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NDA 22-187
INTELENCE® etravirine

Cross Reference IND 113,895
Cross Reference IND 63,646

Response to PREA Non-Compliance Letter

Dear Dr. Birnkrant:

On 15 July 2013, the FDA issued a Notification of Non-Compliance with PREA to NDA 22-187 for failure to fulfill a PREA commitment because Janssen had not yet submitted the pediatric assessment due on 30 June 2013. The PREA commitment is as follows:

Conduct deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 months to 6 years of age. This study will determine the pharmacokinetic profile, safety, and activity of etravirine in pediatric subjects from 2 months to 6 years of age.
Protocol submission: June 2010; Final report submission: June 2013

Under the provisions of section 505B(d) of the Federal Food, Drug, and Cosmetic Act as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), Janssen is providing this response letter to outline the reasons for the delayed pediatric assessment, including the delays in the study initiation, the challenges in subject recruitment, the current study status, and the steps taken by Janssen to mitigate these issues. Janssen intends on submitting a pediatric deferral extension request by September 3, 2013 for the Agency's review and consideration.

To fulfill the PREA commitment noted above, Janssen is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID), as represented by the division of AIDS (DAIDS) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT). The IMPAACT Group has long and outstanding experience in the design and conduct of pediatric clinical studies related to HIV and acquired immunodeficiency syndrome (AIDS).

Cross-reference is made to IND 113,895 for etravirine, in which DAIDS submitted the following protocol, the results of which Janssen intends to submit to fulfill the PREA commitment above: TMC125-C234/P1090: "*A Phase I/II, Open-Label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-Experienced HIV-1 Infected Infants and Children, Aged ≥2 months to <6 years".*

Delays in Study Initiation

The pediatric development program started with the assessment of the efficacy, safety and pharmacokinetics of etravirine in treatment-experienced HIV-1 infected children and adolescents between the ages of 6 and <18 years (study TMC125-C213). A study in a younger age group (≥2 months to <6 years, study TMC125-C234/P1090) was to be initiated after the review of the Week 24 (primary) results of TMC125-C213.

TMC125-C213 was initiated on 1 July 2008, with a recruitment goal of approximately 100 subjects. The study had several recruitment challenges throughout its entire open enrollment period, as patients fitting the eligibility criteria were harder to find than expected. As a consequence full recruitment was reached on 16 July 2010, approximately 15 months later than what was originally projected. These recruitment challenges and the impact on protocol development and initiation of the TMC125-C234/P1090 study were described in correspondences to IND 63,646 (SN 939, 980, 1041) dating back to 2009-2010.

To address challenges in the initiation and enrollment of study TMC125-C234/P1090, Janssen and IMPAACT decided to begin TMC125-C234/P1090 after evaluation of the relevant data at Week 12 on 75 subjects from TMC125-C213 instead of based upon the evaluation of the Week 24 analysis of TMC125-C213. In addition, Janssen and IMPAACT worked closely together on the development of a protocol design that would allow for a faster recruitment by using a mini-cohort approach. DAIDS submitted the initial protocol to the FDA and the clinical investigational sites on 15 November 2011. However, the start of screening for TMC125-C234/P1090 was delayed primarily due to the unanticipated change in the study's pharmacokinetics (PK) lab. Once IMPAACT identified a new PK lab, Janssen expeditiously worked with the newly selected PK lab to validate the necessary analytical methods. Due to this unforeseen event, the first subject was screened only on 16 October 2012, approximately 10 months later than expected.

Current Pediatric HIV Population and Recruitment Challenges

IMPAACT designated the TMC125-C234/P1090 as a high priority protocol, based on the need for additional ARV agents for young children and infants.

With the successful role out of expanded access to perinatal HIV testing, and improved regimens for prevention of mother-to-child transmission of HIV, most countries with IMPAACT certified clinical sites have reported a significant decrease in the number of newly identified HIV-infected infants and children.[1] In addition, for those that are identified, and treated with first and second line highly active antiretroviral therapy (HAART) regimens, virologic suppression is well maintained over an extended period of time. In a study conducted in 266 children, 82% of

[1] UNAIDS report on the global AIDS epidemic 2012: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf

subjects were virologically suppressed after 4 years and 71% of children were still on first-line therapy after a median follow-up of 5 years.[2] These advances have led to a greatly decreased pool of eligible subjects for study TMC125-C234/P1090. The decrease in the potential pool of subjects has resulted in much slower progression of the study timelines.

TMC125/C234 Recruitment Status and Study Challenges

IMPAACT performed a feasibility study prior to study initiation and actively sought sites located in areas with high incidence rates of maternal HIV infection and newly identified HIV-infected infants (South Africa, Thailand and Brazil). At the same time, these sites need to be capable of and experienced with implementation of complex drug protocols, requiring intensive pharmacokinetic sampling.

IMPAACT opened the first site for screening in October 2012. Currently, a total of 21 sites have been opened (USA (19), South Africa (1) and Thailand (1)). To date, these sites have screened 6 patients (USA (2), South Africa (4)), of which 3 were enrolled (USA (1), South Africa (2)) and 3 were screen failures.

With the landscape of HIV infection incidence in the target population for TMC125-C234/P1090 changing rapidly across the globe, the initial feasibility assessment has become obsolete in prediction of recruitment timelines. Therefore, in early 2013, Janssen requested IMPAACT to contact the sites for updated information, which is currently being collected.

The enrollment rate is approximately 1 subject/2 months (3 subjects enrolled from 16 October 2012 to 1 May 2013), which is lower than the anticipated rate of 1 subject enrolled/month. In spite of a possible exhaustion of recruitment in the initial recruiting sites, Janssen estimates that, thanks to the recruitment enhancement activities, the current rate of 1 subject/2 months can be maintained for children between 2-6 yrs of age (Cohort I).

In addition to these recruitment difficulties, an unexpected pharmacokinetic result in this study led Janssen and IMPAACT to halt the screening of the study temporarily and to develop a protocol amendment in order to address this issue. Janssen and IMPAACT expect to submit this amended protocol to the FDA by end of September 2013 and to resume the screening of patients shortly thereafter.

Measures to Address the Challenges Related to the PREA Commitment

Janssen has been working and continues to work closely with IMPAACT to implement a number of measures to address challenges in this pediatric program. First, as noted above, Janssen and IMPAACT decided to initiate TMC125-C234/P1090 after the review of Week 12 results of TMC125-C213. Janssen and IMPAACT also worked together on the modification of the protocol design to a mini-cohort approach, which allowed for a faster initiation of subsequent cohorts. When there was an unexpected change with the PK lab, Janssen expeditiously worked with the newly identified PK lab to validate their analytical methods and open screening. Upon Janssen's request, IMPAACT is currently re-evaluating the projections of eligible subjects, to which Janssen has reviewed and to which it has provided input. For 12 new sites (in USA, South Africa, Thailand, Argentina and Brazil), the site implementation plans (SIP) were approved, and

[2] Babiker A et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis 2011; 11: 273-83.

the site opening is expected 1Q2014. For the most updated site information, please refer to clinicaltrials.gov (identifier: NCT01504841). Janssen and IMPAACT agreed to make darunavir/ritonavir available as study drug to broaden the choice of boosted protease inhibitors (PI), as required per protocol, for children between the ages of 3 and 6 years if darunavir/ritonavir is not locally available. The study protocol team, made up of both members from Janssen and IMPAACT, meets every 2 weeks to discuss systematically with site investigators, and identify possible solutions for topics such as patient recruitment.

Janssen Proposal to fulfill PREA Commitment

Under the provisions of FDASIA, Janssen intends to submit a PREA Deferral Extension Request to the Division no later than 03 September 2013. Janssen is committed to working with the Division in its collaboration with DAIDS/IMPAACT to fulfill this PREA Commitment.

A copy of this response will also be provided to CDER's Pediatric and Maternal Health Staff.

The electronic CTD submission is being submitted via the FDA ESG. Janssen Research & Development, LLC certifies that appropriate precautions have been taken to ensure that this eCTD submission is free of computer viruses via scanning with the Microsoft ForeFront Client Security and authorizes CDER to use anti-virus software as appropriate.

If you have any questions regarding this submission, please contact me at (908) 927-3779 or nnair@its.jnj.com.

Sincerely,

(See appended electronic signature page)

Nancy V. Nair, PharmD, MBA
Associate Director, Global Regulatory Affairs
Janssen Research & Development, LLC

CC: Pediatric and Maternal Health Staff (Lynn P. Yao: HFD-180, Room 5120)

SIGNATURES

Signed by	Date	Justification
Nancy Nair	27Aug2013, 16:09:08 PM, UTC	Document Approval