - Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling. September 2006 (<http://www.fda.gov/cber/gdlms/interactstud.htm>)
8. Furu K. Nordic Prescription Databases (Nordic PD). Oral presentation at a symposium at ICPE, Copenhagen, Denmark. August 2008
9. Summary Minutes of the FDA Endocrinologic and Metabolic Drugs Advisory Committee, "Cardiovascular Assessment in the Pre-Approval and Post-Approval Settings for Drugs and Biologics Developed for the Treatment of Type 2 Diabetes Mellitus". July 1-2, 2008
10. Safety hasn't made us more conservative: Woodcock. FDA Webview. October 16, 2008
11. Johann-Liang Rosemary. Presentation at the FDA Anti-Infective Drugs Advisory Committee, December 14-15, 2006

Published Literature:

1. Pearce DJ, Feldman SR. Update on Infliximab: An Intravenous Biologic Therapy for Psoriasis. *Expert Rev Dermatol.* 2007;2:707-713.
2. Brophy JM. Selling safety--lessons from muraglitazar. *JAMA* 2005;294:2633-5.
3. Ahmad SR. Evolution of the FDA Drug Approval Process. Chapter 3: pp 25-41. In: TR Fulda, AI Wertheimer, editors, *Handbook of Pharmaceutical Public Policy.* Haworth Press, Binghamton, NY, USA. 2007
4. Temple R, Stockbridge N. BiDiI for heart failure in black patients: The U.S. Food and Drug Administration perspective. *Ann Intern Med* 2007;146:57-62.
5. Tubach F., et al. The RATIO observatory: French registry of opportunistic infections, severe bacterial infections, and lymphomas complicating anti-TNF alpha therapy. *Joint Bone Spine.* 2005;72:456-60
6. Askling J, Foreb CM, Geborek P, Jacobsson LT, van Vollenhoven R, Feltelius N, et al. Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis* 2006;65:707-12

SPONSOR'S POST-MARKETING RISK ASSESSMENT PROPOSALS:

In order to address the unanswered potential safety concerns associated with ustekinumab and discussed by DODAC members, the sponsor has come up with what appears to be an elaborate postmarketing risk assessment program. The sponsor has proposed the following elements in its post-approval plan:

1. Large managed care and population-based datasets
2. Registries – PSOLAR and NORDIC
3. Five-year extension of pivotal trials
4. Pharmacovigilance activities

1. Large managed care and population-based datasets

The sponsor is proposing to evaluate safety signals in large managed care and population-based datasets modeled on the FDA's Sentinel Initiative (<http://www.hhs.gov/news/press/2008pres/05/20080522a.html>.) While the FDA's Sentinel initiative which was announced on May 22, 2008 has the potential to lead to more widespread use of large automated databases for pro-active drug safety surveillance, it will take several years to see the results of this system and any system modeled on it. The sponsor's proposal to conduct studies in large health care database is problematic. Conventional observational study designs may pose challenges in assessing safety. It can take many years to accrue enough exposures in the population and large exposed sample size would be needed to study rare events such as malignancy. Also, there can always be questions about unmeasured or residual confounders. In addition, observational studies are notoriously ineffective in documenting long latency adverse outcomes such as malignancy. In some of these databases, turnover of patients may be as high as 25% per year so that long-term follow-up of patients may be very difficult. Incomplete case ascertainment and underestimation of risks (because of misclassification) may also be relevant issues. These studies will have low power to detect rare events such as malignancy. Moreover, biologicals are very expensive products and the economics of healthcare delivery and the involvement of third-party payers have created barriers to the access

of biological therapies. It is not uncommon for health plans to impose restrictions on use of biological therapies. In many cases use of an expensive product such as a biological agent is granted by insurers only after traditional agents have been tried and failed (Daniel J Pearce; Steven R Feldman. Update on Infliximab: An Intravenous Biologic Therapy for Psoriasis. *Expert Rev Dermatol.* 2007;2:707-713).

2. Registries

Registries are systematic collection of events or exposures and can be exposure-based such as drug exposure or disease-based such as cancer registry. The sponsor has proposed two registries (i) PSOLAR and (ii) Nordic Database initiative.

i. PSOLAR:

The sponsor has proposed PSOLAR which is a voluntary registry wherein access to drug is not contingent on being in registry and hence it is less burdensome to both patients and prescribers. In general, patients who enroll in registries are different from those who do not enroll and hence they may not be representative of the population. Voluntary registries are usually incomplete and capture only some of the cases and exposed persons. Ascertainment of disease, death and causes of death may be incomplete or missing. There may be considerable loss to follow-up of patients. In voluntary registries, data may not be verified by medical records and the logistics of following patients for long-latency adverse outcome such as malignancy may be problematic. Over the years, many sponsors have come up with voluntary registries to study the postmarketing risk of their products. However, this reviewer has been unable to find a single voluntary registry which has identified any meaningful safety signal.¹ In addition, enrollment/recruitment in voluntary registries may pose another challenge as seen recently in the case of another biologic approved for psoriasis namely efalizumab. At the time of approval of efalizumab, the sponsor committed to enroll 5,000 patients by June 30, 2008 and recently this sponsor approached the FDA to allow it to close the enrollment with 1,350 efalizumab-

¹ On October 16, 2008, FDA announced strengthening of the labeling for efalizumab when a case of progressive multifocal leukoencephalopathy (PML), a life-threatening and a deadly opportunistic infection was reported in an efalizumab-exposed patient who was enrolled in a voluntary registry which was set up as part of the postmarketing commitment. Considering that the sponsor had apparently stopped enrollment in the registry with 1350 patients, this is a very high reporting rate of PML with efalizumab. Sales of natalizumab, another biologic associated with PML was suspended when this association was observed. Natalizumab is currently available with a mandatory registry and other restrictions in place.

exposed patients only. The DODAC unanimously rejected the sponsor's PSOLAR proposal to study safety concerns.

ii. Nordic Database Initiative:

The sponsor proposes to use the Nordic database to collect postmarketing safety information in 4,000 ustekinumab-exposed patients and follow them for at least 10 years. The sponsor anticipates that it will take them 5 years to accrue 4,000 patients. In the event if ustekinumab uptake is slower than expected the sponsor proposed to extend the number of years these patients will be followed-up.

It is true that all the Nordic countries namely Sweden (population 9.2 million), Denmark (population 5.5 m), Finland (population 5.3 m), Norway (population 4.8 m), and Iceland (population 0.3 m) have full coverage tax-supported public health services independent of socio-economic status. All the citizens in each of these countries have a unique patient identifier and linkage to computerized pharmacy database and to several other registers such as national health registers, medical birth registers, cancer registers, causes of death registers, and hospital discharge registers (Furu K. Nordic Prescription Databases (Nordic PD). Oral presentation at a symposium at ICPE, August 2008). However, in general the uptake of biologics is very slow in these countries. For example, at the June 2008 DODAC, the sponsor said that their biologic product infliximab was used by over 10,000 patients in Sweden, Denmark and Finland for all indications and probably 1% of the use has been in psoriasis patients. In 2007, according to a very crude estimate, the number of patients treated with infliximab for dermatological indications (i.e., psoriasis) is less than 100, possibly only 50. This crude data is from 3 out of 24 counties in Sweden which represents 1 million inhabitants, i.e., 11% of the Swedish population (Anders Sundstrom, Karolinska Institute, Sweden. Personal communication. October 2008). Hence it could take potentially many years to obtain meaningful safety data from this database.

3. Five-year Extension of Pivotal Trials

This allows this biologic to be marketed prior to fully assessing the safety profile. This may be useful but there will be extensive loss to follow-up and quality of information will be questionable. The DODAC unanimously rejected this proposal.

4. Pharmacovigilance Program:

Traditional pharmacovigilance programs rely on passive spontaneous adverse event reporting systems which are best suited to identify rare event with short latency. Adverse event monitoring programs may not be able to capture events with long latency such as malignancy but may capture infections. Underreporting and incomplete or missing information are major limitations of passive surveillance system such as the FDA's Adverse Event Reporting System or AERS. In addition, we cannot calculate the incidence of an event because of lack of data on numerator (actual number of events) and denominator (total population exposed) and hence we can't quantify the risk of an event.

DISCUSSION

Drug Approval is an Evolving Science

The standard of drug approval has evolved over time as we learn from our past experience and this is what common sense requires us to do (Ahmad SR. Evolution of the FDA Drug Approval Process. Chapter 3: pp 25-41. In: TR Fulda, AI Wertheimer, editors, Handbook of Pharmaceutical Public Policy. Haworth Press, Binghamton, NY, USA. 2007). Over the years, we have raised the bar for approval of certain drugs, for example, antidepressants, sleep medications and antihypertensives. In the case of antidepressants we now 'require' that these drugs should be evaluated for their risk of suicidal ideation before approval.

From the early 1980s, there was substantial concern that elderly and women were not adequately represented in the New Drug Applications (NDAs) that were submitted to the FDA for approval. In the late 1990s, regulations regarding NDAs were changed and drug sponsors were required to do analyses in demographics subsets of the patient population (Temple R, Stockbridge N. BiDil for heart failure in black patients: The U.S. Food and Drug Administration perspective. *Ann Intern Med* 2007;146:57-62.). We now require drug sponsors to include a good representation of women and elderly in randomized controlled trials.

The requirement to conduct large cardiovascular outcomes studies with newer COX-2 inhibitors and those already approved went hand in hand and all NSAIDs – traditional and the

new coxibs label now carry boxed warning for adverse cardiovascular outcomes and gastrointestinal bleeding.

Recently, an FDA Endocrinologic and Metabolic Drugs Advisory Committee recommended that the Agency require long-term cardiovascular outcome study pre-approval for all investigational drugs for diabetes mellitus whether or not there was any cardiovascular signal in the phase 2/3 drug development stage. (Summary Minutes of the FDA Endocrinologic and Metabolic Drugs Advisory Committee, "Cardiovascular Assessment in the Pre-Approval and Post-Approval Settings for Drugs and Biologics Developed for the Treatment of Type 2 Diabetes Mellitus". July 1-2, 2008).

In the 1990s, the awareness of drug-drug interactions because of the cytochrome p450 enzyme system led to the withdrawal of anti-allergy medications namely terfenadine and astemizole. In the years following this, the sponsors were "required" to conduct drug interactions studies for their investigational drugs. Finally, FDA issued guidance to the industry suggesting to them that "the metabolism of a new drug should be defined during drug development and that its interactions with other drugs should be explored as part of an adequate assessment of its safety and effectiveness" [Guidance for Industry - Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling September 2006

(<http://www.fda.gov/cber/gdlns/interactstud.htm>)]

"During the late 1990s, ... the Director of Anesthetics, Critical Care and Addiction Drug Products encountered years of significant resistance from industry before sponsors finally agreed to switch from conducting non-inferiority clinical trials to placebo- and active controlled studies in situations where sponsors submitted formulation changes of existing opiate products. It is important to note that when such trials were undertaken, it was discovered that some of the products did not prove to be more effective than placebo, substantiating the concerns regarding non-inferiority trials. The Panel emphasized that as science changes the standards for regulatory approval also must change to reflect what we have learned". (Johann-Liang Rosemary. FDA Anti-Infective Drugs Advisory Committee, December 14-15, 2006 AC presentation)

Given the fact we have so little information about ustekinumab currently and the fact that there are a number of other biologics that are in the pipeline and sponsors are pursuing dermatologic indications which may be relatively easy to study, this reviewer is of the opinion that it may not be prudent to support the approval of a biologic with so many unanswered safety questions and so little safety data. It is indeed true that the Agency has approved other biologics with far less data but while we can be guided by precedent, we are not bound by it, as stated by Dr. Susan Walker, Director, DDDP. It is also true that over the years the science of drug regulation has evolved and the Agency has indeed raised the bar for drug approval in case of other products in the past which had potential safety concerns. Notable examples of such drugs are:

1. The newer selective COX-2 inhibitors: Following the withdrawal of rofecoxib (Vioxx) in October 2004, the FDA discussed the relative benefit and risk of all other NSAIDs including other approved COX-2 inhibitor drugs namely valdecoxib (Bextra) and celecoxib (Celebrex) and required a box warning for cardiovascular outcomes and gastrointestinal bleeding for all approved NSAID drugs. Similarly, FDA required sponsors of newer selective COX-2 inhibitors to conduct long-term cardiovascular outcomes studies pre-approval. The result of this "requirement" was that newer COX-2 inhibitors such as lumirocoxib, parecoxib and etoricoxib were not approved by the FDA even though some of these newer coxibs were approved by some other drug regulatory agencies including EMEA, Canada and Australia. In response to this evolving understanding of product risks, FDA standards also evolved to better protect the public from harm.
2. Tacrine (Cognex) - the first drug to be approved for Alzheimer's disease, where the sponsor had to conduct randomized controlled trials to study the hepatotoxicity risk associated with the drug prior to approval. Because of liver toxicity concern, FDA did not approve tacrine earlier. However, the Agency made this drug available since February 1992 to patients under a "treatment IND or Investigational New Drug" protocol that allowed more than 7,400 patients to receive the drug while the controlled clinical studies were being completed.

Treatment IND is an FDA procedure for promising drugs for serious diseases that provides for wider use than is usual during the pre-approval stage, provided no satisfactory approved treatment exists and patients won't be exposed to unreasonable risk. In March 1993, an FDA advisory panel recommended approval of the drug based on additional studies conducted by the sponsor and FDA approved the drug in September 1993, after reviewing the additional data in the studies.

3. **Telithromycin (Ketek)** – Telithromycin is the first member of a new class of antibiotics known as the ketolides, antibiotics which are closely related to the macrolides (e.g. azithromycin, clarithromycin and erythromycin). In 2001, the sponsor of telithromycin submitted its NDA to the FDA. In July 2001, the European Medicines Agency (EMA), approved telithromycin for use in fifteen member countries. The drug was first launched in October 2001 in Germany and in 2002 in other European markets. By June 2003, telithromycin was marketed in 36 countries around the world, including Canada and Japan. In April 2001, the FDA Anti-infective Advisory Committee recommended approval of this antibiotic. In June 2001, the FDA issued an approvable letter to the sponsor. However, because of safety concerns, FDA required the sponsor to conduct a large (over 20,000 patients) safety study prior to approval to examine adverse events of special interest (cardiac, hepatic, visual). In the US, FDA approved telithromycin on April 1, 2004 (Testimony of FDA Commissioner. Ketek hearing on the Hill.)
4. **Muraglitazar (Pargluva)** – Muraglitazar belongs to a novel class of drugs that target the peroxisome proliferator-activated receptors, both alpha and gamma subtypes and was investigated for the treatment of patients with type 2 diabetes. On September 9, 2005, the FDA Endocrinologic and Metabolic Drugs Advisory committee recommended approval of muraglitazar by a vote of 8:1 for the treatment of type 2 diabetes mellitus. On October 18, 2005, FDA reportedly issued an “approvable letter” to the sponsor. (Brophy JM. Selling safety—lessons

from muraglitazar. JAMA 2005;294:2633-5.) However, FDA required the sponsor to conduct an additional safety study prior to approval.

So, in all the above examples the additional “requirements” , a few of which have been added in guidances issued by the FDA does not in any way or shape mean that the Agency has treated different drug sponsors differently but rather it is making the best use of our experience and the evolving science of drug approval.

REGULATORY OPTIONS FOR CONSIDERATION

1. Additional randomized controlled trials: The sponsor should conduct additional randomized controlled trials pre-approval. The sponsor should pursue other serious non-dermatologic indications such as multiple sclerosis, Crohn’s disease, and rheumatoid arthritis to build the safety database as was done in the case of most other biological therapies, which were first approved for non-dermatologic indications.

2. Treatment IND: While the sponsor conducts additional randomized controlled trials, ustekinumab could be made available through the Treatment IND program, if regulations permit this kind of access for psoriasis which is a rarely life-threatening disease and for which alternative therapies exist.

3. Single-disease-based Psoriasis Registry: FDA should facilitate the creation of a single Psoriasis registry where makers of all biologic agents contribute data. Such an approach has the potential to increase the statistical power and provide meaningful data on the long-term safety of biological therapies. As a first step FDA should consider to organize a forum to discuss this option with all stakeholders. Such a registry can be initiated with the FDA collaboration like the French registry (Tubach F., et al. The.RATIO observatory: French registry of opportunistic infections, severe bacterial infections, and lymphomas complicating anti-TNF alpha therapy. Joint Bone Spine. 2005;72:456-60) of infections/ lymphomas in patients on anti-TNF alpha therapy coordinated by their drug regulatory agency, government research arm, industry and professional societies. Interestingly, efforts to establish registries with different goals and using different approaches exist in several countries such as the ARTIS

(Anti Rheumatic Treatment in Sweden) where clinicians, academicians, and the Swedish drug regulatory agency collaborate with a focus on TNF-blocking agents (Askling J, Fored CM, Geborek P, Jacobsson LT, van Vollenhoven R, Feltelius N, et al. Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis.* 2006;65:707-12). There is precedent for FDA to facilitate creation of a single drug-based registry such as the Ribavirin Pregnancy Registry.

4. **Mandatory Registry:** The sponsor should conduct a mandatory registry rather than a voluntary registry. In mandatory registry since access to drug is tied to being enrolled in registry, complete information on all exposed patients and cases are captured and this reduces selection bias. However, in mandatory registry, prescriber, patient and or pharmacist may have to do some additional tasks which may make prescription, sale and use of drug a little burdensome for all relevant parties. Mandatory registry also require restricted distribution of the drug. Since there may not be any incentive for patient to continue on registry after they discontinue therapy, it may be difficult to attribute the drug for events with long latency such as malignancy. Mandatory registry has the potential to restrict the distribution of this biologic to patients with serious psoriasis. An overwhelming majority of DODAC members, 8 out of 11 spoke in favor of a mandatory registry.

CONCLUSIONS

In conclusion, review of ustekinumab, a novel biologic agent, first in its class, with a novel mechanism of action presents regulatory challenges. Given the fact that ustekinumab is being considered for treatment of psoriasis, a rarely life threatening condition affecting a relatively healthy population; that psoriasis is a condition for which alternative therapies exist; that this product has carcinogenicity signal in the literature and is recommended for long-term use; that it has no prior marketing history in other non-psoriatic populations like most of the other approved biologics for psoriasis; that it has only 18 months of human exposure data on 373 patients; that the total human exposure is in about 2,000 psoriasis patients; and that being an immunosuppressant with potential risk of malignancy and opportunistic infections, the Agency has to make a regulatory decision with all these factors in consideration. We must start somewhere, and have to deal with already approved drugs later and there is precedence for this.

The safety profile for ustekinumab is far from established. Approving ustekinumab for psoriasis at this time would amount to post-approval human experimentation. There is no way to state with any confidence that the benefits exceed the risks, or that the potential superior efficacy exceeds the potential risks, which could be substantial. We simply do not know because the safety database is too scant and inadequate a fact which was unanimously agreed by the DODAC members at the June 17, 2008 meeting. The postmarketing risk assessment plan as currently proposed by the sponsor may be inadequate and insufficient in providing us the much needed safety data in a timely fashion. In addition, the sponsor's plan may not have the power to detect events of interest namely malignancy and serious opportunistic infection and hence may give us a false reassurance on the safety of ustekinumab.

Given all these uncertainty, it may be prudent to require the sponsor to pursue other serious non-dermatologic indications such as rheumatoid arthritis and multiple sclerosis and Crohn's disease prior to approval and build the safety database before this biologic is approved for psoriasis. This requirement will be certainly not an extra-ordinary measure by any regard and in fact will be in line to meet the mandates of last year's FDA Amendments Act (FDAAA) which gave the Agency much needed power to perform its job.

APPENDIX: STATISTICAL REVIEWER'S COMMENTS ON SAMPLE SIZE ISSUES

August 26, 2008

Yu-te Wu, Ph.D., M.P.H.
Mathematical Statistician
Quantitative Safety and Pharmacoepidemiology Group
Division of Biostatistics VI
Office of Biostatistics

OSE consult request:

Ustekinumab is a monoclonal antibody that targets human cytokines IL-12 and IL-23 (first in its class NME). The proposed indication is "treatment of adult psoriasis (18 years and older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy". It is an immunosuppressant with an animal carcinogenicity signal (murine). The safety concerns are serious infections and risk of malignancy (long latency and low frequency events). Please comment on the sample size and power considerations proposed by the sponsor in its latest submission regarding postmarketing studies.

Materials reviewed:

BLA 125261, Sequence 0030

Malignancy Position Paper and Enhanced Risk Management Plan

Sample Size Issues/Reviewer's Comments

Sponsor did not provide the following details for the power calculations shown on pages 42 and 43:

- 1) Did not specify the statistical methods used for power calculations
- 2) Did not specify whether the testing was based on one-sided or two-sided alpha of 0.05
- 3) As stated on pages 42 and 43, the background rate = 0.36% for malignancy and = 1.07% for serious infection were used for the calculations. However, the unit should be presented as per 100 patient-years (source document: Table 36 on page 114, Advisory committee briefing document dated on May 31, 2008).

Statistical reviewer was able to replicate the results of power calculations shown in Figure 2 (page 42) and Table 1 (page 43) based on the following assumptions:

- 1) The calculations were based on 2-sided alpha of 0.05
- 2) The unit of background rate is as per 100 patient-years, not as % shown in the document
- 3) The background rates proposed were adequate
- 4) Power = 0.80

- 5) The calculations were based on the method proposed by Thode²
- 6) Assuming no loss-to-follow-up

- Sponsor needs to provide the estimates of loss to follow-up rate in the study cohorts and take that into account in the power calculations.
- The estimates of background rates were based on all phase 2 and 3 data through 120-day safety update in patients taking ustekinumab. The reviewer was not clear why the sponsor chose the incidence rates in patients taking ustekinumab as the background rate. Based on sponsor's paragraph as below, the malignancy risk in patients taking ustekinumab will be compared to the risk in control subjects. Therefore, the incidence rate in the control cohort should be used as the background rate for the power calculation. Sponsor needs to justify the adequacy of background rate used in the calculation.

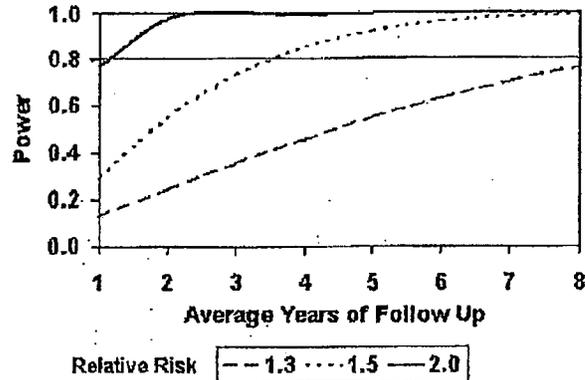
Section 2.2.1.2 Signal detection in all proposed data sources

In order to help establish the upper limit for the relative risk for malignancy serious infection, the rates of these events observed in our clinical development program can be utilized. This relative risk can only be assessed using comparator groups such as in health care databases. The number of patients and the duration of follow-up needed to have 80% power to detect an elevated relative risk can be calculated. Using malignancies as an example, in _____, assuming 4000 ustekinumab-treated patients and 16,000 controls, with an alpha of 0.05, we are able to detect fairly modest increases in relative risk over time. Assuming a baseline rate of malignancy of 0.36%, for example, we will be able to detect a relative rate of 2, after 4000 ustekinumab-treated patients are following for 2 years and a relative risk of 1.5 by after these patients are followed for 5 years.

b(4)

² Thode CH. Power and sample size requirements for tests of differences between two Poisson rates. *The statistician* 1997; 46(2): 227-230.

Power to Detect a Difference: Noncutaneous Malignancies



$\alpha = 0.05$ Background Rate = 0.36%
N = 20,000 4:1 Ratio Control: Ustekinumab

Figure 2 Power calculations and relative risk for solid tumors over proposed observation period

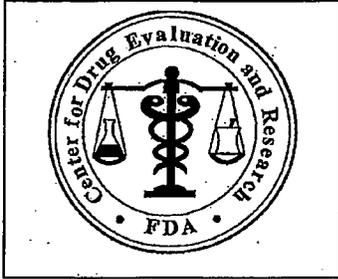
Table 1 Average patient-years of observation to exclude relative risk for aggregate events in PSOLAR, Nordic Database Initiative (NDI) and Health Claims databases						
Database	Aggregate Event (clinical trial baseline rate)	Year 1	Year 2	Year 3	Year 5	Year 8
PSOLAR	Malignancy (0.36%)	2.4	2	1.8	1.5	1.4
	Serious Infection (1.07%)	1.8	1.5	1.4	1.3	<1.2
Healthcare or NDI database	Malignancy (0.36%)	2	1.7	1.5	1.4	1.3
	Serious Infection (1.07%)	1.4	1.4	1.3	<1.2	<1.2

Notes:

- PSOLAR, NDI, and HC Claims databases have intrinsic comparator cohorts. Time to exclude risk in NDI and HC databases is accelerated due to availability of a larger comparator cohort.
- Statistical assumptions - sample cohort is 4000 patients exposed, alpha error 0.05, in Health Claims or NDI databases the control group: sample cohort ratio is 4:1.
- Malignancy rate in aggregate excludes non-melanoma skin cancer.

Design issue/Reviewer's comments

- Loss to follow up is a common problem in the long-term follow-up study. There is no mention how to minimize the loss to follow up in the study cohort and also the power calculation did not account for this bias
- The sponsor needs to discuss the limitations of health plan databases (e.g., PharMetrics, MarketScan, Ingenix/13)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Epidemiology

Date: May 22, 2008

To: Susan Walker, M.D., Director
Division of Dermatologic & Dental Products (DDDP)

Through: Solomon Iyasu, M.D., M.P.H., Director
Division of Epidemiology
Office of Surveillance and Epidemiology
Syed Rizwan Ahmad
5-22-08

From: Syed Rizwanuddin Ahmad, M.D., M.P.H., F.I.S.P.E. *05/22/08*
Medical Epidemiologist

Subject: Study protocol review

Drug Name(s): Drug: Ustekinumab

Submission Number: BLA 125261

Applicant/sponsor: Centocor, Inc.

OSE RCM #: 2008-339

INTRODUCTION

This memorandum is in response to a request from the Division of Dermatologic & Dental Products (DDDP) to the Office of Surveillance and Epidemiology (OSE) to review and comment on a Risk Management Plan submitted by Centocor, Inc., for, ustekinumab.

Ustekinumab is a human monoclonal antibody with an apparently novel mechanism of action that targets the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23). These naturally occurring proteins regulate immune responses and are reported to be associated with some immune-mediated inflammatory disorders, including psoriasis. Within the proposed RMP for ustekinumab, the sponsor included a protocol of Psoriasis Longitudinal Assessment and Registry (PSOLAR), a multi-center, open registry of patients with psoriasis who are candidates for systemic therapy including biologics. This memorandum includes a review of the PSOLAR specifically and a comparison to protocols received for efalizumab (Amevive®) and alefacept (Ratpiva®) which are also biologics approved for moderate-to-severe psoriasis.

MATERIALS REVIEWED

Primary review material consisted of a 38-page document entitled, "Registry C0168Z03: A multicenter, open registry of patients with psoriasis who are candidates for systemic therapy including biologics (09 Nov 2006)," including Amendment 1 dated 07 August 2007. In addition, a separate section of the Risk Management Plan (pages 65-69) entitled, "2.3 Detailed action plan for specific safety concerns" was also reviewed. Protocols submitted by the sponsors of efalizumab for the "RAPTIVA® Epidemiologic Study of Psoriasis Outcomes and Safety Events in Patients with Chronic Moderate to Severe Plaque Psoriasis or RESPONSE" (study protocol # ACD3101g dated 1 February 2005, Dates Amended: 10 November 2005, 13 December 2006) and that for alefacept, "Assessment and Tracking of Long-term Alefacept or ATLAS" (study protocol # C-736, dated 21 February 2003, Version 1. Final) as a part of postmarketing commitments at the time of approval were also reviewed. The Briefing Document for Ustekinumab dated May 13, 2008 as prepared by the sponsor for the FDA Dermatologic and Ophthalmic Drugs Advisory Committee meeting, June 17, 2008 was also reviewed.

Overview of PSOLAR

PSOLAR is a prospective, longitudinal, 8-year, observational study of long-term safety and clinical outcomes in patients at least 18 years of age with all forms of psoriasis, including plaque psoriasis and psoriatic arthritis, who are candidates for systemic therapy (such as methotrexate, acitretin, cyclosporine, or systemic PUVA) or therapy with biologics. The study is being conducted in both academic and community-based practices. The purpose of PSOLAR is to further evaluate the safety of a recombinant immunoglobulin G (IgG) biologic product infliximab (Remicade®), [by the same sponsor, Centocor, Inc., and approved in August 24, 1998] in patients with chronic severe (extensive and/or disabling) plaque psoriasis and all overlapping forms of psoriasis, including plaque psoriasis and psoriatic arthritis, in patients who are candidates for systemic therapies.

The protocol states that PSOLAR is designed to track serious adverse events, and targeted adverse events (such as malignancies, tuberculosis and other opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, congestive heart failure, hepatotoxicity, and hematologic events) in addition to disease activity, quality of life and specific health economic measures. The registry will include approximately 8,000 patients, to include at least 4000 infliximab-exposed patients, and a comparable number of patients who are prescribed other biologics or systemic therapies.

Specific Protocol issues/Reviewer's Commentary

Objectives: The primary objective of the registry is to evaluate the safety of infliximab in patients with chronic severe (extensive and/or disabling) plaque psoriasis and all overlapping forms of psoriasis, including plaque psoriasis and psoriatic arthritis, in patients who are candidates for systemic therapies. The secondary objectives of the registry are (1.) To evaluate clinical outcomes, quality of life, and comorbidities for patients who may receive conventional systemic or biologic therapy for psoriasis. (2.) To assess the proportion of patients exposed to infliximab that meet labeling criteria relative to the number of patients exposed, based on data collected within the registry.

Comment:

The sponsor should clarify the role for PSOLAR at this time. The PSOLAR protocol as submitted and reviewed was focused on infliximab. Going forward, will PSOLAR now be focused on the primary safety of ustekinumab and as part of a postmarketing commitment for ustekinumab. Additionally, was PSOLAR intended to fulfill postmarketing commitment for infliximab?

We recommend that the sponsor describe how they will ensure that ustekinumab is being prescribed per labeling recommendation to the appropriate adult psoriasis patient population with chronic, moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Sample Size: Per page 66 of the sponsor's RMP, PSOLAR "is designed to specifically track AEs in approximately 8000 patients, of whom up to 4000 will be exposed to ustekinumab."

Per page 188 of the sponsor's RMP and the www.clinicaltrials.gov listing for PSOLAR (<http://clinicaltrials.gov/ct2/show/NCT00508547?term=psolar&rank=1>. Accessed May 19, 2008), this registry is planned to include at least 4000 infliximab-exposed patients, and a comparable number of patients who are prescribed other biologics or systemic therapies.

Comment:

The sponsor needs to clarify the number of ustekinumab-exposed patients that will be included in PSOLAR. As noted in the Table (below), protocols for the post-approval safety studies for efalizumab (Amevive®) and alefacept (Ratpiva®) include 5,000 patients each.

Study Design: PSOLAR is proposed to be multicenter involving 500 sites in North America, Europe and Asia. This registry is a prospective, longitudinal, 8-year, observational study of long-term safety and clinical outcomes in patients receiving treatment for psoriasis. Treatment will be provided based on actual clinical practice or standard of care and there will be no restrictions on the use of concomitant medications. As noted under "6 Statistical Methods" of the PSOLAR registry protocol, data from the registry will be evaluated using longitudinal observational cohorts to assess safety, clinical outcomes, quality of life, comorbidities, pharmacoeconomics, and treatment regimens.

Comment:

A multicenter study design is desirable in order to collect enough patients within the proposed time frame. Enrollment criteria should include demographic and clinical attributes to ensure that participants are representative of the target population in which ustekinumab will be used. We note the original PSOLAR protocol was designed with a robust comparator arm. This is distinct from the protocols for efalizumab (Raptiva®) which includes 500 in the comparator arm and the protocol for alefacept (Amevive®) which includes no comparator arm.

Data Collection: Patient demographics, medical history and baseline characteristics, medical history, past history of psoriasis treatments; history of concomitant medications, dose and frequency of infliximab or other systemic therapies, and clinical status will be collected at the time of enrollment, i.e., baseline and on a 6-monthly basis.

The protocol states the reporting timeline for all adverse events including serious adverse events; adverse events of special interest which include malignancies; tuberculosis and opportunistic infections; hypersensitivity reactions; autoimmune disease; neurologic or demyelinating events; congestive heart failure; hepatotoxicity; and hematological events; and pregnancy will be within one week of observation or notification. With respect to deaths, the protocol states that all patient deaths must be reported to the sponsor or its designee by the registry physician/site within 24 hours of observation or notification. Data will be obtained by direct contact with the patient, review of the medical records, contact with the patient's treating physician. The protocol states that the registry will be conducted in accordance with current ethical regulations and guidelines and informed consent will be obtained from all patients prior to data collection.

Comment:

The data collection methods specified appears to be appropriate. In addition, the investigators should collect complete dosing information for ustekinumab and any previous treatments for psoriasis including dose administered, duration of therapy, and therapy start and stop date, if applicable. Patient demographics data including age, and gender; and data on psoriasis severity should also be collected. The investigators should ensure that adequate data quality

assurance measures are in place to maintain uniformity and standardization in data collection in all the possible 450 centers where study will be conducted. Regarding adverse events data, the investigators should try to collect all relevant information such as full description of the event including type and severity; laboratory values; time to onset of event from therapy start date; information about rechallenge and dechallenge; and information about concomitant therapy and comorbid conditions. The protocol should ideally collect adverse events through active surveillance and patients should also be educated regarding reporting of all suspected adverse events to the registry physician or site or the sponsor. The protocol should specify the timeline for reporting all patient deaths to the FDA as well. The protocol mentions the existence of Registry Reference Manual which apparently has additional details. The sponsor should provide full information including a copy of the Registry Reference Manual to the FDA. In addition, the investigators should indicate if the patient questionnaire will be submitted to the FDA for evaluation, and if the questionnaire will be administered by trained healthcare professionals experienced in this activity.

Duration of Observation: The protocol states that patient enrollment phase will last approximately 2 years; the planned observation period for each patient will be 8 years; and the registry will be conducted for a period of approximately 10 years.

Comment

The duration of follow-up (~10 years is similar in length to that advanced in the postmarketing safety study for efalizumab (Amevive®) and longer than alefacept (Ratpiva®) which includes a 5 year follow-up period.

Patient Follow-up and Retention: The protocol states that the patient participation in the registry will be encouraged but patients will have the right to voluntarily withdraw consent at any time.

Comment

The sponsor should indicate if any incentive will be provided to the patients to complete the duration of the study. The patient management and retention plan outlined in the registry appears to be appropriate.

Interim Analyses: The protocol states that interim analyses will be conducted annually and comprehensive annual report with registry accrual rates, number of adverse events, total person years of observation, psoriasis severity, dose and duration of therapy, as well as uptake of the infliximab and ustekinumab will be included. The protocol mentions the existence of a Registry Steering Committee.

Comment:

The report should also provide details of the number of cases of lost to follow up, and an analysis of all adverse events of interest. The protocol should state the composition of the Registry Steering Committee.

Data Integrity: The protocol states that the sponsor or its designee will perform site visit during the course of the registry to monitor the progress of the registry; and maintain the overall quality and integrity of the data.

Comment

The protocol should specify the frequency of site visits that will be conducted over the duration of the registry.

CONCLUSIONS AND RECOMMENDATIONS

Ustekinumab is a human monoclonal antibody with an apparently novel mechanism of action that targets the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23). These naturally occurring proteins regulate immune responses and are reported to be associated with some immune-mediated inflammatory disorders, including psoriasis. This memorandum is the review of the sponsor's protocol PSOLAR to study long-term safety of their products ustekinumab and infliximab and includes a comparison with protocols received for efalizumab

(Amevive®) and alefacept (Ratpiva®) which are already approved biologics for moderate-to-severe psoriasis.

Registries may be complete (mandatory enrolment) or incomplete (voluntary enrolment). In general, incomplete registries such as PSOLAR may not represent the best research design to study long term and rare outcomes such as malignancies, and opportunistic infections due to limited absolute size, voluntary participation, and issues of loss-to-follow-up. As also acknowledged by the sponsor "registries may not have the ability to evaluate rare events or identify lower relative risks." (Sponsor's Briefing Document for Ustekinumab, May 13, 2008, p. 123).

Compared to the protocol for efalizumab which initially included a comparison group of 2,500 cohort treated with other biologics, and alefacept which has no comparison group, the protocol for PSOLAR suggests that data will be compared with other conventional and biologic therapies.

In conclusion, the sponsor need to elaborate and clarify a number of elements of PSOLAR as outlined above under Reviewer's Commentary. As currently proposed PSOLAR is not the best research design to study the long-term safety of ustekinumab. An alternative option could be a mandatory long-term registry where all individuals exposed to ustekinumab are included. Input from the Advisory Committee on the optimal approach would be useful.

Brief Comparison of Protocols Submitted to Study Long-term Safety of Three Biologics for the treatment of Psoriasis			
Characteristic/Feature	Ustekinumab	Efalizumab	Alefacept
Objectives	Primary: To evaluate the safety of infliximab Secondary: To evaluate the clinical outcomes, quality of life, and co-morbidities. To assess the proportion of patients who meet the labeling criteria	Primary: To estimate the incidence of targeted serious adverse events – all malignancies; infections; psoriasis-related events; inflammatory & autoimmune-mediated events; thrombocytopenia, hepatic events Secondary: To explore the association of psoriasis treatments with patient outcomes	Primary: To measure the rates of NonHogkin Lymphoma & infections that require hospitalization Secondary: To estimate the rates of lung, breast, prostate, & colorectal carcinoma, melanoma, and active TB.
Study Design	Prospective multicenter open registry	Prospective, multicenter study	Open-label, observational cohort study
Study Population/Database	Patients who may receive conventional systemic or biologic therapy for psoriasis	Patients who have received efalizumab	Patients treated with alefacept for chronic plaque psoriasis
Setting	North America, Europe, Asia	USA	USA
Duration of Study	Enrollment period= 2 yrs; Observation period for each patient=8 yrs; Total duration: 10 yrs	8-9 years from study initiation	5 years
Age (years)	≥18 years	Not stated in protocol	≥18 years
Criteria for Participation	Male or female patients with psoriasis Patients who can receive or are on conventional systemic agents or biological therapy Ability to understand and sign informed consent form	Patients who are being treated with or initiating efalizumab Willing to fully participate for 5 years	Patients who are prescribed alefacept consistent with the product labeling
Sample Size	4000 infliximab-exposed patients Comparable cohort exposed with other biologics and/or conventional systemic agents	5000 efalizumab-exposed patients Formerly 2500 comparison cohort treated with other biologic	5000 alefacept-exposed patients
Ascertainment of Outcomes of Interest	Plan exists to report and follow-up serious outcomes including adverse events of special interest	Plan exists to elicit and/or discover all serious adverse events at follow-up visits	Study center will contact patients directly for relevant info every 6 months by telephone interview.
Data Collection	At baseline – demographics, medical/ family history, previous psoriasis treatments, history of concomitant meds, health economics info and quality of life assessments At 6 th Month interval thru 8 years – clinical status, disease characteristics, adverse events, concomitant meds, health economics info, and quality of life assessments	Screening/Baseline- Demographics, age at time of psoriasis diagnosis, pregnancy status, psoriasis & medical history, lab evaluations (hematology, chemistries, serum samples of anti-Rapivva and anti-platelet antibody assessments) At 6 th month interval – Psoriasis and medical history, serious adverse events	At enrollment – demographics, medical history, current psoriasis severity & history, medications history, concomitant medications, and alefacept treatment regimen At 6 month interval – Alefacept treatment regimen, concomitant medications, any hospitalizations, biopsies, and any malignancies
Patient Follow-up & Retention	Elaborate plan for follow-up and retention including search in the National Death Index Uniform and standardized form exists for data collection	Plan to follow-up patient exists	Plan to follow-up patient exists
Data Quality Assurance		Electronic case report form exists. CRO will be responsible for data management and quality	Data collection tool exists. Instructions will be provided to sites to ensure accurate, complete and reliable data
Interim Analyses/Annual Report	Yearly interim analyses will be conducted. Annual report will include registry accrual rates, number of AEs, total person years of observation, psoriasis severity, dose and duration of therapy, and total U.S. infliximab use by age, gender, and indication	Not stated in protocol	Study objectives will be assessed annually beginning first year after enrollment of the first patient.

Protocol Date	August 07, 2007	December 13, 2006.	February 21, 2003
ClinicalTrials.gov identifier*	NCT00508547	NCT00096928	NCT00454701
Start date*	June 2007	March 2005	July 2003
Last update*	Not stated	September 2007	October 2007
Status*	recruiting	recruiting	recruiting

*as indicated in the ClinicalTrials.gov database (www.clinicaltrials.gov), Accessed May 19, 2008