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Schweizerisches Tropen- und Public Health-Institut
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Associated Institute of the University of Basel

Swiss Centre for International Health

Market Entry of Improved Paediatric Protease Inhibitor Based Fixed Dose Combinations for Children with HIV/AIDS

Grantee: Drugs for Neglected Diseases *initiative* (DND*i*)

External Mid-Term Evaluation Commissioned by UNITAID

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Acronyms

3TC	Lamivudine
ABC	Abacavir
ACT	Accelerating Children's HIV/AIDS Treatment (ACT) PEPFAR initiative
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine (azidothymidine)
CDC	Centers for Disease Control and prevention
CHAI	Clinton Health Access Initiative
CIFF	Children's Investment Fund Foundation
CMC	Chemistry, Manufacturing and Controls
CSO	Civil Society Organization
DNDi	Drugs for Neglected Diseases initiative
DRV	Darunavir
DRV/r	Darunavir/ritonavir
DTG	Dolutregravir
EDCTP	European & Developing Countries Clinical Trials Partnership
EFV	Efavirenz
EGPAF	Elizabeth Glaser Paediatric AIDS Foundation
FACES	Family AIDS Care and Education Services
FDC	Fixed Dose Formulation
IATT	Inter-Agency Task Team for HIV Prevention and Young People
ICW	International Community of Women Living with HIV
KI	Key Informant
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
MTCT	Mother-to-child transmission
NASCOP	National AIDS and STI Control Program
NEPHAK	National Empowerment Network of People Living with HIV/AIDS in Kenya

NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIH/IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
PADO	Paediatric ARV Drug Optimization
PAWG	Paediatric ARV Working Group
PENTA	Paediatric European Network for the Treatment of AIDS
PEPFAR	U.S. President's Emergency Fund for AIDS Relief
PHTI	Paediatric HIV Treatment Initiative
PIs	Protease inhibitors
PK	Pharmacokinetic
PMTCT	Prevention of mother-to-child transmission
R&D	Research & Development
RTV	Ritonavir
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
TPP	Target product profile
U.S. FDA	U.S. Food and Drug Administration
UNAIDS	Joint United Nations Programme on HIV and AIDS
WHO	World Health Organization

Executive summary

Background and objectives

One of the major obstacles in treating paediatric HIV is the limited availability of paediatric antiretroviral (ARVs) formulations. The World Health Organization (WHO) recommends using the two nucleoside-inhibitors (NRTIs) plus boosted protease inhibitor (PI)-based as the preferred HIV treatment regimen in young children < 3 years of age. Among boosted PIs – only co-formulated lopinavir/ritonavir (LPV/r) is approved for use in children starting at 14 days of life. Paediatric formulation of LPV/r for young children is a poorly tolerated liquid which negatively affects adherence. An alternative LPV/r formulation for young children is urgently needed. There is also an important need for a better formulation of a standing alone PI booster ritonavir (RTV) for children co-infected with HIV and tuberculosis (TB).

The market entry of improved paediatric PI-based fixed dose combinations (FDCs) project implemented by the Drugs for Neglected Diseases initiative (DNDi) was approved by the UNITAID Executive Board for the period of May 2013 - May 2016 with a total budget of USD 17,335,404 The project serves to increase access to optimal ARVs for young children, and has **three main objectives**:

1. To develop and register two solid first-line PI LPV/r-based FDCs with two NRTIs (4-in-1) in the form of heat-stable taste-masked paediatric granules to accommodate weight-band dosing.
2. To develop and register complementary paediatric granules of RTV to be used during simultaneous treatment of HIV and TB.
3. To begin market penetration with the new paediatric products in order to provide better treatments to infants, to create demand for the products, and to promote in-country adoption.

Approach

In October 2015 UNITAID contracted the Swiss Tropical and Public Health Institute (Swiss TPH) to conduct a mid-term evaluation of the project. The evaluation assessed the relevance, effectiveness, efficiency, impact and lessons learned of the project based on the progress made against the activities, outputs, and outcomes.

This mid-term review was conducted in December 2015 analysing available project documentation and conducting interviews with a number of key informants.

Findings

The project outcomes to date are limited, but those achieved are consistent with UNITAID mission to contribute to scale-up innovations for treatment of HIV/AIDS. Progress has been made with regard to all three objectives. However, no new, optimized paediatric appropriate PI-based FDCs have reached the market, nor has a standalone RTV formulation.

The effectiveness of the project has been challenged by an early failure of the candidate product and difficulties in finding an alternative compound. In spite of the very promising preliminary data, highly anticipated taste-masked Cipla Ltd. LPV/r granules demonstrated low and unpredictable bioavailability making them unsuitable for further development. DNDi worked closely with pharmaceutical partner Cipla Ltd. analyzing the failure and testing multiple candidate formulations. After two years of consistent efforts, six taste-masked LPV/r formulations with potentially good bioavailability in humans have been identified and the *three most promising formulations* are being evaluated in phase I studies in healthy human volunteers. Until the full results of the phase I taste-masked LPV/r formulations are available and allow for the 4-in-1 formulations to be developed and evaluated, it is difficult to predict the full impact of the UNITAID funding on target product development.

The project has seven outputs as listed below:

- **Output 1:** Formulate two optimal PI-based 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)
- **Output 2:** Complete clinical studies for two 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)
- **Output 3:** Registration of adapted paediatric ABC/3TC/LPV/r and AZT/3TC/LPV/r FDCs for use in resource-poor settings
- **Output 4:** Formulate a standalone PK booster (RTV)
- **Output 5:** Clinical studies completed for a standalone PK booster (RTV)
- **Output 6:** Registration of adapted paediatric RTV granules for use in resource-poor settings
- **Output 7:** Facilitate the adoption of LPV/r based first-line antiretroviral therapy (ART) and RTV granules in low- and middle-income countries

Out of seven outputs, adjustments and partial progress have been made in four (Outputs 1, 2, 5 and 7), while three outputs (3, 4 and 6) have not advanced, and two outputs (4 and 6) are no longer planned. Adjustments of the outputs and activities were related to the delay in the 4-in1 product development and related delay in the roll out of the implementation studies. A total of 24 activities have been scheduled within the frameworks of seven outputs: two have been completed, 16 are in progress or planned, and six are no longer planned. Given the limited scope of undertaken activities, only 16% of the budget has been spent over the review period. DNDi utilized UNITAID funding efficiently for the amount of work that was carried out.

Activities implemented by the project to date are consistent with the initial and adjusted project plan and in line with UNITAID objectives and strategy. Most important achievements of the project relevant to the UNITAID mission to date include:

- Development of the optimal paediatric weight band dosing for PI-based FDCs from PK modeling and simulations of integrated existing PK data. The weight band based alignment of the PI and NNRTIs dosing has led to the important changes in the paediatric WHO treatment guidelines and had an important influence on developing, manufacturing and forecasting of PI-based FDCs for young children.

- Paediatric PK study in infants and young children co-infected with TB and HIV was conducted in South Africa to supplement existing information and evaluate the effect of the "superboosting" strategy with RTV on the PK of LPV in children concomitantly receiving rifampicin as treatment for TB. An interim analysis of study data showed the safety and efficacy of the superboosting approach. It was shared with the WHO Technical Review Team to support 2015 revisions of the paediatric treatment guidelines for TB and HIV in children.

Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi and Cipla Ltd. have abandoned plans for further development of a standalone RTV booster. With recent availability of the powder and small tablet size RTV paediatric formulation[1] this output has somewhat lost its relevance as a priority for paediatric ARV drug development. For the LPV/r paediatric formulations, DNDi worked on developing taste-masked pellets (mini-tablets) and granules. To date, three most promising candidates of each of this formulations are being evaluated in Phase I bioavailability study. Preliminary results from these studies suggest potential for the development of taste-masked pellets and the need to reformulate the taste-masked granules. Once the development of the taste-masked LPV/r formulation (pellets or/and granules) is complete, the project can move into next stage developing 4-in-1 taste-masked FDCs. Finally, DNDi has been active in promoting paediatric HIV treatment, seeking collaboration with other stakeholders and partners, actively participating in the set-up of the Paediatric HIV Treatment Initiative (PHTI) and sharing llessons learned.

Recommendations

Based on the current progress on the project, the considerations and recommendations for further project implementation within an existing timeline are:

1. Retain the focus on completing the phase I bioavailability study, selecting the best formulation and path for further, development of 4-in-1 FDC. .
2. Consider focusing only on *taste-masked LPV/r pellets* versus moving forward with both *taste-masked LPV/r pellets* and *granules* development.
3. Consider narrowing the product selection by focusing on the development of one 4-in-1 product with ABC/3TC.
4. Reassess of the progress of the LIVING study[2], consider new partnerships to reach recruitment goal within the remaining time.

DNDi has requested a no-cost extension period of 2.5 years to complete on-going and planned activities. Based on the current progress on the project and as a result of the detailed discussions with the DNDi and key informants (KIs), we conclude that the consideration for the no-cost extension can be given **after the following steps**:

1. The results of the bioavailability studies become available in April 2016. Consider awaiting the results of the formal meeting with US Food and Drug Administration (US FDA) (planned for Q2 2016) to review the phase I bioavailability study results and advise about the best regulatory pathway to proceed.

[1] For RTV powder: Salem Ah, et al., Antivir Ther 2015;9:20(4):425-32; registration filed with the European Medicines Agency [EMA]. For the smaller Cipla tablets: PEPFAR/FDA tentative approval - NDA 205040 - http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm

[2] The study protocol is entitled "Prospective study of lopinavir based ART for HIV Infected children globally (LIVING study)"..

2. Recommend gathering the meeting with key stakeholders to conduct current market analysis, reassess/forecast the position of the product on the market within 5 years.
3. Facilitate the approval by the WHO of the new product following anticipated tentative approval by US FDA.
4. Consider broaden collaboration platform within the project by engaging CHAI and other parties that can help reach LIVING study targets.
5. Thoroughly estimate time line and risk mitigation with alternative development plan.
6. Expanding the scope of work to include more diversified outputs and activities such as work with other pharmaceutical agents and partners in advancing introduction of other novel paediatric formulations to avoid activities that are highly contingent upon each other. Revise the budget and consider reduction and/or redistribution of the funds within the new scope of work and partnerships.

1 Background

Despite a progressive decrease in mother-to-child transmission (MTCT) of HIV, the need for treatment of children with HIV remains and is anticipated to increase in the coming 5 years. Only 24% of children eligible for antiretroviral treatment (ART), based on the 2013 WHO HIV treatment guidelines, were reported to receive ART in 2013. In 16 high-burden countries in sub-Saharan Africa, less than 10% of children living with HIV were on ART in 2013. Based on the new 2015 WHO HIV treatment guidelines advocating for universal treatment of HIV, including all children and adolescents, these numbers are even lower, highlighting the urgent need to expanded access to paediatric ART[3]. Within the last 2 years, the global community including the Global Fund to Fight AIDS, Tuberculosis (TB) and Malaria (Global Fund), the Joint United Nations Programme on HIV and AIDS (UNAIDS), the U.S. President's Emergency Fund for AIDS Relief (PEPFAR), and the Children's Investment Fund Foundation (CIFF), has prioritized paediatric HIV and pledged major political commitment and funding initiatives — such as 90/90/90 targets by UNAIDS and PEPFAR-CIFF Accelerating Children's HIV/AIDS Treatment (ACT) initiative — to support the scale-up of paediatric care and treatment.

One of the major obstacles in treating paediatric HIV is the limited availability of paediatric ARVs formulations. In the 2013 WHO HIV Treatment Guidelines, based on previously generated and supported by more recent data, the two NRTIs plus boosted PI-based combination ART remains the preferred HIV treatment regimen in young children < 3 years of age. Among boosted PIs – only co-formulated lopinavir/ritonavir (LPV/r) is approved for use in children starting at 14 days of life, while other paediatric fixed dose co-formulated formulations such as atazanavir/ritonavir (ATV/r) and darunavir/ritonavir (DRV/r) are under development or not currently available for use in infants and children. Moreover, the use of some of the boosted PIs, such as DRV is limited to children older than 3 years of age due to toxicity. Paediatric formulation of LPV/r for infants and young children is in an alcohol- and propylene-glycol based liquid form with a poorly tolerated bitter taste which negatively affects adherence and retention in care. In addition, the liquid LPV/r formulation requires cold chain management, is voluminous and expensive. Moreover, with accumulating evidence suggesting the potential benefits of very early (<4 weeks of age) ART on the viral reservoirs and long-term outcome of HIV, the excipients-based limitation of using the current liquid formulation of the LPV/r during the first 2 weeks of life, further dictates the need for alternative LPV/r formulation.

In addition to the urgent need for an alternative LPV/r formulation for young children, there is an equally important need for a better formulation of a standing alone PK PI booster RTV. High rates of co-infection and associated mortality with TB, particularly in sub-Saharan Africa, create a strong demand for anti- mycobacterial therapy in infants and young children. Quite unfortunately, available anti-TB drugs have significant drug-drug interactions with many ARV medications used to treat HIV. Administration of rifampicin to a child on a LPV/r based ART, for example, significantly decreases blood levels of LPV decreasing its efficacy against HIV and creating viral resistance. This negative interaction requires new or adapted treatments, such as the addition of extra RTV to boost the bioavailability of LPV. This

[3] WHO (2015). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.

therapeutic modality, however, is challenged by poor tolerability of liquid RTV formulation which, similar to LPV/r, has high alcohol content and a short shelf life.

DNDi has taken a leadership role within the framework of various groups including Médecins Sans Frontières (MSF), WHO and the Medicines Patent Pool (MPP), to advance paediatric HIV therapy options for a first-line combination ART for infants and children less than three years of age. In 2010-2011, DNDi became aware of the development of LPV/r sprinkles or pellets by Cipla Ltd., and partnered with the company for the development of two '4-in-1' paediatric NRTI plus PI-based FDCs for young children. Following an expert consultation meeting in April 2011, the target product profile (TPP) was defined to include the following desired characteristics: safety, tolerability and ease of administration, forgiveness with a high threshold to resistance and minimal potential for drug-drug interactions.

The market entry of improved paediatric PI-based FDCs project implemented by DNDi was approved by the UNITAID Executive Board in December 2012 for the period of May 2013 to May 2016. The project started implementation in Q2 2013. The project serves to increase access to optimal ART for children under three years old, and has **three main objectives**:

1. To develop and register two solid first-line PI LPV/r-based FDCs with two NRTIs, Lamivudine (3TC) and either Abacavir (ABC) or Zidovudine (AZT). All components of this combination to be developed in the form of *taste-masked granules* that are heat stable, presented in a single unit (two 4-in-1 LPV/r-based FDCs) and are available in two dosages, each to accommodate weight-band dosing
2. To develop and register complementary *granules of RTV t*o be used in addition to the 4-in-1 LPV/r-based FDCs during simultaneous treatment of HIV and TB (e.g., "superboosted")
3. To begin market penetration with these LPV/r-based granule products immediately, even before the availability of the optimal 4-in-1 LPV/r-based FDC, in order to provide better treatments to infants, to create demand for the products, and to promote in-country adoption

Expected project outputs of the projects included the following deliverables:

- **Output 1:** Formulate two optimal PI-based 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)
- **Output 2:** Complete clinical studies for two 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)
- **Output 3:** Registration of adapted paediatric ABC/3TC/LPV/r and AZT/3TC/LPV/r FDCs for use in resource-poor settings
- **Output 4:** Formulate a standalone PK booster (RTV)
- **Output 5:** Clinical studies completed for a standalone PK booster (RTV)
- **Output 6:** Registration of adapted paediatric RTV granules for use in resource-poor settings
- **Output 7:** Facilitate the adoption of LPV/r based first-line ART and RTV granules in low- and middle-income countries

In October 2015, UNITAID contracted the Swiss TPH to conduct a mid-term evaluation of the project. This report outlines the general and specific objectives of the mid-term evaluation

(chapter 2), the approach and methods (chapter 3), the findings (chapter 4) and the conclusions & recommendations (chapter 5). The annexes further contain the evaluation matrix with comments and summaries (Appendix A), a list of key informants (Appendix B) and an overview of documents reviewed (Appendix C).

2 Objectives of this mid-term evaluation

The objective of this mid-term evaluation is to provide

- UNITAID with a detailed assessment of the programmatic progress of DNDi's development of improved paediatric PI based FDCs
- UNITAID and DNDi with recommendations on how to improve the grant implementation
- UNITAID with insight into the requested no-cost extension.

The evaluation assessed the relevance, effectiveness, efficiency, impact and lessons learned of the project. In addition, the evaluation will review the overall goals of the project, its outputs and activities for each output against specific questions.

3 Approach and methods

The evaluation reviewed the overall goals of the project, its outputs and the activities for each output against the following questions:

- **Relevance -** are the activities implemented by the project to date consistent with the initial and adjusted (during 2014) project plan and in line with UNITAID objectives and strategy?
- **Effectiveness -** have the objectives of the project been achieved and which remain as a target? What are the factors related to achievement or non-achievement of the project's objectives?
- **Efficiency -** is the project utilizing the UNITAID funding in the most efficient manner in order to achieve the objectives?
- **Impact** - To what extent the UNITAID funding affected/accelerated the target product development?
- **Lessons Learned –** Should the project continue in the current path or should changes be made?

The Programmatic Progress Overview will be aligned according to the original 2013 objectives and activities outlined in the Grant Agreement signed in May 2013 between UNITAID and DNDi for a Project to Secure Market Entry of Improved Protease Inhibitor Based Fixed-Dose Combinations for Children with HIV/AIDS.

This mid-term review was conducted according to the following five steps:

Step 1: Review relevant documents and extract **information and data** for the evaluation and reporting.

The following documents shared by UNITAID and DNDi were reviewed see also Appendix C):

- Grant Agreement and all Annexes
- Inception report, Annual and semi-annual reports of the Project for years 2013, 2014, and 2015
- Memorandums of Understanding with manufacturers
- Study reports and relevant publications
- Agreements with Principal Investigators of trials and studies
- Summary of the Pharmaceutical Development of Paediatric HIV "4-in-1" Formulations (provided after November 11, 2015)
- DNDi Paediatric HIV Program Briefing Paper (provided after November 11, 2015)

Step 2: Conduct **key informant interview** for the evaluation and reporting.
We conducted key informant interviews (e.g. with WHO, CHAI) through face-to-face interviews, by phone or Skype (see also Appendix B). The purpose of these interviews was to evaluate the overall progress of the project since its inception, assess the status on each output, assess the product(s) current and future stand in the approval process and market penetration.

Step 3: Meet with **key stakeholders (in Geneva)** for the evaluation and reporting,
We organized a meeting with the key stakeholders in UNITAID and DNDi in Geneva in early December 2015 to discuss the preliminary findings, remaining open questions and steps forward.

Step 4: Draft and finalize **the report.**
Along the process we have documented findings and recommendations and have summarised them in this evaluation reports.

Step 5: Formulate **recommendations** for no-cost extension considerations, further implementation and dissemination.
Following the completion of steps one through four, and follow up discussion with key stakeholders, we formulated two sets of recommendations: for completion of the project within the current timeline and for the consideration of the no-cost extension.

4 Findings

The project has been active since Q2 2013. A formal collaboration was established between DNDi and Cipla Ltd., where Cipla Ltd. is responsible for the pharmaceutical development (formulation screening and process development), product registration and conduct of Phase I, healthy human volunteer bioavailability studies. DNDi is responsible for managing clinical development including the performance of the implementation studies using the LPV/r pellets developed by Cipla Ltd. The project, while being successful in reaching several deliverables, has encountered significant challenges during the first 2 years that were primarily related to the difficulties in achieving objectives 1 and 2, developing taste-masked formulations of

LPV/r and RTV. In August 2015, DNDi requested a no-cost extension of the project for 2.5 years. This report provides an update on the progress and developments concerning the implementation of DNDi's project t*o secure market entry of improved solid protease inhibitor-based fixed-dose combinations for children with HIV/AIDS* during the period between May 2013 and November 2015.

The following chapters outline the programmatic project progress (see also Appendix A) followed by additional activities, aspects on monitoring and evaluation and other evaluation aspects.

4.1 Programmatic Progress Overview

A summary of the programmatic progress is given in "**Table 1: Summary of the outputs/activities progress**" and detailed findings for each output and planned activities are outlined in the chapters 4.1.1- 4.1.7.

Table 1: Summary of the outputs/activities progress

Output/Activities	Projected timeline	Current Status	Comments and updated timeline
Output 1: Formulate two optimal PI-based 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)			
***Output 1_Activity 1**: "Weight Band Dosing", scheduled for Q1 2013	Q1 2013	Completed in 2013	This activity is highly relevant to the project overall and represents indeed the most important early stage project achievement. (detailed summary in the text) **Updated timeline:** N/A
Output 1_Activity 2, 3 & 4: "Development of LPV/r granules plus NRTIs granules into 4-in-1"; "Clinical batch produced for ABC/3TC/LPV/r and AZT/3TC/LPV/r"; "Registration stability studies for ABC/3TC/LPV/r and AZT/3TC/LPV/r (accelerated and real time)"	Q2 2013 - Q4 2013	Not completed, in progress	Initial product candidate failed in 2013. Since the formulation of the 4-in-1FDC can't be advanced without successful development of the taste-masked LPV/r, there was no progress on the remaining activities under Output 1. (detailed summaries in the text) **Updated timeline:** Not available, early estimate
Output 1_Activity 5: "Validation batches produced for ABC/3TC/LPV/r and AZT/3TC/LPV/r"	Q3 2015	Not completed, contingent upon the success of the Output 1_Activities 2-4	See above (detailed summaries in the text) **Updated timeline:** Not available, early estimate
Output 2: Clinical studies completed for two 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)			
Output 2_Activities 1 & 2: "Phase I: Bioavailability & Bioequivalence of LPV/r and 4-in-1 in healthy human volunteers"	Q2 2013 – Q3 2014	Taste masked LPV/r studies (Phase I) are in progress, 4-in-1 studies are contingent upon the success of the Output 1_Activities 2-4	The completion of this activity will require successful LPV/r bioavailability study in healthy adult volunteers in fasted state plus co-formulation of the best candidate with NRTIs for BA/BE studies. (detailed summaries in the text) **Updated timeline:** Not available, early estimate

Output/Activities	Projected timeline	Current Status	Comments and updated timeline
Output 2_Activities 3 & 4: "PK, efficacy, safety and acceptability studies"	Q3 2013 – Q1 2016	Not completed, contingent upon the success of the Output 1_Activities 2-4 and Output 2_Activities 1&2	The PK, efficacy, safety and acceptability studies of the new taste-masked this LPV/r and 4-in-1 FDC formulations depend on the successful product development and have been placed on hold. (detailed summaries in the text) **Updated timeline:** Not available
Output 3: Registration of adapted paediatric ABC/3TC/LPV/r and AZT/3TC/LPV/r FDCs for use in resource-poor settings			
Output 3_Activity 1 & 2: "Regulatory-scientific advice", "Preparation and submission of regulatory dossiers for 4-in-1 FDCs"	Q3 2013, onwards Q4 2013-Q4 2014	Not completed, contingent upon the success of the Output 1 and Output 2, and support of the prequalification process by WHO with tentative FDA approval	Since no 4-in-1 formulation has been developed, it is not available for registration. DNDi seeks UNITAID support in leveraging the approval prequalification process between FDA and WHO to facilitate the registration of the 4-in-1 LPV/r based FDC once it has been fully developed. (detailed summaries in the text) **Updated timeline:** Not available, early estimate
Output 4: Formulate a standalone PK booster (RTV)			
Output 4_Activities 1, 2, and 3: "Development of RTV in granules", "Clinical batch available for RTV granules", "Registration stability studies for RTV granules (accelerated and real time)"	Q2-Q3 2013	Not completed, not planned	Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. **Updated timeline:** N/A
Output 4_Activity 4: "Validation batches produced for RTV"	Q3-Q4 2015	Not completed, not planned	Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. **Updated timeline:** N/A

Output/Activities	Projected timeline	Current Status	Comments and updated timeline
Output 5: Clinical studies completed for a standalone PK booster (RTV)			
Output 5_Activities 1 & 2: "Phase I: Bioavailability & Bioequivalence study of RTV granules in healthy human volunteers (pilot and pivotal)"	Q3 2013- Q3 2014	Not completed, not planned	Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. **Updated timeline:** N/A
***Output 5_Activities 3 & 4: "**PK, safety and efficacy of super-boosted LPV/r"	Q1 2013- Q4 2015	Interim analysis completed, recruitment completed, full analysis in progress	As outlined in Outputs 3 and 4, DNDi has abandoned plans for further development of a standalone RTV booster. However, the clinical studies with available liquid formulation of RTV have been carried out to evaluate the effect of the superboosting. An interim analysis showed the safety and efficacy of the superboosting approach and was shared with the WHO to support the 2015 revision of the paediatric HIV and TB treatment guidelines. (detailed summaries in the text) This activity is among most important achievements of the project to date. **Updated timeline:** scheduled to be completed in Q3-4 2016
Output 6: Registration of an adapted paediatric RTV granules for use in resource-poor settings			
Output 6_Activity 1: "Regulatory-scientific advice"	Q3 2013, onwards, as required	Not completed, not planned	Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. **Updated timeline:** N/A

Output/Activities	Projected timeline	Current Status	Comments and updated timeline
Output 6_Activity 2: "Regulatory dossiers for RTV granules"	Q3 2013 – Q4 2014	Not completed, not planned	Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. **Updated timeline:** N/A
Output 7 - Facilitate the adoption of LPV/r based first-line ART and RTV granules in low- and middle-income countries			
Output 7_Activity 1: "Dosage from acceptability field surveys"	Q1 2013- Q3 2013	Not completed, planned	The dosage from acceptability field studies of the new taste-masked this LPV/r and 4-in-1 FDC formulations depend on the successful product development. Since the product development has not been completed, these activities have been placed on hold. The acceptability of the non-taste masked LPV/r pellets by Cipla Ltd. is ongoing in the LIVING study. (detailed summaries in the text) **Updated timeline:** to be completed in 2016-2017
***Output 7_Activity 2:** "Implementation studies" - Prospective study of Lopinavir based ART for HIV Infected children globally (LIVING study)"	Q1 2014- Q2 2016	Not completed, in progress	DNDi is working with Cipla Ltd. to ensure early access to a newly approved non-taste masked LPV/r pellets formulation through a large implementation LIVING study which started recruitment in Kenya in fall 2015 and is scheduled to initiate recruitment in Uganda in Q1 2016. The project has planned to recruit 350 subjects per country. DNDi is active in seeking other partnerships (with CHAI, NICHD, PENTA etc.) in expanding its spectrum of implementation studies. **Updated timeline**: preliminary data analysis to be completed in Q2-Q4 2016

Output/Activities	Projected timeline	Current Status	Comments and updated timeline
Output 7_Activity 3: "Market analysis results published"	Q2 2013 – Q2 2016	Not completed, in progress	Market analysis results are most likely to be published. **Updated timeline:** to be completed in Q1-Q2 2016
Additional Activities: Raising awareness, Engaging with Civil Society Organizations and Set-up of Pediatric HIV Treatment Initiate (PHTI)	Q2 2013- onwards, as required	In progress	DNDi is working with community leaders from the National Empowerment Network of People Living with HIV/AIDS in Kenya (NEPHAK) and the International Community of Women Living with HIV (ICW) to develop and implement the paediatric HIV treatment toolkit.The set-up of the Paediatric HIV Treatment Initiative (PHTI) is considered among the most important achievements of the project to date by DNDi. **Updated timeline:** to be completed in Q1-Q2 2016

*The achievement of this activity is considered among the five most important achievements of the project to date by DNDi.

4.1.1 Output 1: Formulate two optimal PI-based 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)

Current status: Partially completed, in progress

a) Output 1_Activity 1: "Weight Band Dosing"
Scheduled for: Q1 2013
Current Status: Completed in 2013

Finding
Dosing of ARVs in infants and children in resource-limited settings is based on weight bands. The previous LPV/r and NRTIs dosing ratios recommended by WHO did not align with NRTIs in the lower weight bands, complicating dosing of combinations of ARVs. Population PK modeling and simulations were carried out and integrated existing PK data of LPV, AZT, 3TC and ABC from United States, France and Africa in order to determine the optimal FDCs across all paediatric weight bands. These results led to a WHO review and new dosing for LPV/r, the 4-in-1 LPV/r based FDCs and RTV booster incorporated into Annex 7 of the 2013 WHO HIV treatment guidelines under "urgently needed ARV drugs for children as recommended by the Paediatric ARV Working Group (PAWG)" and further endorsed by Paediatric ARV Drug Optimization (PADO). The full modelling was published in 2014 in the medical journal *Antiviral Therapy*.

Summary observations in respect to **Output 1_Activity 1**:

- The achievement of this activity is considered among the five most important achievements of the project to date by DNDi.
- This activity is highly relevant to the project overall and represents indeed the most important early stage project achievement. This assessment has been shared by all KIs and by the consultant. The weight band based alignment of the PI and NNRTIs dosing has led to the important changes in the paediatric WHO treatment guidelines and had an important influence on the approach to developing, manufacturing and forecasting of PI-based FDCs for young children. This activity also laid the foundation for the successful implementation of the project activities under outputs 1-3 and output 7.

b) Output 1_Activity 2, 3 & 4: "Development of LPV/r granules plus NRTIs granules into 4-in-1"; "Clinical batch produced for ABC/3TC/LPV/r and AZT/3TC/LPV/r"; "Registration stability studies for ABC/3TC/LPV/r and AZT/3TC/LPV/r (accelerated and real time)"
Scheduled for: Q2 2013 - Q4 2013
Current Status: Not completed, in progress, future timeline needs to be specified if project is extended

Finding:
Development of LPV/r granules plus NRTIs granules into 4-in-1: The LPV and RTV molecules are highly insoluble and do not cross the gastro-intestinal barrier easily

(Biopharmaceutical Class IV). They taste very bitter and thus cannot be made into a dispersible tablet and require melt extrusion technology to make the formulation bioavailable and heat-stable. Bioavailability is easily lost when certain taste-masking agents are used. In 2011, DNDi systematically explored formulation options including prodrugs of LPV and RTV, LPV/r nanosuspensions and LPV/r nanoparticles. Development timelines for these options were assessed and estimated to take more than five years. At the same time, DNDi investigated the opportunity offered by the solid formulation of *LPV/r pellets* developed by Cipla Ltd. These pellets demonstrated bioequivalence with LPV/r syrup (standard of care) in a pilot study involving healthy human volunteers and were considered to be good candidates that could be further developed rapidly to meet the defined TPP.

A phase l bioavailability study conducted in India in 2013, using the first highly anticipated *taste-masked* LPV/r *granules* in capsules produced by Cipla Ltd., demonstrated low and unpredictable bioavailability of the initial candidate for the formulation compared to the oral solution Kaletra® produced by Abbott Laboratories, USA and AbbVie. The results showed great variability of the bioavailability of the *taste-masked LPV/r granules* with AUC_{0-t} and $AUC_{0-\infty}$ granules to reference ratios not found to be within the acceptance range of 80% to 125% for LPV and RTV. In spite of the very promising Chemistry, Manufacturing and Controls (CMC) data and excellent taste masking, the low bioavailability meant that the developed *taste-masked LPV/r granules* formulation, the most difficult part of the 4-in-1 formulation was not adequate to pursue the project. A thorough analysis of all data and experimental details did not offer a full explanation, however all possibilities were reviewed and other solid solutions and different proportions of active pharmaceutical ingredients and taste masking agents were reconsidered. DNDi and Cipla Ltd. decided to evaluate, in an animal model, different formulations of LPV/r focusing on bioavailability, stability and taste-masking before moving forward with additional human studies. Various *taste-masked granule* formulations were tested while keeping coated *LPV/r pellet* formulations as backup options.

Despite the technical challenges and failure of the initial candidates, DNDi continued to express firm commitment and testing various candidates. A total of about 40 LPV/r formulations were tested in the beagle dog model. After working for almost two years on the development of the multiple candidate formulations six *taste-masked LPV/r formulations* tested in dogs have been identified which could demonstrate good bioavailability in man. During 2014-2015, DNDi and Cipla Ltd. selected ***three promising taste-masked LPV/r formulations*** (*two taste-masked pellets formulations and one taste-masked granule formulatio*n) to be evaluated in phase l studies in healthy human volunteers.

The phase I PK and bioavailability studies of *taste-masked coated pellets and granules* in healthy volunteers were started in July 2015. The preliminary data from the Phase I PK study was shared by DNDi with the consultant in November 2015. In the **fed state**, *all three formulations* showed an increased bioavailability (150-180%) in humans compared to the reference solution, an outcome which **was not expected based** on the data generated in dogs. The 8% coated variant of the *taste-masked pellets* showed excellent taste masking and high bioavailability when tested in the fed state in man, making it a strong potential candidate for further development. A bioavailability study in the **fasted state** needs to be performed to confirm the higher bioavailability of the *taste-masked pellets* and it is scheduled to take place in **January 2016** with **preliminary data available in April 2016**.

Out of ***three promising taste-masked LPV/r formulations***, taste masking was insufficient for the *smaller-sized taste-masked LPV/r granules* (with the 10% coating). Taste testing of a series of granule formulations, some of which have already been tested in dogs, is scheduled to be undertaken for a last review and selection towards the end of Q4 2015. Those candidates which are most effectively taste masked will be selected for bioavailability testing in dogs and in some cases in man, depending on whether the candidate(s) have already been investigated in the dog model. The goal is to have a choice between a *few granule formulations*, as well as the available "reference" coated *pellet formulations*. DNDi sees strong arguments for preserving focus on *granules* for following rationales: potential for faster scale up in production and decreased production cost compared to pellets/mini-tablets. However, DNDi also confirms a faster time line in making *pellets* (sized 1.8 mm) available versus additional 2-3 months for the granules (sized 200-300 microns) development in the best case scenario of bioavailability for granules, which is not currently the case.

Cipla Ltd. also continues to test the backup LPV/r formulations in the dog model in case bioavailability is not achieved in fasted state phase I testing of the three selected formulations described above. In summary, despite a significant setback in the projects to date, DNDi remains optimistic about developing new taste-masked LPV/r-based FDCs that are heat-stable and are combined with 2 NRTIs. Outside of Cipla Ltd. collaboration, DNDi pursued other possibilities which included offering of test formulations being developed by other companies (e.g. Mylan and Hetero). [redacted]

Clinical batch produced for ABC/3TC/LPV/r and AZT/3TC/LPV/r: The development of 4-in-1 is contingent upon successful development of the *taste-masked LPV/r pellets*. The best formulation from phase I testing is planned to be combined with the two NRTIs (ABC + 3TC and AZT + 3TC) and tested in a phase I healthy adult volunteer study. DNDi is does not anticipate any technical compatibility challenges combining best candidate *taste-masked LPV/r pellets* with two NRTIs. The production of clinical batches of pellets, however, will require technical equipment capable of measuring the exact amount of required ingredients for pellets/mini-tablets. This equipment was recently developed by the German engineering firm for Cipla Ltd. with the support of UNITAID funding and is ready to be shipped to Cipla Ltd. The installation of this equipment within Cipla Ltd. faculties is expected to create the capacity to produce clinical batches of LPV/r pellets.

Registration stability studies for ABC/3TC/LPV/r and AZT/3TC/LPV/r (accelerated and real time): While the three new *taste-masked LPV/r formulations* undergo Phase I testing in healthy human volunteers, DNDi is working with Cipla Ltd. and other partners to ensure its *non-taste-masked LPV/r pellets* developed in collaboration with partners such as the Medical Research Council (MRC), from the United Kingdom, and clinical trial sites in Uganda are registered and adopted through the clinical trial. In May 2015, *LPV/r pellets* developed by Cipla Ltd. outside of the DNDi project received tentative approval from the US FDA which represents an important step towards closing the treatment gap for infants and young children living with HIV. DNDi has played **a prominent role** on the global arena and within the paediatric HIV community informing about the new formulation and advancing its introduction to the WHO guidelines and to the market. DNDi is currently working with Cipla Ltd. to ensure the new *non taste-masked LPV/r pellets* are registered and adopted through an implementation study which is scheduled to be carried out in selected sub-Saharan

African countries. The study titled the *Prospective Study of Lopinavir Based ART for HIV Infected childreN Globally* (LIVING Study) began recruitment in Kenya in September 2015. In fact, the LIVING study results are expected to significantly facilitate registration and introduction of the *non-taste masked LPV/r pellets* by Cipla Ltd. in a number of African countries, as well as a joint regulatory review by east African countries. The study, therefore, represents an important step to getting solid PI-based regimen formulations to the market before the availability of the optimal 4-in-1 LPV/r FDCs and for setting the stage for policy change within countries (in-country registration, inclusion in national treatment guidelines, and adoption in treatment programs. DNDi plans to transition Cipla's *non-taste masked LPV/r pellets* to the taste-masked 4-in-1 LPV/r based FDCs once they become available. DNDi also collaborates closely with the Clinton Health Access Initiative (CHAI) and the Inter-Agency Task Team (IATT) for Prevention and Treatment of HIV Infection in Pregnant Women, Mother and Children in following the registration and/or introduction of the *non taste-masked* LPV/r pellets in countries which started the process of procuring the new LPV/r formulations, such as Mozambique and Cameroon.

An informal conversation was held between the US FDA and DNDi teams in 2015 (confirmed by both parties) who reviewed the non-taste masked Cipla Ltd. The FDA team encouraged DNDi to share the results of the phase l studies as soon as they are available in order to discuss the development strategy. Additionally, the team suggested that DNDi collects additional data on the safety of the pellets in very young children as part of its planned LIVING study (see below).

Summary observations in respect to **Output 1_Activity 2, 3 & 4:**

- In spite of the very promising preliminary data and excellent taste masking, highly anticipated initial product candidate (*taste-masked* Cipla Ltd. *LPV/r granules* in capsules) has failed in 2013, demonstrating low and unpredictable bioavailability compared to the available oral solution product. Since the formulation of the 4-in-1FDC can't be advanced without successful development of the *taste-masked LPV/r*, *pellets or granules* there was no progress on the remaining activities under Output 1. While this risk mitigation was included into the original proposal, the overwhelming optimism about this product has caught the project somewhat off guard and significantly affected the overall capacity to deliver on activities and outcomes, despite evident commitment by DNDi and pharmaceutical partner Cipla Ltd.

- DNDi continued to work closely with Cipla Ltd. analyzing the failure and testing multiple candidate formulations. After two years of consistent efforts, ***six taste-masked LPV/r formulations*** with potentially good bioavailability in human have been identified and ***three most promising formulations*** (two *taste-masked pellets* formulations and one *taste-masked granule* formulation) have been evaluated in phase l studies in healthy human volunteers in fed state only. The preliminary data from shared by DNDi with the consultant in November 2015, shows high bioavailability in humans. While encouraging, it is important noticing that this outcome **was not expected based** on the animal data generated in dogs, pointing out to the potential weakness of prediction in animal model. With good bioavailability in the fed state, it is crucial to evaluate the formulation in **fasted state** as the bioavailability of LPV/r is highly dependent on the food intake. Moreover, taste masking appears to be

successful *in pellets* form of the new formulation, making it a good potential candidate for further development. A bioavailability study of **the *taste-masked LPV/r pellets*** is scheduled to take place in **January 2016** with **preliminary data available in April 2016**.

- With good fed state bioavailability data, ***taste-masked*** granules of new formulations have suboptimal taste-masking. Advancing granules development will require going back to bioavailability testing in man. Taken into consideration limited timeline of the current project, this activity is not realistic to be completed, and might only be considered for the extension stage. Careful consideration should be given to evaluate whether developing granules within the scope of the future paediatric ARV drugs market is cost and time efficient, and whether the final product will be more marketable compared to *LPV/r pellets*. A stakeholders meeting with the participation of the US FDA, CHAI, WHO and the National Institutes of Health (NIH) will be useful to evaluate the potential for *taste-masked granules of LPV/r*.

- Another significant decision will need to be made while selecting the final combination of NRTIs for final FDC development. Strong consideration should be given to narrowing the product selection by focusing on the development of one 4-in-1 product with ABC + 3TC versus two products (ABC + 3TC and ABC + AZT), as AZT + 3TC may not be considered as a preferred ARV combination in 2017 or 2019 WHO paediatric ART guidelines. A stakeholders meeting with the US FDA, CHAI, WHO and NIH will be useful to evaluate the potential for narrowing product development to only one 4-in-1 FDC product.

- In addition to the candidate product development, Cipla Ltd. had to address the challenge of packaging the pellets/granules in capsules. The production of new formulation of LPV/r and 4-in-1 requires technical equipment capable of measuring and packaging the exact amount of required ingredients. This equipment was not available for the large scale production at Cipla Ltd. Under the UNITAID award, this equipment was recently developed by the German engineering firm and is ready to be shipped to Cipla Ltd. The installation of this equipment within Cipla Ltd. faculties is scheduled for 2016 and will significantly increase the capacity to produce LPV/r pellets (including *non-taste masked LPV/r pellets*, tentatively approved by FDA in 2015, see below).

- The approval of Cipla Ltd. LPV/r oral pellets by FDA (May 2015) represents an important step towards closing the treatment gap for infants and young children living with HIV. While not involved in the development of the pellets, DNDi has played **a prominent role** informing about the new formulation and advancing its introduction to the WHO guidelines. DNDi is currently working with Cipla Ltd. to facilitate future registration and adoption of the new LPV/r pellets through an implementation study launched in fall of 2015 in Kenya and scheduled to expand to Uganda in Q1 2016. This activity can be considered as preparatory stage for the registration stability studies for 4-in-1 FDC. This activity will also be useful in obtaining the data on the acceptability and feasibility of *pellets* formulation in infants and young children to be shared with FDA as part of the formal consultation following Phase I bioavailability study completion.

c) Output 1_Activity 5: "Validation batches produced for ABC/3TC/LPV/r and AZT/3TC/LPV/r"

Scheduled for: Q3 2015

Current Status: Not completed, contingent upon the success of the Output 1_Activities 2-4, future timeline needs to be specified if project is extended

Finding

Per Cipla Ltd., the NRTIs granules are already available. The production of the clinical batches for 4-in-1 formulations requires combining the *taste-masked LPV/r pellets* or *granules* with two NRTI's – either *granules* of ABC + 3TC or of AZT + 3TC - for use in accordance with the regional or country recommendations on NRTIs. This activity is contingent upon successful development of the *taste-masked LPV/r pellets or/and granules*. The production of batches of capsules filled with pellets or granules requires technical equipment capable of measuring the exact amount of required ingredients for pellets and/or granules formulations. This equipment was recently developed by the German engineering firm for Cipla Ltd. with the support of UNITAID funding and is ready to be shipped to Mumbai, India Cipla Ltd. facilities. The installation of this equipment within Cipla Ltd. facilities is expected to significantly increase the capacity to produce clinical batches of LPV/r and 4-in-1 pellets from the current capacity of ~10,000 capsules/year to an estimated 216,000,000 capsules/year. Assembling of the PI-based FDCs, however, is dependent upon the success of development of the taste-masked LPV/r pellets/granules.

Summary observations in respect to **Output 1_Activity 5:**

- The advancement has been made to develop and manufacture the equipment capable to produce pellets/granules by German engineering firm. The development of this LPV/r formulation, crucial for the production of the validation batches of 4-in-1 formulations, has not been completed. As a result, the production of validation batches of 4-in-1 has been placed on hold. The completion of the formulation of 1-in-4 FDC is feasible within the current project timeline; however, the production of the validation batches will require additional time and can only be performed during extension stage if granted.

4.1.2 Output 2: Clinical studies completed for two 4-in-1 ARV FDCs (ABC/3TC/LPV/r and AZT/3TC/LPV/r)

Current status: Not completed, contingent upon the success of the Output 1

a) Output 2_Activities 1 & 2: "Phase I: Bioavailability & Bioequivalence of LPV/r and 4-in-1 in healthy human volunteers"

Scheduled for: Q2 2013 – Q3 2014

Current Status: Taste masked LPV/r studies (Phase I) are in progress, 4-in-1 studies are contingent upon the success of the Output 1_Activities 2-4, future timeline needs to be specified

Finding:

Bioavailability/bioequivalence studies of LPV/r in healthy adult volunteer have been completed for the **fed state** and are now ongoing in the fasting stage (scheduled for January-February 2016). The best formulation from phase I testing is planned to be combined with the two NRTIs (ABC/3TC and AZT/3TC) and tested in a phase I healthy adult volunteer study. This activity is contingent upon the successful outcome of Activity 2. DNDi is estimating a timeline of 3-4 months to complete the bioequivalence study with 4-in-1 once the candidate product becomes available. However, current experience with LPV/r phase I bioavailability study suggest more realistic timeline of 5-6 months.

Summary observations in respect to **Output 2_Activities 1 & 2:**

- The completion of this activity will require: successful bioavailability study in healthy adult volunteers in fasted state plus co-formulation of the best candidate with 2 choices of combination of two NRTIs (or one if only one FDC is selected for future development following the stakeholder meeting recommended under Output 1). In addition, the formal consultation with the FDA team after completion of Phase I LPV/r bioavailability study to discuss the development strategy for 4-in-1 formulation is highly advisable before carrying out the activities 1 & 2 for the Output 2. The completion of the formulation of the bioequivalence study for LPV/r is feasible within the current project timeline; however, the completion of the phase I bioavailability study for 4-in-1 formulation (if successful in development) will require additional time and can only be performed during extension stage if granted.

b) Output 2_Activities 3 & 4: "PK, efficacy, safety and acceptability studies"
Scheduled for: Q3 2013 – Q1 2016
Current Status: Not completed, contingent upon the success of the Output 1_Activities 2-4 and Output 2_Activities 1&2, future timeline needs to be specified

Finding:
Following the results of the phase I bioavailability study comparing the first *taste-masked LPV/r granules* in capsules produced by Cipla Ltd. with the AbbVie liquid formulation, the extension of Chapas-2, the phase II study comparing *taste-masked* Cipla Ltd. *LPV/r granules or pellets* formulation with the Kaletra® oral solution in children, has been put on hold until an optimised formulation has been developed and successfully tested in adult healthy normal volunteers. As described above, DNDi will seek FDA advice in Q2-Q3 2016 once phase I study results from bioavailability of LPV/r pellets and/or granules in healthy volunteers are available (fed and fasted state). A decision will be made on the best regulatory pathway (either a pivotal bioequivalence *or* a paediatric phase II study which would be a continuation of the Chapas 2 study in Uganda (https://www.dndina.org/component/content/article/2-events/104) using the new taste-masked formulations).

The current clinical LIVING study began recruitment in Kenya in September 2015. The study is being carried out to provide clinical data on the acceptability, feasibility, effectiveness, safety, and PK of existing *non-taste masked LPV/r pellets* by Cipla Ltd. to demonstrate an advantage of solid PI formulation in comparison with the liquid formulation in children. The study specifically evaluates the acceptability of the pellets LPV/r formulation in infants and young children. The recruitment of infants is limited to date.

Additionally, in April 2014 DNDi signed a Partnership Agreement with the South African National Department of Health to improve access to paediatric HIV treatment in the country. The agreement aims to ensure that clinical studies commence rapidly in order to prepare for the transition from the current alcohol-based liquid LPV/r formulation to the *new non taste-masked LPV/r pellets formulation*. An agreement has been reached to expand the currently active RTV booster studies in South Africa (see output 5) with co-enrolment for the LPV/r pellets. Within the framework of the LIVING study, DNDi also offered to test formulations developed by other companies (Mylan and Hetero etc.) However, to date no other companies have engaged in the project.

Summary observations in respect to **Output 2_Activities 3 & 4:**

- The PK, efficacy, safety and acceptability studies of the new taste-masked this LPV/r and 4-in-1 FDC formulations depend on the successful product development. Since the product development has not been completed, these activities have been placed on hold. The completion of these activities will require additional time and can only be performed during extension stage if granted. Through ongoing LIVING study DNDi will be able to obtain limited preliminary data on the acceptability of the *non-taste masked* existing *LPV/r pellets* formulation by Cipla Ltd. in children within the current project timeline.

4.1.3 Output 3: Registration of adapted paediatric ABC/3TC/LPV/r and AZT/3TC/LPV/r FDCs for use in resource-poor settings

Current Status: Not completed, in progress with activities and outputs contingent upon Output 1 and Output 2

a) Output 3_Activity 1 & 2: "Regulatory-scientific advice", "Preparation and submission of regulatory dossiers for 4-in-1 FDCs"

Scheduled for: Q3 2013-onwards and Q4 2013 – Q4 2014

Current Status: Not completed, contingent upon the success of the Output 1 and Output 2, and support of the prequalification process by WHO with tentative FDA approval

Finding

Currently, no 4-in-1 formulation is available for registration. DNDi had originally planned for the FDA approval process to be able to facilitate the pre-qualification by WHO, however, to date this issue has not been resolved. The "tentative approval" by FDA currently does not guarantee the timely approval of the new product by WHO. DNDi seeks UNITAID support in leveraging the approval prequalification process between FDA and WHO to facilitate the registration of the 4-in-1 LPV/r based FDC once it has been fully developed. The lack of this facilitated mechanism has the potential to significantly delay the registration of the new product in resource-limited settings. For the country approval – the accelerated process of ~60 days could be used after prequalification once the product is available. Currently, DNDi supports Cipla Ltd. in accelerating the *LPV/r non-taste masked pellets* registration process through a priority review in South Africa and a joint regional review coordinated by WHO Prequalification of Medicines Program.

Summary observations in respect to **Output 3_Activity 1 & 2:**

- Since no 4-in-1 formulation has been developed, it is not available for registration. DNDi seeks UNITAID support in leveraging the approval process between FDA and WHO to facilitate the registration of the 4-in-1 LPV/r based FDC once it has been fully developed.

4.1.4 Output 4: Formulate a standalone PK booster (RTV)

Current Status: Not completed, no longer planned

a) Output 4_Activities 1, 2, 3 and 4: "Development of RTV in granules", "Clinical batch available for RTV granules", "Registration stability studies for RTV granules (accelerated and real time)"

Scheduled for: Q2-Q3 2013
Current Status: Not completed, no longer planned

Finding
Since the start of the project, several RTV solid granule and pellet formulations have been evaluated in the dog model. To date, DNDi and Cipla Ltd. have not been successful in developing a standalone RTV formulation that is taste-masked and does not compromise bioavailability. DNDi and Cipla Ltd. have no plans for further development of a *taste-masked RTV formulation.*

It is important to notice tentative FDA approval for the smaller (25 mg/50 mg) RTV tablets by Cipla Ltd. in March 2015 (http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm)

and development of the solid formulation of non-taste masked RTV pellets by AbbVie (Salem Ah, et al., *Antivir Ther* 2015;9:20(4):425-32; registration filed with the European Medicines Agency [EMA]). Following these developments, DNDi has engaged in discussions with AbbVie to use their non-taste-masked (bioequivalent to their registered liquid formulation) oral powder formulation (in a study similar to an ongoing superboosting study in South Africa (see Activity 13, Output 18 below). This small (n=30) bioavailability study, scheduled for implementation in 2016, will evaluate the efficacy of superboosting the Cipla Ltd. Non-taste masked LPV/r pellets with AbbVie's *non-taste-masked RTV granules* in TB and HIV co-infected children. The study protocol is currently under development and review.

Summary observations in respect to **Output 4_Activities 1, 2, 3 and 4:**

- Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi and Cipla Ltd. have abandoned plans for further development of a standalone RTV booster. Taken into consideration the newly developed and approved formulations of RTV suitable for young children, further development of the taste-masked RTV granules, while could be beneficial, is no longer a priority for paediatric ARV drug development. The proposed study of RTV superboosting of the new non-taste masked formulations of LPV/r pellets by Cipla Ltd and with AbbVie RTV powder will contribute to the knowledge on the dosing and PK with co-

administration of these drugs in children with HIV and TB co-infection. This study will can only be performed during extension stage if granted.

b) Output 4_Activity 4: "Validation batches produced for RTV"
Scheduled for Q3-4 2015
Current Status: Not completed, no longer planned

Finding
DNDi and Cipla Ltd. have no plans for further development of a taste-masked RTV formulation.

Summary observations in respect to **Output 4_Activity 4:**

- Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. Taken into consideration the newly developed and approved formulations of RTV suitable for young children, further development of the taste-masked RTV granules, while could be beneficial, is no longer a priority for paediatric ARV drug development.

4.1.5 Output 5: Clinical studies completed for a standalone PK booster (RTV)

Current Status: Not completed, partially in progress

a) Output 5_Activities 1 & 2: "Phase I: Bioavailability & Bioequivalence study of RTV granules in healthy human volunteers (pilot and pivotal)
Scheduled for: Q3 2013 – Q3 2014
Current Status: Not completed, no longer planned

Finding
As above, DNDi and Cipla Ltd. have no plans for further development of a taste-masked RTV formulation.

Summary observations in respect to **Output 5_Activities 1 & 2:**

- Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster. Taken into consideration the newly developed and approved formulations of RTV suitable for young children, further development of the taste-masked RTV granules, while could be beneficial, is no longer a priority for paediatric ARV drug development.

b) **Output 5_Activities 3 & 4: "PK, safety and efficacy of superboosted LPV/r",**
Scheduled for: Q1 2013 – Q4 2015
Current Status: Interim analysis completed, recruitment completed, full analysis in progress

Finding

The superboosting paediatric RTV dose which is safe and efficacious, weight and age-based, needed to be confirmed through PK studies in TB-HIV co-infected paediatric studies. The boosting efficacy of the newly developed powder for suspension has to be verified in combination with the 4-in-1 LPV/r based FDCs. A paediatric PK study is currently underway in infants and young children co-infected with TB and HIV in South Africa to supplement existing information and evaluate the effect of the "superboosting" strategy. Specifically, the study is evaluating the effect of lopinavir/ritonavir in a 1:1 ratio (increased from 1:4 to 1:1) on the PK of lopinavir in children concomitantly receiving rifampicin as treatment for TB. The study used all liquid formulations including RTV formation, which are not adapted for resource limited settings. An interim analysis of data from 80 study participants was conducted in May 2015, showing the safety and efficacy of the superboosting approach. The results were submitted to WHO Guidelines Technical Review Team in view of revisions of the treatment guidelines for TB and HIV in children by the end of 2015. The results were also presented at a Paediatric HIV workshop in July 2015 in Vancouver, Canada. As of October 2015, 271 children were screened, and 95 were enrolled in the study, there were 14 drop outs. 91 children have been included in the study. A first PK study has been completed in 99% (n=90) of expected participants, a second PK study in 74 (97%) and a third PK study in 50 (100%) of expected participants. All study visits have been completed by 68 (100%) of expected participant. DNDi now plans to complete the full analysis and 9 months follow up of the current superboosting study and also plans to initiate the all solid (LPV/r pellets supplied by Cipla Ltd. and LPV/r powder supplied by AbbVie) super-boosting second phase study. The investigators meeting for phase 2 superboosting study was held in November 2015 in South Africa. The study protocol is scheduled to be sent to the ethics committee and regulatory authority in January 2016. The recruitment is scheduled to start in Q2/Q3 2016.

Summary observations in respect to **Output 5_Activities 3 &** 4:

- The achievement of this activity is considered among the five most important achievements of the project to date by DNDi.
- As outlined in Outputs 3 and 4, DNDi has abandoned plans for further development of a standalone RTV booster. However, DNDi has pursued the clinical studies with available liquid formulation of RTV to supplement existing information and evaluate the effect of the "superboosting" strategy. An interim analysis conducted and presented in 2015, showed the safety and efficacy of the superboosting approach and was shared with the WHO to support the 2015 revision of the paediatric HIV and TB treatment guidelines. The full analysis of this study, as well as the proposed study of all solid formulations of and non-taste masked LPV/r formulation by Cipla Ltd. and RTV AbbVie powder are only feasible to be completed during an extension stage if granted.

4.1.6 Output 6: Registration of an adapted paediatric RTV granules for use in resource-poor settings

Current Status: Not completed, no longer planned

a) Output 6_Activity 1: "Regulatory-scientific advice"
Scheduled from: Q3 2013 onwards, as required
Current Status: Not completed, no longer planned

Finding
As above, DNDi and Cipla Ltd. have no plan for further development of a taste-masked RTV formulation.

Summary observations in respect to **Output 6_Activity 1**:

- Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster.

b) Output 6_Activity 2: "Regulatory dossiers for RTV granules"
Scheduled for Q3 2013 – Q4 2014
Current Status: Not completed, no longer planned

Finding
As above, DNDi and Cipla Ltd. have no plan for further development of a taste-masked RTV formulation.

Summary observations in respect to **Output 6_Activity 2**:

- Having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi has abandoned plans for further development of a standalone RTV booster.

4.1.7 Output 7: Facilitate the adoption of LPV/r based first-line ART and RTV granules in low- and middle-income countries

Current Status: In progress

a) Output 7_Activity 1: "Dosage from acceptability field surveys"
Scheduled for Q1 2013 – Q3 2013
Current Status: Not completed, planned

Finding
Field surveys to determine the feasibility of using capsules will be carried out during the implementation studies (see description above and below of the LIVING study) with 4-in-1 FDC once it becomes available.

Summary observations in respect to **Output 7_Activity 1:**

- The dosage from acceptability field studies of the new taste-masked this LPV/r and 4-in-1 FDC formulations depend on the successful product development. Since the product development has not been completed, these activities have been placed on hold. The acceptability of the non-taste masked LPV/r pellets by Cipla Ltd. is ongoing in the LIVING study (see details below).

b) Output 7_Activity 2: "Implementation studies" - Prospective study of Lopinavir based ART for HIV Infected children globally (LIVING study)"

Scheduled for Q1 2014 – Q2 2016
Current Status: Not completed, in progress

Finding

DNDi is working with Cipla Ltd. to ensure early access to a newly approved *non taste-masked pellet LPV/r* formulation through an implementation study. Specifically, DNDi works with Cipla Ltd. to ensure its non-taste-masked LPV/r pellets, which received tentative approval from the U.S. FDA in May 2015, are registered and adopted through a large implementation LIVING study (see above). While not taste-masked, the Cipla Ltd. LPV/r pellets represent a significant improvement over AbbVie's Kaletra® liquid formulation in that they do not require a cold chain, are alcohol free, easy to store and administer.

The implementation study encountered a delay due to the lack of availability of the pellets from Cipla Ltd. The LPV/r pellets are introduced together with existing dual NRTIs dispersible tablets (ABC/3TC and AZT/3TC) produced and marketed by Cipla Ltd. The study started recruitment in Kenya in September 2015. The Institutional Review Board (IRB) approval is expected in December 2015 in Uganda, recruitment through reactivated Chapas 2 sites is expected to be initiated in Q1 2016. IRB approval has been sought in Tanzania, not available yet. The project has planned to recruit 350 subjects per country. Current pilot recruitment is at 25 subjects in Kenya with an age range between 9 months and 8 years old, multiple sites are collaborating and the study team is actively trying to reach younger cohorts for enrolment to evaluate efficacy, safety, acceptability and PK in infants. The labelling for Cipla's pellets tentatively approved by U.S. FDA excludes children below 2 weeks of age and under 5 kg. Data will be required to modify the labelling for a more inclusive use in younger age groups. Therefore, DNDi aims to collect acceptability and safety data in very young children and make it available to Cipla Ltd., FDA and WHO. The usefulness of pellets/mini-tablets in neonates, however, is questionable taken into consideration some pilot unpublished data from Germany (shared by DNDi during interview) which describes significant (43 pellets) dosing requirements of the LPV/r in newborns. The epidemiological data on young HIV infection rates are supportive of the feasibility for the recruitment of the target 350 children in Kenya and Uganda. However, recruitment of young infants is more challenging than recruitment of older children. Even with addition of Uganda sites, currently, an estimated recruitment by March 2016 by DNDi is <75 subjects. To date, internal communication within DNDi on the pilot results suggests high acceptability and satisfaction by prescribers and caregivers. The study is scheduled to be extended to other countries in sub-Saharan African including Zimbabwe, Malawi and South Africa. The negotiations are most advanced with South Africa where recruitment is expected to commence in Q2/Q3 2016.

As mentioned previously, DNDi has also approached two companies involved in developing alternative heat-stable taste-masked LPV/r-based formulations (Mylan and Hetero), and offered the possibility to test their formulations in the implementation study. DNDi plans to transition to the taste-masked 4-in-1 FDCs once they become available. Additionally, DNDi engaged in discussion with the U.S. National Institutes of Child Health and Development (NICHD), International Maternal Pediatric Adolescent AIDS Clinical Trials Group (NIH/IMPAACT), to partner and support a study evaluating LPV/r versus raltegravir-based ART in children < 3 years of age. The sponsor for the study is NIH/IMPAACT. It was

envisioned that DNDi would contribute to write protocols and supply Cipla's LPV/r pellets for the study with an estimated recruitment of 100 infants. For DNDi this partnership represents an excellent opportunity to leverage resources and avoid competition for recruitment between the two studies which will be conducted in the same countries/sites. The NICHD 2006-NEXGEN trial, however, has been recently modified to focus on alternative integrase inhibitor dolutegravir (DTG), and this modification is most likely to delay the roll out of the study and projected collaboration with DNDi. Currently, NICHD estimates the startup of the study in approximately 18 months.

Other implementation studies partnerships were developed by DNDi and include, most importantly, supplying LPV/r pellets for the Paediatric European Network for the Treatment of AIDS *(PENTA)-20/Odyssey trial* comparing DTG-based therapy to standard of care for the cohorts of young children who cannot swallow tablets (Alluvia LPV/r 100/25mg). DNDi also partnered with the *NeoART study* examining the safety, pharmacokinetics and feasibility of very early LPV/r-based ART in HIV-infected neonates followed by passive immunization with HIV-1 broadly neutralizing monoclonal antibody in being developed. The funding proposal for this study is currently under review by European & Developing Countries Clinical Trials Partnership (EDCTP).

DNDi reports that they reached agreement to a memorandum of understanding with CHAI to collaborate and share expertise in R&D, forecasting, product uptake and adoption in countries, pricing and cost of goods and the creation and dissemination of tools to promote product acceptability. DNDI also reports on agreement to partner with CHAI on a pilot study to introduce Cipla's LPV/r pellets in various countries to collect feasibility and acceptability data. [redacted]

Summary observations in respect to **Output 7_Activity 2:**

- The achievement of this activity is considered among the five most important achievements of the project to date by DNDi.

- DNDi is working with Cipla Ltd. to ensure early access to a newly approved non-taste masked LPV/r pellets formulation through a large implementation LIVING study which started recruitment in Kenya in fall 2015 and is scheduled to initiate recruitment in Uganda in Q1 2016. The project has planned to recruit 350 subjects per country. Current pilot recruitment is at 25 subjects in Kenya with an age range between 9 months and 8 years old, and the study team is actively trying to reach younger cohorts for enrolment to evaluate efficacy, safety, acceptability and PK in infants. However, recruitment of young infants is more challenging than recruitment of older children. Even with addition of Uganda sites, currently, an estimated recruitment by March 2016 by DNDi is <75 subjects. DNDi is active in seeking other partnerships (with CHAI, NICHD, PENTA etc.) in expanding its spectrum of implementation studies. The preliminary data will be available from the initial recruitment from LIVING study within the current project time line, however, obtaining additional data and target enrolment is only feasible to be completed during an extension stage if granted.

c) Output 7_Activity 3: "Market analysis results published",
Scheduled for Q2 2013 – Q2 2016
Current Status: Not completed, in progress

Finding
A manuscript entitled "*An analysis of volumes, price trends and pricing trends of the pediatric antiretroviral market in developing countries from 2004 to 2012*" has been submitted for publication to BioMed Central Pediatrics and it is currently under review.

Summary observations in respect to **Output 7_Activity 3:**

- Market analysis results are most likely to be published in Q1-Q2 2016.

4.2 Additional Activities

4.2.1 Raising awareness

Since the start of the project, DNDi has taken an leadership advocacy role for improved paediatric ARV formulations and increased access to treatment and collaborating with multiple international agencies including, but not limited to WHO, IATT, CHAI, Elizabeth Glaser Paediatric AIDS Foundation (EGPAF). Specifically, DNDi is developing and evaluating an advocacy toolkit to raise awareness about early testing, diagnosis and treatment of HIV infection in infants and young children and capture those that have fallen out of the current system (http://www.dndi.org/diseases-projects/paediatric-hiv/paediatric-hiv-advocacy-toolkit/). The toolkit is being developed in collaboration with community organisations and other partners.

4.2.2 Engagement with civil society organizations

Engagement with civil society organizations (CSOs): DNDi is working with community leaders from the National Empowerment Network of People Living with HIV/AIDS in Kenya (NEPHAK) and the International Community of Women Living with HIV (ICW) to develop and implement the paediatric HIV treatment toolkit and has engaged other partners such as the Centers for Disease Control and prevention (CDC)/ PEPFAR, National AIDS and STI Control Program (NASCOP) to adopt and use the toolkit. Within the scope of these activities, advocacy toolkit two day training took place in June 2015 in Kenya and was attended by 22 community and provider members from the University of Nairobi, University of Washington, Gertrudes Hospital, Kenyatta Hospital, Family AIDS Care and Education Services (FACES) project, NASCOP and CDC/PEPFAR. During the workshop the participants shared experiences from the community, provided treatment literacy to community representatives on diagnosis and treatment of children with HIV and shared the latest research on paediatric HIV, including presentation on the LIVING study. CSOs members serve on the Community Advisory Board for DNDi studies and play an intermediate role between the patients and the study sites: CSOs will help to advocate for product uptake and adoption into national

treatment guidelines. The collaboration with NEPHAK is expected to increase the referral of the potential patients to study sites for treatment and screening for inclusion into the study. Importantly, this collaboration is part of an advocacy strategy that, if successful, will be replicated nationwide and in countries where DNDi conducts its implementation study.

4.2.3 Set-up of the Paediatric HIV Treatment Initiative

Set-up of the Paediatric HIV Treatment Initiative (PHTI) in collaboration with the MPP, CHAI and UNITAID: DNDi is an active founding member of the PHTI and contributes its research and development expertise. DNDi has contributed its expertise and data to PHTI and WHO for the population PK modelling of ABC, 3TC and EFV necessary to develop a FDC of the three products for children older than three years of age. Within the PHTI framework DNDi also continues to work with other partners including CHAI, MPP, WHO and the Paediatric ARV Procurement Working Group to ensure access to needed paediatric formulations as soon as they are available.

Summary observations in respect to **additional activities**:

- DNDi is developing and evaluating an advocacy toolkit to raise awareness about early testing, diagnosis and treatment of HIV infection in infants and young children and capture those that have fallen out of the current system. DNDi is working with NEPHAK, in Kenya and the ICW to develop and implement the paediatric HIV treatment toolkit. The collaboration with NEPHAK is expected to increase the referral of the potential patients to study sites for treatment and screening for inclusion into the implementation study.
- The set-up of the PHTI is considered among the five most important achievements of the project to date by DNDi.

4.3 Monitoring and Evaluation

The project has experienced significant delays and changes from original planning. The detailed explanations of the delays have been provided to UNITAID in yearly reports. A letter detailing the delays was submitted to UNITAID in August 2015 as part of the request for no-cost extension of the project for 2.5 years. DNDi has submitted yearly and semi-annual reports in 2013, 2014 and 2015. The project did not have any significant personnel or other incidents such as fraud, loss and incident report.

4.4 Financial progress

The original allocation of funding for the project included USD 17’336’000. UNITAID funds that were available at the time of this reporting period were USD 14’600’000. A total of ~16% from initially allocated funding was spent during the project. The reasons for the significant underspending are two-fold:

1) a significant delay in the timeline resulting from the need to evaluate several LPV/r formulations in a dog model after the first formulation of LPV/r granules that were developed and tested in 2013 showed low bioavailability and a high variability, and
2) a delay due to the lack of availability of the pellets from Cipla Ltd.

The project spending is expected to increase with the projected new product development and scale up of implementation studies. However, that increase in spending will likely not use the full amount of the remaining funding, but just part of it. DNDi, however, estimates the spending to reach full expenditure if the no cost-extension is granted.

Summary observations in respect to **financial progress**:

- Due to the failure of the initial drug candidate and delay in drug development and implementation studies, the project budget has been grossly underspent. DNDi anticipates that spending will increase in the remaining project time with the projected new product development and scale up of implementation studies. Even with this scale up, it is clear that the project will remain significantly underspent. For any no-cost extension funding needs to be thoroughly revised and decreased to be allocated for the achievable deliverables only.

5 Conclusions & Recommendations

The DNDi project to secure market entry of improved solid PI-based FDCs for children with HIV/AIDS in partnership with Cipla Ltd., has shown a great dedication and has advanced the cause of paediatric HIV treatment overall. The project outcomes to date are limited (see Appendix A), but those achieved are consistent with UNITAID mission to contribute to scale-up innovations for treatment of HIV/AIDS. The project started implementation in Q2 2013. Some progress has been made in all three objectives to date, however, no new paediatric PI-based optimized FDCs have been developed, and neither was developed standalone RTV formulation.

The effectiveness of the project has been challenged by an early failure of the candidate product and difficulties in finding an alternative compound. In spite of the very promising preliminary data and excellent taste masking, highly anticipated taste-masked Cipla Ltd. LPV/r granules in capsules demonstrated low and unpredictable bioavailability making them unsuitable for further development. DNDi worked closely with pharmaceutical partner Cipla Ltd. analyzing the failure and testing multiple candidate formulations. After two years of consistent efforts, six taste-masked LPV/r formulations with potentially good bioavailability in human have been identified and *three most promising formulations* are being evaluated in phase I studies in healthy human volunteers. Until the results of these and 4-in-1 studies become available, it is difficult to predict the full impact of the UNITAID funding on target product development.

Out of seven outputs, adjustments and some progress have been made in four (Outputs 1, 2, 5 and 7), while three outputs (3, 4 and 6) have not advanced thereby two outputs (4 and 6) are no longer pursued. Adjustments of the outputs and activities were related to the delay in the main product development and related delay in the roll out of the implementation studies.

A total of 24 activities have been scheduled within the frameworks of the seven expected outputs: two have been completed, 16 are in progress or planned, and six are no longer planned. Given the limited scope of undertaken activities, only 16% of the budget has been spent through the review period. DNDi utilized UNITAID funding efficiently for the amount of work that was carried out.

Activities implemented by the project to date are consistent with the initial and adjusted project plan and in line with UNITAID objectives and strategy. Most important achievements of the project relevant to the UNITAID mission to date include:

- Development of the optimal paediatric weight band dosing for PI-based FDCs from PK modeling and simulations of integrated existing PK data from the United States, France and Africa. The weight band based alignment of the PI and NNRTIs dosing has led to the important changes in the paediatric WHO treatment guidelines and had an important influence on the approach to developing, manufacturing and forecasting of PI-based FDCs for young children.

- Paediatric PK study is in infants and young children co-infected with TB and HIV was conducted in South Africa to supplement existing information and evaluate the effect of the "superboosting" strategy with RTV on the PK of lopinavir in children concomitantly receiving rifampicin as treatment for TB. An interim analysis of data showed the safety and efficacy of the superboosting approach and was shared with the WHO Technical Review Team to support 2015 revisions of the paediatric treatment guidelines for TB and HIV in children.

Following the failure of the best taste-masked candidate for LPV/r in the initial stages of the project and having experienced significant difficulties preserving bioavailability of the product with taste-masking, DNDi and Cipla Ltd. have abandoned plans for further development of a standalone RTV booster. With recent availability of the powder and small tablet size RTV paediatric formulation this output has lost its relevance as a priority for paediatric ARV drug development. Finally, DNDi has been active in promoting paediatric HIV treatment, seeking collaboration and engaging with other stakeholders and partners, actively participating in the set-up of the Paediatric HIV Treatment Initiative and sharing lessons learned with the global community.

At the beginning of the project three components including (a) excellent product candidates, (b) strong advisory board and (c) excellent prospective development appeared to guarantee the success and completion within the expected timeline. While the risk mitigation seemed to be well addressed, the level of difficulties and alternative approaches after the candidate failure has not been anticipated enough. To compensate for this DNDi and Cipla Ltd. worked hard on finding solutions. DNDi has clearly acquired a better understanding of the factors influencing bioavailability and taste-masking of LPV-r solid solution formulations and feels it is in the solid position now with the new product candidates and encouraging early bioavailability pilot data from animal experiments and health human volunteers trials in fed state.

The considerations and recommendations for further project implementation within an existing timeline without extension are:

1. Retain the focus on scheduled outputs and deliverables without expanding the project beyond the current mandate of completing the phase I bioavailability study, and select the best formulation and path for further development of 4-in-1 FDC.

2. Consider focusing only on LPV/r pellets versus moving forward with both pellets and granules development.

3. Consider narrowing the product selection by focusing on the development of one 4-in-1 product with ABC/3TC.

4. Reassess of the progress of LIVING study, which has made great strides in opening new sites, however, still has a low pace of recruitment across existing sites compared to the recruitment target. More engaging collaboration with CHAI and other potential implementers on mutually shared funding platform including direct funding support should be considered.

5. Revise of the budget and reduction of the funds for the remaining scope of work need to be strongly considered.

The interviews with KIs has solicited the same degree of enthusiasm from the main partner Cipla Ltd., while generated much more reserved assessments of future success by the representatives from WHO, US FDA, CHAI and NICHD. The main reservations by KIs are based on the advancement of other drug candidates such as DTG for consideration as first-line ART in young children and the position of LPV/r for future paediatric treatment guidelines, which will eventually determine the market for the LPV/r pellets. Thus based on what is known about candidate formulations and developments of the implementation studies today, and despite significant remaining challenges, DNDi is confident that they could complete the project and requested a no-cost extension period of 2.5 years to complete on-going and planned activities.

Based on the current progress on the project and as a result of the detailed discussions with the DNDi team and KI interviews in November-December 2015, we conclude that the consideration for the no-cost extension can be given **after the following steps**:

1. Consideration for a no-cost extension should be given only after the results of the bioavailability studies become available. Consider awaiting the results of the formal meeting with US FDA (planned for Q2 2016) to review the phase I bioavailability study results and advise about the best regulatory pathway to proceed.

2. To help make the best decision on the way forward, recommend gathering the meeting with KI such as WHO, CHAI, NICHD, FDA and potentially other important stakeholders to conduct current market analysis, reassess and forecast the position of the final product on the market within5 years. DNDi and all KIs have expressed willingness and commitment to such gathering in the future if approved by UNITAID. Q1-Q2 of 2016 would be preferable in order to influence a no-cost extension decision.

3. In conjunction with the KI and stakeholders meeting, revise the prequalification requirements process with WHO to facilitate the pre-approval of the new product following anticipated tentative approval by FDA. DNDi has specifically requested support in using collaborative review process to expedite in country registration.

4. Taken into consideration current development of other paediatric boosted PI FDCs and integrase inhibitors, consider broaden collaboration platform within the project to more than one grantee to better manage market entry timeline, leveraging and making stronger market impact for the final product. Consider broaden collaboration platform within the project by engaging CHAI and other parties that can help reach LIVING study targets.

5. Any consideration for the no-cost extension should include a thorough estimate of the realistic time line and thorough risk mitigation with alternative development plan.

6. Expanding the scope of work to include more diversified outputs and activities such as work with other pharmaceutical agents and partners in advancing introduction of other novel paediatric formulations

7. While spending is expected to increase with the new product development and scale up of implementation studies projected for the no-cost extension stage, such an increase will likely not use the full amount of the remaining budget. Consideration for no-cost extension should include revision of the budget and reduction and/or redistribution of the funds within the new scope of work and partnerships.

Appendix A: Evaluation Matrix

Area / question	Criteria	Sources	Comments
Relevance			
Do the goal (impact) and outcome as indicated in the logframe (annex) align with UNITAID's mission to contribute to scale-up of in			**Yes, the goal and outcomes align with UNITAID mission to contribute to scale-up of innovations for treatment of HIV/AIDS.**
Consistency of the project goal (impact) with UNITAID mission to contribute to scale-up innovations for treatment of HIV/AIDS	Exemplification of guiding principles in project processes and outputs	Project documentation ; UNITAID mission (http://www.unitaid.eu/en/about/mission-mainmenu-89)	The project goal (impact) was found to be consistent with the UNITAID mission to continue scale-up innovations for treatment of HIV/AIDS.
Consistency of the project outcome with UNITAID mission to contribute to scale-up innovations for treatment of HIV/AIDS	Outcomes matched with UNITAID mission statement	Project documentation ; UNITAID mission (http://www.unitaid.eu/en/about/mission-mainmenu-89)	The project outcomes to date are limited, but those achieved are consistent with UNITAID mission to contribute to scale-up innovations for treatment of HIV/AIDS.
Do the goal (impact) and outcome align with the global response (and global health actors) to paediatric HIV/AIDS treatment?			
Position of the PI based formulation of ARVs in global reponse ot pediatric HIV/AIDS	Match to strategic obejcitves and projections	Project documentation, WHO HIV Treatment Approach	The project contributed to better positioning of the PI based formulation of ARVs in global response to pediatric HIV/AIDS by advancing Cipla Ltd. non-taste masked LPV/r formulation through implementation study and preparing for the regulatory approval.
Role of the new ARV formulation in the global response ot pediatric HIV/AIDS	Match to strategic obejcitves and projections	Project documentation, data at global and regional levels; WHO prioritization (http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization/en/)	The new formulation has not been developed by the project to date.
Effectiveness			
Have the outputs in the logframe been achieved (or will they likely be achieved)?			**The majority of the outputs has not been achieved**
Development of the optimized PI and NRTI granules and FDCs	New formulations developed, stability studies performed	Project documentation, KI	The optimized PI and NRTI granules and FDCs have not been developed within the scope of the project.
Clinical studies	Bioavailability/Bioequivalence and palatability tested	Project documentation, KI	Initial clinical studies of bioavailability have failed for the original LPV/r product candidate. The new candidates have been tested in Phase I bioavailability study at fed state only. The palatability data are promising for pellets formulation of LPV/r. No studies have been conducted for the 4-in-1 formulation as it has not been developed to date.
Regulatory approval of the products and manufacturing plans	Projected market price, generated demand	Data at global and regional levels, project documentation; WHO prioritization (http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization/en/)	No regulatory approval of the products and manufacturing plans have taken plans as the product development is still in progress. The project facilitates the approval for non-taste masked LPV/r pellets thorough advancing implementation studies.
Have the activities been achieved (or will they likely be achieved)?			**The majority of the activities have not been achieved. The majority of the activities for the output 1 and 2 are highly contingent upon the success of the activity 2 from the output 1. have been dropped from further planning. T**
Completion of each individual objective	Detailed activities and output	Project documentation, KI	Please, find detailed summary in the Output/Activities table.
Assessment of reaching the projected output	Overall outputs of the project	Project documentaiton, KI	Overall, the project achieved less than half of the projected output.

What have been the main factors influencing (or preventing) the achievement of the outputs?			**The main factors preventing the achievement of the outputs were high contingency of the activities upon each other and insufficient risk mitigation plan.**
Pharmaceutical development of the product	Development and validation	Project documentation, KI	The main challenge in the development and validation of the product was in taste-masking of LPV/r and RTV while preserving their bioavailability.
Clinical studies	Enrollment, retention and completion	Project documentation, KI	Currently two clinical studies are open under the project. The RTV superbooster study recruited successfully and shared interim study analysis with global audience including WHO in summer of 2015. The LIVING implementation/acceptability study of the new Cipla Ltd. LPV/r non-taste masked pellets formulation started recruitment in fall 2015, but current recruitment rates are yet far from reaching the target.
Efficiency			
For achieved outputs and activities, where they completed according to the project timeline and budget?			**A total of 24 activities have been scheduled within the frameworks of 7 outputs: 2 have been completed, 16 are in progress or planned, and 6 are no longer planned.**
Project outcomes and acitvities	Adherence to and adjustment(s) of the timelines	Project documentation, KI	The project has limited number of completed outcomes and activities.
Fiscal responsibility	Adherence to budget per activities and timeline	Project documentation, KI	The budget is grossly underspent due to the limited number of activities that were completed.
For activities not yet achieved, will they be completed on time and on budget?			**Only a couple of activities not yet achieved will be completed on time, the rest will not be completed. The budget will remain underspent even with their completion.**
The approach to completing the acitvities in the remaining timeline	Deviations from the projected timeline, targets and rationale	Project documentation, KI	The project has requested no-cost extension to complete the activities. There is no currently firm timeline for the completion of the outstanding activities during a no-cost extension.
Need for additional funding	Estimates of the remaining costs, under(over) spending estimates	Project documentation, KI	84% of the funding is currently underspent and the spending before the project completion is unlikely to significantly change that number. Even with no-cost extension - it is unlikely that all remaining funds will be spent.

Impact			
Will the project result in the intended impact?			**The intended impact has not been achieved to date. It is possible that it will be achieved partially before the end of the project and during extension period (if granted), however, it depends on the results of the bioavailability studies which are ongoing and the timeline to the final product.**
Validation of access to new formulations	Availability of novel pediatric ARV formulations in young children	Project documentation, KI, data at the global and regional level	The project did not yet develop a novel pediatric ARV formulation to be validated and become available for young children. The project did take a lead role in validating and advancing access to a novel formulation of LPV/r pellets for young children developed outside of this project by Cipla Ltd.
What could be the value for money of UNITAID's investment in this project			**The value for money could be advancement of solid PI formulations for young children.**
Better and more cost effective treatments for infants and young children with HIV	Replacement of the current liquid formulation with new granulated formulation	Project documentation, KI, data at the global and regional level; WHO prioritization (http://www.who.int/hiv/pub/journal_articl es/cost-effectiveness-arv-children/en/)	Replacement of liquid ARV formulations for infants and young children with pellets of LPV/r and, potentially, introduction of 1-in-4 solid formulation FDC depending on the successful development of the new candidates.
Lessons learned and Risk Mitigation			
Does the project plan need to be amended? If so, how?			**The project plan does need to be amended. The no-cost extension has been requested. Involvement of the external stakeholders is advised including consultation with FDA, CHAI, NIH and WHO to determine the best plan forward.**
Modification of the project	Reprioritization of the activities	Project documentation, KII	Depending on the outcome of the bioavailability studies of the new candidates, the project activities need to be reviewed and reprioritized.
Have lessons learnt been documented and widely shared?			**The lessons learned have been documented and widely shared.**
Capacity to amend the project based on the lessons l	Practical application of the available evidence	Project documentation, KII	The opportunities to amend the project based on the lessons were limited, however, the project made multiple attempts and currently has promising product in development
Have risks (programmatic, financial , strategic, etc.) been identified and tracked over grant implementation to date?			**The risks have been identified and tracked, but have not been all mitigated to date.**
Risk management	Budget, logframe, deliverables	Project documentation, KII	A lot of the remaining grant activities are contingent upon the success of the Activities 2, 3 and 4 under Output 1. More parallel activities framework and broader/shared partnership including shared funding support needs to be considered.

Appendix B: List of Interviewees

Name	Organisation	Role and /Relevance for the Project	Contact	Role in mid-term review	Date meeting
Jane Galvão	UNITAID	Project Manager	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Brian Keiser	UNITAID	Manager Strategy & Results	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Jewgeni Bader	UNITAID	M&E Data Officer	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Robert Matiru	UNITAID	Director Operations	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Carmen Perez-Casas	UNITAID	HIV and Cross-Cutting Technical Manager, Strategy & Results team	[redacted]	KII, Face2Face Meeting (possibly)	Dec 07, 2015
Patricia Caldwell	DNDi	Portfolio Grant Manager	[redacted]		Dec 07, 2015
Bernard Pécoul	DNDi	Executive Director	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Marc Lallemant	DNDi	Head of Paediatric HIV Program	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Janice Lee	DNDi	Project Coordinator	[redacted]	KII, Face2Face Meeting	Dec 07, 2015
Jean-René Kiechel	DNDi	Senior Pharma Advisor and Product Manager, R&D		KII, Face2Face Meeting	Dec 07, 2015
Rachel Cohen	DNDi	Regional Executive Director, DNDi North America & HIV Advisor	[redacted]	KII, Face2Face Meeting	Did not meet, obtained information from DNDi team (Patricia Caldwell)
Geena Malhorta	Cipla Ltd.	Head of Integrated Product Development Cipla Ltd.	[redacted]	KII, phone interview	Dec 04, 2015

Dale Kempf	Abbvie, Inc.	Distinguished Research Fellow and Director of Antiviral Research Abbvie	[redacted]	KII, phone interview	Dec 03, 2015

Name	**Organisation**	**Role and /Relevance for the Project**	**Contact**	**Role in mid-term review**	**Date meeting**
Martina Penazzato	WHO	Paediatric focal point; WHO/HIV Department	[redacted]	KII, phone interview	Dec 04, 2015
Yodit Belew	FDA	FDA/CDER/OND/OAP/Division of Antiviral Products	[redacted]	KII, Face2Face interview	Dec 01, 2015
Nandita Sugandhi	CHAI	Partner, Implementer	[redacted]	KII, phone interview	
Rohan Hazra	NICHD/NIH	Partner	[redacted]	KII, Face2Face interview	Dec 01, 2015

Appendix C: Documents consulted

Type	Available for review
Grant Agreement signed in May 2013 between UNITAID and DNDi including all annexes	Reviewed
2013 Inception Report	Reviewed
Annual reports: 2013, and 2014	Reviewed
Semi-annual reports: 2014 and 2015	Reviewed
Memorandums of Understanding with Cipla Ltd.	Reviewed
Study reports: LIVING study (2015), RTV booster (2015)	Reviewed
Agreements with Principal Investigators of trials and studies	Reviewed