21 November 2013
EMA/CHMP/772068/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tivicay

International non-proprietary name: dolutegravir

Procedure No. EMEA/H/C/002753/0000

Note

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

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List of abbreviations

3TC	lamivudine
ABC	abacavir
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C_0	Pre-dose concentration
C_{tau}	Concentration at the end of the dosing period
c/mL	copies per milliliter
C_{avg}	Average of concentrations
DRV	darunavir
DTG	dolutegravir, S/GSK1349572
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FC	Fold change
FDC	Fixed dose combination
FPV	fosamprenavir
FTC	emtricitabine
GCP	Good Clinical Practice
GSS	Genotypic susceptibility score
IC_{50}	Half-maximal inhibitory concentration
INI	Integrase inhibitor
ITT-E	Intent-to-Treat Exposed
LOCFDB	Last observation carried forward (discontinuation equals Baseline)
mITT-E	Modified Intent-to-Treat Exposed
MDF	Missing or Discontinuation = Failure
MSDF	Missing, Switch or Discontinuation = Failure
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OBR	Optimized background regimen
OSS	Overall susceptibility score
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PIQ	Phenotypic inhibitory quotient
PK/PD	Pharmacokinetic/pharmacodynamic
PSS	Phenotypic susceptibility score

RAL	raltegravir
RAM	Resistance associated mutation
RNA	Ribonucleic acid
RTV	ritonavir
TLOVR	Time to Loss of Virologic Response
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WT	Wild type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViiV Healthcare submitted on 17 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tivicay, 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 24 May 2012

The applicant applied for the following indication: "*Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age*."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that dolutegravir was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0088/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0088/2012 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 dolutegravir contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice/Protocol Assistance

The applicant received Scientific Advice from the SAWP / CHMP in 2009 (EMEA/H/SA/1217/1/2008/III), in 2010 (EMEA/H/SA/1217/1/FU/1/2010/II) and in 2011 (EMEA/H/SA/1217/1/FU/2/2011/III). The Scientific Advice pertained to non-clinical and clinical

aspects of the dossier.

Licensing status

Tivicay has been given a Marketing Authorisation in the US on 12 August 2013 and Canada on 31 October 2013.

The product was not licensed in any country at the time of submission of the application. However, a new application was filed in the following countries: United States of America on 17 December 2012, Canada on 17 December 2012 and Switzerland 10 January 2013.

1.2. Manufacturers

Manufacturer responsible for batch release

GLAXO WELLCOME, S.A.
Avda. Extremadura 3,
09400 Aranda de Duero,
Burgos
Spain

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Philippe Lechat

- The application was received by the EMA on 17 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 24 April 2013 (Annex 2).
- During the meeting on 30 May 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 3 June 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 August 2013.
- The integrated Inspection Report of the GCP inspection carried out at the following site(s): Dr Mills Inc., Suite 812, 9201 Sunset Blvd., Los Angeles, 90069, California, United States, Dr Sloan North Texas Infectious Disease Consultants, Suite 710, 3409 Worth Street Dallas, 75246, Texas, United States and at the sponsor site located in Five Moore Drive, Research Triangle Park (RTP), North Carolina 27709, United States between 19 June and 18 July 2013, was issued on 1st August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 September 2013 (Annex 5).

- During the CHMP meeting on 24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 7).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 October 2013.
- During the meeting on 21 November 2013, 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 Tivicay.

2. Scientific discussion

2.1. Introduction

Globally, 34.0 million [31.4 million–35.9 million] people were living with HIV at the end of 2011. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions.

Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults (4.9%) living with HIV and accounting for 69% of the people living with HIV worldwide. Although the regional prevalence of HIV infection is nearly 25 times higher in sub-Saharan Africa than in Asia, almost 5 million people are living with HIV in South, South-East and East Asia combined. After sub-Saharan Africa, the regions most heavily affected are the Caribbean and Eastern Europe and Central Asia, where 1.0% of adults were living with HIV in 2011.

In 2012, there were 35.3 million [32.2 million–38.8 million] people living with HIV. Since the start of the epidemic around 75 million [63 million–89 million] have become infected with HIV.

New HIV infections have fallen by 33% since 2001. Worldwide, 2.3 million [1.9 million–2.7 million] people became newly infected with HIV in 2012, down from 3.4 million [3.1 million–3.7 million] in 2001. New HIV infections among adults and adolescents decreased by 50% or more in 26 countries between 2001 and 2012. New HIV infections among children have declined by 52% since 2001. Worldwide, 260 000 [230 000–320 000] children became newly infected with HIV in 2012, down from 550 000 [500 000–620 000] in 2001.

AIDS-related deaths have fallen by 30% since the peak in 2005. In 2012, 1.6 million [1.4 million–1.9 million] people died from AIDS-related causes worldwide compared to 2.3 million [2.1 million–2.6 million] in 2005. Since the start of the epidemic an estimated 36 million [30 million – 42 million] people have died of AIDS-related illnesses.

Worldwide, around 50% of these infected are women, which differs from some western world regions where males are still those mainly infected. In western/central Europe around 1 million people are infected; in the US around 1.5 million. In the Baltic and some eastern European such as Ukraine, the prevalence is high, around 1%. [UNAIDS report 2012]

Antiretroviral therapy has led to a dramatic reduction in mortality and morbidity in treated HIV-infected individuals. Indeed, those able to get adequate and continuous treatment might expect normal life spans, when adjusting for other medical conditions overrepresented in this population (hepatitis co-infections, smoking habits etc.).

In 2012, around 9.7 million people living with HIV had access to antiretroviral therapy in low- and middle-income countries. This represents 61% of people eligible for treatment under the 2010 WHO guidelines; and 34% of people eligible under the 2013 WHO guidelines. [UNAIDS report 2012]

Dolutegravir is a new integrase inhibitor which has been studied in a full range of HIV treatment populations; in those without prior HIV therapy, in patients with prior failing therapies and resistance to drug classes other than integrase inhibitors, and in patients who also had failed therapy with an integrase inhibitor with consequent integrase inhibitor class resistance. The proposed dosage was 50 mg once daily in the absence of integrase inhibitor resistance, and 50 mg twice daily in the presence of such resistance.

The applicant has generally followed the CHMP Guidance given as part of Scientific Advice from the SAWP / CHMP in 2009 (EMEA/H/SA/1217/1/2008/III), in 2010 (EMEA/H/SA/1217/1/FU/1/2010/II) and in 2011 (EMEA/H/SA/1217/1/FU/2/2011/III).

2.2. Quality aspects

2.2.1. Introduction

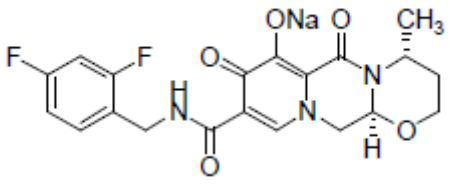
The drug product is an immediate release tablet for oral administration. Tivicay is presented as Film-coated tablet containing 50 mg of dolutegravir (as dolutegravir sodium salt) as active substance.

Other ingredients are: mannitol (E421), microcrystalline cellulose, povidone, sodium starch glycollate and sodium stearyl fumarate. The tablet coating: polyvinyl alcohol-part hydrolyzed, titanium dioxide (E171), macrogol, talc and iron oxide yellow (E172)

The tablets are packed in HDPE (high density polyethylene) bottles closed with polypropylene screw closures, with a polyethylene faced induction heat seal liner.

2.2.2. Active Substance

The chemical name of dolutegravir sodium salt is: 2H-Pyrido[1',2':4,5] pyrazino[2,1-b] [1,3]oxazine-9-carboxamide,N-[(2,4-difluorophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-, sodium salt (1:1), (4R,12aS), and has the following structure:



Dolutegravir is a white to light yellow non-hygroscopic crystalline substance; it is slightly soluble in water, but practically not soluble over the physiological range. It presents 2 chiral centers and pseudo-polymorphism. The most thermodynamically stable form is Form 1 (crystalline anhydrous).

Manufacture

Dolutegravir sodium is manufactured through 5 main steps using commercially available starting materials with acceptable specification; the last step of synthesis is the formation of the salt. The process is described in sufficient detail (raw materials, amounts, process conditions and controls) as well as a flow chart provided. Dolutegravir sodium anhydrous crystalline substance is milled in order to obtain the particle size distribution needed to meet drug product performance requirements.

The current route (Route B) is the intended commercial route and this route has been used to prepare all of the active substance batches used in clinical studies, non-clinical studies, and active substance and finished product primary stability batches.

The active substance has been developed using a Quality by Design (QbD) approach, in line with ICH Q8, Q9, Q10, Q11 and other regulatory guidance. However, no Design Space was proposed.

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. The specified impurities do not exceed the 0.15% w/w ICH qualification threshold [ICH Q3A(R2)] and have no structural alerts for potential mutagenicity and carcinogenicity.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

Satisfactory descriptions are provided for all analytical methods used for specification testing of dolutegravir sodium drug substance. All analytical methods have been validated in accordance to the ICH guidelines. The active substance specification includes tests for: description (visual), identification (IR), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC), water content (KF), solid state (XRPD), particle size distribution (laser diffraction)

Batch analyses data are presented for a substantial amount of batches used during development and also data for the three production scale batches which comply with the specification.

Stability

Primary stability data are presented for three commercial scale batches of dolutegravir sodium active substance manufactured by the commercial process at the commercial manufacturing site. The active substance is packaged in containers representing those intended for market. Data are provided from 18 months of storage at long term condition (25°C/60%RH) and at intermediate condition (30°C/65%RH) and from 6 months storage at accelerated condition (40°C/75%RH). The testing has been performed according to the proposed active substance specification.

For the stressed stability studies, data were presented for short-term storage under stress conditions for one of the three above batches. Samples have been stored exposed to high temperature, high humidity and extreme light. From stress studies a slight increase in the total impurities from 0.10 to 0.26% is seen for the samples exposed to light and a slight decrease in dolutegravir sodium content at the elevated storage conditions but otherwise no changes are seen.

Forced degradation studies were also performed to identify potential degradation products that might be formed in drug substance and drug product and to elucidate the mechanisms of formation. From those studies it can be seen that there is an increase in related substances at all conditions but most pronounced for drug substance in solution and exposed to acidic and alkaline conditions, i.e. impurity GSK1747009A formed by epimerization under acidic conditions, RRT 0.30 and 0.31 formed by hydrolysis under acidic and neutral pH conditions, RRT 0.48 formed by hydrolysis under acidic and basic conditions, RRT 0.43 formed by hydrolysis under basic conditions, and RRT 0.30 formed by photo-oxidation as the principal degradation products. These products have not been observed at significant levels under long-term or accelerated condition.

All dolutegravir sodium samples stressed in solution and the solid state were tested for diastereomer content. Only the acid stressed sample contained any diastereomer.

No co-eluting impurities were found under the dolutegravir sodium peak in any stressed sample using UV diode array detection when using the current method for drug related impurities; the method is therefore considered stability indicating.

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

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The product has been developed using a Quality by Design (QbD) approach, in line with ICH Q8, Q9, Q10, Q11 and other regulatory guidance. No Design Space was proposed.

The Quality Target Product Profile (QTPP) for Dolutegravir tablets was to develop an immediate release dosage form to deliver a clinical dose of 50 mg for once daily administration.

To meet the QTPP the following steps were progressed: Identifying compatible excipients that facilitated tablet manufacture and performance; evaluating potential manufacturing processes; conducting a designed experimental study (DoE) to determine the impact of excipient levels on product performance; employing suitable techniques to characterise process and product performance during development.

Diverse physicochemical attributes of the active substance (description, solid state form, identification, content, related impurities, water content, solubility, particle size distribution, crystal habit and amorphous content) shown sort impact on the drug product CQAs. The scale of impact was clearly discussed and defined on the corresponding section of the dossier.

The CQAs of the finished product are description, identification, content, uniformity of content, drug-related impurities and dissolution. The contributors to Drug Product CQA variability have been established and controls have been defined to ensure that the performance criteria are consistently and reliably met.

Risk assessments, using structured methodologies such as Failure Mode and Effects Analysis (FMEA), in accordance with ICH Q9, were used to establish those process parameters and attributes that are likely to have the greatest impact on product quality. Those risks were

investigated through the use of Design of Experiments (DoE) to evaluate the significance of changing process parameters on the quality and performance of the drug product.

The excipients used in the formulation for Dolutegravir Tablets, 50 mg are of compendial quality and the amounts per tablet fall within typical ranges used. Opadry yellow makes exception and it is controlled in house with adequate specifications. The levels of povidone and sodium starch glycolate were explored in a DoE.

The High Density Polyethylene (HDPE) bottles, closed with polypropylene screw closures, with a polyethylene-faced induction heat seal liner were selected, as it provides protection against moisture, convenient presentation and maintaining the integrity of the drug product through shelf-life.

Adventitious agents

No materials of human or animal origin are used.

Manufacture of the product

The manufacturing process of Tivicay film-coated tablets is a standard process using wet granulation followed by blending, compression, and film-coating. The manufacturing process is satisfactorily described, and it has been clearly detailed in flow-chart diagrams. The finished product is controlled according to an in-house specification.

All batches manufactured using the process described have produced finished product of acceptable quality and performance showing that this product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for the control of this oral preparation.

Process validation has been performed on three batches using production scale for the compression blend and pilot scale for compression and coating. Although the validation does not include complete data regarding blend uniformity, the information provided on the whole validation process guarantees the quality and safety of the product. However based on the available batch data, the CHMP recommends the Marketing authorisation holder (MAH) to provide data on blend uniformity (assay at 10 locations) once they are available or a stratified sampling protocol at commercial scale.

Product specification

The control of finished product quality is done via in-house specifications and analytical procedures which are in general suitably validated. The finished product release specifications are justified based on data for stability and clinical batches.

Release specifications include description (visual), identity of dolutegravir (UV, HPLC), assay (HPLC), uniformity of dosage (HPLC), and dissolution (HPLC). In addition, related substances are specified at shelf-life (HPLC). Microbial testing is performed as a skip test

Stability of the product

Stability studies for the finished product were performed according to ICH Q1 on 6 production scale batches. The batches presented are identical to those proposed for marketing and were

packed in the primary packaging proposed for marketing. The stability studies were intended for 36 months. Stability data of 24 months at 25°C/60% RH and for up to 6 months at 40°C/75% RH were presented.

Tivicay film-coated tablets were evaluated for description, dolutegravir assay, impurities, dissolution and microbiological quality. The microbiological test will not be performed routinely; however, this test will be performed on a minimum of two batches per year. The analytical procedures used are stability indicating

In addition, data were presented following short-term storage of one of the six batches under stress conditions of 50°C/ambient, a freeze/thaw cycle (-20°C/30°C), 40°C/75% RH exposed and exposed photostability testing in accordance with ICHQ1B (Option 2). No significant changes were observed with all results complying with specification.

The results demonstrated the chemical and physical stability and no significant changes in tablet description, dolutegravir content, drug related-impurities and dissolution release were observed with all results complying with specification. Microbial limit testing confirmed the absence of microbial growth. The finished product is stable, only a slight increase in water content was noted.

Based on available stability data, the proposed shelf-life with no special storage conditions as stated in the SmPC are considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Tivicay is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. Information on development, manufacture and control of the active substance 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 the clinic.

Nevertheless, based on the available batch data, the CHMP recommends the marketing authorisation holder (MAH) to complement the validation by obtaining data on blend uniformity (assay at 10 locations). In case of out of specification results occur, the MAH is reminded that such would need to be reported to the Agency and to the Rapporteurs. Alternatively the marketing authorisation holder should undertake a stratified sampling protocol at commercial scale.

2.2.5. 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.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and quality future development, the CHMP recommends the following point for investigation:

- To complement the validation by obtaining data on blend uniformity (assay at 10 locations). In case of out of specification results occur, the MAH is reminded that such would need to be reported to the Agency and to the Rapporteurs. Alternatively the marketing authorisation holder should undertake a stratified sampling protocol at commercial scale.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal studies on safety pharmacology, general toxicity including carcinogenicity and reproduction toxicity studies were conducted in accordance with GLP principles. Toxicokinetic and some pharmacokinetic studies were also conducted according to GLP. Some other studies were not strictly GLP; however these nevertheless conformed to adequate scientific standards of quality as declared by the applicant, which the CHMP found to be acceptable.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Dolutegravir is referred to as a second generation integrase inhibitor, with activity against raltegravir resistant viruses. Dolutegravir binds to the HIV integrase active site blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Dolutegravir caused a dose dependent decrease in integrated HIV-1 DNA and an increase of 2 LTR circles consistent with antiviral activity being a direct consequence of effect on viral integration. Data indicate that dolutegravir enjoys tighter binding and a longer dissociative half-life from integrase than either raltegravir or elvitegravir possibly reflected in a higher barrier for resistance.

The IC_{50} of dolutegravir against the purified enzyme HIV-1 integrase ranged from 2.7 nM to 12.6 nM. Corresponding values using cell based assays ranged from 0.51 to 0.71 nM. In assays using MT-4 cells infected with HIV-1 strain IIIB dolutegravir IC_{50} values ranged from 0.71 nM to 2.1 nM (MTT). A 75 fold increase in IC_{50} was apparent in the presence of human serum. Additive or synergistic effects were noted in combination with other antiretroviral agents.

Secondary pharmacodynamic studies

With respect to activity against other viruses, IC_{50} values of 11.2 µM were reported for HCV also indicating a potential for suboptimal clinical activity at maximum reported clinical plasma levels of approximately 3.7-4.2 µg/ml. The TC_{50} was 96.7 µM, indicating mild cytotoxicity. The IC_{50} against measles was 30.3 µM reflecting some antiviral activity.

Dolutegravir up to 10 µM was evaluated *in vitro* for off target effects in a selectivity profile screen including various receptors, ion channels and enzymes.

In vitro, dolutegravir inhibited the binding of radiolabeled α-melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) receptor by 64% at a concentration equal to the clinical C_{max}. The MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity. The potential effect of dolutegravir on the binding of natural ligands to other melanocortin receptors will be further clarified by conducting *in vitro* binding assays (see RMP in Section 2.8). There were no

findings associated with MC4R in toxicity studies, and no clinically significant patterns of changes in vital signs across the clinical studies.

In studies using isolated tissues no statistically significant effects of dolutegravir were noted, but a 41% inhibition was recorded in the sodium channel site 2 rat brain assays.

Safety pharmacology programme

Results from safety pharmacology studies indicated that single oral doses of dolutegravir up to 500 (rat) and 1000 (monkey) mg/kg have a low likelihood to induce acute effects on major organ function in brain, respiratory and cardiovascular system. In addition, evaluation of cardiovascular parameters incorporated in the repeated dose toxicity studies did not suggest any particular cardiovascular adverse effects.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism and excretion of dolutegravir were studied in mouse, rat and monkey. In addition pharmacokinetic/toxicokinetic data were generated in support of general toxicology studies.

Bioavailability of dolutegravir in rat and monkey ranged from 25 to 34% and increased to levels of 76 to 87% after fasting. With increasing doses systemic exposure levels increased although less than dose-proportionally. Systemic exposure levels were overall similar at similar doses in animals given intramuscular or subcutaneous doses. After repeated doses there was a trend for increased exposure in female animals compared with males although this gender difference was not consistently observed.

Protein binding was high, over 99% in all species including rat, monkey and human.

Distribution studies after single oral doses in partially pigmented rats indicated highest levels of radiolabel at 6 hours post dose and tissues with highest radioactivity included liver, adrenal medulla, myocardium, pigmented skin, renal cortex and renal medulla, lung and lymph nodes. Levels in brain were low, but quantifiable. Studies in pregnant rats showed that dolutegravir crossed the placenta and that foetal radioactivity was highest in blood, myocardium and muscle. In addition lacteal transfer of dolutegravir was evident.

In vitro studies in rat and human liver microsomes showed that a metabolite of dolutegravir, consistent with addition of glutathione through oxidative defluorination was formed. Data indicated that dolutegravir induced a formation of an electrophilic metabolite in rat and human microsomes. The significance of the formation of this metabolite is likely limited at doses relevant for the clinical setting. Studies in human liver microsomes and recombinant CYP enzymes showed that CYP3A4 was the primary CYP enzyme involved in metabolism with formation of metabolite M1 (N-dealkylation) and M7. In addition metabolism to an ether glucuronide, primarily via UGT1A1 was observed in human liver microsomes.

In isolated perfused rat liver dolutegravir was shown to be metabolised via routes involving N-dealkylation (M1), oxidation (M7), hexose conjugation (M2), glucuronidation (M3) and hexose or glucuronide conjugation in combination with N-dealkylation (M4 and M5) or with oxidation (M6 and M8).

Metabolic profiling in mouse showed that dolutegravir was the major radiolabelled compound in plasma, liver and faeces. In bile an ether glucuronide and a metabolite resulting from loss of fluorine and addition of glutathione and oxidation were the major components. In urine the major component was dolutegravir ether glucuronide.

Metabolic profiling in rat showed that dolutegravir was the major radiolabelled compound in rat plasma, liver and faeces. In urine the major component were formed by oxidation and N-dealkylation. In bile the predominant metabolites were formed by glucuronidation and hexose conjugation. Other metabolites resulted from loss of fluorine in combination with oxidation and glutathione addition (11.7% of radiocarbon, 0.8% of dose). In urine, oxidation and N-dealkylation were major biotransformation products. Metabolites resulting from glucuronidation and hexose conjugation were also found in urine.

Metabolic profiling in monkey showed that dolutegravir was the major radiolabelled compound in male and female monkey plasma. In bile major components were glucuronide and hexose conjugates. A notable component was also a metabolite resulting from loss of fluorine and addition of cysteine and oxygen (16% of radiocarbon, 3.1% of dose). In faeces dolutegravir was the major component. In urine the major component was dolutegravir glucuronide (M3) accounting for 68%. Minor components in urine were a hexose conjugate and an N-dealkylated metabolite. Dolutegravir in faeces appeared to be due to a contribution from deconjugation of biliary metabolites as well as from lack of absorption.

No significant metabolic conversion to the respective enantiomer or the two diasteroisomers was apparent in cryopreserved rat, dog, monkey and human hepatocytes.

Dolutegravir was also the major component in milk from lactating rat (82.9 to 97% over 24 hours).

In mouse, rat and monkey the major part of the radioactivity was eliminated in faeces, accounting for 93 to 94.1% in mouse, 90.7 to 92.6% in rat and 67 to 78% in monkey. Urinary excretion was less than 2% of administered dose in mouse, less than 4% in rat and 4.4 to 6% in monkey. The majority of dose was eliminated within 24 hours post dose. No significant differences in rate or extent of elimination between male and females were apparent. In bile duct cannulated animals, biliary excretion accounted for approximately 2.5% of dose in mouse, 7% of the dose in rat and 12% of dose in monkey.

2.3.4. Toxicology

Dolutegravir was investigated for potential to induce toxicity in repeated dose toxicity studies in rat up to 26 weeks and in monkey up to 38 weeks. A treatment free period of 1 month was included in selected studies to evaluate reversibility of changes.

Single dose toxicity

The single dose studies were conducted with the aim to compare pharmacokinetics/toxicokinetics using different administration routes and formulations/vehicles and as such acute toxicity was not investigated. This is acceptable and in accordance with ICH M3.

Repeat dose toxicity

Repeated dose toxicity studies in the mouse were conducted prior to initiating carcinogenicity studies. In the 13 week study, the NOAEL was proposed to be set to 1500 mg/kg. The results indicated though, that dolutegravir at doses of 500 mg/kg had the potential to interfere with liver status reflected in slight increase in bilirubin and liver transaminases and while histopathology did not show any remarkable changes, mucous neck cells in stomach appeared increased.

Table 1. Overview of mouse repeated dose toxicity studies

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
RD2009 /01546	Mouse CD-1 (10M, 10F)	10, 100, 500, 1500, PO	14 days	NOAEL 1500 mg/kg
RD2009 /00028	Mouse CD-1 (10-54M, 10-54F)	0, 10, 50, 500,1500, PO	13 weeks	Bilirubin slight ↑ (M), AP ↑ (M>500 mg/kg), AST ↑ (F>500 mg/kg), K+↑ (F high dose). Stomach- mucous neck cells increased at high dose.

Formulated in 0.5% HPMC with 0.1 w/w% Tween 80.

In rat repeated dose toxicity studies that ranged from 2 weeks to 26 weeks, the principal toxicity was manifested as gastric mucosal changes and lesions. Findings included eosinophilic infiltration, thickening of the limiting ridge mucosa, oedema, acanthosis as well as incidences of microscopic hemorrhage in the glandular stomach at doses of 500 mg/kg and higher. The changes were attributed to local irritating properties and showed reversibility during a 1 month treatment free period. There were also occasional changes in haematology parameters and clinical chemistry in the studies, but without any consistent pattern or dose-dependency. These were considered of limited significance.

Table 2. Overview of rat repeated dose toxicity studies

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
RD2007 /01140 (GLP)	Rat (Sprague-Dawley 10 M, 10 F)	50, 150, 500, PO	14 days	Urine specific gravity ↑ (≥LD). Creatinine ↑ (M). Stomach -edema, mucous cell ↑, eosinophilic infiltration -glandular stomach.
RD2008 /01628 (GLP)	Rat (Sprague-Dawley 10 M, 10 F)	2, 10, 100, 1000, PO	4 weeks (+4 week recovery)	Urine specific gravity ↑ (1000 mg/kg). Glandular stomach -edema, mucous cell ↑, eosinophil infiltration, (≥100 mg). hemorrhage (HD only). Limiting ridge stomach, mixed cell infiltration, edema, acanthosis, (≥100 mg).
RD2009	Rat	5, 50,	26 weeks	At 4 + 6 months -Forestomach –thickening

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
/00410 (GLP)	(Sprague-Dawley 12 M, 12 F)	500, PO	(+4 week recovery)	mucosa limiting ridge (HD), glandular stomach-mucous cell ↑, eosinophil infiltration, globule leukocyte ↑ (≥MD). Mucous neck cells ↑ (MD-HD).

Formulated in 0.5% HPMC with 0.1 w/w% Tween 80.

In a 2 week monkey study, deaths occurred at the high dose of 1000 mg/kg. Clinical chemistry changes in this study included increases in bilirubin and liver transaminases and decreases in red blood cells and reticulocytes and lymphocytes. Microscopic evaluations showed liver hypertrophy and single cell necrosis and atrophy and haemorrhage of mucosal epithelium in the stomach. In the 1 month monkey study the high dose was decreased to 100 mg/kg. No liver related pathology was reported, but an increase in bilirubin in high dose females was apparent. The primary effects consisted of atrophy of cecum, colon, rectum and inflammatory cell infiltration. In the pivotal 38 week study in monkey the high dose was 50 mg/kg, but this was decreased to 30 mg/kg due to intolerance and deaths at 50 mg/kg. Gastrointestinal toxicity seemed the most likely cause of deaths.

Table 3. Overview of monkey repeated dose toxicity studies

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
RD2007 /01142 (GLP)	Cynomolgus monkey (3M, 3F)	0, 100, 300, 1000, PO	14 days	100 mg/kg: TG ↑ (M). ≥300 mg/kg: Diarrhea, vomiting. Bw. ↓.RBC ↓ (F), reticulocytes ↓, platelets ↓ (M). ALT ↑ (M). Lymphocyte ↓paracortex mesenteric lymph nodes. Cecum, colon, rectum -atrophy mucosal epithelium cell debris. Thymus- atrophy cortex. 1000 mg/kg: 1 F died. APTT ↓ (M), γ-GTP, TG ↑ (M). Chol. ↓ (F). AST, ALT, T-Bil., UN, Creat. , fibrinogen ↑. Na, Cl, A/G ↓. Urinary volume↓. Liver, adrenal w. ↑, thymus ↓. Kidney-dilatation. Spleen- atrophy white pulp. Liver- hypertrophy, single cell necrosis. Adrenal-hypertrophy zona fasciculate. Stomach- atrophy mucosal epithelium, hemorrhage. Pancreas-atrophy acinar cells. NOAEL: 100 mg/kg
RD2008 /00107	Cynomolgus monkey (3-5M,	0, 25, 50, 100, PO	1 month +1 month	≥25 mg/kg: Reticulocytes ↑ ≥50 mg/kg: Bw. ↓, neutrophils ↑ (M), TG ↑ (M),

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
(GLP)	3-5F)		recovery	100 mg/kg: Diarrhea, vomiting. Reticulocytes ↑. Fibrinogen ↑ (M), RBC, platelets ↓ (F). UN, Ca, K, Total protein ↑(M), T-Bil ↑ (1 F). Urine Chloride ↓. Cecum inflammatory cell infiltration lamina propria,atrophy mucosal epithelium. Colon –atrophy mucosal epithelium. Rectum-inflammatory cell infiltration. Thymus-atrophy. Pancreas-atrophy acinar cells. NOAEL: 50 mg/kg.
RD2009 /00036 (GLP)	Cynomolgus monkey (7-9M, 7-9F)	0, 3, 10, 15, 50/30, PO	38 weeks +1 month recovery	≥15mg/kg: Diarrhea, salivation, vomiting. Moncoytes, neutrophils ↑ (M). APTT ↑ (F) ≥50/30 mg/kg: Deaths, 2 M. Activity ↓, emaciation. Bw. ↓. Neutrophils, leukocytes ↑. APTT, fibrinogen ↑. RBC, Hb, HCT ↓ (F). Protein, inorg. phosph. ↓ (M). TG ↑ (F). Glucose, chloride ↓. Stomach red mucosa (F). Mononuclear cell infiltration, hemorrhage lamina propria cecum and colon (M), esophagius and tongue inflammatory cell infiltration (M). Stomach inflammatory cell infiltration lamina propria, hemorrhage, erosion (F). NOAEL: 15 mg/kg.

Formulated in 0.5% HPMC with 0.1 w/w% Tween 80.

Genotoxicity

Table 4. Overview of studies on genotoxic potential

Type of test/study ID	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/ Equivocal
Gene mutations in bacteria (WD2007/00514)	Salmonella strains TA98, TA100, TA1535, TA1537, E.coli WP2 uvrA	5 to 849 µg/plate, ± S9	Background bacterial lawn ↓, revertants colonies ↓at 500, 849 µg/plate. Negative.
Gene mutations in mammalian cells (preliminary) (WD2007/01581)	L5178Y mouse lymphoma cells	80 µg/ml, + S9, (3 hours), 20 µg/ml, - S9, (24 hours)	Negative at 3 hr +S9. Weakly positive at 24 hours –S9 (85% cytotoxicity).

Gene mutations in mammalian cells (WD2007/00515)	L5178Y mouse lymphoma cells	85 µg/ml, ± S9, (3 hours), 85 µg/ml, - S9, (24 hours) 10-150, 200 µg/ml, ± S9 (preliminary) 0,1 to 200 µg/ml (± S9 definitive assay), 0, 2.5-70 µg/ml (-S9, 24 hours)	Not genotoxic at 3 hr (81% and 53% ↓total growth +S9, -S9, respectively) and 24 hours –S9 (26 % ↓total growth)
Chromosomal aberrations *in vivo* (WD2007/00513)	Rat, micronuclei in bone marrow (6 M)	0, 50, 100, 500 mg/kg, PO (2 doses 24 hours apart)	No structural or numerical chromosome aberrations. No bone marrow toxicity.

Carcinogenicity

Table 5. Summary of mouse and rat carcinogenicity studies

Type of test / study ID	**Dose / Route / Duration**	**Major findings**
Mouse (CD-1, 65 M, 65 F) (2012N152419) GLP	0, 0, 7.5, 25, 500 mg/kg/d 101-104 weeks	500 mg/kg: F 29.2% survival compared with 41.5% in vehicle and 30.8% in water control
Rat (Sprague-Dawley, 65 M, 65 F) (2012N152418) GLP	0, 0, 2, 10, 50 mg/kg/d 88-95 weeks	Female survival 23.1, 30.8, 26.2% in low, mid and high dose group compared with 41.5% in vehicle. High dose males had also 26.2% survival compared with 33.8% in vehicle males.

Reproduction Toxicity

Reproductive function was evaluated in rat and rabbit.

Table 6. Overview of fertility and early embryonic development studies.

Study type / Study ID	**Species; No / sex / group**	**Route & dose Study design**	**Major findings**
Fertility and early embryonic development XD2009/00368 GLP	Rat (Sprague-Dawley, 20 M, 20 F)	0, 100, 300, 1000 mg/kg, PO M: 4 weeks prior to mating F: 2 week prior to mating to Day 7 of gestation	NOAEL: F0 males, F0 females, F1 litter 1000 mg/kg

Dose formulated in 0.5% HPMC, 0.1% Tween 80

Table 7. Overview of embryo-fœtal development studies.

Study type / Study ID / GLP	**Species; No / sex / group**	**Route & dose, Study design**	**Major findings**
Embryofetal development (XD2009/00367) GLP	Rat (Sprague-Dawley, 20 F)	0, 100, 300, 1000, mg/kg PO GD6-GD17	Preimplantation loss (%) slightly ↑ at 1000 mg/kg. Litter parameters not affected. NOAEL F0 females, F1 litters: 1000 mg/kg.
Embryofetal development (XD2009/00366) GLP	Rabbit (Japanese White, 20 F)	0, 40, 200, 1000, mg/kg, PO GD6-GD18	≥200 mg/kg: Bw. gain, food intake ↓. Scant feces/urine incidence ↑. NOAEL F0 females: 200 mg/kg (general toxicity) 1000 mg/kg (reproductive toxicity) F1 litters: 1000 mg/kg.

Dose formulated in 0.5% HPMC, 0.1% Tween 80

Table 8. Overview of prenatal and postnatal development, including maternal function studies

Study type / Study ID / GLP	**Species; No / sex / group**	**Route & dose Study design**	**Major findings**
Pre and postnatal development including maternal function (2011N121663) GLP	Rat (Sprague-Dawley, 22 F)	0, 5, 50, 1000, mg/kg, PO GD6-LD20	1000 mg/kg: Bw, food intake ↓. NOAEL: F0: 50 mg/kg (general toxicity, 1000 mg/kg (reproductive function) F1: 50 mg/kg

Table 9. Rat juvenile toxicity study

Study ID	**Species / Sex / No. / Group**	**Dose (mg/kg)**	**Duration**	**Major Findings**
CD2009/00409	Rat (Sprague-Dawley 10-20 M, 10-20 F)	5, 50, 100, 500, 1000, PO	D 4-21 post-partum	≥500 mg/kg: Deaths, growth retardation. Alopecia, loss of skin elasticity, decreased body weight and body length.
CD2009/00770	Rat (Sprague-Dawley 20 M, 20 F)	2, 25, 75, 300, PO	D 4-31 post-partum	≥25 mg/kg: Body w. ↓. Peripheral blood T cells ↓. 75 mg/kg: spleen lymphocytes ↓. Eosinophilic infiltrate mucosa of glandular stomach, extramedullary hematopoiesis ↑. 300 mg/kg: Deaths, alopecia activity↓. Skin elasticity ↓. Body w. ↓.Lymphocytes ↓in splenic white pulp, thymus and mesenteric and mandibular lymph nodes. Eosinophilic infiltrate

Study ID	Species/Sex/ No./Group	Dose (mg/kg)	Duration	Major Findings
				mucosa of glandular stomach, cytoplasmic rarefaction hepatocytes liver.
G09229 (GLP)	Rat (Sprague-Dawley 10-20 M, 10-20 F)	0, 0.5, 2, 75, PO	D 4-66 post-partum	75 mg/kg: Body w. ↓. Two deaths. NOAEL 2 mg/kg

Formulated in 0.5% HPMC with 0.1 w/w% Tween 80.

Local Tolerance

Local tolerance studies conducted *in vitro* and *in vivo* showed that dolutegravir had mild irritant effects on abraded skin and slight ocular irritating effects that were reduced with rinsing after exposure. Dolutegravir was non-sensitizing in the mouse local lymph node assay.

Dolutegravir absorbs light in the wavelength of 290-700 nm and the rat distribution study showed that drug-related material reaches the uveal tract as well as the skin. A review of clinical data has been presented by the Applicant. No phototoxicity reactions were identified; however, the data obtained in clinical trials are limited and it is unclear to what extent patients have been exposed to sun. Hence, a phototoxicity study in accordance with the applicable guideline will be performed by the Applicant (see RMP section 2.8).

Other toxicity studies

Immunotoxicity

Table 10. Rat immunotoxicity study

Type of test/ study ID/GLP	Dose/Concentration/ Test system	Major findings
Rat (Sprague-Dawley, 10 m, 10 F) (RD2009/00751) GLP	0, 10, 100, 1000 mg/kg/d, PO 1 month	1000 mg/kg: Spleen w. ↑. No effects in anti-Hemocyanin, Keyhole limpet antibody titers, no effect on T-cell dependent antibody formation.

In a 2 week monkey study spleen atrophy of white pulp was reported at a dose of 1000 mg/kg. Data from the separate juvenile toxicity study that included immunological endpoints did not suggest any particular developmental immunotoxicity of dolutegravir. Overall based on non-clinical data the potential for immunotoxicity would appear a minor concern.

Impurities

Impurities in batches used in major toxicology studies were stated to be representative of those in batches used in clinical studies. Three impurities as intermediates in the synthesis and

manufacturing process were tested positive in *in vitro* genotoxicity studies. The impurities are controlled by specification or control of the manufacturing process.

2.3.5. Ecotoxicity / environmental risk assessment

Table 11. Summary of main study results

Substance (INN / Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107*	Log Dow (pH 5)=-2.28 Log Dow (pH 7)=-2.45 Log Dow (pH 9)=-3.21			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}	-2.45			not B
Persistence	DT50 or ready biodegradability	Not biodegradable			P
Toxicity	NOEC or CMR	***See below***			***Not T***
PBT-statement :	Log Dow is below trigger value. Data taken together do not indicate that the criteria for PBT are met.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.5	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Sorption-activated sludge	OPPTs 835.1110	Kd_{oc} =10609-15367 (activated sludge) Freundich sorption coefficient 14407 (Koc=4.16)			Sorps to sludge
Ready Biodegradability Test	OECD 301 B	Not biodegradable			28 days
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Aerobic: $DT_{50,\ whole\ system}$ >1000 days % shifting to sediment =82.1-88			Once in sediment the system remained generally unchanged
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.0954	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.834	mg/L	Reproduction and survival
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.753	mg/L	*Pimephales promelas* No surviving fry at 11 mg/l, NOEC for hatching success 3.57 mg/l.
Activated Sludge, Respiration	OECD 209	EC	>100	mg/	No inhibitory

Inhibition Test				L	effect
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF			
Aerobic and anaerobic transformation in soil	OECD 307	DT50	>1000 days		for 3 soils (in South Witham soil not possible to determine)
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	985	mg/ kg	EC50 could not be calculated
Water sediment effects	OECD218	NOEC	858	mg/ kg	*Chironomus riparius*
Terrestrial Plants, Growth Test/*Species*	OECD 208	EC50 (growth) wheat, onion, dwarf bean, tomato, turnip, pea	79.9 (pea) to >1000 (wheat, onion)	mg/ kg	Overall NOEC 12 mg a.i. /kg.
Earthworm, Acute Toxicity Tests	OECD 207	NOEC ≥1000 mg/kg dry soil		mg/ kg	*Eisenia fetida*
Collembola, Reproduction Test	OECD 232	NOEC (reproductio n)**	29	mg/ kg	*Folsomia candida*

* The distribution coefficient (Dow) was determined as the partition coefficient only could be determined on unionised material. The distribution coefficient takes into account the total species of the chemical (ionised and neutral).

** An EC50 could not be calculated. A 50% mortality was not reached in any group; EC50 (mortality, reproduction) >1000 mg/kg.

Dolutegravir does not fulfil the criteria to be classified as a PBT substance.

Considering the above data, dolutegravir is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.

The pharmacology of dolutegravir including potential for secondary activity and any pharmacological action on function of major organ systems, were investigated *in vitro* and *in vivo*. The non-clinical studies have shown expected inhibition of HIV integrase and antiviral activity consistent with the mode of action. Secondary pharmacology and safety pharmacology studies were indicative of dolutegravir having little potential for off target effects as well as low likelihood for interference with normal organ function. In vitro, dolutegravir inhibited the binding of radiolabeled α-melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) receptor by 64% at a concentration equal to the clinical C_{max}. The MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity. The potential effect of dolutegravir on the binding of natural ligands to other melanocortin receptors will be further clarified by conducting *in vitro* binding assays (see RMP in Section 2.8).

The pharmacokinetic investigations supported the use of rat and monkey in general toxicity studies. The metabolite profiles in different species showed overall comparable pattern of metabolites with no unique metabolites formed in humans and not found in animals.

In rat repeated dose toxicity studies that ranged from 2 weeks to 26 weeks, the principal toxicity was manifested as gastric mucosal changes and lesions. Findings included eosinophilic infiltration, thickening of the limiting ridge mucosa, oedema, acanthosis as well as incidences of microscopic hemorrhage in the glandular stomach. The changes were attributed to local irritating properties and showed reversibility during a 1 month treatment free period. The repeated dose toxicity studies on dolutegravir showed that the monkey was particularly sensitive species to adverse effects possibly related to gastrointestinal intolerance. Adverse effects of dolutegravir were evident in the stomach, cecum, colon, rectum in both rat and monkey. In monkey, with increasing study duration from 14 days to 38 weeks tolerance appeared to decrease markedly. Indeed, a total dose of 4200 mg over 14 days was relatively well tolerated in contrast to a total dose of 3000 mg over approximately 55-59 days that was related to deaths in the 38 week study.

In both rat and monkey hematopoietic effects such as increases in mean platelets volumes and red cell distribution width as well as increases in reticulocytes were recorded. At a high dose of 1000 mg/kg one male monkey had decreased nucleated cell count upon bone marrow examination. While bone marrow effects occurred at low exposure multiples with respect to expected clinical values, the clinical data has not indicated any signal for such toxicity.

There were indications of a potential for dolutegravir to disturb liver functional activity in the 3 months study in rats. In monkeys, liver effects were reported at doses from 300 mg/kg in the 2 week study with more pronounced reactions, including single cell necrosis and hypertrophy at a dose of 1000 mg/kg. In the high dose monkey study, the safety margin (NOAL for liver reactions) was around 3-4 times the exposure seen in humans. The mechanism of liver injury in monkey is not known. Some clinical data have indicated a potential for liver reactions to dolutegravir and the hepatic effects are further considered in the clinical safety section (see Section 2.6).

Dolutegravir was tested *in vitro* for genotoxicity up to cytotoxic concentrations. Negative results were reported except for a weakly positive result in the mouse lymphoma assay at high cytotoxicity. The *in vivo* rat micronucleus test was negative. The data did not indicate any relevant genotoxic potential of dolutegravir.

Long term carcinogenicity studies were conducted in mouse and rat. Overall dolutegravir did not exhibit any significant neoplastic activity in either study. Indeed, the data are consistent with a lack of any clinically relevant carcinogenicity of dolutegravir.

There were no noteworthy findings with respect to sperm functional parameters and morphology in male rats treated with doses up to 1000 mg/kg. Indeed, male and female fertility did not appear to be affected at doses up to 1000 mg/kg providing exposure multiples of approximately x27 the expected clinical value at a dose of 50 mg bid.

Parameters monitored for embryofoetal development in rat and rabbit after treatment with dolutegravir from the period of implantation to closure of the hard palate, were within normal limits. Doses up to 1000 mg/kg in rat caused a slight increase in pre implantation loss, but no increases in external, visceral or skeletal malformation or variations in offspring were recorded. In rabbits, doses of 1000 mg/kg were associated with slight general toxicity such as decreased food

consumption and body weight, but no significant embryotoxic effects were observed. However, the high dose in rabbit produced systemic exposure levels that did not exceed the expected clinical level.

Reproduction toxicity studies included an investigation on prenatal and postnatal development after administration of dolutegravir at doses of 5, 50 and 1000 mg/kg from the period of implantation to weaning of offspring. Maternal function such as maintenance of pregnancy, delivery and nursing was not affected by treatment with dolutegravir. Dolutegravir also had no effects on development of offspring, early behaviour, physical development, sensory functions, genital development and mating ability and fertility of offspring. Due to decreases in maternal and pup bodyweights the NOAEL for F1 pre and postnatal development was set to 50 mg/kg.

Dolutegravir absorbs light in the wavelength of 290-700 nm and the rat distribution study showed that drug-related material reaches the uveal tract as well as the skin. A review of clinical data has been presented by the Applicant. No phototoxicity reactions were identified; however, the data obtained in clinical trials are limited and it is unclear to what extent patients have been exposed to sun. Hence, a phototoxicity study in accordance with the applicable guideline will be performed by the Applicant (see RMP section 2.8).

A dedicated 1 month immunotoxicity study in rat given oral doses up to 1000 mg/kg did not indicate any important effects on T-cell dependent antibody formation.

Dolutegravir does not fulfil the criteria to be classified as a PBT substance. Considering the ERA data, dolutegravir is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Separate juvenile toxicity studies were conducted where offspring were given oral doses from day 4 to 66 postpartum. Juvenile rats were much more sensitive to adverse effects of dolutegravir compared with adults and deaths occurred at doses of 75 mg/kg/day. Nasal degeneration/regeneration observed at all dose levels were considered a local irritant effect secondary to expelling of gavage material. There were indications that a local irritant effect may be a class effect of integrase inhibitors. The lack of irritant effect in stomach, oesophagus and tongue should also be taken into account. Higher systemic exposures were achieved in pre-weaning pups (day 13) than in juveniles likely reflecting early differential expression of the primary drug metabolizing enzyme, uridine glucuronosyl transferase. The cause of deaths was not identified. The study included immunological evaluation. Dolutegravir did not have any remarkable effects on immunological competence or on lymphocyte subset counts. Overall, the data did not raise specific concern of potential unwanted reactions in the paediatric population.

2.3.7. Conclusion on the non-clinical aspects

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at

doses that produce systemic exposures approximately 21 and 0.82 times the 50 mg twice daily human clinical exposure based on AUC, respectively.

There were indications of a potential for dolutegravir to disturb liver functional activity in the 3 months study in rats. In monkeys, liver effects were reported at doses from 300 mg/kg in the 2 week study with more pronounced reactions, including single cell necrosis and hypertrophy at a dose of 1000 mg/kg. The mechanism of liver injury in monkey is not known. Some clinical data have indicated a potential for liver reactions to dolutegravir and the hepatic effects are further considered in the clinical safety section (see Section 2.6).

In rabbit embryo-fœtal development study, doses of 1000 mg/kg were associated with slight general toxicity such as decreased food consumption and body weight, but no significant embryotoxic effects were observed. Of note, this dose corresponded to 0.40 times the 50 mg twice daily human clinical exposure based on AUC.

Overall, the non-clinical studies have provided sufficient characterisation of the principal aspects of toxicity of dolutegravir.

The CHMP considers the following additional pharmacovigilance activities necessary to further elucidate potential safety issues arising from the non-clinical data, as reflected in the pharmacovigilance plan (see RMP in Section 2.8):

- The potential effect of dolutegravir on the binding of natural ligands to other melanocortin receptors will be further clarified by conducting *in vitro* binding assays.
- A phototoxicity study in accordance with the applicable guideline will be performed by the Applicant.

2.4. Clinical aspects

2.4.1. 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

Protocol No. **(Study Type)**	**Study Objectives**
Pharmacokinetic Studies in HIV-Negative Subjects	
ING111207 (Dose Linearity)	To assess safety, tolerability and PK of single doses of DTG
ING111322 (Dose Linearity)	To assess safety, tolerability and Pharmacokinetics (PK) of repeat doses of DTG To assess safety, tolerability and PK of single doses of DTG suspension and single doses of

Protocol No. (Study Type)	Study Objectives
	DTG tablets with or without food
ING111853 (Mass Balance)	To investigate the recovery, excretion, and PK of 14C-DTG
ING115465 (PK)	To describe DTG exposure in cervicovaginal fluid, cervical and vaginal tissue
ING116195 (PK)	To describe DTG exposure in semen and rectal tissue
ING113125 (PK)	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with severe renal impairment
ING113097 (PK)	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with mild or moderate hepatic impairment based on Child-Pugh category
ING115381 (PK)	To assess safety, tolerability and PK of single doses of DTG in healthy Japanese subjects
ING113099 (Drug Interaction)	To assess the potential for a drug interaction between DTG and rifampin (RIF) and between DTG and rifabutin (RIFABUT)
ING115696 (Drug Interaction)	To investigate the effects of prednisone on the steady-state PK of DTG
ING115697 (Drug Interaction)	To assess the potential for a drug interaction between DTG and telaprevir (TLV) and between DTG and bocepravir (BCV)
ING115698 (Drug Interaction)	To assess the potential for a drug interaction between DTG and methadone
ING111405 (Drug Interaction)	To assess the potential for a drug interaction between DTG and lopinavir (LPV)/ ritonavir (RTV) and between DTG and darunavir (DRV)/ RTV
ING111602 (Drug Interaction)	To assess the potential for a drug interaction between DTG and multivitamin and between DTG and Maalox
ING116898 (Drug Interaction)	To assess the potential for a drug interaction between DTG and calcium carbonate and between DTG and ferrous fumarate
ING111603 (Drug Interaction)	To assess the potential for a drug interaction between DTG and etravirine (ETV)
ING111604 (Drug Interaction)	To assess the potential for a drug interaction between DTG and tenofovir (TDF)
ING111854 (Drug Interaction)	To assess the potential for a drug interaction between DTG and atazanavir (ATV) and between DTG and ATV/RTV

Protocol No. **(Study Type)**	**Study Objectives**
ING111855 (Drug Interaction)	To assess the potential for a drug interaction between DTG and oral contraceptives (ethinyl estradiol (EE) /norgestimate [NGM])
ING112934 (Drug Interaction)	To assess the potential for a drug interaction between DTG, ETV, and LPV/RTV or DRV/RTV
ING112941 (Drug Interaction)	To evaluate the effect of a high fat meal and omeprazole on DTG PK and to evaluate the safety and PK of a 250 mg dose of DTG
ING113068 (Drug Interaction)	To investigate the effects of fosamprenavir (FPV)/ RTV on the steady-state PK of DTG and to evaluate relative bioavailability of tablets with varying particle size
ING113096 (Drug Interaction)	To assess the safety, tolerability and PK of repeat dose co-administration of DTG alone, tipranavir (TPV)/RTV alone, and DTG in combination with TPV/RTV
ING114005 (Drug Interaction)	To evaluate PK of DTG 100 mg versus 50 mg and the effect of efavirenz (EFV) on the PK, safety and tolerability of DTG 50 mg
LAI116181 (Drug Interaction)	To assess the potential for a drug interaction between DTG and rilpivirine (RPV)
ING116265 (PGx)	To evaluate the effects of UGT and CYP polymorphisms on the PK of DTG
Human Pharmacodynamic Studies	
ING111856 (PD)	To evaluate the effect of DTG on cardiac conduction as assessed by 12-lead electrocardiogram compared to placebo and moxifloxacin (Thorough QTc study of DTG)
ING114819 (PD)	To evaluate the effect of DTG on glomerular filtration rate as measured by iohexol and to evaluate creatinine clearance, extra-glomerular creatinine excretion, and renal plasma flow
Pharmacokinetic and PK/PD Studies in Target Patient Population	
ING111521 (PK and PK/PD)	To assess the safety, tolerability and efficacy of repeat dose DTG
ING116070 (PK)	To determine plasma (total and unbound) DTG concentration and evaluate the relationship between DTG concentration in plasma and CSF
ING112276 (PK and PK/PD)	To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/ emtricitabine (FTC) and to evaluate antiviral activity, safety and PK over time
ING113086 (PK and PK/PD)	To assess safety and efficacy of DTG 50 mg once daily to RAL 400 mg BID both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy
ING111762 (PK and PK/PD)	To evaluate safety and efficacy of DTG 50 mg once daily vs. raltegravir (RAL) 400 mg BID, both administered with an investigator-selected background regimen

Protocol No. (Study Type)	Study Objectives
ING112961 (PK and PK/PD)	To assess the antiviral activity of DTG containing regimen
ING112574 (PK and PK/PD)	To assess the antiviral activity of DTG administered with failing background therapy to Day 8 and thereafter with optimised background ART
ING112578 (PK)	To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in ART-naïve adult subjects (ING112276), to evaluate safety, tolerability, and steady-state PK of DTG in combination with other ARTs
ING116529 (PK and PK/PD)	To quantify the antiviral activity of DTG compared to placebo (PCB) when administered with failing background therapy for 7 days

For additional efficacy studies see table in Section 2.5.

2.4.2. Pharmacokinetics

The clinical pharmacology program was aimed at describing the absorption and disposition of dolutegravir. Further, to identify sub-groups of patients in which exposure might be altered and to reveal potential interactions with food and with other medical products.

Thirty phase I trials have been completed to investigate the clinical pharmacology of dolutegravir. Furthermore, population pharmacokinetic (popPK) analyses have been performed using data pooled from Phase II and III studies in HIV infected patients. In addition, ca. 30 *in vitro* studies have been performed to investigate the characteristics of DTG.

The commercial formulation of DTG is identical to the formulation used in the pivotal Phase 3 studies except for minor differences in shape and coating.

Analytical methods

The bioanalytical method for the measurement of DTG concentrations in plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labelled internal standard ([2H7 15N]-DTG) followed by HPLC-MS/MS analysis. DTG has two chiral centres. Generally, the used methods complied with acceptance criteria regarding selectivity, sensitivity, accuracy and precision. Short-term and long-term stability of the analytes in the biological matrix was tested and shown to be satisfactory.

Absorption

DTG is rapidly absorbed, with a t_{max} of 2 h to 3 h after oral dosing of the tablet formulation. The solubility in FeSSIF (fed state simulated intestinal fluid) was 0.170 mg/mL at pH 5. According to *in vitro* studies, DTG is a substrate of P-gp and BCRP transport proteins. However, due to the indicated high permeability and fast absorption (t_{max} is 0.5 h after administration of a suspension) the importance of P-gp and BCRP at the site of absorption is most likely low.

The absolute bioavailability of DTG has not been determined. However, based on data from the mass balance studies in animals (bile duct cannulated animals show low biliary excretion of parent compound) and man (major part of radioactivity recovered in late time points in faeces, >72 h after administration) the fraction absorbed is estimated to be approximately 50% after administration of the tablet formulation. Exposure to DTG is increased when administered with food. A high fat meal increased AUC by 66%, moderate meal by 41% and a low fat meal by 33%.

Co-administration of DTG and multivitamin decreased the exposure of DTG with approx. 30% due to complex binding to polyvalent metal ions. Concurrent administration of Maalox (antacid, polyvalent meta ions) decreased exposure of DTG >70%, while staggered dosing with Maalox, administered 2 h after DTG, reduced the exposure with 20-30%. Co-administration with either calcium or iron supplements led to a decreased exposure to dolutegravir by approximately 40% and 50%, respectively. However, the effect was essentially cancelled out by either staggered dosing (taking dolutegravir 2 hour prior to the supplement) or concomitant intake of a moderate fat meal.

Distribution

Plasma protein binding of DTG is high (approximately 99.3%) and independent of concentration over the therapeutic range based on *in vitro* data. In the hepatic impairment study the unbound fraction (f_u) of DTG increased with decreasing serum albumin concentration, while there was no evident trend in the relation between f_u and α_1-acid glycoprotein. The blood-plasma ratio was in the range 0.44 to 0.54.

Based on the population PK analysis, the apparent volume of distribution (V/F) in patients was determined to be 17-20 L. DTG is distributed to CSF and the resulting steady state concentration is similar to the unbound concentration in plasma. The distribution to the genital tract in males and females is low with an AUC ratio at steady state of <20%.

Elimination

Based on the population PK analysis, CL/F and half-life in patients was determined to be approximately 1 L/h and 14 h, respectively.

Excretion

In the human mass balance study the total mean recovery of the administered radioactive dose was 96%, with relative recovery of 64% in faeces (94% of radioactivity assigned) and 32% in urine (87% assigned). The plasma half-life of total radioactivity and parent compound were both 16 h.

Unchanged DTG constitutes the major part of the radioactivity excreted in faeces (53% of the dose). Virtually no (<1% of dose) DTG was excreted unchanged in the urine. It is likely that the major part of the DTG recovered in faeces originates from biliary excreted glucuronide conjugate, which has been converted back to parent in the gut lumen.

Metabolism

Parent compound accounts for 97% of the total plasma radioactivity. DTG is metabolised by UGT1A1 and approximately 20% of the dose in the mass balance study was found as glucuronide conjugate in urine. DTG is also metabolised by CYP3A4 (~10% of dose in mass balance study).

A reactive intermediate appear to be formed as observed in an *in vitro* study with GSH trapping and also *in vivo* as cysteine conjugate in human faeces. In incubations in human liver microsomes non-extractable radioactivity was detected. These findings are indicative of a reactive metabolic pathway. It is unknown which enzymes could be responsible. No human-specific metabolite was detected *in vitro* or *in vivo*.

Dose proportionality and time dependencies

Due to limitations in solubility, there is an approximate dose-proportional increase in exposure between 25 mg and 50 mg (tablet) while the increase is less than proportional between 50 mg and 100 mg. However, with 50 mg twice daily, the exposure over 24 h was approximately doubled compared to 50 mg once daily. No time dependent PK has been observed. Steady state is reached within five days of dosing.

Pharmacokinetics in Target Population

PK in the treatment-naïve population is similar to PK in healthy volunteers. In the treatment-experienced population, the AUC_{τ}, C_{max} and C_{τ} are lower compared to healthy volunteers. The lower exposure may be a result of the co-administration with drugs that induce the metabolism of DTG. However, the typical clearance in patients is similar to healthy volunteers when extrinsic and intrinsic factors have been taken into account. The intra- and inter-individual variability in exposure to DTG is low to moderate.

Special populations

Exposure to DTG was 40% lower in subjects with severe renal impairment (creatinine clearance 16 to 28 mL/min/1.73 m^2) compared to healthy controls. No dose adjustment is considered necessary for patients with renal impairment.

The unbound clearance of DTG was reduced by 35% to 50% in subjects with moderate hepatic impairment (HI) leading to an approximate 1.5 to 2-fold increase in unbound exposure to DTG. Three HI subjects had a Child-Pugh (C-P) total score of 9 while six subjects had a C-P total score of 7. No dose adjustment is considered necessary for patients with hepatic impairment.

Gender, race and weight had no clinically relevant effects on the PK of DTG. PK in adolescents 12 to 18 years of age was similar to adults (please refer to Section 2.5.2). The PK of DTG in elderly patients is not fully characterized.

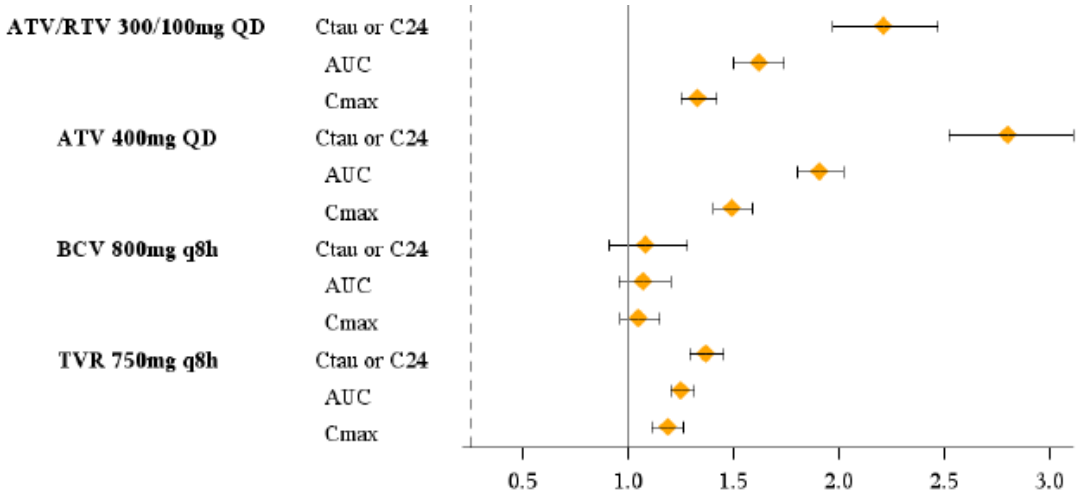
In a meta-analysis using pharmacogenetic samples from healthy volunteers (n=89), the influence of UGT1A1 polymorphism on the DTG exposure was investigated. The AUC_{τ} of DTG in subjects with the low function (*28/*28, *28/*37) and reduced function (e.g. *1/*28, *28/*36) of the UGT1A1 enzyme, increased by 46% and 17%, respectively. The frequency of homozygosity for UGT1A1*28 in Europeans is in the range 9-16%. The activity in subjects with this low function genotype is decreased up to 70%.

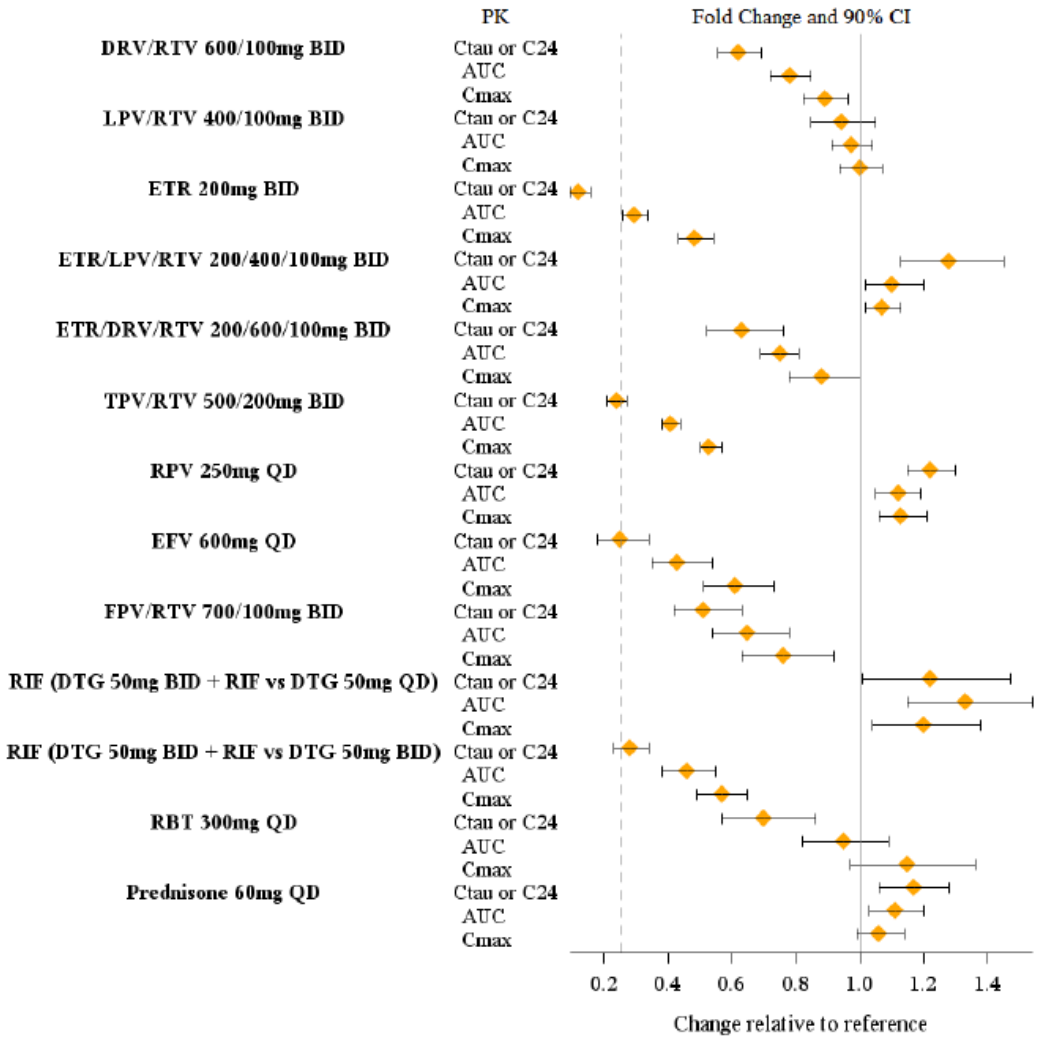
Pharmacokinetic interaction studies

Effects of other medicinal products on the PK of DTG

DTG is a substrate of UGT1A1 and CYP3A4 as well as of the transporter proteins P-pg and BCRP. No mechanistic studies aimed to investigate the relative importance of the elimination pathways have been performed, however a number of co-medications commonly used in clinical practice have been studied. A summary of the effects of co-administered drugs on the PK of DTG is given in plots in Figure 1.

Figure 1 Relative effect of co-administered drugs on DTG exposure (C_{tau}, AUC, C_{max})





ATV=atazanavir; BCV=boceprevir; DRV=darunavir; EFV=efavirenz; ETR=etravirine;FPV=fosamprenavir; LPV =lopinavir; RBT=rifabutin; RIF=rifampin; RPV=rilpivirine; RTV=ritonavir; TLV=telaprevir; TPV= tipranavir; TVR=Telaprevir

Effects of DTG on the PK of other drugs

The potential of DTG to inhibit/induce CYPs and UGTs has been investigated *in vitro* using relevant enzymes and also in two *in vivo* studies with midazolam (CYP3A4 probe) and efavirenz (CYP2B6 probe).

Based on this data the risk of clinically relevant DDIs due to inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 and 2D6 or general enzyme/transporter induction by DTG is considered low.

For CYP3A4 clinically relevant DDIs due to inhibition or induction by DTG at systemic level is considered low.

DTG did not inhibit BCRP, MRP2, MRP4, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and P-pg *in vitro* to any clinically relevant extent.

However, DTG did inhibit OCT2 in vitro, which is supported by the *in vivo* observation of a decrease in creatinine clearance. Based on the data available with cimetidine, a stronger inhibitor on OCT2 than DTG, the risk of interaction between dolutegravir and metformin is expected to be

in a lesser magnitude than observed with cimetidine. No further DDI study was considered necessary. Nonetheless, it is stated in the SmPC that co-administration of dolutegravir has the potential to increase metformin plasma concentration via inhibition of OCT2 transporter and that careful patient monitoring is advised when starting or ending concomitant treatment.

DTG also inhibited OAT1 and OAT3 in vitro. *In vivo*, OAT1 (tenofovir as substrate) was not inhibited by DTG. The DTG glucuronide conjugate did not inhibit MRP2 in vitro.

In vitro data indicate that DTG has the potential to inhibit CYP3A4 *in vivo*, both as competitive and mechanism based inhibitor. The Applicant performed a clinical DDI study with midazolam (CYP3A4 probe) in order to ensure that DTG is neither a CYP3A4 inhibitor nor an inducer. The trial was appropriately designed, except the dose of DTG used. In this study a 25 mg dose (suspension) was used instead of the 50 mg tablet. The AUC for midazolam was slightly lower when co-administered with DTG. C_{max} after a 25 mg dose of suspension and 50 mg tablet was 3.1 and 3.7 µg/mL, respectively, thus the risk of interaction at systemic level is considered negligible. However, there is some uncertainty regarding the concentrations in the entrocytes at intestinal level comparing the two dosing regimens of DTG. Indeed, an inhibition of metabolism of CYP3A4 substrates at the intestinal level by DTG can't be excluded. Therefore, the studied dose of DTG 25 mg was not considered adequate to assess the inhibitory effect of DTG on this isoenzyme and a the Applicant will further address the potential for an interaction between DTG and midazolam: Development of a PBPK model is planned to simulate the exposure of DTG at the enterocyte following a 25 mg suspension dose and a 50 mg commercial tablet dose, to assess any differential impact over the 25 mg suspension the 50 mg tablet formulation may have on the systemic exposure to midazolam (see RMP section 2.8).

2.4.3. Pharmacodynamics

Introduction: In vivo evolution of first generation integrase inhibitor resistance

Evolution of integrase inhibitor resistance is rapid and highly dynamic during failure with the first generations integrase inhibitors (Fransen et al J Virol, July 2012; Winters et al, Plos One, July 2012).

In DTG clinical studies, outcomes were analyzed by baseline resistance, i.e. the same time point that dolutegravir was started. Since it might not be feasible in clinical practice, the Applicant was asked to present resistance data from screening, as well as baseline, from the studies performed in INSTI (integrase strand transfer inhibitor) experienced patients, particularly in the subgroup that remained on failing INSTI therapy during this period. The outcome is discussed below.

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of DNA integration, essential for the HIV replication cycle.

Primary and Secondary pharmacology

***In vitro* findings**

In vitro activity and selection experiments

DTG is a pure isomer (4R-12S) and the IC_{50} of dolutegravir ranged 0.5 to around 2 nM against both HIV-1 lab strains and clinical isolates of various subtypes (a large number of subtype B isolates tested, and a more limited number of subtypes A, C,D,E,F,G and group O).

To be noted, dolutegravir also showed similarly high activity to HIV-2 strains, in vitro. Hence, dolutegravir may be an important option for HIV-2 infected patients in need of therapy. Since that population generally have less treatment options, clinical studies are highly encouraged by the CHMP.

Dolutegravir is highly protein-bound (99.3%), albumin likely being the main binding component (more than α1-acid glycoprotein). When extrapolated to 100% human serum a maximum 75-fold shift was observed with MT-4 assays, resulting in a mean protein-adjusted IC_{50} of 38 nM for Peripheral Blood Mononuclear Cell (PBMCs).

Serial passage is used to study resistance evolution in vitro. When using the lab-strain HIVIII during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and F. The maximum fold change in susceptibility was relatively low, 4 (vs baseline value). None of these mutations have been associated with raltegravir, and they were so far not selected in patients in the clinical studies.

With another strain, NL432; selection was done either starting with wild type or with site directed mutants, where primary integrase inhibitor associated mutations (for raltegravir) had been introduced. Passage was done either at steady concentrations (6.4 nM) or at increasing concentrations (6.4-32 nM), for 56 days. The following findings were seen:

- Starting with NL432 wild type virus, mutations E92Q and G193E (not associated with raltegravir) was selected, with a very slight effect on dolutegravir susceptibility. In the clinical trials these mutations have been selected for in patients treated with dolutegravir, and they are listed as secondary mutations.
- When starting with site directed mutants harboring mutations N155H or E92Q (primary for raltegravir) no further selection of resistance was seen (and fold change (FC) was unchanged).
- In contrast, when starting with a virus harboring the Q148-mutation a rapid selection of a secondary mutation was seen, with a consequent high FC to dolutegravir. Hence, in the presence of mutation Q148 the high resistance barrier seemed to be broken, despite the fact that this mutation per se (without additional secondary) does not cause a reduced susceptibility *in vitro* (FC 1).

In further selection experiments with clinical isolates of subtype B isolates a mutation R263K was seen in all 5 B isolates after 20 weeks and onwards. This mutation does not increase the *in vitro* FC, and was seen in a couple of patients in phase 3 (both with a very low background activity).

In subtype C (n=2) and A/G (n=2) isolates the R263K was only seen in one case, while another mutation, G118R, was selected in 2 isolates. The G118R lowers the susceptibility to dolutegravir in site directed mutants (FC 10), but was so far not selected in the patients in the phase 3 program.

In vitro activity against clinical isolates with various resistance patterns and site directed mutants

In vitro susceptibility (Monogram Biosciences PhenoSense assay) has been studied for a substantial number of clinical isolates obtained from patients with prior treatment failure with an integrase inhibitor (raltegravir for the most). In line with the selection experiments discussed, the *in vitro* activity was not affected in the presence of primary mutations other than Q148H/R/K, also in the presence of secondary mutations, and double primary.

With regards to isolates where the Q148-mutation + secondary mutations are present, the *in vitro* activity is lower, with a wide range of FC. The number of additional secondary mutations (1 or ≥2) in clinical studies could possibly determine whether relevant long-term activity of dolutegravir would be expected. Indeed, during functional monotherapy with a 50mg qd dose in this population, the viral decay was lower in the presence of Q148+ ≥2 secondary mutations. Furthermore, in the phase 3 study (VIKING-3, dose 50 mg bid) the 24 week outcomes was better for patients with Q148 + 1 (19/32, 59% responding) than for those with Q148 + ≥2 secondary mutations at baseline (response in 5/21, 24%). However, when looking at the susceptibility *in vitro* for clinical isolates (FC vs wild type) by the number of secondary mutations in addition to Q148 (1 or ≥2), there is an extensive overlap (median FC being around 5 for both patterns).

The variability of *in vitro* susceptibility (of clinical isolates with the same genotypic resistance pattern) is always higher than that seen in experiments of site directed mutants (SDMs), for methodological reasons. Looking at SDM experiments there is still a rather varied picture for the Q148 +1 vs ≥2 secondary mutations. Some double mutants showed a FC >10, while some triple mutants had a FC around 2, depending on which secondary mutations were introduced.

In contrast, activity of dolutegravir (in SDMs) to other primary mutations was consistent with what was already discussed. All but 1 single mutation showed very limited effects on doluteravir activity. Mutation G118R (selected *in vitro* in 2 non-B isolates, but so far not *in vivo*) caused a FC of 10 in this experiment, but with a high degree of uncertainty (SD 4.7). Very limited effects on activity were seen in for relevant double and triple mutants in the absence of the Q148-mutation.

Minor variants in clinical isolates from the phase 2 studies by deep sequencing techniques

Regarding the issue of resistance dynamics discussed in the introduction of this section, the applicant explored baseline isolates (VIKING pilot, phase 2) with deep sequencing techniques, in addition to the routine population sequencing. With the latter technique a mutation needs to be present in some 20% of the viral in the sample, to be detected, while deep sequencing has a detection limit at around 1%.

The key finding from that analysis was that the more sensitive technique did not detect any additional primary mutations or secondary mutations in baseline isolates from patients with raltegravir on-going at the time of sampling (including those with the Q148 mutation).

For those who had stopped raltegravir prior to this study (i.e. documented integrase resistance in the past), and where no primary mutations were detected by population sequencing, ultra deep sequencing detected primary mutations in a couple of cases, and secondary mutations in varying percentages in some.

These more sensitive analyses were done on the baseline samples (i.e. from one specific moment) and still do not really fully apply to the issue of rapid dynamics, discussed in the introduction. Hence, the Applicant was asked to compare genotypes (as assessed by population sequencing) from screening and baseline samples, respectively. In Viking-3 for the 98 subjects with raltegravir

or elvitegravir as part of the current failing therapy from screening through to Day 1, 88/98 have paired IN genotypes for the investigation of IN pathway evolution. Of these 88 subjects 14/88 (16%) had changes in their IN genotypic profile. Only 4/88 (5%) had changes in their IN genotypic profile that impacted the identification of Q148 pathway virus (in either direction – loss of or addition of Q148 or associated mutations), table below.

Table 12. IN genotypic profile for the 98 subjects in Viking-3 with raltegravir or elvitegravir as part of the current failing therapy from screening through to Day 1

Subject	Screening IN Genotype	Baseline IN Genotype	Screening IN Mutation Category (prespecified)	Baseline IN Mutation Category (prespecified)	Outcome at Week 24 (HIV-1 RNA c/mL)
7	G140S, Q148H, G163G/R	G140S, Q148H	Q148+≥2	Q148+1	<50
487	V151I, N155H	G140S, Q148H, V151I	N155H	Q148+2	<50
572	G140S, Q148R	E138E/A, G140S, Q148R	Q148+1	Q148+2	<50
1243*	G140S, Q148H	G140G/S	Q148+1	No Primary Detected	2805

*Subject 1243 met PDVF criteria at Week 24. Resistance testing at the Week 24 time point showed E138E/K, G140G/S, and Q148Q/H.
b) The Week 24 outcomes for those subjects with a switch that includes changes in Q148 pathway virus identification is provided above. A fifth subject, Subject 343 with only Y143R at Screening had T97T/A, Y143Y/R/H/C, V151V/I, and N155N/H at Baseline and as such was classified as >2 Primary detected in the analysis. This subject at Week 24 had HIV-1 <50 c/mL Therefore a comparison of Week 24 outcomes between Screening defined IN Mutation Groups and Baseline IN Mutation Groups would not provide different efficacy results from those previously.

The turnaround time between screening and baseline would be roughly the same as in clinical practice. During that time frame only 2 (marked blue in the table) had a change in INI resistance from screening to baseline that would be considered as a risk for a worsened outcome with the baseline resistance as compared to that found at screening, out of 88 patients possible to evaluate (both still with a favorable treatment outcome at week 24).

However, as indicated previously, integrase resistance may evolve quickly during failure with first generations integrase inhibitors (RAL/EVG), sometimes with a rapid change in the pattern of mutations that would have consequences for the effect of dolutegravir i.e. from non-Q148 pattern to Q148-pattern (Fransen et al J Virol, July 2012; Winters et al, Plos One, July 2012).

Resistance *in vivo* - in patients failing dolutegravir

In patients naïve to class (prior integrase inhibitor class resistance not present)

In practice *de novo* resistance to the integrase class has not been selected during therapy with dolutegravir in this patient population within the clinical trials:

In the two pivotal studies in patients without prior HIV treatment ("SINGLE" and "SPRING 2) 825 patients treated with dolutegravir in combination with abacavir/lamivudine (583) and tenofovir/emtricitabine (242) were followed for ≥48 weeks. *De novo* resistance to integrase inhibitors were detected from none (nor any resistance to the NRTI backbones).

In patients with treatment failure, and resistance to at least 2 drug classes, but naïve to treatment with an integrase inhibitor (SAILING), there were 19 vs 43 patients with protocol defined virological failure up to week 48 for those treated with dolutegravir (n=354) and raltegravir (n=361), respectively. Among the 19 treated with dolutegravir predefined integrase inhibitor associated mutations emerged in 4 (~1% of the total number treated). In 3 out of these 4 patients no increase in fold change to DTG was seen (FC<2 at time of failure); only secondary DTG-associated mutations with unknown clinical significance was detected. In the 4th patient a FC>25 was seen at time of failure. However, this patient had advanced resistance to the integrase class already at baseline, and likely not naïve to the integrase inhibitor class.

In those failing with raltegravir, emerging mutations was seen in 16 patients, with a resistance pattern typical for this agent.

In patients with prior integrase inhibitor failure (integrase inhibitor resistance present)

In VIKING-3, data from functional monotherapy (7 days) and 24 weeks outcomes is available for all 183 patients (see Section 2.5.2). In the first 114 patients followed for at least 24 weeks, protocol defined virological failure was seen in 35/114 patients, with paired genotypes available for 31. In patients where new mutations were detected at failure (as compared to baseline pattern), this typically occurred in patients with a history of the Q148-mutation and only concerned the selection of mutations previously known to be associated to raltegravir treatment failure. In those patients where several new mutations were selected, this in fact only occurred in patients without detectable primary mutations at baseline (i.e. patients included based on prior documented resistance, and without raltegravir on-going as part of failing therapy when entering the study).

During functional monotherapy, mutation G163G/R was selected (also seen during long term serial passage in WT virus) in 2/183 patients; both had a sensitivity score of 0 in the failing background, and both showed isolates with an unchanged FC to dolutegravir at day 8 as compared to baseline.

2.4.4. Discussion on clinical pharmacology

Absorption

Dolutegravir is rapidly absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for tablet formulation. A high fat meal increased AUC by 66%, moderate meal by 41% and a low fat meal by 33%.

Excretion and Metabolism

The absolute bioavailability is not known, however the fraction absorbed from tablet formulation is estimated to be approximately 50%, based on recovered radioactivity in late faeces samples (>72 h after dose, major part corresponds to parent compound). It is likely that the major fraction of the DTG recovered in faeces originates from biliary excreted glucuronide conjugate, based on similar data from bile duct cannulated Cynomolgus monkeys.

Hepatic metabolism constitutes >25% of the DTG clearance pathway. Thus, it is considered important to determine whether DTG is a substrate of hepatic uptake transporters OATP1B1 and

OATP1B3. The Applicant will therefore perform *in vitro* uptake studies for OATP1B1/1B3 (see RMP section 2.8).

Drug-Drug Interactions

In the absence of class resistance, most interactions can be handled with dose adjustment.

Key anti-epileptic drugs have not been studied. Since, carbamazepine is a known strong enzyme and P-pg inducer, the CHMP recommends the Applicant to perform a DDI study with DTG and carbamazepine.

In vitro data indicate that DTG has the potential to inhibit CYP3A4 *in vivo*, both as competitive and mechanism based inhibitor. The Applicant performed a clinical DDI study with midazolam (CYP3A4 probe) in order to ensure that DTG is neither a CYP3A4 inhibitor nor an inducer. The trial was appropriately designed, except the dose of DTG used (25 mg instead of 50 mg). Therefore, the studied dose of DTG 25 mg was not considered adequate to assess the inhibitory effect of DTG on this isoenzyme and a the Applicant will further address the potential for an interaction between DTG and midazolam: Development of a PBPK model is planned to simulate the exposure of DTG at the enterocyte following a 25 mg suspension dose and a 50 mg commercial tablet dose, to assess any differential impact over the 25 mg suspension the 50 mg tablet formulation may have on the systemic exposure to midazolam (see RMP section 2.8).

Special Populations

The general trend was that renal impaired subjects had lower exposure to DTG. No dose adjustment is considered necessary for patients with renal impairment.

The unbound clearance (CL_u) of DTG in subjects with moderate hepatic impairment was reduced by approximately 35% to 50% compared to healthy controls leading to an approximate 1.5 to 2-fold increase in free exposure to DTG. However, this particular increase in exposure does not constitute a safety concern and no dosage adjustment is considered necessary for patients with hepatic impairment.

Pharmacodynamics

Dolutegravir shows activity at nano-molar levels to HIV-1 of various strains and subtypes. The activity against HIV-2 (only studied in vitro) is similarly high.

The resistance barrier of dolutegravir is high. No relevant integrase resistance was selected throughout the clinical studies in patients naïve to the class, including those who had a suboptimal activity of background agents. This clinical finding is supported by *in vitro* data, where selection of resistance was slow in wild type virus, and only yielded mutations which do not seem clinically relevant.

In patients who failed therapy with a first generation integrase inhibitor, a number of primary mutations (Q148, N155H, Y143, E92), followed by secondary mutations, may be selected. The activity and resistance barrier of dolutegravir does not seem to be relevantly affected by mutations other than the Q148-mutation. The Q148-mutation is seen in around 40% of those who failed raltegravir and where primary integrase resistance mutations were detected. In patients

who failed raltegravir and where the Q148-mutation is detected, 1 secondary mutation is more frequently detected than ≥ 2.

In VIKING 3, the median viral decay during short term functional monotherapy was around -1 log_{10} vs 0.5 log_{10} reduction, and 59% vs 25% respectively at week 24 (<50 copies/mL by snap shot). Given the poor activity of background regimen, dolutegravir shown a clear activity in the Q148 + 1 mutation subset of patients. However, the clinical data from the short term functional monotherapy and long term therapy with an optimised background regimen have shown a difference pending on the number of secondary mutations (1 versus ≥ 2). Please refer to Section 2.5.3 for discussions on the implications of these findings on the dosing recommendations for DTG.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic and pharmacodynamic properties of dolutegravir have in general been adequately characterized in healthy volunteers and HIV patients.

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of DNA integration, essential for the HIV replication cycle. Dolutegravir shows activity at nano-molar levels to HIV-1 of various strains and subtypes. The activity against HIV-2 (only studied in vitro) is similarly high.

In the absence of class resistance, most interactions can be handled with dose adjustment.

The resistance barrier of dolutegravir is high. No relevant integrase resistance was selected throughout the clinical studies in patients naïve to the class, including those who had a suboptimal activity of background agents. This clinical finding is supported by *in vitro* data, where selection of resistance was slow in wild type virus, and only yielded mutations which do not seem clinically relevant.

In patients who failed therapy with a first generation integrase inhibitor (raltegravir), a number of primary mutations (Q148, N155H, Y143, E92), followed by secondary mutations, may be selected. The activity and resistance barrier of dolutegravir does not seem to be relevantly affected by mutations other than the Q148-mutation. The clinical data, both from short term functional monotherapy and long term therapy with an optimized background, have shown a difference pending on the number of secondary mutations (1 versus ≥ 2). (See section 2.5.3)

The CHMP considers the following additional pharmacovigilance activities necessary to further elucidate potential safety issues arising from the pharmacology data, as reflected in the pharmacovigilance plan (see RMP section 2.8):

- Development of a PBPK model is planned to simulate the exposure of DTG at the enterocyte following a 25 mg suspension dose and a 50 mg commercial tablet dose, to assess any differential impact over the 25 mg suspension the 50 mg tablet formulation may have on the systemic exposure to midazolam.
- Hepatic metabolism constitutes >25% of the DTG clearance pathway. Thus, it is considered important to determine whether DTG is a substrate of hepatic uptake transporters OATP1B1 and OATP1B3. The Applicant will therefore perform in vitro uptake studies for OATP1B1/1B3.

2.5. Clinical efficacy

Dolutegravir efficacy and safety has been studied in the trials shown below. Hence, the program contains a full spectrum of patient populations; previously untreated patients and patients failing treatment with at least 2-class resistance but still naïve to integrase inhibitors, as well as patients with advanced resistance including the integrase inhibitors class.

Table 13. Table of clinical studies

Study Number	**Study Design**	**Primary Objectives / Patient Population**	**Duration**	**Regimens**
Exploratory				
ING111521	Dose-ranging, placebo-controlled monotherapy	Safety, tolerability and efficacy of repeat dose DTG Patients without ongoing therapy and without any prior treatment w/ integrase inhibitor.	10 days	DTG:2, 10, 50 mg qd
ING112276 (SPRING-1)	Randomized, dose-ranging	Dose selection Previously untreated.	96 weeks	DTG:10, 25, 50 mg qd Reference: efavirenz 600 mg Backbone: abc/3TC or tdf/FTC
ING112961 (VIKING)	10 days functional monotherapy, followed by optimized therapy.	Antiviral activity Patients with integrase class resistance documented.	96/48 weeks	50 mg qd (cohort 1) 50 mg bid (cohort 2) + OBT
ING116529 (VIKING-4)	Identical to VIKING-3 (below), with the exception that the 7 days period of functional monotherapy was placebo-controlled in VIKING-4 (n=30, 1:1).			
Pivotal				
ING113086 (SPRING-2)	double blind, active-controlled, non-inferiority study	Efficacy and safety for DTG vs RAL. Previously untreated.	48 weeks	DTG 50 mg qd. RAL: 400 mg bid; Backbone: abc/3TC or tdf/FTC
ING114467 (SINGLE)	double blind, active-controlled, non-inferiority study	Efficacy and safety for fixed dose DTG/3TC/abc versus Atripla Previously untreated.	48 weeks	(50/300/600 mg) qd vs Atripla (efavirenz / emtricitabine / tenofovir disoproxil)
ING111762 (SAILING)	double blind, active-controlled, non-inferiority study	Efficacy and safety for DTG 50 mg qd vs. RAL 400 mg BID, both with OBT. Failing patients, without integrase resistance.	24 weeks	DTG 50 mg qd + OBT vs RAL 400 mg BID + OBT
ING112574 (VIKING-3)	Multicenter, open-label, single arm	Activity of DTG during 7 days functional monotherapy, then with OBT. Failing patients, integrase class	24 weeks	DTG 50 mg BID; oral tablet

		resistance documented.		

In addition, ING114915 (FLAMINGO) is an on-going a phase IIIb study comparing DTG 50mg to DRV/RTV 800mg/100mg, both in combination with 2 NRTIs in previously untreated patients (1:1, n=468). Although not part of the application, the Applicant provided safety data for certain rare, but severe adverse events, from this study. These are discussed in the safety section.

2.5.1. Dose response studies

Exploratory studies

Study ING111521 : monotherapy for10 days in patients naïve to the class.

A clear dose response relationship was noted for the doses studied, 2-10-50 mg qd with mean VL decays of 1.5 and 2.0 and 2.5 log_{10}, respectively.

Plasma concentrations of dolutegravir reached steady state by 7 days of dosing, with slightly less than dose proportional increase of exposure. C_{tau} was the PK parameter that best predicted antiviral activity.

The treatment was well tolerated without obvious differences in AEs between arms.

SPRING-1: dose finding combination therapy in previously untreated patients.

Patients were randomized 1:1:1:1 to dolutegravir 10 mg, 20 mg 50 mg qd (blinded for dose), or efavirenz 600 mg qd, all in combination with open label Kivexa (abacavir / lamivudine) or Truvada (emtricitabine / tenofovir disoproxil). The study included 205 patients (around 50 per arm).

Patients were stratified for VL > or < 100.000 copies/ml, and by backbone NRTI.

The primary efficacy endpoint (for dose selection) was the proportion of subjects with HIV-1 RNA< 50 c/mL through Week 16 using the TLOVR algorithm.

The majority of patients across all 4 arms were white (80%) and male (86%) with a mean age of 37 years.

Median baseline CD4 count was ~ 300 cells/µl. The men who have sex with men (MSM) group dominated this study (65%).

Discontinuations (including for AEs) were seen in rather low frequencies with dolutegravir; a higher number of patients stopped efavirenz due to side effects.

No major difference in efficacy was seen for the different doses of dolutegravir. A numerically higher relapse rate was seen with the lowest dose of dolutegravir than with the 50 mg dose, see table below.

Table 14. Proportion with <50 copies/ml over time.

	dolutegravir			**efavirenz**
	10 mg	20 mg	50 mg	
Week 4	37/53 (70)	35/51 (69)	31/51 (61)	9/50 (18)
Week 16	51/53 (96)	46/51 (90)	47/51 (92)	29/50 (58)
Week 24	51/53 (96)	46/51 (90)	47/51 (92)	41/50 (82)
Week 48	48/53 (91)	45/51 (88)	46/51 (90)	40/50 (80)

Week 96	42/53 (79)	40/51 (78)	45/51 (88)	36/50 (72)
Week 96 virological non-response				
Any	7 (13)	4 (8)	2 (4)	4 (8)
NR	1	0	0	0
Rebound	6	4	2	4

No emerging integrase inhibitor resistance was detected. With regards to the RT gene, lamivudine resistance (mut184) emerged in 1 patients treated with dolutegravir at the lowest dose level (10 mg).

VIKING: efficacy in presence of resistance to integrase class

Two sequential cohorts of patients failing therapy and with genotypic resistance to raltegravir (integrase inhibitor) and to ≥2 other classes at baseline were studied in a single-armed design. The dose was 50 mg qd for cohort I (n=27) and 50 mg b.i.d. for cohort II (n=24).

The current failing regimen had to be unchanged for the previous 8 weeks as a minimum. Raltegravir was not necessarily part of the current regimen according the prior documented resistance provided.

Dolutegravir was added to the failing therapy through day 11 (functional monotherapy), followed by optimization of background (OBT). The inclusion of at least one fully active drug in the OBT was required for Cohort II. The data is presented for the 2 cohorts in parallel, to enable a comparison of the 2 doses.

Since the activity of the OBT differed extensively between cohorts (see table 15), the main interest of this study is comparison of viral decay by baseline genotypes and dose (50 mg qd versus bid) during functional monotherapy.

Table 15. Baseline data by cohort, the VIKING study.

	Cohort I (n=27)	**Cohort II (n=24)**
Median CD4+cells/mm3 (range)	114 (19,729)	202 (19, 528)
Median HIV-1 RNA log_{10}c/mL (range)	4.48 (2.64, 6.06)	4.26 (3.32, 5.84)
Mutation categories		
Q148 + ≥1	9 (33%)	11 (46%)
N155 or Y143 or other	18 (67%)	13 (54%)
Median RAL FC (range)	161 (0.57, 165)	128 (0.78, 183)
Median DTG FC (range)	1.5 (0.6, 35)	2.7 (0.9, 9.5)
Median years prior ARV (range)	14 (4, 21)	15 (3, 22)
Raltegravir failure: Current Historical	21 (78) 6 (22)	24 (100) 0
PSS of OBR 0 1 ≥2	 12 7 8	 1 9 14

Numbers by genotype are low, but the higher dose clearly seemed to yield a better effect in the harder to treat genotype (Q148) (see table 16). In contrast, for other primary mutations (N155, Y43 represented in this study), short term efficacy seems very similar for the two doses.

The impact of baseline susceptibilities to the failing regimen has been noted. However, numbers are very low in this VIKING pilot. The issue is further discussed in relation to VIKING-3 results.

Table 16. Outcome data during functional monotherapy, by baseline categories and cohort

Factors	**Cohort I 50 mg qd (N=27)**			**Cohort II 50 bid (N=24)**
	N	Mean [SD]	N	Mean [SD]
VL <10,000 c/mL	8	-1.26 [0.66]	7	-1.71 [0.21]
≥10,000 c/mL	19	-1.54 [0.81]	17	-1.77 [0.63]
Baseline IN Mutation pathway				
Q148 + 2	3	-0.40 [0.25]	2	-1.34 [0.63]
Q148 + 1	4	-1.17 [0.72]	8	-1.65 [0.49]
Mixture [a]	2	-0.29 [0.04]	1	-1.35
N155	4	-1.62 [0.64]	6	-1.57 [0.56]
Y143	12	-1.90 [0.55]	6	-2.10 [0.14]
Other mutations[b]	2	-1.76 [0.21]	1	-2.92
Baseline PSSf to Day 1 to 10 regimen				
0	18	-1.28 [0.78]	15	-1.57 [0.50]
1	6	-1.65 [0.69]	6	-1.89 [0.35]
2	1	-1.61	3	-2.43 [0.47]
>2	2	-2.34 [0.02]	0	

Mixtures: Q148H + Y143H + G140S(n=1); Q148H+ Y143H+ E138A+G140S (n=2)
Others: E92Q (n=1); none (screen; G140G/S, Q148H/Q) (n=1)

Long term outcomes for cohort II (using the higher dose, and with less extreme suboptimal background regimens) are of some interest, despite the low numbers. Virological failure up to week 48 was rather low (5/24), despite 10/24 having background activity of < 2. By baseline genotype, 5/10 patient with the Q148-mutation were responders at week 48 (eight of whom having 1 secondary mutation at baseline) and 12/14 patients with other baseline genotypes. This is in line with the data seen in the phase 3 study (VIKING-3) (see Section 2.5.2).

Dose Selection for phase 3 studies

Dolutegravir 50 mg qd was chosen for patients naïve to the class, the dose 50 mg bid was chosen for patients with class resistant virus in the phase 3 studies (see discussions in Section 2.5.3).

2.5.2. Main studies

Apart from the resistance issue, the same exclusion criteria applied in all studies, mainly:

- Ongoing AIDS-defining disease, excluding cutaneous Kaposi's sarcoma (KS) without need for systemic therapy
- Moderate to severe hepatic impairment as determined by Child-Pugh classification
- Recent history (<3 months) of upper or lower gastrointestinal bleed, with the exception of anal or rectal bleeding.
- Treatment with etravirine, efavirenz or nevirapine within 14 days of first dose of dolutegravir (etravirine accepted if co-administered with LPV/r or DRV/r).
- Treatment with TPV/r, FPV/r within 28 days prior to screening.
- Any verified Grade 4 laboratory abnormality, with the exception of Grade 4 lipids.

- Alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN).
- ALT > 3xULN and bilirubin > 1.5xULN (with >35% direct bilirubin).

In all studies the same non-antiretroviral medications were prohibited (for reasons of possible interactions), namely barbiturates, modafinil, pioglitazone, troglitazone, rifampin and rifabutin, phenytoin, phenobarbital, carbamazepine, oxcarbamazepine and St. John's wort.

Patients infected with HIV without resistance to integrase inhibitor class

ING113086 (SPRING-2)

Methods

A Phase III, randomized, double blind study of the safety and efficacy of Dolutegravir 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects.

Study Participants

Main inclusion criteria are listed here:

- HIV-1 infected, ART-naive adults ≥18 years of age;
- Plasma HIV-1 RNA ≥1000 c/mL at Screening;
- ART-naive (≤10 days of prior therapy with any ART agent).

Subjects starting ABC as part of the non-nucleoside reverse transcriptase inhibitor (NRTI) backbone must have been screened to be negative for the HLA-B*5701 allele.

Treatments

The DTG and RAL doses were administered in a double blind, double-dummy fashion during the Randomized Phase of the study. Subjects randomized to the DTG treatment group received DTG 50 mg once daily, with placebo to match RAL, to ensure subjects were blinded to the treatment arm. Subjects randomized to the RAL treatment group received RAL 400 mg twice daily, with placebo to match DTG. DTG and RAL were taken orally, with either ABC/3TC or TDF/FTC fixed dose combination (FDC) tablets as backbone therapy. DTG, RAL and the backbone NRTI therapy could be administered with or without food. A switch of backbone NRTI therapy to an alternate approved NRTI therapy for toxicity management was allowed once during the study.

Objectives

Primary Objective: To demonstrate the antiviral activity of DTG 50 mg administered QD compared with RAL 400 mg twice daily over 48 weeks in HIV-1 infected therapy naive subjects.

Secondary Objectives:

- To demonstrate the antiviral activity of DTG compared to RAL over 96 weeks.

- To compare the tolerability, long-term safety and antiviral and immunologic activity of DTG to RAL over time.
- To assess the development of viral resistance in subjects experiencing virological failure.
- To characterize the pharmacokinetics (PK) of DTG using a sparse PK sampling strategy and a population modelling approach.
- To explore exposure-response relationships of DTG (e.g., the relationship between DTG plasma exposure and virologic response or occurrence of adverse events (AEs).
- To evaluate the effect of subject characteristics (e.g., demographic factors) and concurrent medications on PK parameters of DTG.
- To evaluate the incidence of HIV-associated conditions in subjects treated with DTG compared to RAL over time.
- To explore the impact of gender, race and/or HIV-1 subtype on response to DTG and RAL over time.
- To explore the change in utility and health-related quality of life for subjects treated with DTG and RAL.

Full data from the primary endpoint/objective at Week 48 were presented. The safety cut-off date was 02 March 2012.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA <50 c/mL through Week 48 using the Missing, Switch or Discontinuation = Failure (MSDF) algorithm, as codified by the FDA's "snapshot" algorithm. Antiviral activity was assessed by quantitative plasma HIV-1 RNA. Immunological responses were assessed by total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts.

Sample size

Data on RAL from studies in treatment-naive HIV-1 infected subjects showed response rates of approximately 86% at Week 48 and 81%-83% at Week 96. The failure rate in any study is a combination of the performance of the drug and discontinuations for reasons less likely to be related to the performance of the drug (lost to follow up, withdrawal of consent, etc.). The rate of discontinuations for non-drug reasons historically has been higher for the Applicant's studies than for the studies of RAL. The control response rate assumed for this study combines the failure rate for drug reasons from the RAL studies with the failure rate for non-drug reasons from the Applicant's studies. This gives response rates of approximately 80% at Week 48 and 75% at Week 96. Using the lower of the two response rates for the power calculation yields ≥ 90% power at each time point.

Assuming a 75% response rate in the RAL arm, the study required 394 evaluable subjects per arm to have 90% power with a 10% non-inferiority margin and a one-sided 2.5% significance level.

Statistical methods

This study was designed to show that the antiviral treatment effect with DTG 50 mg once daily is not inferior to treatment with RAL 400 mg twice daily when each is administered in combination with dual NRTI therapy. The endpoint for the primary comparison is the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48.

The primary efficacy analyses were based on the Intent-to-Treat Exposed (ITT-E) Population that consisted of all randomized subjects who received at least one dose of study medication, and were assessed according to their randomized treatment. The FDA "snapshot" dataset was used to perform the primary efficacy analysis.

Results

Recruitment

Started in October 2010 – ongoing.

Conduct of the study

Major protocol deviations were infrequent and similar in numbers by arm; up to week 48 the PP population constitutes 94% of the ITT-E population.

Baseline data

Eight hundred and twenty two (822) previously untreated patients from 9 countries were included (5 European, Russia, US, Canada, Australia).

In SPRING-2, the vast majority of patients where white (85%) males (86%); the median age was 36 years (18-75). Risk factor for HIV transmission was by MSM contact for 65% of patients, and heterosexual contact for 29%; the numbers infected by intra-venous (IV) drug use was low (5%), and likewise the proportion co-infected with hepatitis B/C.

Table 17. Main disease characteristics, SPRING-2.

	DTG (411) n (%)	**RAL (411)** n (%)	**Total (822)** n(%)
BL VL >100,000, %	4.52 (28)	4.58 (28)	4.55
Median Baseline CD4+ (cells/mm3)	359.0	362.0	360.5
<50	8 (2)	6 (1)	14 (2)
50 to <200	47 (11)	44 (11)	91 (11)
200 to <350	144 (35)	139 (34)	283 (34)
350 to <500	126 (31)	136 (33)	262 (32)
>500	86 (21)	86 (21)	172 (21)
CDC Category			
A: Asymptomatic/ lymphadenopathy/acute HIV	359 (87)	347 (84)	706 (86)
B: Symptomatic, not AIDS	43 (10)	55 (13)	98 (12)
C: AIDS	9 (2)	9 (2)	18 (2)
Hepatitis B (only)	7 (2)	8 (2)	15 (2)
¨C (only)	41 (10)	35 (9)	76 (9)

Note. 1 patient had both hep B and C.

Numbers analysed

A total of 822 subjects were randomized (1:1) to DTG or RAL, and 822 subjects received at least one dose of study medication, defined as DTG or RAL. At the time of the analysis, 719 subjects were on-going.

Outcomes and estimation

The proportion of premature withdrawal is low (dolutegravir 11%, raltegravir 14%), including a very low proportion of loss to follow-up (1%). Stopping for lack of efficacy occurred at similar rates in both arms (4 vs 6%).

Dolutegravir was non-inferior to raltegravir for the primary endpoint, + 2.4%, $CI_{95\%}$ (-2.2, 7.1). A trend for better result in patients with high BL VL and low CD4 count was seen for dolutegravir, see table 18.

Table 18. Response (<50 cps/mL) up to week 48 in SPRING-2(ITT-E).

	DTG (411)	**RAL (411)**	**Diff (CI95)**
Week 4	295 (72)	266 (65)	
Week 24	384 (93)	369 (90)	
Week 48	**361 (88)**	**351 (85)**	+2.5 (-2.2, 7.1%)
BL VL ≤100,000 c/mL	267/297 (90)	264/295 (89)	
>100,000 c/mL	94/114 (82)	87/116 (75)	+5.3% (-3, 18)
BL CD4 <50 cells	5/8	0/6	
50 to <200	38/47 (81)	34/44 (77)	
by NRTI backbone			
ABC/3TC	145/169 (86)	142/164 (87)	-0.8 (-2, 7)
TDF/FTC	216/242 (89)	209/247 (85)	+4.6 (-1.3, 10.6)
VL ≤100,000 ABC/3TC	115/132 (87)	110/125 (88)	
TDF/FTC	152/165 (92)	154/170 (91)	
VL >100,000 ABC/3TC	30/37 (81)	32/39 (82)	
TDF/FTC	64/77 (83)	55/77 (71)	

The median change in CD4 count to week 48 was quite identical and around +230 cells/uL.

Virological non-response was uncommon in both arms; numerically slightly more common with raltegravir treatment. The frequency of safety-related discontinuations was similar.

Table 19. Reasons for non-response, SPRING-2

	DTG (411)	**RAL (411)**
Non-response, total	50 (12%)	60 (15%)
Virologic Non-Response	20 (5%)	31 (8%)
Data in window not <50 c/mL	8	5
Discontinued for lack of efficacy	5	13
Discontinued for other reason, not suppressed	2	11
Change in ART	5	2
No Virologic Data at Week 48	30	29
Discontinued due to AE or Death	9	6
Discontinued for Other Reasons	21	23

De novo resistance

For patients with protocol defined virological failure (PDVF, 20 and 28 respectively), and with successfully paired genotypes (baseline and failure), *de novo* resistance was not seen in any

patient treated with dolutegravir (neither to the integrase class nor NRTIs). For those treated with raltegravir, integrase inhibitor resistance was selected in 1 patient (N155H + secondary), and relevant RT mutations in 3 patients (K65R + M184V in 1; M184I/V (only) in 2 patients).

ING114467 (SINGLE)

Methods

A Phase III, randomized, double-blind study of the safety and efficacy of DTG plus abacavir (ABC)/lamivudine (3TC) fixed-dose combination (FDC) therapy administered once daily compared to Atripla (efavirenz / emtricitabine / tenofovir disoproxil) over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects

Study Participants

Key inclusion criteria included HIV-1 infected, antiretroviral-treatment naïve (ART) adults ≥ 18 years of age with plasma HIV-1 RNA ≥ 1000 copies/millilitre (c/mL) at Screening who had a negative HLA-B*5701 allele assessment.

Treatments

The treatment consisted of dolutegravir + abacavir/3TC (Kivexa) or efavirenz/tenofovir/FTC (Atripla).

The treatment (given as 3 tablets once daily) was fully blinded and recommended to be taken at an empty stomach at bedtime, in accordance with the Atripla SmPC.

- Arm 1: DTG + Kivexa + Atripla placebo
- Arm 2: DTG placebo + Kivexa placebo + Atripla

Objectives

Primary Objectives: To demonstrate the antiviral activity of DTG + ABC/3TC once daily therapy compared to Atripla over 48 weeks in HIV-1 infected ART-naïve subjects.

Secondary Objectives:

- To demonstrate the antiviral activity of the DTG+ ABC/3TC once daily therapy compared to Atripla over 96 weeks
- To compare the tolerability, long-term safety and antiviral and immunologic activity of DTG + ABC/3TC once daily therapy to Atripla over time
- To assess the development of viral resistance in subjects experiencing virological failure
- To assess the change in symptom bother count for subjects treated with DTG +ABC/3TC once daily therapy with Atripla
- To evaluate the incidence of HIV-associated conditions in subjects treated with DTG + ABC/3TC once daily therapy compared to Atripla over time

- To explore the impact of gender, race, and/or HIV-1 subtype on response to DTG + ABC/3TC once daily therapy and Atripla over time
- To explore the change in utility and health related quality of life for subjects treated with DTG + ABC/3TC once daily therapy and Atripla

Full data from the primary endpoint/objective at Week 48 is presented in this report. The safety cut-off date is 14 May2012.

Outcomes/endpoints

The primary endpoint for this study was the proportion of subjects with plasma HIV-1 RNA <50 c/mL through Week 48 using the Missing, Switch, or Discontinuation = Failure (SNAPSHOT or "Snapshot") as codified by the FDA's Snapshot algorithm. Antiviral activity was assessed by quantitative plasma HIV-1 RNA. Immunological responses were assessed by total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts.

Sample size

The power of this study was based on a response rate of 75% at Week 48 which was the mid-range of response rates observed in EFV arms in recent large clinical studies ranges from 71% to 82%. Assuming this response rate in the Atripla arm, the study required 394 evaluable subjects per arm to have 90% power with a 10% non-inferiority margin and a one-sided 2.5% significance level.

Blinding (masking)

Subjects received double blinded DTG doses plus ABC/3TC FDC therapy, or Atripla along with the corresponding matching placebo tablets for one of the two treatment regimens during the Randomized Phase (dosing will continue in this manner through their Week 96 study visit) each of which was to be taken once daily.

Statistical methods

The primary analyses were based on the Intent-to-Treat Exposed (ITT-E) population that consisted of all randomized subjects who received at least one dose of study medication and were assessed according to their randomized treatment. Subjects' responses at Week 48 (e.g. <50 c/mL) were calculated according to a Missing, Switch or Discontinuation = Failure algorithm (Snapshot) as codified by the FDA's Snapshot algorithm. Adjusted estimates of the difference in the rate of responders between the two arms were based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. Overall type I error rate was adjusted within key secondary comparisons to control for type I error.

Results

Recruitment

Started in February 2011, ongoing.

Baseline data

Eight hundred and thirty three (833) previously untreated patients from 12 countries were included (9 European, US, Canada, Australia).

The main demographics in SINGLE are similar to those described for SINGLE-2, with a male predominance (84%), and a median age of 35 years. Only 7 patients were above 65 (1 and 6 respectively). In this study the proportion of patients of black race was higher (24%); the remaining patients being of white race for the most (68%). The proportion of patients with severe immune deficiency was low; only 14% had a CD4 count < 200 cells/m.

Table 20. Baseline main disease characteristics, SINGLE.

	DTG + abc/3tc (414) n (%)	**Atripla (419) n (%)**	**Total (833) n(%)**
BL VL, median log_{10} copies/ml. >100,000, %	4.52 (31)	4.58 (32)	4.55 (32)
Median Baseline CD4+ (cells/mm3)	335	339	338
<50	13 (3)	14 (3)	27 (3)
50 to <200	44 (11)	48 (11)	92 (11)
200 to <350	163 (39)	159 (38)	322 (39)
350 to <500	131 (32)	128 (31)	259 (31)
>500	63 (15)	70 (17)	133 (16)
CDC Category			
A: asymptomatic/ lymphadenopathy/acute HIV	343 (83)	350 (84)	693 (83)
B: symptomatic, not AIDS	53 (13)	52 (12)	105 (13)
C: AIDS	18 (4)	17 (4)	35 (4)
Hepatitis B (only)	1 (<1)	1 (<1)	2 (<1)
¨C (only)	27 (7)	29 (7)	56 (7)

(None had hepatitis B + C)

Numbers analysed

Seven hundred and eighty eight (788) subjects were planned; 844 subjects were randomized and 833 subjects received at least one dose of study medication, defined as DTG plus abacavir/lamivudine fixed dose combination or Atripla. Six hundred ninety-eight remained ongoing at the time of this analysis.

Outcomes and estimation

Patients were stratified by BL viral load (< or > 100.000 cps/ml) and BL CD4 count (< or > 200 cells/µl). The screening failures rate (23%) was similar to that seen in SPRING-2.

The proportion of premature withdrawal differed so far (up to week 60) substantially between arms (12 vs 20%, respectively). The difference was driven by discontinuations related to AEs of Atripla:

- In the dolutegravir arm 10 (2%) stopped therapy for reasons of an AE; 5 withdrew content.
- In the Atripla arm 42 (10%) stopped due to AEs (24 within 2 weeks of therapy), 11 withdrew consent.

By week 48 a total of 18 patients (2%) had major protocol deviations, evenly between arms (11 vs 7 patients).

At week 48, a higher response rate was seen for dolutegravir + abacavir/lamivudine than with Atripla; in fact the dolutegravir arm was superior, +7.4% (95% CI: 2.5 – 12.3%). This was also true when adjusting for BL viral load (< vs > 100.000 c/ml) and CD4 count (< vs > 200 cells/mL), by Cochrane.Mantel Haenszel stratified analysis (p = 0.003).

The difference was driven by the higher frequency of AEs; virological non-response was similar between arms.

Table 21. Response (<50 cps/mL) up to week 48 in SINGLE (ITT-E)

	DTG + abc/3tc (414) n (%)	**Atripla (419) n (%)**
Week 4	261 (63)	59 (14)
Week 24	379 (92)	350 (84)
Week 48	**364 (88)**	**338 (81)**
BL VL ≤100,000 c/mL	253/280 (90)	238/288 (83)
>100,000 c/mL	111/134 (83)	100/131 (76)
BL CD4 count ≤200 cells	45/57 (79)	48/62 (77)
>200	319/357 (89)	290/357 (81)
Virologic Non-Response	**21 (5)**	**26 (6)**
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason, not suppressed	8 (2)	12 (3)
No Virologic Data at Week 48	**29 (7)**	**55 (13)**
Discontinued due to AE or Death	9 (2)	40 (10)
Discontinued for Other Reasons	20 (5)	14 (3)

The mean change from baseline to Week 48 in CD4 count was around 270 and 210 cells respectively, a statistically significant difference. This difference was apparent already from week 4, and onwards.

De novo resistance

The vast majority of patients with confirmed PDVF had low-level viremia, <200 c/mL, in particular those treated with dolutegravir (16/18). The number of paired genotypes is consequently low and *de novo* resistance was very rare for both treatments

In patients treated with dolutegravir, one *de novo* mutation (E157Q/P, likely not relevant) was seen in 1 patient; apart from this no other *de novo* mutations (integrase or RTgene) were detected. In the Atripla arm *de novo* resistance of relevance for efavirenz (K103N and or G190G/A) was selected in 3 patients, and K65R (tenofovir) in a 4th patient.

Patients with previous failure but not exposed to the integrase class

ING111762 (SAILING)

Methods

A Phase III Randomized, Double-blind Study of the Safety and Efficacy of DTG 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator-selected

Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults.

Study Participants

This trial recruited patients with on-going treatment failure (>400 copies/mL), with documented resistance to at least 2 drug classes other than integrase inhibitors, and naïve to the latter class.

Main Inclusion criteria:

- ART-experienced, HIV-1 infected subjects ≥ 18 years of age.
- Integrase inhibitor (INI)-naïve, defined as no prior exposure to any INI (e.g. RAL, elvitegravir, or DTG).
- HIV-1 infection as documented by HIV-1 RNA >400 c/mL at Screening and with at least one consecutive HIV-1 RNA >400 c/mL within the four months prior to Screening (unless the Screening HIV-1 RNA is > 1000 c/mL where no additional plasma HIV-1 RNA assessment is needed).
- Have documented resistance (via Screening resistance test) to two or more different classes of antiretroviral agents; genotypic resistance was defined by current primary mutations and Monogram genotypic results; phenotypic resistance was defined as values greater than lower cut off for agents where available and by a clinical/biological cut off if an upper cut off was not available; CCR5 resistance was defined by an assay which identifies any CXCR4-utilizing virus, e.g. Trofile; fusion inhibitor (FI) T20 resistance is defined as 50% inhibitory concentration (IC_{50}) > susceptibility cutoff in PhenoSense entry assay. If Screening resistance results provided a fully active agent and did not show two class resistance, then historical resistance results from the subject's most recent resistance testing may have been used for subjects off ART for at least 1 month, after consultation with the study virologist and/or medical monitor.

Patients were stratified for:

- BL VL ≤ versus > 50.000 c/ml.
- Darunavir/r use without versus with primary PI mutations (at baseline or historic).

Treatments

The DTG and RAL doses were administered in a double blind, double-dummy fashion during the Randomized Phase of the study. Subjects randomized to the DTG treatment group received DTG 50 mg once daily, with placebo to match RAL, to ensure subjects were blinded to the treatment arm. Subjects randomized to the RAL treatment group received RAL 400 mg twice daily, with placebo to match DTG. DTG and RAL were taken orally, with choice of investigator selected background therapy. DTG and RAL could be administered with or without food (unless dietary restrictions were required by background therapy). A switch of backbone therapy to an alternate approved in class therapy for toxicity management was allowed once during the study.

Optimised background treatment:

For reasons of enzyme induction that may affect dolutegravir efficacy, nevirapine and etravirine were not allowed as single agents; however etravirine was allowed if given in combination with darunavir/r or lopinavir/r.

For the same reason, the following drugs could be given as single agents, but not in combination with tipranavir/r, fosamprenavir/r, efavirenz, etravirine (in combination with darunavir/r or lopinavir/r).

Darunavir/ritonavir (DRV/r) was overall the most commonly used background agent, in combination with tenofovir, with regional differences.

Objectives

Primary: To demonstrate the antiviral efficacy of GSK1349572 (DTG) 50 mg once daily compared to raltegravir (RAL) 400 mg twice daily (BID) both in combination with a background regimen consisting of one to two (1-2) fully active agents in human immunodeficiency virus type 1 (HIV-1) infected, integrase inhibitor-naïve, therapy-experienced subjects at 48 weeks.

Secondary:

- To demonstrate antiviral efficacy of DTG 50 mg once daily compared to RAL 400 mg twice daily both in combination with a background regimen consisting of one to two (1-2) fully active agents in HIV-1 infected, integrase inhibitor-naïve, therapy-experienced subjects at 24 weeks.
- To compare the tolerability, long-term safety, antiviral efficacy, and immunologic activity of DTG 50 mg once daily to RAL 400 mg BID, both in combination with a background regimen, over time.
- To assess the development of viral resistance in subjects experiencing virological failure.
- To characterize the pharmacokinetics (PK) of DTG using sparse PK sampling strategy and population-modeling approach.
- To explore exposure-response relationships (e.g., the relationship between DTG plasma exposure and virologic response or occurrence of adverse events [AEs]).
- To evaluate the effect of patient characteristics (e.g., demographic factors) and concurrent medications on PK parameters of DTG.
- To evaluate the incidence of HIV-associated conditions in subjects treated with DTG 50 mg once daily compared to RAL 400 mg BID.
- To explore the impact of gender, race, and/or HIV-1 subtype on response to DTG 50 mg once daily and RAL 400 mg BID over time.
- To explore the change in utility and health related quality of life for subjects treated with DTG 50 mg once daily and RAL 400 mg BID.

Outcomes/endpoints

The primary efficacy endpoint for this study was the proportion of subjects with HIV-1 ribonucleic acid (RNA) <50 c/mL through Week 48 using the Missing, Switch or Discontinuation = Failure (MSDF) algorithm, as codified by the Food and Drug Administration's (FDA's) "Snapshot"

algorithm. Antiviral activity was assessed by quantitative plasma HIV-1 RNA. Immunological responses were assessed by total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts.

Sample size

The sample size calculation was determined to provide a sufficient number of subjects to detect non-inferiority of DTG vs. RAL in the primary efficacy endpoint (proportion of subjects with plasma HIV-1 RNA below 50 c/mL at Week 48 using the Snapshot algorithm). Assuming a 65% response rate in the raltegravir arm, a sample size of 333 per treatment arm provided 90% power to detect non-inferority based on a 12% non-inferiority margin and a one-sided 2.5% significant level. To allow for a possible group sequential analysis, the planned sample size was increased to 344 per arm.

Patients who received darunavir/r, and with a fully PI susceptible virus, were excluded in one analysis. This population is called AS (Added Sensitivity) population (AS mITT-E). The sample size provided at least 80% power to detect non-inferiority in this population.

Statistical methods

Efficacy analyses were based on the mITT-E population. A stratified analysis using Cochran-Mantel-Haenszel weights was used to estimate an adjusted treatment difference and 95% confidence interval for the proportion of subjects with plasma HIV-1 RNA below 50 c/mL at Week 48 using the Snapshot algorithm, adjusting for Baseline stratification factors.

Results

Recruitment

Started in October 2010, ongoing.

Conduct of the study

After enrollment was completed, the Applicant became aware of GCP noncompliance at one site in Russia where 4 subjects (DTG 3; RAL 1) had been enrolled. Although this non-compliance concerned another Applicant's study performed there; the site was closed. These 4 patients were removed from the ITT-E efficacy population, creating a modified ITT-E (mITT-E), used throughout for the analyses of the study.

Baseline data

One hundred and fifty six (156) sites included patients worldwide (Europe (46), US and Canada (64), Russia (12), South America and Mexico (24), Taiwan (5), South Africa (3), Australia (2).

At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All patients had at least two class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline.

Numbers analysed

A total of 724 subjects were randomized (1:1) to DTG or RAL, and 719 subjects received at least one dose of study medication, defined as DTG or RAL.

After enrolment was completed, the Applicant became aware of GCP non-compliance issues in another ViiV Healthcare-sponsored study at one site in Russia where 4 subjects (DTG 3; RAL 1) were enrolled in ING111762. As a consequence, these 4 subjects were removed from the Intent-to-Treat efficacy (ITT-E) population, creating a modified ITT-E (mITT-E, N=715) Population that was used for analysis of study populations and efficacy endpoints in the study. At the time of the analysis, 494 subjects were on-going.

Outcomes and estimation

Week 48 outcomes (including outcomes by key baseline covariates) for SAILING are shown in Table 22.

Table 22. Response in SAILING at 48 Weeks (Snapshot algorithm, <50 copies/mL)

	Tivicay 50 mg Once Daily + BR N=354§	**RAL 400 mg Twice Daily + BR N=361§**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted treatment difference‡	7.4% (95% CI: 0.7%, 14.2%)	
Virologic non-response	20%	28%
Baseline Viral Load (copies/mL)		
≤50,000 copies/mL	186 / 249 (75%)	180 / 254 (71%)
>50,000 copies/mL	65 / 105 (62%)	50 / 107 (47%)
Baseline CD4+ (cells/ mm^3)		
<50	33 / 62 (53%)	30 / 59 (51%)
50 to <200	77 / 111 (69%)	76 / 125 (61%)
200 to <350	64 / 82 (78%)	53 / 79 (67%)
≥350	77 / 99 (78%)	71 / 98 (73%)
HIV-1 RNA < 50 copies/mL by Background Regimen		
Genotypic Susceptibility Score* <2	155 / 216 (72%)	129 / 192 (67%)
Genotypic Susceptibility Score* =2	96 / 138 (70%)	101 / 169 (60%)
Use of DRV without PI mutations		
Yes	50 / 72 (69%)	54 / 77 (70%)
No	201 / 282 (71%)	176 / 284 (62%)
HIV-1 RNA <50 copies/mL by Gender		
Male	172 / 247 (70%)	156 / 238 (66%)
Female	79 / 107 (74%)	74 / 123 (60%)
HIV-1 RNA <50 copies/mL by Race		
White	133 / 178 (75%)	125 / 175 (71%)
Non white	118 / 175 (67%)	105 / 185 (57%)
HIV-1 RNA <50 copies/mL by Age (years)		
<50	196 / 269 (73%)	172 / 277 (62%)
≥50	55 / 85 (65%)	58 / 84 (69%)
HIV-1 RNA <50 copies/mL by HIV sub type		
Clade B	173 / 241 (72%)	159 / 246 (65%)
Clade C	34 / 55 (62%)	29 / 48 (60%)
Other†	43 / 57 (75%)	42 / 67 (63%)
Mean increase in CD4+ T cell (cells/mm^3)	162	153

‡ Adjusted for baseline stratification factors.
§ 4 subjects were excluded from the efficacy analysis due to data integrity at one study site
*The Genotypic Susceptibility Score (GSS) was defined as the total number of ARTs in BR to which

a subject's viral isolate showed susceptibility at baseline based upon genotypic resistance tests.
†Other clades included: Complex (43), F1 (32), A1 (18), BF (14), all others <10.

In the SAILING study, virologic suppression (HIV-1 RNA <50 copies/mL) in the Tivicay arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.03).

Statistically fewer subjects failed therapy with treatment-emergent integrase resistance on Tivicay (4/354, 1%) than on raltegravir (17/361, 5%) (p=0.003).

Resistant development to the integrase inhibitor class

In line with the results in SPRING-2 and SINGLE, no relevant *de novo* integrase resistance was detected in patients treated with dolutegravir, despite the fact that the PSS of the OBT was 1 (<2) in almost one third of the patients. The K263 mutation was selected in 2 patients, and FC in dolutegravir susceptibility was here <2 in both. Up to week 48, the figure remained 2 (out of 12 patients with paired genotypes tested).

In patients failing raltegravir well known mutations emerged in 9 patients with successfully paired genotypes, with consequent full resistance to raltegravir.

To be noted, in patients who withdrew from study while not suppressed (but not necessarily having protocol defined virological failure), neither genotypic nor phenotypic resistance was detected for either treatments.

In previously treated patients infected with class-resistant virus

Study ING112574 (VIKING 3)

Methods

A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravir in HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen (ING112574 – Week 24 Results of All Subjects Enrolled [N=183])

Study Participants

To be eligible for study entry at Screening, subjects must have been INI-experienced with: ≥500 copies/mL plasma HIV-1 RNA; genotypic evidence of resistance to RAL and/or EVG (or phenotypic evidence to RAL) and genotypic or phenotypic evidence of resistance to at least one drug from two or more of the other approved ART classes. If no evidence of INI-resistance was determined at Screening, subjects were eligible if there was documented historical genotypic and/or phenotypic evidence of resistance to RAL and/or EVG at time of prior INI virological failure. Subjects were also required to be able to receive at least one fully active ART in their background regimen from Day 8.

Treatments

At first (day 1-7) dolutegravir 50 mg bid was as added to the unchanged therapy (raltegravir stopped, if part of current failing regimen), i.e. "functional monotherapy". At day 8 the background regimen was optimized.

Objectives

Primary Objectives

- To assess the antiviral activity of DTG 50 mg twice daily (BID) administered with failing background therapy to Day 8 and thereafter with optimised background ART (OBR) consisting of at least one fully active agent through Week 24 in HIV-infected adult subjects with virological failure on a prior INI containing regimen.
- To evaluate the safety and tolerability of DTG 50 mg BID with background ART over time

Secondary Objectives

- To assess the antiviral and immunologic activity of DTG over time
- To assess the impact of different Baseline INI genotypic resistant patterns and phenotype on treatment response (short and long term) to DTG
- To characterize treatment emergent viral resistance in subjects experiencing virological failure
- To characterize the pharmacokinetics (PK) of DTG using a sparse PK sampling strategy and a population modelling approach
- To evaluate the effect of patient characteristics (e.g. demographic factors) and concurrent medications as covariates on PK parameters of DTG
- To explore, using multivariate models, the impact of Day 1 covariates (e.g. demographics, HIV ribonucleic acid (RNA), resistance to DTG, overall susceptibility score of background ART) and PK on treatment response (e.g. antiviralactivity, development of resistance, and/or AEs).

Outcomes/endpoints

The study's primary efficacy objective was the characterisation of antiviral activity at both Day 8 and Week 24. The primary efficacy endpoints in this study comprised the mean change from Baseline in plasma HIV-1 RNA (log_{10} c/mL) at Day 8, using a last observation carried forward (discontinuation equals Baseline) (LOCFDB) data set and the proportion of subjects with plasma HIV-1 RNA <50c/mL through Week 24 using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm.

Statistical methods

To support the primary objective there were two primary efficacy end-points: one assessed on Day 8 and the other at Week 24. The primary efficacy endpoint for hypothesis testing was the mean change from Baseline in plasma HIV-1 RNA at Day 8 (LOCFDB). The primary endpoint at Week 24 was the proportion of subjects with plasma HIV-1 RNA <50 c/mL using an MSDF (Snapshot) dataset.

The Intent-to Treat Exposed (ITT-E) population was the main population for assessment of efficacy at Day 8 and consisted of all the subjects who received at least one dose of investigational product. The Week 24 ITT-E population was the main population for assessment of efficacy at Week 24 and consisted of the initial 114 subjects recruited in the ITT-E population who had completed the Week 24 visit by the data cut-off or who had been withdrawn.

The Last Observation Carried Forward, Discontinuation =Baseline (LOCFDB) data set was used for the analyses of response at Day 8.The Missing, Switch or Discontinuation = Failure (MSDF) data set was used for the analyses of proportions of responders <50 c/mL overtime and for the primary efficacy analyses at Week 24. Missing or Discontinuation=Failure (MDF) was applied in other instances where specified. The Observed Case (OC) data set was used for safety and the analyses of CD4+ cell changes over time.

Results

Conduct of the study

Started in in May 2011 – on-going.

Baseline data

Twenty three (23) sites in Europe (Belgium, Canada, France, Italy, Portugal, and Spain) and 38 in the United States and Canada, recruited patients to this single arm, open-label study.

The median duration of prior ART for the 24 week ITT-E population was 13 years (range 7 months to 25 years), with similar durations for the full ITT-E population. Previous median time spent on raltegravir was just over 2 years (2.5 for the ITT-E), ranging from 2-132 months in both populations.

One hundred (100)/183 patients had an integrase inhibitor as part of the current failing regimen. This constitutes the most interesting population with regards to outcomes of short term monotherapy, in particular those patients where primary mutations for integrase inhibitors were detected at baseline; 90/183 fulfilled that combined criteria.

Seventy per cent (70%) of patients were white and 25% of black race. In practice only patients with HIV-1 subtype B are represented in this study (non-B subtype represented at higher rates in the SAILING trial, previously discussed). Over half had CDC-class C, mainly related to low CD4-cells, since active AIDS was not allowed.

Around one third of the patients had very high viral loads at baseline, and may in many cases likely either in fact not have been taking any HIV treatment at all, or have been on a “waiting regimen” in order to minimize the risk of further resistance development prior to study entry.

Table 23. Selected baseline demographics in VIKING-3, ITT-E (n=183).

Age (years) Median (Range)	48 (19, 67)
Males Sex, n (%)	141 (77)
Transmission route MSM Heterosexual contact Injectable drug use	 92 (52) 51 (29) 27 (15)
HCV positive	26 (14)
CDC Classification C	102 (56)
CD4 count, median (range)	140 (19, 1100)
HIV RNA c/mL, n (%)	
<1,000	21 (11)
1,000 to <10,000	49 (27)

10,000 to <50,000	52 (28)
>50.000	51(28)
RAL/EVG Ongoing at screening	101 (55)
Primary integrase inhibitor mutations detected	123 (67)
RAL/EVG ongoing AND primary mutation	90 (49)

Prior therapies and baseline resistance scores to background regimen and OBT

Darunavir/r had at some time been part of prior therapy for 75% of the patients, and around 50% had been using enfuvirtide and etravirine, respectivly. The proportion of patients with these therapies on-going as part of failing regimens was lower (e.g. only 5% were on enfuvirtide).

In the optimized background regimen (day 8 and onwards) some 60% used darunavir/r, 1/3 used etravirine, and around 1/3 enfuvirtide. In the ITT-E population (n=183) 65% of patients showed baseline virus with resistance to ≥ 4 ARV classes (integrase inhibitors included), a very advanced population to treat.

Numbers analysed

Three hundred and twenty three (323) patients were screened, and 183 received at least one dose. The main reasons for screening failure were too low screening viral loads and lack of evidence of integrase class resistance.

Outcomes and estimation

Day 8 outcomes

Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4 $\log_{10}$ (95% CI -1.3 – -1.5 $\log_{10}$, p<0.001).

The subset of patients of highest interest for the day 8 response were those with ral/evg on-going in the current failing regimen and with primary mutations detected at baseline. This is because in these patients a very large proportion of the viral load will consist of virus with the resistance mutations of interest (drug pressure), while in those who already stopped their integrase inhibitor (part of a prior failing therapy) the mutations may constitute only a small (but yet detectable) fraction. Such data was provided during the procedure, and is presented in table 24.

In this subset of patients, the viral load decay was quite similar in patients with non-148 primary mutations (N155, Y143, table 24) detected at baseline in comparison to the decay in patients where no primary resistance was detected (around 1.5 $\log_{10}$ reduction, not shown in the table). This is in line with *in vitro* data, where those mutations (N155, E92 etc) had no impact on activity, or on the accumulation of further resistance in selection experiments.

The impact of Q148-mutations + secondary on activity is obvious, and focusing on median values there is also a difference by the number of secondary mutations, 1 or ≥2. This is fully in line with the response by type of resistance category at week 24.

Phenotypic resistance seems to be a less useful predictor of response.

Table 24. Day 8 response by resistance; patients with primary mutations detected and RAL/EVG ongoing until DTG start (N=88), VIKING-3

Resistance Factor	Resistance sub-group	n	mean	SD	median	min	max
Baseline FC to DTG	0 to 2.5	43	-1.62	0.48	-1.68	-2.45	-0.78
	>2.5 to 4	10	-1.47	0.60	-1.53	-2.61	-0.64
	>4 to 8	17	-0.99	0.61	-1.04	-1.82	0.44
	>8 to 10	3	-1.30	0.80	-1.33	-2.08	-0.49
	>10 to 15	5	-0.75	0.90	-0.41	-2.33	-0.19
	>15 to 20	2	-0.30	0.27	-0.30	-0.49	-0.11
	>20 to 25	1	-1.41	N/A	-1.41	-1.41	-1.41
	>25	3	-0.15	0.26	-0.24	-0.36	0.14
	missing	4	-1.31	0.38	-1.17	-1.85	-1.05
Pre-specified IN resistance mutation category at Baseline	Q148+ ≥2[a]	15	-0.93	0.90	-0.57	-2.33	0.44
	Q148 + 1[b]	23	-1.10	0.58	-1.06	-2.61	-0.11
	N155H	24	-1.48	0.50	-1.43	-2.41	-0.78
	Y143	20	-1.68	0.40	-1.67	-2.29	-0.99
	T66	1	-1.85	-	-1.85	-1.85	-1.85
	≥2 primary mutations	5	-1.21	0.88	-1.43	-2.45	-0.24
Derived IN mutation group at Baseline	No Q148[c]	48	-1.59	0.47	-1.64	-2.45	-0.78
	Q148 + 1[d]	26	-1.14	0.61	-1.08	-2.61	-0.11
	Q148+ ≥2[d]	14	-0.75	-0.84	-0.45	-2.33	0.44

Secondary mutations were at codons: G140 (all but one subject);L74; T97; E138; S147; V151; E157; G163; G193. b) The secondary mutation was G140 in all but one subject. c) Included primary IN resistance mutations N155H, Y143C/H/R, T66A, E92Q d) Secondary mutations from G140A/C/S, E138A/K/T, L74I.

Week 24 outcomes

Based on 24-week data for all 183 patients, 126 (69%) had <50 copies/mL RNA at Week 24 (Snapshot algorithm).

The 24 week outcomes by genotype (integrase mutation category) is fairly consistent the day 8 response; a clear difference is seen by the presence or absence of the 148-mutation and also by number of secondary mutations in the latter subset, table 25.

Again, baseline phenotype (FC vs WT) seemed less predictive than baseline genotypic resistance.

The difference in number of active agents by type of score (Overall Susceptibility score based on a combined scoring of both phenotypic and genotypic results versus genotypic only) is explained by the way resistance is differently categorised in phenotypic and genotypic scoring.

Table 25. Outcome (<50 c/mL) at Week 24– Snapshot (MSDF) Analysis (ITT-E Population)

Factor	DTG 50 mg BID (N=183) n/N (%)
All subjects	126/183 (69)
IN resistant mutation categories at Baseline	
Q148+≥2 [a]	5/ 21 (24)
Q148+1[b]	19/ 32 (59)
N155	29/ 33 (88)
Y143	21/ 28 (75)
T66	1/ 1 (100)
≥2 Primary mutations	4/ 8 (50)
Primary not detected	47/ 60 (78)
Baseline OSS to OBR at Day 8	

Factor	DTG 50 mg BID (N=183) n/N (%)
0	7/ 9 (78)
1	48/ 71 (68)
2	53/ 77 (69)
>2	18/ 26 (69)
Baseline GSS to OBR at Day 8	
0	4/ 8 (50)
>0 to 1	43/ 58 (74)
>1 to 2	58/ 87 (67)
>2	21/ 30 (70)

Treatment failures fulfilling protocol defined virological failures (PDVF) occurring trough week 24 are summarized in the table 26. Numbers are low by mutation category, but for the Q148-mutation the pattern of response at week 24 is in line with the short term response discussed previously.

In those with the Q148-mutation (in particular with 2 secondary) failure is mainly caused by non-response (rather than relapse) up to week 24. In contrast, and as expected, failure was caused by rebound in those without primary mutations detected at baseline (as a consequence of lacking an integrase inhibitor in the current failing regimen).

Table 26. Summary of PDVF Criteria through Week24 by Baseline IN Mutation Category.

	Week 24 n (%)
Total (N=183)	36 (20)
Non-response	21
Rebound	15
Q148+≥2 (n=21)	12 (57)
Non-response	10
Rebound	2
Q148+1 (n=32)	9 (28)
Non-response	6
Rebound	3
≥2 Primary mutations (n=8)	2 (25)[b]
Non-response	2
Rebound	0
N155 (n=33)	2 (6)
Non-response	1
Rebound	1
Y143 (n=28)	3 (11)
Non-response	1
Rebound	2
No Primary Detected (n=60)	8 (13)[a]
Non-response	1
Rebound	7

3 subjects with historic Q148 mutations
Both subjects with Q148+≥2 with T66 or Y143 mutations

Since so many factors other than the integrase resistance pattern contribute to the outcome, in particular the OBT activity and the adherence, narratives for all patients with a non-response at week 24 and who had the Q148 mutation + 1 secondary were assessed in detail. In summary, these patients either had very poor background activity, or evidence of quite poor adherence, or both. With regards the activity of the OBT, the scores used seemed to overestimate the activity of the background agents.

Post Week 24 outcomes

For 114 patients data is available also after week 48, table 27. For most of the patients, the response at week 48 is in line with that seen at week 24. Of note, only 1/13 patients who lost response between Week 24 and Week 48 was in the Q148+1 category (at baseline). The subset who lost response the most is those with no primary mutations detected at baseline - which includes patients with the Q148-pattern detected in the past. Again durability is seen also in patients with a low activity of background agents.

Table 27. Responders at Week 24 and Week 48 in VIKING-3 (Snapshot) of the initial 114 subjects enrolled

Factor	**Week 24 <50c/mL N=114 n/N (%)**	**Week 48 <50c/mL N=114 n/N (%)**
All patients	73/114 (64)	64/114 (56)
BL resistance catagory		
Q148+≥2	0/12	1/ 12 (8)
Q148+1	10/20 (50)	9/ 20 (45)
N155	18/21 (86)	15/ 21 (71)
Y143	11/15 (73)	13/ 15 (87)
T66	1/1 (100)	1/ 1 (100)
≥2 Primary mutations	3/5(60)	3/5 (60)
Primary not detected	30/40 (75)	22/ 40 (55)
Baseline OSS to OBR at Day 8		
0	5/6 (83)	4/6 (67)
1	31/48(65)	25/48 (52)
2	26/44 (59)	24/44 (55)
>2	11/16 (69)	11/16 (69)
Baseline GSS to OBR at Day 8		
0	N/A	2/4 (50)
>0 to 1	20/29 (69)[f]	25/39 (64)
>1 to 2	37/62 (60)	26/55 (47)
>2	16/23 (70)	11/16 (69)

VIKING-4

One issue discussed thoroughly in the SAWP advice was the design of the single-armed study in patients with prior failure to the class (VIKING 3). The CHMP stressed the importance of having placebo-control during the first stage of functional monotherapy, since the effect may otherwise be overestimated since patients with remaining activity of the failing regimen perhaps would be more adherence also to that therapy when entering a clinical study. This advice was not taken on board for the study in this patient population (VIKING-3), which had already started to recruit patients. Instead, the applicant has performed a smaller study, VIKING-4, with placebo-control in

place during the functional monotherapy, to use as complementary information. The results from this study are discussed below.

Methods

A Phase III Randomized, Double-blind Study to Demonstrate the Antiviral Activity of Dolutegravir (DTG) 50 mg Twice Daily Versus Placebo Both Co-Administered with a Failing Antiretroviral Regimen over Seven Days, Followed by an Open Label Phase with All Subjects Receiving DTG 50 mg Twice Daily co-administered with an Optimised Background Regimen (OBR) in HIV-1 Infected, Integrase Inhibitor Therapy-Experienced and Resistant, Adults.

The Applicant provided the Day 8 primary end point and secondary endpoints through the data cut-off date of 14 Dec 2012 when all subjects had the opportunity to complete their day 8 visit.

Study Participants

Main Inclusion criteria

- ART-experienced, HIV-1 infected subjects ≥18 years of age with a plasma HIV-1 RNA ≥ 1000 copies/mL at Screening.
- Subject is DTG-naive but is RAL and/or EVG-experienced with current virologic failure to RAL or EVG AND has evidence of genotypic resistance to RAL and/or EVG on Screening resistance testing. Subject harbours virus with Screening or documented genotypic or phenotypic resistance to at least one drug from each of two or more of all other approved classes of ART.
- Subject must be able to receive at least one fully active drug in the OBR (to ensure an OSS ≥1) from Day 8 onwards based on the subject's Screening Monogram resistance test Net Assessment results.

Treatments

From Day 8 patients from both arms received open label dolutegravir and the background regimen was optimized (this on-going second phase is not further discussed in this report).

Objectives

Primary:

- To quantify the antiviral activity of DTG 50 mg twice daily (BID) compared to PCB when administered with failing background therapy for 7 days in HIV-infected adult subjects with virologic failure on a prior INI containing regimen and with INIresistance at Screening.

Secondary:

- To assess the antiviral activity of DTG over time when administered with optimized background regimen (OBR) consisting of at least one fully active agent from Day 8 □ To assess the immunologic activity of DTG 50 mg BID with OBR over time
- To evaluate the safety and tolerability of DTG 50 mg BID with OBR over time

- To describe the relationship between different baseline INI resistance genotypic patterns and DTG phenotype on antiviral response
- To characterise treatment emergent viral resistance in subjects experiencing virologic failure
- To evaluate the pharmacokinetics (PK) of DTG using a sparse PK sampling strategy

Outcomes/endpoints

The primary efficacy endpoint for this study was to quantify the mean change from Baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Day 8, using a last observation carried forward with discontinuation equals Baseline (LOCFDB) dataset.

Sample size

The mean DTG FC at baseline for the whole study population was used to calculate an estimate of the treatment difference between the two arms. The sample size was based on the assumption that the mean (SD) difference in Day 8 change from Baseline in plasma HIV-1 RNA between the DTG and placebo arms is 1 (0.8) log_{10} c/mL. A sample size of 30 subjects (15 subjects per arm) had a 91% power to detect such difference.

Statistical methods

The Intent to Treat Exposed (ITT-E) population was the main population for assessment of efficacy and consisted of all the subjects who received at least one dose of investigational product. For the primary comparison, adjusted estimates and p-value of the difference in the mean change from baseline in plasma HIV-1 RNA at Day 8 between the DTG and placebo arms are presented along with 95% confidence intervals using an analysis of covariance (ANCOVA) model. This analysis model in quantifying the difference of viral reduction adjusted for Baseline plasma HIV-1 RNA (log_{10} copies/ml, Baseline DTG FC (log2) and Overall Susceptibility Score of the failing regimen (0, 1, 2, >2). The primary analysis included an interaction between treatment and DTG FC (log2).

Results

Conduct of the study

18 Apr 2012 – ongoing.

Baseline data

In the table below baseline demographics of main interest are shown, with a comparison to the demographics in VIKING-3. To be noted, this VIKING-3 data concerns all 183 patients, and not only the subset of relevance for a comparison with VIKING-4 data. Overall, parameters are similar between studies, including the predicted activity score of the failing regimen.

Table 28. Baseline demographics in VIKING-4 and VIKING3

	VIKING-4		**VIKING-3**
	DTG (N=14)	**Placebo (N=16)**	**DTG (N=183)**
Age in years), Median (Range)	49.5 (19, 66)	48.0 (32, 63)	48 (19, 67)

Male gender, n (%)	12 (86)	12 (75)	141 (77)
Baseline HIV-1 RNA (c/mL), n (%)			
<1,000	2 (14)	1 (6)	21 (11)
1,000 to <10,000	2 (14)	4 (25)	49 (27)
10,000 to <50,000	8 (57)	5 (31)	52 (28)
>50,000	2 (14)	6 (38)	51(28)
Baseline PSS			
0	4 (29)	7 (44)	98 (54)
1	7 (50)	7 (44)	66 (36)
2	1 (7)	2 (13)	11 (6)
>2	2 (14)	0	8 (4)
Baseline GSS			
0	3 (21)	5 (31)	36 (20)
>0 to 1	8 (57)	10 (63)	119 (65)
>1 to 2	1 (7)	1 (6)	19 (10)
>2	2 (14)	0	9 (5)
Baseline OSS			
0	5 (36)	7 (44)	107 (58)
1	7 (50)	8 (50)	59 (32)
2	1 (7)	1 (6)	11 (6)
>2	1 (7)	0	6 (3)

Numbers analysed

A total of 30 subjects were randomized ~1:1 to the DTG arm (n=14) and the PCB/DTG arm (n=16). By the data cut-off, all subjects had completed the study (Day 8 visit). As one subject withdrew from the study on the day of the Day 8 assessments, 29 subjects entered the open label phase of the study post-Day 8.

Outcomes and estimation

The primary endpoint, adjusted mean change from BL in plasma HIV-1 RNA at Day 8 and overall susceptibility score (OSS) of the failing regimen (0, 1, 2, >2), was overall for all patients -1.2$\log_{10}$ copies/mL and 0.10 $\log_{10}$ c/mL for dolutegravir and placebo, respectively. The Q148-mutation was more frequent in the dolutegravir arm than in the placebo arm (9/14 vs 6/16).

The relevant subset of patients in VIKING-3 for a comparison are those with primary resistance detected at screening and RAL/EVG as part of the current failing regimen. In such a comparison, the viral decay by type of BL resistance was quite similar in VIKING-4 and VIKING-3, next table. For the subset of highest interest (those with Q148 as primary mutation), the median change is quite similar in VIKING-4 (those treated with dolutegravir) and VIKING-3.

Table 29. Change in viral load from BL to day 8 in VIKING-4 and relevant subset* of VIKING-3

	VIKING-4					VIKING-3*		
	DTG			Placebo		DTG		
	N	Mean (SD)	Median	N	Mean (SD)	N	Mean (SD)	median
Q148+≥2	4	-0.64 (0.809)	-0.51	1	0.09	15	-0.93 (0.90)	-0.57
Q148+1	5	-1.07 (0.352)	-0.97	5	-0.03 (0.194)	23	-1.10 (0.58)	-1.06
N155	2	-1.13 (0.971)	-1.13	4	0.11 (0.359)	24	-1.48 (0.50)	-1.43
Y143	2	-1.74 (0.949)	-1.74	4	-0.01	20	-1.68	-1.67

					(0.101)		(0.40)	
T66	0	-	-	0	-	1	-1.85 (-)	-1.85
≥2 primary	1	-1.37	-1.37	1	-0.17	5	-1.21(0.88)	-1.43

* Only including those VIKING3 patients with RAL/EVG as part of failing regimen, and with resistance detected at screening.

In the next table, VIKING-4 results are shown in further detail. Min - max values are in practice being within the precision of the assay for those treated with placebo in VIKING-4. The lack of change in the placebo group verifies that the failing regimen did not contribute to the effects reported for dolutegravir.

Table 30. Change in viral load from BL to day 8, VIKING 4

Group	Category	n	Mean (SD)	Median	Q1	Q3	Min.	Max.
DTG	Q148+≥2	4	-0.64 (0.81)	-0.51	-1.27	-0.01	-1.7 -	0.1
	Q148+1	5	-1.07 (0.35)	-0.97	-1.31	0.76	-1.6	-0.8
	N155	2	-1.13 (0.97)	-1.13	-1.82	0.45	1.8	-0.4
	Y143	2	-1.74 (0.95)	-1.74	-2.41	-1.07	-2.4	-1.1
	≥2 primary	1	-1.37	-1.37	-1.37	-1.37	-1.4	-1.4
Placebo	Q148+≥2	1	0.09	0.09	0.09	0.09	0.1	0.1
	Q148+1	5	-0.03 (0.19)	-0.06	-0.08	0.03	-0.3	0.2
	N155	4	0.11 (0.36)	0.16	-0.11	0.32	-0.4	0.5
	Y143	4	-0.01 (0.10)	-0.05	-0.07	0.04	-0.1	0.1
	≥2 primary	1	-0.17	-0.17	-0.17	-0.17	-0.2	-0.2

Clinical studies in special populations: Paediatric population

There is an on-going study in children and adolescents (ING112578, or P1093), which is performed in the US, and organized by the International Maternal Paediatric Adolescent AIDS Clinical Trials Group (IMPAACT). In total of 160 patients are planned to be recruited, covering all age groups from infants to adolescents. Data is available for a limited number of adolescents (12-18 years).

Study ING112578, P1093

Methods

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of DTG, a Novel Integrase Inhibitor, In Combination Regimens in HIV-1 Infected Infants, Children and Adolescents.

The study concerns only “ARV-experienced children”, with and without currently on-going treatment. In this study ARV-experience also includes previous treatment to prevent mother to child transmission. Hence, both children with and without on-going therapy can be included. For those children currently on therapy, the regimen needs to be unchanged for the last 8 weeks, and the viral load must then be ≥ 1000 cps/mL. For inclusion an available OBT must yield at least 1

active agent. AIDS defining opportunistic infection and known ≥ Grade 3 lab toxicities are exclusion criteria.

Eventually 6 cohorts are planned for, where recruitment is done sequentially. When starting a new cohort, intense PK sampling will be done in 4 children (at least present cohorts), followed by another 6 (=stage 1 for each cohort). When an adequate dose has been decided further recruitment (= stage 2 for each cohort) will proceed for a full cohort of that age span. Hence, in case all cohorts will be equally large, 25-26 patients will be included in each cohort; 10 in stage 1 and 15-16 in stage 2.

Planned cohorts are:

- Cohort I: Adolescents ≥ 12 to <18 years of age (Tablet formulation)
- Cohort IIA: Children ≥ 6 to <12 years of age (Tablet formulation)
- Cohort IIB: Children ≥ 6 to <12 years of age (Paediatric formulation)
- Cohort III: Children ≥ 2 to < 6 years of age (Paediatric formulation)
- Cohort IV: Children ≥ 6 months to < 2 years (Paediatric formulation)
- Cohort V: Infants ≥ 6 weeks to < 6 months (Paediatric formulation)

The rationale for this approach is to get more robust PK data. If the failing regimen would be optimized at the time for starting dolutegravir, PK samples would need to be collected 10-20 days after start of therapy, possibly increasing the duration of sub optimal dosing.

For children in stage 2 of the cohort optimized treatment will be given from start (with the dose of dolutegravir decided by stage 1).

Long term follow-up (minimum 3 years) is planned for those successfully completing 48 weeks of therapy.

The data cut-off date for this report is 17 December 2012.

Study Participants

Eligible subjects presented here were antiretroviral treatment experienced, with no prior treatment with an integrase inhibitor, HIV-1 infected male and female subjects ≥ 12 years to ≤18 years old, with a screening plasma HIV-1 RNA ≥1000 copies/millilitre (c/mL), and must have had available at least one fully active drug for the planned optimized background regimen.

Treatments

Subjects were given DTG once-a-day dose with target dose of ~1 mg/kg according to weight and dosing chart using 10 mg, 25 mg or 50 mg tablets.

Children/adolescents belonging to stage 1 of each cohort will at first receive dolutegravir as monotherapy (functional, if on a failing regimen at baseline) during 10 days, before treatment is optimized. During monotherapy intense PK sampling is performed at days 5-10. For those with on-going treatment, the current failing regimen must not include certain agents which may impact dolutegravir PK (ATV/r, ATV, EFV, NVP, FPV, FPV/r and TPV/r).

Objectives

Primary:

- To select a dolutegravir (DTG) dose for chronic dosing in infants, children and adolescents that achieve similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in antiretroviral therapy (ART)-naïve adult subjects.
- To determine the safety and tolerability of DTG in human immunodeficiency type 1 (HIV-1) infected infants, children and adolescents at 24 and 48 weeks.
- To evaluate the steady-state pharmacokinetics (PK) of DTG in combination with other antiretrovirals (optimized background therapy, OBT) in treatment experienced HIV-1 infected adolescents and to determine the dose of DTG that achieves a targeted AUC_{24} (primary PK endpoint) and drug plasma concentration at the end of the 24 hour dosing interval (C24h, secondary PK endpoint) in this population.

Secondary:

- To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.
- To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.
- To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in subjects experiencing virologic failure.
- To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.
- To determine the extended long term ($\geq$ 48 weeks) safety and tolerability of DTG in HIV-1 infected adolescents.
- To explore the relationship between DTG exposure and the antiviral activity.

Outcomes/endpoints

The primary endpoint concerns dolutegravir PK (to mimic the adult exposure), while tolerability, safety and efficacy are key secondary end points.

Sample size

Total accrual across all age cohorts will depend upon the number of subjects who must be accrued to yield at least 100 evaluable subjects for purposes of the primary safety analyses. There is some uncertainty concerning the number needed to complete the dose finding procedures in Stage 1 and the number who may be lost to follow-up for reasons other than treatment failure. Each successful cohort on Stage 1 will include 10 subjects; the majority of whom will have been treated continuously on the dose that has been chosen for Stage 2. This will likely yield additional subjects from Stage 1 who will contribute to the evaluation of the optimal dose. Thus, the Applicant anticipated accruing approximately 160 subjects to ensure that the total sample includes at least

100 evaluable subjects who have been treated only on the optimal dose and that the quotas for each cohort, specified in the Schema, have been filled.

The selection of a sample size of 10 subjects in Stage 1 for each age cohort is based on feasibility and historical paediatric recruitment experience of the Applicant and IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Group), as well as justification to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance (CL/F) and volume of distribution (Vd) for DTG with an at least 78% power.

Results

Recruitment

20 April 2011 - ongoing

Baseline data

All 23 patients on the full Cohort I enrolled and completed therapy up to week 24, 17, 48. There were no premature withdrawals.

The age was median 15 years, range 12-17. 18/23 patients were females, and 12/23 had an African American heritage. Median CD4-count at baseline was 466 (11-1025) cells/uL.

Numbers analysed

P1093 will screen approximately 160 infants, children and adolescents to allow for a minimum of 100 evaluable subjects. Cohort I, Stage 1 and Stage 2 presented here consists of 23 subjects.

Outcomes and estimation

The geometric mean AUC_{24} for Cohort I, Stage 1, was 46 µg*h/mL and the C_{24h} was 0.902 µg /mL, meeting the pre-defined targeted PK exposure with 1 mg/kg dosing for AUC_{0-24} and C_{24h} (37-67 µg *h/mL and 0.77 – 2.26 µg /mL) supporting dolutegravir 50 mg once daily in 12-18 years of age weighing at least 40 kg.

The proportion of responders (<50 cps/mL) at week 24 were 16/23 (70%) (19/23 with <400 cps/mL).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

DTG 50 mg QD in previously untreated patients

Table 31. Summary of efficacy for trial ING113086 (SPRING-2)

Design	randomized, double-blind, double dummy, active-controlled, non-inferiority study .
	Duration of main phase: 96 weeks

Treatments groups	DTG	DTG 50 mg QD + RAL placebo BID + ABC/3TC or TDF/FTC (N = 411)
	RAL	DTG 50 mg placebo + RAL 400 mg BID + ABC/3TC or TDF/FTC (N = 411)

Results and Analysis

Population and time point description	Intent-to-treat Exposed (ITT-E) Time point: Week 48		
Descriptive statistics	Treatment group	DTG (411)	RAL (411)
	Proportion with HIV-1 RNA <50 c/mL	88%	85%
	<400 c/mL	90%	87%
	Change CD4+ cell counts to week 48, cells/mm3	230	230
Effect estimate per comparison	Proportion w/ HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference: 2.5, 95% CI -2.2, 7.1	

Table 32. Summary of efficacy for trial ING114467 (SINGLE)

Design	Randomized, double-blind, double-dummy, active-controlled, multicentre, non-inferiority study .			
	Duration of main phase: 96 weeks			
Treatments groups	DTG+ABC/3TC	DTG 50 mg QD + ABC/3TC + Atripla placebo (N = 414)		
	Atripla	DTG placebo + ABC/3TC placebo + Atripla (N = 419)		

Results and Analysis

Population and time point description	Intent-to-treat Exposed (ITT-E) Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	DTG/ABC/3TC (414)	Atripla (419)
	Proportion w/ HIV-1 RNA <50 c/mL	88%	81%
	Median time to viral suppression (days)	28	84
	Numbers with HIV-1 RNA ≥1,000 copies/mL weeks 16-24, or ≥ 200 copies/mL at 24 weeks	4	8
	Median change from baseline in HIV-1 RNA (log_{10} c/mL)	-3.04	-3.09
	Change in CD4+ cell counts, cells/uL	267	208
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference: 7.4 95% CI 2.5, 12.3	

DTG 50 mg QD in previously treated - no resistance to integrase inhibitor class

Table 33. Summary of efficacy for trial ING111762 (SAILING)

Design	Randomized, double-blind, double dummy, active-controlled, non-inferiority study.	
	Duration of main phase: 48 weeks	
Treatments groups	DTG	DTG 50 mg QD + RAL placebo + background regimen (N = 357)
	RAL	DTG placebo + RAL 400 mg BID + background regimen (N = 362)

Results and Analysis

Population and time point description	**Intent-to-treat Exposed (ITT-E)** **Time point: Week 48**		
Descriptive statistics and estimate variability	Treatment group	DTG (354)	RAL (361)
	Proportion w/ HIV-1 RNA <50 c/mL	71%	64%
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W24 (%)	Adjusted difference: 7.4 (0.7, 14.2) (p-value: 0.05)	

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The first two studies (SPRING 2 and SINGLE) recruited previously untreated patients. In these studies any primary viral resistance was an exclusion criterion. The third study (SALING) concerns patients with on-going treatment failure, with resistance to at least 2 classes other than integrase inhibitors, for which no experience (or transmitted resistance) was allowed. Finally, the fourth study (VIKING 3), concerns patients with at least 3 class failure (integrase inhibitors included), and where documented resistance to integrase inhibitors (prior or at screening) was an inclusion criterion.

Apart from the resistance issue, the same exclusion criteria applied in all studies. The number of screening failures related to liver chemistry was low (9 patients total throughout the phase 3 studies). Likewise, only 4 patients total were excluded for the GI bleeding criteria, while some 13% patients with a history of conditions (present or past) that may predispose to such bleeding were included. Hence, these exclusion criteria would not impact the generalisability of the studies and were found adequate by the CHMP.

<u>Patients infected with HIV without resistance to integrase inhibitor class</u>

The primary endpoint in all 3 studies (SPRING-2, SINGLE, SAILING) is the proportion of patients with <50 copies/ml at week 48 (window), using the FDA snapshot analysis (Missing, Switch of ART or Discontinuation = Failure).

The non-inferiority margin in the studies of previously untreated patients (SPRING-2 and SINGLE) was set to 10%. In SAILING (resistance to at least 2 classes other than integrase inhibitors) the margin was 12%, which also would be considered adequate, according to EMA guidelines.

Sample sizes were based on the presumption of a 75% response rate was assumed for the control treatments in both SPRING-2, and SINGLE. The intake differs in SINGLE (fasted at bedtime) from that in SPRING-2 (administration with or without food).

The control agents (raltegravir, efavirenz) were considered adequate. DTG was used in combination with the NRTI backbones used in first line treatment (abacavir/3TC and tenofovir/FTC).

<u>In previously treated patients infected with integrase inhibitor resistant virus</u>

In VIKING-3, dolutegravir 50 mg bid was as added in the first phase (day 1-7) to the unchanged therapy (raltegravir stopped, if part of current failing regimen), i.e. “functional monotherapy”. At day 8 the background regimen was optimized.

The primary efficacy objective in this study was the characterisation of antiviral activity at both Day 8 and Week 24. The primary efficacy endpoints in this study comprised the mean change from Baseline in plasma HIV-1 RNA (log_{10} c/mL) at Day 8 and the proportion of subjects with plasma HIV-1 RNA <50c/mL through Week 24.

VIKING-4 was initiated to assess the request from the SAWP/CHMP to address the Day 8 intrinsic activity of DTG vs placebo in a randomized, double-blind, placebo-controlled design. Indeed, there may be a risk that patients would sharpen adherence also to the failing background regimen when starting therapy as part of a clinical study. In that case the activity of the new agent would be overemphasized.

Paediatric study

Eligible subjects in Study P1093 were antiretroviral treatment experienced, with no prior treatment with an integrase inhibitor, HIV-1 infected male and female subjects ≥ 12 years to ≤18 years old, with a screening plasma HIV-1 RNA ≥1000 copies/millilitre (c/mL), and must have had available at least one fully active drug for the planned optimized background regimen. The primary endpoint concerns dolutegravir PK (to mimic the adult exposure), while tolerability, safety and efficacy while key secondary end points. The study design is in line with the Clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02 Rev. 2) and is considered adequate.

Efficacy data and additional analyses

Dosing recommendations

The dose 50 mg qd was chosen for phase 3 studies in patients naïve to the integrase inhibitor class for the following reasons:

- The highest dose (50 mg qd) yielded the best results in monotherapy in Study ING111521,
- A PK/PD analysis from the same study demonstrated that the 50 mg dose was on the plateau of the concentration-response curve after monotherapy,
- In SPRING-1, the three doses (10, 25 and 50 mg qd) were equally well tolerated (yielding similar outcomes),
- Choosing the highest dose would also provide a safer margin with regards to possible drug interactions and suboptimal adherence.

Data from phase 2b (SPRING-1) indicated that the dose of 50 mg qd is adequate in the absence of class resistance, at least as part of a regimen with 2 other fully active agents.

For patients with integrase inhibitor class resistant virus, the Applicant selected the 50mg bid dose for phase 3 studies, based on the suboptimal response with the 50 mg qd during functional monotherapy in patients with the Q148-mutation present in VIKING, cohort I. In addition, data from healthy subjects (ING114005) demonstrated that plasma exposures increased less-than-dose-proportionally from 50 to 100 mg, and that one-third of subjects did not have an

appreciable increase in C_{tau} (the PK parameter that best predicted antiviral activity in Study ING111521) between 50 and 100 mg doses.

As discussed in the pharmacodynamics section, the evolution of integrase inhibitor resistance is rapid and highly dynamic during failure with the first generations integrase inhibitors (Fransen et al J Virol, July 2012; Winters et al, Plos One, July 2012). In patients who failed therapy with a first generation integrase inhibitor, a number of primary mutations (Q148, N155H, Y143, E92), followed by secondary mutations, may be selected. Based on the data presented from the clinical studies, the activity and resistance barrier of dolutegravir does not seem to be relevantly affected by mutations other than the Q148-mutation. The Q148-mutation is seen in around 40% of those who failed raltegravir and where primary integrase resistance mutations were detected. Hence, the CHMP was of the opinion that any reduction in dolutegravir exposure should be avoided in the presence of the integrase inhibitor class resistance. Hence, the CHMP requested the Applicant to modify the dosing recommendations for patients with integrase inhibitor class resistant virus as follows:

Exposure to DTG is increased when administered with food. This increase would be clinically relevant in the presence of certain integrase class resistance. Therefore, the Applicant agreed to modify the SmPC to recommend administration with food for patients with integrase class resistance.

All factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. Hence, in the presence of integrase class resistance, the Applicant agreed to modify the SmPC recommendations regarding the co-administration of with certain medicines e.g. co-administration of DTG with efavirenz, nevirapine, tipranavir/ritonavir, or rifampicin should be avoided in this population.

Finally, the CHMP recommended the Applicant to further discuss the potential treatment optimisation in the patients with integrase class resistance. Using an appropriate viral dynamic PK/PD model (reference is made to the publication from Jacqmin et al. Journal of pharmacokinetics and pharmacodynamics 37.2 (2010): 157-177.), the Applicant is recommended to analyse the short term viral response data from all individuals included in the VIKING and VIKING-3 studies. Relevant covariates (including mutation category, RAL/EVG as part of current failing therapy) are recommended to be tested in order to explain variability in the drug effect. Based on an adequate and sufficiently qualified model (using numerical/visual predictive check), the short term response following a 100 mg bid dosing regimen is recommended to be predicted and illustrated for the patients carrying the Q148+1 INI resistance mutation. The effect of extrinsic factors (inducers, polyvalent cations, food) on the exposure and response is recommended to be investigated and presented.

Patients infected with HIV without resistance to integrase inhibitor class

In the two pivotal studies in previously untreated patients, non-inferiority was shown vs raltegravir in the SPRING-2 study (88 vs 85% response at week 48, 95% CI -2.2;7.1%)) and in the SINGLE study dolutegravir in combination with abacavir/3TC was superior to efavirenz / emtricitabine / tenofovir disoproxil (88 vs 81% response at week 48 (+7.3%, 95% CI 2.3;12.2%). The latter was driven by a higher discontinuation rate in the control arm. These studies included a quite homogenous population (white males with HIV-1 B-subtype).

In SAILING (patients with resistance to at least 2 drug classes other than integrase inhibitors) superiority was shown vs raltegravir; both agents combined with an optimized background regimen (71 vs 64% at week 48 (adjusted difference +7.4%, CI95 (0.7, 14.2)). The difference in response was driven by a lower rate of virological failures with dolutegravir than with raltegravir. The population studied in SAILING included an adequate proportion of females (30%), non-white patients (>40%), and patients with non-B subtypes (just above 30%). No difference in outcome by such baseline parameters was noted.

Previously treated patients infected with class-resistant virus

VIKING-3 concerns patients where resistance to the integrase inhibitor class is present. The majority of patients had very extensive background resistance; around 65% to at least 4 drug classes, and around 50% of patients had <2 active agents as part of the optimized background therapy. Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4$\log_{10}$ copies/mL (95% CI -1.3 – -1.5$\log_{10}$, p<0.001).

The results seen in VIKING-4 indicate that that the short term activity presented in VIKING-3 should be considered as reliable, despite the lack of placebo control in the latter.

Resistance

In the SAILING-2, SINGLE and SAILING studies, the selection of integrase resistance of clear clinical relevance was not seen in any patients treated with dolutegravir with a follow up of ≥ 48 weeks. Of note, around 50% of patients in SAILING had a suboptimal activity of the background regimen (<2 active agents). In addition, in the previously untreated patients, not a single case of *de novo* resistance to backbone NRTIs was detected. This indicates that the resistance barrier of dolutegravir is high.

In the VIKING-3 study, a high response rate was seen for patients for whom the Q148-mutation was not detected as part of the integrase resistance; with a viral decay of around 1.5 $\log_{10}$ during functional monotherapy, and a 24 week response of 75%. This is in line with the *in vitro* data (including selection experiments), where non-148 mutations did not seem to have an impact on activity or resistance barrier. Also, when comparing outcomes during functional monotherapy in phase 2 (cohort 1 versus cohort 2, VIKING study) a similarly high viral decay was seen with 50 mg qd and 50 mg bid for these genotypes.

In contrast, the Q148 primary mutation does have a clear impact on dolutegravir performance. Although response rates were lower than for non-Q148 subsets, data from the VIKING-3 study shows that relevant activity of dolutegravir still remains in the presence of Q148 + 1 secondary mutation. This was clear both by the response seen during short term functional monotherapy and longer term outcomes at weeks 24 and 48 of therapy. Importantly, the response through week 24 was durable to week 48, despite the activity of background regimen being weak in a substantial part of these patients. However, in the presence of Q148 + ≥ 2 secondary mutations (secondary mutations from G140A/C/S, E138A/K/T, L74I) the efficacy is substantially hampered, to a level that may not be clinically relevant. This information is adequately reflected in the SmPC.

The number of active drugs in OBT was not a strong predictor in the SAILING, or in VIKING-3 studies, likely due to adherence issues, or to problems estimating OBT activity. It is clear that the integrase resistance categories are more predictive of the outcome, than is the number of active agents in the OBT, where similar response rates are seen for patients with at least 1 fully active

background agent. This verifies a robust effect by dolutegravir also in patients with class resistance.

Assessment of paediatric data on clinical efficacy

The applicant is applying for an indication in children aged 12-18 years old and with a weight >40 kg, and with a virus without resistance to the integrase class.

Dolutegravir dosed 50 mg qd in 10 such adolescents provided a similar exposure to that seen in adults. No apparent effect of body size (weight) could be seen on primary PK parameters. However, further observations of children of lower age/body weight are needed before the adequacy of a weight based dosing regimen can be assessed as part of future submissions.

The efficacy observed in the limited number of adolescents studied was satisfactory. From a mechanistic point of view, there would be no reasons to believe that dolutegravir would cause specific problems/perform differently in adolescents since the exposure is in line with that seen in adults.

2.5.4. Conclusions on the clinical efficacy

The recommended dose of dolutegravir is 50 mg (one tablet) orally once daily with or without food in patients infected with HIV-1 without resistance to the integrase class.

The evolution of integrase inhibitor resistance is rapid and highly dynamic during failure with the first generations integrase inhibitors (Fransen et al J Virol, July 2012; Winters et al, Plos One, July 2012). In patients who failed therapy with a first generation integrase inhibitor, a number of primary mutations (e.g. Q148), followed by secondary mutations, may be selected. Based on the data presented from the clinical studies, the activity and resistance barrier of dolutegravir does not seem to be relevantly affected by mutations other than the Q148-mutation. The Q148-mutation is seen in around 40% of those who failed raltegravir and where primary integrase resistance mutations were detected. Hence, the CHMP was of the opinion that any reduction in dolutegravir exposure should be avoided in the presence of the integrase inhibitor class resistance. Therefore, the CHMP requested to Applicant to modify the dosing recommendations in the SmPC to recommend administration of dolutegravir is 50 mg (one tablet) twice daily with food for patients with integrase class resistance and to modify the recommendations for co-administration with certain medicines in this population. The Applicant agreed with these changes.

Dolutegravir shows convincing efficacy results. Doltegravir also has a high barrier to resistance in the absence of pre-selected integrase class resistance. This has been confirmed also in patients with a suboptimal activity of background agents.

When taking both clinical data and *in vitro* data into account, it can be concluded that efficacy seems preserved also in the presence of certain integrase class resistance (i.e. non-148-mutations). Hence, the agent seems fully active for a substantial proportion (around 50%) of the patients with prior treatment failure that included raltegravir and for whom integrase resistance had been selected.

In the presence of the Q148 mutation and 1 secondary the effect is lower, but still highly relevant, also during long term therapy. In the presence of Q148 + ≥ 2 secondary mutations the efficacy is

substantially hampered, to a level that may not be clinically relevant. This information is adequately reflected in the SmPC.

Dolutegravir dosed 50 mg qd in 10 such adolescents provided a similar exposure to that seen in adults. Hence, in line with the Clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02 Rev. 2), the CHMP concluded that the efficacy results observed in adults could be extrapolated to the adolescents weighting >40 kg and with a virus without resistance to the integrase class.

2.6. Clinical safety

Patient exposure

Safety data has been collected from 30 Phase I, 4 Phase II, 7 Phase III clinical trials, as well as a compassionate use and an expanded access program, tables below.

For the majority of the Phase IIb and phase III studies, the safety data cut-off occurred prior to the end of June 2012,with the exception of ING111762 (SAILING, data cut-off: August 2012). An additional cut-off date of 26 October 2012 for deaths, other SAEs, and pregnancies was applied.

Table 34. Exposure in long term clinical trials (dose 50 mg qd and bid)

	Exposure duration at time of application	**DTG**	**Comparator**	**Total**
Total Safety population, n		**1571**	**1242**	**2813**
ART-Naïve population, n		**980**	**880**	**1860**
ING112276 SPRING-1 (n with 50 mg qd dose)	96w	155 (51)	50	205
ING113086 SPRING-2	48w	411	411	822
ING114467 SINGLE	48w	414	419	833
ART-Experienced (INI-Naïve) population, n		**357**	**362**	**719**
ING111762 SAILING	24w (357) 48w (164)	357	362	719
ART-Experienced (INI-Resistant) population, n		**234**	-	**234**
ING112961 VIKING Cohort I 50 mg QD	24w	27	-	27
ING112961 Cohort II 50 mg BID	48w	24	-	24
ING112574 VIKING-3 50 mg BID	24w (114) 10d (183)	183	-	183
Paediatric study	>24 w	21	-	-

In the compassionate use programs (data below through 31 May 2013) the dose was always 50 mg bid.

Table 35. Exposure in compassionate use programs (dose 50 mg bid)

Compassionate use Programme	Enrolled Patients	Withdrawn Patients	Ongoing Patients
	N	N	N
ING115502 (Named Patient Programme)	161	21	140
ING114916 (Expanded Access Programme)	87	3	84
Total	248	24	224

Adverse events

The number of patients stopping dolutegravir for reasons of AEs in the randomized studies was low and similar to that seen with raltegravir, 2%. For dolutegravir no specific AE term was seen at a frequency exceeding 1%. To be noted, due to the signal for potential liver toxicity in monkeys, the applicant had strict protocol-defined liver chemistry stopping criteria. Some patients were stopped for this reason; numerically higher for patients treated with dolutegravir than control agents.

Table 36. Numbers stopping for AEs and liver stopping criteria by treatment, randomized phase 3 studies

Name of study	**SPRING-2**		**SINGLE**		**SAILING**	
treatment	DTG +2NRTI (411) n, (%)	RAL +2NRTI (411) n, (%)	DTG + ABC/3TC (414) n, (%)	EFV /TDF/FTC (419) n, (%)	DTG + BR (357) n, (%)	RAL + BR (362) n, (%)
Any AE, n (%)	10 (2)	9 (2)	10 (2)	42 (10)	6 (2)	13 (4)
AE - liver related (A)	3	3	0	3	5	5
Stopping criteria liver (B)	6	1	0	0	11	4
Liver-related AE *or* Liver stopping criteria (A+B)	9 (2.2)	4 (1.0)	0	3	16 (4.5)	9 (2.5)
Withdrew consent	6 (1)	10 (2)	5 (1)	11 (3)	9 (3)	4 (1)
Lost to follow-up	4 (<1)	8 (2)	14 (3)	9 (2)	5 (1)	10 (3)

In VIKING-3 (single-armed, dolutegravir dosed 50 mg bid in combination with OBT) similar low numbers stopped for reasons of an AE (4/183, 2%); this is based on data for 183 patients who started therapy, and with data for 114 patients up to week 24.

Common adverse events

For common adverse events, the most straight forward comparison is dolutegravir versus raltegravir in studies SPRING-2 and SAILING, since the background regimen would be the same or similar in these studies (NRTI backbone stratified in the former, and OBT in the latter), next table.

Raltegravir has a well-defined safety profile. Within mentioned studies the common side effects are quite similar between the two integrase inhibitors, table below.

In parallel, it is of interest to compare the AE frequency in VIKING-3 (dolutegravir dosed 50 mg bid, with OBT) to that seen in SAILING; frequencies being quite similar.

Table 37. Frequency (%) of AEs (≥5%) for DTG 50 mg qd vs RAL in phase 3, and with DTG 50 mg bid dose single arm

	SPRING-2 (+ 2NRTI)		**SAILING (+ OBT)**		**VIKING cohort II+VIKING-3 (+OBT)**
	DTG 50 mg QD	RAL	DTG 50 mg QD	RAL	DTG 50 mg BID
Diarrhoea	12	12	20	17	16
Nausea	15	13	7	8	9
Headache	13	12	9	8	9
Insomnia	5	4	-	-	5
Fatigue	5	5	4	6	8
Dizziness	6	6	-	-	-
Cough	5	4	8	6	8
Depression	5	4	-	-	-
Back pain	4	5	-	-	-
Vomiting	-	-	5	6	-
Rash	-	-	5	5	5
Asthenia	-	-	-	-	3

In the SINGLE study the backbone NRTIs differ between arms complicates the comparison; the main finding here was a much higher number of certain AEs in the Atripla arm, table below.

Table 38. Common AEs*– SINGLE study

Preferred term	**SINGLE**	
	DTG + Kivexa (414)	**EFV/TDF/FTC (Atripla) (419)**
	n (%)[a]	**n (%)[a]**
Any event	369 (89)	387 (92)
Diarrhoea	72 (17)	75 (18)
Nausea	59 (14)	57 (14)
Nasopharyngitis	62 (15)	60 (14)
Headache	55 (13)	56 (13)
Insomnia	64 (15)	43 (10)
Fatigue	54 (13)	50 (12)
Upper resp. infection	36 (9)	43 (10)
Dizziness	37 (9)	148 (35)
Cough	24 (6)	29 (7)
Depression	23 (6)	26 (6)
Pyrexia	23 (6)	22 (5)
Abnormal dreams	30 (7)	72 (17)
Bronchitis	20 (5)	15 (4)
Back pain	23 (6)	17 (4)

*≥5% of Subjects in the combined dolutegravir group.

Adverse events judged to be reasonably related to dolutegravir, with a frequency of at least 1% in the combined database of all dolutegravir treated, were selected for inclusion in the SmPC. Nausea (15%), diarrhoea (16%) and headache (14%) were the most frequents AEs.

Serious adverse events and deaths

At the safety cut-off date (26 October 2012), there were 16 deaths reported across the clinical studies, including the compassionate use program.

In the pivotal and exploratory trials a total of 7 deaths were reported for patients treated with dolutegrair, table below. None of these deaths were considered drug-related.

Four (4) deaths (not drug related) were reported in other on-going studies (ING116529) and the compassionate use program (ING115502), in subjects receiving dolutegravir 50 mg BID (CMV-infection, NHL, Sepsis and Cardiac death in patients with associated medical conditions).

Table 39. Deaths in pivotal and exploratory studies

Trial / Source	Age (yrs)	Sex	Treatment	Exp (days)	Cause of Death
ING112276	35	M	DTG	637	road traffic accident
ING112276	49	M	DTG	935	myocardial infarction, (risk factors, incl previous MI) .
ING113086	42	M	DTG	13	homicide
ING113086	22	M	RAL	116	suicide
ING114467	86	F	Atripla	88	DIC, pneumonia
ING114467	40	M	Atripla	262	renal failure, Systemic candida
ING111762	30	M	RAL +OBT	104	hepatorenal failure
ING111762	53	M	RAL +OBT	220	adenocarinoma
ING112961	48	M	DTG +OBT	45	brain mass
ING112961	55	M	DTG +OBT	144	immunobl bone marrow aplasia
ING112961	45	M	DTG +OBT	233	suicide
ING112574	47	F	DTG +OBT	109	PML

When looking at SAE preferred terms overall, the frequency of "Any event" was similar between treatment arms and the reporting rate per term was <1% across all treatment groups, regardless of dose 50 mg qd or 50 mg bid, table below.

Table 40. Table 1 SAEs, possibly drug-related, by dose and background regimen in phase 2b/3.

	dtg 50 mg qd		dtg 50 mg bid
	ART-naive dtg + 2 NRTI (N=980) n, (%)	SAILING dtg + OBT (N=375) n, (%)	VIKING cohort 2+ VIKING 3 (N=207) n
Patients with event	5	2	2
Drug hypersensitivity	2 (<1)		
Acute myocardial infarction	1 (<1)		
Arrhythmia	1 (<1)		
Hepatitis	1 (<1)	1 (<1)	
Hyperbilirubinemia + increased transaminases			1
Myositis	0	1 (<1)	
Rash + pruritis	0		1
Renal failure	0	1 (<1)	

Adverse Events of Special Interest

Hepatobiliary disorders and liver chemistry

Liver toxicity is a potential safety issue based on findings in repeat dose toxicity in cynomolgus monkeys. Overall, increased liver enzymes were numerically more common with dolutegravir than with raltegravir in the randomized phase 3 studies (SPRING-2, SAILING). Alternative diagnosis (such as acute HCV) explains the vast majority of such events. In addition, in SINGLE the numbers with increased liver enzymes were higher with Atripla, than with dolutegravir+abacavir/lamivudine.

Reactions that would fulfil Hy´s law criteria are the most serious. This is defined as an increase of ALT/AST to >3xULN and bilirubin to >2xULN, while ALP is < 2xULN, and with no other evident cause explaining the event. One patient treated with dolutegravir (SPRING-2) may have fulfilled these criteria; out of some 1500 exposed to dolutegrvir in the clinical studies. This case is the main safety concern of the CHMP. The clinical picture was that of a hypersensitivity reaction, including an intense rash, in addition to the serious liver reaction. In VIKING-3 another patient had a similar HSR, but less intense and with a concomitant ALP-increase (i.e. not fulfilling Hy´s law criteria) and where an association to background therapy may be present. Both events resolved without any sequelae after stopping therapy.

Liver related AEs and liver chemistry in phase 3 - randomized studies (dolutegravir dosed 50 mg qd)

The number of patients with reported liver-related AEs was quite similar between treatments in the randomized phase 3 studies, table below.

Table 41. Summary of Adverse events in Hepatobiliary SOC - ART-Naïve Population, phase 3

	SPRING-2		**SINGLE**		**SAILING**	
	DTG	RAL	DTG	EFV	DTG	RAL
N	411	411	414	419	357	362
Any event in SOC	7 (2)	6 (1)	0	3 (<1)	12 (3)	10 (3)
Autoimmune hepatitis	0	0	0	1 (<1)	In part other AE terms. Jaundice (5 vs 4) more common than in the other studies - related to atazanavir/r as part of OBT). For other terms listed maximum 1 patient per arm and event.	
Cholecystitis	0	0	0	1 (<1)		
Cholelithiasis	0	0	0	1 (<1)		
Cholestasis	0	0	0	0		
Cytolytic hepatitis	1 (<1)	1 (<1)	0	0		
Hepatic cyst	1 (<1)	0	0	0		
Hepatic steatosis	2 (<1)	2 (<1)	0	0		
Hepatitis	1 (<1)	0	0	0		
Hepatitis toxic	0	2 (<1)	0	0		
Hepatomegaly	0	1 (<1)	0	0		
Hypertransaminasaemia	0	1 (<1)	0	0		
Jaundice	1 (<1)	0	0	0		
Portal vein thrombosis	1 (<1)	0	0	0		

The frequency of abnormal or deteriorating liver chemistry is overall rather similar between dolutegravir and control agents (raltegravir and efavirenz, respectively). Numerically higher rates of transaminase increases (ALT>10 xULN) were seen in patients treated with dolutegravir than in those treated with raltegravir, both in SPRING-2 (previously untreated) and in SAILING

(previously treated, but without integrase class resistance). In contrast, in SINGLE, dolutegravir + abacavir+lamivudine yielded similar or lower rates of such reactions than did Atripla.

Table 42. Liver chemistry in the randomized phase 3 studies.

parameter	SPRING-2 (+ 2NRTI)		SINGLE abc/3TC tdf/FTC		SAILING (+OBT)		DTG	Control
X ULN	DTG (411) n	RAL (411) n	DTG (414) n	EFZ (419) n	DTG (357) n	RAL (362) n	(1182) n, (%)	(1192) n, (%)
ALT/AST>3,BILI>=2 ALP<2	2	1	0	0	3	1	5 (0.4) *	2 (0.2)
ALT >=10 (grade 4)	5	2	1	1	4	1	10 (0.8)	4 (0.3)
ALT >=5 (grade 3)	9	7	1	2	9	7	19 (1.6)	16 (1.3)
ALT >=3 (grade 2)	15	17	5	15	20	13	60 (5.1)	45 (3.8)
BIL >2	3	4	2	1	27	24	32 (2.7)	29 (2.4)
ALP >1.5	7	8	1	19	18	19	26 (2.2)	46 (3.9)

In the randomised phase 3 studies, dolutegravir was dosed 50 mg qd and given with OBT. In these studies, 5 patients treated with dolutegravir experienced a combined increase of transaminases and bilirubin (ALP< 2ULN).

One case was quite severe, with a clinical picture of severe HSR which included liver chemistry possibly fulfilling Hy´s law, although the latter is not fully clear. There is no data on ALP at the time when ALT and BIL was severely increased. GGT was increased to 5 x ULN, which may implicate that ALP may have been >2 ULN at that occasion. A chemistry pattern fulfilling Hy´s law at the one and same date for sampling has actually not been shown. Regardless the reaction is severe and no other firm diagnosis or treatment is present. A reaction to abacavir (associated with HSR reactions) cannot be ruled out, but seems not likely since both HLAB5701 and an abacavir skin patch test was negative. It is also noted that the patient was taking a number of supplements including herbal extracts that may also be a risk factor for severe reactions. Still a reaction on dolutegravir cannot be ruled out.

For the other 4 patients, alternative diagnoses are present (1 gallstone disease, 1 acute hepatitis C, and 2 cases of liver flares in patients with chronic hepatitis B, where tenofovir and lamivudine was (wrongly) withdrawn when constructing the optimized background regimen).

In VIKING-3 (single-armed) dolutegravir was dosed 50 mg bid, and given with OBT. In this study 4/183 patients were reported to have ALT >3, BIL ≥2 and ALP <2 xULN. Out of these 4 patients, 1 patient is of interest. In this case, a HSR was also seen, starting some 14 days after starting dolutegravir and 7 days after optimizing OBT. After stopping therapy (all agents) the reaction resolved without sequele. No re-challenge has been made with the background agents. The reaction is also compatible with his new co-treatments (darunavir/r + etravirine, taken for the first time), but an association to dolutegravir cannot be ruled out. With regards the other three, one (co-infected with hepatitis B) had a liver flare after withdrawal of tenofovir, and the other two

(both hepatitis co-infected) continued dolutegravir therapy (despite meeting liver stopping criteria), and did well, events resolving.

When summarizing all cases with ALT >10 x ULN (= ALT grade 4) in the randomized studies, alternative diagnoses seem to be present practically without exceptions (table below).

Table 43. Table 2 Cases with ALT >10xULN in randomized phase 3 studies.

Treatment	ALT /ULN	Bil /ULN	Comment	Study Withdrawal? Yes/No (Y/N), Reason
SPRING-2				
DTG	28	1	HBV IRIS	Y, Stopping Criteria
DTG	15	1	Acute HCV	Y, AE
DTG	13	1	Acute HCV	Y, AE
DTG	11.5	11	Gall stone disease (mentioned above in text)	Y, Stopping Criteria
DTG	11	1	HCV; resolved without interrupting DTG	N
RAL	12.5	0.5	Possible DILI	Y, Stopping Criteria
RAL	10	1	Acute HCV	Y, Stopping Criteria
SINGLE				
Atripla	17	1	Acute HCV	Y, AE
DTG	10.5	0.5	HCV, resolved, without interrupting DTG	N
SAILING				
DTG	15	0.5	Possible Hepatitis C IRIS	Y, Stopping Criteria
DTG	10	2	Hepatitis C IRIS	Y, Stopping Criteria
DTG	54	20	Hepatitis B flare (tenofovir stopped)	N
DTG	27	3.5	Hepatitis B flare (lamivudine stopped)	Y, Stopping Criteria
RAL	15.5	7.5	Choledocolithiasis, post op complications	Yes, AE

The liver stopping criteria that were used (throughout the clinical studies) were the following:

- Regardless of symptoms:

- ALT ≥ 3xULN and bilirubin ≥2xULN (>35% direct BIL)
- ALT ≥8xULN
- ALT ≥5xULN to <8xULN for > 2 weeks or where test cannot be repeated within 2 w.

- If symptoms (worsening/acute hepatitis, signs of hypersensitivity)

- ALT ≥3xULN (if baseline ALT is < ULN) and symptoms
- ALT ≥3 fold increase from baseline ALT and symptoms

The next table summarizes all patients *who stopped therapy* for reasons of liver chemistry in the randomized phase 3 studies (including that patient in SINGLE-2 with a concomitant HSR reaction discussed previously).

In SPRING-2 (5 in the dolutegravir-arm, 3 in the raltegravir arm), 2 out those 5 who stopped dolutegravir had confirmed other causes (HBV-IRIS, acute HCV) and another two had other conditions that may have been implicated (gallstone disease with signs of inflammation of the gallbladder, HCV co-infection). In SINGLE 0/414 patients stopped dolutegravir for reasons of liver reactions, while 3 stopped Atripla.

In the experienced patients (SAILING) 9 stopped dolutegravir for this reason versus 5 for raltegravir. As seen in the table, among those 9 who stopped dolutegravir 5 had definite other causes that fully explains the reaction, while the other 4 had other causes that may be implicated but where an association to dolutegravir cannot be ruled out.

Of all these events, case 4529 that had a liver chemistry as part of a severe HSR reaction is the most serious safety concern, discussed previously.

Table 44. Patients discontinuing for reasons of liver chemistry, randomized studies (1:1), phase 3.

agent	ALT /ULN	BIL /ULN	Comment	Definition for withdrawal (time to start of event)
SPRING-2 (previously untreated)				
DTG	>10	>3	HSR reaction, discussed above. Possible DILI.	AE (9 days)
DTG	>10	>3	Confounded by gallstone disease, narratives previously discussed. DILI cannot be ruled out.	Stopping Criteria (week16)
DTG	28	0.91	Confirmed HBV IRIS	Stopping Criteria (week 4)
DTG	13	1.00	Confirmed acute HCV	AE (week 24)
DTG	9	1.64	HCV co-infection.	AE (week 40)
RAL	12	0.68	Possible DILI	Stopping Criteria
RAL	10	0.77	Acute HCV	AE
RAL	6	0.59	Possible DILI	AE
				DTG: 5/411 (stop criteria 2, AE 3)
				RAL: 3/411 (stop criteria 1, AE 2)
SINGLE (previously untreated)				
Atripla	17	0.82	Acute HCV	AE
Atripla	4	0.45	Systemic candida, multi-organ failure.	AE
Atripla	3	0.45	HCV	AE
				DTG: 0/414
				Atripla: 3/419 (all 3 AE)
SAILING (treatment failures, i.e OBT)				
DTG	>10	>3	Verified acute hepatitis C	AE (week 8)
DTG	>10	>3	HBV flare (due to incorrect	AE (week 12)

			change to OBT, w/o HBV active drugs).	
DTG	>10	>3	HBV flare (due to incorrect change to OBT, w/o HBV active drugs).	AE (week 8)
DTG	15	0.45	Possible Hepatitis C IRIS	Stopping Criteria (week 2)
DTG	10	1.77	Hepatitis C IRIS	Stopping Criteria (week 8)
DTG	27	3.64	HBV flare (due to incorrect change to OBT, w/o HBV active drugs).	Stopping Criteria (week 8)
DTG	10	6.27	Verified acute HCV	Stopping Criteria (week 8)
DTG	9	0.45	A numbe r of co-treatments including tipranavir/r may be implicated. DILI cannot be ruled out.	Stopping Criteria (week 32)
DTG	10	1.36	Possible HBV IRIS	Stopping Criteria (week 8)
RAL	16	7.45	Choledocolithiasis	AE
RAL	7	0.45	Hepatitis C	AE
RAL	5	1.91	Hepatitis C	Stopping Criteria
RAL	8	1.55	Acute infection	AE (Death)
				DTG: 9/354 (stop criteria 6, AE 3)
				RAL: 4/361 (stop criteria 1, AE 3)
TOTAL:				DTG: 14/1179 (stop criteria 8, AE 6) Control: 10/1191 (stop criteria 2, AE 8)

From the table above, it is noted that patients who were treated with dolutegravir and stopped therapy for reasons of the predefined stopping criteria all had marked enzyme elevations (>10 ULN); the criteria did in practice not stop patients with reactions < grade 4.

Liver chemistry toxicity by hepatitis co-infection status

The applicant has summarized emergent ALT/AST and BIL toxicities by treatment population, and hepatitis co-infection status. Data on AST elevation did not reveal any further toxicity as compared to ALT. To be noted, for hepatitis C also acute hepatitis C occurring during the study was counted.

In previously untreated patients (background regimen less prone to give reactions) grade 3-4 reactions were rare and occurred evenly between treatments in patients without co-infection. Reactions were also rare in those with co-infection (cases shown in previous tables).

Table 45. Emergent ALT and BIL Toxicities by hepatitis co-infection status. Previously untreated patients (test + 2 NRTIs)

	HBV and/or HCV coinfected			**No HBV or HCV infection**		
	DTG	**RAL**	**Atripla**	**DTG**	**RAL**	**Atripla**
n	90	43	30	885	363	385
ALT n(%)						
Grade 1	16 (18)	10 (23)	3 (10)	75 (8)	41 (11)	40 (10)
Grade 2	8 (9)	9 (21)	7 (23)	17 (2)	6 (2)	13 (3)
Grade 3	2 (2)	1 (2)	0	3 (<1)	4 (1)	1 (<1)

Grade 4	3 (3)	0	0	3 (<1)	2 (<1)	1 (<1)
BILI n(%)						
Grade 1	2 (2)	3 (7)	0	37 (4)	14 (4)	1 (<1)
Grade 2	1 (1)	1 (2)	0	14 (2)	7 (2)	1 (<1)
Grade 3	0	0	0	2 (<1)	1 (<1)	1 (<1)
Grade 4	0	0	0	1 (<1)	0	0

In the SALING study grade 3-4 ALT elevations occurred at similar rates (dolutegravir vs raltegravir) in those patients without co-infection. A numerically higher number of patients with co-infection and treated with dolutegravir had grade 3-4 elevations (again, cases shown in a previous table).

Table 46. Emergent ALT and BIL toxicities by hepatitis co-infection stats. Previously treated, not integrase class resistance (test + OBT, the SAILING study)

	HBV and/or HCV co-infected		No HBV or HCV infection	
	DTG	RAL	DTG	RAL
n	50	65	289	272
ALT				
Grade 1	4 (8)	17 (26)	19 (7)	11 (4)
Grade 2	4 (8)	2 (3)	8 (3)	5 (2)
Grade 3	3 (6)	2 (3)	2 (<1)	2 (<1)
Grade 4	4 (8)	0	0	1 (<1)
BILI*				
Grade 1	2 (4)	2 (3)	11 (4)	7 (3)
Grade 2	4 (8)	6 (9)	16 (6)	15 (6)
Grade 3	1 (2)	2 (3)	14 (5)	6 (2)
Grade 4	1 (2)	0	2 (<1)	2 (<1)

*For those patients with a known HBV/HCV status in the SAILING study, treatment emergent hyperbilirubinemia grade ≥3 was related to atazanavir as part of OBT in 16/18 patients in the dolutegravir-arm, and in 8/10 patients in the raltegravir-arm. (Data on HBV and HCV status was missing for 42 patients (17 in the dolutegravir arm, 25 in the raltegravir arm)).

In the table below data is shown on toxicity by type of hepatitis co-infection (B and C separate).

Four (4) patients with hepatitis B co-infection (left part of the table) and treated with dolutegravir had grade 3-4 ALT increases. Shown in previous tables, 2 of these patients was considered to have a HBV IRIS event, and the other 2 were incorrectly not receiving HBV-active NRTIs when the background regimen was optimized.

Overall, four subjects (DTG: 2, RAL: 2) with acute or chronic (n=3) hepatitis C met liver stopping criteria and were withdrawn for liver chemistry elevations (cells marked in the table above). One (1) of the 2 patients with grade 4 elevation in the dolutegravir had a verified acute HCV infection. HCV co-infected subjects in both treatment arms were also noted to have Grade 1 and 2 elevations in liver transaminases at baseline and during the course of treatment, which were not treatment-limiting or progressive, and in some cases were sporadic or self-limiting.

Table 47. Emergent ALT and BIL Toxicities by type of co-infection, SAILING study.

	HBV infected		**HCV infected**	
	DTG	**RAL**	**DTG**	**RAL**
n	17	16	32	48
ALT				
Grade 1	1 (6)	4 (25)	3 (9)	13 (27)

Grade 2	0	0	4 (13)	2 (4)
Grade 3	2 (12)	0	0	2 (4)
Grade 4	2 (12)	0	2 (6)	0
Total bilirubin				
Grade 1	2 (12)	0	0	2 (4)
Grade 2	2 (12)	2 (13)	2 (6)	4 (8)
Grade 3	1 (6)	0	0	1 (2)
Grade 4	1 (6)	0	0	0

In summary, when carefully reviewing the data, the overall liver safety profile of dolutegravir seems roughly comparable with that of control agents, regardless of hepatitis co-infection status.

The frequency of increased liver chemistry in VIKING cohort-II and VIKING-3, where dolutegravir was dosed 50 mg bid is shown below. The study is single-armed, and the rates can only be roughly compared to the rates of reactions seen in the dolutegravir arms in the other studies. Those 4 patients with reactions including increased bilirubin were previously mentioned above (causes other than dolutegravir exposure seemingly present in 2/events resolving without stopping therapy in 2).

Table 48. Table 3 Liver chemistry with dolutegravir dosed 50 mg bid vs qd.

X ULN	DTG 50 mg bid +OBT (N=207) n, (%)	DTG 50 mg qd (phase 3, randomized) (N=1182) n, (%)
ALT/AST>3,BILI>=2, ALP<2	4 (2)	5 (0.4)
ALT >=10 (grade 4)	2 (<1)	10 (0.8)
ALT >=5 (grade 3)	7 (3)	19 (1.6)
BIL >2	5 (2)	32 (2.7)

Exposure safety margin and interacting drugs

In the high dose monkey study, the safety margin (NOAL for liver reactions) was around 3-4 times the exposure seen in humans. In practice there is one main agent that causes a moderate increase of dolutegravir exposure; atazanavir/r s (C_{max} +60%, AUC +30%). Higher increases are seen with non-boosted atazanavir (regimen not approved in the EU) around +90% and +60%, respectively. Other antiretrovirals including protease inhibitors either do not affect dolutegravir exposure, or lower it.

The number of patients that used atazanavir/r and non-boosted atazanavir as part of OBT was 51 in SAILING (50 mg qd) and 3 in VIKING-3 (50 mg bid). The applicant showed that there was no increased risk of unexplained liver reactions in these patients, as compared to the rates seen with other co-treatments.

Rash with or without Systemic Involvement

Severe skin reactions have been reported for raltegravir, and abacavir (prevalent backbone in the clinical studies) is associated with skin rash and hypersensitivity reactions. Therefore, this was considered an AE of special interest.

Rash of any grade was infrequent in those treated with dolutegravir (comparable with raltegravir, and lower than observed for efavirenz Atripla). No serious rashes, such as SJS/TEN or erythema multiforme, have been reported for the dolutegravir development program to date. With regards

to hypersensivity reactions (including rash and systemic symptoms), only two cases have been reported. These patients also had liver reactions, and were discussed in the previous section.

Renal Disorders

Mild non-progressive changes in serum creatinine were seen for dolutegravir in the Phase IIb studies, and therefore of particular interest in phase 3. Dolutegravir blocks the organic cation transporter 2 (OCT-2) and the applicant states this to be the reason of this finding. Kidneys were not considered a target organ for toxicity in animal studies.

In phase 2b, a slight increase of creatinine levels was noted already at week 1, and from the lowest dose level of 10 mg qd. While the change was stable over time with the 50 mg dose (~ + 10 µmol/L), there was a trend for normalization with time for the lower doses (~+5 µmol/L by week 24).

In phase 3, the same was seen and without any difference in creatinine increase by background NRTI (Kivexa (n=634) versus Truvada (n=346)) when pooling data from SPRING-2 and SINGLE (an increase of around 10 µmol/L by week 48 for both combinations). A similar increase was seen also for dolutegravir in SAILING (dose 50 mg qd + OBT) and in VIKING-3 (dose 50 mg bid + OBT).

Urinary protein was assessed both by dip stick, and by urine albumin/creatinine ratios, and without discrepancies between those treated with dolutegravir and control agents.

Renal failure was reported for 3 patients treated with dolutegravir, and they all had pre-existing underlying disease (i.e. reported as renal failures, despite that the renal impairment was present already at baseline).

Gastrointestinal Disorders

GI toxicity (lesions, mucosal irritation and related symptoms) was the main toxicity in non-clinical studies, but here considered related to local toxicity, not caused by the systemic exposure.

In the randomized phase 3 studies, diarrhoea, nausea, and vomiting occurred at similar frequencies across treatment arms (dolutegravir, raltegravir and efavirenz). In addition, in the dose ranging study (SPRING-1) there was no dose relation (dolutegravir 10-20-50 mg qd) for these events.

Hence, at present there are no concerns for gastrointestinal toxicity with the doses proposed for human treatment.

Immune Reconstitution Inflammatory Syndrome (IRIS)

It has been discussed whether IRIS would be more common with integrase inhibitors, due to high potency and rapid viral load decays (and in parallel a faster increase of CD4 counts).

The only study of interest for this issue would be the SINGLE study (dolutegravir vs efavirenz), since raltegravir was the control agent in the other randomized studies. However, IRIS would typically occur in patients with advanced immune deficiency at baseline, and baseline CD4 counts were quite high in this study and AIDS diagnoses was an exclusion criteria in this this study.

In SINGLE 3 definite cases were seen in the dolutegravir group (related to toxoplasmosis, tuberculosis and MAC-infection), and 1 definite (cryptococcal meningitis) and 3 possible with

efavirenz (extrapulmonary cryptococcosis, and 2 cases of HCV IRIS). Hence, the frequency of typical IRIS was low and without a meaningful difference between arms.

Laboratory findings

Liver and renal chemistry were discussed in the previous sections. The other common laboratory findings didn't raise specific concerns. Abnormalities in haematology, electrolytes, and metabolism indices (glucose, calcium, phosphorus) were uncommon and without difference between treatments.

Treatment emergent CK increase (included in the EU SmPC for raltegravir) are common during HIV therapy in general. While grade 4 increases were more common for dolutegravir than with raltegravir in SPRING-2 (16 vs 7 patients), the opposite was reported for dolutegravir+abc/3TC as compared to Atripla in SINGLE (5 vs 12 patients), and where "any grade" again occurred at similar rates. No patients stopped therapy due to CK increase. In conclusion, there was no signal for muscle toxicities with dolutegravir.

SPRING-2 is the most adequate study to evaluate the changes in blood lipids (raltegravir control, same NRTI backbones). From this study it is clear that dolutegravir, in line with other agents of the class,doesn't have an effect on blood lipids. When comparing the treatments in SINGLE; a very similar increase, likely without clinical relevance, is seen with the two regimens (abacavir/3TC + dolutegravir and tenofovir/FTC/efavirenz).

Table 49. Table 4 Lipids, ART-Naïve patients, phase 3

	SPRING-2 abc/3TC (n=319) or tenofovir/FTC (n=489)		**SINGLE**	
	dtg	ral	dtg +abc/3TC	efv /tdf/FTC
Total Cholesterol				
Baseline (mean)	4.2	4.1	4.1	4.1
Week 24	+0.05	+0.11	+0.38	+0.46
LDL				
Baseline (mean)	2.5	2.4	2.4	2.4
Week 24	-0.03	-0.02	+0.1	+0.2
Triglyceride				
Baseline (mean)	1.3	1.3	1.3	1.3
Week 24	-0.04	+0.04	+0.21	+0.26

Safety in special populations

Paediatric patients

Clinical adverse events were mild (only grade 1-2). Rash of grade 1 was seen in 2 patients, and of grade 2 in 2 patients. No clinically significant trends in change from Baseline in liver chemistries were observed.

Pregnancies

Dolutegravir did not show signs of being teratogenic in the pre-clinical studies.

As of 31 May 2013 the Sponsor's global safety database contained 36 pregnancies in women directly exposed to dolutegravir or control agents in the clinical studies and compassionate use program up. The review did not identify any reproductive toxicity for DTG. Few cases resulted in an adverse pregnancy outcome (e.g., spontaneous abortion or ectopic pregnancy), and were comparable for DTG, RAL and Atripla, and no congenital anomalies were reported.

Safety related to drug-drug interactions and other interactions

The agent of interest is mainly atazanavir (with or without ritonavir), since the exposure of dolutegravir is increased. In the limited number of patients treated with that combination there was no signal for a worsened safety profile.

2.6.1. Discussion on clinical safety

Overall, the safety profile of dolutegravir was similar to that of control agents in phase 3 (raltegravir and efavirenz). The number of patients stopping for reasons of adverse events was low, 2%.

None of the 11 deaths occurring in patients treated with dolutegravir throughout the clinical trials and the compassionate use program was likely attributable to dolutegravir.

Serious AEs were uncommon, and also fully comparable in numbers between treatments. The same applied for common AEs (except for dizziness being much more common with efavirenz).

Two patients experienced liver reactions. Hy´s law criteria (ALT/AST and BIL > 3 xULN, ALP < 2xULN) was fulfilled for one of the patients. This patient treated with dolutegravir did not have a likely other cause for the event. In addition to extensive increases of the liver enzymes, the clinical picture was that of a hypersensitivity reaction, starting some 10 days after start of therapy (dolutegravir + abacavir/lamivudine). A detailed investigation was done while initially hospitalized and at follow-up after discharge. Dolutegravir cannot be ruled out as the causative agent in that case. A second patient, part of the VIKING-3 study, also had a HSR-like reaction 14 days after starting dolutegravir, and 7 days after optimizing the background regimen. This case, also with skin rash and a liver reaction, did not fulfil Hy´s law criteria. In this latter case, the co-treatment agents (darunavir/r and etravirine) could be alternative causes of the reaction.

Although such presumed hypersensitivity reactions were infrequent, not necessarily caused by dolutegravir and resolved without sequelae in both cases, the liver reaction associated with the presumed hypersensitivity in one of the patients was considered as important for the safety profile of dolutegravir.

During the procedure the Applicant was asked to update on any new cases of severe hypersensitivity reaction (HSR) reactions and / or hepatotoxicity. This review also included patients in an on-going phase 3 study which is not part of this application (FLAMINGO; previously untreated patients randomized to dolutegravir or darunavir/r, both with 2 NRTIs). The review included 2829 patients treated with at least one dose of DTG in the Phase 1 to 3b clinical trials and the compassionate use programmes. No further cases of severe HSR reactions or cases fulfilling Hy´s law were seen. There was no tendency for more frequent liver reactions with dolutegravir than darunavir/r in the FLAMINGO study.

The risk of HSR is adequately reflected in the RMP. The SmPC contains an adequate warning concerning such events. In addition, the applicant has committed to undertake a Prospective Observational Cohort Study in patients receiving DTG, where a large number of patients exposed to dolutegravir will be compared to others within the EuroSida Cohort. The focus of this PASS is to determine the frequency of such possible events in a cohort where the denominator of exposed patients is known, and where further investigations into mechanisms and risk factors are possible, if this proves an issue of concern. A draft protocol for this study was submitted by the Applicant as an Annex to the RMP and was endorsed by the Committees. (see Section 2.8 RMP).

Liver safety was followed closely since a signal for such toxicity was seen at high doses in a monkey study. As a consequence, the applicant had instituted conservative liver stopping criteria in all studies. When pooling all patients stopping treatment due to increased transaminases, this occurred at similar rates with dolutegravir and control agents in the randomized phase 3 studies. Importantly, when carefully reviewing these patients, additional likely causes (i.e. hepatitis co-infection, such as verified acute hepatitis C and liver flares in patients with chronic hepatitis B) were present almost without exceptions in all treatment arms. When restricting the assessment to patients without hepatitis co-infection, grade 3-4 increases of transaminases occurred at low and fully similar rates between arms. Hence, the overall liver safety of dolutegravir seemed roughly comparable with that of the control agents, regardless of hepatitis co-infection status.

However, given the potential severity of this event, this risk will also be investigated further in the Prospective Observational Cohort Study in patients receiving DTG (EuroSIDA cohort). (see RMP Section 2.8)

Mild/moderate rash was an uncommon event with dolutegravir, and no patient stopped therapy for this reason; severe rash with mucocutanous involvement has so far not been reported.

However, given the potential severity of this event, this risk will also be investigated further in the Prospective Observational Cohort Study in patients receiving DTG (EuroSIDA cohort) (see RMP Section 2.8).

No relevant findings were noted in the common lab chemistry. An immediate but mild and non-progressive increase in creatinine is seen already at low doses of dolutegravir. The effect (around +10 µmol/l) was the same regardless which background agents that were used (including tenofovir and ritonavir), and is considered to be caused by an inhibition of the transporter OCT2. The increase of serum creatinine is not considered clinically relevant.

Dolutegravir, in line with other agent in the class, doesn't have an effect on blood lipids.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Assessment of paediatric data on clinical safety

There were no specific concerns around safety in the limited number of adolescents studied.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall the safety profile of dolutegravir is deemed favourable. The agent was well tolerated. As other agents in class, dolutegravir has a favourable metabolic profile.

Among the ~2800 patients exposed to dolutegravir (around 2000 longer term), there was one severe case of hypersensitivity which included a severe liver reaction fulfilling Hy´s law criteria. This case resolved after stopping therapy; however, an association to dolutegravir could not be ruled out. A second case, less severe from a liver point of view and where other co-treatment may have been involved, was reported. The SmPC contains an adequate warning concerning such events.

Based on the findings in monkeys in non-clinical studies, liver safety was the main focus of the assessment. When carefully reviewing liver safety in the phase 3 studies, the overall liver safety of dolutegravir seemed roughly comparable with that of the control agents, regardless of hepatitis co-infection status.

Mild/moderate rash was an uncommon event with dolutegravir, and no patient stopped therapy for this reason; severe rash with mucocutanous involvement has so far not been reported.

The Applicant has committed to undertake a Prospective Observational Cohort Study in Patients Receiving DTG (EuroSIDA cohort) to investigate further the risks of hypersensitivity, hepatobiliary disorder and serious rash (see Section 2.8 RMP).

An immediate but mild and non-progressive increase in creatinine is seen already at low doses of dolutegravir. The effect (around +10 µmol/l) was the same regardless which background agents that were used (including tenofovir and ritonavir), and is considered to be caused by an inhibition of the transporter OCT2. The increase of serum creatinine is not considered clinically relevant.

In line with the agents of the same class, dolutegravir doesn't have an effect on blood lipid.

With these measures now in place, the CHMP considers that the dolutegravir safety profile is acceptable.

The CHMP considers the following additional pharmacovigilance activities necessary to further elucidate potential safety issues arising from the safety data presented (see Section 2.8 RMP):

- Prospective Observational Cohort Study in Patients Receiving DTG (Eurosida Cohort).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 50. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions Hepatobiliary disorders Drug Interactions Drug resistance
Important potential risks	Serious rash (DAIDS Grade 3 or 4) Renal disorders GI Intolerance and erosions Muscoskeletal events/ elevated CPK elevations Lipase elevations (Grade 3 and 4) Psychiatric disorders Increased occurrence of IRIS Phototoxicity
Missing information	Use in the elderly Use in pregnancy/ breastfeeding Use in patients with severe hepatic impairment Long term safety data Affinity of DTG to melanocortin receptors

- **Pharmacovigilance plans**

Table 51. Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Prospective Observational	To investigate the risk of HSR,	HSR	Planned	Final report anticipated April

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Cohort Study in Patients Receiving Dolutegravir (category 3)	hepatotoxicity and serious rash (DAIDS category 3 or 4)	Hepatotoxicity Serious rash		2020 or 10 months after study completion
Affinity of DTG to melanocontin receptors (category 3)	To asses the affinity of DTG to melanocontin receptors	Interaction with melanocontin receptors	Planned	Q4 2014
Phototoxicity study (category 3)	To assess phototoxicity of DTG	Phototoxicity	Planned	Q4 2014
In vitro study to determine if DTG is a substrate of OATP1B1 and OATP1B3 (category 3)	To determine if DTG is a substrate of OATP1B1 and OATP1B3	Potential drug interaction	Planned	Q2 2014
Midazolam drug interaction study justification (category 3)	To asses the potential for an interaction with midazolam	Potential drug interaction	Planned	Jan 2014

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Hypersensitivity reactions	As part of routine risk minimisation a contraindication in patients with hypersensitivity to DTG is included in section 4.3 of the SmPC. A warning around hypersensitivity is also included	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	in section 4.4 and hypersensitivity is included as an ADR in section 4.8 of the SmPC.	
Hepatobiliary disorders	As part of routine risk minimisation a warning is included in section 4.4 of the SmPC with respect to management of HBV/HCV infected patients. Hepatitis is also included as an ADR in section 4.8 of the SmPC.	None proposed
Drug Interactions	As part of routine risk minimisation a contraindication with dofetilide is included in section 4.3 of the SmpC and further information is provided in section 4.5.	None proposed
Drug resistance	As part of routine risk minimisation information on the recommended dose of DTG in patients infected with HIV-1 with resistance to the integrase classis is included in section 4.2 of the SmpC. Section 4.4 includes a warning around the use of dolutegravir in the presence of integrase class resistance. Section 5.1 of the SmPC also provides responses by pre-existing mutational patterns in ING112574, names the observed treatment-emergent mutations with DTG in subjects with and without pre-existing resistance to INIs, and contains information for the INI-resistant population.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential Risks		
Serious Rash (DAIDS Grade 3 or 4)	As part of routine risk minimisation rash is included as an ADR in section 4.8 of the SmPC. A warning and precaution around rash as part of a hypersensitivity reaction is included in section 4.4 of the SmpC.	None proposed
Renal Disorders	As part of routine risk minimisation information on increases in serum creatinine levels with DTG is included in section 4.8 of the SmPC.	None proposed
Gastrointestinal erosion and intolerance	Information around GI intolerance is included in section 4.8 of the SmPC. Pre-clinical data around GI intolerance is also presented in Section 5.3 of the SmPC	None proposed
Lipase elevations (Grade 3 or 4)	None proposed	None proposed
Psychiatric disorders	Insomnia is included in section 4.8 of the SmPC	None proposed
Musculoskeletal events and CK elevations	Data on asymptomatic CPK elevations is included in section 4.8 of the SmPC	None proposed
Increased occurrence of IRIS	Information on IRIS is included in section 4.4 and 4.8 of the SmPC.	None proposed
Phototoxicity	None proposed	None proposed
Missing Information		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in the elderly	As part of routine risk minimisation information on the use of DTG in the elderly is included in section 4.2 and 5.2 of the SmPC.	None proposed
Pregnant/ breastfeeding women	As part of routine risk minimisation information on the use of DTG in pregnant/ breastfeeding women is included in section 4.6 of the SmPC.	None proposed
Long term safety	None proposed	None proposed
Use in Severe Hepatic impairment	As part of routine risk minimisation a statement to use with caution in severe hepatic impairment is included in section 4.2 of the SmPC and further information provided in section 5.2.	None proposed
Affinity of DTG to melanocortin receptors	None proposed	None proposed

The CHMP endorsed this advice without changes.

2.9. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

A high efficacy of dolutegravir has been confirmed in studies in patients infected with HIV without resistance to integrase inhibitor class. Adequate control agents (raltegravir, efavirenz) were used

and DTG was administered in combination with the two main NRTI backbones used in first line treatment (abacavir/3TC and tenofovir/FTC).

In previously untreated patients, dolutegravir was non-inferior to raltegravir in the SPRING-2 study (88 vs 85% response at week 48, 95% CI -2.2;7.1%)). In the SINGLE study, DTG in combination with abacavir/3TC was superior to efavirenz / emtricitabine / tenofovir disoproxil also in previously untreated patients (88 vs 81% response at week 48 (+7.3%, 95% CI 2.3;12.2%).

For patients with previous treatment failures and resistance to other drug classes than integrase inhibitor, dolutegravir proved to be superior to raltegravir in the SAILING study (71 vs 64% at week 48 (adjusted difference +7.4%, CI95 (0.7, 14.2)).

VIKING-3 concerns patients where resistance to the integrase inhibitor class is present. The majority of patients had very extensive background resistance; around 65% to at least 4 drug classes, and around 50% of patients had <2 active agents as part of the optimized background therapy. Mean change from baseline in HIV RNA at day 8 (primary endpoint) was -1.4$\log_{10}$ copies/mL (95% CI -1.3 – -1.5$\log_{10}$, p<0.001). In this study, the efficacy seems to remain unhampered in the absence of the Q148 primary mutation.

Dolutegravir provides a high barrier to resistance. This barrier protects not only the agent itself but also the co-treating agents. Indeed, not a single case of *de novo* resistance to the integrase class or to NRTIs where seen in previously untreated patients receiving dolutegravir in the SPRING-2 and SINGLE studies, with a follow up of ≥ 48 weeks. The high resistance barrier was even more clearly manifested in the SAILING study, where no development of clinically significant integrase inhibitor resistance was seen in patients treated with dolutegravir, despite suboptimal activity of the background regimen in a substantial proportion of these patients.

In patients already having integrase inhibitor class resistant virus due to prior selection, but with resistance patterns other the Q148 primary mutation, the efficacy of DTG and its resistance barrier seems to be unaffected.

The primary endpoint in the paediatric study P1093 is dolutegravir PK (to mimic the adult exposure). The study design is in line with the Clinical development of medicinal products for treatment of HIV infection (CPMP/EWP/633/02 Rev. 2) and is considered adequate. In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, dolutegravir dosed 50 mg q.d., provided a similar exposure as in adults.

Uncertainty in the knowledge about the beneficial effects.

In the presence of the Q148 primary mutation, the efficacy of DTG is compromised and the resistance barrier is lowered to varying extents depending on the secondary mutations.

Although response rates were lower than for non-Q148 subsets, data from the VIKING-3 study shows that relevant activity of dolutegravir still remains in the presence of Q148 + 1 secondary mutation. This was clear both by the response seen during short term functional monotherapy and longer term outcomes at weeks 24 and 48 of therapy. Importantly, the response through week 24 was durable to week 48, despite the activity of background regimen being weak in a substantial part of these patients. However, in the presence of Q148 + ≥ 2 secondary mutations (secondary mutations from G140A/C/S, E138A/K/T, L74I) the activity of dolutegravir is considerably

compromised. To what extent dolutegravir provides added efficacy in the presence of such integrase class resistance is uncertain. This information is adequately reflected in the SmPC.

The Q148-mutation is seen in around 40% of those who failed raltegravir and where primary integrase resistance mutations were detected. Given that the evolution of integrase inhibitor resistance is rapid and highly dynamic during failure with the first generations integrase inhibitors, the CHMP concluded that any reduction in dolutegravir exposure should be avoided in the presence of the integrase inhibitor class resistance. Since DTG exposure is increased with food intake, the recommended dosage for dolutegravir is 50 mg twice daily with food for patients with integrase class resistance.

Risks

Unfavourable effects

Dolutegravir was well tolerated. In line with the agents of the same class, dolutegravir has an unremarkable metabolic profile and doesn't have an effect on blood lipids.

Among the ~2800 patients exposed to dolutegravir (around 2000 longer term), there was one severe case of hypersensitivity which included a severe liver reaction fulfilling Hy's law criteria. This case resolved after stopping therapy; however, an association to dolutegravir could not be ruled out.

The risk of hypersensitivity reactions (HSR) is adequately reflected in the RMP. The SmPC contains an adequate warning concerning such events. In addition to routine pharmacovigilance monitoring, the applicant has committed to undertake a Prospective Observational Cohort Study, where a large number of patients exposed to dolutegravir will be compared to others within the EuroSida Cohort.

An immediate but mild and non-progressive increase in creatinine is seen already at low doses of dolutegravir. The effect (around +10 µmol/l) was the same regardless which background agents that were used (including tenofovir and ritonavir), and is considered to be caused by an inhibition of the transporter OCT2. The increase of serum creatinine is not considered clinically relevant.

There were no specific concerns around safety in the limited number of adolescents studied.

Uncertainty in the knowledge about the unfavourable effects

Based on the findings in monkeys in non-clinical studies, liver safety was the main focus of the assessment. When carefully reviewing liver safety in the phase 3 studies, the overall liver safety of dolutegravir seemed roughly comparable with that of the control agents, regardless of hepatitis co-infection status.

Mild/moderate rash was an uncommon event with dolutegravir, and no patient stopped therapy for this reason; severe rash with mucocutanous involvement has so far not been reported.

The frequency and causality of putative dolutegravir-related risks (hypersensitivity reactions, hepatobiliary toxicity and severe skin reaction) is not known. This will be further investigated in the Prospective Observational Cohort Study in Patients Receiving DTG (EuroSIDA cohort).

Benefit-risk balance

Importance of favourable and unfavourable effects

Dolutegravir has demonstrated its efficacy in large scales studies covering previously untreated patients as well as those with advanced treatment histories and multi class resistance. In particular, a high barrier to resistance was demonstrated in the absence of integrase inhibitor class resistance. In addition, dolutegravir presented a favourable tolerability profile. The CHMP noted a potential risk for infrequent but potentially severe hypersensitivity reactions with dolutegravir. In addition to routine monitoring, the Applicant has committed to undertake a Prospective Observational Cohort Study in Patients Receiving DTG (EuroSIDA cohort) to investigate further the risks of hypersensitivity but also hepatobiliary disorder and serious rash.

In adolescents (aged from 12 to 17 years and weighing at least 40 kg) infected with HIV-1 without resistance to the integrase class, the CHMP considered that the proposed dose of DTG dosed 50 mg q.d was sufficiently substantiated. The efficacy and safety of DTG in this population was in line with the data from the studies supporting the indication in the older age group.

Benefit-risk balance

The overall benefit-risk balance for dolutegravir is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tivicay in the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age in combination with other anti-retroviral medicinal products is favourable and 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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 data on the quality properties of the active substance, the CHMP considers that dolutegravir is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0088/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.