SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

IMPAACT 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

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 5.0, dated 10 March 2016

The information contained in this protocol amendment impacts the IMPAACT P1090 study and must be submitted to site Institutional Review Boards (IRBs) and Regulatory Ethics Committees (RECs) as soon as possible for review and approval. This amendment impacts the study informed consent forms (ICFs); all study sites must prepare updated informed consent forms and obtain IRB approval of the updated forms. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon receiving IRB/EC and any other applicable regulatory entities approvals for this amendment, this amendment is to be implemented immediately and using the updated ICFs.

All study sites must submit an amendment registration packet to the DAIDS Protocol Registration Office (PRO); however, approval from the DAIDS PRO is not required prior to implementing the amendment.

This Summary of Changes, Version 5.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB correspondence should be retained in each site's essential document files for IMPAACT P1090.

Summary of Revisions and Rationale

The primary purposes of this full version amendment are to 1) incorporate changes that will enable the team to revise the cohort management plan so that Cohort III (eligible children ≥ to 2 months of age to < 1 year who are treatment experienced) may open to enrollment upon release of Version 5.0 provided that available Cohort II safety and PK are acceptable and 2) include changes implemented via Letter of Amendment #1, dated 22 January 2016. We are using this opportunity to also make additional adjustments to the study roster, to revise one of the study objectives for internal consistency, to reduce expected blood volumes from Cohort III participants and to correct formatting issues throughout the protocol.

Detailed Listing of Modifications

Detailed modifications of the protocol text in this summary of changes are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions). Unless otherwise stated section numbers reflect the current version of the protocol.

1. Protocol roster has been updated.

2. Schema:

   a) Two qualifications have been added to Stratification:

   This is a sequential study which started accrual with the oldest age cohort and will progress down to the youngest age cohort. **Cohort III will open with the activation of Version 5.0**

   Children will be stratified by age, as follows:

   - Cohort I: ≥ 2 year to < 6 years who are treatment experienced*
   - Cohort II: ≥ 1 year to < 2 years who are treatment experienced*
   - Cohort III: ≥ 2 months to < 1 year who are treatment experienced*, †

   […]

   † **subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.**

   Note that this latter qualification has also been added to Section 3.2 Table 6 and Section 8.1.

   b) The fifth secondary objective has been revised to reflect the planned analyses described in Section 9.4.

   To explore the relationship between subject-specific gene CYP profile, **sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers** and pharmacokinetics of ETR.

   Note that this same revision has been made to Section 2.25.

3. Section 1.32. Pediatric Studies. There have been two changes to this section:

   Justification and rationale for revising the cohort management plan to allow earlier opening of Cohort III and for the planned approach for dosing are outlined in a new section: **Data from the second P1090 mini-cohort and a) rationale for opening Cohort III and b) dose selection for Cohort III**

   The following paragraph has been added to the end of the section titled: "Additional Safety Data":

   As of February 12th, 2016, fourteen participants between the ages of 2 to 6 years have been enrolled into P1090. To date, adverse events have been primarily unrelated to study product; none raised concerns regarding the safety of ETR in this population. Specifically, there has been no reported skin rashes related to study med, nor any safety events related to EKGs obtained on the day of pharmacokinetic testing.

4. Section 3.0. Study Design.

   Figure 2 has been retitled as "Algorithm for Cohort Management **as of Version 5.0**" and has been completely revised. Detailed explanations of the changes are provided in Section 3.3 and (new) Section 3.5 (see below).

5. Section 3.3. Mini-Cohorts. This section was revised as follows:

   ~~Enrollment will move~~ **Under prior versions of the protocol, enrollment moved** in a sequential manner, from the oldest cohort to the next youngest cohort ~~and then the youngest cohort~~ (Cohort I →Cohort II~~→ Cohort III~~). **Upon release of Version 5.0, the team will consider opening Cohort III while the first mini-cohort of Cohort II may still be enrolling based on available PK and safety data to ongoing participants. Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects of at least 6 months of age and less than 1 year of age (see Figure 2 and Section 3.5).**

   […]

   The P1090 core protocol team will review the PK and safety results of each mini-cohort, and if acceptable, enrollment will resume, at that dose, to complete enrollment of the remaining 6 slots. ~~Enrollment into the next (younger) mini-cohort, will begin once 4-week safety data for the older mini-cohort are deemed appropriate, and sufficient PK data are available to assess the most appropriate starting weight-based dose for the mini-cohort. The team may request SMC review and advice at this time.~~

6. Section 3.5. A new section has been created entitled "**Cohort III**."

   Upon release of Version 5.0, the P1090 core protocol team will review the available PK and safety results of Cohort II to determine whether Cohort III may be opened to enrollment of infants ≥ 6 months and < 1 year of age.

   3.5.1 Available Cohort II PK and safety data are acceptable

   If the available PK and safety data are acceptable, enrollment into Cohort III will commence starting with infants ≥ 6 months and < 1 year of age.

   In the event that Cohort III is open to accrual at the time that Cohort II completes accrual of a mini-cohort (N=6), accrual into both cohorts will be paused as per Section 3.3.

   3.5.2 Available Cohort II PK and safety data are not acceptable

   If available safety and/or PK data from Cohort II are unacceptable at this time, Cohort III will remain closed to enrollment; Cohort II will continue to enroll to complete the mini-cohort of six subjects. At that point, the team will evaluate the mini-cohort as described in Section 3.3.

   If the 4-week safety data from the six subjects in the Cohort II mini-cohort are deemed appropriate, and sufficient PK data are available to confirm the starting weight-based dose for the older infants in Cohort III as per Dosing Table 2, Cohort III will open to enrollment of infants > 6 months and < 1 year of age.

If the 4-week safety data from the six subjects in the Cohort II mini-cohort are not deemed appropriate, and/or PK data confirm the starting weight-based dose for the older infants in Cohort III as per Dosing Table 2, Cohort III will remain closed to enrollment and a new mini-cohort will be enrolled into Cohort II as per Section 3.3.

3.5.3 Enrollment of Cohort II is paused at time of release of Version 5.0

If enrollment of Cohort II is paused for review of mini-cohort data at the time of release of Version 5.0, opening of Cohort III will be held until Cohort II is re-opened.

Once there are sufficient data of infants ≥ 6 months and < 1 year of age to assess the impact of age on the pharmacokinetics, enrollment of the youngest group of infants in Cohort III (≥ 2 months and < 6 months of age) will commence.

7. Section 8.0 has been edited as per 2a above and as follows:

   a) 8.1 General Design Issues

   […]
   Accrual to the study will follow an algorithm in which younger children's **(Cohort II and Cohort III)** exposure to the study medication is contingent upon the older age cohort **(Cohort I)** having passed the safety criteria. In addition, sufficient pharmacokinetic data will be required to determine the starting dose for the younger cohort (see Section 3.3-3.4 for details).

   Initial tests of safety and PK will examine data from the first 6 subjects (mini-cohort) of Cohort I to determine whether Cohort II **and Cohort III** will be allowed to open for its mini-cohort of 6 subjects. **Subjects below 6 months of age will not be enrolled until there are initial safety and PK data from subjects between 6 months and 1 year of age.** These tests will proceed as follows: […]

   b) 8.512 First Six Subjects Started at a Given Dose Level in Each Cohort

   For each **study** cohort **(Cohort I, Cohorts II & III combined)**, the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 6 subjects. The data will extend to the week 4 visit for subjects not requiring dose adjustment or until the visit on which the dose is adjusted, as described above. Further accrual into this cohort will be contingent upon meeting the following safety guidelines:

   If any of the first 6 subjects has a life threatening SADR or any Grade 4 event or death that is probably or definitely attributable to the study medication or 3 or more subjects have terminated study drug due to a Grade 3+ at least possibly treatment related SADR, stop accrual into this **study cohort (Cohort I, Cohorts II & III combined)** ~~dose group~~ until a safety review by the P1090 core protocol team is conducted. If none of the first 6 subjects has experienced a life-threatening SADR or a Grade 4 event or death that is probably or definitely attributable to the study medication and at most 2 of these 6 subjects has terminated study drug due to a Grade 3+ at least possibly treatment related SADR, then this cohort has passed the initial safety guidelines. If these 6 subjects also meet the PK guidelines, accrue ~~6~~ more subjects to this cohort and evaluate the safety and PK results of the overall cohort ~~of 12 subjects~~. […]

c) 8.513 Revision in title of: Total Group of ~~Twelve~~ Subjects **(Minimum of Twelve)** Started at a Given Dose Level of Each Cohort

d) 8.522 Accrual Rate Evaluation. A second paragraph was added to this section:

A trial go/no-go decision point will be set approximately 2 years after opening of Cohort 2 At that time, an analysis across all age cohorts (irrespective of the number of enrolled subjects or length of follow-up within each age group and across the age groups) will be performed, for the purpose of complying with regulatory requirements for Janssen R&D. In addition, accrual rate and all of the relevant safety and pharmacokinetic data will be examined to determine whether it is safe and worth to continue the trial in an attempt to find an optimal dose for Cohorts II and III.

8. Section 9.32 Starting Dose. The last paragraph has been updated as follows:

[…]
All available etravirine PK data in pediatric subjects, including the P1090 subjects, were used in a modeling and simulation approach to better inform the choice of a revised starting dose for ETR for Cohort I and the starting dose for other cohorts in this study. It was also decided that instead of a ~~dose~~ **mg**/kg dose **across all ages** it would be more appropriate to develop dosing based on weight bands. The starting doses for Cohorts II and III ~~will also be~~ **are** also informed and chosen by the results ~~and the sequential opening of the older cohorts~~ **of Cohort I**, as detailed in Section 8.1. For example, **after evaluation of** the first 6 subjects of Cohort I **and** ~~meet the~~ criteria were met, ~~then~~ Cohort I ~~will~~ re-opened to accrual of ~~6~~ additional subjects to complete the full cohort. Opening of Cohort II to accrue the first mini-cohorts of 6 subjects **was done based** ~~will depend~~ on the assessment by the protocol team that sufficient data (PK and safety) ~~are~~ **were** available to appropriately inform the choice of starting dose regimen for this cohort. **The same applies for opening of Cohort III. Within Cohort III, subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.** Appendix III gives the tables for the revised starting dose for Cohort I**, starting doses for Cohort II and III** and guidelines about re-evaluating the dose regimen if warranted based on the PK data.

9. Appendix IA, IB and IC: the following changes have been made to all of these Appendices:

a) A new footnote 4 has been added: "**Study drug may be dispensed at other clinic study visits."**

b) The footnote pertaining to the population PKs has been revised as follows: "1.0mL [**0.5mL** for Appendix IC] of blood will be collected for each of the population pharmacokinetic samples. NOTE: An absolute minimum of 0.5 mL ~~of plasma~~ is necessary for population PK sample."

10. Appendix IC. To reduce the burden of collection on the youngest participants, the following additional changes have been made to Appendix IC:
    a) In the table, volumes have been reduced across all visits for hematology, lymphocyte subsets and both intensive and population PKs. The volume of chemistry was reduced but is now combined with the volume needed for the cholesterol/triglycerides. The total volumes have been adjusted.

    b) Footnote 1 has been revised: "Informed consent must be obtained prior to performing Screening evaluations. The entry (Day 0) evaluations should be completed within 60 days following

screening. **For children of low weight, the screening laboratory evaluations may be split over 2 visits. Safety labs and lymphocyte subsets should be obtained at the first time point and HIV RNA and HIV genotyping and phenotyping a week later."**

c) Footnote 7 has been revised: "**Cholesterol/triglycerides should be tested from the sample drawn for chemistries.** If a subjects lab results show elevated cholesterol/triglycerides AND if the subject is ≥1 year old, the subject should be asked to return to clinic for fasting cholesterol/triglycerides."

d) The volumes in the priority listing have been updated as per the table.

Note that the Sample Informed Consent (Appendix VIII) has been updated to reflect the lower volumes of blood to be collected from the youngest participants.

11. Appendix III: "**Dosing Table 2**" has been added.