20 September 2018
EMA/874672/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Delstrigo

International non-proprietary name: doravirine / lamivudine / tenofovir disoproxil

Procedure No. EMEA/H/C/004746/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

3TC	lamivudine
DOR	doravirine
DRV	darunavir
EFV	efavirenz
ETV	etravirine
FTC	emtricitabine
INI	integrase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non- nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PI/r	protease inhibitor in combination with low dose ritonavir (“boosted PI”)
r	ritonavir
RPV	rilpivirine
TDF	tenofovir disoproxil as fumarate
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CPP	Critical process parameter
CQA	Critical Quality Attribute
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
MS	Mass Spectrometry
NAS	New active substance
NMR	Nuclear Magnetic Resonance
NMT	Not more than
PAR	Proven Acceptable Range
PDE	Permitted Daily Exposure
PE	Polyethylene

Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 3 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Delstrigo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2017.

The applicant applied for the following indication:

Doravirine/Lamivudine/Tenofovir Disoproxil (as fumarate) MSD is indicated for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.

During the evaluation phase, the applicant was changed from Merck Sharp & Dohme Limited (Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom) to Merck Sharp & Dohme B.V. (Waarderweg 39, Haarlem, 2031 BN, The Netherlands).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0116/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0116/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance doravirine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2805/1/2014/III	26 June 2014	non-clinical, clinical
EMEA/H/SA/2805/1/FU/1/2015/II	26 February 2015	clinical
EMEA/H/SA/2805/2/2016/I	13 December 2016	quality

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	3 November 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 April 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two clinical investigator sites in the US and Chile and at CRO site in Germany between February and April 2018. The outcome of the inspection carried out was issued on	1 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	05 June 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	28 June 2018

The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Delstrigo on	20 September 2018

2. Scientific discussion

2.1. Problem statement

Infection with human immunodeficiency virus (HIV) and the resulting Acquired Immunodeficiency Syndrome (AIDS) are having a significant human and socio-economic impact.

WHO reported that around 37 million people around the world were living with HIV-1 infection in 2016, with around 2 million newly infected in that year, and an estimated 1 million deaths. The majority of new infections and deaths (64% and 73%) occurred in sub-Saharan Africa. Approximately 2.1 million adults and children were living with HIV infection in western and central Europe and North America, where 73,000 were estimated to have been infected that year.

A large number of antiretrovirals are available, as part of 6 different drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs), fusion inhibitors (i.e. enfuvirtide) and CCR5 inhibitors (i.e. maraviroc).
Present treatment guidelines recommend 2 NRTIs in combination with an NNRTI, a PI (in combination with a pharmacokinetic enhancer) or an INI. Doravirine belongs to the NNRTI class. This class has been downgraded to be “an alternative regimen” by some treatment guidelines (including the European EACS guideline) for reasons of a tolerability (efavirenz associated with CNS side effects , nevirapine with liver reactions and rash) and efficacy (rilpivirine, which is not indicated for patients with a high baseline viral load, and where commonly used proton pump inhibitors are contra-indicated as co-medication). The third available NNRTI, etravirine, is indicated as a second line agent (previously treated), and needs to be taken twice daily.

Globally, NNRTI-based regimens has prevailed, and been recommended as first line by the WHO, since the start of the ”roll-out” of HIV therapy in low and middle income countries, which started around 2004. This is because such regimens have been available at low costs, and until recently the only regimens that were available as fixed dose products, a quality considered of high importance in such settings. Alarming figures on an increasing prevalence of NNRTI resistance, with figures >10% in those newly diagnosed with HIV-infection, are reported from some regions (WHO HIV Drug Resistance Report 2017). As long as an NNRTI regimen is taken with adequate compliance, the efficacy is as high as with other regimens. However, the regimens used so far cannot be considered to have a “high resistance barrier”, and are prone for resistance development in case therapy is stopped for a prolonged time as a consequence of the very long half-life of the present agents (i.e. resulting in functional monotherapy for a couple of weeks if therapy is halted). Consequently, the WHO is now introducing dolutegravir, a second generation INI with a high resistance barrier, as the basis for an alternative first line regimen.

Hence, there is room for improvement within the NNRTI class, both with regards to efficacy and safety aspects. Doravirine has been developed with the aim to address the potential short comings of available NNRTIs.

2.2. About the product

Doravirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI). Mutations selected *in vitro*, and in a limited number of failing subjects *in vivo*, are partially the same, and partially different from those seen at failure with the other agents of the class. The reduction in *in vitro* susceptibility is not very pronounced in the presence of the most prevalent NNRTI mutations seen at failure with the available agents (included transmitted resistance typically seen in lower income settings). However, the efficacy of doravirine has only been evaluated in patients without prior therapy, and in the absence of NNRTI resistance, since full set of such mutations (as listed by IAS-USA) were part of exclusion criteria in the clinical trials. Consequently, no threshold for defining phenotypic resistance to DOR has yet been clinically defined.

Doravirine has a low protein binding (around 75%) in comparison to available NNRTIs (>99%). The free Cmin concentration with the chosen dose of 100 mg qd covers the EC95 of wild type virus several fold, and also the EC95 of virus harbouring the most prevalent NNRTI mutations typically seen at failure with efavirenz. For reasons mentioned, it remains to be studied whether such resistance is devoid of a negative impact on efficacy in clinical practice.

The food impact on absorption is moderate, and not considered clinically relevant; doravirine was given without regards to food in the phase 3 studies. On the basis of studies in HIV-negative subjects, doravirine can be given without dose adjustment to patients with renal impairment (including severe) as well as to patients with hepatic impairment (Child Pugh B studied, Child Pugh C not studied). The terminal half-life of around 15 hrs is considerably shorter than that of efavirenz and rilpivirine (around 40-45 hrs). This may reduce the risk of resistance development in case of halted therapy, a problem often discussed for the NNRTI class.

The current application concerns the use of doravirine, combined with tenofovir disoproxil and lamivudine in standard doses, as a fixed dose combination product.

2.3. Type of Application and aspects on development

- Legal basis

This application is submitted in accordance with article 8(3) of Directive 2001/83/EC, with claim for a new active substance.

- Accelerated procedure

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This is because doravirine belongs to an established class of antiretrovirals (NNRTI), is not indicated for rescue therapy (resistance profile is not clinically evaluated), and there is a large number of available antiretrovirals with favourable efficacy and safety profiles.

- Conditional approval - NA
- Exceptional circumstances - NA
- Biosimilar application - NA
- 1 year data exclusivity - NA

- Significance of paediatric studies

A Paediatric Investigational Plan (PIP) has been agreed on 28/04/2017 (PIP decision number P/0116/2017). No paediatric data has been provided as part of the application, where the indication concerns adult use.

- Clinical development programme

The clinical development programme of doravirine is considered to be in compliance with the CHMP guidance.

Short-term monotherapy was undertaken with a low (25 mg qd) and a high dose (200 mg qd), and the following dose response combination therapy with four dose levels in the same span, using efavirenz as control agent. The phase 3 studies were blinded and used adequate control agents (darunavir/r and efavirenz). In a previous CHMP advice, it was clearly stated that the primary endpoint should concern <40 copies/ml using the FDA snap shot approach. The <50 copies/ml cut off was still used as primary endpoint; however, outcomes with the lower cut-off are presented, and regardless of what level is used point estimates favour doravirine over control. It was also clearly stated that safety endpoints (comparing frequency of side effects that are common during therapy with the agents chosen for control) are not to be part of the SmPC.

All studies concerned are stated to have been performed in compliance with GCP. Routine inspections, with satisfactory outcomes, were carried out at two sites, one in the US and one in Chile.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 100 mg of doravirine, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil as active substances.

Other ingredients are: hypromellose acetate succinate, lactose monohydrate, croscarmellose sodium (E468), anhydrous colloidal silica (E551), microcrystalline cellulose (E460), magnesium stearate (E470b), sodium stearyl fumarate, hypromellose (E464), titanium dioxide (E171), triacetin (E1518) and carnauba wax (E903), iron oxide yellow (E172).

The product is available in high-density polyethylene (HDPE) bottles with a polypropylene child-resistant closure with silica gel desiccants as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The drug product contains the three active substances doravirine, lamivudine and tenofovir disoproxil fumarate.

The active substance doravirine is a New Active Substance (NAS) and full information has been included in the dossier.

Lamivudine is a known active substance described in a Ph. Eur. Monograph. granted a Certificate of Suitability (CEP) by the EDQM.

Tenofovir disoproxil fumarate is a known active substance described in a monograph in the International Pharmacopoeia (WHO, June 2010) and in a USP Pending monograph but not in any Ph. Eur. monograph. For this substance the ASMF procedure is used.

Doravirine

General information

The chemical name of doravirine is 3-chloro-5-({1-[(4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}oxy)benzonitrile corresponding to the molecular formula $C_{17}H_{11}ClF_3N_5O_3$. It has a relative molecular mass of 425.75 g/mol and the following structure:

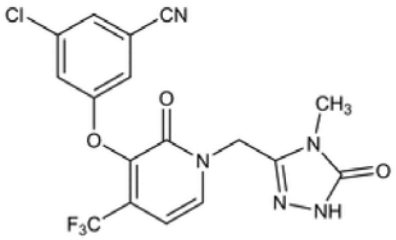


Figure 1: active substance structure

The chemical structure of doravirine was elucidated by a combination of UV, IR, NMR-^{1}H and ^{13}C, and MS. The solid state properties of the active substance were measured by DSC, TGA, and XRPD.

Doravirine is a white to off-white, non-hygroscopic, crystalline powder which is practically insoluble in water.

Doravirine has a non - chiral molecular structure.

Polymorphism has been observed for doravirine.

Doravirine is considered a Biopharmaceutical Classification System (BCS) class II compound (i.e., low solubility and high permeability at a human dose of 100 mg).

Doravirine is a New Active Substance (NAS). Evaluation of the structure of doravirine active substance proved that there is no metabolite of doravirine formed *in vitro* or *in vivo* which is a chemical active substance previously authorized as a medicinal product in the European Union. Also, there is no evidence that doravirine is either an ether or ester analog, derivative, different salt form, polymorph, co-crystal of an authorized active substance. Additionally, doravirine is not a mixture of isomers related to an existing active substance, or a single isomer of an existing active substance containing a mixture of isomers. Doravirine is entirely composed of covalent bonds and none of its bonds are ionic or associated with counter-ions. Therefore, by definition, doravirine is not a salt.

Similarly, the applicant provided data to demonstrate that doravirine or any sub-structure of doravirine is not the therapeutic moiety of an already authorised active substance.

The body of information provided demonstrates that doravirine active substance meets the criteria presented in the Reflection Paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance status of chemical substances and therefore qualifies as a NAS.

Manufacture, characterisation and process controls

Doravirine is synthesized using commercially available well defined starting materials with acceptable specifications.

The synthetic route has been demonstrated at multiple scales, from laboratory to commercial, within the ranges specified and has been shown to produce doravirine active substance meeting all in-process and release specifications.

The selection of regulatory starting materials was discussed in connection with a CHMP Scientific Advice received in 2016. The definition of starting materials is considered justified and acceptable. The control of raw materials including the starting materials is sufficient.

The in-process controls and the critical process parameter have been acceptably described and are considered adequate.

The control of the isolated intermediates is satisfactory.

The extensive development of the synthesis process has been described in detail. Elements of Q8-Q11 have been used but the control strategy is claimed to be traditional. The applicant does not propose design spaces, however, proven acceptable ranges are claimed. Based on these studies, proven acceptable ranges have been defined for all the described steps of the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed proven acceptable range (PAR)s.

Summary descriptions of the developmental studies performed have been provided. They included one factor at a time (OFAT) and multiple factor at a time (MFAT) experiments. Part of the first synthesis step uses a continuous flow reactor and this has been described in sufficient detail.

The active substance doravirine and intermediates have been characterised using adequate analytical techniques. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Extensive information and discussions regarding potential impurities including potentially mutagenic impurities and non-mutagenic carcinogenic impurities and the control strategies of the same have been provided. The mutagenic impurities emerging from the starting materials, intermediates and active substances have been identified. However, in this procedure, the CHMP has concluded that the classification of HIV in the ICH M7 document is no longer supported due to the anticipated duration of therapy in HIV, which may well be more than 5-10 years. Therefore, the CHMP considers that mutagenic impurities must be limited to 1.5 µg/day limit, rather than 10 µg/day proposed by the applicant.

Doravirine container closure system used for its long-term storage is a double, low density polyethylene (LDPE) liner in an outer containment of a fibreboard drum or HDPE drum or packaging providing equivalent or enhanced protection from light. The LDPE materials comply with European Pharmacopoeia 3.1.3, EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), and water content (KF).

The proposed doravirine active substance specifications are acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from several manufacturing scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance critical quality attributes (CQA).

The specifications for doravirine active substance were established after review of the analytical method capabilities, a detailed and comprehensive understanding of the process and finished product CQAs, as well as an extensive review of the batch and stability data. The release specifications are also used through re-test. Batch release data for lots used in toxicological and safety assessment studies, clinical trials, and production scale manufacturing were included in the review.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in in double LDPE liners within a fiberboard container for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The results for three additional primary commercial stability batches for 12 months at 25°C/60%RH and 6 months at 40°C/75%RH showed comparable results to prior stability studies.

Stability testing on doravirine active substance at each time point included description, assay and impurities by HPLC, and water content by KF titration. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No notable trends were observed at any of the stability conditions.

Photostability testing following the ICH guideline Q1B was performed.

Results upon exposure to stress conditions (thermal, oxidative, and photolytic stresses, acidic and basic conditions) were examined. These stress studies were intended to generate degradation products in order to demonstrate the selectivity and stability-indicating nature of the HPLC methods.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed containers.

Lamivudine

General information

The chemical name of lamivudine is 4-amino-1-[(*2R*,*5S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one corresponding to the molecular formula $C_8H_{11}N_3O_3S$. It has a relative molecular mass of 229.3 g/mol and the following structure:

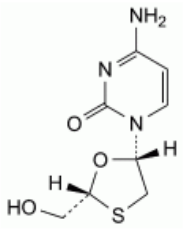


Figure 2 : active substance structure

As there is a monograph of lamivudine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Lamivudine is a white or almost white powder. It is soluble in water, sparingly soluble in methanol, slightly soluble in ethanol. Three relevant crystalline forms of lamivudine had been identified (Form I, Form II and Form III). Form II, anhydrous, is the most stable form, was used to manufacture the finished product. The kinetic solubility of lamivudine Form II in water is 98 mg/mL at 25°C and is considered a BCS class III compound.

Lamivudine exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC.

Manufacture, process controls and characterisation

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

As indicated in the CEP, lamivudine is packaged in double polyethylene bags (outer black) placed in a polyethylene drum.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Acceptable information relating to the specification and controls applied by the finished product manufacturer for their control of the active substance lamivudine has been submitted. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

The active substance specification includes tests for: description, solubility (Ph.Eur.), identity (IR, HPLC, chiral HPLC, DSC, UV), impurities (HPLC), water content (Ph. Eur.), and residue on ignition (Ph. Eur.)

Stability

No retest period is stated on the CEP, and the applicant has provided stability data for three validation batches of the active substance from the proposed manufacturer stored at long term conditions (25°C/60% RH) for 24 months and accelerated conditions (40°C/75% RH) for 6 months according to the ICH guidelines. The batches were stored in in the intended commercial package double polyethylene (PE) bags, placed inside HDPE drum.

The following parameters were tested: description, identification (IR, DSC), water content (KF), enantiomeric purity (chiral HPLC), related substances (HPLC), assay (HPLC). At both storage conditions no out of specification results and no trends are observed for any of the parameters tested.

Based on the stability data provided, the retest period and the storage conditions proposed by the applicant are acceptable.

Tenofovir Disoproxil Fumarate

General information

The chemical name of tenofovir disoproxil fumarate is [[(*2R*)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethyl-(propan-2-yloxycarbonyloxymethoxy)phosphoryl] oxymethyl propan-2-yl carbonate;(*E*)-but-2-enedioic acid corresponding to the molecular formula $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$. It has a relative molecular mass of 635.51 g/mol and the following structure:

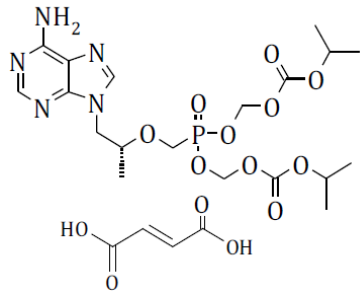


Figure 3: active substance structure

The chemical structure of tenofovir disoproxil fumarate was elucidated by a combination of ^{1}H-NMR, ^{13}C-NMR, MS, IR, UV and HPLC. The solid state properties of the active substance were measured by XRPD.

Tenofovir disoproxil fumarate is a white to off-white slightly hygroscopic powder. It is slightly soluble in water and sparingly soluble in pH buffers 2.0-8.0.

Tenofovir disoproxil exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for tenofovir disoproxil fumarate. Tenofovir disoproxil fumarate exists in two polymorphic forms with indistinguishable solubility. Therefore, any solid-state differences are unlikely to result in clinical consequences. The manufacturing process of tenofovir disoproxil fumarate proposed in the present application, consistently produces one polymorph.

Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Tenofovir disoproxil fumarate is synthesized using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls (IPC) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. An evaluation of potentially mutagenic impurities has been performed. However, in this procedure, the CHMP has concluded that the classification of HIV in the ICH M7 guideline is no longer supported and considers that a limit of 1.5 µg/day has to be applied for mutagenic impurities, rather than 10 µg/day.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Tenofovir disoproxil fumarate for commercial dispatch is packed in a primary transparent low density polyethylene bag (LDPE), followed by another transparent LDPE bag. The secondary pack is a triple laminated sunlight barrier bag (TLSB) with heat sealed kept in a HDPE drum. The packaging material complies with the EC Commission Regulation (EU) No 10/2011, European Pharmacopeia 3.1.3.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-MS), and residue on ignition (Ph. Eur.)

There is a monograph for tenofovir disoproxil fumarate in the International Pharmacopoeia (WHO) from June 2010 and there is an authorized USP monograph.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of several commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of the active substance from the proposed manufacturer stored in similar packages to the commercial package for up to 18 months under long term conditions (5 ± 3°C) and for up to six months under accelerated conditions (25 ± 2° C /60 ± 5% RH) according to the ICH guidelines were provided.

The parameters tested were the same as for release except for melting range, residue on ignition, fumaric acid and residual solvents by GC. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period and the storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The product is a yellow, oval-shaped, bilayer film-coated tablet, debossed with the corporate logo and 776 on one side and plain on the other side. Each tablet is 21.59 mm long by 11.30 mm wide. 30 tablets will be packaged into HDPE bottle with a polypropylene child-resistant closure and silica gel desiccant.

The pharmaceutical development of the finished product contains QbD elements.

The primary strategy of the tablet development program was aimed at developing a solid oral dosage form that meets the quality target product profile (QTPP) throughout the product's shelf life. The safety, efficacy, and patient compliance considerations were used to guide decisions about the dosage form and packaging choices. The finished product has been developed as a solid immediate release oral dosage form. The daily single tablet would be suitable for global market with a shelf life of at least 2 years amongst other relevant requirements. Other safety and efficacy considerations included the control of impurities and degradation products and suitable pharmacokinetic performance for all the actives substances as single entities.

During formulation development, selected target product profile categories were translated into product Critical Quality Attributes (CQA) used to aid in risk assessments made during development.

The key physical properties of the active substances have been described and considered as part of the development program:

- Doravirine

Doravirine is a white to off-white, non-hygroscopic, crystalline powder which is practically insoluble in water.

Polymorphism: As mentioned above, polymorphism has been observed for doravirine. Aqueous solubility: It is classified as a BCS class II compound.

- Lamivudine

Polymorphism: Lamivudine exhibits polymorphism but a single polymorph was selected for development. Aqueous solubility: Lamivudine is considered a BCS class III compound.

Stability: Lamivudine is chemically and physically stable when stored at room temperature.

- Tenofovir disoproxil fumarate

Polymorphism: The active substance manufacturing process is controlled to produce a single tenofovir disoproxil fumarate polymorph.

Aqueous solubility: Tenofovir disoproxil fumarate is considered a BCS class III compound.

Hygroscopicity: Tenofovir disoproxil fumarate is slightly hygroscopic.

Stress stability: Tenofovir disoproxil fumarate is sensitive to temperature and moisture, and can undergo hydrolysis in solution as well as in the solid state. The main hydrolysis degradation product, the tenofovir isoproxil monoester, is a metabolite.

The choice of the excipients as well as their functions has been discussed in the dossier for each of the different layers.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Drug excipient compatibility studies included long term and stressed (accelerated) storage conditions.

During early development different types of fixed dose combination products were evaluated and compared in human bioequivalence studie. The single bilayer tablet formulation was selected for further development.

During dissolution method development, both USP apparatus I (baskets) and USP apparatus II (paddles) were evaluated, as well as multiple rotation speeds and buffers. The sensitivity of the dissolution method to different process parameters and product quality attributes has been evaluated. The discriminatory power of the dissolution method has been demonstrated. Based on the data presented, the dissolution methodology was concluded to be suitable to control the quality of doravirine/lamivudine/tenofovir disoproxil fumarate tablet.

For the development of the manufacturing process a systematic risk-based development program was applied in accordance with the principles of ICH Q8, Q9 and Q10. The proposed control strategy for the manufacture of doravirine/lamivudine/tenofovir disoproxil fumarate film-coated tablets consists of process parameter PARs and design spaces and in-process controls. The manufacturing process development focussed on factors that potentially posed a moderate to high risk to achieving CQAs. This evaluation was based on a risk assessment, followed by both multi-factor designs and OFAT experimental approaches. Based on the results from these studies, flexible approaches to the final proposed control strategy, specifically operational flexibility within multivariate design spaces, is being proposed for the tablet film coating unit operation.

Finished product development was conducted in pilot scale facilities at multiple sites and at the intended commercial site to understand the impact of process parameters and minimize risk to CQAs. The process was scaled up to the intended commercial scale.

The process development studies conducted for doravirine tablet product can be divided in the following stages:

- Pilot Process Development Studies: The objective of the pilot process development studies was to build process understanding and identify any potential linkages between process inputs (raw material attributes and process parameters) and process outputs (in-process material attributes and finished product quality attributes), as well as provide an initial starting point for proven acceptable ranges to be further evaluated at commercial scale. These studies were designed as multi-factor studies across unit operations, i.e., assessing the potential for interactions between process parameters from one unit operation to another.

- Commercial Process Development Studies: The objective of the commercial process development studies was to further develop the proven acceptable ranges identified from the pilot process development studies and establish the final control study at the intended manufacturing site and scale. These studies were also designed as multi-factor studies across unit operations.

The primary packaging is a HDPE bottle with PP induction child-resistant closure. Silica gel desiccant is added in the bottle to provide moisture protection. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The process is considered to be a standard manufacturing process consisting of spray drying, blending, lubrication, roller compaction, tablet compression, film coating and packaging.

Briefly, doravirine spray dried intermediate (SDI) is manufactured by spray drying a solution of hypromellose acetate succinate and doravirine dissolved in purified water and solvent. The spray dried intermediate is combined with excipients, blended and roller compacted to produce doravirine granules. Lamivudine and tenofovir disoproxil fumarate are combined with excipients, blended and roller compacted to produce lamivudine/tenofovir disoproxil fumarate granules.

The granules are then compressed into bilayer tablet cores. The compressed bilayer tablets are film coated. The film-coated tablets are placed into containers for storage, shipping and packaging operations.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

A design space has been proposed for the following step of the manufacturing process of the medicinal product: film-coating. The design space has been developed at commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Proven acceptable ranges have been defined for the rest of manufacturing steps of the medicinal product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Product specification

The finished product release specifications includes appropriate tests for this kind of dosage form: description, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC), dissolution (HPLC) and microbial quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 30 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, water activity, microbial quality, dissolution and crystallinity. The analytical procedures used are stability indicating. All results complied with the specification.

In addition, 3 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of all samples met the proposed specifications.

The applicant proposed that the calculations of expiry date for the finished product (start of shelf-life) to begin with the date of the addition of the spray-dried intermediate to the other excipients and not with the date of active substance addition during spray-drying. The applicant provided data of batches that represent the full proposed holding intervals of the bulk product (intermediate) in the finished product stability program. Since the applicant has presented acceptable data for finished products manufactured with aged SDI the approach is accepted.

The applicant provided supportive drug product intermediate and bulk hold time studies to support the manufacturing process.

In-use stability study was carried out by simulating a patient's in-use practice the doravirine/lamivudine/tenofovir disoproxil fumarate tablets are considered stable after an in-use periods when stored at 30ºC/75%RH or at 30ºC/65%RH.

Based on available stability data, the proposed shelf-life of 30 months and the storage condition “Store in the original bottle and keep the bottle tightly closed to protect from moisture. Do not remove the desiccant. This medicinal product does not require any special temperature storage conditions” as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

GMO

Not Applicable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The proposed finished product tablet is formulated as a bilayer consisting of doravirine in the core and a layer and lamivudine and tenofovir disproxil fumarate in the other. The reason for developing a bilayer tablet for this product was to preserve the PK performance of the doravirine component (relative to co-dosing) and was not driven by physical or chemical incompatibilities.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Pharmacology

Primary pharmacodynamic studies

Doravirine has been pharmacologically characterised as a potent HIV-1 non-nucleoside reverse transcriptase inhibitor. In biochemical assays, doravirine displays IC50s <15 nM in the inhibition of the ribonucleic acid (RNA)-dependent deoxyribonucleic acid (DNA) polymerization catalyzed by HIV-1 RT variants (WT, K103N, and Y181C). In cell-based assays, DOR showed EC50s of 12, 21, 31, 55 and 33 nM against the WT virus, K103N, Y181C, G190A, and K103N/Y181C mutants, respectively, in the presence of 100% human serum. Doravirine also exhibited similar antiviral activities (in the range from 1.2 nM to 10.0 nM) against a panel of 93 wild-type viruses comprised of several isolates from each of 10 different HIV-1 subtypes (A through H).

No activity data for doravirine on HIV-2 and other viruses (HBV and HCV), which is recommended by the EMA HIV Note for Guidance on antiretrovirals, has been provided. It is acknowledged that HIV-2 is considered to be naturally resistant to the class, but EC50 values differ between available agents, and data may still be of interest. While hepatitis C does not have the RT enzyme, and may be irrelevant to study, data on hepatitis B should be considered. The applicant was initially asked to submit in vitro data on doravirine activity for HIV-2 and hepatitis B. The applicant has provided data on activity of doravirine against HBV as analyzed in a HepG2 cell line infected with HBV. In this assay, the EC50 of the test compound was >10 µM (10 µM was the highest concentration tested), suggesting that doravirine is not active against HBV. Moreover, in PBMCs infected with HIV-2, the antiviral activity of doravirine (EC50 = 1.25 µM) in suppressing the replication of HIV-2 was lower compared to the activity on HIV-1.

Cytotoxicity was investigated using different in vitro cell system including proliferating (MT4, HL60, and SupT1), stationary, and activated cells (CD4, PBMC, macrophages, and monocytes). Doravirine displayed no cytotoxic activity in any cell types tested (CC_{50} > 100 µM). These results indicate that the antiviral activity of doravirine is not derived from effects on cell viability, this is endorsed.

Secondary pharmacodynamic studies

Doravirine and its major human metabolite M9 were evaluated for off-target activity in an in vitro battery of binding assays. Doravirine seems to show affinity only to the 5-HT2B receptor using a ligand binding assay (IC50=2.5 µM), while in a subsequent cell based functional 5-HT2B assay, no agonist or antagonist activity was observed. Consequently, binding of doravirine to 5-HT2B is not related to 5-HT2B function. In the first round of this procedure the full data report from the PanLabs pharmacology activity testing was lacking for doravirine and its human major metabolite M9. The requested study reports of binding data and functional activity for doravirine and M9 metabolite have been presented by the Applicant.

The potential for off-target activity of doravirine against mechanistically similar enzymes was also evaluated by assessing the inhibitory activity of doravirine with human cellular DNA polymerases α, β and mitochondrial DNA polymerase γ. DOR exhibited greater than 10,000-fold selectivity with respect to the cellular DNA polymerases α, β and γ with IC50s >100 µM. Therefore, doravirine is not likely to inhibit the human cellular DNA polymerases α, ß, and mitochondrial DNA polymerase γ.

The human major metabolite M9 did not display antiviral activity against wild-type HIV-1 virus or the mutants K103N, V106A, and Y181C (IC50 > 8.4 µM). In addition, M9 did not display activity against a panel of endogenous targets including >100 different receptors, transporters and enzymes.

Based on the above, the CHMP considers that both doravirine and M9 seem to have low potential for off-target effects.

Safety pharmacology programme

Doravirine was tested in a battery of safety pharmacology assays in vitro and in vivo including assessing effects on central nervous system (CNS)/neurobehavior in rats and mice, and cardiovascular and respiratory function in dogs. There were no doravirine-related effects on blood pressure, heart rate, or any of the ECG parameters including QT or QTc prolongation in conscious dogs (through 1000 mg/kg, C_{max} = 32.7 µM, 14-fold above clinical C_{max}). Except for a few isolated findings in rat on righting reflex and forelimb grip, oral dosing of doravirine had no obvious neurobehavioral effects in rodents (≥ 450 mg/kg, C_{max} ≥ 15.2 µM, 6.5-fold above the unbound clinical C_{max}).

In vitro pharmacology studies showed that doravirine has low potency on the hERG channel in transfected cells with an IC50 of 88 µM (>160-fold above the unbound clinical C_{max}).

In conclusion, the CHMP is of the view that doravirine does not appear to have a low potential for adverse effects on cardiovascular, nervous system, and respiratory functions.

Pharmacodynamic drug interactions

The applicant conducted specific pharmacodynamic drug interaction studies.

In two-drug in vitro antiviral combination studies, DOR exhibited no antagonistic effects on the antiviral activity of any of the 18 licensed antiretroviral drugs from different mechanistic classes within the concentration ranges examined, including combinations of DOR with 3TC or TDF.

2.5.2. Pharmacokinetics

The absorption, distribution, metabolism, and excretion properties of doravirine were studied in mouse, rat, rabbit, and dog. In vitro studies investigating the plasma protein binding, blood-to-plasma distribution ratios and involvement of enzymes and transporters were also conducted. No in vitro or in vivo studies were performed with lamivudine or tenofovir disproxil fumarate.

Methods of analysis

Bioanalytical methods using liquid chromatography (LC) coupled with tandem mass spectrometry (MS/MS) were used for the analysis of doravirine in plasma, urine, muscle, and milk samples collected during preclinical studies. The bioanalytical methods used in support of GLP studies for the analysis of mouse, rat, rabbit, and dog, plasma, and rat milk were validated in accordance with regulatory guidances in effect at the time the studies were conducted. The lower limit of quantification was 12 ng/mL, in mouse plasma an assay with lower limit of 4.0 ng/mL was also validated. The upper limit of quantification was up to 4900 ng/mL.

For metabolism and excretion studies, total radioactivity in plasma, blood, urine, and bile was determined by liquid scintillation counting (LSC).

Absorption

The pharmacokinetic behaviour of doravirine was studied following single intravenous (IV) and oral (P.O.) administration to mouse, rat, rabbit and dog. The plasma concentration of doravirine decreased in a mono-exponential manner in mice, rats, rabbits, and dogs. The plasma clearance was low (mouse 6.05, rat 2.6, rabbit 4.0 (ml/min/kg) or very low (dog 0.44 ml/min/kg). The volume of distribution at steady state (VdSS) was moderate (mouse 0.99, rat 1.4, rabbit 2.67, dog 0.9 L/kg). Oral administration of doravirine resulted in rapid absorption in mouse and dog (tmax 1 and 0.8 h respectively) and a slightly prolonged absorption in rat and rabbit (tmax 3.3 and 3.5 h respectively). The half-life in dog was long (21.7 h) compared to the other investigated species (mouse 2.7, rat 6.4, rabbit 9.0 h). The exposures at 100 mg/kg were found to be less than dose proportional.

The bioavailability of doravirine was limited by poor solubility. The oral bioavailiability of several different formulations of doravirine was investigated in rats (spray dried, crystalline in 10% polysorbate 80 or in emulsifying lipids, ball milled in 10% polysorbate 80 and nanosuspension in HPC-dextrose in water) and dogs (spray dried, jet milled doravirine in 10% polysorbate 80 and a suspension of nano-milled material) in order to increase the exposure. The oral bioavailability was moderate across all species (mouse 39%, rat 46%, rabbit 41%, dog 47%) for the spray-dried formulation. However, the formulation in the mass balance studies resulted in an even higher bioavailability than the spray-dried formulation in mouse and rat, similar in dog, and lower in rabbit.

	Bioavailability	
Species	**PK study**	**Excretion study**
mouse	39%	66%
rat	46%	80%
rabbit	41%	29%
dog	47%	40-59%

Distribution

Doravirine was moderately bound to plasma proteins with small differences in fraction unbound across nonclinical species and human (at 3 µM, fraction unbound: 0.25 in mouse, 0.28 in rat, 0.26 in rabbit, 0.19 in dog, and 0.23 in human). The plasma protein binding in rat increases from 65% at 0.1 µM to 73% at

5 µM, indicating some concentration dependency in plasma protein binding in rats. The major metabolite M9 had a smaller unbound fraction in human (at 1 µM 0.09) compared with rat and dog 0.20 and 0.25 respectively.

Doravirine does not partition preferentially into the blood cellular compartment in rat, rabbit, dog, and human (blood to plasma partitioning 0.90-1.1), in mouse the value was lower (0.65-0.71). Thus, in mouse the blood clearance is slightly higher than the plasma clearance, whereas similar blood and plasma clearance is expected in rat, rabbit, dog, and human. The metabolite M9 had a lower blood-to-plasma ratios (0.7-0.9) in rat, dog, and human.

The tissue distribution of doravirine was assessed in Wistar and Long Evans rat by QWBA following a single oral dose of 5 mg/kg 14C-labelled doravirine. The distribution pattern of doravirine was similar in the non-pigmented and pigmented rat. The highest levels of radioactivity were observed at 2 h post dose in the following tissues: small intestine, liver, adrenal gland, kidney cortex, Harderian gland, stomach, pancreas, and caecum. The highest overall concentrations were observed in the contents of the alimentary canal, bile, and urine. Low levels of radioactivity in the brain suggested that doravirine does not readily cross the blood-brain-barrier. Doravirine does also not readily cross the plasma-testis barrier. In the pigmented rat, the radioactivity in eye tissues and pigmented skin tissue were similar as in the non-pigmented rat, suggesting that doravirine does not bind to melanin. Elimination of radioactivity was nearly complete from most tissues by 48 hr (Wistar rats) or 168 h (LE rats, 48 h not measured) post-dose.

Doravirine was observed in foetal plasma suggesting that doravirine can cross the placental barrier. In rabbits the ratio fetal/maternal plasma concentration was 0.48-0.52 and in rabbits 0.36-0.40.

Metabolism

The metabolism of doravirine was investigated in vitro in liver microsomes or hepatocytes of rat, dog and human, and in vivo in mouse, rat, rabbit, and dog. Metabolism in vitro was slow (<10% was metabolised over a period of 120 min in microsomes), only small amounts of metabolites were observed. In the studies with human liver microsomes the metabolites M9 and M10 were identified, with dog microsomes only M9 was identified, and with rat microsomes M5, M8, M9, and M10 were identified.

In clinical studies, M9 was identified as a major metabolite circulating in human plasma (accounting for 12.9% of the dose). M9 circulating in plasma in the investigated nonclinical species was only identified in the mouse (approximately 50% parent and 50% M9). In rats, only trace amounts of some metabolites (M1, M8, M11, M12, M13) were identified in plasma. In the rabbit, trace amounts of circulating metabolites (M6, M9, M11, and M17) were identified. Also in dog, only trace amounts of metabolites in plasma were identified (M15, M16, and M17). The plasma metabolism data indicate that doravirine is metabolised more extensively to M9 in humans compared to rats and dogs. Only at much higher dosages compared to humans (130-fold and 292 fold) similar unbound exposures to M9 are obtained in rat and dog. The biotransformation in mouse is rapid and high exposure to M9 is obtained. In rabbit, M9 is only present in trace amounts in plasma.

In the mouse, 43% of the absorbed dose was observed as M9 in the urine and 25% in faeces. In rat, M9 was detected only in low levels in urine and bile (≤5% of the absorbed dose). The glucuronide of an oxidative metabolite, M7, was identified as the major metabolite in bile (≤24% of the absorbed dose). M7 is the glucuronide of M9, but is not detected in rat plasma. It is known that some glucuronides are unstable and may be degraded in plasma, it appears however that M7 is stable in rat plasma. The data indicate that M7 is formed in rat hepatocytes and is directly and efficiently excreted into bile with no or a limited distribution to plasma. The major identified metabolite in rabbit was M9 which accounted for 68% of the absorbed dose in urine and 16% of the absorbed dose in faeces. In dog, M9 was present in urine (16% of the absorbed dose) and faeces (9.8% of the absorbed dose), but not in bile. In bile, M14 and M15

were the major metabolites (13% and 12% of the absorbed dose, respectively). Doravirine accounted for 6% in mouse, 23% in rat, 24% in rabbit, and 39% in dog of the absorbed dose.

Overall, the in vitro and in vivo data indicate that oxidation, primarily via formation of M9 is the major metabolism pathway in all species. In addition, in dog, doravirine is also directly metabolised to its N-acetylcysteine conjugate (M15). Furthermore, in rat M9 is further conjugated via glucuronidation (M7 ~25% of the absorbed dose) and in dog via glucosidation (M14 ~15% of the absorbed dose). Overall, metabolism to M9 and to metabolites of M9 is the major metabolism route in the non-clinical species and humans. Elimination of unchanged doravirine via urine is limited, except in dog where ~40% of the absorbed dose is excreted unchanged via urine.

Excretion

The excretion of doravirine was studied in mass-balance studies in mice, bile-duct-cannulated rats, rabbits, and bile duct-cannulated dogs. In the in vivo studies, unchanged doravirine was found to be excreted in mouse, rat, rabbit, and dog.

Following oral administration to pregnant/lactating rats, doravirine was shown to be secreted into milk at day 14 postpartum. Milk/maternal plasma ration 2 h post dose was 1.47 (5 mg/kg/day) and 1.32 (450 mg/kg/day).

2.5.3. Toxicology

The pivotal toxicity studies were performed in mouse, rat, and dog in which the animals were dosed orally for up to 9 months. The mouse/rat and dog were selected as the rodent and non-rodent species for doravirine toxicity assessment based on in vitro and in vivo metabolic profiles and the demonstration of satisfactory pharmacokinetics. The applicant's justification is considered acceptable and consequently, the data generated in these studies are regarded as relevant.

Single dose toxicity

The applicant has not presented any pivotal GLP single dose toxicity studies, which is acceptable by the CHMP.

Repeat dose toxicity

Morbidity and mortality

No morbidity or mortality related to doravirine was observed.

Clinical observations

In both rat and dog, sporadic salivation was observed post dose. In dogs (≥10 mg/kg/day) a transient clear discharge from the eyes was observed in the 9-month toxicity study.

In dogs administered 1000 mg/kg/day the animals were observed with discoloured faeces (pale brown to white). It is likely that the discolouration is due to non-absorbed whitish doravirine formulation. The presence of non-absorbed substance was also reflected in the TK-data where a 100 time increase in dose (between 10 and 1000 mg/kg/day), resulted in only approximately 2-fold increase in AUC. In males (≥1 mg/kg/day) an increased incidence of unformed stools was also observed.

No test-item related findings were found regarding ophthalmic and ECG examinations.

Body weight and food consumption

A reduction in body weight gain was observed in the 3 month toxicity study in mice. In the 450 mg/kg/day group the reduction in gain was 16% in females and 33% in males.

Haematology

Changes in haematological parameters were only observed in the 6-month study in rats. In male animals administered 30 and 450 mg/kg/day a mild increase in prothrombin time was observed (control 11.6 sec, 450 mg/kg/day 12.6 sec). The activated partial thromboplastin time was also increased (control 18.8 sec, 450 mg/kg/day 20.6 sec).

Clinical chemistry and urinalysis

In the 6-month study in rats, female rats administered 450 mg/kg/day were observed with a decreased urinary volume (-56%), increased urine specific gravity, and low individual urinary pH values (3 out of 13 pH=5.5). Furthermore, in several studies in rats including the juvenile toxicity study, yellow-brown, needle-like urinary crystals were observed. This occurred mainly in the high dose group (450 mg/kg/day) but sporadic findings in lower dose-groups (30 mg/kg/day) were also observed. Water consumption was not measured in the studies where the precipitations were observed. The presence of the crystals in urine was further investigated in an exploratory study in which it was shown that precipitation of the crystals in urine occurred only when urine was collected by metabolism caging and not via cystocentesis. The study revealed a high solubility of doravirine in urine and precipitation seemed to be due to sample handling and occur ex vivo. In the first round of the procedure, the applicant was asked to further discuss this finding and its clinical relevance since it was noted in the 6-month study in rats, that the urinary volume was decreased and urine specific gravity increased. The applicant described that urine sediment had been assessed in patients and healthy volunteers with no observed treatment-or dose related findings. Thus it is agreed that the observed crystals in the urine apparently consisted of unchanged doravirine observed when collected ex vivo.

No test-item related findings in serum clinical chemistry analysis were observed.

Macroscopic and microscopic observations

There were no test-item related macroscopic or microscopic findings in any of the studies.

Toxicokinetics

Toxicokinetic evaluation was performed in all repeat dose toxicity studies (mouse, rat, and dog). There were no substantial (i.e. more than 2-fold) sex-related differences in mean systemic exposure. However, a larger exposure in female vs male mice and rats was observed. Mean systemic exposure and mean Cmax was less than dose proportional over the dose range, with a more pronounced effect in the higher dose steps.

Summary

Overall, doravirine was well tolerated by the animals with no morbidity, mortality or macroscopic and microscopic observations. In the first round of the procedure the NOAELs suggested in the application were in some studies lowered following agency assessment. After assessment of the Applicant's response, the NOAELs were re-assessed and consequently the exposure margins. The animal AUC (mean M and F) at NOAEL was compared with the human therapeutic AUC rendering the following exposure margins in the pivotal studies: in the dog studies, exposure at the NOAEL was 16-20 fold above the human therapeutic AUC, in the mouse study 5-fold the human, and in the rat studies 7 fold.

Genotoxicity

Doravirine was not genotoxic in any of the studies performed (Ames assay, chines hamster ovary cells, and a rat bone marrow micronucleus study). The top doses investigated were however limited, and as a consequence also the margin to human exposure. The *in vitro* genetic toxicity studies were limited by solubility and the top dose was 300 µg/plate in the microbial mutagenesis assay and 300µM in the chromosomal aberration test in vitro. Exposure in the *in vivo* chromosomal aberration study was limited

by the maximum feasible dose and the margin to human exposure was 5-6 times based on AUC. Distribution to the bone marrow was confirmed in the quantitative whole body autoradiography studies in rat where the concentration of doravirine in bone marrow was approximately 2-fold the concentration in blood.

Carcinogenicity

The carcinogenic potential of doravirine was evaluated in a 6 month study in Tg.rasH2 mice and a two year study in Wistar Han rats. There were no test article related unscheduled deaths or differences in mortality in any of the studies.

In the mouse study, 2/25 male mice were observed with adenomas in the harderian gland. No other neoplastic or non-neoplastic changes were observed in the animals administered doravirine. The highest dose level in this study was (300 mg/kg/day) which correspond to approximately 5-7 times the clinical exposure (based on AUC).

In the 2-year rat study, an increased incidence of benign thyroid c-cell adenomas was observed in females administered the highest dose doravirine (450 mg/kg/d) (5 of 50). This finding is not discussed in the toxicology written summary. In the study report reference to historical controls are made, the link to the actual reference is however not valid. In the first round of the procedure the applicant was asked to further discuss this finding and its clinical relevance and possible mechanism. The applicant presented the requested historical data and the number of thyroid c-cell adenomas in the high-dose female rat in the doravirine carcinogenicity study was within the range observed in vehicle treated female animals from the Applicant and from the animal supplier. Furthermore, there was no evidence of progression from hyperplasia to adenoma. The findings in the carcinogenicity study could be considered not related to the test item, this is endorsed by the CHMP.

In the male rats, a centrilobular (hepatocellular) hypertrophy in the livers from the high dose group was observed (11 of 50). This was explained by hepatic enzyme induction. In the first round of the procedure the applicant was asked to provide other observations or references to substantiate the claim that there is a hepatic enzyme induction. The applicant discussed this further and supported with references to previous data and literature. Furthermore, in an *in vitro* study in rat hepatocyte cultures an increase in Cyp 3A mRNA by doravirine was observed. Thus the explanation that the centrilobular (hepatocellular) hyperthrophy is secondary to hepatic enzyme induction is agreed upon by the CHMP.

Reproduction Toxicity

Fertility and early embryonic development

Doravirine was evaluated in combined male and female fertility and early embryonic studies with no test item-related effects in any of the investigated parameters up to the highest dose levels evaluated. Thus, for doravirine, the NOAEL for male and female fertility and early embryonic development in rats was 450 mg/kg/day. No toxicokinetic parameters were collected in this study but the estimated average exposure (AUC0 24h) in male and female animals at 450 mg/kg/day was estimated to 279 µM·hr based on exposures from the 6-month repeat dose studies in rats. Based on this prediction, the exposure margins at the NOAEL were approximately 7.4-fold the clinical AUC exposure (37.8 µM·hr) at the 100 mg/day dose.

Embryo-foetal development

Doravirine was evaluated in separate embryo-foetal development studies in rats and rabbits, respectively.

Rat: In the exploratory rat dose-range finding study, no adverse maternal or embryo-foetal effects were observed at doravirine doses of up to 450 mg/kg/day. Similarly, in the pivotal rat EFD study, no adverse

maternal or embryo-foetal effects were observed at doses up to the maximum feasible dose of 450 mg/kg/day. Thus, the NOAEL for maternal toxicity and embryo-foetal development was 450 mg/kg/day (AUC0-24hr: 345 µM·hr), which is approximately 9-fold above the clinical AUC exposure (37.8 µM·hr) at the human 100 mg daily dose.

In the pivotal EFD study, a high incidence of skeletal abnormalities (malformations and variations) has been observed across all dose groups, including the controls. The applicant was asked to discuss these results in detail especially in relation to historical control data, which were initially missing. The applicant has presented the requested historical data in the Wistar Han rat. The common alterations found in this rat strain were generally within the historical control range in the laboratory of the applicant and the findings were observed with comparable incidences between the treated and corresponding control groups with no dose-response relationship. Thus it is agreed that the fetal abnormalities observed in the pivotal rat EFD study are not apparently related to doravirine treatment.

Placental transfer was confirmed in rats after oral dosing of doravirine (5 and 450 mg/kg/day). The placental transfer on GD 20 was similar at both doses and ranged between 48% and 52%. Lactational transfer on LD 14 was approximately 147% (low dose) and 132% (high dose).

Rabbit: In exploratory DRF studies conducted with doravirine in non-pregnant and pregnant rabbits, there was no maternal toxicity at the maximum feasible dose (450 mg/kg/day). Thus, the maternal NOAEL was 450 mg/kg/day with an estimated exposure (AUC) of 364 µM·hr. In one litter of 4 fetuses at 450 mg/kg/day there was external findings (malformations) consisting of open eyelids in all 4 fetuses and a cleft palate in 2 fetuses.

In the pivotal EFD study, there were signs of maternal toxicity based on a decrease in mean maternal body weight gain observed from GD 7 to 21 and from GD 7 to adjusted GD 28 (12% and 62% below control, respectively) at the maximum feasible dose of 300 mg/kg/day. At the high dose level there were no other effects related to mortality, clinical signs and gross examination. Thus, the NOAEL for F0 maternal toxicity was 15 mg/kg/day based on decreased mean maternal body weight gain at 300 mg/kg/day, providing an exposure (AUC) of 81 µM•hr, which is approximately 2.1-fold above the clinical AUC exposure at the human 100 mg daily dose.

Assessment of developmental toxicity in the F1 generation indicates no obvious effects on embryonic/fetal viability, fetal weights and sex ratios. However, external fetal examinations revealed that 2 fetuses from 2 litters showed multiple external malformations (open eyelids and cleft palate) and skeletal abnormalities (skull bone malformations). Initially there were concerns that the results of the EFD studies in the rabbit indicate doravirine-related developmental toxicity based on multiple external abnormalities (malformations) occurring at ≥ 300 mg/kg/day (AUC exposure ≥315 µM·hr). The Applicant provided historical control data for the findings observed in the embryo-fetal developmental toxicity studies in rabbits and it is agreed that all embryo-fetal findings which might be of concern in the pivotal study fell within historical control range, were single occurrences, or were restricted to ≤2 litters and lacked a dose response relationship. Thus, the fetal abnormalities observed in the rabbit EFD studies are not considered to be related to doravirine treatment.

Placental transfer was confirmed after oral dosing of doravirine (300 mg/kg/day) in the rabbit. On GD 20, the foetal exposure represented between 36 to 40% of the maternal plasma concentration at 4 and 24 hours post-dose, respectively.

Prenatal and postnatal development

Doravirine was evaluated in rat pre- and post-natal development studies after oral dosing. Doravirine was well tolerated up to the maximum feasible dose (450 mg/kg/day) and there were no test item-related deaths, clinical signs or any other effects of the investigated parameters. Therefore, for doravirine, the

NOAEL for F0 maternal and reproductive performance and for viability and growth in the F1 offspring was ≥ 450 mg/kg/day.

There was no evidence of preweaning F1 toxicity and lack of adverse postweaning toxicity. When excluding the increase in motor activity in the 45 and 450-mg/kg/day female F1 animals, which were generally within the laboratory's historical control animal ranges, but not observed in males, the F1 generation toxicity NOAEL was ≥ 450 mg/kg/day. At NOAEL, the estimated doravirine AUC exposure in the F0 generation was 345 µM·hr, corresponding to approximately 8-fold the clinical doravirine exposure (37.8 µM·hr) at the human 100 mg daily dose.

Toxicokinetic data

Two juvenile studies in rats were conducted: one oral dose-range-finding toxicokinetic study and one pivotal juvenile toxicity study. The objectives of the exploratory non-GLP study were to determine the tolerability and the TK profile of doravirine following repeat daily dose administrations by oral gavage to F1-generation juvenile rats from PND 14 to 55. In the pivotal rat juvenile toxicity study (0, 10, 45, 300 mg/kg/day) there were no doravirine-related deaths, clinical observations, or effects on body weight, food consumption, developmental landmarks (vaginal opening and preputial separation), open field motor activity, alterations in hematology, and serum biochemistry parameters, or organ weight changes, or histomorphologic changes in juvenile rats at the highest oral dose tested (300 mg/kg/day, mean AUC for male and females: 333 µM·hr).

The only study finding in doravirine-treated juvenile rats was presence of urine crystals observed *ex vivo* following overnight urine collection. This finding was also observed in the repeat dose rat toxicity studies, and was stated to be the result of ex vivo formation. The applicant has discussed these data regarding the urinary crystals and findings from the toxicity studies regarding possible negative effects on the kidney. It is agreed with the applicants suggestion that the urinary crystals consists of unchanged doravirine formed during *ex vivo* conditions and the crystals were not observed by direct *in vivo* collection of urine from rat bladders. The applicant has also described that assessment of urine sediment was part of the clinical studies. There were no treatment- or dose related observations in the investigation of the urine sediment in either patients or healthy individuals and there were no relevant kidney clinical safety signals.

Local Tolerance

Local tolerance of doravirine was investigated in two alternative models to the Draize methodology; isolated bovine corneas and MatTekEpiDerm tissue samples. Doravirine was classified as a non-irritant.

Other toxicity studies

Antigenicity

There were no observations or changes considered to be due to potential antigenicity induced by doravirine. No antigenicity evaluations were thus conducted.

Immunotoxicity

The weight of evidence indicated that there is no cause for concern regarding immunotoxicity resulting from treatment with doravirine. A local lymph node assay (LNNA) in mice showed no test-article related increase in the stimulation index.

Dependence

No studies on animal abuse potential were conducted; this was considered acceptable since doravirine did not readily cross the blood-brain-barrier. Furthermore, there was no indication of a pharmacologic profile consistent with drug abuse liability potential.

Metabolites

M9 was identified in plasma in rats and dogs in the chronic safety studies and peak areas were calculated. M9 was also measured in human plasma after administration of 240 mg doravirine per day. The average exposure margin in rat (450 mg/kg/day) was in average 0.52, and in dog (1000 mg/kg/day) 0.51. The exposure margins for M9 in rat and dog were just above the level to consider M9 as qualified. However, the dose of doravirine in the clinical study was slightly higher (240 mg/day) than the highest therapeutic dose (200 mg/day) and unbound fraction of M9 in human plasma was lower than in rat and dog plasma (0.08 vs 0.18 and 0.24 respectively). Furthermore, in the *in vivo* metabolism studies in mice, M9 was present in plasma after a single oral dose of doravirine (5 mg/kg) at similar levels as doravirine itself. The M9 was thus probably sufficiently covered in the 3-month oral toxicity study in mice. Taken together with the data from the rat and dog studies, the exposure levels of M9 in patients were adequately covered in the chronic toxicity studies.

Impurities

An assessment regarding the qualification of several impurities has been made (process impurities, degradation products, intermediates, or starting materials) has been conducted.

A new batch of doravirine was evaluated in a 3-month GLP toxicity study in rat (115 mg/kg/day). In the study the mean serum triglyceride level was decreased in the doravirine treated animals. No other test article related findings were observed. A known phenol degradate was also investigated in a 3-month study in rat (30 mg/kg/day doravirine, 0.4% phenol degradate). No test article related findings were observed in the study.

The fixed dose combination product, Doravirine-Lamivudine-Tenofovir disoproxil (as fumarate) contains 100 mg of doravirine, 300 mg of lamivudine, and 245 mg of tenofovir disoproxil (as fumarate). The drug product contains an impurity, the tenofovir degradant G. To qualify it was investigated in a 3-month repeat-dose oral toxicity study in rats. The animals were administered 0.3 mg/kg/day of tenofovir degradant G with or without doravirine. No test article-related findings were observed. Furthermore, the micronucleus assay was negative.

Potential mutagenic impurities were assessed by in-silico analyses for structural alerts followed by Ames testing. Three impurities were found to be positive in the Ames assay. Five impurities were negative in the Ames assay. In the first round of the procedure the individual assay data was not provided and the report for semicarbazide was lacking. Furthermore the assays were not performed under GLP and the applicant was requested to provide the data. It was agreed that according to ICH M7(R1) Ames assays performed before publication of the guideline which were not performed according to GLP can be acceptable and do not have to repeated. The applicant further states that no positive controls for treatment without metabolic activation are needed as "the strain-specific positive controls without metabolic activation were tested during phenotypic characterization of the working stocks of all the bacteria used in the Ames tests". The Applicant provided the positive control data from the phenotypic characterization of the bacterial stocks used in the Bacterial Mutagenicity (Ames) assays of potential mutagenic impurities. In these experiments, all strains responded appropriately to their respective positive controls. The Ames assay for semicarbazide was considered negative for mutagenicity after the applicant had provided the bacterial stock codes for the phenotypic characterization and specific Ames tests.

Regarding bisacylhydrazide, in the first round of this procedure the study reports from the in-silico analyses for structural alerts using the DEREK software (for Windows or Nexus, Lhasa Ltd) and MultiCASE (MC4PC) were lacking. The requested reports for the in silico analyses of BAH and BACH have been presented by the applicant. BACH had been further tested and shown to be negative in the bacterial (Ames) mutagenicity assay. The classification of BACH as a Class 5 impurity and BAH as a Class 4 impurity is agreed upon.

Phototoxicity

To evaluate the potential phototoxic effects of doravirine, Long-Evans pigmented male rats were administered doses of doravirine (0, 30, 450 mg/kg/day) for three consecutive days followed by exposure to radiation from a xenon lamp to simulate sunlight. There were no doravirine-related cutaneous or ocular findings indicative of phototoxicity.

2.5.4. Ecotoxicity / environmental risk assessment

Doravirine: The water solubility of doravirine is 2.73mg/L (pH 7) and its n-octanol/water partition coefficient was determined to be log K_{OW} =2.08 (pH 7). The Phase I surface water PEC (PEC_{SW}) was calculated using a default Fpen (0.01) to PEC_{SW} = 1.0µg/L (>0.01 µg/L action threshold), triggering ERA phase II assessment. The environmental fate of doravirine in sludge was assessed with OECD TG314B, indicating that doravirine is not rapidly degraded in sludge (an estimated DT_{50} of 158d and an ultimate biodegradation of 2.1%) and that the absorption to sludge solids is weak (Kdoc = 114-157L/kg).

The degradation kinetics were recalculated by the rapporteur, exchanging the applicant's SFO based kinetics with the one recommended by the FOCUS Degradation Kinetics Workgroup. In sediment/water systems, the empirical DT_{50} at 20°C were 129d-880d in sediment and 76-418d in water. The estimated DT_{50} for 12°C was 274d-402d – indicating doravirine to be very persistent in sediment/water systems. A large proportion of doravirine shifts to the sediment relatively quickly (>10% within 10d, 40-47% within 13d) but there were no signs of extensive biodegradation. Only some minor transformation products were detected (<10% AR) and the overall mineralization of DOR to CO_2 was between 2.04% and 5.06%.

The aquatic toxicity profile of doravirine is incomplete as a full activated sludge respiration inhibition test report (OECD TG209) is missing. The CHMP requests the applicant to submit this study. The NOEC for algae is ≥5.8 mg/L. For daphnids, the initial reported NOEC was ≥6.7mg/L. This NOEC value was based on a one-sided statistical analysis. As significantly increased reproduction was seen at a LOEC of 0.78 mg/l, a two-sided statistical test was considered more appropriate. As increased reproduction can be considered a relevant effect as well, it is recommended to use the precautionary NOEC of 0.38 mg/L for PNEC derivation and to include this value in the summary of main test results in the ERA and EPAR. For fish (i.e. the FELS test), the NOEC is ≥1mg/L. The NOEC and carbon normalized NOEC for the harlequin fly (i.e. sediment-dweller toxicity) was 81 and 450mg/kg respectively.

Lamivudine: In the original market application for the dolutegravir, abacavir and lamivudine fixed-dose combination (Triumeq®) in 2014, it was concluded that "the ERA dossier for lamivudine dossier is incomplete". The applicant has not performed the Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD TG308), and the Fish, Early Life Stage toxicity test (OECD TG210) studies. Antimicrobial effects were not tested using the recommended guideline i.e. activated Sludge, respiration Inhibition Test (OECD TG209). This was subsequently addressed by the MAH for Triumeq® in a type IB variation procedure. The applicant is asked to submit a full ERA for lamivudine as all active ingredients in a combination product should be assessed for their individual environmental risk.

Tenofovir: The applicant is also asked to submit a full ERA for tenofovir. The applicant is committed to generating and submitting new studies for a new independent tenofovir ERA (planned to be initiated in 3Q18).

2.5.5. Discussion on non-clinical aspects

Pharmacology

Pharmacological characterisation of doravirine, a non-nucleoside reverse transcriptase inhibitor, demonstrates potent antiviral activity in the low nanomolar range against different HIV-1 subtypes (A

through H). The potential antiviral activity of doravirine against HIV-2, and hepatitis B virus (HBV) were during the first round not presented by the applicant. The provided activity data indicate a lower activity in suppressing the replication of HIV-2 (EC50 in human PBMCs expressing HIV-2 = 1.25µM) compared to HIV-1. Moreover, doravirine was not active against HBV at test concentrations up to 10 µM in vitro. No secondary pharmacological targets were identified for doravirine in the in vitro screening for off-target activity. In addition, the submitted study report for the pharmacological activity of the major metabolite M9 indicates no anti-HIV activity in cellular assays and in receptor assays there were no off-target activities observed with M9 (at 10 µM). In the non-clinical safety pharmacology studies there were no apparent safety issues identified. Consequently, no additional non-clinical investigations are considered necessary by the CHMP.

Pharmacokinetics

The non-clinical pharmacokinetic profile of doravirine is considered to have been adequately characterized. The exposure of doravirine in the investigated species was low and less than dose-proportional over the dose range investigated, with a more pronounced effect in the higher doses. The efforts made to increase the exposure are acknowledged. Different formulations were investigated. The spray dried formulation resulted in the highest absorption in rat after investigating different formulations. However, the formulation in the mass balance studies resulted in an even higher bioavailability than the spray-dried formulation. Moreover, the data indicate that absorbed doravirine is most extensively metabolised in mouse (~90%), followed by rat and rabbit (~70%) and least in dog and humans (~60%). Doravirine is primarily metabolised to M9 in the non-clinical species and humans. M9 is excreted via urine or bile or further conjugated in rat and dog. Excretion of doravirine is mainly as metabolite via urine. However, in dog ~40% of the dose is excreted as parent compound via urine.

In the tissue distribution study doravirine was found mainly in the alimentary canal, bile and urine. The distribution pattern was similar in non-pigmented and pigmented rats.

The major metabolite in human, M9, seemed to have been adequately covered in the chronic toxicity studies. M9 did not inhibit wild-type HIV-1 reverse transcriptase, common mutants, and no off-target activity against a wide range of endogenous pharmacological targets. However, only at dosages ~200-fold higher compared to humans similar exposures to M9 were obtained in rat and dog.

Doravirine was shown to be directly glucuronidated in rat to a limited extent only (≤2.9% of the absorbed dose in bile). However, metabolite M9 (≤5.1% of the absorbed dose in rat bile and urine and not detected in rat plasma) appears rapidly glucuronidated to M7 in rat (≤24.4% of the absorbed dose). In rat hepatocytes M9 is metabolised to M7 and efficiently excreted into bile with no or a limited distribution to plasma.

The metabolism profile in plasma was investigated in the pre-clinical species mouse, rat, rabbit, and dog. Oxidation, primarily via formation of M9 is the major metabolism pathway in all species. In addition, in dog, doravirine is also directly metabolised to its N-acetylcysteine conjugate (M15). Furthermore, in rat M9 is further conjugated via glucuronidation (M7 ~25% of the absorbed dose) and in dog via glucosidation (M14 ~15% of the absorbed dose).

Toxicology

The toxicology documentation for doravirine and its fixed dose combination with the approved drugs tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) is comprehensive and studies in general have been conducted in accordance with relevant guidelines and GLP. The Applicant has sought scientific advice for the non-clinical program, and followed the recommendations received.

As doravirine has low solubility in water, the effect of formulation and dose defined the maximum feasible exposures in all toxicology species. For doravirine, at the highest dose tested, the maximum achieved plasma exposures (AUC0-24hr) in the chronic toxicity studies of the longest duration were 279 µM·hr (at 450 mg/kg/day) and 673 µM·hr (at 1000 mg/kg/day) for the rat and dog, respectively. These exposure levels correspond to 7.4-fold and 18-fold the clinical exposure at the therapeutic dose of 100mg/day (AUC0-24h,ss 37.8 µM·h), respectively.

Doravirine was not found to be genotoxic in any of the studies performed (Ames assay, chines hamster ovary cells, and a rat bone marrow micronucleus study). The top doses investigated were however limited, and as a consequence also the margin to human exposure is low.

Doravirine was well tolerated also in the two carcinogenicity studies. Initially there was a concern regarding observations in the 2-year rat study regarding increased incidence of benign thyroid c-cell adenomas in the female, and in the male rats and a centrilobular (hepatocellular) hypertrophy in the livers. The applicant provided historical control data and references to previous data and literature. The findings in the carcinogenicity study could be considered not related to the test item.

There was no cause for concern regarding the potential of doravirine to have a potential effect on antigenicity, immunotoxicity, or dependence. Furthermore, in vivo studies in Long-Evans pigmented rats showed no potential doravirine-related cutaneous or ocular findings that were indicative of a phototoxic effect of doravirine.

The reproductive and developmental toxicology program for doravirine has been evaluated in rats and rabbits, respectively. There were no doravirine-related findings in any of the rodent studies with NOAELs at maximal feasible dose levels, corresponding to exposure margins of 8.5-fold compared to the clinical AUC exposure (at the human 100 mg/day dose).

Initially there were potential concerns of doravirine-related developmental toxicity in the rabbit based on multiple external abnormalities (e.g. malformations) and a range of visceral, coronal and skeletal abnormalities occurring at ≥ 300 mg/kg/day (AUC exposure ≥315 µM·hr). The Applicant provided historical control data for the findings observed in the embryo-fetal developmental toxicity studies in rabbits and it is agreed that all embryo-fetal findings which might be of concern in the pivotal study fell within historical control range, were single occurrences, or were restricted to ≤2 litters and lacked a dose response relationship. Thus, the fetal abnormalities observed in the rabbit EFD studies are not considered to be related to doravirine treatment.

Environmental risk assessment

Doravirine: A Phase IIA ERA assessment plus sediment-dweller toxicity studies has been conducted for Doravirine. The overall risk assessment was based on the default (Fpen 0.01) Phase I PECSW (1.0ug/L), giving a ground water and sludge micro-organism PEC of 0.25ug/L and 1.00ug/L respectively. The sediment PEC was calculated to 60ug/kg. Data for activated sludge, respiration inhibition test (OECD TG209) is missing and is requested. The applicant is committed to provide the study in 4Q2018, submitting it as a PAM (cf. section 2.3.5).

While doravirine likely is very persistent in sludge and sediment/water systems, the PBT hazard assessment does not indicate that doravirine is a PBT substance. There were also some issues with the choice of NOEC/LOEC in the Daphnia test based on statistical test design, resulting in the use of a pre-cautionary NOEC of 0.38 mg/L. The conclusion of the ERA does not change with the revision of the associated PNEC and RQ values. Beyond that, a full assessment cannot be conducted until all necessary studies have been submitted together with an updated ERA.

Table 1 Summary of main study results for Doravirine

Substance (INN/Invented Name): Doravirine
CAS-number (if available): 1338225-97-0

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	2.08	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{OW}	2.08	not B
	BCF	NA	not B
Persistence	DT50 or ready biodegradability	$DT_{50,\ water}$ > 60d $DT_{50,\ Sed}$ > 180d	vP
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{\ Surface\ water}$, default (Fpen = 0.01)	1.0	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	NA	NA	(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD TG105	2.48mg/L (pH 5) 2.73mg/L (pH 7) 3.27mg/L (pH 9)	
Adsorption-Desorption	OECD TG106	*Soils* *1.* K_{oc} = 477 L/kg *2.* K_{oc} = 506 L/kg *3.* K_{oc} = 514 L/kg *4.* K_{oc} = 717 L/kg *Sludges* *5.* K_{oc} = 157 L/kg *6.* K_{oc} = 114 L/kg	1: Loam 2: Loamy sand 3: Sandy loam 4: Clay No trigger of terrestrial studies as <10000L/kg.
Simulation biodegradation test (active sludge, 28d)	OECD TG314B	DT_{50} = 158d DT_{90} = 523d *Primary degradation*: 2 minor (<10% AR) TPs *Ultimate biodegradation*: 2.1% AR CO_2	Biotic sludge results
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	*20°C empirical* $DT_{50,water}$ =76-418d $DT_{50,sed.}$= 129-880d $DT_{50,whole}$ = 129-144d *12°C estimate* $DT_{50,system}$ = 402-274d *Mineralization:* CO_2: 2.04-5.06% *Shifting to sediment:* > 10% AR (3d)	No major transformation products (<10% AR). DT50 (20°C) values from rapporteur reassessment (based on the FOCUS Degradation Kinetics Workgroup) of applicant SFO kinetics calculations. Triggers an OECD TG218 study as >10% AR is shifted to sediment after 3d.
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species* (72h)	OECD TG201	NOEC	≥5.8	mg/L	*P. subcapitata,* Growth rate
Daphnia sp. Reproduction Test	OECD TG211	NOEC	0.38	mg/L	*Daphnia* Survival, reproduction & growth.
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	≥1.0	mg/L	*Fathead minnow* Hatching, survival & growth.
Activated Sludge, Respiration Inhibition Test	OECD TG209	EC	NA	mg/L	Missing study report/invalid study report Applicant committed to provide study as PAM.
Phase IIb Studies					
Sediment-dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	≥81 ≥450	mg/kg mg/kg	*C. riparius,* *Max measured concentration for NOEC in the absence of a clear dose-response relation.*

Lamivudine: The applicant is asked to submit full ERA for lamivudine as all active ingredients in a combination product should be assessed for their individual environmental risk. All applicants have to submit their own ERA in accordance with Directive 2001/83/EC (as amended) or a letter of consent to use studies from other applicants. The applicant is committed to provide a letter of consent allowing the applicant to reference studies for lamivudine from ViiV Healthcare UK Limited. This is stated to be currently in progress (cf. section 2.3.5).

Tenofovir: The applicant is asked to submit a full ERA for tenofovir (cf. section 2.3.5). The applicant is committed to conduct studies for a new ERA for tenofovir (stated to be initiated during 3Q18).

2.5.6. Conclusion on the non-clinical aspects

The review of non-clinical data available for doravirine indicates no issues for concern.

However, as a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Doravirine to the environment.

The applicant therefore commits to perform the following studies as follow-up measures:

- The applicant will repeat the Activated sludge, respiration inhibition test (OECD TG209). The report will be available in 4Q2018 and will be submitted as a post-authorisation measure. The ERA should be updated based on the results of the study.
- The applicant is committed to providing an ERA letter of consent from the MAH for lamivudine.
- The applicant is committed to generating and submitting new studies for a new independent tenofovir ERA (planned to be initiated in 3Q18).

2.6. Clinical aspects

2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Studies providing key efficacy and safety data

Trial	Design	Treatment Groups
P007	Phase 2b double-blinded (in-house), randomized	Dose response combination therapy 2-part study comparing doravirine dosed 25-50-100 or 200 mg to efavirenz 600 mg qd, all in combination with tenofovir/emtricitabine (Truvada). In part 1, 210 patients were randomized to the different dose groups in equal proportions (about 40 per arm). When all patients had passed week 24, a single dose was chosen (the 100 mg dose), and patients treated with doravirine were switched to this dose on their next visit, still blinded for a total treatment duration of 96 weeks. Part 2 was initiated once the dose was selected in part 1; here another 132 patients were randomized 1:1 to doravirine 100 mg qd or efavirenz 600 mg qd, for 96 weeks of blinded therapy.
P018	Phase III double blind, treatment-naïve patients	Test: doravirine 100 mg qd Control: darunavir + ritonavir 800/100 mg qd (double blind) Both in combination with tenofovir disoproxil/emtricitabine (~90%) or abacavir/lamivudine (~10%) Resistance screening (exclusion criteria) NNRTI: L100I, K101E/P, K103N/S, V106A/M/I, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188H/L, G190A/S, H221Y, P225H, F227C/L/V, M230L/I, L234I NRTIs and PI: In accordance with IAS-USA
P021	Phase III double blind, treatment-naïve patients	Test: doravirine/tenofovir disoproxil/lamivudine (100/300/300 mg, fixed-dose) Control: efavirenz/tenofovir disoproxil/emtricitabine (600/300/300 mg, fixed-dose) Resistance screening (exclusion criteria) NNRTI: Same as P018 NRTIs: In accordance with IAS-USA

2.6.2. Pharmacokinetics

The Doravirine/Lamivudine/Tenofovir Disoproxil fumarate 100/300/300 mg fixed dose combination (FDC) tablet contains the new chemical entity doravirine and the well-known substances lamivudine and tenofovir disoproxil (as fumarate salt). The FDC tablet is a bilayer tablet consisting of doravirine in one layer and lamivudine and tenofovir disoproxil in the other layer. The FDC tablet is supposed to provide a complete regimen for the treatment of HIV-1 infection.

Thirty-six trials were conducted as part of the clinical pharmacology program; the majority of the trials were performed with doravirine as mono-component. An overview of the phase 1 trials is presented in the table below.

Table 3

Trial type	
PK and initial tolerability trials	
Single Rising Dose, Multiple Rising Dose and Drug Interaction with Midazolam	P001
Supratherapeutic Single and Multiple Rising Dose	P006
Human Absorption, Metabolism, and Excretion	P008 (+nonclinical report PK006/PK008)
PK of Long Acting Parenteral Intramuscular Injections[1]	P031
Intrinsic Factor PK Trials	
PK in Male vs. Female and Young vs. Elderly Subjects	P009
PK in Patients with Hepatic Impairment	P019
PK in Patients with Severe Renal Impairment	P051
Extrinsic Factor PK Trials	
Drug Interaction with Tenofovir Disoproxyl Fumarate	P003
Drug Interaction with Ritonavir	P002
Drug Interaction with Ketoconazole	P010
Drug Interaction with Rifampicin	P011
Drug Interaction with Rifabutin	P035
Pharmacokinetic Effect of Switching From Efavirenz to MK-1439[2]	P020
Drug Interaction with Aluminum and Magnesium Containing Antacid and a Protonpump Inhibitor	P042
MK-1439A[3] Component Interaction	P038
Drug Interaction with Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel)	P012
Drug Interaction with Dolutegravir	P016
Drug Interaction with Atorvastatin	P036
Drug Interaction with Metformin	P048
Drug Interaction with Methadone	P045
Drug Interaction with Elbasvir / Grazoprevir	P050
Drug Interaction with Ledipasvir / Sofosbuvir	P053
PD and PK/PD Trials	
Multiple Dose in HIV-1 Infected Patients	P005
QT/QTc Trial	P017
Biocomparison and Bioequivalence Trials	
Bioavailability of Two Probe MK-1439A[3] Formulations	P014
Bioavailability of a Probe MK-1439A[3] Formulation	P015
MK-1439A Comparative Bioavailability	P026
Comparative Bioavailability of Nanoparticle Formulations[1]	P034
Bioequivalence of Coated and Uncoated Tablets	P039
Comparative Bioavailability of Oral Pediatric Minitablets[1]	P043
Bioavailability of Nanoparticle Formulations[1]	P046

Comparative Bioavailability of Pediatric Oral-Granules[1]	P049
Comparative Bioavailability of 2nd Generation Pediatric Oral-granules[1]	P052
Bioavailability Trials	
Food Effect	P037
IV Microdose	P044
MK-1439A[3] Food Effect	P029

1These were exploratory formulation trials and are not relevant to the present submission; therefore, the trials are not summarized and evaluated by the reviewer; 2MK-1439, doravirine; 3MK-1439A, the fixed dose combination of doravirine, lamivudine and tenofovir disoproxil fumarate.

Lamivudine and tenofovir disoproxil fumarate

The pharmacokinetics of lamivudine and tenofovir disoproxil fumarate are well characterised and are not further discussed in this report.

Doravirine

Absorption

Doravirine is a poorly soluble compound with a solubility that is pH independent across physiological pH values (pKa 9.47). The compound may be classified as a BCS II (low solubility, high permeability) or BCS IV (low solubility, low permeability) compound. At doses higher than the therapeutic dose (100 mg QD) the exposure to doravirine increases less than dose proportional, this is likely explained by the solubility limited absorption of doravirine. Doravirine is a substrate of the transport protein P-glycoprotein (P-gp), but the influence of P-gp on the absorption of doravirine appears to be minor (refer to the paragraph on Interactions below).

A relative bioavailability study between the commercial doravirine/lamivudine/tenofovir disoproxil fumarate tablet formulation and the single entity tablets was performed aiming at evaluating the comparative bioavailability between the fixed dose combination (FDC) doravirine/lamivudine/tenofovir disoproxil fumarate (100 mg/300 mg/300 mg) tablet and co-administration of the single entity tablets doravirine 100 mg, lamivudine 300 mg (Epivir®), and tenofovir disoproxil fumarate 300 mg (Viread®), in healthy male and female subjects under fasted conditions. Doravirine, lamivudine and tenofovir displayed similar plasma concentration exposures (AUC and Cmax) when given as the FDC tablet and as the single entity tablets. The Cmax of tenofovir following administration of the FDC was slightly lower compared to following administration of tenofovir disoproxil fumarate 300 mg (Viread®), and would not pass the conventional bioequivalence level (GMR 0.87; 90% CI 0.78, 0.97). The FDC tablet is the formulation that was given in the pivotal phase III study (study P021), and the somewhat reduced tenofovir Cmax is not considered clinically meaningful.

The effect of food intake on the commercial FDC tablet was evaluated, and it was concluded that a high-fat meal did not change the exposure to any of the components to any clinically meaningful extent.

Distribution

After a single dose intravenous (iv) dose of 100 µg, doravirine had a volume of distribution of 60 L. The plasma protein binding was assessed by equilibrium dialysis in human plasma. Two separate assays were performed: one at 0.1 µM ad 1.0 µM doravirine concentration levels, and one at 3.0 µM and 5.0 µM doravirine concentration levels. The protein binding was moderate across the concentration levels tested with a fraction unbound of approximately 25%. The plasma protein binding in the hepatic and renal impairment studies was not reported.

Elimination

In an iv microdose study, doravirine had a clearance (CL) estimated to 4 L/h. The terminal half-life ($t_{1/2}$) reported in different studies was about 15 hours.

Following a single dose of 350 mg [^{14}C]doravirine approximately 90% of the radioactivity was excreted in faeces and 11% of the radioactivity was excreted into urine (mean recovery 101%) (n=6 subjects).

In faeces, unchanged doravirine accounted for 84% of the radioactivity. It is uncertain to what extent unchanged doravirine recovered in faeces was unabsorbed drug or biliary excreted drug. Of note is that the systemic exposure to doravirine was low in mass balance study (likely caused by that the formulation used was based on the crystalline form of doravirine), which suggests that doravirine recovered in faeces to a large extent could be attributed to unabsorbed drug.

In urine, the primary components were M9 (6.7%) and doravirine (2.2%). Metabolites M8, M10, and M18 were also detected in urine, but combined, represented only approximately 0.5% of the administered dose. Trace amounts of other metabolites (M5, M11, M14, M15, and M19) were also detected in urine. The low recovery of unchanged doravirine in urine was supported by data from the SAD study (dose level of 50 mg), where ~6% was recovered in urine following a 24-hour collection period (although the renal recovery was likely underestimated in this study due to limited collection period).

Additional data obtained for the 100 mg tablet formulation (unlabelled drug) using semi-quantitative analysis of pooled plasma indicated that M9 was present in amounts that were approximately 5.6% and 6.7% of the total drug-related components on day 1 and day 10, respectively, while doravirine levels were about 86% and 80% on day 1 and day 10, respectively. These results indicated agreement in the levels of M9 observed in the ADME study and those observed following multiple once daily administration with the doravirine tablet despite the different formulations used in these trials. In the semi-quantitative analysis also metabolite M16 was identified as a metabolite, at levels comparable to M9 (4.5 and 5.3%, respectively).

Renal excretion is the main elimination pathway for the tablet formulation. The metabolite M9 was the major metabolite excreted in urine (6.7% of the administered dose, 39.4% of the absorbed dose). Including other minor metabolites identified in urine M8, M10, M18), at least 55% of the absorbed dose was recovered in urine as either unchanged parent compound or its metabolites. The metabolite M9 was a major metabolite excreted in faeces (2.7% of the administered dose, 15.9% of the absorbed dose). In total 71% of the absorbed dose could be accounted for.

As more than 25% of the total clearance of doravirine occurs via metabolism and biliary secretion, it is recommended to investigate whether the compound is a substrate for the hepatic uptake transporters OATP1B1 and OATP1B3. The in vitro substrate assays were performed at only one concentration level, which limited the interpretation of the results. However, the single dose rifampicin interaction study indicated that the transporters OATP1B1/3 do not have a major influence on doravirine in vivo pharmacokinetics (1.4-fold increase in doravirine Cmax).

In vitro doravirine was shown to be metabolized by CYP3A4, and this was confirmed in vivo by co-administering the strong CYP3A4 inhibitors ketoconazole and ritonavir. The major metabolite circulating was metabolite M9, which accounted for 13% of the total radioactivity in plasma.

Dose proportionality and time dependencies

In the single- and multiple ascending dose study, a less than dose proportional increase in doravirine was observed. The nonlinearity appeared to arise at doses higher than the proposed therapeutic dose (100 mg); in addition, the popPK model with a linear clearance from the central compartment captured the pharmacokinetics of doravirine up to dose of 200 mg. The time to achieve steady state (2-4 days) and

the accumulation ratios were consistent with the apparent terminal half-life observed and the dosing interval. Hence, there were no data indicating time-dependent changes in doravirine pharmacokinetics.

Population pharmacokinetics

The population pharmacokinetics (popPK) model was developed based on 20 Phase I trials, 1 Phase IIb trial, and 2 Phase III trials (341 healthy subjects; 959 HIV-1 infected subjects). The final model was a 1-compartment model with first order absorption. The covariates age on CL and body weight on V were included in the model. C_{min} appeared to be reasonably predicted. Attempts could have been made to further improve the model, for example: a 2-compartment model seemed to better describe doravirine pharmacokinetics and the model was only developed for doses up to 200 mg. These issues may have to be considered if the model is used in the future, but they do not have an impact for conclusions drawn about the pharmacokinetics and exposure-response of doravirine in the current application.

Doravirine pharmacokinetics between healthy subjects and HIV-1 infected patients are comparable. Population pharmacokinetic estimates indicate at a 100 mg q.d. dose a steady state AUC0-24h of 37.8 µM*h, a Cmax of 2.26 µM and a C24h of 0.93 µM. Doravirine pharmacokinetics showed a moderate between-subject variability in AUC0-24h, Cmax and C24h of about 27%, 18% and 42%, respectively. Intra-subject variability was not evaluated.

Special populations

A study in subjects with severe renal impairment (n=8 subjects with renal impairment; n=8 matched control subjects), did not indicate any clinically meaningful effect of reduced renal function on doravirine pharmacokinetics. The doravirine $AUC_{0-\infty}$ and C_{24h} were increased by 31% and 31%, respectively, and C_{max} was reduced by 18%.

A study in subjects with moderate hepatic impairment (n=8 subjects with hepatic impairment; n=8 matched control subjects) was also performed. However, the majority of the subjects with hepatic impairment had values within the normal range for bilirubin, INR and albumin, and were categorized into “moderate” hepatic impairment (CP score 7-9) due to high scores of the encephalopathy and ascites. The effects of hepatic impairment on doravirine pharmacokinetics in subjects with reduced metabolic capacity therefore remains somewhat uncertain. But based on the seemingly wide therapeutic window of doravirine and also considering that the effect of moderate hepatic impairment probably is less pronounced compared to what was observed with strong CYP3A4 inhibitors, the recommendation on no dose adjustment in this subpopulation is considered acceptable. The exposure to doravirine has not been evaluated in subjects with severe hepatic impairment, and this is reflected in the proposed SmPC.

The covariates gender, race, body weight, and age (≥18 years of age) are not expected to have a clinically relevant effect on doravirine pharmacokinetics.

Pharmacokinetic interaction studies

Doravirine in the combination with lamivudine and tenofovir disoproxil fumarate

Upon single-dose administration, doravirine did not affect the pharmacokinetics of lamivudine or tenofovir (when co-administered as Epivir and Viread) and was not affected by co-administration of Epivir and Viread. Any interaction between the three components was not anticipated based on what is known *in vitro* and *in vivo* about the interaction potential of the compounds.

Multiple doses of tenofovir disoproxil fumarate (300 mg QD) reduced doravirine Cmax by 20%. The reduction in Cmax is not considered to be clinically meaningful.

Effects on Doravirine PK exerted by concomitant medicines

As shown both in vitro and in vivo, doravirine pharmacokinetics is affected by changes in CYP3A4 activity and potentially also by changes in P-gp activity:

Ketoconazole (400 mg QD) increased the AUC0-∞ of doravirine approximately 3-fold. The effect appears to be primarily mediated by ketoconazole inhibiting CYP3A4 mediated metabolism of doravirine, but inhibited P-gp may also contribute to the interaction. The small effect on doravirine Cmax (1.25-fold increase) suggests that ketoconazole does not affect the first pass extraction of doravirine to any major extent, but exerts its effect during the elimination of doravirine.

Ritonavir (100 mg QD) increased the AUC0-∞ and Cmax of doravirine approximately 3-fold and 1.3-fold, respectively. The underlying interaction mechanism(s) are similar to ketoconazole.

Rifampicin (600 mg QD, 14 days) reduced doravirine $AUC_{0-\infty}$ by 88%. In addition, the C24hr was below the clinical efficacy target concentration of 54 nM. The clinical efficacy of doravirine may be reduced when co-administered with rifampicin or other strong CYP3A4 inducers, and strong CYP3A inducers are therefore contraindicated in the proposed SmPC.

Rifabutin (300 mg QD) reduced doravirine $AUC_{0-\infty}$ by 50%. The interaction is likely caused by CYP3A induction. As rifabutin may be a viable treatment alternative for HIV patients co-infected with Mycobacterium tuberculosis infection, the applicant used nonparametric superposition to optimize the dosing of doravirine and allow for co-administration with rifabutin. The superposition principle approach is rather simplistic, but was considered to provide adequate information based on the seemingly wide therapeutic window of doravirine and the linear pharmacokinetics within the relevant dose range. The exposure to doravirine administered alone at a dosing regimen of 100 mg QD was similar as compared to when doravirine at a dosing regimen of 100 mg BID was co-administered with 300 mg QD rifabutin.

Efavirenz (600 mg QD, pretreatment) reduced doravirine $AUC_{0-24hrs}$ by 62% and C24hrs by 85%. The interaction is likely caused by CYP3A induction. The applicant proposes that patients may switch from efavirenz to doravirine without any dose adjustments. This is supported since the C24 levels of doravirine are expected to reach Emax relatively quickly and since the effect of efavirenz is expected to be sustained during the initial period following the switch (efavirenz t1/2 40-55 h). Also, the other components of the patient's antiretroviral regimen are not expected to be affected.

The effects of an **aluminum- and magnesium containing antacid** and a **proton-pump inhibitor** (pantoprazole) on the absorption of doravirine was also investigated and provided data to support co-administration of doravirine with such agents. No clinically meaningful changes in doravirine pharmacokinetics were observed.

Effect exerted by Doravirine on the PK of concomitant medicinal products

Based on in vitro data it could not be excluded that doravirine in vivo was an inducer of CYP3A (and PXR mediated enzymes/transporters), and inhibitor of the transporters OATP1B1/3, and OAT3. However, the interaction studies performed by the Applicant provided sufficient data to conclude that doravirine only weakly induces CYP3A and does not affect any other of the enzymes and transporters investigated:

- The geometric mean ratios and 90% CIs for the sensitive CYP3A4 substrate **midazolam** were 0.82 (0.70, 0.97) and 1.02 (0.81, 1.28) for midazolam $AUC_{0-\infty}$, and C_{max}, respectively. This suggests that doravirine may be a weak inducer; compounds are typically being categorized as weak inducers if they reduce the AUC of a sensitive CYP3A4 probe substrate by 20%-50%. Other interactions with CYP3A4 substrates were performed (atorvastatin, methadone, elbasvir/grazoprevir), and these studies indicated even smaller effects on exposure parameters. However, those studies were limited by a shorter period of doravirine treatment (5 days).

- The geometric mean ratios and 90% CIs for the moderately sensitive CYP3A4 substrate **atorvastatin** were 0.98 (0.90, 1.06) and 0.67 (0.52, 0.85) for $AUC0_{-\infty}$, and C_{max}, respectively.
- Doravirine did not change the pharmacokinetics of **metformin**, a probe substrate for OCT1, OCT2, and MATE1/2K.
- Doravirine did not change the pharmacokinetics of **methadone**, a compound that is primarily cleared via CYP3A4 and CYP2B6. Based on comparison with historical data methadone reduced the exposure to doravirine. The reduced doravirine exposure observed in the study as compared to historical data may be caused by between-study variability. It is also possible that methadone has some inducing effects on doravirine elimination, as the clearance of methadone is known to have a time-dependent increase presumably caused by CYP3A4 autoinduction.
- Doravirine increased the exposure to **dolutegravir**: AUC0-24hr and Cmax were increased by 36% and 43%, respectively. The generalizability of these results is however limited by the high dose of doravirine used in the trial (200 mg QD). Similar increases in dolutegravir exposure are accepted without dose adjustment in the Tivicay SmPC, and the recommendation on no dose adjustment in proposed Doravirine SmPC is therefore accepted. Doravirine exposure was unaffected by dolutegravir.
- Doravirine did not change the pharmacokinetics of **elbasvir and grazoprevir**. Grazoprevir is a sensitive OATP1B1/3 with several-fold increase in exposure when being co-administered with the OATP1B1/3 inhibitor rifampicin. Hence, these results suggest that doravirine is not an in vivo relevant OATP1B1/3 inhibitor. Both grazoprevir and elbasvir are also sensitive CYP3A4 substrates.

Exposure-response

The exposure-response analyses indicated a close to flat exposure-response relationship for doravirine: a similar response was seen with the exposures yielded by the four doses (25 mg, 50 mg, 100 mg, and 200 mg QD) in the Phase IIb study. There was no apparent difference in response at week 48 by Cmin quartiles (see figure below). It would also be of interest to see the exposure-response analysis for week 24. This is further discussed under clinical efficacy section.

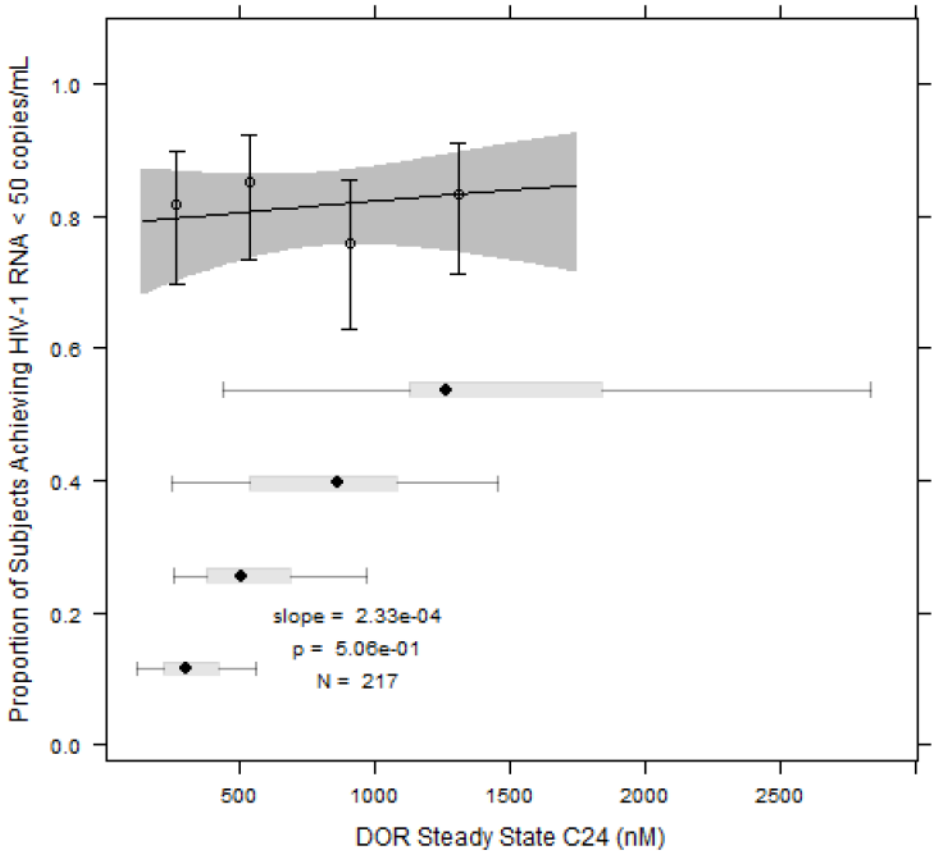


Figure 4 Predicted and Observed Proportion of Subjects Achieving HIV-1 RNA <50 copies/mL (Snapshot Approach) as a Function of Doravirine Steady State C24 Quartiles Following Administration of 25 mg to 200 mg QD Doravirine with FTC/TDF (P007, N=217)

The exposure-safety analysis did not cover exposures from higher doses than 200 mg. Hence, any potential issues regarding safety at higher exposures (e.g., upon co-administration with CYP3A4 inhibitors) were not covered by the exposure-safety analysis.

Discussion of Pharmacokinetics

The CHMP is of the view that the pharmacokinetics of doravirine has been adequately characterised.

The applicant has justified that the recommendations upon co-administration with CYP3A4 inhibitors and moderate inducers are adequate. The recommendation that no dose adjustment is needed in case of co-treatment with a strong CYP3A inhibitor is considered acceptable (See Discussion on Clinical Safety). The applicant has discussed dose adjustment when doravirine is co-medicated with moderate CYP3A inducers other than rifabutin. The applicant states that it is difficult to predict the effect of moderate inducers not studied *in vivo* and as a general recommendation should not be given. This is agreed by the CHMP. Thus, based on *in vivo* data the recommendation to dose doravirine 100 mg BID when co-administrated with rifabutin is acceptable by the CHMP, while other moderate CYP3A inducers has not been studied. This is reflected in the SmPC.

2.6.3. Pharmacodynamics

Mechanism of action

Doravirine is a non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). X-ray crystal structure analyses show that the compound binds to the classic NNRTI binding pocket.

Lamivudine and tenofovir disoproxil are nucleoside analogues (cytidine and adenosine, respectively), inhibiting the reverse transcriptase step of the viral life cycle via DNA chain termination after incorporation of the active moiety (i.e. phosphyrlized) analogue.

Primary and Secondary pharmacology

Lamivudine and tenofovir disproxil

The pharmacodynamics of lamivudine and tenofovir disproxil are well characterised and are not further discussed in this report. Both are metabolized sequentially by intracellular kinases to tenofovir diphosphate and lamivudine triphosphate, the active moieties, with extended intracellular half-lives supporting once daily dosing. Both agents are also active to hepatitis B virus, where tenofovir disoproxil has been a first line agent for the treatment of this infection for many years. No antagonistic activity was shown in vitro when doravirine was combined with lamivudine and with tenofovir dispoproxil.

Antiviral activity in vitro - study PD002

Antiviral assays were performed using variants of a laboratory HIV-1 isolate, R8, and MT-4 human T-lymphoid cells during low multiplicity of infection (moi) conditions, in the presence of normal human serum (NHS) in a proportion of 10%, 50% (using MT-4 human T-lymphoid cells) and 100% (using MT4-gag-GFP cells).

In these experiments both wild type (WT) and mutant variants were used, and doravirine was studied in parallel with rilpivirine and etravirine. Outcomes are shown below. It is noted that addition of serum (protein) has less impact on doravirine activity, than on the activity of the other NNRTIs. This is linked to the lower protein binding of doravirine (76%), where the protein binding of the other NNRTIs is >99%. The minimum C_{min} target exposure that was chosen when deciding the doses for doravirine monotherapy (efficacy section) was ≥54 nM; the EC95 value for the K103N/181C variant in the presence of 50% normal human serum.

Figure 5 Antiviral activity of DOR, EFV, ETR, and RPV against HIV-1 variants assayed in the MT4(-GFP) cell lines in the presence of 10%, 50% and 100% NHS

	WT	K103N	Y181C	K103N/Y181C
EC 95 (nM), 10% NHS				
DOR	11.0±2.6 (n=11)	13.4±3.3 (n=11)	16.4±3.2 (n=9)	30.5±3.9 (n=8)
EFV	5.0±3.2 (n=203)	247±83 (n=152)	8.6±4.5 (n=45)	297±129 (n=41)
ETR	4.4±2.1 (n=29)	5.3±3.9 (n=28)	23.5±12 (n=11)	52.5±23.9 (n=11)
RPV	2.0±1.0 (n=8)	1.7±1.0 (n=5)	4.3±3.1 (n=6)	12.9±9.9 (n=6)
EC95 (nM), 50% NHS				
DOR	20±6.7 (n=9)	43±7.8 (n=7)	27±14 (n=5)	55±14 (n=7)
EFV	41±24 (193)	1427±53 (n=22)	80±34 (n=25)	2943±903 (n=12)

ETR	38±22 (n=42)	36±9.8 (n=24)	263±191 (n=19)	653±216 (22)
RPV	37±16 (n=11)	48±18 (n=7)	120±26 (n=6)	407±153 (6)
		EC50 (nM), 100%		
DOR	12 ± 4.4 (61)	21 ± 6.8 (45)	31 ± 10 (44)	33 ± 4.2 (7)
EFV	30 ± 9.0 (93)	1173 ± 447 (70)	90 ± 21 (77)	3119 ± 506 (8)
ETR	67 ± 26 (73)	67 ± 23 (56)	382 ± 128 (55)	479 ± 192 (2)
RPV	56 ±16 (61)	56 ± 15 (37)	169 ± 45 (38)	318 ± 74 (7)

The antiviral activity of doravirine and the other NNRTIs was also evaluated against 10 different subtypes, where the activity was compared to that of a reference strain (doravirine EC50 = 4.2 nM). Activity is similar across subtypes, as well as NNRTI agents, where free concentrations *in vivo* differ between agents (discussed previously).

Table 4 Fold change of inhibitory potency of doravirine, efavirenz, etravirine and rilpivirine in different HIV-1 subtypes, as compared to control virus

Control	Subtype	DOR	EFV	ETR	RPV
drug-sensitive reference strain (CNDO) with PR and RT sequence derived from laboratory HIV strain NL4-3. (doravirine EC50 = 4.2 nM)	Subtype A (n=5)	0.84±0.33	0.81±0.34	0.76±0.36	0.84±0.45
	Subtype A1 (n=13)	0.68±0.19	0.70±0.16	0.73±0.36	0.73±0.32
	Subtype AE (n=5)	0.79±0.44	0.75±0.27	072±0.28	0.71±0.27
	Subtype AG (n=18)	0.92±0.40	0.75±0.21	0.66±0.15	0.68±0.17
	Subtype B (n=7)	0.99±0.42	1.02±0.52	0.79±0.22	0.75±0.20
	Subtype BF (n=4)	1.44±0.73	1.02±0.39	1.02±0.37	0.92±0.32
	Subtype C (n=22)	1.07±0.36	0.89±0.27	0.77±0.19	0.72±0.19
	Subtype D (n=9)	0.94±0.29	0.91±0.16	0.74±0.12	0.71±0.15
	Subtype G (n=8)	0.93±0.27	0.74±0.16	0.62±0.15	0.61±0.15
	Subtype H (n=2)	0.30±0.01	0.29±0.01	0.18±0.08	0.17±0.07

Selection experiments – study PD003

Resistance selection was conducted with doravirine and efavirenz (EFV) under low- and high-multiplicity-of-infection (moi) conditions in cell cultures.

Under low moi conditions HIV-1 subtypes A, B and C were studied, in the presence of 10% fetal calf serum. Here supernatants are removed every three to four days to infect new wells with 1, 2 and 4 times the previous drug concentration, i.e. exposing any mutants to gradually increasing concentrations of the drug. Concentrations of doravirine were increased from 1x EC95 to 50x EC95. Main results are depicted in a coming table.

For subtype B, two main pathways were seen, where V106A was reported to be the signature mutation, seen at lower concentrations, and where F227L or L234I developed in addition to V106 at higher concentrations. Other minor pathways were also identified; the one specifically mentioned being the V108I mutant followed by the emergence of V106A and L234I substitutions.

The V108I and V106A mutant viruses per se conferred approximately 4- and 12-fold resistance to doravirine (as evaluated in subtype B virus) and where the addition of F227 or L234 yields a high fold change (>100). Other minor mutations identified were V106I, F227V, H221Y, M230I, P236L, and Y318F.

In subtype A virus the pathway also started with V106A, but with minor populations found with V016M, with the addition of F227L (minor populations with C or V substitutions), followed by triple mutants including L234I or V106 A. Again, a minor pathway started with V108I as the first mutant.

In subtype C, again V106A was a signature mutation, followed by added F227I in one pathway. V106M started another pathway, where F227C emerged in a second step.

Subtype	Pathway	Pattern
B	1 (major)	V106A (FC ~ 10) →V106A/F227L (FC>500)
	2 (major)	V106A → V106A/L234I (FC~150) → V106A/L234I/F227L
A	1 (major)	V106A(M) → V106A(M)/F227L(C/V)
	2 (minor)	V108I → V108I/L234I → V108I/L234I/V106A(I)
C	1 (major)	V106A → V106A/F227I
	1 (major)	V106M → V106M/F227

In summary, in subtypes A, B and C, V106A (signature mutation) and F227 (evolving thereafter) account for the majority of mutants in the breakthrough viruses under low moi conditions, where the 106A mutation per se confers around 10-fold decrease in susceptibility (FC only evaluated in subtype B virus), and double mutants conferring a high fold change (>100).

- The V106A mutation is listed as a major mutation for nevirapine, but not the other NNRTIs.
- The V106 M mutation (one signature mutation in subtype C and A), is the second most common substitution seen at failure with efavirenz in subtype C-infection (seen in around 20% of failures, K103N being the most common, seen in >50% of cases). When looking at the prevalence of NNRTI mutations (by common population sequencing) in newly diagnosed patients in low income regions where efavirenz has been used for long times, V106M is much less frequent than the K103N substitution (~factor 10) (WHO Drug Resistant report 2017), indicating that the V106 mutations has a higher negative impact on viral fitness.

Subtype B virus was also studied under high moi conditions at set selection pressures (3x, 10x and 30x the IC95 for WT virus), where no supernatant from lower to higher was distributed at time of passage. Findings were in line with those seen in low moi conditions. Substitutions V106A, L234I, F227L, and V108I substitutions were most frequent, and mainly selected at concentrations 3X EC95 for the WT virus. The V108I mutation is involved in several minor mutation pathways, but not listed as a key mutation.

NNRTI mutations – impact on doravirine susceptibility *in vitro*

Monogram Biosciences evaluated the antiviral activity of doravirine, EFV, ETR, and RPV against a panel of 96 NNRTI resistant clinical isolates by, using their Phenosense assay, table below (HIV subtypes not specified in the report, likely subtype B).

As noted, some NNRTI mutations (or combinations of mutations) that are selected by other NNRTIs, but not reported from the selection experiments with doravirine, yield a high FC. A single mutation (Y188L), not selected in vitro in the study PD003, but seen in one patient failing doravirine in phase 3, yields per se a FC of around 100. This mutation is seen infrequently at failure with efavirenz and nevirapine, and is distinctly rare in previously untreated patients, also in settings with a high prevalence of NNRTI resistance suh as African regions (e.g. Kityo 2017). For other NNRTI mutations tested, a combination of several mutations is needed to yield a higher fold change to doravirine. Of note though, a cut off for a FC that would be clinically relevant has not been established, since NNRTI-mutations were part of exclusion criteria in the phase 2B/3 studies.

Upon request, further data was presented for K101P, E138A/G/Q, Y181I, G190E, and M230L as single mutations (major NNRTI resistance mutations listed by the Stanford database). The results have been added to the table below. M230L and G190E ar mutations that yielded high fold changes (besides G190S, V106A and Y188L which were identified in the first round). The mutant containing G190E was actually a mutant containing also M41L, L74V and T215F. However, these last three mutations are not known among the mutations causing relevant decreases in susceptibility to doravirine. The reduced susceptibility of the G190E mutant can therefore be assumed to be mostly due to G190E. Mutations M230L and G190E were not selected in *in vitro* selection experiments with doravirine.

Table 5 Susceptibility (FC vs that seen in WT virus) to doravirine, efavirenz, etravirine and rilpivirine of clinical isolates harbouring various NNRTI mutations (Biogram Phenosense assay). * Results added during procedure.

	Fold change vs WT virus				EC50 (nM)			
Resistance Mutations	**MK-1439**	**EFV**	**ETR**	**RPV**	**MK-1439**	**EFV**	**ETR**	**RPV**
A98G/Y181C	3.3	3.4	5.3	2.1	13.2	13.8	12.7	2.2
A98G	3.3	1.5	1.3	1.3	13.2	6.2	3.1	1.4
A98G/K103N	4.0	25.0	1.6	1.9	15.9	101	3.8	2
E138A	2.1	1.3	2.8	2.3	9.5	5.4	6.7	2.1
E138A (n=4)*	1.25	-	-	-	22.2	-	-	-
E138G (n=2)*	1.03	-	-	-	18.3	-	-	-
E138K	0.5	0.5	0.7	0.6	2.1	1.9	1.6	0.5
E138K	0.7	0.6	1.0	0.8	3	2.4	2.3	0.8
E138K	0.6	0.8	0.8	0.7	3	3.3	2.1	0.7
E138K	1.2	1.2	1.9	1.6	5.3	5	4.5	1.4
E138Q (n=3)*	3.25	-	-	-	57.6	-	-	-
E138K/V179E/V189V/I	1.0	1.4	3.5	1.9	4.5	5.7	8.5	1.7
E138K/Y181C/M230L	>111	12.0	>206	>82	>500	48.6	>500	>500
G190A	1.8	3.7	0.8	0.7	7.2	14.8	2	0.8
G190A	3.6	13.0	1.3	1.0	14.4	51.1	3.1	1.1
G190E (n=1)*	>111	-	-	-	>500			
G190S	4.6	38.0	0.4	0.3	18.2	151.4	1	0.3
G190S	5.9	43.0	0.8	0.5	23.6	171.7	1.9	0.5
G190S	11.0	81.0	1.1	0.7	42.6	326.7	2.6	0.8
G190S	1.5	>124	0.4	0.3	5.9	>500	1.1	0.4
K101E	4.5	11.0	6.5	10.0	20.1	45.7	15.8	9.2
K101P* (n=1)	1.08				19.1			
K101E/G190A	0.9	25.0	0.8	0.7	3.4	100.4	1.9	0.7
K101E/G190A	1.8	37.0	1.8	1.9	7.4	148	4.3	1.9
K101E/G190A	3.3	89.0	2.6	2.5	13.3	359.3	6.3	2.6
K101E/Y181C/G190A	2.0	45.0	6.4	4.5	8	179	15.4	4.7
K101E/Y181C/G190A	2.4	66.0	7.9	6.9	9.7	264.4	19.1	7.2
K101E/Y181C/G190S	18.0	>124	62.0	40.0	72.4	>500	149.6	42.1
K101H/K103N/G190A	1.2	>124	0.5	0.4	4.7	>500	1.2	0.5
K101Q/E138K	1.1	1.1	1.7	1.6	5	4.3	4	1.4
K103N	1.3	9.5	0.7	0.6	5.7	37.9	1.7	0.6
K103N	1.2	9.6	0.5	0.5	5.3	38.2	1.3	0.5
K103N	0.6	16.0	0.3	0.5	2.7	63.9	0.8	0.5
K103N	3.0	18.0	0.9	0.9	13.2	69.8	2.3	0.9
K103N	1.2	19.0	0.5	0.8	5.1	76.2	1.2	0.8
K103N/G190A	1.9	>124	0.4	0.4	7.6	>500	1	0.4
K103N/G190A	2.0	>124	0.8	0.8	7.9	>500	1.9	0.9
K103N/G190A	3.6	>124	1.3	1.1	14.5	>500	3.1	1.1
K103N/P225H	5.7	41.0	0.9	0.7	22.9	166	2.2	0.7

K103N/P225H	10.0	101.0	1.4	1.2	41.5	407	3.4	1.2
K103N/V108I	5.5	40.0	1.6	3.1	21.9	159.9	3.8	3.2
K103N/V108I	3.7	96.0	0.4	0.4	15.9	381.5	1	0.4
K103N/V108I/G190A	1.2	>124	0.3	0.3	4.7	>500	0.6	0.3
K103N/V108I/Y181C	2.0	42.0	2.6	2.8	8.4	174.8	6.1	2.7
K103N/V108I/Y181C	4.9	65.0	9.9	17.0	20.9	269.9	22.7	16.3
K103N/V108I/Y181C	5.6	79.0	3.4	2.6	24.3	325.9	7.7	2.5
K103N/V108I/Y181C	4.8	>122	6.4	8.4	21.6	>500	15.5	7.6
K103N/Y181C	5.7	22.0	15.0	13.0	24.4	88.7	33.9	11.9
K103N/Y181C	2.6	25.0	6.4	3.9	11.3	104.7	14.6	3.7
K103N/Y181C	3.9	26.0	3.7	2.6	16.6	109.2	8.5	2.5
K103N/Y181C	5.0	103.0	4.9	2.8	21.7	426.2	11.2	2.7
K103N/Y181C/G190A	1.3	>124	4.6	2.1	5	>500	11.1	2.2
K103N/Y181C/G190A	4.8	>124	7.7	2.5	19.1	>500	18.6	2.6
K103N/Y188L	>124	>124	2.3	29.0	>500	>500	5.5	30.8
K103N/Y188L	>124	>124	4.8	69.0	>500	>500	11.5	72.3
K103N/Y188L	>124	>124	5.0	71.6	>500	>500	12.1	>500
K103N/Y188L	>124	>124	12.0	71.6	>500	>500	29.6	>500
K103R/V108V/I/V179D/Y181C	4.9	>121	69.0	11.0	20.9	>500	157.8	10.6
K103R/V179D/G190A	1.0	>124	1.7	1.3	4.2	>500	4	1.3
K103S	1.7	3.3	0.8	0.8	7.4	13.8	1.7	0.7
K103S	3.0	5.5	1.4	1.3	13	22.6	3.2	1.2
K103S/G190A	1.2	34.0	0.5	0.5	5	134.6	1.2	0.6
L100I	0.6	4.3	0.5	0.4	2.4	17.7	1.1	0.4
L100I	1.5	11.0	1.5	0.6	6.5	43.5	3.5	0.6
L100I	2.7	14.0	2.1	1.0	11.5	57.8	4.9	1
L100I/K103N	2.7	>121	3.8	8.0	11.5	>500	8.6	7.6
L100I/K103N	8.4	>121	3.9	9.5	36.3	>500	8.9	9
L100I/K103N	4.5	>121	5.7	8.6	19.3	>500	13.1	8.2
L100I/K103N	4.6	>121	7.9	8.1	19.9	>500	18.2	7.7
L100I/K103N	10.0	>121	16.0	41.0	45.1	>500	36.8	39.2
L100I/K103N	5.1	>121	20.0	78.7	21.8	>500	47	>500
L100I/K103N	11.0	>121	29.0	43.0	48.3	>500	67.5	41.4
L100I/K103N	19.0	>121	33.0	78.7	79.8	>500	75.6	>500
L100I/K103N/V108I	27.0	>121	17.0	78.7	117.2	>500	39.5	>500
P236L	1.7	0.3	0.5	0.4	7.7	1.2	1.2	0.4
P236L	3.9	0.5	0.8	0.7	17.8	2.1	2	0.6
V106A	7.1	1.3	0.9	1.0	32.1	5.4	2.1	0.9
V106A	28.0	4.2	1.4	1.5	126	17.3	3.3	1.4
V106A/G190A/F227L	>106	>118	0.7	1.2	>500	>500	2	1.3
V106I	1.4	1.1	1.2	1.2	6.4	4.5	2.9	1.1
V106I/Y188L	>110	>122	8.5	24.0	>500	>500	20.5	22
V106M	3.4	106.0	0.8	0.5	16.1	446.9	2.1	0.5
V108I	4.0	1.6	1.0	1.2	18.2	6.4	2.3	1.1
V108I/Y181C	7.8	4.3	7.4	5.0	33.7	17.8	17.1	4.7
V108I/Y181C	6.0	7.1	7.8	5.0	27	29	18.8	4.5
V179D	1.0	4.5	1.6	1.1	4	18	3.7	1.2
V90I	1.6	1.2	1.3	1.2	6.3	4.9	3.2	1.2
V90I/K103N	2.8	36.0	1.6	1.6	11.2	146.1	4	1.7
Y181C	1.2	1.3	2.7	1.6	5.1	5.3	6.1	1.5
Y181C	1.3	1.4	3.8	2.1	5.8	5.7	8.6	2
Y181C	1.5	3.3	5.1	5.2	6.4	13.6	11.7	5

Y181C	6.0	4.9	14.0	6.8	25.8	20.2	33	6.5
Y181C/G190A	2.4	10.0	1.9	1.2	10.4	40.9	4.3	1.1
Y181C/G190A	3.5	46.0	14.0	4.0	15.3	191.7	32.2	3.8
Y181V	1.0	1.1	61.0	9.4	4.4	4.6	140.3	8.9
Y181V	9.2	3.6	40.0	20.0	39.5	15	91.3	19.2
Y181I (n=2)	1.6	-	-	-	28.6	-	-	-
Y188C	0.3	2.8	0.2	0.3	1.4	11.6	0.6	0.3
Y188H	2.8	3.9	0.3	0.3	12.8	16.1	0.7	0.2
Y188L	95.0	37.0	2.5	15.0	410.1	152.5	5.7	14.3
Y188L	>116	53.0	2.5	6.9	>500	217.8	5.6	6.5
Y188L	>116	>121	27.0	72.0	>500	>500	62.3	68.7
M230L (n=1)*	>111	-	-	-	>500	-	-	-

The previous table, indicate that the resistance pattern per se (FC vs wild type) seems rather similar for doravirine, etravirine and rilpivirine. To what extent that FC equals resistance in vivo is another issue. The clinical cut-off for a FC in reduced susceptibility (and associated NNRTI resistance patterns) to doravirine has not been established.

NNRTI RAMs selected *in vivo*, in the phase 3 studies

To be noted, both in the phase 2b study (P007, dose ranging) and the phase 3 studies (P018, P021), the full set of NNRTI-associated mutations (as listed by the IAS-USA) were part of exclusion criteria. This was (more or less) a necessity in study P007 and P021, efavirenz being the control agent, but not in study P018, darunavir/ritonavir being the control agent.

In the discussion on in vitro dynamics the company proposes that the NNRTI mutations yielding at least a 10-fold decrease in susceptibility may be clinically relevant. Further, to quote the Clinical study reports, "Doravirine is intended for use in the treatment-naïve population, in whom rates of transmitted NNRTI resistance are low, but is also expected to be active against several common NNRTI resistance mutations, specifically K103N, Y181C, and G190A".

NNRTI mutations that were part of exclusion criteria in the phase 3 studies are shown below, where substitutions conferring a FC of around 10 or more are underlined. To recall, for some of these substitutions there was no data on *in vitro* susceptibility presented in the files (K101P, E138A/G/Q, Y181I, G190E, and M230L as single mutations).

Those written in **bold type** were those (pre-) defined as potentially yielding resistance to DOR in isolates from patients who failed DOR therapy. Substitutions **P236L** and **Y318F** were not part of exclusion criteria, but instead part mutations that were considered in the genotypic analysis in those who failed therapy.

L100I, K101E, K101P, K103N, K103S, **V106A, V106I, V106M, V108I, E138A,** E138G, **E138K,** E138Q, E138R, V179L, Y181C,Y181I, Y181V, Y188C, Y188H, **Y188L, G190A, G190S, H221Y, L234I, M230I, M230L, P225H, F227C, F227L, F227V**

In phase 3 (doravirine given to 747 patients), de novo resistance was evaluated in cases of protocol defined virological failure, PDVF (41= 8 non-responders, 33 rebounders) and in patients who discontinued for other reasons (n=75). Protocol defined virologic failure (PDVF) was defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

Successful genotypic tests (baseline + failure) were achieved for 20/41 and 11/75 of these cases, total 31/116 (others in practice having viral loads of <400 copies/ml, where no test was done). Out of 31 with successful testing, numbers failing with de novo NNRTI substitutions were low (table 13). The pattern, notably yielded in a population screened for the mentioned NNRTI mutations prior to therapy, is consistent with that obtained in the *in vitro* selection experiments.

Table 6 Individual data on treatment failure cases, with successful genotyping and de novo NNRTI RAMs, following treatment with doravirine 100 mg in studies (P007),P018 and P021

(Study), subtype	Type of failure	Day of test, (type of visit), Viral load		
(P007) Subtype A	Non-response PDVF: Wk 24	D.171 (VFC)	E138E/G, V179D	S (0.9)
	D/C (noncompliance): Wk 24	D.197 (D/C)	E138E/G, V179D	S (0.8)
1 (P018) Subtype B	D/C (noncompliance): Wk 24	D.169 (D/C) 55,708 c/mL	V106I, H221Y, F227C	R (>96.6)
2 (P021) Subtype AE	Rebound PDVF: Wk 48	D.366 (D/C) 1,256 c/mL	Y188L	R (>181.6)
3 (P021) Subtype C	Non-response PDVF: Wk 36	D.338 (D/C) 7,498 c/mL	Y318Y/F	S (0.4)
4 (P021) Subtype B	Non-response PDVF: Wk 24	D.195 (VFC) 12,691 c/mL	V106I, F227C	R (>105.5)
6(P021) Subtype B	Non-response PDVF: Wk 24	D.169 (VF) 33,250 c/mL	H221H/Y, F227C	R (>88.4)
		D.182 (VFC) 34,944 c/mL	V106V/I, H221H/Y, F227C	R (>109.9)
7 (P021) Subtype B	Non-response PDVF: Wk 24	D.251 (VFC)	F227C	R (>93.3)
8 (P021) Subtype B	Non-response PDVF: Wk 24	D.176 (VF) 80,038 c/mL	V106V/A, P225P/H	R (32.0)
		D.212 (D/C) 106,092 c/mL	V106A, P225H, Y318Y/F	R (>210.8)
9 (P021) Subtype C	Non-response PDVF: Wk 24	D.170 (VF) 71,727 c/mL	V106M, V108V/I, F227F/C	R (103.3)
		D.196 (VFC) 32,799 c/mL	V106M/T, F227C/R	R (>98.2)

VF virologal failire, VFC: virological failure confirmation visit, D/C discontinuation

In phase 2b (study P007, doravirine dosed 25-50-100-200 mg until all patients had passed week 24, followed by 100 mg qd), 15/232 (6.4%) of those treated with doravirine had PDVF, where 3/15 had viral isolates at failure with de novo resistance; 2 in the 25 mg group and 1 in the 100 mg group. Only 1 of 15 cases (25 mg dose, not shown in the previous table) had resistance with an impact on doravivine (V106V/I, F227C, FC 66).

When including all assessable cases from phase 2b (all dosing groups) and phase 3 with any de novo NNRTI resistance the V106 substitution was seen in 6 of 11 isolates, accompanied by F227C in 5 of 6 cases.

In patients who failed doravirine therapy with doravirine resistance (prior table), the presence of these mutations as part of baseline isolates were studied retrospectively with the use of deep sequencing. In the 5 case studied at present, none of the baseline isolates harboured any mutations (cut off level of 1%).

With regards the issue of the V106M mutation and subtype C virus (discussed previous part of this section), actual numbers of subtype C-infected patients treated in the phase 2/3 studies were presented. A total of 67 subtype C-infected patients were treated with doravirine 100 mg in phase 2b/3, and the response rate was fully in line with that seen for other subtypes. Of those 67 treated, the V106M mutation

was seen at failure in 1 patient. It can be concluded that doravirine does not seem to select V106M particularly easily in subtype C-infection.

The prior table on resistance outcomes concern pooled data, but in column 1 it is evident that a single case with NNRTI + NRTI resistance was found in study P018 (n=383) versus 6 in study P021 (n=364). The difference between the doravirine regimens in these studies is the NRTI backbone, with tenofovir/emtricitabine as co-treatment in the vast majority of patients in P018, and with tenofovir/lamivudine (all patients) in study P021.

Table 7 Resistance development, in PDVF population + early D/C population, study P018

	DOR (383) + TDF/**FTC (333)** or abc/3TC (50)	DRV/r (383) + TDF/**FTC (335)** or abc/3TC (48)
PDVF	19 (5.0)	24 (6.3)
Successful genotype	7	8
RAM test drug; DOR , DRV/r	0/7	0/10
NRTI mutation	0/7	0/10
D/C for reasons other than PDVF	40 (10.4)	53 (13.8)
Successful genotype	2	2
RAM (test drug)	1/2	0/10
NRTI mutation	1/2	0/10
M184V	1	

Table 8 PDVF and resistance development, study P021

	DOR/TDF/**3TC** (364)	EFZ/TDF/FTC (364)
PDVF	22 (6.1)	14 (3.8)
Successful genotype	13	10
NNRTI RAM (of relevance)	6/13	9/10
NRTI mutation	6/13	5/10
M184V	4	3
M184I + K219K/E		1
K65R (only)	1	
K65R + M184V	1	1
D/C for reasons other than PDVF	35 (9.6)	50 (13.7)
Successful genotype	9	13
RAM (test drug)	0/9	3/13
Relevant NRTI mutation	0/9	0/13

The difference is in line with large analyses on the risk of failure with the M184V mutation (resistance to both cytidine analogues) with lamivudine versus emtricitabine (Casper Rokx et al on the Dutch Athena cohort, CID 2014; The TenoRes Study Group, Lancet Infect Dis 2016; 16: 565–75).

The sampling schedule differed between the two phase 3 studies, with more frequent samples specifically aimed for resistance testing drawn in study P021 (in parallel with every HIV-RNA sample) than in P018 (at the virologic failure (VF) confirmation visit or discontinuation visit). However, when looking at details it was clear that cases with de novo resistance was in practice only yielded by patients in the so called PDVF population. There was no cases of resistance in those patients who stopped therapy “for other reasons” in study P021 (where samples could be used for resistance screening also in such cases). To maximize the information around this finding, the applicant was asked by the CHMP for further analysis of HIV-RNA

samples in study P018 (drawn for viral load counts), if such samples are still available. However, these samples had not been stored, and a post-hoc analysis could not be made.

NNRTI resistance and proposed labelling

Issues discussed in the prior sections, i.e. the lack of in vivo data on doravirine outcomes in vivo in the presence of NNRTI mutations, have implications for the proposed labelling. The CHMP is of the opinion that the data presented does not support an indication in the absence of "doravirine resistance", which was initially suggested by the MAH. During the procedure the MAH accepted a revised indication, i.e. where doravirine/lamivudine/tenofovir disproxil is indicated in the absence of past or present evidence of resistance to the NNRTI class, lamivudine and tenofovir disoproxil.

2.6.4. Discussion on clinical pharmacology

Doravirine is a new non-nucleoside reverse transcriptase inhibitor, with a similar in vitro activity, measured by EC50 and EC95 values, to HIV lab strains of subtype B to that seen with available NNRTI agents. The protein binding is considerably lower for doravirine (around 75%) as compared to that of the other agents (>99%), and therefore the shift in EC95 values is less marked (or absent) in cell cultures , again in comparison to that seen for the other NNRTIs. The activity was similar for the 10 HIV-1 subtypes tested (A through H).

In selection experiments, undertaken in HIV-1 subtype A, B and C virus, substitutions in V106 and F227 accounted for the majority of mutants in the breakthrough viruses. This pattern is consistent with that seen in those few patients failing doravirine-based therapy with documented resistance in the clinical studies. In panels of viruses with various types of NNRTI resistance substitutions, the patterns of reduced susceptibility (fold change versus the values seen in wild type/control virus) was fairly similar for doravirine, rilpivirine and etravirine. What fold change that is associated with a reduction if efficacy in vivo, dependent on the exposure of free drug concentrations, cannot be fully predicted by in vitro data, but would need to be clarified in clinical trials. However, a very cautious approach was taken when designing the phase 3 studies, where the complete list of established NNRTI mutations (IAS-USA, with the addition of yet one more doravirine-associated substitution) was part of exclusion criteria, also in study P018, where darunavir/r (protease inhibitor) served as control. Consequently, there is a lack of clinical back-up to support the use of doravirine in patients with resistance to the class; a breakpoint for a relevant fold change in phenotypic susceptibility is not established. A study (P0030) was undertaken in patients where NNRTI resistance was detected prior to therapy. However, the study is limited to 10 patients, 2 of whom stopped therapy prior to week 48. Hence, a follow-up is available for 7 patients with a baseline virus carrying the K103N mutation, and 1 patient with the G190A mutation. Although the 7 patients were responders at week 48, this data is too limited to clear the issue.

When looking at failures in the two phase 3 studies, numbers with de novo NNRTI (and NRTI) resistance was low. However, it is noted that the risk of failure with de novo resistance seems higher when doravirine was given with tenofovir plus lamivudine (the combination chosen for the fixed dose product) rather than with tenofovir plus emtricitabine. A higher risk of resistance with lamivudine, as compared to with emtricitabine, as part of the NRTI backbone has been reported from large scale analyses of real world data. The number of failures with resistance in the doravirine phase 3 studies was too low to provide any conclusive evidence on this issue.

2.6.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted are considered satisfactory by the CHMP.

2.7. Clinical efficacy

This section shows the main outcomes of doravirine short term monotherapy, exploring 25 mg and 200 mg qd for 7 days (study P005), the dose response combination therapy (study P007) where doses 25-50-100 and 200 mg was studied with efavirenz as control, all in combination with tenofovir disoproxil/emtricitabine, and finally the phase 3 studies (P018 and P021). In the latter darunavir+ritonavir and efavirenz were used as control agents. The efficacy studies were undertaken in previously untreated patients, infected with HIV-1 without any resistance to any of the agents in the regimens used; any resistance substitutions to the NNRTI class constituted exclusion criteria.

2.7.1. Dose response study(ies)

Doravirine short term monotherapy - study P005

This study was conducted at a single centre in Berlin (October 2011 to April 2012). Results were also published (Schűrmann, AIDS 2016)

The PK target chosen as a minimum exposure was a C24 concentration ≥54 nM, a drug level that would be 95% effective in the presence of 50% normal human serum against the NNRTI K103N/Y181C double substitution (see pharmacodynamics section). Pharmacokinetic data in healthy subjects (Protocol MK-1439-001) suggested that 25 mg qd would yield a mean C24 on Day 1 of 213 nM (4-fold higher than target), and that >95% of the dosed population was predicted to achieve C24 >148 nM (2.7-fold above that target).

Men aged 18-55, with a stable health (other than HIV-1 infection), with a VL >10.000 copies/ml, no NNRTI resistance mutations (population sequencing), a CD4 count>200 could enter the study. In order to minimize the risk for resistance development, once the subject completed the treatment phase of the study, initiation of a non-NNRTI-containing, suppressive ART regimen for at least 10 days following doravirine treatment was recommended.

18 patients were included and fulfilled treatment; 9 patients were randomized to doravirine 25 mg (n=6) or placebo (n=3) in a panel A. In panel B, another 6 were randomized to doravirine 200 mg and 3 to placebo. The treatment duration was 7 days.

17 patients had subtype B, the other CRF29_BF. Median baseline viral loads were 4.79 (25 mg group), 4.55 (200 mg) and 4.79 (placebo) log10 copies/ml. Outcomes are shown below, where the viral decay was similar between arms. Also when looking at a plotted graph, there is no tendency for a higher activity with the 200 mg than with the 25 mg dose (data not shown).

Table 9 Change From BL in log10 Plasma HIV RNA (log10 copies/mL) on Day 7

Treatment	N	LS mean (95% CI)	Treatment difference	LS mean difference (90% CI)	P-value	rMSE †
DOR 25 mg	6	-1.52 (-1.71, -1.32)	25 mg - Placebo	-1.37 (-1.60, -1.14)	<0.001	0.221
DOR 200 mg	6	-1.41 (-1.61, -1.21)	200 mg - Placebo	-1.26 (-1.51, -1.02)	<0.001	
Placebo	6	-0.15 (-0.35, 0.06)	200 mg - 25 mg	0.11 (-0.13, 0.34)	0.4371	

† rMSE: Square root of conditional mean square error (residual error) from an analysis of covariance (ANCOVA) model for log10 plasma HIV RNA. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation. LS = Least-squares; CI = Confidence interval.

Viral resistance was evaluated at baseline and prior to initiation of suppressive ART on Day 8. In 3 subjects treated with doravirine the VLs were too low to evaluate resistance on day 8. No resistance development was seen in the other 9 cases.

Doravirine exposure increased slightly less than dose proportional; the exposure was similar to that observed in HIV-negative men of similar weight dosed 25 and 200 mg qd. All patients (25 mg dose included) had a C24 concentration following the first dose that exceeded the C24 target, and the geometric mean trough concentrations were approximately 3- to 19-fold above target during days 3-7.

Dose response combination therapy – study P007

Design: double-blinded (in-house), randomized, 2-part study comparing doravirine dosed 25-50-100 or 200 mg to efavirenz 600 mg qd, all in combination with tenofovir/emtricitabine (Truvada).

Centres (73): US (25), Canada (3), Puerto Rico (4), Australia (6)
Belgium (2), France (6), Germany (9), the Netherlands (4), Poland (2), Romania (4), Spain (5), Russia (4)

In part 1, 210 patients were randomized to the different dose groups in equal proportions (about 40 per arm). *When all patients had passed week 24*, a single dose was chosen (the 100 mg dose), and patients treated with doravirine were switched to this dose on their next visit, still blinded for a total treatment duration of 96 weeks.

Part 2 was initiated once the dose was selected in part 1; here another 132 patients were randomized 1:1 to doravirine 100 mg qd or efavirenz 600 mg qd, for 96 weeks of blinded therapy.

Part I and Part II combined were to provide data to confirm the overall safety and efficacy of doravirine 100 mg versus efavirenz at Week 24. (i.e. around a total of 100 had received the selected dose of 100 mg doravirine)

Stratification: Screening viral load ≤ or >100,000 copies/mL.

Primary efficacy end point: Proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24 in Part I and in Part I/II combined.

Main inclusion/exclusion criteria of interest

Inclusion

- Treatment naïve patients, with a CD4 count ≥ 100 cells/mm^3.
- Serum creatinine within normal range (applying to the NRTI backbone).

Exclusion

- “Resistance to emtricitabine, tenofovir or efavirenz”.
- Patient with active Hepatitis C virus (HCV) co-infection (defined as detectable HCV RNA) or Hepatitis B virus (HBV) co-infection (defined as HBsAg positive).

The minimum CD4 count was low, having in mind that this is a dose ranging study. The list of NNRTI mutations that were part of exclusion criteria (“resistance to efavirenz”) was not stated in the CRF or protocol, and was not clarified by applicant. Since the resistance evaluation was performed at a central lab (Monogram, US) the issue was dropped.

On the basis of doravirine pharmacokinetics, potent inducers/inhibitors of CYP3A4 and potent inhibitors of glucuronidation were disallowed, and naturally also medicines not recommended in combination with efavirenz (in accordance with the efavirenz SmPC).

The full analysis set (FAS), all randomized who received at least one dose, was the population analysed for efficacy. The term “per protocol population” was not used. Instead, missing values were handled as follows:

• **Observed Failure (OF)** Subjects who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter.
- This population also includes patients who stopped therapy “for other reasons”, and who had a detectable viral load in the latest sample prior to discontinuing the study.

• **Treatment-Related Discontinuation=Failure (TRD=F):** Subjects who prematurely discontinued assigned treatment due to lack of *efficacy or adverse experiences* were considered failures thereafter.

• **Non-Completer=Failure (NC=F)**: Subjects who prematurely discontinued assigned treatment *regardless of reason* were considered as failures thereafter.
Results

The numbers stopping therapy early, for various non-efficacy reasons, was high, around 30% in the important dose finding part 1. In part 2, the discontinuation rate was lower, around 15%.

The disposition and outcomes at week 24 (i.e. during the dose ranging part, of main interest when considering PK/PD and choice of dose) are shown in the tables below.

There was no tendency for dose response to week 24, and proportions that discontinued the study up to week 24 was even between DOR treatment arms.

Table 10 Overall Disposition of Patients Part I (Weeks 0 - 24) All Patients Randomized (P007)

	MK-1439 25mg		MK-1439 50mg		MK-1439 100mg		MK-1439 200mg		Efavirenz		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Randomized	41		43		42		41		43		210	
Never Treated	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)	2	(1.0)
Treated	40	(97.6)	43	(100.0)	42	(100.0)	41	(100.0)	42	(97.7)	208	(99.0)
Discontinued the study	4	(9.8)	4	(9.3)	2	(4.8)	3	(7.3)	7	(16.3)	20	(9.5)
Adverse Event	1	(2.4)	2	(4.7)	1	(2.4)	0	(0.0)	2	(4.7)	6	(2.9)
Lost to Follow-up	0	(0.0)	0	(0.0)	1	(2.4)	1	(2.4)	3	(7.0)	5	(2.4)
Physician Decision	1	(2.4)	1	(2.3)	0	(0.0)	1	(2.4)	1	(2.3)	4	(1.9)
Withdrawal by Subject	2	(4.9)	1	(2.3)	0	(0.0)	1	(2.4)	1	(2.3)	5	(2.4)

Note: Both MK-1439 and Efavirenz were administered with TRUVADA™.

Table 11 Outcome at Week 24 (<40 copies/mL, FDA Snapshot), Part I (P007)

	Doravirine 25mg (N=40) n (%)	Doravirine 50mg (N=43) n (%)	Doravirine 100mg (N=42) n (%)	Doravirine 200mg (N=41) n (%)	Doravirine Combined (N=166) n (%)	Efavirenz 600mg (N=42) n (%)
HIV-1 RNA <40 copies/mL	32 (80.0)	32 (74.4)	30 (71.4)	33 (80.5)	127 (76.5)	27 (64.3)
HIV-1 RNA ≥40 copies/mL[†]	5 (12.5)	9 (20.9)	11 (26.2)	7 (17.1)	32 (19.3)	13 (31.0)
No Virologic Data at Week 24 Window						
Discontinued study due to AE or Death[††]	1 (2.5)	2 (4.7)	1 (2.4)	0 (0.0)	4 (2.4)	2 (4.8)
Discontinued study for Other Reasons[‡]	2 (5.0)	0 (0.0)	0 (0.0)	1 (2.4)	3 (1.8)	0 (0.0)
On study but missing data in window	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[†] Includes subjects who discontinued study before Week 24 for lack of efficacy and subjects who are equal to or above 40 copies/mL in the 24 week window.

[††] Includes subjects who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[‡] Other includes: Physician Decision, Patient Withdrew Consent, Lost to Follow-up, among others.

Note: Both doravirine and efavirenz were administered with TRUVADA™.

Secondary endpoint - response at week 48 and 96

With the common snapshot approach doravirine 100 mg (n=108) and efavirenz (n=107) yielded similar response rates at week 48 (78 vs 79%), and the same was true for the OF population ananlysis (81/95 (83%) vs 82/92 (86%), next table. The pattern was similar at week 96, with lower response rates across arms due to further discontinuations.

Table 12 Response at week 48, P007, Part 1 + 2 combined.

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†]
		n/N	% (95% CI)	(95% CI)[††]
Non-Complete=Failure (NC=F)	Doravirine 25 mg	29/40	72.5 (56.1, 85.4)	-7.9 (-25.1, 6.9)
	Doravirine 50 mg	31/43	72.1 (56.3, 84.7)	-8.7 (-25.3, 5.7)
	Doravirine 100 mg	84/108	77.8 (68.8, 85.2)	-1.9 (-12.9, 9.2)
	Doravirine 200 mg	34/41	82.9 (67.9, 92.8)	4.1 (-11.7, 16.5)
	Doravirine Combined	178/232	76.7 (70.7, 82.0)	-3.0 (-11.9, 6.9)
	Efavirenz 600 mg	85/107	79.4 (70.5, 86.6)	
Treatment-Related Disc.=Failure (TRD=F)	Doravirine 25 mg	29/36	80.6 (64.0, 91.8)	-1.5 (-18.9, 12.1)
	Doravirine 50 mg	31/41	75.6 (59.7, 87.6)	-6.8 (-23.5, 7.3)
	Doravirine 100 mg	84/104	80.8 (71.9, 87.8)	-0.3 (-11.2, 10.4)
	Doravirine 200 mg	34/39	87.2 (72.6, 95.7)	6.5 (-8.9, 18.1)
	Doravirine Combined	178/220	80.9 (75.1, 85.9)	-0.3 (-8.9, 9.4)
	Efavirenz 600 mg	85/105	81.0 (72.1, 88.0)	
Observed Failure (OF)	Doravirine 25 mg	29/35	82.9 (66.4, 93.4)	-4.2 (-21.4, 8.5)
	Doravirine 50 mg	31/38	81.6 (65.7, 92.3)	-5.9 (-22.5, 6.9)
	Doravirine 100 mg	84/101	83.2 (74.4, 89.9)	-2.9 (-13.2, 7.3)
	Doravirine 200 mg	34/39	87.2 (72.6, 95.7)	1.6 (-13.6, 12.8)
	Doravirine Combined	178/213	83.6 (77.9, 88.3)	-2.6 (-10.6, 6.6)
	Efavirenz 600 mg	85/99	85.9 (77.4, 92.0)	
FDA Snapshot Approach	Doravirine 25 mg	29/40	72.5 (56.1, 85.4)	-7.1 (-24.3, 7.7)
	Doravirine 50 mg	31/43	72.1 (56.3, 84.7)	-7.9 (-24.5, 6.6)
	Doravirine 100 mg	84/108	77.8 (68.8, 85.2)	-1.1 (-12.2, 10.0)
	Doravirine 200 mg	34/41	82.9 (67.9, 92.8)	4.9 (-11.0, 17.3)
	Doravirine Combined	178/232	76.7 (70.7, 82.0)	-2.2 (-11.2, 7.7)
	Efavirenz 600 mg	85/108	78.7 (69.8, 86.0)	

De novo resistance to doravirine, as captured within patients with PDVF, was very uncommon, and concerned only one case (25 mg dose group), discussed in the pharmacodynamics section.

Dose Selection for phase 3

The company considered that efficacy and safety findings were comparable across all tested DOR doses (25, 50, 100 and 200 mg). In a PK/PD analysis of study P007, including the four doravirine dosing arms, there was no relevant difference in response by steady state C24 quartiles. The 100 mg dose was chose for further study, in study P007, and in the phase 3 studies. This dose was considered the best choice, since it would be compatible with moderate inducers as well as CYP3A inhibitors as part of co-treatment and likely sufficient to cover for virus harbouring several common HIV-1 mutations that confer resistance to other NNRTIs, specifically, RT K103N, Y181C, K103N/Y181C, and G190A. The latter point has not yet been explored.

2.7.2. Main studies – *P018 and P021*

The two phase 3 studies are described below, both exploring doravirine dosed 100 mg versus a control agent (both with 2 NRTIs) in previously untreated patients.

The inclusion/exclusion criteria were the same, except for the list of mutations that were part of the exclusion criteria (i.e. tailored with regards to NRTI backbones used, and choice of control (darunavir in study P018, efavirenz in study P021). Resistance to the NNRTI class was not allowed, as discussed in the prior section.

- The screening viral load needed to be at least 1000 copies/ml
- There was no minimum CD4 count, and AIDS/opportunistic infections are not mentioned as part of exclusion criteria.
- Creatinine clearance (CG GFR) needed to be at least 50 ml/min (applying to NRTI backgrounds).

Primary objectives and hypotheses:

P018 + P021

Non-inferiority vs control regimen (darunavir/ritonavir and efavirenz, respectively) at week 48, using a 10% margin, for the key efficacy end points, i.e. <40 and <50 copies/ml at week 48 (FDA snapshot approach).

Study P021: Also safety as part of primary objectives, with the hypothesis that doravirine/tenofovir/lamivudine is superior to efavirenz/tenofovir/emtricitabne with regards to typical efavirenz-related side effects (dizziness, sleep disorder, altered sensorium).

Secondary objectives and hypothesis:

P018 + P021

Non-inferiority versus control regimen (same margin and efficacy end points) at week 96

Safety: particularly concerning serum lipids, where the hypothesis was that doravirine is superior to darunavir/ritonavir (P018) and efavirenz (P021) with regards to (lack of) increase in LDL and non-HDL cholesterol at week 48.

Sample size (both studies)

The power calculations assumed a true response rate of 80% at Week 48 for doravirine and control regimens in both studies, using the FDA Snapshot approach. With around 340 subjects randomized to each treatment (both studies), the studies had 90% power to demonstrate that the doravirine regimens were non-inferior to the control regimens at an overall one-sided 2.5% alpha level.

Extension phase (for a total of approximately 4 years)

There is a planned extension phase for another 96 weeks (total study duration of approximately 4 years) for both phase 3 studies, to evaluate longer term efficacy and safety for doravirine dosed 100 mg qd.

Study P018

Methods

Doravirine 100 mg or Darunavir + ritonavir 800/100 mg (double blind) , both in combination with TDF/FTC or abc/3TC (TRUVADA or EPZICOM) in treatment-naïve patients, and without any resistance to the agents in the regimens at screening; resistance to the NNRTI class disqualifying.

Trial dates: Dec-2014 (first patient enrolled) to Nov-2016 (week 48 database lock)

Study Participants

Centres allocating study subjects(125):

US (37), Canada (5), Puerto Rico (3)
Chile (5), Argentina (4)
DE (12), UK (8), ES (10), FR (7), Romania (6), Austria (4), DK (3), Italy (1)
Russian Federation (11), South Africa (3)

Matching placebos were used, meaning that the total number of daily pills = 4.

Stratification: HIV-1 RNA level at screening (≤ or > 100,000 copies/mL) and NRTI background therapy (FTC/TDF or ABC/3TC). Patients were randomized within each of these 4 strata in a 1:1 ratio.

Prohibited medications: Moderate or strong inducers of CYP3A4 (linked to doravirine), and additionally in accordance with the Prezista SmPC.

1027 individuals were screened, with 252 screening failures (25%), where resistance to any study drug was the most common screen failure (13% of screened subjects).

Table 13 Patient Disposition by week 48, P018

	Dor		drv/r		Total	
	n	%	n	%	N	%
Total Randomized	385		384		769	
Not Treated	2	(0.5)	1	(0.3)	3	(0.4)
Treated (=Full set Analysis, FAS)	383	(99.5)	383	(99.7)	766	(99.6)
Discontinued Study	56	(14.5	71	(18.5)	127	(16.5)
Adverse Event	4	(1.0)	12	(3.1)	16	(2.1)
Death	1	(0.3)	0	(0)	1	(0.1)
Lack Of Efficacy	12	(3.1)	14	(3.6)	26	(3.4)
Lost To Follow-Up	17	(4.4)	19	(4.9)	36	(4.7)
Non-Compliance	7	(1.8)	4	(1.0)	11	(1.4)
Physician Decision	3	(0.8)	3	(0.8)	6	(0.8)
Pregnancy	1	(0.3)	0	(0)	1	(0.1)
Protocol Deviation	1	(0.3)	6	(1.6)	7	(0.9)
Withdrawal By Subject	10	(2.6)	13	(3.4)	23	(3.0)

Results were also presented for a per protocol population, where numbers and reasons for exclusions are shown below. Site 0020 was closed when the sponsor was informed that the principal investigator was no longer employed (reasons not discussed). Patients were not willing to transfer to another site.

Table 14 Details on the Per Protocol population.

Reason for Exclusion†	DOR 100 mg QD	DRV/r 800/100 mg QD	Total
FAS	383	383	766
Per protocol population	353	341	694
Excluded from FAS, any reason	**30**	**42**	**72**
Discontinuation for Reasons Not Related to Treatment	**20**	**29**	**49**
D/C prior to wk 48 for reasons other than lack of efficacy, AE, or death and the last on-treatment HIV- 1 RNA value is <50 copies/mL	11	15	26
D/C prior to wk 8 visit due to non-treatment-related	9	15	24
Major Protocol Deviations That Have the Potential to Affect Efficacy	**7**	**15**	**22**
Entry Criteria	4	11	15
- Randomized with an exclusionary mutation	2	9	11
- Did not have a screening HIV-1 RNA value of ≥1000 copies/mL available from the central lab within the 45-day screening window	2	1	3
- Screening HIV-1 RNA <1000 copies/mL at central lab	0	1	1
Clinical Supplies	3	3	6
- Received the wrong study treatment	2	2	4
- Improper storage of study therapy ty	1	1	2
	0	1	1
Noncompliance With Study Medication	**3**	**5**	**8**
Full compliance with study drug through Week 48 was <70% and HIV-1 RNA at Week 48 was not <50 copies/mL	3	5	8
GCP Noncompliance	**3**	**3**	**6**
All subjects at site 0020	3	3	6

The majority of patients were white men and around half were included at European sites (Russia included). Non-B subtype was more common than in many other recent studies (30%). Around 90% had tenofovir disoproxil/emtricitabine as backbone NRTIs.

Table 15 Baseline characteristics, P0018

	DOR (N = 383) n (%)		DRV/r (N = 383) n (%)		Total (N = 766) n (%)	
Male gender	319	(83)	326	(85)	645	(84.2)
Race, white	280	(73)	280	(73)	560	(73.1)
Black or African American	86	(22)	88	(23)	174	(22.7)
Region, Africa	23	(6)	22	(6)	45	(5.9)
Asia/Pacific	12	(3)	3	(1)	15	(2.0)
Europe	170	(44)	179	(47)	349	(45.6)
Latin America	38	(10)	33	(9)	71	(9.3)
North America	140	(37)	146	(38)	286	(37.3)
Mean age	34.8		35.7		35.2	
CD4 count, cells/mm^3 mean (SD)	433		412		422.2 (219.4)	
CD4¤ >200	341	(89)	316		657	(85.8)
non-B subtype	117	(30)	111	(29)	228	(29.8)
HIV-RNA >100,000 copies/mL	83	(22)	74	(19)	157	(20.5)
>500,000 copies/mL	17	(4)	12	(3)	29	(3.8)
Hep B and/or C Positive	11	(3)	18	(5)	29	(3.8)
NRTI background TRUVADA	333	(87)	335	(87)	668	(87.2)
EPZICOM/KIVEXA	50	(13)	48	(13)	98	(12.8)

Reported compliance was similar for the DOR and DRV+r treatment groups; ≥90% compliance was reported by around 95% in both groups.

Outcomes/endpoints

The outcomes and main reasons for non-response by Snapshot using <50 copies/ml were summarised in the next table. Outcomes are similar for the two regimens (non-inferiority reached vs darunavir/ritonavir). It should be noted that subjects who met defined virological failure criteria (PDVF) were to be discontinued regardless of compliance with study therapy. The snapshot algorithm and the definition of PDVF differ in several aspects. This explains the discrepancy in the proportions with HIV-RNA levels ≥50 copies/ml and the proportions with PDVF (an issue clarified during pre-submission meeting, not discussed further in the application).

Table 16 Virologic outcome at week 48, FDA Snapshot (<50 cps/mL), study P018

	DOR (383)	DRV/r (383)
HIV-1 RNA <50 copies/mL	321 (83.8)	306 (79.9)
HIV-1 RNA ≥ 50 copies/mL	43 (11.2)	50 (13.1)
PDVF *	19 (5.0)	24 (6.3)
No Virologic Data at Week 48 Window	19 (5.0)	27 (7.0)
D/C due to AE or Death	5 (1.3)	11 (2.9)
D/C for Other Reasons	11 (2.9)	15 (3.9)
On study, missing data	3 (0.8)	1 (0.3)

* Protocol defined virological failure (PDVF)

1) Rebounder: confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 after having had HIV-1 RNA <50 at any time during the study, or 2) Non responder: confirmed HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36, or confirmed HIV-1 RNA ≥ 50 copies/mL at Week 48.

The expected cut-off is <40 copies/ml (i.e. the lower limit of quantification of the HIV-RNA assay used, the Abbott RealTime HIV-1 Assay). Results by 40 copies/ml and baseline parameters are presented next. Point estimates are similar, and in favour of doravirine for baseline parameters of interest. Point estimates for response by age, gender and race were fully similar between arms (data not shown).

Table 17 Proportions with Plasma HIV-1 RNA <40 Copies/mL at Week 48, FDA Snapshot, P018

	DOR		DRV/r		Difference % (95% CI)
	n/N	%	n/N	%	
Total	319/383	83.3	303/383	79.1	4.2 (-1.4, 9.7)
By BL parameters					
VL ≤100,000L cps/mL	256/300	85.3	248/308	80.5	4.8 (-1.3, 10.8)
>100,000	63/83	75.9	54/74	73.0	1.1 (-13.5, 15.8)
>500,000	14/17	82.4	6/12	50.0	30.9 (-4.1, 65.9)
CD4 ≤50	5/6	83.3	12/19	63.2	20.4 (-20.0, 60.8)
>50, ≤200	29/36	80.6	31/48	64.6	15.7 (-3.0, 34.4)
>200	285/341	83.6	260/316	82.3	1.4 (-4.4, 7.2)
Region Africa	19/23	82.6	15/22	68.2	13.2 (-13.2, 39.5)
Asia/Pacific	9/12	75.0	2/3	66.7	4.5 (-68.3, 77.4)
Europe	148/170	87.1	148/179	82.7	4.2 (-3.5, 11.9)
Latin America	37/38	97.4	28/33	84.8	14.1 (0.2, 28.0)
North America	106/140	75.7	110/146	75.3	0.7 (-9.4, 10.8)
Subtype B	222/266	83.5	219/272	80.5	2.5 (-4.1, 9.1)
Non-B	97/117	82.9	84/111	75.7	6.2 (-4.6, 16.9)
TRUVADA™	276/333	82.9	267/335	79.7	3.2 (-2.8, 9.1)
EPZICOM/KIVEXA	43/50	86.0	36/48	75.0	11.0 (-5.3, 27.2)
Immunologial response					
CD4 increase	193		186		

Similar outcomes were seen between arms also in the PP population.

Table 18 Efficacy analysis (snapshot week 48), per protocol population, P018

	DOR n/N (%)	DRV/r n/N (%)	Estimated Difference	95% CI
VL <50 copies/mL	316/353 (89.5)	298/341 (87.4)	2.1	(-2.725, 6.924)
VL <40 copies/mL	314/353 (89.0)	295/341 (86.5)	2.4	(-2.544, 7.350)

Week 96 results were consistent with the week 48 result, with a point estimate favouring the doravirine treatment arm.

Table 19 Efficacy response (<40 copies/mL, Snapshot approach) through week 96, in the pivotal studies

	DOR + 2 NRTIs (383)	DRV+ rtv + 2 NRTIs (383)
Week 48	83 %	79 %
Difference (95 % CI)	4.2 % (-1.4%, 9.7 %)	
Week 96*	72 % (N=379)	64 % (N=376)
Difference (95 % CI)	7.6 % (1.0 %, 14.2 %)	
to week 48	193	186
to week 96	224	207

Study P021

Methods

Doravirine/lamivudine/tenofovir disoproxil (100/300/300 mg) or efavirenz/emtricitabine/tenofovir disoproxil (100/300/300 mg), double blinded, in treatment-naïve patients, and without any resistance to the agents in the regimens at screening; resistance to the NNRTI class disqualifying.

Study Participants

The trial was conducted at 126 sites:

33 in the United States, 4 in Canada 3 in Mexico, 3 in Puerto Rico, 4 in Chile, 3 in Colombia, 4 in Guatemala, 1 in Honduras, 7 in Peru, 2 in Australia, 1 in New Zealand
7 in the United Kingdom; 6 in Germany, 5 in Portugal, 4 in Spain, 3 in Belgium, 3 in Switzerland, 2 in Denmark, 8 in Russia, 2 in Israel, 9 in South Africa, 6 in Taiwan, 6 in Thailand.

Trial dates: June 2015 (first patient enrolled) to March 2017 (last visit for primary endpoint).
Stratification: HIV-1 RNA level at screening (≤ or > 100,000 copies/mL) and hepatitis B and/or C co-infection status, yes/no.

Prohibited medications: Moderate or strong inducers of CYP3A4 (linked to doravirine) and in accordance with the efavirenz SmPC.

992 individuals were screened, with 241 screen failures. 141 out of 992 screened (15%) were excluded for reasons of baseline resistance (certainly mainly NNRTI-mutations), a high figure in a treatment naïve population.

A slightly higher proportion in the efavirenz-treated arm discontinued study, the difference driven by a higher rate of AEs as a reason in this arm (6.3 vs 2.7%), next table. A somewhat higher proportion of patients stopped doravirine due to lack of efficacy (4.9 vs 2.7%).

Table 20 Patient Disposition by week 48, P021

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Total	
	n	(%)	n	(%)	n	(%)
Total Randomized	368		366		734	
Not Treated	4	(1.1)	2	(0.5)	6	(0.8)
Treated (=FAS)	364	(98.9)	364	(99.5)	728	(99.2)
Discontinued Study	51	(13.9)	61	(16.7)	112	(15.3)
Adverse Event	10	(2.7)	23	(6.3)	33	(4.5)
Death	1	(0.3)	3	(0.8)	4	(0.5)
Lack Of Efficacy	18	(4.9)	10	(2.7)	28	(3.8)
Lost To Follow-Up	6	(1.6)	7	(1.9)	13	(1.8)
Non-Compliance With Study Drug	1	(0.3)	2	(0.5)	3	(0.4)
Physician Decision	2	(0.5)	2	(0.5)	4	(0.5)
Pregnancy	1	(0.3)	1	(0.3)	2	(0.3)
Protocol Deviation	4	(1.1)	2	(0.5)	6	(0.8)
Withdrawal By Subject	8	(2.2)	11	(3.0)	19	(2.6)

FAS: Full Analysis set

The proportion of patients that were excluded to form the Per Protocol population was similar between arms, and for similar reasons, next table.

Table 21 Details on the Per Protocol population, P021.

Reason for Exclusion†	DOR/3TC/TDF QD (N=364)	EFV/FTC/TDF QD (N=364)	Total (N=728)
Any reason	**26**	**25**	**51**
Discontinuation for Reasons Not Related to Treatment	**18**	**16**	**34**
Subject discontinued prior to Week 8 visit due to non-treatment-related reasons (reasons other than lack of efficacy, AE, or death)	9	10	19
Subject discontinued prior to Week 48 window (no HIV-1 RNA data in the week 48 window) due to non-treatment-related reasons (reasons other than lack of efficacy, AE, or death) and the last on-treatment HIV-1 RNA value is <50 copies/mL	9	8	17
Major Protocol Deviations That Have the Potential to Affect Efficacy	**10**	**9**	**19**
Clinical Supplies	6	6	12
- Received the wrong study treatment from what they were assigned (i.e., received incorrect study therapy or an incorrect dose)	5	2	7
- Improper storage of study therapy that could affect efficacy and/or safety	1	3	4
- Blinded active study therapy was unblinded during the trial (not according to protocol)	0	1	1
Entry Criteria	4	3	7
- Randomized with an exclusionary mutation	4	2	6
- Did not have a screening HIV-1 RNA ≥1000 copies/mL available from the central lab within the 60-day screening window	0	1	1
Noncompliance With Study Medication	**5**	**10**	**15**
Full compliance with study drug through Week 48 was <70% and HIV-1 RNA at Week 48 was not <50 copies/mL	5	10	15

Demographics were similar to that seen in P018, but with a lower proportion of patients with white race (around half), and a higher proportion of patients recruited in non-US, non-EU regions. Baseline factors were balanced; the proportion with non-B subtype was somewhat higher in the doravirine treatment arm

(36 vs 30%), next table. Reported compliance was similar; ≥90% compliance was reported by around 95% of patients in both arms.

Table 22 Baseline characteristics, P021

	DOR/3TC/TDF (N = 364) n, (%)	EFV/FTC/TDF (N = 364) n, (%)	Total (N = 728) n, (%)
Male gender	305 (83.8)	311 (85)	616 (84.6)
Age, mean (SD)	33.6 (10.5)	32.7 (10)	33.1 (10.2)
American Indian/Alaska Native	10 (3)	6 (2)	16 (2.2)
Asian	59 (16)	65 (18)	124 (17.0)
Black or African American	67 (18)	68 (19)	135 (18.5)
Multiple	51 (14)	55 (15)	106 (14.6)
White	177 (49)	170 (47)	347 (47.7)
Region, Africa	37 (10)	27 (7)	64 (8.8)
Asia/Pacific	59 (16)	62 (17)	121 (16.6)
Europe	88 (24)	94 (26)	182 (25.0)
Latin America	89 (24)	87 (24)	176 (24.2)
North America	91 (25)	94 (26)	185 (25.4)
CD4 count, mean	435	415	425
>200 cells/mm ^{3} , n (%)	320 (88)	318 (87)	638 (87.6)
HIV-RNA <=100,000 copies/mL	291 (80)	282 (77)	573 (78.7)
Hep B and/or C Positive	11 (3)	9 (2)	20 (2.7)
Hep B Positive Only	9 (3)	8 (2)	17 (2.3)
Hep C Positive Only	2 (0.5)	1 (0.3)	3 (0.4)
Non-B subtype	130 (36)	111 (30)	241 (33)

Outcomes / endpoints

Doravirine/lamivudine/tenofovir disoproxil was non-inferior to efavirenz/emtricitabine/tenofovir disoproxil for the primary endpoint, tables below. Although the proportion of responders was somewhat higher for the doravirine regimen, the point estimate for PDVF was higher with the doravirine than with the efavirenz regimen. The issue of lamivudine (3TC) versus emtricitabine (FTC) as a potential cause of a higher rate of PDVF (and de novo resistance) was raised by the CHMP (please refer to the pharmacodynamics section), without any conclusive results.

Table 23 Virologic outcome at week 48, FDA Snapshot (<50 cps/mL), study P021

	DOR/3TC/TDF (N=364)	EFV/FTC/TDF (N=364)
HIV-1 RNA <50 copies/mL	307 (84.3)	294 (80.8)
HIV-1 RNA ≥ 50 copies/mL	39 (10.7)	37 (10.2)
PDVF *	22 (6.0)	14/364 (3.0)
No Virologic Data at Week 48 Window	18 (4.9)	33 (9.1)
D/C due to AE or Death	9(2.5)	24(6.6)
D/C for Other Reasons	9 (2.5)	8 (2.2)
On study, missing data	0	1 (0.3)

PVDF: polyvinylidene fluoride

In this study there is a tendency for lower point estimates with doravirine than with control, for subjects who have low CD counts. However, numbers are low, and the differences are far from significant. In contrast, in subjects with a CD4 count >200, the point estimate favours doravirine (significant), next table.

Table 24 Response by baseline parameters (FDA snap shot, <40 copies/ml), study P021

	Response				Difference % (95% CI)
	DOR/TDF/3TC		EFZ/TDF/FTC		
	n/N	%	n/N	%	
Total	305/364	83.8	290/364	79.7	4.1 (-1.5, 9.7)
By BL parameters					
VL ≤100,000L cps/mL	251/291	86.3	234/282	83.0	3.3 (-2.6, 9.2)
>100,000	54/73	74.0	56/82	68.3	6.4 (-8.1, 20.8)
>500,000	5/10	50.0	11/18	61.1	-6.3 (-47.5, 35.0)
CD4 ≤50	5/9	55.6	6/10	60.0	-11.1 (-65.4, 43.2)
>50, ≤200	22/35	62.9	29/36	80.6	-18.1 (-38.8, 2.7)
>200	278/320	86.9	255/318	80.2	6.6 (0.9, 12.3)
<200	27/44	61.4	35/46	76.1	
Male	255/305	83.6	246/311	79.1	4.3 (-1.8, 10.4)
Female	50/59	84.7	44/53	83.0	1.2 (-13.1, 15.5)
Region, Africa	29/37	78.4	22/27	81.5	-3.1 (-24.1, 18.0)
Asia/Pacific	55/59	93.2	50/62	80.6	12.9 (0.5, 25.3)
Europe	74/88	84.1	77/94	81.9	-0.1 (-10.8, 10.6)
Latin America	77/89	86.5	74/87	85.1	1.6 (-9.1, 12.3)
North America	70/91	76.9	67/94	71.3	6.8 (-5.6, 19.1)
Subtype B	194/232	83.6	199/253	78.7	5.2 (-1.7, 12.1)
Non-B	109/130	83.8	91/111	82.0	1.7 (-8.1, 11.4)
Immunologial response					
CD4 increase, mean	198		188		

Again, outcomes in the per protocol population mirror those seen in the FAS population, next table.

Table 25Efficacy analysis (Snapshot week 48), per protocol population

	DOR/3TC/TDF n/N (%)	EFV/FTC/TDF n/N (%)	Difference % (95% CI)
<50 cps/mL	302/338 (89.3)	291/339 (85.8)	3.6 (-1.4, 8.5)
<40 cps/mL	300/338 (88.8)	287/339 (84.7)	4.2 (-0.9, 9.2)

The week 96 results were in line with the week 48 outcomes, with a point estimate favouring the doravirine treatment arm, table below.

Table 26 Efficacy response (<40 copies/mL, Snapshot approach) in the pivotal studies

	DOR/3TC/TDF (364)	EFV/FTC/TDF (364)
Week 48	84 %	80 %
Difference (95 % CI)	4.1 % (-1.5 %, 9.7 %)	
Week 96*	76 %	73 %
Difference (95 % CI)	3.3 % (-3.1 %, 9.6 %)	
Mean CD4 Change from baseline		
to week 48	198	188
to week 96	238	223

Summary of main efficacy studies

The next tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on the clinical efficacy and benefit risk assessment sections.

Table 27 Summary of Efficacy (Snapshot week 48) for trials P018 and P021

	Response n/N (%)		Difference % (95% CI)
Study P018 (DRIVE-FORWARD) double blind, treatment-naïve patients. *Test:* doravirine 100 mg qd *Control:* darunavir + ritonavir 800/100 mg qd (double blind) Both in combination with tenofovir disoproxil/emtricitabine (~90%) or abacavir/lamivudine (~10%), in treatment-naïve patients. Resistance screening (exclusion criteria) NNRTI: L100I, K101E/P, K103N/S, V106A/M/I, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188H/L, G190A/S, H221Y, P225H, F227C/L/V, M230L/I, L234I NRTIs and PI: In accordance with IAS-USA			
	doravirine	darunavir/r	
<40 cps/mL, FAS, snapshot	319/383 (83.3)	303/383 (79.1)	4.2 (-1.4, 9.7)
<40 cps/ml, PP, snapshot	314/353 (89.0)	295/341 (86.5)	2.4 (-2.5, 7.3)
Study P021 (DRIVE-AHEAD) double blind, treatment-naïve patients. *Test:* doravirine/tenofovir disoproxil/lamivudine (100/300/300 mg, fix dose) *Control:* efavirenz/tenofovir disoproxil/emtricitabine (600/300/300 mg, fix-dose), Resistance screening (exclusion criteria) NNRTI: Same as P018 NRTIs: In accordance with IAS-USA			
	DOR/TDF/3TC	EFV/TDF/FTC	
<40 cps/mL, FAS, snapshot	305/364 (83.8)	290/364 (79.7)	4.1 (-1.5, 9.7)
<40 cps/ml, PP, snapshot	300/338 (88.8)	287/339 (84.7)	4.2 (-0.9, 9.2)

Analysis performed across trials (pooled analyses and meta-analysis)

The company did mainly present pooled results in overviews and summaries. With regards to efficacy, the pooling of results is not supported from the CSRs. This is because the NRTI backbone used in combination with doravirine differed across studies. Hence, without pooling, outcomes by viral subtypes are shown below. The CHMP notes that the response was similar between subtypes, and not markedly different between arms.

Table 28 Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Week 48 by Viral Subtype, P018 , FDA Snapshot Approach

Prognostic and Demographic Factors	Response			
	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD	
	n/N	% (95% CI)	n/N	% (95% CI)
Viral Subtype				
Subtype B	222/266	83.5 (78.4, 87.7)	219/272	80.5 (75.3, 85.1)
Non-Subtype B	97/117	82.9 (74.8, 89.2)	84/111	75.7 (66.6, 83.3)
A	6/7	85.7 (42.1, 99.6)	6/8	75.0 (34.9, 96.8)
A1	27/34	79.4 (62.1, 91.3)	15/19	78.9 (54.4, 93.9)
A2	0/0	N/A	1/1	100.0 (2.5, 100.0)
AB	1/1	100.0 (2.5, 100.0)	0/0	N/A
AE	2/2	100.0 (15.8, 100.0)	3/3	100.0 (29.2, 100.0)
AG	7/8	87.5 (47.3, 99.7)	4/8	50.0 (15.7, 84.3)
BF	10/10	100.0 (69.2, 100.0)	4/5	80.0 (28.4, 99.5)
C	21/26	80.8 (60.6, 93.4)	17/22	77.3 (54.6, 92.2)
Complex	15/15	100.0 (78.2, 100.0)	18/24	75.0 (53.3, 90.2)
D	0/0	N/A	1/1	100.0 (2.5, 100.0)
F1	7/12	58.3 (27.7, 84.8)	14/18	77.8 (52.4, 93.6)
G	1/2	50.0 (1.3, 98.7)	0/1	0.0 (0.0, 97.5)
Undetermined	0/0	N/A	1/1	100.0 (2.5, 100.0)

Table 29 Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Week 48 by Viral Subtype, P021 , FDA Snapshot Approach

Prognostic and Demographic Factors	Response			
	DOR/3TC/TDF QD		EFV/FTC/TDF QD	
	n/N	% (95% CI)	n/N	% (95% CI)
Viral Subtype				
Subtype B	194/232	83.6 (78.2, 88.1)	199/253	78.7 (73.1, 83.5)
Non-Subtype B	109/130	83.8 (76.4, 89.7)	91/111	82.0 (73.6, 88.6)
A	6/7	85.7 (42.1, 99.6)	2/2	100.0 (15.8, 100.0)
A1	9/10	90.0 (55.5, 99.7)	9/15	60.0 (32.3, 83.7)
AB	0/0	N/A	1/1	100.0 (2.5, 100.0)
AE	30/33	90.9 (75.7, 98.1)	35/42	83.3 (68.6, 93.0)
AG	3/3	100.0 (29.2, 100.0)	7/7	100.0 (59.0, 100.0)
BC	1/1	100.0 (2.5, 100.0)	1/2	50.0 (1.3, 98.7)
BF	6/7	85.7 (42.1, 99.6)	2/3	66.7 (9.4, 99.2)
C	30/38	78.9 (62.7, 90.4)	21/24	87.5 (67.6, 97.3)

Complex	19/23	82.6 (61.2, 95.0)	8/10	80.0 (44.4, 97.5)
D	1/1	100.0 (2.5, 100.0)	0/0	N/A
F1	2/4	50.0 (6.8, 93.2)	2/2	100.0 (15.8, 100.0)
G	2/3	66.7 (9.4, 99.2)	3/3	100.0 (29.2, 100.0)
Missing	2/2	100.0 (15.8, 100.0)	0/0	N/A

Clinical studies in special populations

Elderly

In practice doravirine has not been studied in elderly patients, a consequence of studies performed in treatment naïve patients only. In studies P007, P018 and P021 combined there was a total of 11 patients aged 65 and above.

The relative bioavailability of 100 mg doravirine (single dose) was studied in young vs elderly (>65) men and women, without a clinically relevant difference in exposure (comparisons within gender).

Renal and hepatic impairment

Efficacy and safety has not been studied specifically for these subpopulations, and that is not considered necessary. PK studies in HIV-negative patients with severe renal impairment (not end stage with dialysis) and moderate hepatic impairment (Child Pugh class B, not child Pugh C) yielded results that do not call for dose adjustments by renal/hepatic dysfunction.

Hepatitis B/C co-infection

The number of patients with hepatitis co-infection in the phase 3 studies were quite limited (n=49), and in the phase 2b study (P007), hepatitis co-infection was part of exclusion criteria. Since doravirine has no effect on these viruses per se, and no dose adjustment is necessary in patients with hepatic impairment, the main interest for this subpopulation is an adequate DDI program allowing for dose recommendations of direct antivirals for the treatment of hepatitis C. For patients with hepatitis B co-infection, the issue is in practice solved by co-treatment with adequate NRTIs.

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies

On the basis of doravirine in vitro data and pharmacokinetics in healthy adults, short term monotherapy (P005) was studied with 25 mg and 200 mg qd, with a similar viral decay. The lower dose is predicted to cover (on the basis of free concentration of C_{min} values) for both wild type virus and virus harbouring some common NNRTI mutations with severe impact on the efficacy with efavirenz.

The same span was tested in dose ranging combination therapy (25-50-100-200 mg qd), with efavirenz as control agent and tenofovir disoproxil emtricitabine as NRTI backbone (P007). The 200 mg dose was used to study the safety with that higher exposure, kinetics being close to linear. According to the presented analysis, a similar response was seen with the exposures yielded by these 4 doses (no apparent difference in response at week 24 by C_{min} quartiles). The design and choice of dose for this study is supported by the CHMP. The 100 mg dose was chosen for the second part of study P007 and for the phase 3 studies. This is also accepted by the Committee, since that dose yields an exposure where both a

substantial decrease and increase in exposure, as a consequence of potential DDIs, is likely compatible with an unaffected efficacy and safety profile.

The two pivotal studies are double blinded, with adequate control regimens (darunavir+ritonavir and efavirenz). A study with a boosted PI as blinded control is quite welcomed by the CHMP. The CHMP is of the opinion though that the main draw back with the design of the phase 3 studies, in particular study P018 where darunavir/r served as control, is the full set of NNRTI mutations that were part of exclusion criteria. In vitro results indicate that a lower number of more specific mutations could have served as exclusion criteria, at least in study P018 (darunavir/r being control agent). At present this has not been evaluated in vivo, apart from in a study of too limited size (n=8 followed 48 weeks). Consequently, the CHMP considers that the indication needs to be restricted as discussed in the pharmacodynamics section. Apart from that no main design issues are seen for the pivotal studies. The non-inferiority margin of 10% is endorsed. The discontinuation rate in the phase 3 studies are rather high but acceptable (~15%) by the CHMP, and the rate of loss to follow-up was low.

Efficacy data and additional analyses

The company has presented outcomes (snapshot approach) using a cut-off of both <40 cps/ml and <50 cps/ml. The lower cut off is favoured by the CHMP (also mentioned in previous advice), since this is the cut off level for the HIV-RNA assay used. Results with the lower cut-off are therefore presented in the SmPC, following CHMP requests. When looking at overall outcomes, doravirine was non-inferior to the control regimens in the two separate phase 3 studies. Point estimates by various relevant baseline parameters were in line with the overall results, for the most slightly in favour of the doravirine regimen.

As part of summaries, the company has chosen to pool data (100 mg qd dose vs each control regimen). Pooling is not supported for reasons discussed in the prior section on dynamics (different NRTI backbones).

The relevance of safety comparisons as part of formal safety objectives is questioned (i.e. rate of CNS side effects with doravirine vs efavirenz and LDL increase with doravirine vs efavirenz and vs darunavir + ritonavir). These AEs are well known, and are not seen with the other NNRTIs (rilpivirine, etravirine) or other first line agents. These results are therefore not to be part of the SmPC (in line with prior CHMP advice).

2.7.4. Conclusions on the clinical efficacy

Doravirine yielded similar efficacy as darunavir/r, both in combination with 2 NRTIs (in practice tenofovir disoproxil/emtriciabine, as Truvada), and doravirine in fixed dose with tenofovir disoproxil/lamivudine yielded similar results as efavirenz/tenofovir disoproxil/emtricitabine (i.e. Atripla), in two double blind studies in previously untreated patients without any resistance to the agents included in the regimens. The CHMP notes that the MAH did not choose to study the potential impact of NNRTI mutations associated with none to moderate impact on the doravirine in vitro susceptibility in study P018 where that could have been done (darunavir + ritonavir being control agent). Very limited data was presented on outcomes in patients with baseline virus harbouring 2 common mutations, K103N (8 patients), G190A (2 patients), whereof 8 stayed within the study for 48 weeks. This data is too limited to clear this issue.

Therefore, the CHMP is of the opinion that the available efficacy data support an approval of:

- doravirine (single agent) as part of treatment of patients infected with HIV-1, without past or present evidence of NNRTI resistance (including prior failure with an NNRTI-based regimen);

- the fixe dose product, doravirine/tenofovir disoproxil/lamivudine, for the treatment of patients infected with HIV-1, without past or present evidence of resistance to the NNRTI class, tenofovir or lamivudine.

2.8. Clinical safety

Doravirine (DOR, also known as MK-1439) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by the Applicant as a once-daily (QD) oral treatment for human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adults aged 18 years and older. It is being developed as both the single agent DOR (100 mg) and as a fixed-dose combination (FDC) with lamivudine (3TC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg) (also known as MK-1439A but hereafter referred to as DOR/3TC/TDF).

DOR (in combination with other antiretroviral medicinal products) and DOR/3TC/TDF are being developed in a hybrid clinical development program that includes mutually supportive Phase 2 and Phase 3 trials of the DOR single entity and DOR/3TC/TDF.

Patient exposure

The trials supporting this Application and contributing data to this Summary of Clinical Safety include 36 Phase 1 trials, 1 Phase 2b dose-ranging trial (P007), and 2 Phase 3 trials (P018 and P021). A total of 1657 subjects received at least 1 dose of DOR or DOR/3TC/TDF in these trials.

The subjects are included as follows:

- 678 subjects in 36 Phase 1 trials.
  - Of the 678 subjects, 650 were healthy subjects. Other subject populations included 12 subjects infected with HIV-1, 8 subjects with moderate hepatic impairment, and 8 subjects with severe renal impairment.
- 232 subjects in P007, a Phase 2 trial that was conducted as a 2-part dose-ranging trial in treatment-naïve HIV-1 infected subjects.
  - Part I: 166 subjects received DOR (in QD doses of 25 mg [40 subjects], 50 mg [43 subjects], 100 mg [42 subjects], and 200 mg [41 subjects]) and 42 subjects received efavirenz (EFV), each in combination with open label emtricitabine (FTC)/TDF (supplied as TRUVADA™).
  - Part II: After dose selection, Part I subjects who were in the DOR 25 mg, 50 mg and 200 mg dose treatment groups who continued in the trial were switched to the 100 mg dose of DOR at their next planned study visit between Week 36 and Week 72, while maintaining the study blind. An additional 132 subjects were randomized (66 in each treatment group) and received treatment with DOR 100 mg QD and EFV in combination with FTC/TDF.
- 747 subjects in two Phase 3 trials, P018 and P021 (treatment-naïve HIV-1 infected subjects).
  - Safety follow-up in both trials through Week 48 is provided to support this Application. The trials are ongoing to evaluate long term safety and efficacy through Week 96. These two international, multicentre, trials were conducted at different investigation sites. Out of 125 participating sites in P018 and 126 participating sites in P021, there were only 39 sites that participated in both trials.
  - P018 is a Phase 3, multicentre, double-blind, randomized, active comparator controlled trial to evaluate the safety and efficacy of DOR 100 mg QD versus darunavir 800 mg QD plus ritonavir 100 mg QD (DRV+r), each in combination with FTC/TDF (supplied as TRUVADA™) or

abacavir (ABC)/3TC (supplied as either EPZICOM™ or KIVEXA™). A total of 766 treatment-naïve HIV-1 infected subjects received treatment (383 in the DOR treatment group, 383 in the DRV+r treatment group).

- P021 is a Phase 3, multicentre, double-blind, randomized, active comparator controlled clinical trial to evaluate the safety and efficacy of DOR/3TC/TDF QD versus EFV/FTC/TDF (supplied as ATRIPLA™) QD. A total of 728 treatment-naïve HIV-1 infected subjects received treatment (364 in the DOR/3TC/TDF treatment group, 364 in the EFV/FTC/TDF treatment group).

Limited preliminary safety data are available from other ongoing trials, including 2 Phase 2 (P028, P030) and 1 Phase 3 (P024) trials. Data from these trials are not included in the individual safety analyses or integrated analysis of this application, the only reported data are narratives of adverse events (AEs) leading to discontinuation, serious AEs, and deaths.

- P028 is a Phase 2b trial to evaluate a switch from EFV/FTC/TDF (supplied as ATRIPLA™ or generic versions of this FDC) or its components [EFV, FTC plus TDF) to DOR/3TC/TDF in virologically-suppressed, HIV-1 infected subjects for a total duration of 36 weeks (base study). All subjects who complete the base study are eligible for the study extension and, if they provide consent, will receive open-label DOR/3TC/TDF for another 96 weeks. There are two treatment groups. Subjects were assigned randomly in a 1:1 ratio to either the Immediate Switch Group or to the Deferred Switch Group.
  - Immediate Switch Group: Immediate Switch (at Study Day 1) from a baseline regimen of EFV/FTC/TDF or its components to DOR/3TC/TDF (+ a placebo matched to EFV/FTC/TDF to maintain blinding) for 12 weeks followed by treatment with open-label DOR/3TC/TDF for an additional 12 weeks.
  - Deferred Switch Group: Subjects to receive EFV/FTC/TDF (+ a placebo matched to DOR/3TC/TDF to maintain blinding) for the first 12 weeks of the study followed by treatment with open-label DOR/3TC/TDF for 24 weeks.
- P030 is a Phase 2 trial to evaluate the safety and efficacy of DOR/3TC/TDF in antiretroviral treatment-naïve subjects with HIV-1 infection with selected NNRTI transmitted resistance mutations. The trial includes a 96 week base study and a 96 week trial extension to collect long-term efficacy and safety data with DOR/3TC/TDF.
- P024 is a Phase 3 trial to evaluate a switch from a baseline regimen of a boosted protease inhibitor (PI), NNRTI, or integrase inhibitor based regimen to DOR/3TC/TDF in virologically-suppressed, HIV 1-infected subjects for 48 weeks (base study). All subjects who complete the base study are eligible for the study extension to receive open-label DOR/3TC/TDF for an additional 96 weeks. Subjects were assigned randomly in a 2:1 ratio to either an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or a delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group).

Table 30 Summary of Subjects who Received Doravirine (as either DOR or DOR/3TC/TDF) in the Clinical Development Program, All Trials (Completed & Ongoing)

	Subjects Who Received DOR or DOR/3TC/TDF (N)[a]
Phase 1	**678**
Phase 2	**261**
P007 – Total	232
(P007 100 mg only) [b]	(108)
P028[c]	19
P030[c]	10
Phase 3	**1320**
P018	383
P021	364
P024[c]	573
Total Overall Clinical Program	**2259**
Treatment-naive HIV-1 Subjects	1593
Total in P007, P018, P021 (Integrated Safety Populations)	**979**
DOR 100 mg only	615
DOR/3TC/TDF	364

a. Subjects who received ≥1 of any dose of doravirine as either DOR or DOR/3TC/TDF.
b. Subjects who received 100 mg in Part I/Part II combined
c. Studies are ongoing, safety narratives provided for subjects who experienced an SAE(s) or discontinued due to an AE are included in the application.

Abbreviations: AE = adverse event; DOR = doravirine; DOR/3TC/TDF = doravirine/ lamivudine/ tenofovir disoproxil fumarate; HIV-1= Human Immunodeficiency Virus type 1; SAE = serious AE

Table 31 Last Patient Last Visit/ Data Cut-off Date and Database Lock Dates for Phase 2/3 Trials

Trial	**Last Patient Last Visit Date/ Data Cutoff Date**	**Database Lock Date**
P007 Week 96 analysis	22-Mar-2016	12-Aug-2016 (Week 96)
P018 Week 48 analysis	29-Sep-2016	23-Nov-2016
P021 Week 48 analysis	20-Mar-2017	26-Apr-2017
P024	20-Mar-2017	05-May-2017
P028	20-Mar-2017	03-May-2017
P030	20-Mar-2017	03-May-2017

P007: Last subject last visit (LSLV) date is the last visit of last subject

P018 and P021: Last subject's last visit for primary endpoint analysis

P024, P028 and P030: Data cutoff date of 20-Mar-17 is used as the cut off for events in scope occurring on or before that date.

Patient groups not included in the clinical studies include:

- Patients below 18 years of age
- Pregnant and lactating women
- Patients treated for hepatitis B with an agent that is active against HIV-1

- Patients with liver cirrhosis or Child-Turcott Pugh score of >9
- Patients with severe renal impairment

Adverse events

The focus of this safety section is the safety outcomes in the phase 3 studies. However, phase II subjects receiving the final 100 mg doravirine dose are included in the integrated safety pools and some comments are also given on the safety findings in the dose finding phase II study.

Study P017

This was a phase I single dose trial to assess the effect of MK-1439 on QTc Interval in healthy adult volunteers. Subjects participated in 3 treatment periods and received a 1200 mg supra-therapeutic dose of oral MK-1439, 400 mg oral moxifloxacin and placebo in a randomized sequence. It was concluded that MK-1439 does not prolong the QTc interval to a clinically relevant degree, as the true mean difference (MK-1439 – placebo) in change from baseline was less than 10 msec. Assay sensitivity was affirmed by significant QTc changes observed in relation to moxifloxacin.

Study P007

In Part I of P007, the overall safety profile at Week 24 was similar for each of the DOR groups. No evidence of dose related toxicity was observed. Drug-related AEs were reported for a lower proportion of subjects in each of the DOR dose groups (range: 16.7% to 46.5% and 36.7% combined) compared with EFV (57.1%). Overall, the proportion of subjects who discontinued due to drug-related AEs was low (range: 0 to 4.7% for individual doses and 2.4% for DOR combined versus 4.8% for EFV).

At Week 96, the proportion of subjects with 1 or more AEs was comparable across the individual DOR treatment groups, and between the DOR Combined treatment group (91.4%) and the EFV treatment group (96. 3%).

There were no obvious correlations between doravirine dose and the frequency of overall or specific AEs. AEs related to skin and subcutaneous tissue disorders were only seen in the 100 mg and 200 mg groups, but numbers are too limited to allow any conclusion. In comparison to EFV, the frequency of dizziness was clearly lower in all doravirine groups.

Table 32 Subjects With Drug-Related Adverse Events - Overall: Related to Blinded Therapy With Doravirine or Efavirenz or Open-Label TRUVADA™ (Incidence ≥5% in One or More Treatment Groups) by System Organ Class, Part I / II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96), All Subjects as Treated (P007)

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	40		43		108		41		232		108		340	
With one or more drug-related adverse events	18	(45.0)	21	(48.8)	38	(35.2)	19	(46.3)	96	(41.4)	63	(58.3)	159	(46.8)
With no drug-related adverse events	22	(55.0)	22	(51.2)	70	(64.8)	22	(53.7)	136	(58.6)	45	(41.7)	181	(53.2)
Gastrointestinal disorders	6	(15.0)	8	(18.6)	12	(11.1)	7	(17.1)	33	(14.2)	20	(18.5)	53	(15.6)
Diarrhoea	4	(10.0)	1	(2.3)	1	(0.9)	2	(4.9)	8	(3.4)	7	(6.5)	15	(4.4)
Nausea	1	(2.5)	4	(9.3)	8	(7.4)	4	(9.8)	17	(7.3)	7	(6.5)	24	(7.1)
General disorders and administration site conditions	4	(10.0)	4	(9.3)	4	(3.7)	6	(14.6)	18	(7.8)	12	(11.1)	30	(8.8)
Fatigue	2	(5.0)	4	(9.3)	4	(3.7)	5	(12.2)	15	(6.5)	5	(4.6)	20	(5.9)

Table 33 Subjects With Drug-Related Adverse Events - Overall:Related to Blinded Therapy With Doravirine or Efavirenz or Open-Label TRUVADA™ (Incidence ≥5% in One or More Treatment Groups) by System Organ Class, Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96), All Subjects as Treated

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	4	(10.0)	8	(18.6)	12	(11.1)	5	(12.2)	29	(12.5)	38	(35.2)	67	(19.7)
Dizziness	1	(2.5)	2	(4.7)	8	(7.4)	2	(4.9)	13	(5.6)	29	(26.9)	42	(12.4)
Headache	0	(0.0)	1	(2.3)	3	(2.8)	3	(7.3)	7	(3.0)	6	(5.6)	13	(3.8)
Somnolence	2	(5.0)	0	(0.0)	1	(0.9)	0	(0.0)	3	(1.3)	1	(0.9)	4	(1.2)
Psychiatric disorders	7	(17.5)	14	(32.6)	22	(20.4)	5	(12.2)	48	(20.7)	34	(31.5)	82	(24.1)
Abnormal dreams	3	(7.5)	9	(20.9)	6	(5.6)	3	(7.3)	21	(9.1)	16	(14.8)	37	(10.9)
Insomnia	1	(2.5)	3	(7.0)	7	(6.5)	2	(4.9)	13	(5.6)	3	(2.8)	16	(4.7)
Nightmare	1	(2.5)	1	(2.3)	6	(5.6)	0	(0.0)	8	(3.4)	9	(8.3)	17	(5.0)
Sleep disorder	1	(2.5)	2	(4.7)	5	(4.6)	0	(0.0)	8	(3.4)	7	(6.5)	15	(4.4)
Reproductive system and breast disorders	2	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	3	(2.8)	5	(1.5)
Skin and subcutaneous tissue disorders	0	(0.0)	0	(0.0)	5	(4.6)	2	(4.9)	7	(3.0)	14	(13.0)	21	(6.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that

system organ class.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Note: Both doravirine and efavirenz were administered with TRUVADA.

Study P018

In P018, similar proportions of subjects reported AEs in the DOR group (80.2%) and in the DRV+r group (78.3%). The majority of these events were mild to moderate in intensity and were considered by the investigator to be unrelated to study drug. The proportions of subjects who reported an SAE or a drug-related AE were similar for the 2 treatment groups.

Table 34 Analysis of Adverse Event Summary Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	307	(80.2)	300	(78.3)	1.8 (-3.9, 7.6)
with no adverse events	76	(19.8)	83	(21.7)	-1.8 (-7.6, 3.9)
with drug-related[‡] adverse events	117	(30.5)	123	(32.1)	-1.6 (-8.1, 5.0)
with serious adverse events	19	(5.0)	23	(6.0)	-1.0 (-4.4, 2.3)
with serious drug-related adverse events	1	(0.3)	1	(0.3)	0.0 (-1.2, 1.2)
who died	1	(0.3)	0	(0.0)	0.3 (-0.7, 1.5)
discontinued[§] due to an adverse event	6	(1.6)	12	(3.1)	-1.6 (-4.0, 0.6)
discontinued due to a drug-related adverse event	4	(1.0)	8	(2.1)	-1.0 (-3.1, 0.8)
discontinued due to a serious adverse event	1	(0.3)	2	(0.5)	-0.3 (-1.6, 1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(0.3)	-0.3 (-1.5, 0.7)

[†] Based on Miettinen & Nurminen method.

[‡] Determined by the investigator to be related to the drug.

[§] Study medication withdrawn.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Note: DOR 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM/KIVEXA.

The most frequently reported AEs (≥5% of subjects in either treatment group presented in descending order of DOR frequency) were diarrhoea, headache, nausea, upper respiratory tract infection, fatigue, nasopharyngitis, back pain, dizziness, upper abdominal pain, and cough. Diarrhoea was more frequently observed for DRV+r (22.5%) compared with DOR (14.1%) (treatment difference -8.4% [-13.8, -2.9]). In the DOR group, back pain, sleep disorder, cough, and sinus congestion occurred more often. In the DRV+r group, diarrhoea, influenza-like illness, oral candidiasis, hypercholesterolaemia and lethargy occurred more often.

Table 35 Analysis of Subjects With Adverse Events (Incidence ≥4 Subjects in One or More Treatment Groups), Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	307	(80.2)	300	(78.3)	1.8 (-3.9, 7.6)
with no adverse events	76	(19.8)	83	(21.7)	-1.8 (-7.6, 3.9)
Blood and lymphatic system disorders	**12**	**(3.1)**	**15**	**(3.9)**	**-0.8 (-3.6, 1.9)**
Anaemia	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Lymphadenopathy	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Cardiac disorders	**5**	**(1.3)**	**4**	**(1.0)**	**0.3 (-1.5, 2.1)**
Ear and labyrinth disorders	**10**	**(2.6)**	**5**	**(1.3)**	**1.3 (-0.7, 3.6)**
Eye disorders	**4**	**(1.0)**	**6**	**(1.6)**	**-0.5 (-2.5, 1.3)**
Gastrointestinal disorders	**137**	**(35.8)**	**162**	**(42.3)**	**-6.5 (-13.4, 0.4)**
Abdominal discomfort	6	(1.6)	4	(1.0)	0.5 (-1.3, 2.5)
Abdominal distension	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Abdominal pain	12	(3.1)	17	(4.4)	-1.3 (-4.2, 1.5)
Abdominal pain upper	19	(5.0)	10	(2.6)	2.3 (-0.4, 5.3)
Constipation	11	(2.9)	6	(1.6)	1.3 (-0.9, 3.7)
Diarrhoea	54	(14.1)	86	(22.5)	-8.4 (-13.8, -2.9)
Dyspepsia	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Faeces soft	1	(0.3)	6	(1.6)	-1.3 (-3.1, 0.1)
Flatulence	7	(1.8)	11	(2.9)	-1.0 (-3.5, 1.2)
Haemorrhoids	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Nausea	41	(10.7)	46	(12.0)	-1.3 (-5.9, 3.2)
Toothache	7	(1.8)	10	(2.6)	-0.8 (-3.1, 1.4)
Vomiting	12	(3.1)	10	(2.6)	0.5 (-2.0, 3.1)
General disorders and administration site conditions	**62**	**(16.2)**	**57**	**(14.9)**	**1.3 (-3.9, 6.5)**
Asthenia	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Chest pain	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)
Fatigue	31	(8.1)	20	(5.2)	2.9 (-0.7, 6.6)
Influenza like illness	1	(0.3)	7	(1.8)	-1.6 (-3.5, -0.2)
Pyrexia	12	(3.1)	7	(1.8)	1.3 (-1.0, 3.8)
Infections and infestations	**193**	**(50.4)**	**184**	**(48.0)**	**2.3 (-4.7, 9.4)**
Bronchitis	11	(2.9)	18	(4.7)	-1.8 (-4.8, 0.9)
Conjunctivitis	9	(2.3)	5	(1.3)	1.0 (-1.0, 3.3)
Folliculitis	6	(1.6)	3	(0.8)	0.8 (-0.9, 2.7)
Fungal skin infection	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Infections and infestations	**193**	**(50.4)**	**184**	**(48.0)**	**2.3 (-4.7, 9.4)**
Gastroenteritis	11	(2.9)	12	(3.1)	-0.3 (-2.9, 2.3)
Gonorrhoea	4	(1.0)	7	(1.8)	-0.8 (-2.8, 1.1)
Herpes zoster	7	(1.8)	4	(1.0)	0.8 (-1.1, 2.8)
Influenza	10	(2.6)	11	(2.9)	-0.3 (-2.8, 2.2)
Nasopharyngitis	30	(7.8)	39	(10.2)	-2.3 (-6.5, 1.7)
Oral candidiasis	2	(0.5)	9	(2.3)	-1.8 (-3.9, -0.2)
Oral herpes	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Pharyngitis	7	(1.8)	10	(2.6)	-0.8 (-3.1, 1.4)
Pneumonia	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Proctitis gonococcal	5	(1.3)	1	(0.3)	1.0 (-0.3, 2.8)
Respiratory tract infection	8	(2.1)	12	(3.1)	-1.0 (-3.6, 1.3)
Respiratory tract infection viral	8	(2.1)	4	(1.0)	1.0 (-0.8, 3.1)
Rhinitis	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Sinusitis	8	(2.1)	7	(1.8)	0.3 (-1.9, 2.5)
Syphilis	17	(4.4)	13	(3.4)	1.0 (-1.8, 4.0)
Tonsillitis	3	(0.8)	5	(1.3)	-0.5 (-2.3, 1.1)
Tracheobronchitis	1	(0.3)	5	(1.3)	-1.0 (-2.8, 0.3)
Upper respiratory tract infection	36	(9.4)	23	(6.0)	3.4 (-0.4, 7.3)
Urinary tract infection	4	(1.0)	4	(1.0)	0.0 (-1.7, 1.7)
Viral infection	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Injury, poisoning and procedural complications	**17**	**(4.4)**	**20**	**(5.2)**	**-0.8 (-4.0, 2.3)**
Investigations	**43**	**(11.2)**	**37**	**(9.7)**	**1.6 (-2.8, 6.0)**
Alanine aminotransferase increased	8	(2.1)	6	(1.6)	0.5 (-1.5, 2.7)
Aspartate aminotransferase increased	8	(2.1)	8	(2.1)	0.0 (-2.2, 2.2)
Blood creatine phosphokinase increased	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Blood pressure increased	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Lipase increased	1	(0.3)	6	(1.6)	-1.3 (-3.1, 0.1)
Weight increased	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)
Metabolism and nutrition disorders	**22**	**(5.7)**	**31**	**(8.1)**	**-2.3 (-6.1, 1.3)**
Decreased appetite	6	(1.6)	6	(1.6)	0.0 (-2.0, 2.0)
Hypercholesterolaemia	1	(0.3)	7	(1.8)	-1.6 (-3.5, -0.2)
Musculoskeletal and connective tissue disorders	**58**	**(15.1)**	**40**	**(10.4)**	**4.7 (-0.0, 9.5)**
Arthralgia	10	(2.6)	6	(1.6)	1.0 (-1.1, 3.4)
Back pain	21	(5.5)	8	(2.1)	3.4 (0.7, 6.4)
Musculoskeletal pain	6	(1.6)	3	(0.8)	0.8 (-0.9, 2.7)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Musculoskeletal and connective tissue disorders	**58**	**(15.1)**	**40**	**(10.4)**	**4.7 (-0.0, 9.5)**
Myalgia	8	(2.1)	4	(1.0)	1.0 (-0.8, 3.1)
Neck pain	1	(0.3)	4	(1.0)	-0.8 (-2.4, 0.5)
Pain in extremity	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11**	**(2.9)**	**10**	**(2.6)**	**0.3 (-2.2, 2.8)**
Anogenital warts	5	(1.3)	5	(1.3)	0.0 (-1.9, 1.9)
Nervous system disorders	**86**	**(22.5)**	**73**	**(19.1)**	**3.4 (-2.4, 9.2)**
Dizziness	19	(5.0)	15	(3.9)	1.0 (-2.0, 4.1)
Dysgeusia	4	(1.0)	1	(0.3)	0.8 (-0.5, 2.4)
Headache	53	(13.8)	41	(10.7)	3.1 (-1.5, 7.8)
Lethargy	0	(0.0)	6	(1.6)	-1.6 (-3.4, -0.6)
Migraine	4	(1.0)	2	(0.5)	0.5 (-1.0, 2.2)
Paraesthesia	6	(1.6)	1	(0.3)	1.3 (-0.1, 3.1)
Somnolence	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Psychiatric disorders	**51**	**(13.3)**	**51**	**(13.3)**	**0.0 (-4.9, 4.9)**
Abnormal dreams	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Anxiety	4	(1.0)	8	(2.1)	-1.0 (-3.1, 0.8)
Depression	5	(1.3)	8	(2.1)	-0.8 (-2.9, 1.2)
Insomnia	14	(3.7)	18	(4.7)	-1.0 (-4.1, 1.9)
Irritability	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Nightmare	1	(0.3)	5	(1.3)	-1.0 (-2.8, 0.3)
Sleep disorder	10	(2.6)	1	(0.3)	2.3 (0.8, 4.5)
Stress	4	(1.0)	2	(0.5)	0.5 (-1.0, 2.2)
Renal and urinary disorders	**4**	**(1.0)**	**8**	**(2.1)**	**-1.0 (-3.1, 0.8)**
Reproductive system and breast disorders	**16**	**(4.2)**	**10**	**(2.6)**	**1.6 (-1.1, 4.4)**
Menorrhagia	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Respiratory, thoracic and mediastinal disorders	**51**	**(13.3)**	**36**	**(9.4)**	**3.9 (-0.6, 8.5)**
Cough	19	(5.0)	6	(1.6)	3.4 (0.9, 6.2)
Oropharyngeal pain	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Rhinitis allergic	8	(2.1)	5	(1.3)	0.8 (-1.2, 2.9)
Rhinorrhoea	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Sinus congestion	5	(1.3)	0	(0.0)	1.3 (0.3, 3.0)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Skin and subcutaneous tissue disorders	**60**	**(15.7)**	**62**	**(16.2)**	**-0.5 (-5.7, 4.7)**
Acne	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Dermatitis contact	4	(1.0)	1	(0.3)	0.8 (-0.5, 2.4)
Eczema	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Pruritus	3	(0.8)	4	(1.0)	-0.3 (-2.0, 1.4)
Rash	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Rash erythematous	8	(2.1)	5	(1.3)	0.8 (-1.2, 2.9)
Rash macular	3	(0.8)	7	(1.8)	-1.0 (-3.0, 0.7)
Rash maculo-papular	3	(0.8)	4	(1.0)	-0.3 (-2.0, 1.4)
Rash papular	5	(1.3)	9	(2.3)	-1.0 (-3.3, 1.0)
Vascular disorders	**5**	**(1.3)**	**6**	**(1.6)**	**-0.3 (-2.2, 1.6)**
Hypertension	4	(1.0)	4	(1.0)	0.0 (-1.7, 1.7)

[†] Based on Miettinen & Nurminen method.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Note: DOR 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

In line with what is expected from protease inhibitors, diarrhoea is more common in the DRV+r group. Also, DOR seems to have a more favourable lipid profile compared to DRV+r. Cough, sinus congestion and back pain were more common in the DOR group; as similar trends are not seen in the P0021 study (see below) this is likely a random effect rather than causally related to DOR.

Study P021

In study P021, a lower observed proportion of subjects experienced AEs in the DOR/3TC/TDF group (82.7%) compared with the EFV/FTC/TDF group (90.7%) (treatment difference -8.0% [-13.0, -3.1]). A substantially lower proportion of subjects reported drug-related AE(s) in the DOR/3TC/TDF treatment group (31.0%) compared with the EFV/FTC/TDF treatment group (62.9%) (treatment difference -31.9% [-38.6, -24.8]). There were also lower proportions of subjects with discontinuations due to AEs (3.0%, vs.6.6%) (treatment difference -3.6% [-6.9, -0.5]) and discontinuations due to drug related AEs (2.2%, vs. 5.8%) (treatment difference -3.6% [-6.7, -0.8]) in the DOR/3TC/TDF group compared with the EFV/FTC/TDF group.

Table 36 Analysis of Adverse Event Summary Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	301	(82.7)	330	(90.7)	-8.0 (-13.0, -3.1)
with no adverse events	63	(17.3)	34	(9.3)	8.0 (3.1, 13.0)
with drug-related[‡] adverse events	113	(31.0)	229	(62.9)	-31.9 (-38.6, -24.8)
with serious adverse events	13	(3.6)	21	(5.8)	-2.2 (-5.5, 0.9)
with serious drug-related adverse events	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
who died	0	(0.0)	2	(0.5)	-0.5 (-2.0, 0.5)
discontinued[§] due to an adverse event	11	(3.0)	24	(6.6)	-3.6 (-6.9, -0.5)
discontinued due to a drug-related adverse event	8	(2.2)	21	(5.8)	-3.6 (-6.7, -0.8)
discontinued due to a serious adverse event	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
discontinued due to a serious drug-related adverse event	1	(0.3)	3	(0.8)	-0.5 (-2.2, 0.8)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [P021V01MK1439A: analysis-adsl] [P021V01MK1439A: tabulations-aeplus]

The most frequently reported AEs in either treatment group were dizziness, headache, rash, diarrhea, nasopharyngitis, nausea and abnormal dreams. Dizziness was reported more frequently for the EFV/FTC/TDF group compared with the DOR/3TC.TDF group (37.1% vs 8.8%) (treatment difference -28.3% [-34.0, -22.5]).

Dizziness, rash, abnormal dreams, somnolence, dermatitis allergic and vertigo were reported for a higher proportion of subjects in the EFV/FTC/TDF group compared with the DOR/3TC/TDF group. Hypertension was reported more often in the DOR/3TC/TDF group (2.5%) than in the EFV/FTC/TDF group (0.8%).

Table 37 Analysis of Subjects With Adverse Events (Incidence ≥4 Subjects in One or More Treatment Groups), Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	301	(82.7)	330	(90.7)	-8.0 (-13.0, -3.1)
with no adverse events	63	(17.3)	34	(9.3)	8.0 (3.1, 13.0)
Blood and lymphatic system disorders	**15**	**(4.1)**	**12**	**(3.3)**	**0.8 (-2.0, 3.8)**
Lymphadenopathy	6	(1.6)	4	(1.1)	0.5 (-1.3, 2.6)
Cardiac disorders	**6**	**(1.6)**	**4**	**(1.1)**	**0.5 (-1.3, 2.6)**
Ear and labyrinth disorders	**6**	**(1.6)**	**16**	**(4.4)**	**-2.7 (-5.6, -0.3)**
Ear pain	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Vertigo	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Eye disorders	**10**	**(2.7)**	**11**	**(3.0)**	**-0.3 (-2.9, 2.3)**
Gastrointestinal disorders	**120**	**(33.0)**	**136**	**(37.4)**	**-4.4 (-11.3, 2.5)**
Abdominal pain	9	(2.5)	13	(3.6)	-1.1 (-3.8, 1.5)
Abdominal pain lower	1	(0.3)	5	(1.4)	-1.1 (-2.9, 0.3)
Abdominal pain upper	8	(2.2)	2	(0.5)	1.6 (-0.1, 3.8)
Aphthous ulcer	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Colitis	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
Constipation	8	(2.2)	5	(1.4)	0.8 (-1.3, 3.1)
Diarrhoea	39	(10.7)	49	(13.5)	-2.7 (-7.6, 2.0)
Dyspepsia	6	(1.6)	8	(2.2)	-0.5 (-2.8, 1.6)
Food poisoning	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Gastritis	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Gastrooesophageal reflux disease	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Haemorrhoids	5	(1.4)	6	(1.6)	-0.3 (-2.3, 1.7)
Nausea	28	(7.7)	39	(10.7)	-3.0 (-7.3, 1.2)
Toothache	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Vomiting	15	(4.1)	27	(7.4)	-3.3 (-6.9, 0.1)
General disorders and administration site conditions	**56**	**(15.4)**	**53**	**(14.6)**	**0.8 (-4.4, 6.1)**
Asthenia	3	(0.8)	8	(2.2)	-1.4 (-3.6, 0.5)
Fatigue	21	(5.8)	22	(6.0)	-0.3 (-3.8, 3.3)
Influenza like illness	8	(2.2)	9	(2.5)	-0.3 (-2.7, 2.1)
Pyrexia	13	(3.6)	6	(1.6)	1.9 (-0.4, 4.6)
Hepatobiliary disorders	**4**	**(1.1)**	**3**	**(0.8)**	**0.3 (-1.4, 2.1)**
Immune system disorders	**4**	**(1.1)**	**6**	**(1.6)**	**-0.5 (-2.6, 1.3)**

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Infections and infestations	**183**	**(50.3)**	**174**	**(47.8)**	**2.5 (-4.8, 9.7)**
Acute sinusitis	4	(1.1)	3	(0.8)	0.3 (-1.4, 2.1)
Bronchitis	7	(1.9)	11	(3.0)	-1.1 (-3.6, 1.3)
Chlamydial infection	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Conjunctivitis	5	(1.4)	2	(0.5)	0.8 (-0.8, 2.7)
Folliculitis	6	(1.6)	4	(1.1)	0.5 (-1.3, 2.6)
Gastroenteritis	11	(3.0)	9	(2.5)	0.5 (-2.0, 3.2)
Gonorrhoea	6	(1.6)	2	(0.5)	1.1 (-0.5, 3.1)
Herpes virus infection	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Herpes zoster	3	(0.8)	6	(1.6)	-0.8 (-2.8, 0.9)
Influenza	8	(2.2)	11	(3.0)	-0.8 (-3.4, 1.6)
Nasopharyngitis	39	(10.7)	31	(8.5)	2.2 (-2.1, 6.6)
Onychomycosis	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Oral candidiasis	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Oral herpes	4	(1.1)	5	(1.4)	-0.3 (-2.2, 1.6)
Pharyngitis	20	(5.5)	15	(4.1)	1.4 (-1.8, 4.7)
Proctitis chlamydial	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Respiratory tract infection	4	(1.1)	5	(1.4)	-0.3 (-2.2, 1.6)
Respiratory tract infection viral	4	(1.1)	3	(0.8)	0.3 (-1.4, 2.1)
Sinusitis	4	(1.1)	11	(3.0)	-1.9 (-4.4, 0.2)
Subcutaneous abscess	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Syphilis	8	(2.2)	8	(2.2)	0.0 (-2.3, 2.3)
Tonsillitis	14	(3.8)	8	(2.2)	1.6 (-0.9, 4.4)
Upper respiratory tract infection	33	(9.1)	23	(6.3)	2.7 (-1.2, 6.8)
Urethritis	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Urinary tract infection	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Viral infection	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Injury, poisoning and procedural complications	**21**	**(5.8)**	**34**	**(9.3)**	**-3.6 (-7.6, 0.3)**
Contusion	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Ligament sprain	3	(0.8)	4	(1.1)	-0.3 (-2.1, 1.4)
Investigations	**29**	**(8.0)**	**43**	**(11.8)**	**-3.8 (-8.3, 0.5)**
Alanine aminotransferase increased	10	(2.7)	10	(2.7)	0.0 (-2.6, 2.6)
Aspartate aminotransferase increased	9	(2.5)	12	(3.3)	-0.8 (-3.5, 1.7)
Blood alkaline phosphatase increased	0	(0.0)	4	(1.1)	-1.1 (-2.8, -0.0)
Blood creatine phosphokinase increased	7	(1.9)	14	(3.8)	-1.9 (-4.7, 0.6)
Blood pressure increased	5	(1.4)	0	(0.0)	1.4 (0.3, 3.2)
Weight decreased	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Metabolism and nutrition disorders	**26**	**(7.1)**	**35**	**(9.6)**	**-2.5 (-6.6, 1.6)**
Decreased appetite	8	(2.2)	7	(1.9)	0.3 (-2.0, 2.6)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Metabolism and nutrition disorders	**26**	**(7.1)**	**35**	**(9.6)**	**-2.5 (-6.6, 1.6)**
Hypercholesterolaemia	0	(0.0)	5	(1.4)	-1.4 (-3.2, -0.3)
Hypertriglyceridaemia	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Musculoskeletal and connective tissue disorders	**34**	**(9.3)**	**48**	**(13.2)**	**-3.8 (-8.5, 0.8)**
Arthralgia	11	(3.0)	8	(2.2)	0.8 (-1.6, 3.4)
Back pain	9	(2.5)	15	(4.1)	-1.6 (-4.5, 1.0)
Myalgia	4	(1.1)	8	(2.2)	-1.1 (-3.3, 0.9)
Pain in extremity	3	(0.8)	6	(1.6)	-0.8 (-2.8, 0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**15**	**(4.1)**	**12**	**(3.3)**	**0.8 (-2.0, 3.8)**
Anogenital warts	9	(2.5)	8	(2.2)	0.3 (-2.1, 2.7)
Nervous system disorders	**95**	**(26.1)**	**177**	**(48.6)**	**-22.5 (-29.3, -15.6)**
Disturbance in attention	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
Dizziness	32	(8.8)	135	(37.1)	-28.3 (-34.0, -22.5)
Headache	47	(12.9)	45	(12.4)	0.5 (-4.3, 5.4)
Somnolence	12	(3.3)	27	(7.4)	-4.1 (-7.6, -0.9)
Psychiatric disorders	**62**	**(17.0)**	**122**	**(33.5)**	**-16.5 (-22.7, -10.2)**
Abnormal dreams	17	(4.7)	42	(11.5)	-6.9 (-11.0, -3.0)
Anxiety	8	(2.2)	10	(2.7)	-0.5 (-3.1, 1.9)
Depressed mood	4	(1.1)	7	(1.9)	-0.8 (-3.0, 1.1)
Depression	8	(2.2)	12	(3.3)	-1.1 (-3.7, 1.4)
Insomnia	19	(5.2)	32	(8.8)	-3.6 (-7.4, 0.1)
Irritability	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Nightmare	12	(3.3)	17	(4.7)	-1.4 (-4.4, 1.6)
Sleep disorder	4	(1.1)	11	(3.0)	-1.9 (-4.4, 0.2)
Renal and urinary disorders	**8**	**(2.2)**	**7**	**(1.9)**	**0.3 (-2.0, 2.6)**
Reproductive system and breast disorders	**13**	**(3.6)**	**18**	**(4.9)**	**-1.4 (-4.5, 1.6)**
Respiratory, thoracic and mediastinal disorders	**49**	**(13.5)**	**33**	**(9.1)**	**4.4 (-0.2, 9.1)**
Cough	16	(4.4)	14	(3.8)	0.5 (-2.5, 3.6)
Epistaxis	4	(1.1)	1	(0.3)	0.8 (-0.5, 2.5)
Nasal congestion	5	(1.4)	7	(1.9)	-0.5 (-2.7, 1.5)
Oropharyngeal pain	11	(3.0)	6	(1.6)	1.4 (-0.9, 3.9)
Rhinitis allergic	5	(1.4)	1	(0.3)	1.1 (-0.3, 2.9)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Respiratory, thoracic and mediastinal disorders	**49**	**(13.5)**	**33**	**(9.1)**	**4.4 (-0.2, 9.1)**
Rhinorrhoea	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Sinus congestion	4	(1.1)	4	(1.1)	0.0 (-1.8, 1.8)
Skin and subcutaneous tissue disorders	**61**	**(16.8)**	**95**	**(26.1)**	**-9.3 (-15.3, -3.4)**
Alopecia	6	(1.6)	2	(0.5)	1.1 (-0.5, 3.1)
Dermal cyst	4	(1.1)	1	(0.3)	0.8 (-0.5, 2.5)
Dermatitis allergic	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Pruritus	5	(1.4)	6	(1.6)	-0.3 (-2.3, 1.7)
Rash	17	(4.7)	44	(12.1)	-7.4 (-11.6, -3.5)
Rash erythematous	0	(0.0)	4	(1.1)	-1.1 (-2.8, -0.0)
Rash generalised	0	(0.0)	6	(1.6)	-1.6 (-3.6, -0.6)
Rash maculo-papular	3	(0.8)	4	(1.1)	-0.3 (-2.1, 1.4)
Vascular disorders	**14**	**(3.8)**	**7**	**(1.9)**	**1.9 (-0.6, 4.7)**
Hypertension	9	(2.5)	3	(0.8)	1.6 (-0.2, 3.9)

[†] Based on Miettinen & Nurminen method.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Adverse Events of Special Interest - Neuropsychiatric Events

The proportion of participants with AEs in prespecified neuropsychiatric categories by Week 48 were pre-defined safety endpoints in P021. A selected list of neuropsychiatric adverse event categories was examined (mapped according to the supplemental statistical analysis plan), including the following:

- Prespecified Tier-1 categories/primary endpoints: Dizziness, sleep disorders/disturbances, altered sensorium (including disturbance in attention)
- Prespecified Tier-2 categories/secondary endpoints: Depression/suicide/self-injury, psychosis/psychotic disorders.

The Tier 1 safety endpoints were subject to inferential testing for statistical significance with p values and 95% CIs provided for between-group comparisons.

Table 38 Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48 (P021)

	DOR/3TC/TDF QD (N=364)		EFV/FTC/TDF QD (N=364)		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)	2-Sided
	n	%	n	%	Estimate (95% CI)[†]	P-value[‡]
Subjects in population	364		364			
with one or more neuropsychiatric adverse events	86	(23.6)	207	(56.9)	-33.2 (-39.8, -26.4)	
with no neuropsychiatric adverse events	278	(76.4)	157	(43.1)	33.2 (26.4, 39.8)	
Dizziness	32	(8.8)	135	(37.1)	-28.3 (-34.0, -22.5)	<0.001
Sleep Disorders and Disturbances	44	(12.1)	93	(25.5)	-13.5 (-19.1, -7.9)	<0.001
Altered Sensorium	16	(4.4)	30	(8.2)	-3.8 (-7.6, -0.3)	0.033
Depression and Suicide/self-injury	15	(4.1)	24	(6.6)	-2.5 (-5.9, 0.8)	nps[*]
Psychosis and Psychotic Disorders	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)	nps[*]

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method.

[‡] Superiority is tested sequentially for dizziness, sleep disorders and disturbances, and altered sensorium.

[*] Not prespecified for statistical testing.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

The rate of neuropsychiatric events is significantly lower in the DOR group compared to EFV where this is a well-known concern. A statistically significantly lower proportion of Delstrigo-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium. In clinical practice, it is however noted that the EFV tolerability improves after 2-3 weeks and it is of interest to compare not only cumulative rates of neuropsychiatric events but also the incidence and point prevalence over time. Such data was requested by the CHMP during the procedure, table below. With time the difference in prevalence of these side effects are less marked. This data is fully in line with previous data presented for rilpvirine vs efavirenz; around 10% of patients who are treated with efavirenz continue to have neuropsychiatric side effects, mainly dizziness and impact on sleep. To some extent this may also be an adjustment, where the patients get used to remaining side effects, which could be realised would the patient switch to another treatment.

Table 39 Prevalence of Neuropsychiatric Adverse Events P021

Time	AE Category		DOR/3TC/TDF QD (N=364) n	%	EFV/FTC/TDF QD (N=364) n	%
Week 0-12	Total	Prevalence	69	(19.0)	186	(51.1)
	Dizziness	Prevalence	27	(7.4)	128	(35.2)
	Sleep Disorders and Disturbances	Prevalence	33	(9.1)	79	(21.7)
	Altered Sensorium	Prevalence	14	(3.8)	26	(7.1)
	Depression and Suicide/self-injury	Prevalence	7	(1.9)	12	(3.3)
	Psychosis and Psychotic Disorders	Prevalence	1	(0.3)	3	(0.8)
Week 12-24	Total	Prevalence	41	(11.3)	95	(26.1)
	Dizziness	Prevalence	12	(3.3)	42	(11.5)
	Sleep Disorders and Disturbances	Prevalence	21	(5.8)	50	(13.7)
	Altered Sensorium	Prevalence	7	(1.9)	14	(3.8)
	Depression and Suicide/self-injury	Prevalence	10	(2.7)	12	(3.3)
	Psychosis and Psychotic Disorders	Prevalence	0	(0.0)	1	(0.3)
Week 24-36	Total	Prevalence	38	(10.4)	78	(21.4)
	Dizziness	Prevalence	10	(2.7)	35	(9.6)
	Sleep Disorders and Disturbances	Prevalence	19	(5.2)	42	(11.5)
	Altered Sensorium	Prevalence	7	(1.9)	9	(2.5)
	Depression and Suicide/self-injury	Prevalence	9	(2.5)	11	(3.0)
	Psychosis and Psychotic Disorders	Prevalence	0	(0.0)	0	(0.0)
Week 36-48	Total	Prevalence	42	(11.5)	75	(20.6)
	Dizziness	Prevalence	11	(3.0)	34	(9.3)
	Sleep Disorders and Disturbances	Prevalence	22	(6.0)	33	(9.1)
	Altered Sensorium	Prevalence	6	(1.6)	9	(2.5)
	Depression and Suicide/self-injury	Prevalence	10	(2.7)	11	(3.0)
	Psychosis and Psychotic Disorders	Prevalence	0	(0.0)	1	(0.3)

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a category is counted a single time for that category.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

The rate of rash is lower in the DOR group. Similarly to the P018 study, there is a trend towards a higher rate of respiratory, thoracic and mediastinal disorders in the DOR group but random effects cannot be excluded and the causality is not clear.

Serious adverse event and deaths

Study P018

Deaths

One death was reported in P018 by Week 48. A subject in the DOR treatment group experienced an AE recorded as "death." The last reported dose of the study therapy was administered on Day 222. The subject had a medical history of tuberculosis, seizures, hypertension, and HIV-1 infection (diagnosed approximately 1.5 years prior to first dose of study medication). The subject's HIV-1 ribonucleic acid (RNA) at screening was 70,280 copies/mL; it was 73 copies/mL on Study Day 173. On Study Day 222 (the date of the last reported dose), the subject reported dizziness, and subsequently collapsed and died. At the time of the death, the subject's non-serious AEs of mild muscle spasms, mild cough, and mild diarrhea were ongoing; the subject had no reported deterioration of health prior to death. No autopsy was performed. In the opinion of the investigator, the death was not related to study drug.

Serious Adverse Events

By Week 48, 42 (5.5%) of the 766 treated subjects in P018 reported AEs that met the criteria of SAE. The proportion of subjects with SAEs was similar in the DOR treatment group (5.0%) compared with the DRV+r treatment group (6.0%). No single SAE was experienced by more than 2 subjects in the study; the most common SAEs (>1 subject in either treatment group) were anal fistula (1 subject each in both groups), tuberculosis (2 subjects in the DRV+r group), and back pain (2 subjects in the DRV+r group).

Two subjects (1 in each treatment group) experienced SAEs that were considered by the investigator to be drug related SAEs.

- One subject in the DOR treatment group experienced drug-related SAEs of nausea and vomiting. The subject experienced acute kidney injury on Day 1 prior to starting study drug. The subject developed SAEs of nausea and vomiting on Day 4 and was admitted to the hospital on Day 6. The subject was discontinued from the trial on Day 1 due to acute kidney injury. The drug-related SAEs of nausea and vomiting were concurrent, and both resolved without dose interruption or modification on Day 7.
- One subject in the DRV+r treatment group experienced edema peripheral, which resulted in the discontinuation of the subject from the trial after 2 months of treatment.

Study P021

Deaths

In P021, two deaths were reported for the EFV/FTC/TDF treatment group by Week 48. Both were considered by the investigator to be not drug-related.

- One subject in the EFV/FTC/TDF treatment group was found unconscious on Day 58. No autopsy report or death certificate was available; thus, the reported cause of death was not known. It was reported that the subject had not taken study medication on Day 58 and the reported last dose of study medication was on Day 57.
- One subject in the EFV/FTC/TDF treatment group committed suicide on Day 337. The study medication that had been dispensed the previous day was unopened. The subject had experienced traumatic events prior to the suicide and the investigator considered the suicide as not related to study therapy.

Two additional subject deaths were reported as post-treatment (1 in each treatment group) and were considered by the investigator to be not drug-related. These deaths have been displayed as post-treatment since the last recorded dose of study medication was >14 days from the date of death. However, this reflects the subjects' last study visit, and not necessarily the day they took the last dose of study drug.

- One subject in the DOR/3TC/TDF treatment group died on Day 87. The subject was not hospitalized and had last been seen by the investigator on Day 58 at the last scheduled study visit. An autopsy was not performed and the cause of death was reported to be unknown. The last recorded dose of study medication was on Day 58 at the subject's study visit. It is unknown but presumed the subject was taking study medication at the time of death.
- One subject in the EFV/FTC/TDF treatment group died on Day 384. The last recorded dose of study medication was on Day 338 at the subject's last scheduled study visit. It is unknown but presumed the subject was taking study medication at the time of death.

Serious Adverse Events

By Week 48, 34 (4.7%) of the 728 treated subjects in P021 experienced an SAE. The proportion of subjects with SAEs was comparable for the DOR/3TV/TDF treatment group (3.6%) against the EFV/FTC/TDF treatment group (5.8%). No single SAE was experienced by more than 2 subjects in the study. The most commonly reported SAEs (>1 subject in either treatment group) were anogenital warts (2 subjects in the DOR/3TC/TDF group), appendicitis, endometritis and pneumonia (each of these AEs were experienced by 1 subject in the DOR/3TC/TDF group and 1 subject in the EFV/FTC/TDF group).

Five subjects (1 in the DOR/3TC/TDF group and 4 in the EFV/FTC/TDF treatment group) experienced SAEs that were considered by the investigator to be drug related SAEs:

One subject in the DOR/3TC/TDF group experienced 3 drug-related SAEs: asthenia, insomnia, and nightmare. The subject was discontinued from the study on Day 272. The asthenia was resolving and by the data cutoff date, the insomnia had not yet resolved, and the nightmare had resolved with a duration of 3.14 weeks.

Four subjects in the EFV/FTC/TDF group experienced 1 drug-related SAE each as follows:

- Hypertriglyceridaemia (dose interrupted and SAE resolved in 1.54 months)
- Rash generalized (subject discontinued and SAE resolved in 1.14 weeks)
- Rash macular (subject discontinued and SAE resolved in 2.86 weeks)
- Rash maculo-papular (subject discontinued and SAE resolved in 2 weeks)

Overall, the rates of SAEs are comparable between the DOR groups and the respective comparator groups. As expected, a very low death rate during the 48 week period makes any comparison between groups futile.

Laboratory findings

In general, treatment with DOR and DOR/3TC/TDF was well tolerated in the phase 2 and 3 studies. Few Grade 3 or 4 lab abnormalities were reported.

A higher proportion of subjects with Grade 1 and/or Grade 2 values for total bilirubin were observed for the DOR regimen compared with the comparator group. In P007, the proportion of Grade 1 bilirubin elevations was 6.1% of the DOR group and 2.8% in the EFV group. In P018, Grade 1 and/or Grade 2 bilirubin elevations were observed in 6.6% of the DOR group and 1.4% of the DRV+r group. In P021, Grade 1 and/or Grade 2 bilirubin elevations were observed in 6.1% of the DOR group and 0.0% of the EFV group. No subject in either treatment group met the criteria for DILI. The majority of elevations in the DOR group were Grade 1, single, transient elevations, with no pattern of the elevation occurring early or late relative to dosing.

Differences of the DOR regimen were noted versus comparators with respect to fasting lipid test results. For LDL-C, non-HDL-C, total cholesterol, and triglycerides, the differences in the mean change from baseline at Week 48 between DOR and DRV+r and DOR/3TC/TDF and EFV/FTC/TDF favoured the doravirine-treatment group in P018 and P021, respectively. The LDL and non-HDL comparisons were pre-specified and the differences were statistically significant showing superiority for DOR for both parameters.

Study P007

In Part I of study P007, all subjects were assigned to 25, 50, 100 or 200 mg or doravirine for a total of 24 weeks.

Table 40 Subjects With Laboratory Findings that Met Predetermined Criteria (PDLC), Part I (Doravirine All Doses vs. Efavirenz; Weeks 0-24), All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion†	Grade	Number (%) with PDLC					
			Doravirine 25 mg (N=40) n/m(%)	Doravirine 50 mg (N=43) n/m(%)	Doravirine 100 mg (N=42) n/m(%)	Doravirine 200 mg (N=41) n/m(%)	Doravirine Combined (N=166) n/m(%)	Efavirenz 600 mg (N=42) n/m(%)
Hematology Tests								
absolute neutrophil count (10[3]/microL)	0.800 - 1.000	Grade 1	1/40 (2.5)	0/42 (0.0)	1/41 (2.4)	0/40 (0.0)	2/163 (1.2)	1/42 (2.4)
	0.600 - 0.799	Grade 2	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	0.400 - 0.599	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	<0.400	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
hemoglobin (gm/dL)	M- 10.0 - 10.9; F- 9.5 - 10.4	Grade 1	0/40 (0.0)	1/42 (2.4)	0/41 (0.0)	0/40 (0.0)	1/163 (0.6)	0/42 (0.0)
	M- 9.0 - <10.0; F- 8.5 - <9.5	Grade 2	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	1/42 (2.4)
	M- 7.0 - <9.0; F- 6.5 - <8.5	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	M- <7.0; F- <6.5	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
platelet count (10[3]/microL)	100 - <124.999	Grade 1	1/40 (2.5)	0/42 (0.0)	1/41 (2.4)	1/40 (2.5)	3/163 (1.8)	0/42 (0.0)
	50 - <100	Grade 2	0/40 (0.0)	0/42 (0.0)	1/41 (2.4)	0/40 (0.0)	1/163 (0.6)	0/42 (0.0)
	25 - <50	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	1/40 (2.5)	1/163 (0.6)	0/42 (0.0)

platelet count (10[3]/microL)	<25	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
Blood Chemistry Tests								
fasting(non-random) serum LDL-C (mg/dL)	130 - <160	Grade 1	2/39 (5.1)	0/40 (0.0)	0/41 (0.0)	2/38 (5.3)	4/158 (2.5)	5/38 (13.2)
	160 - <190	Grade 2	0/39 (0.0)	0/40 (0.0)	1/41 (2.4)	0/38 (0.0)	1/158 (0.6)	1/38 (2.6)
	≥190	Grade 3	0/39 (0.0)	0/40 (0.0)	0/41 (0.0)	0/38 (0.0)	0/158 (0.0)	0/38 (0.0)
fasting(non-random) serum cholesterol (mg/dL)	200 - <240	Grade 1	3/39 (7.7)	0/42 (0.0)	1/41 (2.4)	2/39 (5.1)	6/161 (3.7)	9/38 (23.7)
	240 - <300	Grade 2	0/39 (0.0)	1/42 (2.4)	0/41 (0.0)	0/39 (0.0)	1/161 (0.6)	1/38 (2.6)
	≥300	Grade 3	0/39 (0.0)	0/42 (0.0)	0/41 (0.0)	0/39 (0.0)	0/161 (0.0)	0/38 (0.0)
fasting(non-random) serum triglyceride (mg/dL)	150 - 300	Grade 1	6/39 (15.4)	1/42 (2.4)	3/41 (7.3)	4/39 (10.3)	14/161 (8.7)	7/38 (18.4)
	>300 - 500	Grade 2	1/39 (2.6)	0/42 (0.0)	1/41 (2.4)	4/39 (10.3)	6/161 (3.7)	3/38 (7.9)
	>500 - 1000	Grade 3	0/39 (0.0)	0/42 (0.0)	0/41 (0.0)	0/39 (0.0)	0/161 (0.0)	0/38 (0.0)
	>1000	Grade 4	0/39 (0.0)	0/42 (0.0)	0/41 (0.0)	0/39 (0.0)	0/161 (0.0)	0/38 (0.0)
fasting(non-random) serum glucose test (mg/dL)	110 - 125	Grade 1	2/39 (5.1)	3/42 (7.1)	2/41 (4.9)	2/39 (5.1)	9/161 (5.6)	3/39 (7.7)
	>125 - 250	Grade 2	0/39 (0.0)	1/42 (2.4)	1/41 (2.4)	0/39 (0.0)	2/161 (1.2)	1/39 (2.6)
	>250 - 500	Grade 3	0/39 (0.0)	0/42 (0.0)	0/41 (0.0)	0/39 (0.0)	0/161 (0.0)	0/39 (0.0)
	>500	Grade 4	0/39 (0.0)	0/42 (0.0)	0/41 (0.0)	0/39 (0.0)	0/161 (0.0)	0/39 (0.0)
total serum bilirubin (mg/dL)	1.1 - <1.6 x ULN	Grade 1	2/40 (5.0)	0/42 (0.0)	0/41 (0.0)	1/40 (2.5)	3/163 (1.8)	0/42 (0.0)
	1.6 - <2.6 x ULN	Grade 2	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	2.6 - <5.0 x ULN	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	≥5.0 x ULN	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>2.5 - 5.0 x Baseline		1/40 (2.5)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	1/163 (0.6)	0/42 (0.0)
	>5.0 - 10.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>10.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>5.0 - 10.0 x Baseline		1/40 (2.5)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	1/163 (0.6)	0/42 (0.0)

direct bilirubin (mg/dL)	>10.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>5.0 - 10.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>10.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>1.3 - 1.8 x ULN or Increase of >0.	Grade 2	1/40 (2.5)	2/42 (4.8)	0/41 (0.0)	2/40 (5.0)	5/163 (3.1)	0/42 (0.0)
	>1.8 - <3.5 x ULN or Increase of 1.	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	≥3.5 x ULN or Inc	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>2.5 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
serum aspartate aminotransferase (IU/L)	1.25 - <2.5 x ULN	Grade 1	4/40 (10.0)	1/42 (2.4)	3/41 (7.3)	3/40 (7.5)	11/163 (6.7)	5/42 (11.9)
	2.5 - <5.0 x ULN	Grade 2	0/40 (0.0)	2/42 (4.8)	0/41 (0.0)	2/40 (5.0)	4/163 (2.5)	1/42 (2.4)
	5.0 - <10.0 x ULN	Grade 3	1/40 (2.5)	1/42 (2.4)	0/41 (0.0)	0/40 (0.0)	2/163 (1.2)	0/42 (0.0)
	≥10.0 x ULN	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)

serum aspartate aminotransferase (IU/L)	>2.5 - 5.0 x Baseline		5/40 (12.5)	0/42 (0.0)	1/41 (2.4)	2/40 (5.0)	8/163 (4.9)	3/42 (7.1)
	>5.0 x Baseline		1/40 (2.5)	3/42 (7.1)	0/41 (0.0)	0/40 (0.0)	4/163 (2.5)	1/42 (2.4)
serum alanine aminotransferase (IU/L)	1.25 - <2.5 x ULN	Grade 1	1/40 (2.5)	3/42 (7.1)	1/41 (2.4)	3/40 (7.5)	8/163 (4.9)	4/42 (9.5)
	2.5 - <5.0 x ULN	Grade 2	0/40 (0.0)	3/42 (7.1)	0/41 (0.0)	0/40 (0.0)	3/163 (1.8)	0/42 (0.0)
	5.0 - <10.0 x ULN	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	≥10.0 x ULN	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>2.5 - 5.0 x Baseline		3/40 (7.5)	2/42 (4.8)	3/41 (7.3)	2/40 (5.0)	10/163 (6.1)	5/42 (11.9)
	>5.0 x Baseline		2/40 (5.0)	2/42 (4.8)	0/41 (0.0)	0/40 (0.0)	4/163 (2.5)	0/42 (0.0)
serum alkaline phosphatase (IU/L)	1.25 - <2.5 x ULN	Grade 1	2/40 (5.0)	1/42 (2.4)	0/41 (0.0)	1/40 (2.5)	4/163 (2.5)	4/42 (9.5)
	2.5 - <5.0 x ULN	Grade 2	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	5.0 - <10.0 x ULN	Grade 3	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	≥10.0 x ULN	Grade 4	0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
	>2.5 - 5.0 x Baseline		0/40 (0.0)	1/42 (2.4)	0/41 (0.0)	0/40 (0.0)	1/163 (0.6)	1/42 (2.4)
	>5.0 x Baseline		0/40 (0.0)	0/42 (0.0)	0/41 (0.0)	0/40 (0.0)	0/163 (0.0)	0/42 (0.0)
serum pancreatic amylase test (IU/L)	1.1 - <1.5 x ULN	Grade 1	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)
	1.5 - <3.0 x ULN	Grade 2	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)
	3.0 - <5.0 x ULN	Grade 3	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)
	≥5.0 x ULN	Grade 4	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)
serum lipase test (IU/L)	1.1 - <1.5 x ULN	Grade 1	3/40 (7.5)	1/42 (2.4)	7/41 (17.1)	1/40 (2.5)	12/163 (7.4)	8/42 (19.0)
	1.5 - <3.0 x ULN	Grade 2	4/40 (10.0)	2/42 (4.8)	2/41 (4.9)	4/40 (10.0)	12/163 (7.4)	4/42 (9.5)
	3.0 - <5.0 x ULN	Grade 3	1/40 (2.5)	1/42 (2.4)	1/41 (2.4)	0/40 (0.0)	3/163 (1.8)	1/42 (2.4)
	≥5.0 x ULN	Grade 4	0/40 (0.0)	0/42 (0.0)	1/41 (2.4)	0/40 (0.0)	1/163 (0.6)	0/42 (0.0)

† For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X. A subject was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULN). Grading is based on DAIDS toxicity criteria.

N=Number of subjects randomized and treated in each treatment group.

n/m = number of subjects with PDLC/number of subjects with baseline and at least one on-treatment value of the laboratory test.

DAIDS=Division of AIDS.

Note: Both doravirine and efavirenz were administered with TRUVADA

In conclusion, the CHMP is of the view that the safety profile of doravirine in part I of the P007 study appeared similar or superior to efavirenz. There is an apparent U-shape in the rates of lipid abnormalities when comparing the doravirine dose arms with higher rates of abnormalities in the 25 mg and 200 mg groups, but given the limited size of the respective dose groups this is likely a random effect rather than a U-shaped correlation.

Study P018

There were no negative trends in haematology or blood chemistry during the 48 week period, apparent on a group level. Proportions of subjects meeting pre-defined levels of change and pre-specified comparisons between study arms are presented below.

Table 41 Study P018, Subjects With Laboratory Findings That Met Predetermined Criteria, Worsening Grade; Weeks 0-48

Criterion[†]	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
HEMATOLOGY						
Neutrophils (10^9/L)						
Grade 1: 0.800 - 1.000	6/379	(1.6)	3/378	(0.8)	9/757	(1.2)
Grade 2: 0.600 - 0.799	1/379	(0.3)	4/378	(1.1)	5/757	(0.7)
Grade 3: 0.400 - 0.599	0/379	(0.0)	1/378	(0.3)	1/757	(0.1)
Grade 4: <0.400	1/379	(0.3)	2/378	(0.5)	3/757	(0.4)
Hemoglobin (g/dL)						
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	7/380	(1.8)	8/378	(2.1)	15/758	(2.0)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	3/380	(0.8)	6/378	(1.6)	9/758	(1.2)
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	1/380	(0.3)	0/378	(0.0)	1/758	(0.1)
Grade 4: Male: <7.0 Female: <6.5	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Platelets (10^9/L)						
Grade 1: 100 - <124.999	3/379	(0.8)	4/376	(1.1)	7/755	(0.9)
Grade 2: 50 - <100	1/379	(0.3)	2/376	(0.5)	3/755	(0.4)
Grade 3: 25 - <50	0/379	(0.0)	0/376	(0.0)	0/755	(0.0)
Grade 4: <25	1/379	(0.3)	0/376	(0.0)	1/755	(0.1)
CHEMISTRY						
Fasting LDL Cholesterol (mg/dL)						
Grade 1: 130 - <160	23/332	(6.9)	34/320	(10.6)	57/652	(8.7)
Grade 2: 160 - <190	1/332	(0.3)	23/320	(7.2)	24/652	(3.7)
Grade 3: ≥190	1/332	(0.3)	9/320	(2.8)	10/652	(1.5)
Fasting Cholesterol (mg/dL)						
Grade 1: 200 - <240	33/335	(9.9)	48/327	(14.7)	81/662	(12.2)
Grade 2: 240 - <300	4/335	(1.2)	32/327	(9.8)	36/662	(5.4)
Grade 3: ≥300	0/335	(0.0)	1/327	(0.3)	1/662	(0.2)
Fasting Triglyceride (mg/dL)						
Grade 1: 150 - 300	41/335	(12.2)	71/327	(21.7)	112/662	(16.9)
Grade 2: >300 - 500	9/335	(2.7)	13/327	(4.0)	22/662	(3.3)
Grade 3: >500 - 1000	2/335	(0.6)	2/327	(0.6)	4/662	(0.6)
Grade 4: >1000	0/335	(0.0)	2/327	(0.6)	2/662	(0.3)

Criterion†	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Fasting Glucose (mg/dL)						
Grade 1: 110 - 125	23/335	(6.9)	26/327	(8.0)	49/662	(7.4)
Grade 2: >125 - 250	7/335	(2.1)	9/327	(2.8)	16/662	(2.4)
Grade 3: >250 - 500	4/335	(1.2)	1/327	(0.3)	5/662	(0.8)
Grade 4: >500	0/335	(0.0)	0/327	(0.0)	0/662	(0.0)
Total Bilirubin (mg/dL)						
Grade 1: 1.1 - <1.6 x ULN	19/380	(5.0)	4/378	(1.1)	23/758	(3.0)
Grade 2: 1.6 - <2.6 x ULN	6/380	(1.6)	1/378	(0.3)	7/758	(0.9)
Grade 3: 2.6 - <5.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Grade 4: ≥5.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>2.5 - 5.0 x Baseline	5/380	(1.3)	1/378	(0.3)	6/758	(0.8)
>5.0 -10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Direct Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	0/380	(0.0)	1/378	(0.3)	1/758	(0.1)
>5.0 - 10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Indirect Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	2/380	(0.5)	0/378	(0.0)	2/758	(0.3)
>5.0 - 10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>10.0 x Baseline	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	1/380	(0.3)	0/378	(0.0)	1/758	(0.1)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	10/380	(2.6)	16/378	(4.2)	26/758	(3.4)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	5/380	(1.3)	10/378	(2.6)	15/758	(2.0)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	1/380	(0.3)	0/378	(0.0)	1/758	(0.1)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	30/380	(7.9)	26/378	(6.9)	56/758	(7.4)
Grade 2: 2.5 - <5.0 x ULN	17/380	(4.5)	12/378	(3.2)	29/758	(3.8)

Criterion†	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Aspartate Aminotransferase (IU/L)						
Grade 3: 5.0 - <10.0 x ULN	2/380	(0.5)	6/378	(1.6)	8/758	(1.1)
Grade 4: ≥10.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>2.5 - 5.0 x Baseline	21/380	(5.5)	15/378	(4.0)	36/758	(4.7)
>5.0 x Baseline	11/380	(2.9)	12/378	(3.2)	23/758	(3.0)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	33/369	(8.9)	27/375	(7.2)	60/744	(8.1)
Grade 2: 2.5 - <5.0 x ULN	10/369	(2.7)	7/375	(1.9)	17/744	(2.3)
Grade 3: 5.0 - <10.0 x ULN	4/369	(1.1)	6/375	(1.6)	10/744	(1.3)
Grade 4: ≥10.0 x ULN	0/369	(0.0)	3/375	(0.8)	3/744	(0.4)
>2.5 - 5.0 x Baseline	27/369	(7.3)	15/375	(4.0)	42/744	(5.6)
>5.0 x Baseline	8/369	(2.2)	13/375	(3.5)	21/744	(2.8)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	3/380	(0.8)	8/378	(2.1)	11/758	(1.5)
Grade 2: 2.5 - <5.0 x ULN	1/380	(0.3)	2/378	(0.5)	3/758	(0.4)
Grade 3: 5.0 - <10.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
Grade 4: ≥10.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)
>2.5 - 5.0 x Baseline	2/380	(0.5)	1/378	(0.3)	3/758	(0.4)
>5.0 x Baseline	0/380	(0.0)	2/378	(0.5)	2/758	(0.3)
Lipase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	20/380	(5.3)	23/378	(6.1)	43/758	(5.7)
Grade 2: 1.5 - <3.0 x ULN	14/380	(3.7)	20/378	(5.3)	34/758	(4.5)
Grade 3: 3.0 - <5.0 x ULN	6/380	(1.6)	6/378	(1.6)	12/758	(1.6)
Grade 4: ≥5.0 x ULN	4/380	(1.1)	3/378	(0.8)	7/758	(0.9)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	22/380	(5.8)	22/378	(5.8)	44/758	(5.8)
Grade 2: 6.0 - <10.0 x ULN	9/380	(2.4)	12/378	(3.2)	21/758	(2.8)
Grade 3: 10.0 - <20.0 x ULN	7/380	(1.8)	7/378	(1.9)	14/758	(1.8)
Grade 4: ≥ 20.0 x ULN	6/380	(1.6)	7/378	(1.9)	13/758	(1.7)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	16/380	(4.2)	16/378	(4.2)	32/758	(4.2)
Grade 2: 1.5 - <3.0 x ULN	8/380	(2.1)	9/378	(2.4)	17/758	(2.2)
Grade 3: 3.0 - <5.0 x ULN	0/380	(0.0)	2/378	(0.5)	2/758	(0.3)
Grade 4: ≥ 5.0 x ULN	0/380	(0.0)	0/378	(0.0)	0/758	(0.0)

†For graded criteria: subjects are counted once per test in the highest grade reported.

For baseline criteria: subjects are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

n = Number of subjects with postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication. Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA or EPZICOM/KIVEXA.

DOR-treated subjects present with higher rates of bilirubin elevation in comparison to the DRV+r study arm. DOR appears to have a more favourable lipid profile with lower rates of LDL, total cholesterol and triglyceride elevations, in comparison to DRV+r. Both issues are further discussed below.

Table 42 Protocol 018: Change From Baseline in Fasting Lipids at Week 48

Treatment	N	Baseline Mean	Change from Baseline at Week 48 Mean Change (SD)	95% CI[†]	Difference Estimates (Doravirine - Darunavir) Difference[‡] 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	326	91.10	-4.51 (20.64)	(-6.76, -2.26)	-14.61 (-18.15, -11.06)	<0.0001
Darunavir/ritonavir 800/100 mg QD	318	91.76	9.92 (27.31)	(6.91, 12.94)		
Fasting Non-HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	113.34	-5.30 (23.28)	(-7.83, -2.78)	-19.34 (-23.33, -15.35)	<0.0001
Darunavir/ritonavir 800/100 mg QD	325	114.44	13.75 (31.08)	(10.36, 17.14)		
Fasting Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	156.92	-1.37 (25.47)	(-4.13, 1.39)	-19.50 (-23.82, -15.17)	nps*
Darunavir/ritonavir 800/100 mg QD	325	157.71	17.90 (33.95)	(14.20, 21.61)		
Fasting Triglyceride (mg/dL)						
Doravirine 100 mg QD	329	111.16	-3.14 (68.81)	(-10.61, 4.32)	-27.87 (-38.71, -17.02)	nps*
Darunavir/ritonavir 800/100 mg QD	325	117.02	21.97 (92.59)	(11.86, 32.07)		
Fasting HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	43.58	3.94 (10.66)	(2.78, 5.09)	-0.15 (-1.75, 1.45)	nps*
Darunavir/ritonavir 800/100 mg QD	325	43.27	4.15 (11.01)	(2.95, 5.36)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

[†] Within group 95% CIs were based on t-distribution.

[‡] The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.

[*] Not pre-specified for statistical testing

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM/KIVEXA.

N = Number of subjects with baseline and at least one postbaseline test result.

The lipid profile of DOR is significantly more favourable than that of DRV+r. However, although these biomarkers (especially LDL) are correlated to cardiovascular disease in subjects with endogenous hypercholesterolaemia and statins have been shown to lower the risk of cardiovascular events, it does not necessarily mean that favourable differences between ART lipid profiles translate to clinical benefit.

Study P021

Similar to the P018 study, there were no trends in overall haematology and blood chemistry up to week 48, apparent on a group level in study P021. Proportions of subjects meeting pre-defined levels of change and pre-specified comparisons between study arms are presented below.

Table 43 Study P021, Subjects With Laboratory Findings That Met Predetermined Criteria, Worsening Grade; Weeks 0-48

Criterion†	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
HEMATOLOGY						
Neutrophils (10^9/L)						
Grade 1: 0.800 - 1.000	2/362	(0.6)	2/359	(0.6)	4/721	(0.6)
Grade 2: 0.600 - 0.799	2/362	(0.6)	3/359	(0.8)	5/721	(0.7)
Grade 3: 0.400 - 0.599	0/362	(0.0)	2/359	(0.6)	2/721	(0.3)
Grade 4: <0.400	3/362	(0.8)	2/359	(0.6)	5/721	(0.7)
Hemoglobin (g/dL)						
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	9/362	(2.5)	6/359	(1.7)	15/721	(2.1)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	3/362	(0.8)	1/359	(0.3)	4/721	(0.6)
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	1/362	(0.3)	1/359	(0.3)	2/721	(0.3)
Grade 4: Male: <7.0 Female: <6.5	0/362	(0.0)	0/359	(0.0)	0/721	(0.0)
Platelets (10^9/L)						
Grade 1: 100 - <124.999	2/359	(0.6)	2/357	(0.6)	4/716	(0.6)
Grade 2: 50 - <100	2/359	(0.6)	0/357	(0.0)	2/716	(0.3)
Grade 3: 25 - <50	0/359	(0.0)	0/357	(0.0)	0/716	(0.0)
Grade 4: <25	0/359	(0.0)	0/357	(0.0)	0/716	(0.0)
CHEMISTRY						
Fasting LDL Cholesterol (mg/dL)						
Grade 1: 130 - <160	15/332	(4.5)	22/309	(7.1)	37/641	(5.8)
Grade 2: 160 - <190	3/332	(0.9)	15/309	(4.9)	18/641	(2.8)
Grade 3: ≥190	1/332	(0.3)	5/309	(1.6)	6/641	(0.9)
Fasting Cholesterol (mg/dL)						
Grade 1: 200 - <240	21/336	(6.3)	44/318	(13.8)	65/654	(9.9)
Grade 2: 240 - <300	2/336	(0.6)	24/318	(7.5)	26/654	(4.0)
Grade 3: ≥300	2/336	(0.6)	1/318	(0.3)	3/654	(0.5)
Fasting Triglyceride (mg/dL)						
Grade 1: 150 - 300	32/336	(9.5)	51/318	(16.0)	83/654	(12.7)
Grade 2: >300 - 500	13/336	(3.9)	20/318	(6.3)	33/654	(5.0)
Grade 3: >500 - 1000	2/336	(0.6)	8/318	(2.5)	10/654	(1.5)
Grade 4: >1000	0/336	(0.0)	0/318	(0.0)	0/654	(0.0)
Fasting Glucose (mg/dL)						

Grade 1: 110 - 125	12/336	(3.6)	13/318	(4.1)	25/654	(3.8)
Grade 2: >125 - 250	6/336	(1.8)	5/318	(1.6)	11/654	(1.7)
Grade 3: >250 - 500	0/336	(0.0)	2/318	(0.6)	2/654	(0.3)
Grade 4: >500	0/336	(0.0)	0/318	(0.0)	0/654	(0.0)
Total Bilirubin (mg/dL)						
Grade 1: 1.1 - <1.6 x ULN	15/363	(4.1)	0/359	(0.0)	15/722	(2.1)
Grade 2: 1.6 - <2.6 x ULN	9/363	(2.5)	0/359	(0.0)	9/722	(1.2)
Grade 3: 2.6 - <5.0 x ULN	1/363	(0.3)	0/359	(0.0)	1/722	(0.1)
Grade 4: ≥5.0 x ULN	1/363	(0.3)	1/359	(0.3)	2/722	(0.3)
>2.5 - 5.0 x Baseline	2/363	(0.6)	0/359	(0.0)	2/722	(0.3)
>5.0 - 10.0 x Baseline	2/363	(0.6)	0/359	(0.0)	2/722	(0.3)
>10.0 x Baseline	1/363	(0.3)	1/359	(0.3)	2/722	(0.3)
Direct Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	1/363	(0.3)	0/359	(0.0)	1/722	(0.1)
>5.0 - 10.0 x Baseline	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)
>10.0 x Baseline	3/363	(0.8)	1/359	(0.3)	4/722	(0.6)
Indirect Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	2/363	(0.6)	0/359	(0.0)	2/722	(0.3)
>5.0 - 10.0 x Baseline	1/363	(0.3)	0/359	(0.0)	1/722	(0.1)
>10.0 x Baseline	1/363	(0.3)	1/359	(0.3)	2/722	(0.3)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	8/363	(2.2)	5/359	(1.4)	13/722	(1.8)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	8/363	(2.2)	3/359	(0.8)	11/722	(1.5)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	0/363	(0.0)	1/359	(0.3)	1/722	(0.1)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	32/363	(8.8)	39/359	(10.9)	71/722	(9.8)
Grade 2: 2.5 - <5.0 x ULN	8/363	(2.2)	9/359	(2.5)	17/722	(2.4)
Grade 3: 5.0 - <10.0 x ULN	1/363	(0.3)	7/359	(1.9)	8/722	(1.1)
Grade 3: 3.0 - <5.0 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)
Grade 4: ≥ 5.0 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)

Criterion†	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Aspartate Aminotransferase (IU/L)						
Grade 4: ≥10.0 x ULN	1/363	(0.3)	2/359	(0.6)	3/722	(0.4)
>2.5 - 5.0 x Baseline	20/363	(5.5)	38/359	(10.6)	58/722	(8.0)
>5.0 x Baseline	6/363	(1.7)	10/359	(2.8)	16/722	(2.2)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	35/363	(9.6)	51/359	(14.2)	86/722	(11.9)
Grade 2: 2.5 - <5.0 x ULN	13/363	(3.6)	14/359	(3.9)	27/722	(3.7)
Grade 3: 5.0 - <10.0 x ULN	2/363	(0.6)	6/359	(1.7)	8/722	(1.1)
Grade 4: ≥10.0 x ULN	1/363	(0.3)	1/359	(0.3)	2/722	(0.3)
>2.5 - 5.0 x Baseline	24/363	(6.6)	50/359	(13.9)	74/722	(10.2)
>5.0 x Baseline	15/363	(4.1)	22/359	(6.1)	37/722	(5.1)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	13/363	(3.6)	29/359	(8.1)	42/722	(5.8)
Grade 2: 2.5 - <5.0 x ULN	0/363	(0.0)	2/359	(0.6)	2/722	(0.3)
Grade 3: 5.0 - <10.0 x ULN	0/363	(0.0)	1/359	(0.3)	1/722	(0.1)
Grade 4: ≥10.0 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)
>2.5 - 5.0 x Baseline	6/363	(1.7)	7/359	(1.9)	13/722	(1.8)
>5.0 x Baseline	0/363	(0.0)	1/359	(0.3)	1/722	(0.1)
Lipase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	18/363	(5.0)	19/359	(5.3)	37/722	(5.1)
Grade 2: 1.5 - <3.0 x ULN	20/363	(5.5)	16/359	(4.5)	36/722	(5.0)
Grade 3: 3.0 - <5.0 x ULN	3/363	(0.8)	5/359	(1.4)	8/722	(1.1)
Grade 4: ≥5.0 x ULN	3/363	(0.8)	2/359	(0.6)	5/722	(0.7)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	19/363	(5.2)	17/359	(4.7)	36/722	(5.0)
Grade 2: 6.0 - <10.0 x ULN	11/363	(3.0)	8/359	(2.2)	19/722	(2.6)
Grade 3: 10.0 - <20.0 x ULN	8/363	(2.2)	7/359	(1.9)	15/722	(2.1)
Grade 4: ≥ 20.0 x ULN	2/363	(0.6)	6/359	(1.7)	8/722	(1.1)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	10/363	(2.8)	14/359	(3.9)	24/722	(3.3)
Grade 2: 1.5 - <3.0 x ULN	3/363	(0.8)	5/359	(1.4)	8/722	(1.1)
Grade 3: 3.0 - <5.0 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)
Grade 4: ≥ 5.0 x ULN	0/363	(0.0)	0/359	(0.0)	0/722	(0.0)

†For graded criteria: subjects are counted once per test in the highest grade reported.

For baseline criteria: subjects are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

n = Number of subjects with postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Similarly to study P018, DOR-treated subjects present with higher rates of bilirubin elevation in comparison to the EFV comparator arm. There is also a slightly higher rate of anaemia in the DOR-group, without any indication of haemolytic background. This issue of bilirubin elevation and the differences in lipid abnormalities are further discussed below.

Table 44 Protocol 021: Change From Baseline in Fasting Lipids at Week 48

Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (DOR/3TC/TDF - EFV/FTC/TDF)	
			Mean Change (SD)	95% CI[†]	Difference[‡] 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	330	92.03	-1.58 (22.12)	(-3.98, 0.81)	-10.01 (-13.53, -6.49)	<0.0001
EFV/FTC/TDF QD	305	90.75	8.74 (25.54)	(5.86, 11.62)		
Fasting Non-HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	115.23	-3.83 (22.59)	(-6.27, -1.40)	-17.02 (-20.89, -13.16)	<0.0001
EFV/FTC/TDF QD	314	114.84	13.26 (28.76)	(10.07, 16.45)		
Fasting Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	157.38	-1.97 (25.67)	(-4.74, 0.79)	-23.44 (-27.57, -19.32)	nps*
EFV/FTC/TDF QD	314	156.21	21.77 (30.74)	(18.35, 25.18)		
Fasting Triglyceride (mg/dL)						
DOR/3TC/TDF QD	333	119.45	-12.40 (67.30)	(-19.66, -5.15)	-35.96 (-47.10, -24.82)	nps*
EFV/FTC/TDF QD	314	122.97	22.01 (93.03)	(11.68, 32.34)		
Fasting HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	42.15	1.86 (9.59)	(0.83, 2.89)	-6.47 (-7.97, -4.96)	nps*
EFV/FTC/TDF QD	314	41.37	8.51 (10.66)	(7.32, 9.69)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

[†] Within group 95% CIs were based on t-distribution.

[‡] The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.

[*] Not pre-specified for statistical testing

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

N = Number of subjects with baseline and at least one postbaseline test result.

DOR-treated subjects present with lower cholesterol and triglyceride levels compared to EFV.

Bilirubin elevation in DOR-treated subjects (P018 and P021)

Cases with graded bilirubin toxicity were summarized and discussed. Overall, around 6% of doravirine treated subjects had graded bilirubin toxicity, vs around 1.5% of those treated with darunavir/ritonavir (P018) and 0% of those treated with efavirenz (P021). Still, the MAH concluded that their analysis of the data does not suggest a causal relationship between DOR and increases in bilirubin. This is endorsed for reasons discussed below. The majority of cases were grade 1 and intermittent, without associated increases in transaminases. When looking at doravirine treated subjects with graded bilirubin toxicity, 2 cases with grade 4 toxicity were clearly linked to other causes (acute hep A, bile duct stone). One case with grade 3 elevation was in fact associated with atazanavir treatment (doravirine had been switched to atazanavir due to treatment failure).For cases with grade 2 elevations (9 with grade 2, another 7 with grade 1 and grade 2), there were co-treatments (various kinds) that had hyperbilirubinaemia as a labeled potential side effect in the majority of cases. The incidence in grade 2 elevations was fairly similar between doravirine and control treatment arms.

Cases with grade 1 elevations (n=44), where the difference in incidence of grade 1 toxicity was clearly higher with doravirine than with control, had for the most an elevation already at screening and in some cases they were taking co-meds during the trial with this potential. Co-meds with potential to increase bilirubin were assessed for this group, with no specific pattern (azithromycin 6 subjects, otherwise for the most 1-2 subjects per co-med listed).

When comparing graded bilirubin toxicity in studies P018 and P021 to that seen in previous pivotal studies of other approved agents, the following is noted:

- The incidence of grade 1 elevations during therapy with other antiretroviral regimens presumably lacking effects on bilirubin levels have been in the order of 5%, i.e similar to that seen with doravirine in the present studies. E.g. in the ECHO study, comparing rilpivirine to efavirenz (ECHO study), the incidence were 4% (rilpivirine) vs 0% (efavirenz). In the SPRING-2 study grade 1 elevations were seen in 4% of patients treated with dolutegravir as well as with raltegravir. In the FLAMINGO study, again 4% had grade 1 elevations during therapy with dolutegravir vs 2% (at least numerically lower) of those treated with darunavir/ritonavir.

With regards to eavirenz, there is a clear evidence for a lowering effect on bilirubin levels. Mezger et al showed that the level of total bilirubin decreased by 30% in healthy volunteers who received efavirenz monotherapy (Curr Ther Res Clin Exp. 2014 ;76: 64-9). Lee et al showed a 40% reduction in levels of bilirubin in a limited number of HIV patients initiating efavirenz therapy (Ann Acad Med Singapore 2012 ;41(12): 559-62). Darunavir + ritonavir is also an inducing regimen, and may consequently lower bilirubin levels, as indicated in the FLAMINGO study.

In summary, the difference in graded bilirubin toxicity between doravirine and control agents seems rather an effect caused by a bilirubin lowering effect of the control agents (efavirenz > darunavir + ritonavir), and where the incidence of bilirubin increases during therapy with doravirine in the phase 3 studies is in line with that seen with other agents deemed to have no effects. The few cases of more severe elevations of bilirubin during therapy with doravirine have been shown to have other very likely causes.

Safety in special populations

There were only a total of 11 subjects aged 65 years and above (of whom 5 received DOR), and none aged 75 years and above. The very limited number of participants aged 65 years and above precludes any relevant analysis of a potential age-related risk of adverse events.

Immunological events

Rash

Although rash was not defined as an ECI for any of the trials included in this application, it is considered to be an important clinical event because rash is commonly associated with use of EFV and other members of the NNRTI class. To evaluate this event, an analysis of all preferred terms related to rash (rash, exfoliative rash, erythematous rash, follicular rash, genital rash, generalized rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, vesicular rash, and viral rash) was performed for a pooled safety dataset (MSP, main safety pool).

A lower proportion of subjects experienced ≥1 AE with a PT related to rash in the Main Combined DOR (7.1%) treatment group compared with the Main Combined EFV treatment group (15.7%). The proportions of subjects with the PT of “rash” were notably lower for the Main Combined DOR (3.0%) treatment group compared with the Main Combined EFV treatment group (11.0%).

In the Main Combined DOR treatment group, 7.1% of subjects experienced AEs with a preferred term related to rash. Most of these were mild (6%) or moderate (1.3%) in intensity; only 1 was considered to be severe (0.1%). Nineteen subjects (2.2%) had their rash events considered to be related to study drug by the investigator. Two subjects (0.2%) were discontinued from the study due to the event of rash.

In the Main DRV+r treatment group 8.4% of subjects experienced AEs with a PT related to rash. Most of these were mild (6.8%) or moderate (1.3%). Ten subjects (2.6%) had their rash events considered to be related to study drug by the investigator. One subject (0.2%) discontinued from the study due to the event of rash.

In the Main Combined EFV treatment group, a higher proportion of subjects (15.7%) experienced AEs with a PT related to rash, compared to the Main Combined DOR. Most of these were mild (9.3%) or moderate (5.5%) in intensity. Four subjects (2.9%) had events of severe intensity. Forty eight subjects (10.2%) had rash events considered to be related to study drug by the investigator. Ten subjects (2.1%) were discontinued from the study due to the event of rash.

Table 45 Rash, Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined) Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	61	(7.1)	32	(8.4)	74	(15.7)
with no adverse events	794	(92.9)	351	(91.6)	398	(84.3)
Infections and infestations	**3**	**(0.4)**	**1**	**(0.3)**	**1**	**(0.2)**
Rash pustular	2	(0.2)	1	(0.3)	0	(0.0)
Viral rash	1	(0.1)	0	(0.0)	1	(0.2)
Reproductive system and breast disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Genital rash	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**57**	**(6.7)**	**32**	**(8.4)**	**73**	**(15.5)**
Exfoliative rash	0	(0.0)	0	(0.0)	1	(0.2)
Rash	26	(3.0)	6	(1.6)	52	(11.0)
Rash erythematous	8	(0.9)	5	(1.3)	4	(0.8)
Rash follicular	2	(0.2)	2	(0.5)	0	(0.0)
Rash generalised	4	(0.5)	0	(0.0)	7	(1.5)
Rash macular	3	(0.4)	7	(1.8)	3	(0.6)
Rash maculo-papular	6	(0.7)	4	(1.0)	4	(0.8)
Rash papular	7	(0.8)	9	(2.3)	1	(0.2)
Rash pruritic	2	(0.2)	0	(0.0)	2	(0.4)
Rash vesicular	1	(0.1)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Main Combined DOR: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.

Main Combined EFV: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

The frequency of study subjects presenting with rash is similar in the DOR och DRV+r groups; both clearly lower than the EFV group. Rash is a well-known adverse event in EFV-treated subjects, but is usually manageable without discontinuing treatment and disappears over time.

Immune Reconstitution Syndrome

In the MSP, 14 subjects (<1% of the MSP) experienced at least 1 AE identified by the investigator as probably related to IRIS. A similar proportion of subjects were observed in all three treatment groups (Main Combined DOR 0.5%, Main DRV+r 1.8%, and Main Combined EFV 0.8%).

Three subjects had AEs associated with IRIS that met the criteria to be considered SAE: tuberculosis (1 subject in the Main Combined DOR group), tuberculosis of central nervous system (1 subject in the Main Combined DOR group), and meningitis tuberculosis (1 subject in the Main Combined DOR group). Each of these events were not considered to be true cases of IRIS by the investigator.

Table 46 Immune Reconstitution Syndrome, P018 and P021 Combined, Weeks 0-48

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Subjects in population	747		383		364	
with one or more adverse events	4	(0.5)	7	(1.8)	3	(0.8)
with no adverse events	743	(99.5)	376	(98.2)	361	(99.2)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Lymphadenopathy	0	(0.0)	1	(0.3)	0	(0.0)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Gastrointestinal disorder	0	(0.0)	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Pyrexia	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Hepatitis	1	(0.1)	0	(0.0)	0	(0.0)
Infections and infestations	**1**	**(0.1)**	**5**	**(1.3)**	**3**	**(0.8)**
Acute sinusitis	0	(0.0)	0	(0.0)	1	(0.3)
Folliculitis	0	(0.0)	1	(0.3)	0	(0.0)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.3)
Hepatitis B	0	(0.0)	1	(0.3)	0	(0.0)
Herpes simplex	1	(0.1)	0	(0.0)	0	(0.0)
Herpes zoster	0	(0.0)	0	(0.0)	1	(0.3)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Molluscum contagiosum	0	(0.0)	1	(0.3)	0	(0.0)
Oral herpes	1	(0.1)	0	(0.0)	0	(0.0)
Tuberculosis	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eczema	0	(0.0)	1	(0.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eosinophilic pustular folliculitis	1	(0.1)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

AIDS-Defining Conditions

Seven subjects (<1% of the MSP) in the MSP experienced ≥1 AE identified as related to an AIDS-defining condition. None of the AEs were considered to be drug-related.

Of the 2 subjects in the Main DOR group, 1 subject had a high grade B-cell unclassifiable lymphoma and 1 subject had Kaposi's sarcoma. Of the 4 subjects in the Main DRV+r group, 3 had tuberculosis and 1 had

both meningitis tuberculosis and tuberculosis of the central nervous system. One subject in the Main Combined EFV group had cytomegalovirus infection. With the exception of the cases of tuberculosis and the cytomegalovirus infection, all of these events were classified as SAEs.

Table 47 AIDS Defining Condition, Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined), Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
with one or more adverse events	2	(0.2)	4	(1.0)	1	(0.2)
with no adverse events	853	(99.8)	379	(99.0)	471	(99.8)
Infections and infestations	**0**	**(0.0)**	**4**	**(1.0)**	**1**	**(0.2)**
Cytomegalovirus infection	0	(0.0)	0	(0.0)	1	(0.2)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis	0	(0.0)	3	(0.8)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**
B-cell unclassifiable lymphoma high grade	1	(0.1)	0	(0.0)	0	(0.0)
Kaposi's sarcoma	1	(0.1)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Main Combined DOR: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.

Main Combined EFV: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

The rates of IRIS and AIDS-defining conditions were similar between DOR, EFV and DRV+r groups. The very low number of total events precludes any comparison of subgroups or individual types of events.

Safety related to drug-drug interactions and other interactions

There were 16 Phase 1 trials conducted to investigate potential drug-drug interactions (DDI) with DOR. Across all DDI trials, the safety profile was similar to that observed when DOR was not co-administered with another medication.

Table 48 Subjects With Drug-related Adverse Events (Incidence ≥5% in One or More Treatment Groups)

	MK-1439 alone		MK-1439A alone		MK-1439 + MK-1439A		MK-1439 + Other	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	578		101		664		167	
with one or more adverse events	106	(18.3)	28	(27.7)	134	(20.2)	31	(18.6)
with no adverse events	472	(81.7)	73	(72.3)	530	(79.8)	136	(81.4)
Gastrointestinal disorders	**31**	**(5.4)**	**7**	**(6.9)**	**38**	**(5.7)**	**9**	**(5.4)**
Investigations	**3**	**(0.5)**	**5**	**(5.0)**	**8**	**(1.2)**	**2**	**(1.2)**
Nervous system disorders	**68**	**(11.8)**	**20**	**(19.8)**	**88**	**(13.3)**	**15**	**(9.0)**
Headache	42	(7.3)	8	(7.9)	50	(7.5)	10	(6.0)
Somnolence	23	(4.0)	9	(8.9)	32	(4.8)	3	(1.8)

Only CYP3A modulators have the potential to affect the exposure of DOR to a clinically meaningful extent. Moderate and strong inhibitors are expected to increase DOR AUC ~2 to 3 fold.

Based on the safety and tolerability data from the Phase 1 trials, the use of strong inhibitors was permitted in Phase 3 trials. Supporting data include Phase 1 trials where single doses as high as 1200 mg and multiple once-daily doses as high as 750 mg were administered to subjects without any apparent safety issues. Other supporting data include the DDI trials with strong inhibitors (P002 and P010) and preclinical safety margins that provided at least a 3-fold exposure multiple over the increased DOR exposure when co-administered with strong inhibitors.

Concomitant use of strong and moderate CYP3A inducers is likely to reduce DOR PK to a clinically meaningful extent, which has the potential to affect efficacy of DOR but without impact on safety.

Clinical AE summary and counts tables were reviewed for subgroups based on concomitant use (for at least 7 days at any time during DOR treatment) of moderate or strong CYP3A inhibitors for subjects in the Main Combined DOR treatment group in the MSP. There were fewer subjects with concomitant use of moderate or strong CYP3A inhibitors (N=67) compared to the subjects without concomitant use of moderate or strong CYP3A inhibitors (N=788); this difference should be considered in the analysis and interpretation of data in these subgroups. Of the 67 subjects who were co-administered moderate or strong CYP3A inhibitors, 8 received co-administration after the initial 48-week period. The safety profile for these subjects while co-administered moderate or strong CYP3A inhibitors was similar to subjects without concomitant use of moderate or strong CYP3A inhibitors. Concomitant use of moderate or strong CYP3A inhibitors did not appear to affect the incidence of AEs, drug-related AEs, SAEs, deaths, or discontinuations due to AEs.

Table 49 Subjects With Adverse Events by Concomitant Use of Moderate or Strong CYP3A4 Inhibitor (Incidence ≥ 2% in Any Column), Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined), Weeks 0-48

	Main Combined DOR			
	With CYP3A4 Inhibitor Use		Without CYP3A4 Inhibitor Use	
	n	(%)	n	(%)
Subjects in population	67		788	
with one or more adverse events	66	(98.5)	635	(80.6)
with no adverse events	1	(1.5)	153	(19.4)
Blood and lymphatic system disorders	**6**	**(9.0)**	**24**	**(3.0)**
Lymphadenopathy	3	(4.5)	10	(1.3)
Cardiac disorders	**2**	**(3.0)**	**13**	**(1.6)**
Ear and labyrinth disorders	**2**	**(3.0)**	**17**	**(2.2)**
Eye disorders	**3**	**(4.5)**	**14**	**(1.8)**
Ocular hyperaemia	2	(3.0)	1	(0.1)
Gastrointestinal disorders	**37**	**(55.2)**	**261**	**(33.1)**
Abdominal pain	4	(6.0)	21	(2.7)
Abdominal pain upper	3	(4.5)	26	(3.3)
Aphthous ulcer	2	(3.0)	3	(0.4)
Constipation	3	(4.5)	18	(2.3)
Diarrhoea	17	(25.4)	89	(11.3)
Dyspepsia	2	(3.0)	14	(1.8)
Gastritis	2	(3.0)	5	(0.6)
Nausea	13	(19.4)	68	(8.6)
Proctalgia	3	(4.5)	2	(0.3)
Vomiting	4	(6.0)	29	(3.7)
General disorders and administration site conditions	**11**	**(16.4)**	**120**	**(15.2)**
Fatigue	3	(4.5)	54	(6.9)
Pyrexia	5	(7.5)	24	(3.0)
Infections and infestations	**48**	**(71.6)**	**388**	**(49.2)**
Abdominal abscess	2	(3.0)	0	(0.0)
Bronchitis	4	(6.0)	17	(2.2)
Conjunctivitis	3	(4.5)	16	(2.0)
Fungal skin infection	2	(3.0)	7	(0.9)
Gastroenteritis	3	(4.5)	26	(3.3)
Herpes zoster	5	(7.5)	10	(1.3)
Influenza	1	(1.5)	19	(2.4)
Nasopharyngitis	8	(11.9)	73	(9.3)

	Main Combined DOR			
	With CYP3A4 Inhibitor Use		Without CYP3A4 Inhibitor Use	
	n	(%)	n	(%)
Infections and infestations	**48**	**(71.6)**	**388**	**(49.2)**
Onychomycosis	2	(3.0)	5	(0.6)
Oral candidiasis	5	(7.5)	1	(0.1)
Oropharyngeal gonococcal infection	2	(3.0)	2	(0.3)
Pharyngitis	5	(7.5)	26	(3.3)
Proctitis gonococcal	2	(3.0)	7	(0.9)
Sinusitis	2	(3.0)	14	(1.8)
Syphilis	0	(0.0)	27	(3.4)
Tonsillitis	0	(0.0)	17	(2.2)
Tooth infection	2	(3.0)	2	(0.3)
Upper respiratory tract infection	5	(7.5)	73	(9.3)
Urethritis	3	(4.5)	8	(1.0)
Urinary tract infection	3	(4.5)	4	(0.5)
Viral infection	2	(3.0)	9	(1.1)
Injury, poisoning and procedural complications	**7**	**(10.4)**	**43**	**(5.5)**
Investigations	**8**	**(11.9)**	**69**	**(8.8)**
Alanine aminotransferase increased	1	(1.5)	17	(2.2)
Aspartate aminotransferase increased	2	(3.0)	15	(1.9)
Blood creatine phosphokinase increased	2	(3.0)	14	(1.8)
Metabolism and nutrition disorders	**5**	**(7.5)**	**49**	**(6.2)**
Musculoskeletal and connective tissue disorders	**12**	**(17.9)**	**97**	**(12.3)**
Arthralgia	2	(3.0)	21	(2.7)
Back pain	4	(6.0)	29	(3.7)
Muscle spasms	2	(3.0)	4	(0.5)
Myalgia	2	(3.0)	14	(1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(4.5)**	**28**	**(3.6)**
Nervous system disorders	**20**	**(29.9)**	**191**	**(24.2)**
Dizziness	5	(7.5)	56	(7.1)
Dysgeusia	2	(3.0)	5	(0.6)
Headache	8	(11.9)	106	(13.5)
Somnolence	3	(4.5)	13	(1.6)

	Main Combined DOR			
	With CYP3A4 Inhibitor Use		Without CYP3A4 Inhibitor Use	
	n	(%)	n	(%)
Psychiatric disorders	**14**	**(20.9)**	**130**	**(16.5)**
Abnormal dreams	5	(7.5)	24	(3.0)
Anxiety	3	(4.5)	12	(1.5)
Insomnia	5	(7.5)	37	(4.7)
Nightmare	1	(1.5)	20	(2.5)
Sleep disorder	1	(1.5)	18	(2.3)
Renal and urinary disorders	**1**	**(1.5)**	**17**	**(2.2)**
Reproductive system and breast disorders	**5**	**(7.5)**	**29**	**(3.7)**
Respiratory, thoracic and mediastinal disorders	**19**	**(28.4)**	**88**	**(11.2)**
Cough	9	(13.4)	28	(3.6)
Oropharyngeal pain	1	(1.5)	19	(2.4)
Rhinitis allergic	3	(4.5)	11	(1.4)
Rhinorrhoea	3	(4.5)	7	(0.9)
Sinus congestion	4	(6.0)	6	(0.8)
Skin and subcutaneous tissue disorders	**21**	**(31.3)**	**120**	**(15.2)**
Acne	2	(3.0)	5	(0.6)
Actinic keratosis	2	(3.0)	0	(0.0)
Dermal cyst	2	(3.0)	3	(0.4)
Pruritus	3	(4.5)	9	(1.1)
Rash	6	(9.0)	20	(2.5)
Rash erythematous	2	(3.0)	6	(0.8)
Rash papular	2	(3.0)	5	(0.6)
Seborrhoeic dermatitis	2	(3.0)	2	(0.3)
Vascular disorders	**2**	**(3.0)**	**21**	**(2.7)**

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Main Combined DOR: Doravirine 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

Main DRV+r: Darunavir/ritonavir 800/100 mg administered with FTC/TDF or ABC/3TC in P018.

Main Combined EFV: Efavirenz 600 mg administered with FTC/TDF in P007, or fixed dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

The proportions of subjects with diarrhea, nausea, and cough were higher in subjects with concomitant use of moderate or strong CYP3A inhibitors compared to the subjects without concomitant use of moderate or strong CYP3A inhibitors (25.4% vs 11.3%, 19.4% vs 8.6%, and 13.4% vs 3.6%, respectively)

The frequency of several types of AEs is higher ($p<0.001$ using Fisher's exact test) in the DOR-treated subjects who comedicate with CYP3A4 inhibitors. There was no specific pattern that indicates that the differences in AE rates are related to increased doravirine exposure. On the contrary, the most types of CYP3A4 inhibitors used in the studies indicate a reverse causality; that the clinical events leading to the need of a co medication also were associated with clinical symptoms that are registered as an adverse event (e.g. bacterial airway infection with cough requiring antibiotic treatment with azithromycin).

To provide further justification that co-treatment with CYP inhibitors does not cause safety problems, the Applicant listed CYP3A4-inhibitors used in the phase 3 studies together and the rate of adverse events was presented separately for those with temporary use of CYP3A4 inhibitors (< 4 weeks) and those with concomitant use for more than 3 months. It was clarified that very few patients had used strong inhibitors; in practice moderate inhibitors had been used in relevant numbers for a safety evaluation. With that said, the AE pattern in those treated for >3 months with such inhibitors were not markedly

different from that seen in all DOR treated patients. It was also shown that in the phase 3 studies there was no tendency of an association to DOR exposure (by AUC quartiles) for the incidence of the most common side effects (Headache, Diarrhea and Nausea). Taken into account that there are no signals for serious AEs related to doravirine from the phase 2/3 studies performed, and there is no issue around for example QT effects. The recommendation that no dose adjustment is needed in case of co-treatment with a strong CYP3A inhibitor is therefore considered acceptable.

Discontinuation due to adverse events

Study P018

Through Week 48, a total of 18 subjects experienced AEs that resulted in discontinuation from the study: 6 subjects (1.6%) in the DOR group and 12 subjects (3.1%) in the DRV+r group.

Twelve of these 18 subjects discontinued due to drug-related AEs: 4 subjects (1.0%) in the DOR group (rash [2 subjects], nausea and nausea/abdominal pain), and 8 subjects (2.1%) in the DRV+r group.

For 3 subjects (1 in the DOR group and 2 in the DRV+r group), discontinuation was due to an SAE (unrelated death in the DOR group; related peripheral edema and unrelated tuberculosis in the DRV+r group).

In P018, there was a smaller risk of discontinuation due to AE in the DOR treatment group (4 events) compared with the DRV+r treatment group (12 events). Results of the log-rank test indicate that the time to discontinuation due to any AE through Week 48 was longer for DOR compared with DRV+r (p = 0.040, not adjusted for multiplicity). Note that for this analysis, 2 subjects in the DOR treatment group who discontinued (a subject whose death was reported as the reason for discontinuation on the disposition form and a subject who discontinued after the Week 48 window) were censored from the analysis of time to discontinuation due to AE.

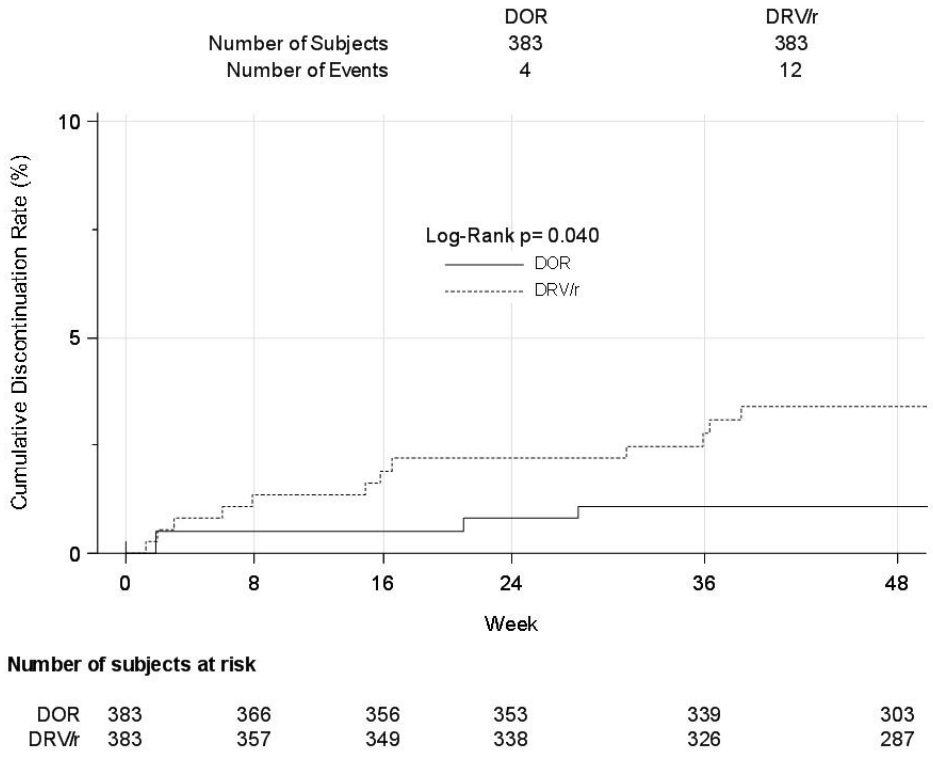


Figure 6 Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event Weeks 0-48 (P018)

Study P021

By Week 48, 35 subjects in P021 experienced AEs that led to discontinuation. A lower proportion of subjects in the DOR/3TC/TDF treatment group (11 subjects, 3.0%) were discontinued from the study due to an AE, compared with the EFV/FTC/TDF treatment group (24 subjects, 6.6%). The most common AE leading to discontinuation was rash, which occurred only in the EFV/FTC/TDF group (12 subjects. No single AE leading to discontinuation in the DOR/3TC/TDF group occurred in more than 1 subject.

A lower proportion of subjects discontinued from the study due to drug-related AEs in the DOR/3TC/TDF treatment group (8 subjects [2.2%]) compared with the EFV/FTC/TDF group (21 subjects [5.8%]) by Week 48. The main reasons for discontinuation were:

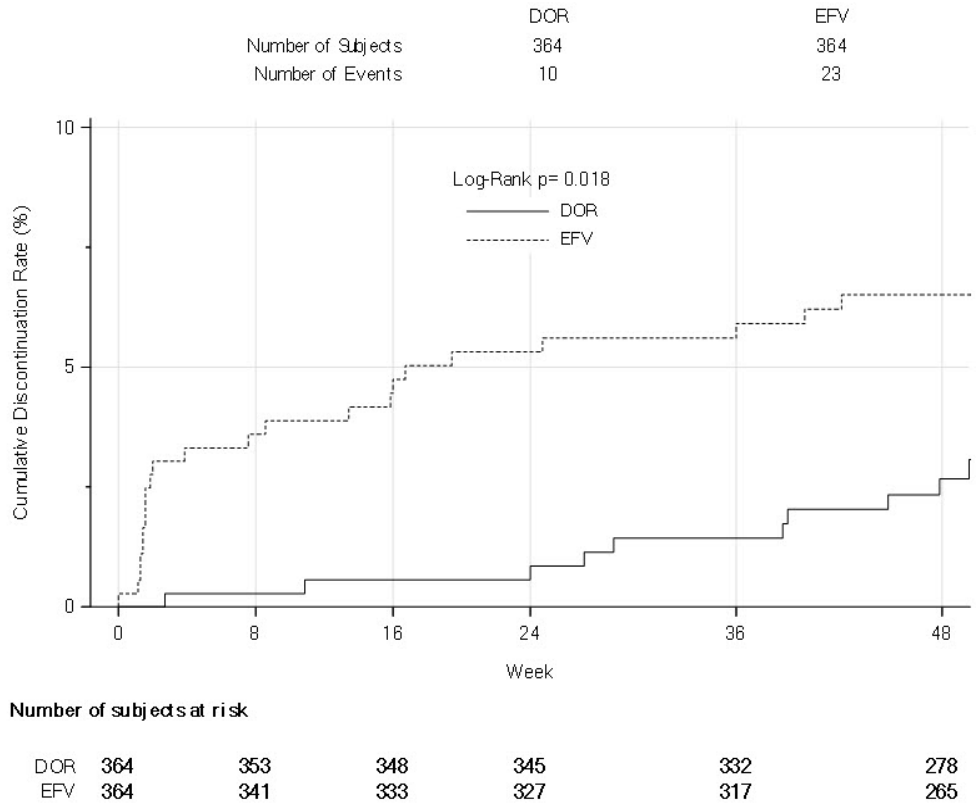
- DOR/3TC/TDF group: 4 subjects discontinued from the study due to a drug-related CNS AE, 1 subject due to drug-related alopecia, 1 subject due to drug-related abdominal pain upper, and 1 subject with drug-related vomiting.
- EFV/FTC/TDF group: 12 subjects discontinued from the study due to a drug-related AE of rash and 9 subjects due to drug-related CNS-AE.

Six (2 in the DOR/3TC/TDF group and 4 in the EFV/FTC/TDF group) of the 35 subjects discontinued from the study due to an SAE(s):

- DOR/3TC/TDF group: 1 subject with drug-related asthenia, insomnia, and nightmare and 1 subject with esophageal obstruction
- EFV/FTC/TDF group: 1 subject each with acute kidney injury, rash generalized, rash macular, and rash maculo-papular.

Overall, the CHMP notes that there was a lower risk of discontinuation due to AE in the DOR/3TC/TDF treatment group (10 events) compared with the EFV/FTC/TDF treatment group (23 events). Results of the log-rank test indicate that the time to discontinuation due to any AE was longer for DOR/3TC/TDF compared with EFV/FTC/TDF ($p = 0.018$, not adjusted for multiplicity. Subjects in the EFV treatment group experienced AEs that led to discontinuation from the study earlier in the trial (~Week 1 to 2 of the study) than the subjects in the DOR/3TC/TDF treatment group, and this difference was maintained thereafter.

Three subjects (0.8%) in the DOR/3TC/TDF treatment group compared with 6 subjects (1.6%) in the EFV/FTC/TDF treatment group discontinued study drug due to neuropsychiatric events.



DOR=DOR/3TC/TDF QD; EFV=EFV/FTC/TDF QD
Source: [P021V01MK1439A: analysis-adtte]

Figure 7 Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event Weeks 0-48 (P021)

The 48 week tolerability (estimated as time to discontinuation) of DOR appears to be at least comparable to DRV+r and superior to EFV. This is in line with the overall safety profiles of the respective study groups in the P018 and P021 studies.

2.8.1. Discussion on clinical safety

The clinical safety profile of doravirine has been established in two pivotal phase 3 studies (P018 and P021), with supporting data from the P007 phase 2 study (P007), rendering a total of 667 patients that have been exposed to 100 mg doravirine daily for more than 48 weeks. Both comparators used (efavirenz and boosted darunavir) are current preferred (DRV+r) or alternate (EFV) options in the treatment of HIV according to EACS guidelines.

Overall the CHMP is of the view that the safety profile of doravirine (with or without TDF and 3TC) appears favourable, with comparable or superior tolerability compared to darunavir (+ritonavir) and superior tolerability compared to efavirenz, with a longer time to discontinuation in the doravirine arms in both pivotal studies. Compared to efavirenz (also belonging to the NNRTI-group of antiretroviral drugs) subjects treated with doravirine present with fewer neuropsychiatric adverse events, a lower risk of rash and a more favourable lipid profile. Compared to darunavir boosted with ritonavir, doravirine treated subjects present with a more favourable lipid profile and less gastrointestinal adverse events. Airway symptoms such as cough slightly more common in the doravirine groups, but could be a random effect of the high statistical multiplicity arising when comparing a large number of AE categories between groups.

Low grade bilirubin elevations were more frequent in the doravirine treatment arms (around 6%) than with control (darunavir +ritonavir around 1.5%, efavirenz 0%), and this was raised as an "Other Concern". The effect was not dose/exposure dependent within the dose span tested (phase 2b study included, where 200 mg was used in one arm), and it concerned mainly intermittent grade 1 elevations. After a thorough discussion, the difference seems more likely explained by the very low frequency of bilirubin increases with the control agents, where there is evidence for a lowering effect on bilirubin by efavirenz (enzyme induction), and where darunavir + ritonavir also have inducing effects. The frequency of bilirubin increases with doravirine was in fact in line with those seen in other trials with other agents deemed to have no effect of bilirubin clearance. In summary the CHMP considers that no specific further investigations are needed on this matter.

In the phase 3 studies, concomitant medication with moderate and strong CYP3A4 inhibitors were allowed although this could elevate doravirine exposure more than 3-fold. The SmPC (section 4.5) states that no dose adjustment is needed during co-treatment with strong inhibitors. To provide further justification that such co-treatment does not cause safety problems, the safety outcomes in the phase 3 studies were further evaluated. It was clarified that very few patients had in fact used strong inhibitors as part of co-treatment. In practice only moderate inhibitors had been used in relevant numbers for a safety evaluation. The AE pattern in those treated for >3 months with such CYP inhibitors were not markedly different though from that seen in all DOR treated patients. It was also shown that there was no tendency of an association to DOR exposure (by AUC quartiles) for the incidence of the most common side effects (headache, diarrhoea and nausea). Preclinical safety was favourable, there are no signals for serious AEs related to doravirine in the phase 2/3 studies, and there is no issue around for example QT effects. The recommendation that no dose adjustment is needed in case of co-treatment with a strong CYP3A inhibitor is therefore considered acceptable by the CHMP.

2.8.2. Conclusions on the clinical safety

The overall safety profile of doravirine, as a single entity and in fixed dose combination with TDF and 3TC, appear favourable to the CHMP. No specific safety issues have been identified.

2.9. Risk Management Plan

Safety concerns

Table 50 Summary of the Safety Concerns

	Attributable Component of DOR/3TC/TDF	Safety Concern for DOR/3TC/TDF
Important identified risks	3TC, TDF	Severe acute exacerbations of hepatitis B
	TDF	New onset or worsening renal impairment/Renal toxicity
	TDF	Decreases in bone mineral density (BMD)/bone events due to proximal renal tubulopathy
Important potential risks	N/A	None
Missing information	DOR, 3TC, TDF	Safety during pregnancy
	DOR, 3TC, TDF	Safety during lactation
	DOR, 3TC, TDF	Safety in elderly patients
	DOR	Long-term safety

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to monitor the safety profile of DOR, 3TC, TDF. Only data collection from participation in the Antiretroviral Pregnancy Registry (APR) is planned for the fixed dose combination to monitor the treatment safety in pregnant women.

There are no additional pharmacovigilance activities proposed for DOR, 3TC, TDF.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
Severe acute exacerbations of hepatitis B	Section 4.4 of the Product Information. What you need to know before you take Delstrigo and Possible side effects sections of the Patient Information	Routine pharmacovigilance activities
New onset or worsening renal impairment/Renal toxicity	Section 4.2 Section 4.4, Section 4.8 and Section 5.2 of the Product Information. What you need to know before you take Delstrigo and Possible side effects sections of the Patient Information	Routine pharmacovigilance activities
Decreases in bone mineral density (BMD)/bone events due to proximal renal tubulopathy	Section 4.4 and Section 4.8 of the Product Information. What you need to know before you take Delstrigo and Possible side effects section of Patient Information	Routine pharmacovigilance activities
Important Potential Risk		
None	N/A	N/A
Missing Information		
Safety during pregnancy	Section 4.6 and Section 5.3 of the Product Information. What you need to know before you take Delstrigo section of Patient Information	Routine pharmacovigilance activities; APR
Safety during lactation	Section 4.6 and Section 5.3 of the Product Information. What you need to know before you take Delstrigo section of Patient Information	Routine pharmacovigilance activities
Safety in elderly population	Section 4.2 and Section 5.2 *Ps* of the Product Information	Routine pharmacovigilance activities
Long-term safety	Section 4.8 of the Product Information	Routine pharmacovigilance activities

During the assessment, PRAC considered that additional Risk minimisation measures for TDF in the form of education materials regarding renal toxicity and bone events were no longer needed for TDF-containing

products since health care prescribers are well aware of those risks.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.10. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 30 August 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.11. New Active Substance

The applicant compared the structure of doravirine / lamivudine / tenofovir disoproxil with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers doravirine / lamivudine / tenofovir disoproxil to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.12. Product information

2.12.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.12.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Delstrigo (doravirine/lamivudine/tenofovir disoproxil) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. In addition, it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In 2016, around 37 million people around the world were living with HIV-1 infection, around 2 million in western and central Europe and North America. Around 2 million were newly infected, and an estimated 1 million deaths occurred, the majority in sub-Saharan Africa. To address this global public health challenge, the United Nations AIDS program has led global efforts to establish new targets for HIV treatment. The "90-90-90" goal for 2020 is that 90% of all people living with HIV will know their HIV status, 90% of all people diagnosed with HIV infection will receive sustained ART and 90% of all people receiving ART will have achieved viral suppression. Modeling suggests that if these targets are achieved, the HIV/AIDS epidemic can be controlled globally by 2030, resulting in profound health and economic benefits.

3.1.2. Available therapies and unmet medical need

A large number of antiretrovirals are available, as part of 6 different drug classes: NRTIs, NNRTIs, PIs, INIs, fusion inhibitors (i.e. enfuvirtide) and CCR5 inhibitors (i.e. maraviroc), where the NNRTI class has been an important anchor as part of first-line therapy for long, in particular in the low/middle-income regions. However, the NNRTI class has been downgraded to an alternative regimen by many treatment guidelines, since available agents are associated with some various disadvantages. In some regions, NNRTI resistance is increasing at a pace that calls for other first-line options, in particular, if lacking the means for resistance screening prior to therapy.

Doravirine is a new NNRTI that was developed to address these shortcomings, both with regards to safety and efficacy. In vitro studies indicate a potential for doravirine to be used in the presence of common NNRTI resistance and with an improved barrier to resistance.

3.2. Main clinical studies

Doravirine as single agent (100 mg given once daily), and in parallel a fixed-dose product consisting of doravirine/lamivudine/tenofovir disoproxil (100/300/300 mg given once daily) has been studied in two pivotal double-blind studies in previously untreated patients. Of note, any resistance to the agents in the regimens, including to the NNRTI class, were part of exclusion criteria.

In study P018 doravirine was compared to darunavir + ritonavir, both in combination with either tenofovir disoproxil/emtricitabine (as Truvada) or abacavir/lamivudine (as Kivexa/Epzicom); around 90% had Truvada as backbone NRTIs.

In study P021, the fixe dose product was compared to efavirenz /emtricitabine/tenofovir disoproxil (i.e. blinded Atripla). Therefore, P021 does not provide a direct comparison of doravirine and efavirenz (cytidine analogues being lamivudine and emtricitabine, respectively). Further, the difference in backbone between studies for those treated with doravirine precludes pooling of the two doravirine treatment arms, and results are presented for the separate studies.

In a supportive study (P007, dose ranging phase 2b), a direct comparison to efavirenz was done; here both agents were given with tenofovir disoproxil/emtricitabine as backbone NRTIs. Similar response rates were seen for doravirine 100 mg qd (n=108) and efavirenz 600 mg qd (n=108).

3.2.1. Favourable effects

Doravirine was non-inferior to darunavir + ritonavir in study P018, and doravirine/lamivudine/tenofovir disoproxil to efavirenz /emtricitabine/tenofovir disoproxil in study P021, with the primary end point being proportions with HIV-RNA <40 copies/ml at week 48, using the FDA snapshot approach. Point estimates were slightly in favour of doravirine on both studies, and results were consistent between arms for relevant baseline parameters, including by baseline CD4 count, baseline viral loads, race and gender. The immunological improvement was fully similar between regimes.

Patients failing therapy with documented de novo resistance was very low for doravirine-treated patients in study P018 (a single case of 383 treated), and in line with those treated with darunavir + ritonavir (0 cases/383 treated). In study P021 de novo resistance was documented in 6/364 treated with doravirine and in 12/364 treated with efavirenz. Whether the somewhat higher number of cases with de novo resistance development with the fixed dose combination in study P021 is explained by the difference in cytidine analogues (lamivudine vs emtricitabine) is unclear. There are disputing findings on that issue in the public domain.

3.2.2. Uncertainties and limitations about favourable effects

The pivotal studies support that doravirine is similarly effective to the two relevant control agents used in the clinical studies; as stated above, these excluded patients with resistance relevant to the NNRTI class.

A small study (P0030) was undertaken in patients where NNRTI resistance was detected prior to therapy. However, the study is limited to 10 patients, 2 of whom stopped therapy prior to week 48. Hence, a follow-up is available for 7 patients with a baseline virus carrying the K103N mutation, and the G190A mutation in the remaining case. Although the 7 patients were responders at week 48, this data set is too limited to clear the issue. Hence, the potential for doravirine to be also used in the setting of certain NNRTI resistance has not been evaluated in a way that would support therapy in the setting of any NNRTI resistance. There is a lack of knowledge what resistance and what breakpoints for phenotypic resistance are associated with a lowered efficacy. Available data therefore support an indication in patients with virus lacking resistance to the NNRTI class, and in addition to the NRTI backbone agents for the fixed dose product.

3.2.3. Unfavourable effects

The clinical safety profile of doravirine has been established in two pivotal phase 3 studies (P018 and P021), with supporting data from the P007 phase 2 study (P007), rendering a total of 667 patients that have been exposed to 100 mg doravirine daily for more than 48 weeks.

Overall the safety profile of doravirine (with or without TDF and 3TC) appears favourable, with comparable or superior tolerability compared to control in the phase 3 studies, darunavir (+ritonavir) and efavirenz. A lower proportion stopped therapy due to AEs with doravirine than with both control regimens. Rash, frequently seen with efavirenz (same NNRTI class), was uncommon; 2/747 stopped doravirine therapy due to rash in the phase 3 studies. Doravirine does not seem to yield CNS side effects, typically seen with efavirenz. The frequency of such AEs was much less frequent with doravirine than with efavirenz, and similar in those treated with doravirine and darunavir/r. The frequency of gastrointestinal side effects were similarwith doravirine and efavirenz, and less frequent with doravirine than with darunavir/r. In contrast to the control regimens, doravirine is lipid neutral. In summary, there are few side effects that can be linked with certainty to doravirine therapy, and those reported were of mild intensity for the very most. Of note, there was a lack of findings in the pre-clinical repeat dose toxicity studies, where indeed no target organ of toxicity was found.

3.2.4. Uncertainties and limitations about unfavourable effects

In the phase 3 studies, elevated bilirubin was seen in around 6% of those patients treated with doravirine (vast majority grade 1 elevation), as compared to in around 1.5% of those treated with darunavir + ritonavir and in none of those treated with efavirenz. Bilirubin elevations, unconjugated, were most often low-grade, isolated and sporadic, but in some cases more severe (grade 2) occurring intermittently or repeatedly. No other signs of liver toxicity were seen in these cases. The effect was not dose/exposure dependent within the dose span tested (phase 2b study included, where 200 mg was used in one arm). Doravirine is not expected to have any relevant effects on CYPs, or tested drug transporters, where an inhibition would yield an increase in unconjugated bilirubin. When comparing graded bilirubin toxicity in studies P018 and P021 to that seen in previous pivotal studies of other approved agents, it is noted that graded bil elevations is in line with those seen with other antiretroviral regimens presumably lacking effects on bilirubin levels. With regards to the control agents, there is a clear evidence for a lowering effect on bilirubin levels by efavirenz (Mezger 2014, Lee 2012), likely due to induction of clearing enzymes. Darunavir + ritonavir is also an inducing regimen, and may consequently lower bilirubin levels, as indicated also in studies other than study P018. In summary, the difference in graded bilirubin toxicity between doravirine and control agents seems rather an effect caused by a bilirubin lowering effect of the control agents (efavirenz > darunavir + ritonavir).

Doravirine is a CYP3A substrate, and concomitant medication with moderate and strong CYP3A4 inhibitors, allowed for use in the phase 3 studies, could elevate doravirine exposure more than 3-fold. The SmPC (section 4.5) states that no dose adjustment is needed during co-treatment with strong inhibitors. The number of patients who in fact used strong inhibitors as part of co-treatment in the phase 3 studies is very limited. In practice co-treatment in relevant numbers for a safety evaluation concerned moderate inhibitors. That said, the AE pattern in those treated for >3 months with such CYP inhibitors was not markedly different from that seen in all DOR treated patients. There was no tendency of an association to DOR exposure (by AUC quartiles) for the incidence of the most common side effects (headache, diarrhoea and nausea), preclinical safety was favourable and there are no signals for serious AEs related to doravirine in the phase 2/3 studies. Doravirine has no relevant effect on QT. The recommendation that no dose adjustment is needed in case of co-treatment with a strong CYP3A inhibitor is therefore considered acceptable, notwithstanding the increased exposure.

3.2.5. Effects Table

Table 51 Effects Table for doravirine/lamivudine/tenofovir disoproxil (Delstrigo) indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir:

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
<40 cps/mL, FAS	Week 48 outcome	cps/ml	319/383 (83.3)	303/383 (79.1)	4.2 (-1.4, 9.7)	Study P018
<40 cps/ml, PP	Week 48 outcome	cps/ml	314/353 (89.0)	295/341 (86.5)	2.4 (-2.5, 7.3)	Study P018
Change in CD4 count	Week 48 outcome	cells/µL	198	186	-	Study P018
<40 cps/mL, FAS	Week 48 outcome	cps/ml	305/364 (83.8)	290/364 (79.7)	4.1 (-1.5, 9.7)	Study P021
<40 cps/ml, PP	Week 48 outcome	cps/ml	300/338 (88.8)	287/339 (84.7)	4.2 (-0.9, 9.2)	Study P021

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Change in CD4 count	Week 48 outcome	cells /µL	198	188	-	Study P021
Unfavourable Effects						
Bilirubin elevation		Grade 1-4 elevations	49/743 (6.6%)	6/737 (0.8%)	Significant difference to comparators. The difference is considered to be driven by a lowering effect on bilirubin levels by control agents, rather than an effect by doravirine.	

Notes:

Study P018 (DRIVE-FORWARD), double blind, treatment-naïve patients.
Doravirine 100 mg qd vs darunavir + ritonavir 800/100 mg qd (double blind)

Both in combination with tenofovir disoproxil/emtricitabine (~90%) or abacavir/lamivudine (~10%).

Resistance screening (exclusion criteria)

NNRTI: Class resistance in accordance with IAS-USA plus mutation L234I
NRTIs and PI: In accordance with IAS-USA

Study P021 (DRIVE-AHEAD), double blind, treatment-naïve patients.

Doravirine/tenofovir disoproxil/lamivudine (100/300/300 mg, fix dose) vs efavirenz/tenofovir disoproxil/emtricitabine (600/300/300 mg, fix-dose)
Resistance screening (exclusion criteria)

NNRTI: Same as P018

NRTIs: In accordance with IAS-USA

3.3. Benefit-risk assessment and discussion

3.3.1. Importance of favourable and unfavourable effects

Doravirine in combination with 2 NRTIs yielded similar efficacy in previously untreated patients infected with HIV free from resistance to the NNRTI class as two valid controls, efavirenz and darunavir/r. In this setting, the resistance barrier seemed somewhat higher with doravirine than with efavirenz, while, as anticipated darunavir/r was associated with the lowest risk of resistance in cases of treatment failure (no cases).

The safety profile is clearly favourable, with improvements both as compared to the prior standard NNRTI treatment, efavirenz, and the recommended first line boosted PI, darunavir/r.

During the development of doravirine, a third class has moved forward as perhaps the main first line therapy in the EU and the US - the integrase inhibitor class. Agents of this class are also highly effective, some with a very high barrier to resistance, and well tolerated. Hence, some of the advantages shown with doravirine as compared to the regimens that were chosen as controls in the doravirine program are also seen with the integrase inhibitor class.

In this procedure, the CHMP has concluded that the classification of HIV in the ICH M7 document is no longer supported due to the anticipated duration of therapy in HIV, which may well be more than 5-10 years. The CHMP considers the 1.5 µg/day limit to be relevant for mutagenic impurities, rather than the 10 µg/day. The applicant should commit to adjusting their control strategy accordingly.

3.3.2. Balance of benefits and risks

The favourable effects of doravirine, which is in line with that of present standard-of-care, clearly outweigh unfavourable effects which seem limited and mild.

Since doravirine single agent as well as this fixed dose product has been clinically evaluated in the absence of NNRTI-resistance, this balance applies to patients infected with HIV lacking resistance to the NNRTI-class, and for this fixed dose product in addition the absence of resistance to lamivudine and tenofovir disoproxil.

3.4. Conclusions

The overall benefit-risk of Doravirine/Lamivudine/Tenofovir (Delstrigo) is positive for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Delstrigo is favourable in the following indication:

"Delstrigo is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that doravirine is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.