EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/580654/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Triumeq

International non-proprietary name: dolutegravir / abacavir / lamivudine

Procedure No. EMEA/H/C/002754/0000

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
ATV	atazanavir
AST	Aspartate aminotransferase
AUC	Area under the curve
BE	Bioequivalence
BID	Twice daily
C_{max}	Maximum observed concentration
CSF	Cerebrospinal fluid
CI	Confidence Interval
COBI	cobicistat
CrCL	Creatinine clearance
CYP	Cytochrome P450
CV%	Coefficient of variance
DRV	darunavir
DTG	dolutegravir, S/GSK1349572
EFV	efavirenz
EMA	European Medicines Agency
FPV	fosamprenavir
FTC	emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INI	Integrase inhibitor
ITT-E	Intent-to-Treat Exposed
LOCFDB	Last observation carried forward (discontinuation equals Baseline)
LPV	Lopinavir
mg	Milligram
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OBR	Optimized background regimen
OCT2	Organic cation transporter 2
OMP	Omeprazole
PBMC	Peripheral blood mononuclear cell
PI	Protease inhibitor
PK	Pharmacokinetic
PD	Pharmacodynamic
RAL	raltegravir
RIF	Rifampin
RNA	Ribonucleic acid
RTV	ritonavir
SE	Single Entity
SJS	Stevens Johnson Syndrome
SOC	System organ class
t1/2	Terminal phase half-life
TLOVR	Time to Loss of Virologic Response
TDF	tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
UGT	Uridine diphosphate glucuronyltransferase
VL	Viral load

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ViiV Healthcare UK Limited submitted on 25 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Triumeq, 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 "*Triumeq is a fixed-dose combination of dolutegravir, abacavir and lamivudine. It is indicated as a complete regimen for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in Triumeq (see sections 4.4 and 5.1).*

*Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see "Management after an interruption of Triumeq therapy"). Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8)*".

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0287/2012 on the agreement of a paediatric investigation plan PIP.

At the time of submission of the application, the PIP P/0287/2012 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

At the time of the submission of this application, 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

The applicant received Scientific Advice from the CHMP on 22 January 2009, 20 May 2010 and on 17 November 2011. The Scientific Advice Protocol Assistance pertained to non-clinical, clinical pharmacology and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

GLAXO WELLCOME, S.A.
Avda. Extremadura, 3, Allendeduero,
Aranda de Duero,
Burgos, 09400
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: Johann Lodewijk Hillege

- The application was received by the EMA on 25 October 2013.
- The procedure started on 20 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2014.
- During the meeting on 20 March 2014, 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 21 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 June 2014.
- During the meeting on 26 June 2014, 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 Triumeq.

2. Scientific discussion

2.1. Introduction

Around 34 million people are presently living with HIV, including >3 million children under the age of 15; at present around 2.5 million people are newly infected each year. 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.

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).

A substantial number of highly effective agents have already been approved. However, there is still a need for new drugs with improved tolerability and safety, with simple dosing regimens (once daily and small pill size) and which are less prone for resistance development when adherence is not optimal. From a global perspective, such “forgiving” drugs with a high resistance barrier, and which are also easy to co-formulate to suitable fixed dose products are in fact still lacking and highly warranted, in particular for use in ART roll-out programs in high epidemic areas.

A once-daily fixed-dose combination (FDC) single tablet regimen (STR) that combines the integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC) was developed for use in the treatment of human immunodeficiency virus (HIV) infection.

DTG is a novel, potent, low nanomolar inhibitor of HIV integrase that provides the excellent antiviral activity and tolerability demonstrated for the INI class, while also offering once-daily dosing without the need for pharmacokinetic (PK) boosting.

Co-formulated ABC 600 mg/3TC 300 mg is available as a once-daily FDC worldwide.The new STR was developed is a FDC of DTG 50 mg + ABC 600 mg + 3TC 300 mg with once-daily dosing for antiretroviral therapy (ART)-naïve and ART-experienced (INI-naïve) patients, and is referred to as the DTG/ABC/3TC FDC.

2.2. Quality aspects

2.2.1. Introduction

Triumeq is presented as film-coated tablets containing a fixed combination of dolutegravir sodium equivalent to 50 mg dolutegravir, 600 mg of abacavir (as sulfate) and 300 mg of lamivudine.

Other ingredients are: mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide black, iron oxide red.

Triumeq is available in HDPE (high density polyethylene) bottles closed with polypropylene screw closures, with a polyethylene faced induction heat seal liner as described in section 6.5 of the SmPC.

Active Substance

Three active substances are used in this fixed combination product, dolutegravir, abacavir and lamivudine.

Dolutegravir

General information

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:

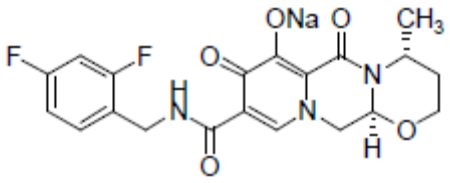


Figure 1 – Chemical structure of dolutegravir.

Dolutegravir sodium 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 centres and polymorphism. The most thermodynamically stable polymorphic form is Form 1. The enantiomeric purity is controlled routinely by chiral HPLC and polymorphism is also tested routinely by XRPD.

The chemical structure elucidation has been performed by infrared spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and x-ray diffraction.

Manufacture, characterisation and process controls

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) and a flow chart has been provided. Dolutegravir sodium anhydrous crystalline substance is milled in order to obtain the particle size distribution needed to meet finished product performance requirements.

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.

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

The active substance specification includes tests description (visual), identification (IR), sodium content (IPC-AES), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC), water content (KF), solid state (XRPD), particle size distribution (laser diffraction).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on 3 production batches of the active substance. All the batches were manufactured according to the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) and intermediate condition (30°C/65%RH) for up 18 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

Data were also 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 the 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 observed.

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. These impurities have not been observed at significant levels under long-term or accelerated condition.

All dolutegravir sodium samples stressed in solution and solid state were tested for diastereomer content. Only the acid stressed sample was found to contain diastereomer impurity.

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.

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

Abacavir

General information

Abacavir sulfate is white to off-white crystalline powder and the solubility is pH dependent with minimal solubility at basic pH and increased solubility at acid. This active substance is slightly soluble in diethyl ether and ethanol. Abacavir exhibits stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC. Abacavir produced by the proposed active substance supplier is a crystalline form. Polymorphism has not been found, although the active substance is of a crystalline nature.

The chemical name of Abacavir is [4R-(2-Amino-6-cyclopropylamino-purin-9-yl)-cyclopent-2-en-1S-yl]-methanol sulfate (2:1)and has the following structure:

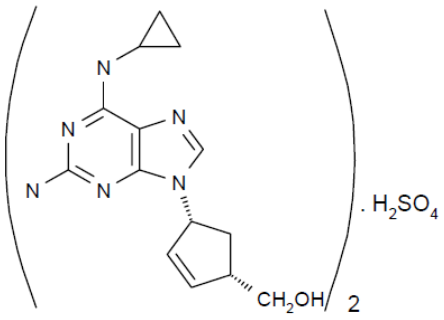


Figure 2: Chemical structure of Abacavir

The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, x-ray diffraction and MS. The molecular formula of this active substance is confirmed by elemental analysis.

Manufacture, characterisation and process controls

Abacavir is manufactured by three different manufacturing processes, which are very similar. In all three manufacturing processes the active substance is synthesised in three steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation. The different routes of synthesis have been described in sufficient detail and it was noted that different solvents have been used in the different manufacturing processes. The choice of starting materials is justified based on their structure and the number of steps involved. The designation of the starting materials for the synthesis of the active substance has been also justified with respect to their impurity profiles and the potential for carry-over into the final active substance. Information provided adequately describes the three manufacturing processes including reactions conditions, quantities of raw materials and yields in the processes.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed. The impurity profile of the active substances for the three manufactures is identical.

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

The active substance is packaged in plastic containers lined with anti-static low-density polyethylene bags and sealed with plastic ties. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for description (visual), identification (IR; chiral-HPLC), sulfate content (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), assay (HPLC), residual solvents (GC), water content (Ph Eur) and residue on ignition (Ph Eur).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on nine production batches produced by each. All the batches were manufactured according to the proposed synthetic routes, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packaged in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (30°C/60%RH) for up 60 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance (visual), water content (HPLC), impurities content (HPLC) and abacavir sulfate content (HPLC). Description of an alternative method for abacavir sulfate content and impurities (HPLC) has been provided. The alternative method has been validated with respect to specificity, linearity, precision, stability of solution and robustness. The analytical methods used for release and were stability indicating.

Forced degradation studies were conducted by exposing the active substance solution to light, high temperature, aqueous hydrolysis, acid and base. The major decomposition products were identified under all conditions except in water where formation of an unidentified degradation product is also significant.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

All stability studies indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

Lamivudine

General information

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

The chemical name of Lamivudine is (2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3]oxathiolan-5S-yl)-1H-pyrimidin-2-one and has the following structure:

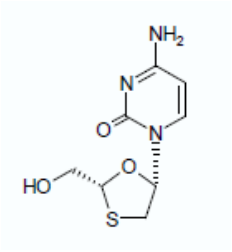


Figure 3: Chemical structure of Lamivudine

The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, MS and x-ray diffraction. The molecular formula of this active substance is confirmed by elemental analysis.

Manufacture, characterisation and process controls

Lamivudine is sourced from two manufacturers and both manufacturers used the same route of synthesis. This active substance is manufactured through a four main steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation.Enantiomeric purity and polymorphism is well controlled during the manufacturing process. The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the active substance, respectively. Information provided adequately describes the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed. The impurity profile of the active substances for both manufactures is identical.

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

The active substance is packaged in anti-static low density polyethylene bags and sealed with plastic ties. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for appearance, identification (IR; chiral HPLC), assay (chiral-HPLC), impurities (HPLC), residual solvents (GC), water content (Ph Eur), appearance of solution (Ph Eur), heavy metals (Ph Eur) and sulphated ash (Ph Eur).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on six production batches produced by one manufacture and three production batches produced by the second manufacturer. All the batches were manufactured according to the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Six production scale batches of the active substance packaged in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (30°C/65%RH) for up 60 months and three production scale batches under accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, assay (chiral HPLC), and impurities (HPLC). The analytical methods are the same as used for release testing were stability indicating.

Forced degradation studies were performed at solid state (heat and light) and solution (acid, base, hydrolysis, heat, oxidation and photolysis). No decrease on lamivudine content or increase of impurities was observed at solid state stress conditions.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

All stability studies results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

2.2.1. Finished Medicinal Product

Description of the product and Pharmaceutical development

The aim of the drug development was to develop a pharmaceutical form combining the currently approved doses of dolutegravir, abacavir and lamivudine into a single film-coated tablet to be administered once daily in order to support patient adherence to treatment.

The particle size of dolutegravir sodium as well as the granulate is the same as used in support of the MA containing Dolutegravir 50 mg tablets. As part of the manufacturing process development studies it was demonstrated that particle size of dolutegravir had no practical impact on the manufacturing process or product performance. Particle size is not considered to be a critical quality attributes for dolutegravir sodium.

Development studies showed no impact of particle size on the drug product manufacturing process and performance as would be expected for a highly soluble molecule.

Development studies showed no impact of particle size on the drug product manufacturing process and performance as would be expected for a highly soluble molecule.

The excipients were selected based on the commercial formulation of the fixed-dose combination abacavir/lamivudine tablets and the monocomponent dolutegravir 50 mg tablets. A risk assessment by Failure Modes and Effect Analysis (FMEA) showed no excipient attributes with a strong relationship to any product critical quality attributes. No additional controls beyond those listed in the European Pharmacopoeia are required. Compatibility of the active substances with the excipients was confirmed by the results of the forced degradation studies on the finished and the results of the formal stability studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. All information regarding the choice of the active substance and the excipients are sufficiently justified.

For the development of the drug product and development of the manufacturing process a Quality by Design (QbD) approach was followed, including the determination of a Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA's), Critical Process Parameters (CPPs) and material attributes by a risk assessment and the control strategy. Design of Experiments (DoE) studies and process stretching studies were performed to evaluate the significance of changing process parameters on the quality and performance of the finished product. It is important to underline that no design space has been established or claimed. The critical quality attributes identified were description, identity, content, uniformity of content, drug-related impurities and dissolution.

The development of the medicinal product was based on prior knowledge of the fixed-dose combination abacavir/lamivudine tablets and the recently developed monocomponent dolutegravir 50 mg tablets. The pharmaceutical formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

The pivotal bioequivalence (BE) study has been performed comparing the finished product according to its finalised formulation with co-administration of one dolutegravir 50 mg tablet and one tablet containing 600 mg/300 mg abacavir/lamivudine administered concurrently under fasted conditions. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is described as stated in the SmPC. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of nine main steps: wet granulation, wet milling, drying, dry milling, post-mill blending, blending, lubricant blending, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

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

The validation of the manufacturing process has been evaluated on eleven consecutive production scale batches. The quality of the production batches was evaluated through the results of in process testing as well as the results of finished product testing. The process validation is supported by batch data on three production scale batches.

Product specification

The finished product release specifications include appropriate tests for this type of dosage form: description, identification (HPLC and UV), uniformity of dosage Units (Ph Eur), assay (HPLC), impurities (HPLC), dissolution (Ph Eur) and microbiological quality (Ph Eur).

Batch analysis data of five production scale batches of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of six production scale batches for of finished product stored under long term conditions for 18 months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The parameters tested are appearance, assay (HPLC), impurities (HPLC), dissolution (Ph Eur), microbiological quality (Ph Eur) and water content (Ph Eur). The analytical methods used during the stability studies are the same as used for release testing of the finished product with the exception of microbial limits, water activity determination, water content by KF and determination of dolutegravir free-acid content. A description of these methods has been provided, validated and they were stability indicating.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions including, humidity, UV-visible light, high temperature, aqueous hydrolysis, acid and base conditions. One production scale batch packed in the primary packaging proposed for marketing was stored for 30 days and 90 days respectively at 25°C/60% RH after removal of the induction seal and re-placing the cap. A patient use study was also performed using three 30 count stability batches stored at 30 ºC / 75% RH for 30 days with and without desiccant. Based on the results of stress stability studies and in-use stability, it was concluded that the finished product might be slightly affected by the humidity. Therefore, it was decided to add the following warning in the PI: “Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant”.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.2. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The main goal of the drug development was to develop a pharmaceutical form combining the currently approved doses of dolutegravir, abacavir and lamivudine into a single film-coated tablet to be administered once daily in order to support patient adherence to treatment. The development of the product includes elements of Quality by Design (QbD), but no design space has been established or claimed. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.3. 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.

2.2.4. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant applied for registration of Triumeq film-coated tablets, a fixed dose combination (FDC) product containing dolutegravir, abacavir and lamivudine. No new studies were performed with the combination dolutegravir, abacavir and lamivudine. Characteristics of the separate components are summarised. Of note the single components of the FDC have been extensively evaluated, therefore the current evaluation is focussed on the necessity to perform additional studies with the combination.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Abacavir

Abacavir is a nucleoside analogue with reverse transcriptase inhibition activity. It is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-t'-triphosphate (dGTP). Antiviral efficacy has been assessed in primary cell cultures (mononuclear cells, macrophages) and in cell lines that are susceptible to HIV-1 and HIV-2. Tested

viruses included T-cell line adapted viruses and primary isolates. These in vitro studies in experimental models included combinations with ZDV, ddI, ddC, amprenavir and nevirapine. A significant antiviral effect of abacavir in HIV-1 and HIV-2 was supported but the combination studies were not performed with primary isolates. Mutations associated with abacavir resistance selected during in vitro passage were K65R, L74V, Y115F, and M184V.

Dolutegravir

Dolutegravir is referred to as a second generation integrase inhibitor, with activity against raltegravir resistant viruses. The mode of action seems well established involving inhibition of viral integration by inhibition of integrase strand transfer. Data indicate that dolutegravir enjoys tighter binding and a longer dissociative half-life from integrase than either raltegravir or evitegravir possibly reflected in a higher barrier for resistance. The IC50 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. This x5 to x10 fold difference in IC50 values between purified enzyme and cell based assays could be interpreted as virus replication being inhibited at concentrations lower than the biochemical data for the proposed mechanism, but differences in protein binding may influence data.

With respect to activity against other viruses, IC50 values of 11.2 µM were reported for hepatitis C virus also indicating a potential for suboptimal clinical activity at maximum reported clinical plasma levels of approximately 3.7-4.2 µg/ml. The TC50 was 96.7 µM, indicating mild cytotoxicity. The IC50 against measles was 30.3 µM reflecting some antiviral activity.

Lamivudine

Lamivudine is a pyrimidine nucleoside analogue. After intracellular uptake, it is sequentially phosphorylated by host cell intracellular kinases to its respective 5'-triphosophates (TP). Thereafter, the monophosphate compound is inserted into the DNA transcript by the viral enzyme reverse transcriptase (RT). However, due to lack of a 3'-OH group, the nucleic acid strand extension is terminated. Lamivudine is also a competitive inhibitor of the viral RT. Lamivudine inhibited viral replication of several laboratory strains and clinical isolates of HIV-1 and HIV-2 in different monocyte or lymphocyte cell lines or fresh human peripheral blood lymphocytes. The IC50 ranged from 2nM to 15 µM. In addition, lamivudine-TP inhibited viral RT with a Ki value of 10-12 µM. The in vitro intracellular half-life of lamivudine TP was 10-15 h. Antiviral effects have been demonstrated at extracellular concentrations of 10 nM. Lamivudine had no activity against a number of other pathogens [RNA and DNA viruses (except hepatitis) bacteria and fungi] normally occurring during HIV disease, indicating anti-HIV specificity.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown.

Secondary pharmacodynamic studies

Abacavir

The effect of abacavir at the following receptors was assessed in isolated tissue preparations: cholinergic (guinea-pig ileum), adrenergic (rabbit aorta, guinea-pig atria and trachea), histaminergic (guinea-pig atria) and serotonergic (rat fundus). In addition, the ability of abacavir to affect tissue responsiveness to arachidonic acid (rat fundus), bradykinin (guinea-pig ileum) and angiotensin II (rabbit aorta) was determined. There were no direct effects of abacavir on any of the isolated tissue preparations, and no significant effects on contractile responses to any of the substances studied.

Dolutegravir

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. A 64% inhibition was recorded in the melanocortin receptor binding assay. The significance of this receptor has not been fully characterized, but a particularly high expression is reported in brain and it appears to play a role in energy homeostasis. 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 assay. Dolutegravir does not appear to have been tested for potential inhibitory activities against DNA topoisomerase I and II that are involved in DNA replication, recombination and transcription.

Lamivudine

Cytotoxicity was investigated using different in vitro cell systems (e.g. human erythroid precursors, human bone marrow progenitor cells). LC50 (concentration reducing cell viability by 50%) was >30 µM. Depending on the test systems used, the therapeutic index (i.e. the ratio between LC50 and IC50) was in general large. No data are available regarding receptor screen with lamivudine.

Safety pharmacology

Abacavir

A range of in vitro and in vivo safety pharmacology studies showed no adverse effects of abacavir on central and autonomic nervous system, or respiratory and cardiovascular systems, at doses exceeding the maximum proposed therapeutic dose 300 mg (base) bid, equivalent to 12 mg (base)/kg/day based on a 50 kg person. These studies involved mouse, rat and dog.

Dolutegravir

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. Although the maximum concentration of dolutegravir tested in the hERG assay was rather low (20 µM) this was justified based on limitations due to use of the solvent DMSO. In addition, evaluation of cardiovascular parameters incorporated in repeated dose toxicity studies did not suggest any particular cardiovascular adverse effects. In view of results from toxicology studies it would have been of interest to determine any potential acute effects on the gastrointestinal system, however, considerable clinical safety data is now available that may allow relevant conclusions on the potential for gastrointestinal toxicity.

Lamivudine

Safety pharmacology studies with lamivudine showed no major effects on cardiovascular or respiratory parameters or on intestinal transport.

Pharmacodynamic drug interactions

Abacavir

Published data have reported on an in vitro synergy of amprenavir and abacavir.

Dolutegravir

No non-clinical interaction studies were performed.

Lamivudine

The extent of lamivudine triphosphorylation was not impaired by the presence of zidovudine concentrations of 5 to 50 µM. Effects of lamivudine on zidovudine triphosphorylation have not been reported. In vitro studies of lamivudine given in combination with other antimicrobial agents showed that ganciclovir reduced the antiviral activity (IC50) of lamivudine by a factor of 2-3, which is within experimental variation.

Combination abacavir + dolutegravir + lamivudine

No non-clinical studies with the combination were performed.

2.3.3. Pharmacokinetics

Triumeq contains dolutegravir, abacavir and lamivudine, therefore any interactions identified for these drugs individually are relevant for Triumeq. The Applicant concludes that due to different routes of metabolism and elimination, and the minimal effect of these agents on drug metabolizing enzymes or transporters, no clinically significant drug interactions are expected between dolutegravir, abacavir and lamivudine.

Methods of analysis

Abacavir

Plasma abacavir concentrations were measured by methods based on protein precipitation with trichloroacetic acid, then chromatographic analysis by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) ranged between 50 and 70 ng/mL, depending on study requirements. Analysis methods were validated across the calibration range with respect to specificity, accuracy, precision, and stability under a variety of conditions. The methods and limits of quantification were adequate with regard to specificity and sensitivity to support the kinetic analyses of abacavir.

Determination of the radioactivity in *in vitro* or *in vivo* biological samples following administration of [^{14}C]-abacavir was carried out by either direct liquid scintillation counting (LSC) or by LSC following combustion of the sample. For radioactivity concentrations in tissues, quantitative whole body autoradiography was used.

The metabolic profiling of abacavir was conducted by using chromatographic separation with radiometric detection and identification of metabolites performed by using LC-MSn.

Immunoblotting experiments for metabolic bioactivation assessments were carried out following SDS-polyacrylamide gel electrophoresis of exhaustively extracted protein samples, using anti-abacavir antibodies as probes. The antibodies were raised in rabbits against abacavir conjugated to keyhole limpet hemocyanin.

Dolutegravir

Plasma dolutegravir concentrations were measured by methods based on protein precipitation followed by chiral or achiral liquid chromatographic separation and tandem mass spectrometric (LC/MS/MS) detection. The lower limit of quantification (LLQ) ranged between 4.75 and 500 ng/mL, depending on study requirements. The chiral and achiral methods used for analysis were validated across the calibration range with respect to specificity, recovery, accuracy, precision and stability under a variety of conditions. The methods and limits of quantification were adequate with regard to specificity and sensitivity to support the kinetic analyses of dolutegravir.

Determination of the radioactivity in *in vitro* or *in vivo* biological samples following administration of [^{14}C]-dolutegravir was carried out by either direct liquid scintillation counting (LSC) or by LSC following combustion of the sample. For radioactivity concentrations in tissues, quantitative whole body autoradiography was used.

The metabolic profiling of dolutegravir was conducted by using chromatographic separation with radiometric detection and identification of metabolites performed by using LC-MSn; nuclear magnetic resonance (NMR) methods were used to confirm structures not confirmed by mass spectrometric methods.

Lamivudine

Plasma lamivudine concentrations were measured by methods based on protein precipitation with trichloroacetic acid, then chromatographic analysis by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) ranged between 5 and 100 ng/mL, depending on study requirements. The methods and limits of quantification were sufficiently adequate with regard to specificity and sensitivity to support the kinetic analyses of lamivudine.

Determination of the radioactivity in *in vitro* and *in vivo* biological samples following administration of [^{3}H]-lamivudine was carried out by either direct LSC or by LSC following combustion of the sample. For radioactivity concentrations in tissues, quantitative whole body autoradiography was used.

The metabolic profiling of lamivudine was conducted by using chromatographic separation with radiometric detection and identification of metabolites performed by using LC-MSn; nuclear magnetic resonance (NMR) methods were used to confirm structures not confirmed by mass spectrometric methods.

Absorption

Abacavir

The pharmacokinetics of abacavir have been investigated in mouse, rat, rabbit, and monkey after single IV or single and repeated oral administration.

Kinetics after IV administration

Following single intravenous administration of abacavir (10 and 55 mg/kg) to mice (studies TEIN/94/0004 and TEIN/94/0005), the elimination half-life was 0.27-0.78 hour. The volume of distribution (Vd) was 0.9-1.3 L/kg, indicating equilibrium of abacavir with total body water. The $AUC_{0-\infty}$ was 13 µM × h at the 10 mg/kg dose and 103 µM × h at the 55 mg/kg dose. A lower total body clearance rate (CL) was observed at the 55 mg/kg dose (1.9 L/h/kg) compared to the 10 mg/kg dose (2.7 L/h/kg), leading to a more than dose proportional increase in the AUC.

Following single IV bolus dose of abacavir (10 or 25 mg/kg) to Cynomolgus monkeys (study TEIN/94/0015), $AUC_{0-\infty}$ values were 41 µM × h at 10 mg/kg and 129 µM × h at 25 mg/kg. Thus, the AUC increased more than dose proportional. The elimination half-life was 1.3 hours and the volume of

distribution was 1.1-1.2 L/kg. The total body clearance was slightly faster at 10 mg/kg (0.87 L/h/kg) compared to 25 mg/kg (0.71 L/h/kg).

Kinetics after oral administration

In mice, the bioavailability of abacavir was 92% at a dose of 10 mg/kg and 76% at a dose of 55 mg/kg after single oral dosing (study TEIN/94/0004). T_{max} was 0.17 hour and C_{max} values of 15 µM (10 mg/kg dose) and 52 µM (55 mg/kg dose) were observed. $AUC_{0-\infty}$ was 12.2 µM × h at a dose of 10 mg/kg and 78.5 µM × h at a dose of 55 mg/kg. Based on a repeated dose studies, C_{max} and AUC increased less than dose proportional. The bioavailability of abacavir was high (76 to 77%) at both 10 and 25 mg/kg in Cynomolgus monkeys received a single oral dose of abacavir (study TEIN/94/0015). C_{max} values of 15 µM at 10 mg/kg and 29 µM at 25 mg/kg occurred 1.5 and 2.0 hours after dosing, respectively. The t½ was 1.2 hours. There were no statistically significant differences in dose normalised $AUC_{0-\infty}$ and C_{max} following single oral administration of the succinate and hemisulphate salts of abacavir (study RD1997/01258). There were no differences in the values for $t_{½}$, T_{max} and mean residence time (MRT) between the salt forms.

Systemic exposure to abacavir following repeat dosing was investigated in mice receiving oral doses of abacavir (195, 312, 496 or 793 mg/kg/day) twice daily with a 6 hour interval for 3 days (study TTDR/92/0036). The AUC_{0-4h} for abacavir increased with increasing dose at Day 2. The AUC_{0-4h} for the carboxylate metabolite was approximately 20% of that for abacavir and the AUC_{0-4h} for the glucuronide increased from 25 to 42% of that for abacavir as the dosage increased at Day 2. In another study, mice were administered abacavir (496, 694 or 793 mg/kg/day) twice daily with a 6 hour interval for 21 days (study TTDR/92/0035). No significant differences were apparent in the plasma concentrations of abacavir between different dose levels, except for possibly higher concentrations on Day 21 than Day 2 in animals dosed with 793 mg/kg/day. During a 30 day repeat oral dose study in which mice received abacavir (78, 234 or 708 mg/kg/day) twice daily with a 6 hour interval between doses (study TTEP/94/0006), systemic exposure was significantly higher on Day 30 than on Day 5. In contrast, AUC_{0-6h} values were significantly lower on Day 91 compared to Day 2 in a 3 month repeat oral dose study in which mice received abacavir twice daily with a 6 hour interval between doses at dose levels of 78, 234 or 708 mg/kg/day (study TTEP/94/0035). Also in a 6 month repeat oral dose study in which mice received abacavir twice daily with a 6 hour interval at dosages of 39, 788 and 234 mg/kg/day (study RD1996/00245), AUC_{0-24h} values were lower on Day 180 than Day 2 at 234 mg/kg/day but was similar on Days 2 and 180 at lower doses.

The kinetics of abacavir were investigated in rats during a 30 day repeat dose oral range finding study in which abacavir (100, 200 or 400 mg/kg/day) was administered twice daily with a 6 hour interval for 30 days (study TEZA/91/0025). Plasma concentrations of abacavir increased proportionally with increasing dose and were 50 to 90% higher on Day 24 than on Day 2. No gender-related differences in plasma concentrations were observed. In a 90 day repeat dose oral study, rats received abacavir twice daily with a 6 hour interval at a dose of 25, 96 and 375 mg/kg/day (study RD1997/03595). The AUC_{0-24h} appeared dose-proportional except for 35 and 530 mg/kg/day in females on Day 3, and was higher in males compared to females on Days 3 and 90. The C_{max} was less than dose-proportional. Furthermore, the kinetics of abacavir (35, 135 and 530 mg/kg/day) in rats was determined during a 1-month study (study RD1997/04062). Plasma levels increased with increasing dose, generally less than proportionally on Day 1 but proportionally on Day 28. There were no gender-related differences in plasma concentrations of abacavir. The kinetics of abacavir (64, 194 or 648 mg/kg/day) were also determined in pregnant rats following oral administration twice daily with a 6 hour interval from Days 6 to 17 of pregnancy (study RD1997/01057). C_{max} increased less than dose-proportional. Values for AUC_{0-24h} generally increased proportional to increasing dose.

In pregnant rabbits, kinetic data have been obtained following oral administration of abacavir (81, 227 or 453 mg/kg/day) twice daily with a 6 hour interval from Days 6 to 20 of pregnancy during reproductive toxicity studies (study RD1997/01059). Systemic exposure to abacavir was demonstrated at each dose level. C_{max} increased dose-proportional and AUC_{0-24h} increased dose-proportional.

During a dose range finding study, Cynomolgus monkeys received abacavir by oral administration twice daily with a 6 hour interval at a dosage of 354 mg/kg/day for 10.5 days (study TTDR/93/0001). Pre-dose plasma levels of abacavir (16 hours after the previous dose) were high on Day 2 but lower on Day 10. Peak plasma levels were generally higher in females than males, due to the greater production of the 5'-glucuronide by males than females. Plasma concentrations of abacavir were lower on Day 10 than Day 2. In contrast the 5'-glucuronide metabolite and 1459U89 (major metabolite) were approximately ~2.5-fold and ~3-fold higher on Day 10 than Day 2. Following, repeated oral dosing twice daily with a 6 hour interval for 30 days with 100 and 200 mg/kg/day (study TEZA/91/0073), mean plasma concentrations of abacavir increased dose-proportional. There were no significant differences in concentrations between Days 3 and 29. In a 28 day study, Cynomolgus monkeys received orally administered abacavir twice daily with a 6 hour interval at dosages of 35, 99 and 297 mg/kg/day (study TTEP/94/0007). On Day 26, C_{max} and AUC_{0-4h} were lower than on Day 3. T_{max} appeared to be longer on Day 26. In a 3-month study in which Cynomolgus monkeys received abacavir (35, 99, and 297 mg/kg/day) by oral administration twice daily with a 6 hour interval (study TTEP/94/0047). At 297 mg/kg/day, C_{max} and AUC_{0-8h} values were lower on Day 87 than on Day 3, although there were no apparent differences at lower dosages. In a 12-month study in which Cynomolgus monkeys received abacavir (35, 99 and 212 mg/kg/day) by oral administration twice daily with a 6 hour interval, no evidence of accumulation of abacavir following multiple oral dosing was observed.

Kinetics in juvenile rats

The kinetics of abacavir following repeated oral administration were determined in juvenile rats in a 1-month preliminary study and a 2-month toxicity study. In the preliminary study, abacavir (50, 150 and 450 mg/kg/day) was administered twice daily with a 6 hour interval, for 31 days starting from Day 3 of lactation (study RD1998/00110). In the 2-month study, abacavir (40, 120 and 360 mg/kg/day) was administered twice daily with a 6 hour interval, for 60 days starting from Day 3 of lactation (study RD1997/04060). In the 1-month and 2-month studies, plasma concentrations increased proportionally with increasing dose and were 1.5 to 3 times greater on Day 10 than on Day 34/63. There were no sex-related differences in systemic exposure to abacavir. Plasma concentrations from the 2-month study were comparable to plasma concentrations observed for abacavir following dosing for 1 month in adult rats.

Dolutegravir

Studies investigating the absorption and pharmacokinetics of dolutegravir after single IV and oral administration have been performed in rat, dog and monkey and after repeated oral administration in mouse, rat, rabbit, dog and monkey.

Kinetics after IV administration

Following intravenous administration of dolutegravir (1 mg/kg) to rats, the clearance (0.229 mL/min/kg) and volume of distribution (103 mL/kg) were low, with a half-life of 6.2 hours (study RH2007/00101). Following intravenous administration of dolutegravir (1 mg/kg) to non-fasted male beagle dogs, the clearance (2.2 mL/min/kg) and volume of distribution (352 mL/kg) were low, with a half-life of 5.2 hours (study RH2007/00102). Following intravenous administration of dolutegravir (1 mg/kg) to Cynomolgus monkeys, the clearance (2.1 mL/min/kg) and volume of distribution (279 mL/kg) were low, with a half-life of 6.0 hours (study RH2007/00103).

Kinetics after oral administration

In fasted rat, the oral bioavailability of dolutegravir solution (5 mg/kg) was 76% (study RH2007/00101). The bioavailability of a suspension of dolutegravir (5 mg/kg) was 34% in non-fasted rats and 52% in fasted rats. In fasted rats, the oral bioavailability after capsule administration of dolutegravir sodium (~7.3 mg/kg) and free acid dolutegravir (~7.8 mg/kg) was 48% and 35%, respectively. The systemic exposure after oral administration of dolutegravir in suspension increased less than dose proportional with dose from 50 to 500 mg/kg. In non-fasted beagle dogs, a bioavailability of 39% was observed after oral administration of dolutegravir (5 mg/kg) (study RH2007/00102). Plasma exposure increased less than dose proportional with increasing dose (30-500 mg/kg) in dog (study RD2009/00963). In rabbit dosed with 30, 100, 300 and 1000 mg/kg dolutegravir (study RD2008/01760), C_{max} values increased less than dose-proportionally between 30 and 300 mg/kg while C_{max} at 1000 mg/kg was approximately the same as at 300 mg/kg. Mean AUC_{0-24} values increased dose-proportionally between 30 and 300 mg/kg while those values at 1000 mg/kg were approximately the same as at 300 mg/kg. In fasted Cynomolgus monkeys, the bioavailability was 87% following oral administration of free acid dolutegravir (5 mg/kg) (study RH2007/00103). Following oral administration of dolutegravir sodium (5 mg/kg) to non-fasted Cynomolgus monkeys, the bioavailability was 25%. After single oral administration of 1, 3, 10 and 50 mg/kg, the systemic exposure to dolutegravir was dose-proportional (study RD2008/01762). No dose relationship was noted in the exposure values after oral administration of 50 to 500 mg/kg; the systemic exposure was considered to have attained the steady state at 125 mg/kg. Overall, the bioavailability results suggest that the absorption of free acid dolutegravir could be limited by the solubility and dissolution rate.

After repeated dosing with dolutegravir (10-1500 mg/kg/day) in mice, no evidence of accumulation was observed after 14 days, 13 weeks and 104 weeks (studies RD2009/01546, RD2009/00028 and 2012N152419). In rat, no accumulation was observed after repeated oral dosing with dolutegravir (2-1000 mg/kg/day) for 14 days, 4 weeks, 26 weeks and 104 weeks (studies RD2007/01140, RD2008/01628, RD2009/00410 and 2012N152418). In non-pregnant and pregnant rabbits orally dosed with dolutegravir (30-1000 mg/kg), no obvious effects of repeat dosing on the systemic exposure values were observed (studies RD2008/01760 and XD2009/0366). After repeated dosing with dolutegravir (25-1000 mg/kg/day), no accumulation was observed after 14 days, 4 weeks in Cynomolgus monkeys (study RD2007/01142, RD2008/00107). In a 38 week study, accumulation was observed after repeated oral dosing with dolutegravir (3-30 mg/kg/day) at Day 120 in female monkeys, but not in male monkeys. In addition, no accumulation was observed at Day 270 compared to Day 1 (study RD2009/00036/01).

Kinetics in juvenile rats

Juvenile rats were given oral doses of dolutegravir (5, 50, 100, 500 and 1000 mg/kg/day) from Days 4 to 21 post-partum (study CD2009/00409) or dolutegravir (2, 25, 75 and 300 mg/kg/day) from Days 4 to 31 post-partum (study CD2009/00770). The systemic exposure increased much less than dose proportional. Systemic exposure following 300 mg/kg/day was essentially not different from that following 75 mg/kg/day in either sex. In another study, juvenile rats were dosed orally with dolutegravir (0.5, 2 and 75 mg/kg/day) from Days 4 to 66 post-partum (study CD2010/00023). The systemic exposure (C_{max} and AUC_{0-24}) to dolutegravir was generally lower on Day 32 compared to that on Day 13.

Lamivudine

Site of absorption

In order to investigate the site of absorption in the gastrointestinal tract, anaesthetised, laparotomised rats were prepared with *in situ* loops of the stomach, duodenum, jejunum and ileum (study

NME/96/019). A solution of [^{3}H]-lamivudine (2 mg/kg) was injected into each loop. Following injection each loop was restored to its original location in the abdominal cavity and the animal was sutured. Lamivudine showed absorption of approximately 50 to 85% of the dose within 2 hours from the small intestine (duodenum, jejunum, ileum) which is consistent with the known pharmacokinetic properties of lamivudine. Little absorption (4 to 5% of the dose) from the stomach was observed.

Kinetics after IV administration

Following IV administration of [^{3}H]-lamivudine (45 mg/kg) to rat (studies GDM/91/015 and GDM/91/077), there was close agreement between serum concentrations of lamivudine and radiolabel, indicating that any metabolites produced are cleared rapidly. Clearance was 4 mL/min and the volume of distribution was 540 mL, suggesting that the distribution of lamivudine was greater than could be attributed to distribution in total body water. Renal clearance was estimated to be approximately 3.3 mL/min. This value is higher than the glomerular filtration rate, indicating that tubular secretion plays a significant role in the clearance of lamivudine. No gender differences were observed. Following IV administration of lamivudine at 2000 mg/kg to rat (study GDM/91/021), clearance was 2.0 mL/min which suggests a non-linear relationship between clearance and dose. The apparent volume of distribution was approximately 1070 mL, suggesting that lamivudine was distributed extra-vascular. The elimination half-life was 1.5 at a dose of 45 mg/kg and 6.5 hours at a dose of 2000 mg/kg.

In addition, the kinetics of lamivudine (30 mg/kg) following IV administration have been studied in dogs (studies GDM/91/008 and GDM/91/080). The elimination half-life was 1.7 hours, and when compared with plasma radioactivity levels, accounted for 40-58% of the drug-related material. The magnitude of the proportion of radiolabel not attributable to lamivudine suggests that metabolic clearance is of greater importance in the dog than in the rat. Clearance was approximately 5.5-5.7 L/h and renal clearance accounted for about 1.5-2.3 L/h. The renal clearance value is lower than the glomerular filtration rate, indicating that tubular secretion does not play a significant role in the elimination in dog. The volume of distribution was 12.4 L, which equated to the volume occupied by total body water.

Kinetics after oral administration

After single oral administration of [^{3}H]-lamivudine (45 mg/kg) to rats (studies GDM/91/015 and GDM/91/077), the oral bioavailability was approximately 60%. Peak concentrations (4 µg/mL) were detected at 1.5 hours post-dose. No gender differences were observed. In rats dosed orally with lamivudine at 600, 800, 1000, 1200, 1500 or 2000 mg/kg (study GDM/91/003), the maximum plasma concentrations ranged from 41 µg/mL at the lowest dose level to 107 µg/mL at the highest dose level at 1 to 2 hours after dosing. The plasma half-life increased from 3.7 hours at 600 mg/kg to 4.6 hours at 1500 and 2000 mg/kg. Both C_{max} and AUC in the dose range 600 to 2000 mg/kg were dose proportional. Following single oral administration of [^{3}H]-lamivudine (45 mg/kg) to rabbits, peak concentrations (13.7 µg/mL) were detected within 1 hour after dosing (study GDM/91/058). Lamivudine declined with an elimination half-life of approximately 3.6 hours. After single oral administration of [^{3}H]-lamivudine (30 mg/kg), the oral bioavailability of lamivudine in the dog was 67-83% (studies DM/91/008 and GDM/91/080). Peak plasma concentrations (13.6-26.6 µg/mL) were observed at approximately 40 minutes. The elimination half-life ranged from 1.3 to 1.6 hours. Following oral administration of lamivudine at dose levels of 500, 1000, 1500 or 2000 mg/kg (study GDM/91/036), both C_{max} and AUC increased less than dose proportional.

In mice administered 1000 mg/kg BID of lamivudine for 37 days (study WPT/93/572), the AUC was 153-217 µg × h/mL. Oral gavage and administration of lamivudine via the diet did not lead to different kinetics in mice (study WPT/92/419). In rat following repeated oral dosing with lamivudine (45, 300 or 2000 mg/kg BID) for 1 month (study WPT/91/104), C_{max} and AUC were similar on Day 1 and 35. In a 13 week oral toxicity study in rats, lamivudine was administered at dosages of 45, 300 or 2000 mg/kg

BID (study WPT/91/435). At all dose levels the plasma AUC values calculated for Day 92 were higher than for Day 1. The plasma level time profiles for Days 1 and 92 showed no evidence of a change in the plasma clearance of lamivudine, but suggest that some form of secondary absorption could be responsible for the difference in AUC values. In a 6-month toxicity study in rats, animals received lamivudine at doses of 90, 425 or 2000 mg/kg BID (12 hour dose interval) (study WPT/93/361). Plasma AUC values did not show any consistent change over the 6 month dosing period with the exception of those in high dose female rats where an increase was observed. Oral gavage and administration of lamivudine via the diet did not lead to different kinetics in rat (study WPT/92/323). Following repeated oral dosing with lamivudine (45, 150 or 500 mg/kg BID with a 12 hour dose interval) to rabbits (study WPT/92/014), a significant increase in the plasma concentrations of lamivudine between the first and last administration. In another study in rabbits, lamivudine was administered at dosages of 7.5, 20 or 45 mg/kg BID (study WPT/92/184). A significant increase in the plasma concentrations of lamivudine between the first and last administration at all three dose levels was observed. Following repeated oral dosing with lamivudine (1500 mg/kg BID) for 14 days in dog (study WPT/91/222), an increase in plasma AUC was observed. In a 13-week oral toxicity study in dogs, lamivudine was administered at dosages of 45, 260 or 1500 mg/kg BID (study WPT/92/132). At all 3 dose levels, AUC values for Day 91 were higher than those for Day 1. In a 52-week oral toxicity study, lamivudine was administered at 45, 260 and 1000 (females) or 1500 (males) mg/kg BID (study WPT/92/407). AUC values in Week 52 were higher than those on Day 1 at all dose levels.

Kinetics in juvenile rats

The kinetics of lamivudine (45 or 2000 mg/kg) after single oral administration were investigated in juvenile rats on litter Day 16 (study WPT/92/190). The mean AUC and C_{max} values obtained at both dose levels were considerably higher than those in adult. The data suggest that the systemic exposure to lamivudine of a juvenile rat is at least twice that of an adult rat receiving an equivalent dose.

Combination of dolutegravir, abacavir and lamivudine

The Applicant did not provide non-clinical *in vivo* kinetic studies in which the combination of dolutegravir, abacavir and lamivudine was administered.

Distribution

Abacavir

Membrane permeability

Abacavir (1 to 100 µM) is passively transported over Caco-2 and MDCK-hMDR1 cells (study RD1998/00626). In an *in vitro* blood-brain barrier model, abacavir (1 and 200 µM) penetrated the endothelial cells by passive diffusion (study RD1997/02021).

Plasma protein binding

The *in vitro* plasma protein binding of abacavir (0.03 to 10.3 µg/mL) was 18.5% in mouse, 38.7% in monkey and 49.4% in humans (study TBZZ/93/0010).Plasma protein binding was independent of concentration over the range tested.

Blood-to-plasma ratio

The Applicant provided no data on the blood-to-plasma ratio of abacavir.

In vivo distribution

Tissue distribution of [^{14}C]-abacavir was assessed in albino and pigmented fasted mice following a single oral dose of 10 mg/kg (study RD1996/00065). Concentrations 15 minutes after dosing were highest in the gall bladder, gastrointestinal tract, urinary bladder, kidney, adrenal gland, uveal tract of

the eye and nasal turbinates. Although radioactivity penetrated into the CSF, penetration into the brain was minimal. Ratios of CSF:blood and brain:blood were 0.51 and 0.09 at 15 minutes, respectively, and 0.36 and 0.11 at 2 hours, respectively. By 16 hours, levels in most tissues were below the limit of quantitation. Seven days following dose administration, radioactivity concentrations were low but still quantifiable in the oesophagus, uveal tract of pigmented mice, liver, nasal turbinates, outer ear and skin, indicating binding to melanin.

In addition, tissue distribution of [^{14}C]-abacavir was investigated in pregnant rats following a single oral dose of 10 mg/kg (study RD1997/04000). Radioactivity was rapidly absorbed and widely distributed. Highest concentrations were detected in the kidney and stomach mucosa at 1 hour and in the kidney, liver, adrenal and gastrointestinal tract mucosa 6 hours following dosing. By 48 hours after dosing, concentrations were only quantifiable in the liver and adrenal.

Placental transfer

The placental transfer of [^{14}C]-abacavir was investigated in pregnant rats following single oral administration at 10 mg/kg (study RD1997/04000). Abacavir related radioactivity is able to cross the placental barrier, with highest radioactivity concentrations in fetal tissues at 1 hour when concentrations were comparable to those in maternal blood.

The placental transfer of [^{14}C]-abacavir was also investigated in pregnant rabbits following a single oral dose of 10 mg/kg (study RD1997/04000). By 1 hour after dosing, maximum blood concentrations were achieved in dams, and radioactivity was shown to cross the placental barrier. Radioactivity concentrations were generally quantifiable in all fetal tissues, but generally less than half those in maternal blood.

Dolutegravir

Membrane permeability

The passive membrane permeability of [^{14}C]-dolutegravir (3 µM) at pH 7.4 and the absorptive membrane permeability at pH 5.5 and 7.4 in the presence of FaSSIF (fasted state simulated intestinal fluid) was investigated *in vitro* in MDCKII-hMDR1 cells (study RD2008/00360). Dolutegravir was determined to have high passive membrane permeability at pH 7.4. The absorptive membrane permeability of [^{14}C]-dolutegravir in the presence of FaSSIF were both high at pH 7.4 and pH 5.5. These high permeability values are consistent with good absorption of dolutegravir when administered as a solution, and the high permeability values and the low solubility of dolutegravir classify it as a BCS II compound.

Plasma protein binding

The *in vitro* protein binding of dolutegravir at 10 µM (4.2 µg/mL) was 99.9% in rat, 95.4% in dog, 99.1% in monkey and 99.3% in human serum (study RH2007/00106). In another study, the *in vitro* protein binding of dolutegravir (0.21 to 21 µg/mL = 0.5 to 50 µM) was 91.5 to 93.8% in human plasma and tended to decrease with increasing concentration of dolutegravir in plasma. In a second *in vitro* human plasma protein binding study with dolutegravir (0.5 to 25 µM), the plasma protein binding was high (99.3%) and concentration independent.

Blood-to-plasma ratio

The blood-to-plasma ratios were determined for radioactivity in *in vivo* studies in mouse, rat and monkey. In mice, the blood to plasma ratios of radioactivity ranged from 0.49 to 0.54. The blood to plasma ratios of total radioactivity ranged from 0.51 to 0.53 in rat. In monkey, the blood-to-plasma ratio ranged from 0.64 to 0.79 through 24 hours post-dose. Overall, these data indicate that radioactivity was largely associated with plasma components of blood.

Tissue distribution

A whole body autoradiography study was conducted using partially pigmented Lister-Hooded male rats administered a single oral dose of [^{14}C]-dolutegravir (50 mg/kg) (study CD2008/00195). Radioactivity was widely distributed with most tissues containing peak levels at 6 hours. Peak blood concentrations of radioactivity also occurred at 6 hours and declined to below the limit of quantification at 28 days. Concentrations of radioactivity in the brain were low (~2% of the blood radiocarbon concentration). By 28 days post-dose, only bone and skin contained quantifiable levels of radioactivity.

Placental transfer

The distribution and placental transfer of radioactivity were determined following administration of a single oral dose of [^{14}C]-dolutegravir (50 mg/kg) to pregnant rats on gestation Day 18 (study 2012N137348). Placental transfer of radioactivity was evident. Radioactivity was rapidly and widely distributed to most dam and fetal tissues, with the highest values obtained from 2 to 10 hours post-dose. The concentration in the whole fetus was 2410 ng equiv/g at 2 hours post-dose, and steadily increased to 3950 ng equiv/g at 10 hours post-dose before decreasing to 1250 ng equiv/g at 24 hours post-dose.

Lamivudine

Plasma protein binding

The plasma protein binding of [^{3}H]-lamivudine was studied in vitro in rat, dog and human by equilibrium dialysis over the concentration range 0.1 to 100 µg/mL. The binding of lamivudine to rat plasma proteins was concentration-dependent. At the lowest concentration, the percentage binding was 49% which decreased to 16% at 1 µg/mL and <10% at 10 and 100 µg/mL (study GDM/91/010). In dog, the plasma protein binding was also concentration-dependent. At 0.1 µg/mL, the percentage binding was 42% which decreased to 12% at 1 µg/mL and <10% at 10 and 100 µg/mL(study GDM/91/010). The binding of lamivudine to plasma proteins was also concentration-dependent in human plasma. The binding was 36% at 0.1 µg/mL and <10% at 1, 10 and 100 µg/mL (study GDM/91/010). In addition, the *in vitro* binding of lamivudine (0.01, 0.1, 1 or 10 µg/mL) to plasma proteins of blood obtained from rats, dogs and humans was investigated after incubation for 22 hours in dialysis cells (study NME/96/011). All 3 species showed very low binding (3 to 7%) of lamivudine to plasma proteins.

Blood-to-plasma ratio

The blood-to-plasma ratio of [^{3}H]-lamivudine was investigated for rat, dog and human *in vitro* over the concentration range 0.1 to 100 µg/mL. The amount of radioactive material associated with rat erythrocytes was in the range 41 to 47%, and was independent of concentration (study GDM/91/010). In dog, the amount of radioactive material associated with erythrocytes was 39 to 47% and independent of concentration (study GDM/91/010). In humans, the amount of radiolabelled material associated with erythrocytes was 53 to 57% (independent of concentration) (study GDM/91/010). Rat, dog and human showed erythrocyte distribution similar to haematocrit values that was independent of concentration, thus demonstrating no specific binding of lamivudine to erythrocytes (study NME/96/011).

In vivo distribution

The *in vivo* distribution of lamuvidine (30 mg/kg) was investigated albino and pigmented rats using whole body autoradiography with optical densitometry (study GDM/90/040). In the albino rat, radioactivity was widely distributed throughout tissues and peak concentrations were observed at approximately 1 hour after dosing in most tissues with the highest concentrations seen in the kidney and bladder. Tissue levels were generally higher than those seen in blood at corresponding time points.

Clearance from the tissues was rapid and by 8 hours, the only tissue to have significant levels of radioactivity was the kidney. By 96 hours, no radiolabelled material could be detected in any tissue. In pigmented rats, there was no evidence of binding to melanin containing tissues.

Placental transfer

The placental transfer of lamivudine (45 mg/kg) was investigated in pregnant rats and rabbits using whole body autoradiography with optical densitometry or liquid scintillation counting (study GDM/91/050 and GDM/91/059). Rats were killed 1 hour after oral administration on Day 12 of pregnancy or 1, 4 and 24 hours after the same treatment on Day 19 of pregnancy. One hour after dosing on Day 12 or Day 19, the levels in maternal blood and placentae were markedly higher than those in the fetuses. Radiolabelled material was evenly distributed throughout the fetuses with no localisation in any particular organ or tissue. At 24 hours post-dose, radiolabelled material had been eliminated from both maternal and fetal tissues. Rabbits on Day 20 of pregnancy were killed approximately 1, 4 and 24 hours after oral administration. The extent of placental transfer was low and less than 0.007% of the administered dose reached each fetus.

Metabolism

Abacavir

In vitro metabolism

[^{14}C]-abacavir (3 µg/mL) was incubated with rat and human hepatocytes in the presence and absence of the ADH inhibitor, 4-methyl pyrazole (4-MP), or the CYP inhibitor, aminobenzotriazole (ABT) (study RD2000/02309). Non-extractable abacavir-derived residues were observed in both human and rat hepatocyte incubations. Both 4-MP and ABT markedly inhibited (33 to 77%) non-extractable residue levels in incubations of abacavir with both rat and human hepatocytes, demonstrating the enzymatic nature of abacavir bioactivation. To determine if oxidation of abacavir to the carboxylic acid via an aldehyde intermediate results in covalent binding to protein in human or rat in vitro systems, [^{14}C]-abacavir (3 µg/mL) was incubated rat and human liver cytosol (study RD2001/01777). NAD (co-factor)-dependent, protein bound residues were observed in rat and human liver cytosol and was ADH mediated. These observations are consistent with ADH involvement in carboxylic acid and protein bound residue formation in rat and human *in vitro* systems. Incubations of [^{14}C]-abacavir (3 µg/mL) with pooled rat and human liver microsomes resulted in low, but detectable levels of NADPH (co-factor)-dependent, non-extractable, protein bound residues (study RD2002/01227). These were decreased in the presence of a non-isozyme selective CYP inhibitor. Only human and rat CYP1A2 yielded notable co-factor-dependent non-extractable residues, indicating the potential for a similar bioactivation process in the rat compared to humans.

The two major metabolites of abacavir in humans are 2269W93 and 361W94. Production of 361W94 is mediated by UGT2B7. However, metabolic turnover with UGT2B7 was thus only detectable at concentrations in significant excess of the usual plasma concentrations encountered clinically. However, in contrast to the other isozymes examined under identical conditions, UGT2B7 was the only isoform that showed any abacavir glucuronidation *in vitro* (study RD2000/02310). UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A9, 1A10 and 2B15 were not capable to glucuronidate abacavir. Alcohol dehydrogenase αα (ADH αα) is involved in the formation of 2269W93 from abacavir (study RD2001/01777).

In vivo metabolism

The Applicant provided no information on the metabolite profile in plasma. It is therefore unknown if the major human metabolites are also present in the non-clinical species.

Dolutegravir

In vitro metabolism studies

Dolutegravir (1 µM) was stable in rat, monkey and human S9 fractions up to 60 minutes (study RH2007/00076). Dolutegravir (0.5 µM) was also stable in rat cryopreserved hepatocytes and in both fresh and cryopreserved human hepatocytes ($t_{½}$ >360 minutes) (study RH2007/00076). In fresh rat hepatocytes, the intrinsic clearance was 25 mL/min/kg bw and the t½ was 268 minutes. In addition, no metabolites were detected when dolutegravir was incubated up to 24 hours with cryopreserved rat, dog, monkey and human hepatocytes (study RH2007/00060). In another study, the metabolic turnover of [^{14}C]-dolutegravir in rat and monkey hepatocytes was low and similar to human hepatocytes (approximately 3.5 to 9.4% turnover) (study RD2007/01496). In human hepatocytes, the notable route of metabolism for [^{14}C]-dolutegravir was glucuronidation. Metabolite profiles of the non-clinical species and human were qualitatively similar and the human glucuronidation metabolite was observed in hepatocytes from the two non-clinical species. In perfused rat liver, dolutegravir was metabolised to M1 (N-dealkylation), M7 (oxidation), M2 (hexose conjugation), M3 (glucuronidation), M4 and M5 (hexose or glucuronide conjugation in combination with N-dealkylation), and M6 and M8 (hexose or glucuronide conjugation in combination with oxidation) (study RD2007/01493).

Metabolites M1 (N-dealkylation) and M7 (oxidation) of dolutegravir were formed by CYP3A4 (study RD2008/00373/00). Incubations with recombinant CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 showed no metabolism. The data suggest that CYP3A4 is the primary CYP enzyme involved in the Phase I metabolism of dolutegravir *in vitro*. In addition, dolutegravir was conjugated to an ether glucuronide (M3) by UGT1A1 (study RH2007/00104). Dolutegravir glucuronidation was also observed in recombinant UGT1A3 and 1A9 incubations, but to a lesser extent in comparison to UGT1A1 (study RD2008/01339). Glucuronidation was not observed in recombinant UGT1A4, 1A6, 2B4, 2B7, and 2B15 incubations. These data suggest that UGT1A1 is the primary UGT enzyme involved in the glucuronidation of dolutegravir *in vitro*, with contribution from UGT1A3 and 1A9.

Dolutegravir has two chiral centers, so the potential for metabolism of dolutegravir (10 M) to its respective enantiomer and two diastereomers was investigated in incubations with cryopreserved rat, dog, monkey and human hepatocytes (study RH2007/00105). Although low amounts (~0.4% of the peak area of dolutegravir) of the enantiomer (GSK1426983) were detected at all incubation times, concentrations of GSK1426983 did not increase with time and no peak that corresponded with the diastereomer (GSK1747005) was detected. Formation of the diastereomer of its enantiomer (GSK1747009) could not be determined, because GSK1747009 could not be separated chromatographically from dolutegravir.

Dolutegravir (100 µM) was tested in a glutathione reactive metabolite trapping assay using rat and pooled human liver microsomes (study RH2007/00058). The results showed *in vitro* evidence for formation of a metabolite consistent with addition of glutathione through oxidative defluorination in both rat and human liver microsomes.

In vivo metabolism

The *in vivo* metabolism of dolutegravir was investigated in male and female mice following a single oral dose of [^{14}C]-dolutegravir at 100 mg/kg (study RD2009/00723). Dolutegravir was the principal radiolabeled component in mouse plasma (78-90% of plasma radioactivity). Two unknown metabolites were present in mouse plasma through 24 hours post-dose and represented 1.3 to 6.6% of the plasma radiocarbon. The *in vivo* metabolism of dolutegravir was also investigated in rats following a single oral dose of [^{14}C]-dolutegravir at a dose level of 50 mg/kg (study RD2008/00220). The only quantifiable radiolabeled component in plasma was unchanged dolutegravir representing 90-98% of plasma radioactivity. There was no evidence for *in vivo* epimerization of dolutegravir to any of its

stereoisomers, GSK1747005, GSK1747009 or GSK1426983, in juvenile rat plasma samples following repeat oral administration of dolutegravir. Furthermore, the *in vivo* metabolism of dolutegravir was investigated in monkeys following a single oral dose of 10 mg/kg of [^{14}C]-dolutegravir (study RD2008/00899). Through 24 hours post-dose, dolutegravir was the principal radiolabeled component in plasma (85-99% of the plasma radioactivity). Dolutegravir glucuronide (M3) was present at low concentrations (~3.5% of plasma radioactivity). In monkey, no notable differences in the metabolic profile between males and females were observed.

Lamivudine

In vitro metabolism

The Applicant did not provide any *in vitro* metabolism studies. It is therefore, unknown which enzymes are involved in the metabolism of lamivudine.

In vivo metabolism

No information on the metabolism pattern in plasma from the non-clinical species was provided by the Applicant.

Chiral conversion

Plasma samples were obtained from pharmacokinetic studies conducted with lamivudine in dogs and humans (study WD1997/00356). Chiral analysis was performed to determine if chiral inversion of lamivudine occurs *in vivo*. No chiral inversion of lamivudine was observed.

Excretion

Abacavir

In vivo elimination

The recovery of [^{14}C]-radioactivity in urine and faeces was investigated following single oral administration of [14C]-abacavir to mice (38 mg/kg) (study TEIN/94/0001), rat (15 mg/kg) (study RD1999/00510) and monkey (15 µg/kg) (study TEIN/94/0006). The cumulative recovery of radioactivity in the urine was 74-90% of the total dose in mice, with the majority excreted over the first 8 hours (70-83%). In the faeces, recovery was 21% (16% within the first 8 hours). In rat, most of the dose (~74%) was excreted via urine, indicating extensive absorption following oral administration. In monkey, also the majority (79% of the total dose) was excreted in urine within 8 hours, with total urinary and faecal excretion representing 92% and 7.4% of the total dose, respectively, from 0 to 72 hours after dosing.

Metabolism pattern in the excreta

The major excretion route was via urine. Therefore, metabolite profiles were determined in urine. No metabolite profiles were determined in bile and faeces. In mice administered a single oral dose of 38-40 mg/kg, the major compounds detected from 0-48 hours in urine were parent drug (10.5% of the total dose), 2269W93 (23.6%), 361W94 (11.5%) and four unidentified abacavir-related peak regions (representing 10.2, 6.1, 4.1 and 3.4% of the total dose) (studies TEIN/94/0001). 139U91 (2, 6-diamino analogue of abacavir), carbovir (1144U88; guanine analogue of abacavir) and 2083U88 (5'-carboxylate of carbovir) were detected as only 1.7, 1.8 and 0.7% the total dose, respectively. Six additional unidentified abacavir-related radiochromatographic peak regions represented a total of 9.1% of the dose. There were no sex-related differences in the metabolism of abacavir. In rats following a single oral dose of 15 mg/kg [^{14}C]-abacavir (study RD1999/00510), the metabolite profile in urine (0-72 h) was 11% as parent compound and approximately 64% of the oral dose as metabolites. The major metabolites in rat urine were 2269W93 (~39% of dose) and an unidentified metabolite that

appeared to be less polar than abacavir (~11% of dose). In addition, following a single oral administration of [^{14}C]-abacavir to monkeys (21 mg(salt)/kg) (study TEIN/94/0006), abacavir was extensively metabolised with 361W94 and 2269W93 detected at 32 and 20% of the total dose, respectively, during the first 72 hours after dosing. Parent drug was 12.6% of the total dose. One unidentified abacavir-related peak region comprised 15% of the total dose, whereas others generally comprised less than 1% each during the same time interval following dosing.

Milk excretion

The milk transfer of drug-related material following a single oral dose of [^{14}C]-abacavir (35 mg/kg) was investigated in rats (study RD1997/01909). Concentrations of abacavir in milk were generally slightly higher than those in plasma. This demonstrates the excretion of drug-related material into the milk of lactating rats.

Dolutegravir

In vivo elimination

The elimination of radioactivity was investigated following a single oral administration of [^{14}C]-dolutegravir (100 mg/kg) to intact and bile duct cannulated (BDC) mice (study RD2009/00562). Faecal excretion was the primary route for elimination of radioactivity in intact mice (93-94% of the administered dose), while urinary elimination accounted for less than 2% of the administered dose. Elimination of radioactivity was rapid with the majority of the dose (>92%) being recovered within 24 hours post-dose. In BDC mice, biliary secretion accounted for a mean of 2.5% of the dose, while means of 86 and 1.8% were eliminated via faeces and urine, respectively.

The elimination of radioactivity was also investigated in intact and BDC rats following a single oral administration of 50 mg/kg of [^{14}C]-dolutegravir (study RD2008/00108). The major route of elimination of drug-related material in intact rats was via the faeces (91-93%). Urinary elimination accounted for less than 4% of the dose. Elimination of radioactivity was rapid with the majority of the dose (>83%) being recovered within 24 hours post-dose. In BDC rats, means of 7.0%, 86% and 2.5% of the dose were eliminated via the bile, faeces and urine, respectively.

Furthermore, the elimination of radioactivity were investigated in intact and BDC monkeys after a single oral administration of [^{14}C]-dolutegravir (10 mg/kg) (studies RD2008/01300 and RD2008/01299). The predominant route of elimination of radioactivity in intact monkeys was via faecal excretion (67-78). Urinary excretion accounted for 4.4-6.0% of the dose. In BDC monkeys, biliary secretion accounted for a mean of 12% of the administered dose. Mean faecal and urinary recoveries of radioactivity were 70% and 7.2%, respectively.

Metabolism pattern in the excreta

In mice, dolutegravir glucuronide (M3) and a metabolite resulting from fluorine loss and the addition of glutathione and oxidation were the principal components in mouse bile accounting for 0.7 and 0.5% of the dose, respectively. Other identified metabolites in the bile each represented ~0.2% of the dose. Dolutegravir glucuronide (M3) was also the major component in the urine (0.6-0.9% of the dose). Metabolites resulting from hexose conjugation of parent, N-dealkylation and an oxidation at the benzylic carbon were also observed as minor components in urine (~0.1% of the dose). Dolutegravir represented ~0.1% of the dose in urine, 0.2% of the dose in bile and 89% of the dose in faeces.

In rat, the majority of the radioactivity was unchanged dolutegravir in faeces (86% of the dose). Oxidation and N-dealkylation were the major biotransformation products in the urine (1.2 and 0.7% of the dose). Other notable metabolites observed in rat urine resulted from glucuronidation (M3) and hexose conjugation (each representing 0.4% of the dose). The predominant metabolites in rat bile resulted from glucuronidation (M3) and hexose conjugation (together 4.0% of the dose). Other notable

metabolites in bile included loss of fluorine in combination with oxidation and glutathione addition (0.8% of the dose) and pentose conjugation (0.1% of the dose). Biliary and renal elimination of unchanged dolutegravir was very low over the time period examined (~0.1% of the dose).

In monkey, biliary and renal elimination of dolutegravir was very low (~0.3% of the dose). Conjugation was the primary biotransformation process for the formation of biliary and urinary metabolites. Glucuronide (M3) (~4.5% of dose) and hexose conjugates (3.5% of dose) were the principal components in bile. A metabolite, resulting from fluorine loss and the addition of cysteine and oxygen, was a notable radioactive component in bile (<2.0% of the dose), but was not measurable in urine. Dolutegravir glucuronide (M3) was the major component in the urine (3.1% of the dose). A hexose conjugate and N-dealkylated metabolite were also observed as minor components in urine (<0.5% of the dose). Dolutegravir was the only notable component in faeces (64% of the dose).

Milk excretion

Lacteal excretion of radioactivity was determined following administration of a single oral dose of [^{14}C]-dolutegravir (50 mg/kg) to lactating rats (study 2012N137348). Mean milk to blood concentration ratios were 0.45 at 1 hour post-dose, steadily increased to a maximum of 2.3 at 8 hours post-dose, and then decreased to 1.3 at 24 hours post-dose.

Identification of dolutegravir-related material in samples was accomplished by radio-HPLC/MS/MS. Dolutegravir was the predominant component in the rat milk (83-97% of the radiocarbon over the 24 hours sampling period). In addition, minor uncharacterized components were observed that were below the quantifiable limit (LLQ).

Lamivudine

In vivo elimination

Following IV administration of [^{3}H]-lamivudine (45 mg/kg) to mice (study GDM/92/045), the mean total recovery was ~68% (range 51% to 98%). Urinary excretion accounted for ~55% of the administered dose, the majority in the first 24 hours after dosing. Faecal excretion accounted for ~5% of the administered dose. After oral administration of [^{3}H]-lamivudine (45 mg/kg) to mice (study GDM/92/045), the mean total recovery of radioactivity was ~89%. Urinary excretion accounted for approximately 54% of the administered radioactivity, the majority in the first 24 hours after dosing. Faecal excretion accounted for ~29% of the administered dose.

Following oral administration of [^{3}H]-lamivudine (45 mg/kg) to rats, the mean total recovery of radioactivity was approximately 96% (study GDM/91/014). Renal clearance was the principal route of elimination with 61% of the dose excreted in the urine and approximately 34% in the faeces. The majority of the dose was excreted within 24 hours. In another study, the mean total recovery of radioactivity was approximately 93% (study GDM/94/076). Urinary and faecal excretion accounted for approximately 57% and 35% of the dose, respectively. A study in pregnant rat showed that pregnancy has no effect on the excretion pattern for the elimination of drug-related material (study GDM/91/050). The biliary excretion of radioactivity following a single oral administration of [^{3}H]-lamivudine (2 mg/kg) has been investigated in rat (study NME/96/007). Levels of radioactivity excreted within 48 hours of dosing were 82% of the dose in urine, 19% of the dose in faeces and 0% in bile.

Following oral administration of [^{3}H]-lamivudine (45 mg/kg), there were no differences in the routes of excretion between pregnant and non-pregnant rabbits (study GDM/91/059). Renal clearance was the principal route of elimination with approximately 50% of the dose excreted in the urine and between 3 and 30% in the faeces. The majority of the dose was excreted within 24 hours.

Following IV administration of [^{3}H]-lamivudine (30 mg/kg) to dogs (studies GDM/91/008 and GDM/91/080), urinary excretion accounted for 82-91% of the administered dose. Faecal elimination accounted for 1-3% of the dose. Elimination was rapid with the majority of the dose excreted within 24 hours after dosing. Following oral administration of [^{3}H]-lamivudine (30 mg/kg) to dogs (studies GDM/91/008 and GDM/91/080), 78-90% of the dose was excreted via urine. Faecal elimination accounted for 1-3% of the dose.

Metabolism pattern in the excreta

The urinary metabolic profile of lamivudine was determined in mice following a single IV dose of [^{3}H]-lamivudine at 45 mg/kg (study GDM/92/045). Analysis of 0 to 24 hour urine samples indicated that unchanged lamivudine accounted for approximately 90% of the urinary radioactivity. The remainder of the urinary radioactivity was accounted for by the trans-sulphoxide (GI138870X) and the cis-sulphoxide in approximately equal proportions. Following oral administration, the metabolic profile was qualitatively and quantitatively similar to that following IV administration (study GDM/92/045).

The metabolic profile of lamivudine was determined in urine from rats following IV administration of [^{3}H]-lamivudine at 45 mg/kg (studies GDM/91/014 GDM/94/076). Unchanged lamivudine accounted for approximately 92-96% of the urinary radioactivity. Two metabolites were detected, with GI138870X present as the major metabolite (<4% to 6%). Following the oral administration, the metabolic profile was similar to that following intravenous administration (study GDM/91/014). Following oral administration, 98% of the radiolabelled material in faeces corresponded to unchanged lamivudine. The metabolic profile of lamivudine in pregnant rats is the same as that in non-pregnant rats (study GDM/91/050). Following either oral or intravenous administration of [^{3}H]-lamivudine (2 mg/kg) to rat (study NME/96/017), the majority of drug-related material was excreted in the urine as unchanged lamivudine within the first 10 hours of dosing. Low levels (2 to 3%) of radioactivity were present as the trans-sulphoxide metabolite.

In rabbit, also unchanged lamivudine was the major component present in urine (80% of urinary radioactivity) following oral administration of [^{3}H]-lamivudine at 45 mg/kg (study GDM/91/059). Two metabolites were detected, each of which accounted for between 7 and 16% of the urinary radioactivity. Unchanged lamivudine accounted for more than 95% of the faecal radioactivity. One minor metabolite was detected which accounted for approximately 5% of the faecal radioactivity.

The metabolism profile of lamivudine has been studied in dogs following IV administration of [^{3}H]-lamivudine at 30 mg/kg (studies GDM/91/008 and GDM/91/080. Unchanged lamivudine accounted for 27-48% of the dose. Two major metabolite peaks accounted for 11-22% (cis-sulphoxide) and 17-28% (trans-sulphoxide) of the dose. The chromatographic retention time of the principal metabolite corresponded for the trans-sulphoxide of lamivudine. Following oral administration, unchanged lamivudine accounted for 20-39% of the dose (studies GDM/91/008 and GDM/91/080). The remaining radioactivity was attributable by trans-sulphoxide (33% of the dose) and cis-sulphoxide (18% of the dose). Following a single oral dose of [^{3}H]-lamivudine (2 mg/kg) to dogs (studies NME/97/014 and NME/97/010), cytosine (17-20% of the radioactivity), trans-sulphoxide (30-35% of the radioactivity) and lamivudine (30-32% of the radioactivity) were observed in urine. There was no gender difference in the pattern of urinary excretion of the metabolites.

Milk excretion

The milk transference of lamivudine (45 mg/kg) after oral administration was studied in rat at least 14 days post-partum (study GDM/92/017). Plasma concentrations of lamivudine were highest (mean 11 µg/mL) at 0.5 hours after dosing and decreased steadily to a mean concentration of 0.3 µg/mL at 8 hours. Milk concentrations of lamivudine were highest (14 µg/mL) at 4 hours after dosing and fell to 4.8 µg/mL at 8 hours. Lamivudine was not detected in milk after 24 hours.

2.3.4. Toxicology

Single dose toxicity

Abacavir

Abacavir had a low potential for toxicity in mice and rats. The median lethal doses were more than 100 times higher than the dose of 600 mg once daily.

Dolutegravir

No single dose studies were performed with dolutegravir. Investigations for acute effects were incorporated in repeat dose toxicity studies. Dolutegravir was not tolerated at doses ≥300 mg/kg/day in the 14 day monkey toxicity study and resulted in severe gastrointestinal intolerance leading to morbidity and mortality. A single dose toxicokinetics study in dogs was conducted at doses up to 500 mg/kg. Dolutegravir was not tolerated and resulted in vomiting at doses ≥150 mg/kg.

Lamivudine

Single dose toxicity of lamivudine after intravenous or oral administration was studied in rodents. The acute toxicity was low, where doses up to 2000 mg/kg i.v. (both species) or 2x2000 mg/kg orally (mice only) were well tolerated without signs of target organ toxicity.

Repeat dose toxicity

Abacavir

Studies were conducted in mice with doses up to 708 mg/kg/day for 1 and 6 months, and in cynomolgus monkeys with doses up to 297 mg/kg/day for 1, 3 and 12 months. In addition, a 3-month study was performed in rats with doses up to 452 mg/kg/day. The primary target organ for toxicity of abacavir is the liver in mice, rats and monkeys. Increased liver weight was observed at 234 mg/kg/day in mice and 200 mg/kg/day in rats associated with mild hepatocellular hypertrophy, increased pigment deposits in the centrilobular hepatocytes and/or Kupffer cells in both species at these dosages. All treatment-related findings reversed following the recovery period. Slight increase in some CYP450 enzymes activity was observed after 6-month administration to rodents. In monkeys, there were minor changes in serum triglyceride concentrations and equivocal increases in alanine aminotransferase were seen at 297 mg/kg/day. Abacavir caused changes in the haemapoietic system. In rats these changes, occasionally noted at all doses, included minimal decrease in red blood cell parameters and increased leucocytes count (especially lymphocytes). There was no evidence of an effect on bone marrow. These changes reversed in the recovery period. In monkeys, the haematological changes noted at all doses were mild and corresponded to slight decreases in red blood cell counts occasionally accompanied by decreased haemoglobin concentrations and haematocrit. In the 3-month study in rats, germ cell loss in the testis was seen in males at the highest dose of 452 mg/kg/day. The reversibility of the finding was not investigated, but the no effect level for this finding was 96 mg/kg/day, at which systemic exposure was 13 times higher than in humans following a once daily 600 mg dose.

Dolutegravir

In a 13-week study in mice, dolutegravir at 500 mg/kg induced slight increases in bilirubin and liver transaminases and mucous neck cells in stomach appeared increased. Systemic exposure at a dose of 500 mg/kg corresponded to approx. x15 expected clinical.

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, edema, acanthosis as well as incidences of microscopic hemorrhage in the glandular stomach at doses of 500 mg/kg and higher, providing considerable

exposure multiples (x17-23) to expected human exposure. The changes were attributed to local irritating properties and showed reversibility during a 1 month treatment free period.

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 liver single cell necrosis (at 1000 mg/kg) and atrophy and haemorrhage of mucosal epithelium in the stomach. The doses at which liver toxicity was recorded corresponded to x4 to x5 the expected clinical exposure. In a 1-month monkey study, the NOAEL was 50 mg/kg/day at which dose a slight decrease in body weight and an increase in neutrophils were noted. The primary effects consisted of atrophy of cecum, colon, rectum and inflammatory cell infiltration. No liver related pathology was reported, but an increase in bilirubin in high dose females was apparent. 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. Moribund animals had mononuclear cell infiltration and slight haemorrhage in the lamina propria in the cecum and colon. Gastrointestinal toxicity seemed the most likely cause of deaths. A high dose male that had to be euthanized had elevated bilirubin and aspartate aminotransferase, but no other indications of liver malfunction. The NOAEL in the 38 week study was considered 15 mg/kg. The doses in this study corresponded to systemic exposure multiples below unity in comparison with expected clinical values.

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.

Taken together the studies on dolutegravir toxicity showed that monkey was particularly sensitive 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, but based on both systemic exposure as well as on dose, monkeys tolerated much lower doses than rat. Concerning the gastrointestinal targets, comparisons based on mg/m2 may be more relevant

than systemic exposure levels and at the NOAEL multiples would approach x2-x3 the expected human values. It is notable that in monkey with increasing study duration from 14 days to 38 weeks tolerance appeared to decrease markedly in that 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.

Lamivudine

Repeated dose toxicity of lamivudine after oral administration was studied in rats (up to 6 months) and dogs (up to 12 months). The target organ of toxicity was the haematopoietic system (anaemia, decreased platelet count, leukopenia and splenic hemosiderosis). Furthermore, following high doses and extended exposure periods, impaired liver function (raised ALT and AST without major histological effects), and gastrointestinal effects (ulcers, inflammation) were observed. Non observable effect level (NOEL) was 300-425 mg/kg/day b.i.d. in rats and <45 mg/kg/day b.i.d. in dogs.

Combination abacavir + dolutegravir + lamivudine

No non-clinical studies were performed with the combination abacavir, dolutegravir and lamivudine. The applicant refers to ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995), stating that for most combinations which involve two late stage entities and for which there is adequate clinical experience with co-administration, combination toxicity studies would generally not be recommended to support clinical studies or marketing unless there is significant toxicological concern (e.g., similar target organ toxicity). With late stage experience is meant experience from Phase III studies and/or post-marketing. The applicant also refers to ICH guideline M3(R2) – questions and answers

(EMA/CHMP/ICH/507008/2001), regarding Combinations, question 9, in which is stated that combination toxicity studies on advanced cancer, tuberculosis, and HIV products are generally not warranted unless there is a specific cause for concern under clinically relevant conditions.

Both abacavir and dolutegravir caused treatment-related hepatic effects, the findings in abacavir-treated animals were believed to be adaptive changes related to metabolic enzyme induction, and with dolutegravir the findings were observed only at doses that exceeded the maximum tolerated dose (the liver effects hepatocellular single cell necrosis, diffuse hepatocellular hypertrophy and elevated liver enzymes only occurred in the monkey 14 day toxicity study at doses that were not tolerated and exposures ~5 to 9X above the anticipated clinical exposure). Cumulative data suggest a hepatic safety profile for dolutegravir/abacavir/lamivudine that is comparable to the combination efavirenz + emtricitabine + tenofovir), raltegravir + abacavir/lamivudine and darunavir +ritonavir + abacavir/lamivudine. There were no other common target organs of toxicities identified for the 3 compounds. The potential for additive or synergistic toxicity at clinically relevant concentrations is therefore considered low.

Genotoxicity

Abacavir

Abacavir was not mutagenic in bacterial tests but showed activity in vitro in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the in vivo micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir has a weak potential to cause chromosomal damage both in vitro and in vivo at high test concentrations.

Dolutegravir

Dolutegravir was tested *in vitro* for genotoxicity in a bacterial mutation assay and mouse lymphoma L5178Y cell assay up to cytotoxic concentrations. Negative results were reported except for a weakly positive result in the mouse lymphoma assay at high cytotoxicity. A previous non-GLP mouse lymphoma test was positive at high dose but cytotoxicity may have confounded results. The *in vivo* rat micronucleus test was negative. Taken together the data did not indicate any relevant genotoxic potential of dolutegravir.

Lamivudine

Lamivudine was negative in the Ames test but induced gene mutations in the mouse lymphoma assay (at 1000 µg/ml and above). It was also clastogenic in an in vitro cytogenicity test in human lymphocytes at 300 µg/ml which is 150 times higher than the concentrations observed at clinical use. Lamivudine induced gene mutations in the mouse lymphoma assay (at 1000 µg/ml and above). It was also clastogenic in an in vitro cytogenicity test in human lymphocytes at 300 µg/ml which is 150 times higher than the concentrations observed at clinical use. In mouse embryo cells, lamivudine did not induce morphological transformation at concentrations up to 320 µg/ml without S9 or 5000 µg/ml with S9. In vivo, lamivudine was not clastogenic in the rat bone marrow metaphase analysis assay, the rat bone marrow micronucleus assay or the rat liver UDS assay following oral doses of up to 2000 mg/kg.

Combination abacavir + lamivudine

A rat bone marrow micronucleus assay was performed (study R25531). Male rats were treated orally by gavage on two consecutive days with vehicle or left untreated, abacavir at 500, 1000, 2000 mg/kg/day, lamivudine at 2000 mg/kg/day, abacavir/lamivudine at 500/2000, 1000/2000 or 2000/2000 mg/kg/day or with cyclophosphamide at 20 mg/kg once (positive control). Signs of toxicity (among others decreased activity) were observed in animals receiving abacavir at 2000 mg/kg/day or

in animals receiving abacavir/lamivudine 2000/2000 mg/kg/day. At the combination 2000/2000 mg/kg/day, two animals died. No significant increase in micronucleated erythrocytes was observed.

Carcinogenicity

Abacavir

An increased incidence of malignant and non-malignant tumours was noted, including in both species carcinoma in the preputial gland of males and in the clitorial gland of females. In female rats, carcinoma in the liver, urinary bladder, lymph nodes and subcutis hemangiosarcoma were observed. These neoplastic findings occurred at the highest doses tested: 330 mg/kg/day in mice and 600 mg/kg/day in rats, with the exception of preputial gland carcinoma in male mice which occurred at 110 mg/kg/day. These doses gave a systemic exposure of respectively around 24 fold and 33 fold higher than the expected exposure in humans treated with 600 mg/day. The non-effect dose levels were 55 mg/kg/day in mice which corresponds to 3 times the human AUC in humans, and 120 mg/kg/day in rats, which corresponds to 7 times the AUC in humans. Furthermore, in the carcinogenicity studies in mice and rats, myocardial degeneration was observed at high dose.

Dolutegravir

Long term carcinogenicity studies were conducted in mouse and rat. Overall dolutegravir did not exhibit any significant neoplastic activity in either study. There were some apparent increases in tumours of the kidney, liver and urinary bladder in mouse when compared with vehicle control, but not when considering water control. Similarly in rat there were some increases such as hyperplasia of the non-glandular stomach, hepatocellular adenoma in high dose animals, but there was no dose-response and incidences were within historical values and likely the relevance of these findings is limited. In rat, 3 oligodendrogliomas, a rare neoplastic finding, were reported at mid dose. Exposure at the high dose was only 2.1 to 1.6 fold higher than at mid dose. However, the data taken together are consistent with a lack of any clinically relevant carcinogenicity of dolutegravir.

Lamivudine

The carcinogenic potential of lamivudine was studied in conventional 24 months studies in rats and mice. No signs of carcinogenic effects were seen. In these studies, the systemic exposure of animals was 10 - 58 higher than the systemic exposure of humans at clinical use.

Reproduction Toxicity

No reproductive toxicity studies were performed with the combination abacavir / dolutegravir / lamivudine.

Complete packages of reproductive and developmental toxicity studies were performed for all compounds. Abacavir was teratogenic but dolutegravir and lamivudine were not. Aggravation of reproductive toxicity due to the combination is not expected. Additional studies with the combination are not warranted.

Local Tolerance

Abacavir

Abacavir did not induce skin or eye irritancy.

Dolutegravir

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.

Lamivudine

Lamivudine did not induce skin or eye irritancy.

Other toxicity studies

Antigenicity

Abacavir

Abacavir did not induce sensitization in guinea pigs using the Magnusson and Kligman Maximisation test.

Dolutegravir

Dolutegravir was non-sensitizing in the mouse local lymph node assay.

Lamivudine

Lamivudine did not induce skin sensitising or antigenic potential.

Immunotoxicity

Dolutegravir

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. An increase in spleen weight was noted, but with no accompanying histopathological changes. 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.

Mitochondrial toxicity studies

Abacavir and lamivudine showed a very low cytotoxic potential. Abacavir and lamivudine did not change the mitochondrial content or change lactate production, cell growth, glucose consumption and LDH leakage in a human leukaemic cell line.

Phototoxicity

In the registration procedure for dolutegravir, a post-authorisation measure is proposed that phototoxicity should be investigated. Dolutegravir absorbs light in the wavelength of 290-700 nm and a rat distribution study showed that drug-related material reaches the uveal tract as well as the skin (mainly the pigmented skin) where it is still quantifiable at up to 7 and 28 days -post-dose.

Abacavir and lamivudine do not absorb light in the 290 to 700 nm wavelength range. Phototoxicity studies have therefore not been performed with abacavir and lamivudine.

2.3.5. Ecotoxicity / environmental risk assessment

Dolutegravir

The ERA dossier for dolutegravir is complete. Dolutegravir is not PBT, nor vPvB.

On the basis of the environmental risk assessment, it is concluded that the use of dolutegravir in Triumeq results in negligible risk for the sewage treatment plant, the surface water, groundwater, soil and sediment compartment.

Substance (INN/Invented Name): Dolutegravir					
CAS-number (if available): 1051375-16-6 (free acid)					
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
	BCF				Not performed
Persistence	DT50 or ready biodegradability	Not biodegradable			P
Toxicity	NOEC or CMR				***See below***
PBT-statement :	Dolutegravir is not considered PBT nor vPvB				
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)	Not investigated				(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 Inhibition Test	OECD 209	EC	>100	mg/L	No inhibitory effect
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF			Not performed
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 a)*	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 (reproduction)**	29	mg/kg	*Folsomia candida*

Abacavir

The ERA dossier for abacavir is incomplete. The applicant has not performed the Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308) and the Fish, Early Life Stage toxicity test (OECD 210) studies. The Applicant will submit the final reports two years following approval.

Substance (INN/Invented Name): Abacavir			
CAS-number (if available): 188062-50-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow (ph 5) = 0.88 Log Dow (ph 7) = 1.18 Log Dow (pH 9) = 1.20	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	1.20	Not B
Persistence	ready biodegradability	not readily biodegradable	Potentially P
	inherent biodegradability	inherently biodegradable	Not P
	DT50		Not submitted
Toxicity	NOEC or CMR		Not submitted
PBT-statement :	Abacavir is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default	3.0	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-activated sludge	Pagga and Taeger protocol	Kb 154 (3 h), 11169 (24 h)	
Soil adsorption study	TAD 3.08	Sandy silt loam Koc = 934 Clay loam Koc = 298	

		Sandy loam Koc = 147			
Ready Biodegradability Test	OECD 301B	DOC = 27 % Primary degradation = 41-94 %			Not ready biodegradable
Inherent Biodegradability	OECD 302B	Primary degradation (14 days) >99 %			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not submitted
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	25.62	mg/L	*Selenastrum capricornutum*
Daphnia sp. Acute effects	OECD 202	EC_{50}(48 h) NOEC	119 61.60	mg/L	
Ceriodaphnia dubia Chronic effects, Reproduction	EPA 821-R02-013	LOEC(7 d) NOEC(7 d)	8.50 4.80	mg/L	*Ceriodaphnia dubia*
Fish, Acute effects	TAD 4.11	EC_{50}(96 h) NOEC(96 h)	>103 103		Rainbow trout
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Not submitted
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	61	mg/L	

Lamivudine

The ERA dossier for lamivudine dossier is incomplete. The applicant has not performed the Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308), and the Fish, Early Life Stage toxicity test (OECD 210) studies. Antimicrobial effects were not tested using the recommended guideline i.e. activated Sludge, Respiration Inhibition Test (OECD 209) . The Applicant will submit the final reports two years following approval.

Substance (INN/Invented Name): Lamivudine			
CAS-number (if available): 134678-17-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow (pH 5) = -1.86 Log Dow (pH 7) = -1.44 Log Dow (pH 9) = -1.17	Potential PBT (N)
PBT-assessment			
Bioaccumulation	LogKow	-1.17	Not B
Persistence	ready an inherent biodegradability	not readily biodegradable; not inherently biodegradable	potentially P
	DT50		OECD 308 not submitted
Toxicity	NOEC CMR	Not investigated	Potentially T
PBT-statement :	Lamivudine is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	Not investigated		(N)

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106		see TAD 3.08
Soil adsorption study	TAD 3.08	Clay loam Koc = 32 Sandy loam Koc = 30.2 Sandy silt loam Koc = 108	
Ready Biodegradability Test	OECD 301B	Not readily biodegradable Ultimate biodegradation (DOC) = 1%	
Inherent Biodegradability	OECD 302B	Not Inherently Biodegradable DOC = 0 % Primary degradation = 4 %	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =	Not submitted

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥ 96.90	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	
Fish, Acute effects	TAD 4.11	EC_{50}(96 h) NOEC(96 h)	>97.90 97.90	mg/L	Rainbow trout
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Not submitted
Microbial Growth inhibition Test	TAD 3.02	EC_{50}	> 1000	mg/L	*Azotobacter beijerinckii* *Aspergillus niger* *Nostoc commune* *Pseudomonas aeruginosa* *Trichoderma harzianum* **Remark:** Not the recommended test, not the recommended STP micro-organisms
Microbial Inhibition Control Readily Biodegradability Test 5 day Bacterial Inhibition Test	OECD 301B/301D	NOEC	23.9	Mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209				Not submitted

2.3.6. Discussion on non-clinical aspects

Non-clinical studies on the combination with dolutegravir, abacavir and lamivudine has not been performed. This is accepted. The non-clinical profiles of each active substance have been established.

2.3.7. Conclusion on the non-clinical aspects

The presented non-clinical package is considered sufficient for approval of TRIUMEQ.

Dolutegravir, abacavir or lamivudine are not PBT substances. Updated Environmental Risk Assessments were provided for acabavir and lamivudine. Dolutegravir is not expected to pose a risk to the environment. The available data do not allow concluding definitively on the potential risk of abacavir or lamivudine to the environment. Additional studies are required, please refer to section 2.3.5. The Applicant will submit the final reports two years following approval.

2.4. Clinical aspects

2.4.1. Introduction

The DTG/ABC/3TC FDC development program consisted of one pivotal study and five supportive studies that provided safety and efficacy data on this combination medicinal product. These studies were conducted in the intended populations, and they provide data from subjects taking all three DTG/ABC/3TC FDC components concomitantly and/or DTG + 2 NRTIs (or at least 1 fully-active agent in the case of the ART-experienced, INI-naive study ING111762). These studies are:

- ING114467 (SINGLE), which is also part of the DTG single entity development program, is considered the pivotal DTG/ABC/3TC FDC study because this trial evaluated a regimen of once-daily DTG 50 mg + ABC/3TC 600/300 mg FDC as one of two randomized study treatments.
- ING113086 (SPRING-2), ING114915 (FLAMINGO), and ING112276 (SPRING-1), which are clinical studies within the DTG single entity development program, are considered supportive in demonstrating the safety and efficacy of the DTG/ABC/3TC FDC as they all include subjects administered once-daily ABC/3TC 600/300 mg FDC as a background treatment option in combination with DTG 50 mg once daily.
- ING116070 (CSF Study) and ING111762 (SAILING), which are clinical studies within the DTG single entity development program, are considered supportive in demonstrating the safety and efficacy of the DTG 50 mg tablet in combination with ABC/3TC or other active antiretroviral drugs. The numbers of subjects from these studies contributing data for once daily DTG 50 mg + ABC/3TC 600/300 mg are small for both of these studies.

Five other studies are considered a part of the clinical development of the individual DTG/ABC/3TC FDC components, including:

ING111521 provided proof of concept (POC) for the DTG component and was included in the original DTG submission.

CNA30021, EPV20001, EPV40001, and COLA4005 supported regulatory submissions for the approval of once daily dosing of ABC 600 mg or 3TC 300 mg. Other studies (CAL30001, ESS30008, EPZ104057, CNA109586, and COL101004) conducted with the ABC/3TC FDC were provided as relevant background information.

Finally, clinical pharmacology studies have been conducted to bridge between the various formulations over time and form an important component to support the efficacy and safety of DTG/ABC/3TC FDC. Underpinning all the clinical efficacy studies is the bioequivalence (BE) study ING114580, establishing that the DTG/ABC/3TC FDC tablet is bioequivalent to DTG+ABC/3TC FDC administered concomitantly.

Clinical studies of main relevance for the Triumeq application

Study Number	Study Design	Primary Objectives / Patient Population	Regimens
Clinical pharmacology study			
ING114580 (BE)	Phase I, open label, randomized, two part, crossover single dose	To evaluate the bioequivalence between FDC tablet formulation of DTG/ABC/3TC 50/600/300 mg vs. co-administration of the separate tablet formulations of DTG 50 mg plus FDC of ABC/3TC 600/300 mg	Part A: Treatment A=FDC of DTG/ABC/3TC 50/600/ 300 mg; Treatment B = DTG 50+FDC of ABC/3TC 600/300 mg; Part B: Treatment C = FDC of DTG/ABC/3TC 50/600/300 mg; high fat meal
Clinical studies of efficacy and safety (previously untreated patients, dolutegravir Phase 3 program)			
ING114467 (SINGLE) N=833	double blind, active-controlled, non-inferiority study	Efficacy and safety for fixed dose DTG/3TC/ABC versus Atripla.	DTG/3TC/ABC (50/300/600 mg) qd vs Atripla
ING113086 (SPRING-2) N=822	double blind, active-controlled, non-inferiority study	Efficacy and safety for DTG vs RAL.	DTG 50 mg qd. versus Raltegravir 400 mg bid; Backbone: abc/3TC or tdf/FTC (backbone open label)
ING114915 (FLAMINGO) N=484	Open-label	Efficacy and safey for DTG vs darunavir/ritonavir	DTG 50 mg qd versus Darunavir/ritonavir 800/100 mg qd Backbone: abc/3TC or tdf/FTC

GCP

The Clinical trials were performed in accordance with Good Clinical Practice 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.

As part of the assessment of Dolutegravir single entity, a request for GCP inspection has been adopted for the clinical studies ING112574 (SAILING) and ING113086 (SPRING-2). These studies are also part of the dossier for the FDC. Based on the quality identified in these two clinical sites and sponsor site inspections it is likely that the deviations and findings identified during the inspections did not in any major sense influence or change the results as they were presented in the final study report of DTG single entity.

2.4.2. Pharmacokinetics

The PK properties of the individual components DTG (Tivicay) and ABC/3TC (Kivexa) have been subject to comprehensive development programs to support their respective Marketing Authorisations. The development strategy for the DTG/ABC/3TC FDC tablet focused on the compatibility of the active ingredients with each other and with the other excipients of the formulation. In addition, the program for the FDC aimed to demonstrate bioequivalence between the FDC tablet and the concurrently administered individual dosage forms, i.e. DTG (Tivicay) and ABC/3TC (Kivexa).

During development of the FDC, a Phase I bioavailability study (study ING114581) has been carried out using two different tablet formulations of DTG/ABC/3TC tablets. Based upon the results of this study, the so-called Formulation 1 was optimised to obtain the proposed commercial formulation. A pivotal bioequivalence and food effect study with the DTG/ABC/3TC 50/600/300mg FDC tablet versus

and the separate co-administered tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) was carried out to proof bioequivalence between the FDC tablet and the separate co-administered tablet formulations (ING114580).

No other clinical pharmacology studies have been conducted with the DTG/ABC/3TC FDC formulation proposed for marketing. Statements regarding the FDC are based on the clinical pharmacology of the individual components.

Furthermore, the outcome of the clinical pharmacology studies with DTG, ABC or 3TC (the individual components of DTG/ABC/3TC FDC) are summarised.

Analytical methods

For the analysis of DTG, ABC and 3TC in study ING114581 and ING114580, LC-MS/MS methods were applied.

Dolutegravir

Validation:

DTG was extracted from plasma by protein precipitation using acetonitrile. The calibration curve range from 20 – 20000 ng/ml. Within-run and between run precision and accuracy were within normal criteria. Stability has been proven over the handling and storage conditions of study samples, e.g. 5 freeze/thaw cycles at -20ºC and -70ºC, long term stability over 257 days at -20ºC and -70ºC, long term stability over 373 days at -20ºC, short term stability at room temperature for about 26 h, stability in whole blood and wet extract stability for 96.5 h at 5ºC and 147 h at 4ºC.

Furthermore stability has been proven in the presence of ABC and 3TC (plasma at room temperature for 18.4h, through freeze/thaw cycles, and following long-term storage (104 days at -20°C).

No interference is observed with abacavir, lamivudine, prednisone, prednisolone, rilpivirine, rifampin, rifabutin, norgestrel, norelgestromin, ethinyl estradiol, boceprevir, and telaprevir.

Analysis of study samples:

Study ING114581:

The precision of the QCs for DTG ranged from 4.8% to 6.4% while the accuracy ranged from 96.8% to 100.2%. Within-run criteria were met. One sample was reanalysed.

Study ING114580:

The precision of the QCs for DTG ranged from 3.4% to 5.2% while the accuracy ranged from 97.7% to 101.7%. Within-run criteria were met. No sample had to be reanalysed.

Abacavir

Validation:

For study ING114581, ABC was separately measured in plasma. ABC was extracted from plasma after protein precipitation. The calibration curve range from 5 – 5000 ng/ml. Within-run and between run precision and accuracy were within normal criteria. Stability has been proven over the handling and storage conditions of study samples, e.g. 3 freeze/thaw cycles at -70ºC, long term stability over 80 days at -70ºC, short term stability at room temperature for about 15 h, and wet extract stability for 110 h at 4ºC.

Stability has been proven in the presence of 3TC.

For study ING114580, ABC was simultaneous analysed with 3TC. The calibration curve range from 2.5 – 2500 ng/ml. Within-run and between run precision and accuracy were within normal criteria. Stability has been proven over the handling and storage conditions of study samples, e.g. 5 freeze/thaw cycles, long term stability over 212 days at -20ºC and -70ºC, short term stability at room temperature for about 29 h, wet extract stability for 90 h at 5ºC and whole blood stability at 37ºC for 4 h.

Analysis of study samples:

Study ING114581:

The precision of the QCs for ABC ranged from 3.4% to 6.2% while the accuracy ranged from 96.8% to 103.5%. Within-run criteria were met. 39 samples were reanalysed due to concentration >ULOQ, and 4 upon client request. Regarding the latter, for 2 samples the original value was kept. For the other 2 samples the repeated value (i.e. BLQ). As this is not the pivotal study, no concern will be raised.

Study IND114580:

The precision of the QCs for ABC ranged from 3.4% to 6.7% while the accuracy ranged from 97.0% to 103.2%. Within-run criteria were met. Samples had to be reanalysed due to concentration > ULOQ and concentration < LLOQ (n=1).

Lamivudine

Validation:

For study ING114581, 3TC was measured in plasma. 3TC was extracted from plasma after protein precipitation. The calibration curve range from 2 – 2000 ng/ml. Within-run and between run precision and accuracy were within normal criteria. Stability has been proven over the handling and storage conditions of study samples, e.g. 3 freeze/thaw cycles at -70ºC, long term stability over 310 days at -70ºC, short term stability at room temperature for about 5 h, and wet extract stability for 137 h at room temperature.

For study ING114580, 3TC was simultaneous analysed with ABC. The calibration curve range from 2.5 – 2500 ng/ml. Within-run and between run precision and accuracy were within normal criteria. Stability has been proven over the handling and storage conditions of study samples, e.g. 5 freeze/thaw cycles, long term stability over 212 days at -20ºC and -70ºC, short term stability at room temperature for about 29 h, wet extract stability for 90 h at 5ºC and whole blood stability at 37ºC for 2 h.

Analysis of study samples:

Study ING114581:

The precision of the QCs for DTG ranged from 2.1% to 4.7% while the accuracy ranged from 97.2% to 104.7%. Within-run criteria were met. 124 samples were reanalysed due to concentration >ULOQ, and 1 upon client request. Regarding the latter, the first analysis was BLQ while the second was 1553 ng/ml, which was also reported. As this is not the pivotal study, no concern will be raised.

Study IND114580:

The precision of the QCs for 3TC ranged from 3.5% to 7.3% while the accuracy ranged from 98.6% to 101.9%. Within-run criteria were met. Samples had to be reanalysed due to concentration > ULOQ and concentration < LLOQ (n=2).

Pharmacokinetic data analysis

Pharmacokinetic variables, e.g. AUC_{0-t}, AUC_{inf}, C_{max}, C_{min}, t_{max}, and $t_{½}$ were calculated according to standard procedures.

The population pharmacokinetic analysis, was performed separately for HIV-Infected Treatment-Naive and HIV-1 Infected Treatment-Experienced adult patients using pooled data from phase 2 and phase 3 studies. PopPK modeling was carried out using NONMEM 7 with FOCE-I as estimation method.

Statistical analysis

For comparison in most cases the 90% confidence intervals were calculated in case of equivalence testing. In addition, in case significance levels were used, the significance level was normally 5%.

Absorption

Bioavailability

DTG, ABC and 3TC are rapidly absorbed following oral administration. The absolute bioavailability of DTG has not been established. In the single dose mass balance study (ING111853), 31.6% of the administered dose was recovered in urine indicating that at least 1/3 of the dose is absorbed systemically.

The absolute bioavailability of oral ABC and 3TC in adults is 83% and 80 to 85% respectively. The mean time to maximal serum concentrations ($t_{max)}$ is about 2 to 3 hours (post dose for tablet formulation), 1.5 hours and 1.0 hours for DTG, ABC and 3TC respectively.

At steady state, the C_{max} and AUC_{0-24h} of DTG 50 mg once daily is 3.67 µ/ml and 53.6 µg.h/ml, respectively. Following a single oral dose of 600 mg of ABC, the mean C_{max} is 4.26 µg/ml and the mean AUC_{0-inf} is 11.95 µg.h/ml. Following multiple-dose oral administration of 3TC 300 mg once daily for seven days the mean steady-state C_{max} is 2.04 µg/ml and the mean AUC_{0-24h} is 8.87 µg.h/ml.

Study ING114581:

This was a single dose, randomised, 3 period crossover study evaluating the relative bioavailability of two experimental fixed-dose combination tablet formulations of DTG/ABC/3TC 50mg/600mg/300 mg compared to co-administered DTG 50 mg and abacavir/3TC (ABC 600 mg/3TC 300 mg) tablets in healthy adult subjects. The formulations were administered under fasted conditions. The washout period between periods was 7 days. Blood samples were taken up to 48 h after administration of the formulation.

18 subjects (8 females and 10 males), aged 19 – 45 years, were included in the study and completed the study.

The following formulations were administered:

Identity of Investigational Products

	Study Treatment			
Product name:	**DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 1 (AA)**	**DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 2 (AC)**	**DTG 50 mg (BC)**	**EPZICOM**
Formulation description:	dolutegravir, abacavir sulfate, lamivudine D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, Opadry II purple 85F90057	dolutegravir, abacavir sulfate, lamivudine microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, Opadry II purple 85F90057	dolutegravir, D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, Opadry II white 85F48011	Abacavir sulfate, lamivudine, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C Yellow No 6, hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide
Manufacturing Method:	Wet granulation/ Direct compression	Roller compaction	Wet granulation	Direct compression
Dosage form:	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)/ Dosage level(s):	DTG 50 mg/ ABC 600 mg/ 3TC 300 mg	DTG 50 mg/ ABC 600 mg/ 3TC 300 mg	50 mg = 1 tablet Dose = 50 mg	ABC 600 mg/ 3TC 300 mg. Dose = ABC 600 mg/3TC 300 mg
Route/ Administration/ Duration:	Administered orally as a single dose	Administered orally as a single dose	Administered orally as a single dose	Administered orally as a single dose
Dosing instructions:	Administered with 240mL of water	Administered with 240mL of water	Administered with 240mL of water	Administered with 240mL of water
Physical description:	11 x 22mm oval, purple, film coated tablets	10.4 x 20mm caplet, purple, film coated tablets debossed 123 on one side	9 mm white, film-coated, round tablets debossed with SV 572 on one side and 50 on the other side	Capsule-shaped, orange, film-coated tablets debossed with GS FC2 on one side
Manufacturer/ source of procurement:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
Method for individualizing dosage:	One tablet	One tablet	One tablet	One tablet
Batch numbers	111287002	111287172	101258084	R491552

The pharmacokinetic results for DTG, ABC and 3TC are shown in Tables 1, 2 and 3.

Table 1. The pharmacokinetic variables of DTG of the test Formulation 1 and 2 and reference DTG 50 mg+Epzicom (as mean ± s.d)

n=18	Form 1 (AA) 50/600/300mg	Form 2 (AC) 50/600/300mg	DTG 50mg+Epzicom 50/600/300mg
$AUC_{(0-t}$ (µg.h/ml)	44 ± 9	67 ± 16	51 ± 15
$AUC_{(0-inf}$ (µg.h/ml)	49 ± 11	75 ± 19	57 ± 17
C_{max} (µg/ml)	2.6 ± 0.6	3.9 ± 1.0	3.0 ± 0.8
t_{max} (h)	3.1 ± 1.1	3.0 ± 0.8	2.5 ± 0.9
$t_{½}$ (h)	14 ± 2	14 ± 3	14 ± 2

Table 2. The pharmacokinetic variables of ABC of the test Formulation 1 and 2 and reference Epzicom (as mean ± s.d)

n=18	Form 1 (AA) 50/600/300mg	Form 2 (AC) 50/600/300mg	DTG 50mg+Epzicom 50/600/300mg
$AUC_{(0-t}$ (µg.h/ml)	17.4 ± 5.3	17.0 ± 4.6	18.1 ± 5.3
$AUC_{(0-inf}$ (µg.h/ml)	17.4 ± 5.3	17.0 ± 4.6	18.1 ± 5.3
C_{max} (µg/ml)	5.3 ± 1.8	4.8 ± 1.1	5.8 ± 2.4
t_{max} (h)	1.6 ± 0.7	2.0 ± 0.7	1.4 ± 0.6
$t_{½}$ (h)	2.7 ± 0.7	2.5 ± 0.6	2.3 ± 0.6

Table 3. The pharmacokinetic variables of 3TC of the test Formulation 1 and 2 and reference Epzicom (as mean ± s.d)

n=18	Form 1 (AA) 50/600/300mg	Form 2 (AC) 50/600/300mg	DTG 50 mg+Epzicom 50/600/300mg
$AUC_{(0-t}$ (µg.h/ml)	14.6 ± 3.6	15.5 ± 3.8	15.6 ± 3.7
$AUC_{(0-inf}$ (µg.h/ml)	15.0 ± 3.4	15.9 ± 3.9	16.0 ± 3.8
C_{max} (µg/ml)	2.5 ± 0.6	2.6 ± 0.6	2.8 ± 0.6
t_{max} (h)	3.0 ± 0.8	2.7 ± 0.8	2.6 ± 0.9
$t_{½}$ (h)	15 ± 9	16 ± 7	14 ± 5

The statistical analysis is shown in Table 4.

Table 4. Statistical comparison of DTG, ABC, and 3TC pharmacokinetic parameters

	Ratio of GLS Means (90% CI)	
	FDC (AA) vs DTG (BC) + EPZ	FDC (AC) vs DTG (BC) + EPZ
DTG PK Parameters		
AUC(0-∞)	0.871 [0.792, 0.958]	1.33 [1.21, 1.46]
AUC(0-t)	0.870 [0.789, 0.959]	1.32 [1.20, 1.46]
Cmax	0.875 [0.785, 0.975]	1.32 [1.18, 1.47]
C24	0.902 [0.813, 1.00]	1.37 [1.24, 1.52]
ABC PK Parameters		
AUC(0-∞)	0.960 [0.906, 1.02]	0.948 [0.895, 1.01]
AUC(0-t)	0.960 [0.906, 1.02]	0.947 [0.894, 1.00]
Cmax	0.925 [0.821, 1.04]	0.867 [0.770, 0.977]
3TC PK Parameters		
AUC(0-∞)	0.937 [0.902, 0.973]	0.994 [0.957, 1.03]
AUC(0-t)	0.927 [0.886, 0.969]	0.988 [0.944, 1.03]
Cmax	0.879 [0.820, 0.942]	0.940 [0.877, 1.01]

FDC (AA): DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 1
FDC (AC): DTG 50 mg/ABC 600 mg/3TC 300 mg Formulation 2
DTG (BC) + EPZ: DTG 50 mg tablet plus a single EPZICOM tablet

Bioequivalence

Bioequivalence between Triumeq FDC and Epzicom/Kivexa (ABC/3TC) and Tivicay (DTG) should be demonstrated, which is required to bridge from the dosing regimen (FDC ABC/3TC and DTG) used in

the clinical effect and safety studies. The Epzicom tablet (marketed in US and Japan) used in the BE study is identical to the Kivexa tablet which is marketed in EU. One bioequivalence study has been conducted specific to the ABC/3TC/DTG FDC program (ING114580)

ING114580: Bioequivalence between the fixed dose combination tablet (TRIUMEQ) and the fixed dose combination ABC/3TC (EPZICOM/KIVEXA) administrated together with individual tablet of DTG (TIVICAY) was evaluated in a single-dose (fasting condition), randomized, two-treatment sequences (AB, BA), crossover study conducted in healthy male and female subjects (n=62 evaluated in pharmacokinetic analysis). In the second part (n=12), the effect of food on the FDC tablet was investigated. Blood samples were collected pre-dose and up to 48 h post-dose. Plasma concentrations were determined with two LC-MS/MS methods (dolutegravir separately and abacavir/lamivudine was co-analysed). For $AUC_{(0-\infty)}$, AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Bioequivalence evaluation:

The pharmacokinetic results for DTG, ABC and 3TC are shown in Table 5, 6 and 7.

Table 5. The pharmacokinetic variables of DTG of the proposed commercial formulation and the reference DTG 50 mg + Epzicom (as mean ± s.d)

n=62	DTG/ABC/3TC 50/600/300mg commercial formulation	DTG 50 mg + Epzicom 50/600/300mg Reference
$AUC_{(0-t}$ (µg.h/ml)	42.8 ± 13.2	45.4 ± 13.6
$AUC_{(0-inf}$ (µg.h/ml)	47.1 ± 15.4	49.8 ± 15.5
C_{max} (µg/ml)	2.5 ± 0.7	2.6 ± 0.7
t_{max} (h)	3.3 ± 1.3	3.2 ± 1.7
$t_{½}$ (h)	13 ± 3	13 ± 2

Table 6. The pharmacokinetic variables of ABC of the proposed commercial formulation and the reference DTG 50 mg + Epzicom (as mean ± s.d

n=62	DTG/ABC/3TC 50/600/300mg commercial formulation	DTG 50 mg + Epzicom 50/600/300mg Reference
$AUC_{(0-t}$ (µg.h/ml)	14.3 ± 3.5	14.9 ± 3.4
$AUC_{(0-inf}$ (µg.h/ml)	14.4 ± 3.5	14.9 ± 3.4
C_{max} (µg/ml)	4.1 ± 0.9	4.5 ± 1.1
t_{max} (h)	1.7 ± 0.9	1.6 ± 0.8
$t_{½}$ (h)	2.7 ± 0.8	2.6 ± 0.7

Table 7. The pharmacokinetic variables of 3TC of the proposed commercial formulation and the reference DTG 50 mg + Epzicom (as mean ± s.d)

n=62	DTG/ABC/3TC 50/600/300mg commercial formulation	DTG 50 mg + Epzicom 50/600/300mg Reference
$AUC_{(0-t}$ (µg.h/ml)	12.7 ± 3.2	13.1 ± 2.8
$AUC_{(0-inf}$ (µg.h/ml)	13.1 ± 3.2	13.4 ± 2.8
C_{max} (µg/ml)	2.2 ± 0.6	2.4 ± 0.6
t_{max} (h)	2.7 ± 0.9	2.3 ± 0.8
$t_{½}$ (h)	16 ± 8	14 ± 5

The mean extrapolated area was less than 20% for all 3 analytes.

The statistical analysis is shown in Table 8.

Table 8. Study Part A: Statistical comparison of plasma DTG, ABC and 3TC PK parameters for BE assessment

PK Parameter	GLS Mean		Ratio of GLS Means [90% CI]
	FDC Fasted (n = 62)	DTG + EPZ Fasted (n = 62)	FDC Fasted vs DTG + EPZ
DTG PK Parameters			
AUC(0-∞) (µg.h/mL)	44.73	47.36	0.945 [0.889, 1.00]
AUC(0-t) (µg.h/mL)	40.86	43.34	0.943 [0.888, 1.00]
Cmax (µg/mL)	2.44	2.54	0.961 [0.906, 1.02]
ABC PK Parameters			
AUC(0-∞) (µg.h/mL)	13.92	14.51	0.960 [0.939, 0.980]
AUC(0-t) (µg.h/mL)	13.90	14.48	0.960 [0.939, 0.980]
Cmax (µg/mL)	4.03	4.38	0.920 [0.867, 0.977]
3TC PK Parameters			
AUC(0-∞) (µg.h/mL)	12.75	13.12	0.972 [0.940, 1.01]
AUC(0-t) (µg.h/mL)	12.30	12.81	0.960 [0.928, 0.994]
Cmax (µg/mL)	2.11	2.28	0.926 [0.885, 0.968]

GLS=Geometric least squares

Data from food-interaction studies

Effect of food

Study ING114580 also evaluated the effect of food on the proposed commercial formulation. Subjects in the food effect assessment were to receive the dose at 30 (± 5) minutes after the start of a high fat meal (53% fat, 869 calories). The meal consisted of: toasted white bread with 2 tsp butter, 2 slices eggs fried in butter, 2 bacon (2 slices), hash-browned (fried shredded) potatoes (4 oz), whole milk (8 oz.).

The pharmacokinetic results are shown in Tables 9, 10 and 11 and the statistical analysis in Table 12.

Table 9. The pharmacokinetic variables of DTG of the proposed commercial formulation under fasting and fed conditions (as mean ± s.d)

n=12	DTG/ABC/3TC 50/600/300mg commercial formulation fasting	DTG/ABC/3TC 50/600/300mg commercial formulation fed
$AUC_{(0-t}$ (µg.h/ml)	39.1 ± 12.0	56.3 ± 14.2
$AUC_{(0-inf}$ (µg.h/ml)	42.7 ± 14.0	62.1 ± 17.7
C_{max} (µg/ml)	2.3 ± 0.6	3.1 ± 0.6
t_{max} (h)	3.0 ± 1.3	4.8 ± 1.8
$t_{½}$ (h)	13 ± 3	13 ± 2

Table 10. The pharmacokinetic variables of ABC of the proposed commercial formulation under fasting and fed conditions (as mean ± s.d).

n=12	DTG/ABC/3TC 50/600/300mg commercial formulation fasting	DTG/ABC/3TC 50/600/300mg commercial formulation fed
$AUC_{(0-t}$ (µg.h/ml)	13.5 ± 4.1	12.5 ± 3.9
$AUC_{(0-inf}$ (µg.h/ml)	13.5 ± 4.1	12.5 ± 3.9
C_{max} (µg/ml)	3.9 ± 0.9	3.2 ± 1.2
t_{max} (h)	1.7 ± 0.8	2.9 ± 1.1
$t_{½}$ (h)	2.3 ± 0.6	2.9 ± 0.9

Table 11. The pharmacokinetic variables of 3TC of the proposed commercial formulation under fasting and fed conditions (as mean ± s.d)

n=12	DTG/ABC/3TC 50/600/300mg commercial formulation fasting	DTG/ABC/3TC 50/600/300mg commercial formulation fed
$AUC_{(0-t}$ (µg.h/ml)	12.3 ± 4.7	12.7 ± 3.7
$AUC_{(0-inf}$ (µg.h/ml)	12.7 ± 4.6	13.1 ± 3.7
C_{max} (µg/ml)	2.1 ± 0.9	2.0 ± 0.6
t_{max} (h)	2.8 ± 1.1	3.5 ± 1.2
$t_{½}$ (h)	18 ± 9	17 ± 5

Table 12. Study part B - Statistical comparison of DTG, ABC and 3TC pharmacokinetic parameters for food effect assessment

PK Parameter	GLS Mean		Ratio of GLS Means [90% CI]
	FDC Fasted (n = 12)	FDC Fed (n = 12)	FDC Fed vs FDC Fasted
DTG PK Parameters			
AUC(0-∞) (µg.h/mL)	40.54	60.11	1.48 [1.36, 1.62]
AUC(0-t) (µg.h/mL)	37.38	54.85	1.47 [1.35, 1.60]
Cmax (µg/mL)	2.25	3.08	1.37 [1.26, 1.48]
ABC PK Parameters			
AUC(0-∞) (µg.h/mL)	12.96	12.00	0.926 [0.899, 0.953]
AUC(0-t) (µg.h/mL)	12.94	11.96	0.924 [0.898, 0.952]
Cmax (µg/mL)	3.84	2.97	0.774 [0.662, 0.905]
3TC PK Parameters			
AUC(0-∞) (µg.h/mL)	12.08	12.61	1.04 [0.971, 1.12]
AUC(0-t) (µg.h/mL)	11.61	12.18	1.05 [0.963, 1.14]
Cmax (µg/mL)	1.95	1.87	0.960 [0.879, 1.05]

The results from the statistical comparisons for DTG showed that plasma exposures following administration of the FDC tablet formulation administered with a high fat meal were approximately 48% higher for AUC and 37% higher for C_{max} than following administration of the FDC tablet formulation in the fasted condition.

For both ABC and 3TC, the results from the statistical analyses indicate that plasma exposures from the FDC tablet formulation administered with a high fat meal were similar to those from administration in the fasted condition, although the C_{max} for ABC was approximately 23% lower when the FDC tablet was taken with food.

Distribution

Abacavir. Following intravenous administration, the apparent volume of distribution is about 0.8 L/kg. *In vitro*, the plasma protein binding at therapeutic concentrations is 49%. Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44%.

Lamivudine. From intravenous studies the mean volume of distribution is 1.3 L/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and binding to serum albumin *in vitro* is <16-36%. The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%.

Dolutegravir. Plasma protein binding of DTG was 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_d/F) in patients was determined to be 17 to 20 L. DTG is distributed to CSF and the resulting steady state concentration is similar to the unbound concentration in plasma. In healthy volunteers (human ADME study, oral 20 mg, suspension) V_d/F (CV%) was determined to 12.5 L (9%).

Metabolism

Abacavir. The primary metabolism pathways are by alcohol dehydrohgenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the dose. These metabolites are excreted in the urine. The PK profile of intracellular active anabolite carbovir triphosphate (TP) following administration of an abacavir 300 mg BID containing regimen in HIV infected patients was characterised. This study demonstrated carbovir-TP has an intracellular half-life of 20.6 h.

Lamivudine. Metabolism is a minor route of elimination of lamivudine. The extent of hepatic metabolism is low (5-10%). The active moiety, intracellular lamivudine-TP, has a terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 h) after 300 mg once daily.

Dolutegravir. DTG is metabolised by UGT1A1 and also to some extent by CYP3A4 (~10% of dose in mass balance study). The fraction in urine was represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose). Dolutegravir is the predominant circulating compound in plasma.

Elimination

Excretion

Abacavir. The mean half-life of ABC was about 1.5 h. Approximately 2% of the administrated dose was renally exctreded as unchanged compound. Unchanged ABC and metabolites thereof accounted for about 83% of the administered dose in urine, the remaining was eliminated in faeces.

Lamivudine. Lamivudine was predominately cleared by renal excretion as unchanged compound. The mean systemic clearance was approximately 0.32 L/h/kg, with renal clearance (~70%) via the organic cationic transport system. The observed lamivudine elimination half-life was 5-7 h.

Dolutegravir. Based on the population PK analysis, CL/F and half-life in patients was determined to be approximately 1 L/h and 12 h, respectively. Based on phase I meta-analysis in healthy volunteers the corresponding data was 1.14 L/h and 14.4 h, respectively.

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). Unchanged DTG constitutes the major part of the radioactivity excreted in faeces (53% of the dose). Virtually no DTG (<1% of dose) 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.

Dose proportionality and time dependencies

Dose proportionality

A population pharmacokinetic analysis of studies ING111521, ING112276 and ING113086 suggested a less than dose-proportional increase in DTG exposure between 10 mg and 25 mg but a dose-proportional increase between 25 mg and 50 mg.

A phase 1 study was performed in HV with the aim to evaluate the effect of rifampin and rifabutin on DTG PK (ING113099). As part of the study 50 mg DTG was administered both once and twice daily to the same subject. Following 7 days repeated dosing exposure over 24 hours was determined. The geometric mean exposure to DTG in terms of AUC0-24 was 32 µg*h/mL and 93 µg*h/mL for once and twice daily dosing, respectively.

Time dependency

After administration of multiple once daily doses (study ING111322), the accumulation index for AUC was 1.4 for the 10 mg and 50 mg doses and 1.2 for the 25 mg dose. The ratio of AUC_T on Day 10 to AUC(0-inf) on Day 1 was 1.06 and 1.01 for the 10 mg and 50 mg doses, respectively, with 95% confidence intervals being within 0.8-1.25 for both dose groups. For the 25 mg group the ratio [95%CI] was estimated to 0.892 [0.841-0.946].

Abacavir and lamivudine show no unexpected steady state data.

Special populations

No clinically relevant effect on the PK of race, gender and weight was observed for any of the three active components. There is limited data in elderly patients for all three active components. In children above 12 years of age, the exposure was comparable to those observed in adults for all three compounds. 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_T 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. This is considered not to be clinical relevant.

Impaired renal function

Abacavir. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Lamivudine. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction is required for patients with creatinine clearance of < 50 ml/min.

Dolutegravir. 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. The mechanism for the decrease is unknown.

Impaired hepatic function

Abacavir. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dose reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure.

Lamivudine. The PK profile of 3TC is not significantly affected in patients with moderate to severe hepatic impairment.

Dolutegravir. 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.

No dose adjustment is considered necessary for patients with mild to moderate HI. The effect of severe hepatic impairment on PK of DTG has not been studied.

Pharmacokinetic interaction studies

No interaction study has been performed with the FDC tablet and no specific DDI study to investigate potential interaction between the three compounds has been performed. Interaction studies have been performed with the individual components dolutegravir, abacavir and lamivudine and any interaction identified for these individually are also relevant to Triumeq.

Abacavir. CYP450 does not play a major role in the metabolism of abacavir. *In vitro*, abacavir has been shown to not inhibit CYP3A4, CYP2C9 or CYP2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may via their action on UDP-glucuronyltransferases slightly decrease the plasma concentrations of abacavir, but are not expected to clinically impact on the exposure levels of abacavir. Two *in vivo* interaction studies has been performed: one with zidovudine and lamivudine and the second with alcohol. The results of those studies did not justify any specific dose recommendations. In the interaction study with ethanol AUC of abacavir was increased by 41%. Retinoid compounds are eliminated via alcohol dehydrogenase and interaction with abacavir is possible but has not been studied. Abacavir is not a substrate of the transporter P-glycoprotein. However, the investigated concentrations were lower than the maximal intestinal concentrations and it is therefore unknown if abacavir is a substrate for P-glycoprotein in the intestine. Literature data indicate that abacavir is a substrate for P-glycoprotein at intestinal concentrations. No other transporter information was provided for abacavir.

Lamivudine. Lamivudine is not significantly metabolised by CYP450 enzymes (such as CYP3A4, 2C9 and 2D6) nor does it inhibit or induce this enzyme system. *In vitro*, Lamivudine has been found to be an OCT2 substrate. Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 43% increase in lamivudine exposure, because of the trimethoprim component (a known OCT2 and MATE1 inhibitor); the sulfamethoxazole component did not interact.

Dolutegravir. DTG is a substrate of UGT1A1 and CYP3A4 as well as of the transporter proteins P-pg and BCRP. No mechanistic *in vivo* 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.

2.4.3. Pharmacodynamics

No other clinical pharmacology study has been conducted with the DTG/ABC/3TC FDC formulation proposed for marketing besides a pivotal bioequivalence and food effect study with the DTG/ABC/3TC FDC as described before. Statements regarding the FDC are based on the clinical pharmacology of the individual components.

Mechanism of action

DTG Component

DTG inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. In vitro, DTG dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{1/2}$ 71 hours).

ABC and 3TC Component

ABC and 3TC are NRTIs, and are potent, selective inhibitors of HIV-1 and HIV-2. Both ABC and 3TC are metabolized sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties and display extended intracellular half-lives supporting once daily use. 3TC-TP and carbovir-TP (the active triphosphate form of ABC) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. ABC and 3TC triphosphates show significantly less affinity for host cell DNA polymerases.

Effect on cardiac conduction

DTG Component

In a randomized, placebo-controlled, cross-over trial (study ING111856), 42 healthy subjects received single dose oral administrations of placebo, a supratherapeutic dose of DTG at 250 mg as suspension (exposures approximately 2-3-fold of the 50 mg twice daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. DTG did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

ABC and 3TC Component

There was no requirement to conduct thorough QTc studies at the time of development and registration of the marketed ABC- and 3TC- containing products. AE preferred terms indicative of clinical manifestations of TdP are not listed in the Company RSI or any approved local country labelling for ABC/3TC or the individual single entities ABC and 3TC. There is no evidence for risk of TdP for ABC and 3TC base on non-clinical data.

Effect on renal function

The effect of DTG on serum creatinine clearance (CrCL), glomerular filtration rate (GFR) using iohexol as the probe, and effective renal plasma flow (ERPF) using paraaminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3 arm, parallel, placebo-controlled study (study ING114819) in 37 healthy subjects, who were administered DTG 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease (about 10%) in CrCL was observed with DTG within the first week of treatment, consistent with that seen in clinical studies. DTG at both doses had no significant effect on actual GFR or ERPF. These data support findings from in vitro studies which suggest that the small increases in creatinine observed in clinical studies are due to the likely benign inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Genetic differences in PD response

Before initiating treatment with ABC, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patients. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Abacavir should not be used in patients known to carry the HLA-B*5701 allele as carriage of this allele is associated with a significantly increased risk of hypersensitivity reaction to abacavir. This restriction also applies to the FDC tablet.

Resistance profile

A dual nucleoside backbone plus a third potent drug is the standard of care in antiretroviral naive HIV positive patients. As the potency and barrier to resistance of the third drug in the combination increases (ie, NNRTI to PI to INI), the percent of protocol defined virologic failures (PDVFs) decreases as does the incidence of resistance to the nucleoside backbone and to the third drug. The combination of ABC + 3TC has proven efficacy when used as a nucleoside backbone for third drugs of multiple classes. While 3TC and ABC each select for M184V, this mutation alone does not cause high level resistance to ABC and antiretroviral activity is preserved unless additional mutations in the RT gene occur. The combination of ABC + 3TC has a well-defined and clinically robust resistance profile.

In the four studies of antiretroviral naive subjects, DTG + ABC/3TC resulted in a very low number of PDVF; none of these subjects had resistance to either DTG or to ABC/3TC. This is consistent with the evidence of higher barrier to resistance for DTG shown by the lower frequency of emergent INI resistance against DTG compared with RAL in both treatment naive and treatment experienced, but INI naive subjects. Protection of the nucleoside backbone and associated preservation of antiretroviral agents for future regimen options is a hallmark of an antiviral agent with a high barrier to resistance.

Nonclinical Virology

The following information is based on what is known from the individual components and briefly summarized.

Dolutegravir (DTG) 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. It has low nM activity against wild type HIV-1 and HIV-2 in a variety of cells lines, regardless of subtype. Human serum (100%) causes approximately 75-fold increase in DTG IC50. DTG is additive or synergistic when assayed in combination with other antiretroviral agents.

Susceptibilities to DTG and raltegravir (RAL) were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants. DTG retained activity against a vast majority of these mutants (95% had <10 FC to DTG). Additionally, susceptibilities to DTG and RAL were determined for over 700 RAL resistant clinical isolates, with DTG retaining activity (<10 FC) against >90% of them.

The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of INI resistance and dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single, double, and up to four residues clinically relevant IN substitutions.

Analysis of site directed mutants at IN polymorphic sites (101 and 124) as either single or double mutants, demonstrated no effect on DTG susceptibility.

Abacavir (ABC) has shown antiviral activity in vitro, with synergistic activity when combined with 3TC. ABC selects for RT mutations M184V, K65R, L74V, and Y115F in vitro.

Lamivudine (3TC) is a potent and selective inhibitor of HIV-1 and HIV-2 replication in vitro and appears to show synergistic antiviral activity in vitro in combination with AZT, ABC, or other inhibitors such as the protease inhibitor Saquinavir. It has been shown to be metabolised intracellularly to the 5'-triphosphate which has a long half-life of 10.5 to 15.5 hours. 3TC 5'-triphosphate inhibits HIV-1 RT with a Ki of 12.3 µM, and but its major action is as a chain terminator of reverse transcription. 3TC 5'-triphosphate is a weak inhibitor of DNA polymerase α, ß and γ, hence, there is little predicted toxic effect on human cell lines.

Clinical Virology

DTG Treatment-naïve population

DTG + ABC/3TC demonstrated long term durability in ING114467 (SINGLE) with a low rate of discontinuation due to virologic failure through 96 weeks. No treatment emergent primary INI or NRTI resistance mutations were observed through 96 weeks in ING114467 (SINGLE) for those subjects on DTG plus ABC/3TC FDC with PDVF. In contrast, both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.

Overall, there was a low rate of discontinuation in ING113086 (SPRING-2) due to virologic failure in both treatment arms (DTG or RAL plus 2 NRTIs), with only three additional subjects with PDVF identified after Week 48. The durability of the virologic response on DTG and RAL was maintained through Week 96. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.

No treatment-emergent Primary INI or NRTI resistance mutations were observed for subjects in the DTG or Darunavir plus ritonavir (DRV+RTV) treatment groups of ING114915 (FLAMINGO).

DTG Treatment-experienced population

DTG in combination with various backbone regimens (n=8 ABC/3TC) exhibits a higher barrier to treatment failure than RAL in the study of treatment experienced, INI naive subjects, ING111762 (SAILING); there was a statistically significant difference in favor of DTG for the proportion of subjects who failed therapy with treatment-emergent evidence of INI resistance through Week 48. A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects (one receiving EFV and TDF and the other receiving DRV/r and TDF as their background regimens) enrolled in ING111762 (SAILING) with little change in susceptibility to DTG and to RAL.

ABC and 3TC

For ABC, significant breakpoints were identified for both the AntivirogramTM and the PhenoSenseTM HIV assays. For the PhenoSenseTM HIV assay, breakpoints were identified at 4.4-fold and 6.3-fold. Breakpoints for the AntivirogramTM assay were slightly different (3.2- and 7.5-fold). In general the number of mutations correlated very closely with phenotype. The M184V mutation alone had no discernible effect on the response to ABC for subjects enrolled in five clinical trials (Glaxo Wellcome studies CNA2003, CNA3001, CNA3002, CNA3003 and CNA3009) versus those entering with wildtype virus, with 88% of subjects with M184V viruses responding at week 4. The M184V mutation in isolation has a negligible effect on ABC efficacy.

ABC/3TC plus a potent third agent results in very low incidence of M184V and only very rarely L74V or K65R (the latter two are ABC-associated resistance mutations) in ART naive subjects with PDVF. Increased potency of the third agent results in reduced incidence of PDVF and reduced treatment emergent mutations in those subjects with PDVF.

3TC selects rapidly for M184V which causes high level resistance to 3TC, reverses the effects of AZT resistance mutations, and delays the appearance of AZT resistance mutations.

2.4.4. Discussion on clinical pharmacology

Bioequivalence

Bioequivalence between Triumeq FDC and Tivicay and Epzicom/Kivexa administered as mono-components has been demonstrated which is crucial in order to bridge from the monotherapy tablet of

Tivicay and FDC Epzicom/Kivexa used in the clinical effect and safety studies. The bioequivalence study was adequately designed.

Effect of food

The effect of food on Triumeq has been sufficiently evaluated. For DTG a larger food effect on exposure has previously been reported for Tivicay (ca. 70% increase with a high fat meal) compared to what was found with the Triumeq FDC (40-50% increase). DTG can be taken with or without food according to the Tivicay SmPC, i.e. this discrepancy is considered to be of minor importance. The food effect on ABC and 3TC for Triumeq was roughly similar as previously reported for Kivexa. Also Kivexa can be taken regardless of food according to the SmPC. Triumeq can be taken with or without food according to the proposed SmPC recommendation, which is adequate.

Interactions

Abacavir and lamivudine were approved as mono therapy compounds for more than 10 years ago and therefore the interaction potential of these has not been evaluated in compliance with the current Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev.1, 2012). However, the non-compliance is acceptable based on long clinical experience and no evident negative effects related to metabolizing enzyme or transporter interactions has been identified.

In a FDC application the interaction between the substances should be considered and appropriate data should be submitted to either exclude PK interaction or establish magnitude of the interaction(s) (Guideline on clinical development of fixed combination medical products, CHMP/EWP/240/95 rev.1). The Applicant has not performed any specific DDI study to investigate potential interaction between the three compounds. Based on *in vitro* data, there is a risk for clinically relevant drug-drug interactions due to inhibition of OCT2 and MATE1 by DTG and thus this includes the OCT2 substrate lamivudine. The approach of not conducting a specific DDI study between the components of the FDC was justified with a cross study comparison. The exposure was found to be similar for both abacavir and lamivudine independent of DTG administration. In addition, safety data from phase III trials supported the absence of clinically relevant DDI; Treatment related AEs were not more frequent with the TRIUMEQ combination, as compared to what was seen with abacavir/lamivudine combined with raltegravir or darunavir/r. Thus, there seem to be no effect on PK of lamivudine or abacavir by dolutegravir. The inhibition of OCT2 and MATE-1 by dolutegravir is acceptably reflected in the SmPC section 4.3, 4.4 and 4.5 and also for lamivudine as an OCT2 substrate in 4.5.

There are no known mechanistic reasons for a PK drug-drug interaction affecting DTG due to co-medication with ABC and 3TC. In addition, as discussed above there is no safety issues identified with the combination in the clinical studies. Thus the risk of any clinical relevant PK interaction caused by ABC and 3TC on the exposure of DTG is considered low.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of the new fixed dose combination (FDC) tablet has been established to a sufficient extent.

2.5. Clinical efficacy

The new single tablet regimen (STR) being developed is a FDC of DTG 50 mg + ABC 600 mg + 3TC 300 mg with once-daily dosing for antiretroviral therapy (ART)-naïve and ART-experienced (INI-naïve) patients, and is referred to in this document as the DTG/ABC/3TC FDC.

No efficacy and safety studies were performed with DTG/ABC/3TC FDC. The bioequivalence study ING114580 is considered pivotal for the FDC tablet to allow bridging of efficacy and safety data obtained with the loose combination. For the DTG/ABC/3TC FDC development program, the main supportive study is study ING114467 (SINGLE, ART-naïve patients, 96 weeks) in which all patients used the backbone of interest. Supportive data are available from studies ING113086 (SPRING-2, ART-naïve patients, 96 weeks), and ING114915 (FLAMINGO, ART-naïve patients, 48 weeks) in which a subgroup of patients used DTG in combination with ABC/3TC.

2.5.1. Dose response studies

The doses selected for the DTG/ABC/3TC FDC tablet (i.e., 50 mg/600 mg/300 mg) were based on the doses previously selected for once-daily dosing of DTG, ABC, and 3TC. DTG 50 mg once-daily is the dose that was recently approved in the EU (21 November 2013, CHMP approval) and already approved in the US for ART-naïve and ART-experienced, INI-naïve populations. ABC 600 mg and 3TC 300 mg are the approved once-daily doses in the intended populations, and these are also the approved doses for the FDC of ABC/3TC.

2.5.2. Main study

ING114467 (SINGLE), which is also part of the DTG single entity development program, is considered the main supportive DTG/ABC/3TC FDC efficacy study because this trial evaluated a regimen of once-daily DTG 50 mg + ABC/3TC 600/300 mg FDC as one of two randomized study treatments. Study design and week 48 data (primary efficacy endpoint) were assessed within the dossier for the DTG single entity. The current submission also includes data until week 96.

This was a multicenter study conducted in US, Canada, EU and Australia. The study started 01 Feb 2011 and is ongoing.

Title of Study

Study ING114467 (SINGLE): 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 over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects.

Diagnosis and study entry criteria

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

The main exclusion criteria were pregnancy and breastfeeding, active centers for disease control and prevention (CDC) Category C disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm^3), any degree of hepatic impairment, Grade 4 laboratory abnormality, recent history (≤3 months) of upper or lower gastrointestinal bleed (without anal or rectal bleeding), estimated creatinine clearance <50 mL/min, alanine aminotransferase (ALT) >5x upper limit of normal (ULN) or ALT ≥3xULN associated with bilirubin ≥1.5xULN, use of disallowed therapy, history of malignancy within the past 5 years, historical or evidence of viral resistance.

Treatment

Subjects were randomized 1:1 to receive double blinded DTG 50 mg plus ABC/3TC FDC therapy once daily or Atripla once daily along with the corresponding matching placebo tablets during the randomized phase (i.e. through their week 96 study visit). Subjects were stratified by screening HIV-1 Ribonucleic acid (RNA) and CD4 cell count.
Since Atripla is recommended to be taken on an empty stomach preferably at bedtime, all three blinded tablets were also recommended to be taken in this manner. Upon completion of the week 96 visit subjects were given the opportunity to continue to receive treatment during the open-Label phase of the trial.

Objectives

Primary objective: To demonstrate non-inferior (non-inferiority margin 10%) antiviral activity of DTG plus ABC/3TC FDC once daily therapy compared to Atripla over 48 weeks in HIV-1 infected ART-naïve subjects.

Secondary objectives:

- Antiviral activity over 96 weeks;
- tolerability, long-term safety and antiviral and immunologic activity over time;
- development of viral resistance in subjects experiencing virological failure;
- health outcomes based on symptom bother count;
- incidence of HIV-associated conditions;
- health related quality of life.

Primary and secondary 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 algorithm).

Key secondary endpoints included the time to viral suppression (<50 copies/mL), the change from baseline in CD4 at Week 48, and the change in symptom bother count from baseline to week 4 of the Symptom Distress Module (SDM, also referred to as “Symptoms Impact Questionnaire”).

For subjects confirmed as virological failures, viral genotyping and phenotyping analyses were conducted to explore the relationship between treatment with DTG + ABC/3TC and Atripla and the evolution of HIV-1 resistance.

Health outcomes were assessed by two summary scores estimated from the HIV Symptom Index (Symptom Distress Module also known as the HIV Symptom Impact Questionnaire). In addition, the EQ-5D scale was also used, which rates patient’s health status on 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). A utility score was estimated by combining scores from each of the 5 dimensions. Changes in health-related quality of life were estimated using a visual analogue scale.

Safety and tolerability evaluations included electrocardiogram (ECG), hematology, clinical chemistry, serum lipids, creatinine concentration and urinalysis. Other assessments including height, weight, vital signs and concomitant medications were recorded.

Statistical methods

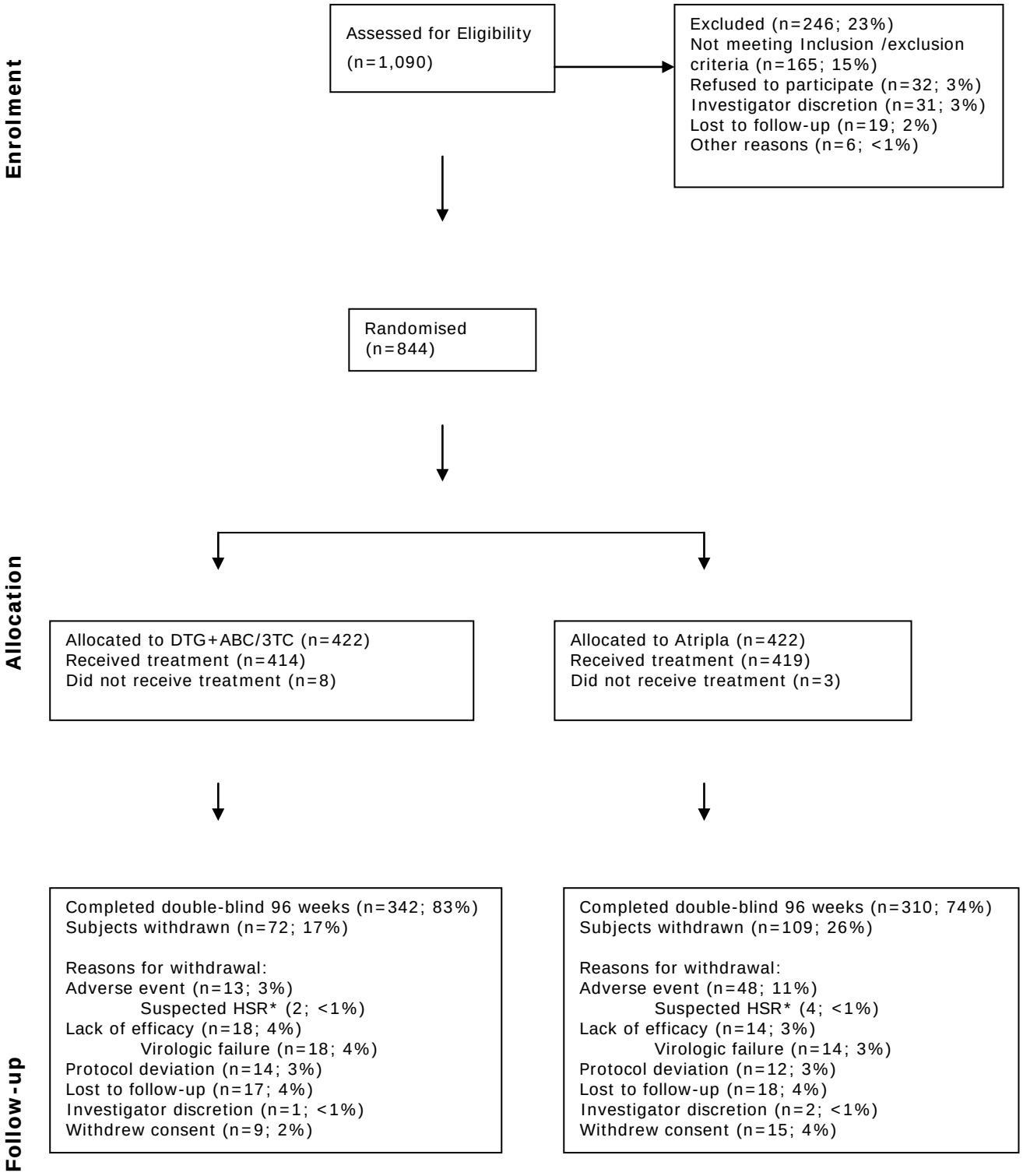
The power of this study was based on a response rate of 75% at week 48 which was the mid-range of response rates observed in EFV arms in recent large clinical studies ranges from 71% to 82%. Assuming this response rate in the Atripla arm, the study required 394 evaluable subjects per arm to have 90%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

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.

If non-inferiority was observed in ITT-E and PP primary analysis, with additionally the lower end of the 95% confidence interval over 0%, superiority of DTG was to be concluded.

Results

Participant flow



Disposition of subjects through week 96. *HSR=hypersensitivity reaction

Twenty-three percent of screening subjects (246/1090) failed to be enrolled. The reasons for screening failure were mainly due to inclusion/exclusion criteria (n=165, 15%), withdrew consent (n=32, 3%) , investigator discretion (n=31, 3%), and lost to follow-up (n=19, 2%).

A total of 844 subjects were randomized, 833 subjects received at least one dose of study drug, and 652 subjects continued through week 96. More subjects in the Atripla treatment group withdrew from the trial prematurely (26% versus 17%, respectively), with the most common reason being due to an AE compared to the DTG + ABC/3TC treatment group (11% versus 3%, respectively). Adverse events are further discussed in the safety section.

The proportion of withdrawals due to lack of efficacy or lost to follow up was similar across both treatment arms (4%). Eighteen (4%) subjects in the DTG+ABC/3TC group and 14 (3%) in the Atripla arm withdrew due to lack of efficacy (virologic failure).

A total of 35 subjects had protocol deviations leading to exclusion from the Per Protocol (PP) population (DTG + ABC/3TC 18, Atripla 17). Two subjects (DTG+ABC/3TC n=1, Atripla n=1) had deviations specific to the Inclusion or Exclusion Criteria. Three subjects were excluded from the PP population, because they had interrupted investigational product (IP) for >10% of the total time they were on treatment (DTG+ABC/3TC 2, Atripla 1). Ten subjects (DTG+ABC/3TC 6, Atripla 4) permanently discontinued IP due to protocol deviations. These withdrawals were due to pregnancy (n=5), use of prohibited meds (n=1), non-compliance with IP (n=6), and non-compliance with protocol procedure (n=3).

Twenty-six (3%) subjects (DTG+ABC/3TC 14, Atripla 12) permanently discontinued IP due to protocol deviations. These withdrawals were due to pregnancy (n=9), use of prohibited meds (n=3), non-compliance with IP (n=9), and non-compliance with protocol procedure (n=7).

Baseline data

The majority of subjects were white (68%) and male (84%); the median age of the ITT-E population was 35 years. In the DTG + ABC/3TC treatment group, only one subject was age 65 years or older, and in the Atripla treatment group, 6 subjects were age 65 years or older. A total of 53 patients on DTG and 44 on Atripla were ≥ 50 years of age. About 68% of the patients included were white Caucasian. Demographic and disease characteristics were comparable between treatment groups.

Table 13. Summary of baseline characteristics (ITT-E population) (ING114467, SINGLE)

	DTG 50 mg + ABC/3TC N=414 n (%)	**Atripla N=419 n (%)**	**Total N=833 n (%)**
BL VL, median log_{10} copies/ml (range)	4.67 (3.06, 6.46)	4.70 (2.48, 6.35)	4.68 (2.48, 6.46)
HIV-1 RNA (c/ml)			
≤ 100,00	280 (68)	288 (69)	568 (68)
>100,000	134 (32)	131 (31)	265 (32)
Median Baseline CD4+ (cells/mm^3) (range)	334.5 (19, 1027)	339 (19, 1123)	338 (19, 1123)
<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 and C

The mean time of exposure during the double-blind phase to DTG + ABC/3TC (N=414) was 606 days. In the Atripla group (N=419), the mean time of exposure was 554 days. The difference between treatment arms is driven by the fact that more subjects on Atripla discontinued the study early.

Outcomes

The primary analysis at week 48 demonstrated that DTG + ABC/3TC is non-inferior to Atripla, with 88% of DTG+ABC/3TC subjects and 81% of Atripla subjects achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA based on outcomes of MSDF (Snapshot) algorithm. This was supported by the PP-analysis (90% versus 81% responders in the DTG and Atripla group, respectively). In addition, superiority of DTG + ABC/3TC vs. Atripla was concluded at week 48.

The week 96 results continue to support the results seen at Week 48. DTG+ABC/3TC demonstrated sustained antiviral activity over 96 weeks. This result is supported by the PP analysis (83% and 75% responders on DTG + ABC/3TC and Atripla, respectively). Statistical analysis also demonstrated superiority of DTG over Atripla.

Table 14. Proportion of subjects responding based on plasma HIV-1 RNA <50 c/ml at week 48 and 96 (ITT-E population) (ING114467, SINGLE)

Responders	**DTG 50 mg + ABC/3TC once daily N=414 n (%)**	**Atripla once daily N=419 n (%)**	**Difference in proportion (95% CI) (DTG – Atripla)**	**Adj. difference[a] in proportions (95% CI) (DTG - Atripla)**
Week 48	364 (88)	338 (81)	7.3 (2.3, 12.2)	7.4 (2.5, 12.3)[b]
Week 96 – Double blind data	319 (77)	293 (70)	7.1 (1.2, 13.1)	7.3 (1.4, 13.3)[c]
Week 96 – Snapshot windowed data	332 (80)	303 (72)	7.9 (2.1, 13.6)	8.0 (2.3, 13.8)[d]

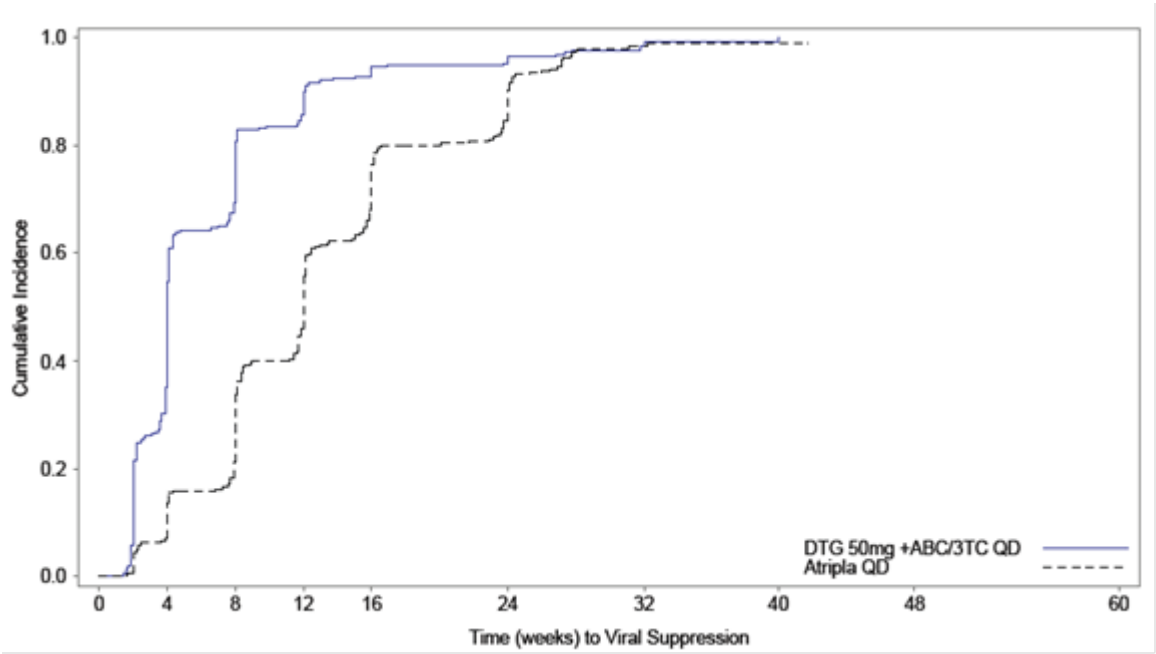
a. Adjusted difference based on Cochran-Mantel Haenzsel stratified analyses for the following baseline stratification factors: Baseline plasma HIV-1 RNA (≤ vs > 100,000 c/ml) and baseline CD4 cell count (≤ vs > 200 cells/mm^3).
b. Test for superiority: p=0.003; c. Test for superiority: p=0.016; d. Test for superiority: p=0.006

DTG+ABC/3TC was associated with a rapid virologic response, which was sustained through week 96. Median time to viral suppression was 28 days with DTG + ABC/3TC and 84 days with Atripla.

Sensitivity analyses supporting the primary endpoint were conducted: Kaplan-Meier estimates of the proportion of subjects without treatment related failure (TRDF) by Week 96 were numerically greater with the DTG + ABC/3TC compared to the Atripla treatment group (93% versus 84%) and supportive of the primary results, while the proportion of subjects without efficacy related failure (ERDF) was essentially the same on both treatment groups (94% for both groups).

The time to viral suppression was much shorter with abacavir/lamivudine + dolutegravir than.

Kaplan-Meier Plot of Time to Viral Suppression (VL <50 c/mL), SINGLE



Subgroup analyses of the primary endpoint

At week 96, DTG showed higher proportions of responders compared to Atripla in patients with low baseline viremia (85% versus 73%, respectively), whereas proportion of responders were comparable in patients with high baseline viremia (71% and 72%, respectively). This difference between viral load strata was not seen at week 48 (Table 15).

Higher response rates were observed in the DTG + ABC/3TC treatment group for baseline CD4+ cell counts above 200 c/mL; similar response rates were observed within the <50 c/mL and 50 to <200 c/mL CD4+ cell count subgroups.

Table 15. Summary of proportion of subjects responding on HIV-RNA < 50 c/mL at week 48 and week 96 by baseline HIV-1 RNA and CD4 strata , snapshot analysis (ING114467, SINGLE)

	DTG 50 mg + ABC/3TC N=414 n/N (%)	**Atripla N=419 n/N (%)**	**Difference in proportion (95% CI)[a]**
Week 48			
Baseline HIV-1 RNA (c/mL)			
≤ 100,000	253/280 (90)	238/288 (83)	7.7 (2.1, 13.3)
>100,000	111/134 (83)	100/131 (76)	6.5 (-3.2, 16.2)

CD4+ cell count (cell/mm^3)			
≤ 200	45/57 (79)	48/62 (77)	1.5 (-13.3, 16.4)
>200	319/357 (89)	290/357 (81)	8.1 (3.0, 3.3)
Week 96			
Baseline HIV-1 RNA (c/mL)			
≤ 100,000	237/280 (85)	209/288 (73)	12.1 (5.4, 18.7)
>100,000	95/134 (71)	94/131 (72)	-0.9 (-11.7, 10.0)
CD4+ cell count (cell/mm^3)			
≤ 200	39/57 (68)	45/62 (73)	-4.2 (-20.6, 12.2)
>200	293/357 (82)	258/357 (72)	9.8 (3.7, 15.9)

Stratified analysis by baseline viral load showed that in the high viral load subgroup, there were more "discontinuations due to other reasons" in the DTG + ABC/3TC group, with 14 (10%) in the DTG group vs. 8 (6%) in the EVF/TDF/FTC group (Table 16). Further, there is a slightly higher rate of "virologic non-response" for DTG + ABC/3TC than EVF/TDF/FTC (15% versus 12%, respectively), driven by data in window not <50 c/mL (6% versus 4%, respectively). The difference between treatment arms in withdrawals due to AE is consistent in both the high and low viral load subgroups.

Table 16. Study outcomes (Plasma HIV-1 RNA < 50 c/ml) at week 96 snapshot analysis by viral load strata (ITT-E population) (ING114467, SINGLE)

	DTG 50mg once daily (N=414) n (%)		**Atripla once daily (N=419) n (%)**	
Outcome	**≤ 100,000 c/ml N=280**	**> 100,000 c/ml N=134**	**≤ 100,000 c/ml N=288**	**≤ 100,000 c/ml N=131**
Virologic Success	**237 (85%)**	**95 (71%)**	**209 (73%)**	**94 (72%)**
Virologic Non-Response[a]	**11 (4%)**	**20 (15%)**	**17 (6%)**	**16 (12%)**
Data in window not <50 c/mL	5 (2%)	8 (6%)	2 (<1%)	5 (4%)
Discontinued for lack of efficacy	2 (<1%)	7 (5%)	6 (2%)	5 (4%)
Discontinued for other reason while not <50 c/mL	4 (1%)	5 (4%)	9 (3%)	6 (5%)
No Virologic Data at Week 96	**32 (11%)**	**19 (14%)**	**62 (22%)**	**21 (16%)**
Discontinued due to AE or Death	10 (4%)	3 (2%)	35 (12%)	13 (10%)
Discontinued for other reason while <50 c/mL	22 (8%)	14 (10%)	27 (9%)	8 (6%)
Missing data during window but on study	0	2 (1%)	0	0

a. Virologic failure

Subgroup analyses by age (<50 and ≥ 50 years), gender and race at week 48 showed that the treatment differences between treatment arms were maintained within demographic subgroups.

Immunological response

The mean change from baseline to week 96 in CD4+ cells in the DTG +ABC/3TC group was + 325 cells/mm^3, compared with + 281 cells/mm^3 in the Atripla arm. These results confirm the improved immunological response seen at week 48 (change in CD4 cell count of 267 cells/mm^3 versus 208 cells/mm^3 with DTG and Atripla, respectively).

De novo resistance

A total of 25/414 (6%) subjects in the DTG + ABC/3TC treatment group and 25/419 (6%) subjects in the Atripla treatment group met the definition of PDVF (two consecutive HIV-1 RNA values <50 c/mL HIV-1 RNA on or after Week 24). The majority of subjects who met PDVF in the study had low-level viremia (28/50). At confirmed failure, 20/25 (80%) and 17/25 (68%) of subjects with PDVF on DTG + ABC/3TC and Atripla, respectively, had <200 c/mL HIV-1 RNA. Of the 134 subjects on DTG + ABC/3TC with >100,000 c/mL HIV-1 RNA at baseline, 21 (16%) had PDVF similar to the 17/131 (13%) subjects

on Atripla. In the group with low baseline viral load, 9/280 (3%) subjects on DTG + ABC/3TC and 12/288 (4%) subjects on Atripla had PDVF.

Thirteen subjects in the DTG + ABC/3TC treatment arm had integrase (IN) genotype and phenotype at both baseline and at the time of PDVF, while 10 subjects in the Atripla treatment arm had IN genotype at and phenotype at both baseline and time of PDVF.

None of the 23 subjects in neither the DTG + ABC/3TC treatment group or the Atripla treatment group had treatment emergent integrase inhibitor (INI) resistance mutations. In patients treated with dolutegravir, 1 de novo mutation without relevance (E157Q/P) was seen in 1 patient at week 24; apart from this no other de novo mutations (integrase or reverse transcriptase (RT)gene) were detected.

Seventeen subjects in the DTG + ABC/3TC treatment group had NNRTI genotypic and phenotypic data at both baseline and time of PDVF. There were no treatment emergent NNRTI resistance mutations or treatment emergent NNRTI phenotypic changes in any of the subjects with PDVF in the DTG + ABC/3TC treatment group. Twelve subjects in the Atripla treatment group had NNRTI genotypic and phenotypic data at both baseline and time of PDVF. Six subjects in the Atripla arm had treatment emergent non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations. De novo resistance of relevance for efavirenz (K103N and or G190G/A) was selected in 5 patients at week 96 which also resulted in phenotypic changes. One patient developed a K101E (EFV) mutation which as an individual mutation was not of clinical relevance (NNRTI phenotype 1.9 FC to EFV).

Clinical studies in special populations

DTG/ABC/3TC FDC is not currently recommended for treatment of children less than 12 years of age as DTG and once daily dosing of ABC and 3TC are currently not approved in these children.

No studies have been performed with the FDC in the paediatric population. The indication in adolescents (12-18 years) is based on the approval of the individual components within that age span, which is acceptable. The applicant has submitted a PIP (EMEA-001219-PIP01-11). The PDCO has granted a waiver for the paediatric population from birth to less than 24 months and a deferral for the submission of DTG/ABC/3TC FDC data for subjects from 2 to 18 years of age.

Supportive studies

ING113086 (SPRING-2) is a phase III study including 822 ART-naïve subjects who received at least one dose of study medication; 169 received DTG 50 mg + ABC 600 mg/3TC 300 mg FDC. Week 48 data were discussed previously, the current submission includes 96 weeks data.

Subjects were stratified by baseline HIV-1 RNA (≤or >100,000 c/mL) and choice of NRTI. Main inclusion criteria were HIV-1 infected, ART-naive adults ≥18 years of age with plasma HIV-1 RNA ≥1000 c/mL at screening and 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.

Main exclusion criteria were women who were pregnant or breastfeeding; any evidence of an active Center for Disease and Prevention Control (CDC) Category C disease , except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm^3; moderate to severe hepatic impairment as determined by Child-Pugh classification; history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma; treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening, or treatment with radiation therapy,

cytotoxic chemotherapeutic agents, or any immunomodulator within 28 days of Screening; any evidence of primary viral resistance in the Screening result or, if known, any historical resistance test result; any verified Grade 4 laboratory abnormality; alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN); ALT ≥ 3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin); estimated creatinine clearance <50 mL/min via Cockroft-Gault method; recent history (≤3 months) of any upper or lower gastrointestinal bleed, with the exception of anal or rectal bleeding.

Subjects were randomized (1:1) and treated with either DTG 50 mg once daily or RAL 400 mg twice daily. Subjects also received a dual combination NRTI backbone (TDF/FTC or ABC/3TC) chosen by the investigator. Subjects received double blinded DTG or RAL plus matching placebo tablets during the randomized phase of the study (i.e., through the Week 96 study visit).

The primary objective was to demonstrate the antiviral activity of DTG 50 mg administered once daily compared to RAL 400 mg twice daily over 48 weeks using the Snapshot algorithm. Secondary objectives included: antiviral and immunological responses over time (including through Week 96); incidence, severity, and changes over time in laboratory and clinical safety parameters; assessment of population-based PK and PK/pharmacodynamic (PD) relationship; and changes in virologic genotype and phenotype.

The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA < 50 c/mL using the Missing, Switch or Discontinuation = Failure (MSDF), or “snapshot” algorithm. Non-inferiority of DTG 50 mg will be concluded if the lower bound of a two-sided 95% confidence interval (CI) for the difference in proportions (DTG - RAL) is greater than -10%.

The primary analysis took place after the last subject completed 48 weeks on therapy, and an additional analysis was conducted after the last subject completed Week 96. Data through Week 96 is presented herein. The primary analysis population is the ITT-E population.

Sensitivity analyses were performed using the Treatment Related Discontinuation = Failure (TRDF) data and Efficacy Related Discontinuation = Failure (ERDF) data. For TRDF, subjects who have not met PDVF criteria and are ongoing in the study, or who have discontinued for reasons other than those related to treatment, will be censored. For ERDF, subjects who have not met PDVF criteria and are ongoing in the study, or who have discontinued for reasons other than lack of efficacy, will be censored.

Key secondary analyses included the proportion of subjects with plasma HIV-1 RNA <50 c/mL at week 96 suppression; proportion of subjects with plasma HIV-1 RNA <400 c/mL at Weeks 48 and 96; change from baseline in plasma HIV-1 RNA over time; the change from baseline in CD4 and CD8 over time, incidence of disease progression ((HIV-associated conditions, AIDS and death).

For subjects confirmed as virological failures, viral genotyping and phenotyping analyses were conducted. Proportion of subjects with detectable virus that has genotypic and/or phenotypic evidence of INI resistance at Weeks 48 and 96 was assessed.

The primary safety population consisted of all subjects who received at least one dose of investigational product (i.e., DTG or RAL). Safety assessment included incidence and severity of AEs and laboratory abnormalities; absolute values and changes over time in laboratory parameters; proportion of subjects who discontinue treatment due to AEs; incidence of any clinically significant changes in ECG profiles; change from baseline in vital signs.

Outcomes

Eight hundred twenty-seven subjects were randomized (DTG: n=413, RAL: n=414), and 822 received at least one dose of study drug (n=411 in both arms). At baseline the median age was 36 years, 14% were female, 15% non-white, 28% had HIV-1 RNA >100,000 c/mL, and 41% used ABC/3TC as their background dual NRTI. Demographic and disease characteristics were comparable between treatment arms.

Table 17. Main disease characteristics (ING113086, SPRING-2)

	DTG (411) n (%)	RAL (411) n (%)	Total (822) n (%)
Baseline HIV-1 RNA (log_{10} copies/ml) Median (range)	4.52 (1.59, 6.61)	4.58 (2.67, 6.70)	4.55 (1.59, 6.70)
HIV-1 RNA (c/ml)			
≤ 100,000	297 (72)	295 (72)	592 (72)
> 100,000	114 (28)	116 (28)	230 (28)
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)
Backbone			
ABC/3TC	169 (41)	164 (40)	333 (41)
TDF/FTC	242 (59)	247 (60)	489 (59)

The proportion of subjects achieving the primary endpoint at week 48 (proportion with HIV-1 RNA <50 c/mL) was 88% for DTG and 85% for RAL; the difference (2.5%; 95% CI: -2.2% to 7.1%) met the 10% non-inferiority criteria. At week 96, a sustained response was observed in both treatment arms, with 81% of DTG subjects and 76% of RAL subjects achieving <50 c/mL plasma HIV-1 RNA and non-inferiority was reached. The trend for higher virologic success is driven by the subgroup of subjects with baseline HIV-1 RNA >100,000 c/mL, the response rate being 78% for DTG vs. 63% for RAL at week 96 (Table below).

Stratified analysis by baseline viral load and NRTI backbone showed that the results were consistent across both backbone regimens at week 48: DTG and RAL were relatively similar in efficacy and their activity was comparable regardless of NRTI-combination or baseline viral load. Only when TDF/FTC was used in combination with RAL in subjects with a high baseline viral load, differences were evident (83% vs 71% of DTG vs RAL and 71% vs 82% of RAL+TDF/FTC vs RAL+ABC/3TC). At week 96, comparable or slightly better efficacy is also seen for DTG versus RAL, especially in patients with a high baseline viral load: 78% vs 63% for DTG vs RAL in the overall population. Overall, the NRTI-combination TDF/FTC resulted in higher virologic response at week 96 than ABC/3TC regardless of use of DTG or RAL, or viral load at baseline.

Table 18. Proportion of responders based on plasma HIV-1 RNA <50c/ml at week 48 and week 96 and stratified for baseline viral load, CD4+ count and backbone NRTI and (ITT-E) (ING113086, SPRING-2).

	Week 48		Week 96	
	DTG (411)	**RAL (411)**	**DTG (411)**	**RAL (411)**
Number of responders	361/411 (88%)	351/411 (85%)	332/411 (81%)	314/411 (76%)
Difference in proportion (95% CI)	2.4 (-2.2, 7.1)		4.4 (-1.2, 10.0)	
Adjusted difference[a] in proportion (95% CI)	2.5 (-2.2, 7.1)		4.5 (-1.1, 10.0)	
By Baseline viral load				
BL VL ≤100,000 c/mL	267/297 (90)	264/295 (89)	243/297 (82)	241/295 (82)
>100,000 c/mL	94/114 (82)	87/116 (75)	89/114 (78)	73/116 (63)
BL CD4 <50 cells	5/8 (62)	0/6 (0)	5/8 (62)	0/6 (0)
50 to <200	38/47 (81)	34/44 (77)	34/47 (72)	28/44 (64)
200 to <350	128/144 (89)	118/139 (85)	116/144 (81)	103/139 (74)
350 to < 500	111/126 (88)	123/136 (90)	103/126 (82)	111/136 (82)
≥ 500	79/86 (92)	76/86 (88)	74/86 (86)	72/86 (84)
By NRTI backbone				
ABC/3TC	145/169 (86)	142/164 (87)	125/169 (74)	124/164 (76)
TDF/FTC	216/242 (89)	209/247 (85)	207/242 (86)	190/247 (77)
VL ≤100,000 ABC/3TC	115/132 (87)	110/125 (88)	98/132 (74)	98/125 (78)
TDF/FTC	152/165 (92)	154/170 (91)	145/165 (88)	143/170 (84)
VL >100,000 ABC/3TC	30/37 (81)	32/39 (82)	27/37 (73)	26/39 (67)
TDF/FTC	64/77 (83)	55/77 (71)	62/77 (81)	47/77 (61)

a Adjusted difference based on Cochrane-Mantel Haenszel stratified analysis adjusting for the baseline stratification factors: Baseline HIV-1 RNA and backbone dual NRTI.

Subgroup analyses stratified for different demographic or other disease characteristics yielded similar proportions of subjects with HIV-1 RNA <50 c/mL at week 96.

ING114915 (FLAMINGO) is a phase IIIb study including 484 ART-naïve subjects who received at least one dose of study medication; 79 received DTG 50 mg + ABC 600 mg/3TC 300 mg FDC.

Main inclusion criteria were HIV-1 infected adults ≥18 years of age, screening plasma HIV-1 ribonucleic acid (RNA) ≥1000 copies/milliliter (c/mL), and antiretroviral therapy (ART)-naïve (≤10 days of prior therapy with any ART agent). Subjects starting ABC as part of the NRTI background were to be screened and be negative for the *HLA-B*5701* allele.

Main exclusion criteria were pregnancy or breastfeeding, any active CDC category C disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm3; moderate to severe hepatic impairment (Class B or C) as determined by Child-Pugh classification; anticipated need for hepatitis C virus (HCV) therapy during the study; history of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma; treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening; or treatment with radiation therapy, cytotoxic chemotherapeutic agents, or any immunomodulator within 28 days of Screening; any

evidence of primary viral resistance in the screening result or in history, any verified Grade 4 laboratory abnormality; alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN); ALT ≥3 × ULN and bilirubin ≥1.5 × ULN (with >35% direct bilirubin); creatinine clearance of <50 mL/min via Cockroft-Gault method; recent history (≤3 months) of any upper or lower GI bleed, with the exception of anal or rectal bleeding.

Appropriate subjects were randomly assigned 1:1 to receive DTG 50 mg once daily or DRV+RTV 800 mg+100 mg once daily, each in combination with fixed-dose combination NRTI therapy (either ABC/3TC or TDF/FTC), for 96 weeks. Subjects were stratified by baseline HIV-1 RNA (≤ or >100,000 c/mL) and choice of NRTI (ABC/3TC or TDF/FTC).

The primary objective was to demonstrate the non-inferior antiviral activity of dolutegravir (DTG) 50 mg administered once daily compared to darunavir + ritonavir (DRV+RTV) 800 mg+100 mg once daily over 48 weeks in human immunodeficiency virus type 1 (HIV-1)-infected therapy naïve subjects.

Secondary objectives included: antiviral activity over 96 weeks, effects on fasting glucose and lipid over time; tolerability and long-term safety; incidence of HIV-associated conditions; antiviral and immunologic activity over time, and changes in virologic genotype and phenotype.

The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA < 50 c/mL using the Missing, Switch or Discontinuation = Failure (MSDF), or “snapshot” algorithm. Non-inferiority will be concluded if the lower bound of a 2-sided 95% confidence interval (CI) for the difference in response rates between the 2 treatment arms is greater than -12%.

The primary analysis took place after the last subject completed 48 weeks on therapy, and an additional analysis will be conducted after the last subject completed Week 96. Data through week 48 is presented herein.

Key secondary endpoints included:

- time to viral suppression (<50 c/mL) through week 48;
- proportion of subjects with plasma HIV-1 RNA <50 c/mL at week 96;
- proportion of subjects with plasma HIV-1 RNA <400 c/mL at weeks 48 and 96;
- absolute values and change from Baseline in plasma HIV-1 RNA, CD4+, and CD8+ T cell over time;
- and incidence of disease progression.

Safety endpoints included incidence and severity of adverse events (AEs) and laboratory abnormalities over time, absolute values and changes over time in laboratory parameters, change from baseline in fasting low-density lipoprotein (LDL) cholesterol at weeks 48 and 96, incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 48 and 96, proportion of subjects who discontinue treatment due to AEs, change from baseline in vital signs, and incidence of clinically significant changes in electrocardiogram profiles.

The virology endpoint was the incidence of treatment-emergent genotypic and phenotypic resistance to DTG, DRV+RTV and other on-study ART.

Health outcomes endpoints included change from baseline in symptom count and symptom bother score for DTG and DRV+RTV at Weeks 4, 24, 48 and 96, change from Baseline in utility and health-related quality of life for DTG and DRV+RTV at Weeks 24, 48 and 96, and treatment satisfaction for DTG and DRV+RTV at Weeks 24, 48 and 96.

The primary population used for study population, efficacy and health outcome summaries, analyses, and figures was the mITT-E Population, defined as all randomized subjects who received at least 1 dose of investigational product (IP) and who were not at a specific study center. The primary population used for safety analyses was the mSafety Population,

defined as all subjects who received at least 1 dose of IP (i.e., DTG or DRV+RTV) and who were not at a specific study center.

Tolerability and long-term safety over time of DTG compared to DRV+RTV was assessed by the incidence of AEs and serious AEs (SAEs) and graded laboratory toxicities, as well as summaries of laboratory tests, vital signs, and incidence of electrocardiogram abnormalities.

Outcomes

A total of 488 subjects were randomly assigned to a study treatment (DTG 243, DRV+RTV 245). Of these, 484 subjects were included in the Modified Safety (mSafety) Population and 484 subjects were included in the Modified Intent-to-Treat Exposed (mITT-E) Population, 242 in each treatment arm. The majority of patients were ongoing after week 48 (93% on DTG and 88% on DRV/r).

A total of 18 subjects (7%) prematurely withdrew from the DTG arm and 29 subjects (12%) from the DRV/r arm. Most common reasons were lost to follow-up (6 subjects (2%) and 10 subjects (4%) in the DTG and DRV/r treatment arm, respectively) and adverse events (3 subjects (1%) and 9 subjects (4%) in the DTG and DRV/r treatment arm, respectively).

A total of 5 subjects (2%) in the DTG treatment arm and 7 subjects (3%) in the DRV/r treatment arm had major protocol violations leading to exclusion from the PP population.

The majority of subjects were white (72%) and male (85%); the median age of the mITT-E Population was 34 years. Three subjects in the DTG treatment group and 1 subject in the DRV+RTV treatment group were age 65 years or older. Baseline demographic and disease characteristics were distributed similarly across treatment groups (Table below).

At the start of the study, 33% of subjects were prescribed ABC/3TC as background NRTI, with the remainder receiving TDF/FTC (67%). Switch of NRTI therapy to an alternative approved NRTI therapy for toxicity management was allowed once during the study. At the time of this analysis, 8 subjects had permanently switched therapy: 2 subjects (DTG 1, DRV+RTV 1) switched from ABC/3TC to TDF/FTC, and 6 subjects (DTG 4, DRV+RTV 2) switched from TDF/FTC to ABC/3TC.

The median time of exposure to both DTG (N = 242) and DRV/r (N = 242) was 337 days. The proportion of subjects receiving therapy for more than 48 weeks in the DTG treatment group (186, 77%) was similar to the DRV+RTV treatment group (181, 75%).

Table 19. Main disease characteristics (mITT-E population) (ING114915, FLAMINGO)

	DTG 50 mg once daily N=242 n (%)	DRV+RTV 800 mg+100 mg once daily N=242 n (%)	Total N=484 N (%)
Baseline HIV-1 RNA (log_{10} copies/ml) Median (range)	4.49 (2.74, 6.43)	4.48 (2.41, 6.22)	4.49 (2.41, 6.43)
≤ 100,000	181 (75)	181 (75)	362 (75)
> 100,000	61 (25)	61 (25)	122 (25)
Median Baseline CD4+ (cells/mm^3) (range)	390.0 (19, 1010)	400.0 (19, 1090)	395.0 (19, 1090)
<50	4 (2)	4 (2)	8 (2)
50 to <200	19 (8)	20 (8)	39 (8)
200 to <350	73 (30)	51 (21)	124 (26)
350 to <500	80 (33)	92 (83)	172 (36)
>500	66 (27)	75 (31)	141 (29)
CDC Category			
A: Asymptomatic/ lymphadenopathy/acute HIV	203 (84)	204 (84)	407 (84)
B: Symptomatic, not AIDS	30 (12)	32 (13)	62 (13)
C: AIDS	9 (4)	6 (2)	15 (3)
Hepatitis B (only)	9 (4)	4 (2)	13 (3)
C (only)	17 (7)	15 (6)	32 (7)
Selected NRTI backbone			
ABC/3TC	79 (33)	80 (33)	159 (33)
TDF/FTC	163 (67)	162 (67)	325 (67)

1 patients in the DRV treatment arm had both Hep B and C

At week 48, 90% of DTG subjects and 83% of DRV+RTV subjects had achieved <50 c/mL plasma HIV-1 RNA. The primary analysis demonstrated that DTG is non-inferior to DRV+RTV at week 48 (treatment difference 7%, lower end 95% CI: -0.9%). This result was supported by the PP analysis (response rates of 91% and 84% for DTG and DRV+RTV, respectively, lower end 95% CI: 1.4%).

Subgroup analyses of the primary analysis showed the trend for higher efficacy of DTG was driven by the difference in subjects with high baseline viremia, whereas similar results were obtained in subjects with low baseline viral load (Table 20). Further, subgroup analyses by backbone and baseline viral load showed comparable efficacy between backbone regimens in combination with DTG independent of baseline viral load, although numbers with high baseline viremia are low.

Table 20. Proportion of responders based on plasma HIV-1 RNA <50c/ml at week 48 and stratified for baseline viral load and backbone NRTI (mITT-E) (ING114915, FLAMINGO)

	DTG 50 mg once daily N=242 n (%)	DRV+RTV 800 mg+100 mg once daily N=242 n (%)
Number of responders	**217/242 (90)**	**200/242 (83)**
Difference in proportion (95% CI)	7.0 (0.9, 13.1)	
Adjusted difference in proportion (95% CI)[a]	7.1 (0.9, 13.2)[b]	
By Baseline viral load		
BL VL ≤100,000 c/mL	160/181 (88)	157/181 (87)
>100,000 c/mL	57/61 (93)	43/61 (70)
By NRTI backbone		
ABC/3TC	71/79 (90)	68/80 (85)
TDF/FTC	146/163 (90)	132/162 (81)
VL ≤100,000 ABC/3TC	59/66 (89)	60/68 (88)
TDF/FTC	101/115 (88)	97/113 (86)

VL >100,000 ABC/3TC	12/13 (92)	8/12 (67)
TDF/FTC	45/48 (94)	35/49 (71)

a. Adjusted difference based on Cochrane-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/ml vs > 100,000 c/ml) and background dual NRTI therapy (ABC/3TC vs TDF/FTC).
b. Test for superiority: p=0.025

Beginning at week 4, the rates of absolute change in HIV-1 RNA had a more rapid rate of decline up to week 24 in the DTG treatment group, although both treatment groups had sustained average decreases from baseline over time through week 48. The median time to viral suppression was 28 days for subjects in the DTG treatment group compared to 85 days in the DRV+RTV treatment group.

Differences in virologic response rates between DTG and DRV/rtv were primarily driven by discontinuations due to AEs (DTG 1%, DRV/rtv 4%) and other reasons (DTG 2%, DRV/rtv 5%) prior to week 48 (Table below). The proportion of virologic non-responders by the "snapshot" algorithm through week 48 was 6% in the DTG group and 7% in the DRV+RTV group, while 4% of subjects in the DTG treatment group and 10% in the DRV+RTV treatment group were considered virologic non-responders due to lack of virologic data at Week 48.

Table 21. Summary of study outcomes (Plasma HIV-1 RNA <50 c/mL) at week 48, snapshot analysis (mITT-E Population) (ING114915, FLAMINGO)

Outcome	**DTG 50 mg once daily N=242 n (%)**	**DRV+RTV 800 mg+100 mg once daily N=242 n (%)**
Virologic Success	**217 (90)**	**200 (83)**
Virologic Non-Response[a]	**15 (6)**	**18 (7)**
Data in window not <50 c/mL	6 (2)	11 (5)
Discontinued for lack of efficacy	1 (<1)	1 (<1)
Discontinued for other reason while not <50 c/mL	3 (1)	5 (2)
Change in ART	5 (2)	1 (<1)
No Virologic Data	**10 (4)**	**24 (10)**
Discontinued due to AE or Death	3 (1)	9 (4)
Discontinued for other reason while <50 c/mL[b]	6 (2)	11 (5)
Missing data during window but on study	1 (<1)	4 (2)

a. Virologic failure; b. Included protocol deviation, lost to follow-up, and withdrew consent

Subgroup analysis by demographic and baseline characteristics, including race, sex, age, HIV risk factors, baseline CDC category, Baseline CD4+ and country, generally supported the primary results.

Kaplan-Meier estimates of the proportion of subjects without treatment- and efficacy related failure at Week 48 were similar for DTG and DRV+RTV and supportive of the primary results.

Median (IQR) baseline CD4 counts were 390 cells/mm^3 (290, 500) and 400 cells/mm^3 (300, 530) in the DTG and DRV+RTV treatment arm, respectively. The median change from Baseline to Week 48 in CD4+ cells was 210 cells/mm^3 in both treatment groups.

ING11762 (SAILING) is a phase III study including 715 ART-experienced, INI-naïve subjects who received at least one dose of study medication; 8 received DTG 50 mg + ABC/3TC 600/300 mg FDC. This study formed the basis for the ART-experience population within the DTG single entity submission.

Main inclusion criteria were HIV-1 infected, INI-naïve, ART-experienced adults ≥18 years of age with ongoing treatment failure (>400 copies/mL), with documented resistance to at least 2 drug classes other than integrase inhibitors.

Main exclusion criteria included: screening resistance test showing no fully active ART available for the background regimen, subject-virus did not yield results using genotype/phenotype/tropism at screening, pregnancy and breastfeeding, active CDC Category C disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell levels <200 cells/mm^3), moderate to severe hepatic impairment, Grade 4 laboratory abnormality, recent history (≤3 months) of upper or lower gastrointestinal bleed (without anal or rectal bleeding), ALT >5x upper limit of normal (ULN) or ALT ≥3xULN associated with bilirubin ≥1.5xULN, use of disallowed therapy, history of malignancy within the past 5 years, any agent with documented activity against HIV-1 *in vitro* (with the exception of entecavir) within 28 days the first dose of investigational product (IP).

Subjects were randomized to DTG 50 mg once daily or RAL 400 mg twice daily (BID), both in combination with investigator selected background therapy based on screening and historic resistance results. The background therapy was limited to no more than two antiretroviral agents, of which one is fully active. Patients were stratified for baseline viral load (≤ 50,000 vs > 50,000 c/ml) and darunavir/r use in the background regimen (treated without primary PI mutations versus not treated or having primary PI mutations).

The primary objective of the study is to assess the non-inferior antiviral activity of DTG to RAL through week 48 by snapshot algorithm as the primary endpoint.

The population for the primary analysis was the mITT-E population, excluding patients from one site with GCP non-compliance. The non-inferiority margin was set at -12%.

Secondary objectives included: antiviral and immunological response over time; incidence, severity and changes over time in laboratory and clinical safety parameters; assessment of population-based PK and PK/PD parameters; and changes in virologic genotype and phenotype.

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) "snapshot" algorithm. An interim analysis was conducted after the last subject completed Week 24.

Secondary endpoints included the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the MSDF algorithm (principal secondary endpoint); proportion of subjects with detectable virus that has genotypic or phenotypic evidence of INI resistance by Week 48 (or Week 24); proportion of subjects with plasma HIV-1 RNA <400 c/mL at Week 24 and Week 48; absolute values and changes from baseline in CD4+ and CD8+ cell counts over time; incidence of disease progression (HIV-associated conditions, AIDS and death); change from baseline in the number of drug classes available at Week 48 (or Week 24). Health outcomes were assessed by the European Quality of Life – 5 Dimensions (EQ-5D) scale that rates subject's health status on five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

Virology:

The virology endpoint was the incidence of treatment emergent genotypic and phenotypic resistance to DTG, RAL and other on-study ART. This was assessed at week 24 and week 48.

Safety and tolerability evaluations included electrocardiogram (ECG), hematology, clinical chemistry, serum lipids, creatinine concentration and urinalysis. Other assessments including height, weight, vital signs and concomitant medications also were recorded.

Outcomes and estimation

Seven hundred and nineteen subjects were randomized (DTG n=357, RAL n=362) into the study and received at least one dose of investigational product. The mITT-E population included 715 subjects

(DTG n=354; RAL, n=361). At baseline, the median age was 43 years, 32% were female, and 42% were African American/African Heritage. Subjects had an overall median duration of prior ART of greater than 6 years, 47% of subjects had been exposed to 3 or more ART classes, 49% had resistance to 3 or more ART classes (and possibly other archived resistance), and subjects had one to two antiretroviral drugs in their background regimen. Most subjects had received the triple combination NRTI+ NNRTI + PI (40%) or the double combination NRTI + NNRTI (39%) before starting the study.

Table 22. Baseline main disease characteristics (ING111762, SAILING)

Baseline characteristic	DTG N=354	RAL N=361	Total N=715
HIV-RNA, median (range)	**4.2 (1.6, 6.8)**	**4.2 (1.6, 6.5)**	**4.2 (1.6, 6.8)**
HIV-RNA copies/ml			
<50,000	294 (70)	254 (70)	503 (70)
50,000 to 100,000	38 (11)	34 (9)	72 (10)
>100,000	67 (19)	73 (20)	140 (20)
Cd4-count, median (range)	**204 (19, 1017)**	**193 (19, 1219)**	**200 (19, 1219)**
<50	62 (18)	59 (16)	121 (17)
50 to <200	111 (31)	125 (35)	236 (33)
200 to <350	82 (23)	79 (22)	161 (23)
350 to <500	56 (16)	59 (16)	115 (16)
≥500	43 (12)	39 (11)	82 (11)
CDC catagory			
A	111 (31)	114 (32)	225 (31)
B	70 (20)	89 (25)	159 (22)
C	173 (49)	158 (44)	331 (46)
Hepatitis B & C, n (%)			
B only	17 (5)	16 (4)	33 (5)
C only	31 (9)	48 (13)	79 (11)
B and C	1 (<1)	1 (<1)	2 (<1)
Neither	288 (81)	271 (75)	559 (78)
Missing	17 (5)	25 (7)	42 (6)

Background regimens received during the treatment phase of the study were diverse, with boosted PIs being a component of the most commonly prescribed regimens (a total of 605 subjects received a boosted protease inhibitor [DTG: 305/354, 86%; RAL: 300/361, 83%]). DRV/r with tenofovir was the most commonly used regimen (18% and 20% in DGT and RAL treatment arms, respectively).

A total of 59% of patients did not have DRV/r use in the background ART regimen, 21% had DRV/rtv without primary PI mutations and 20% DRV/r with primary PI mutations as background ART regimen.

Only 8 patients received the backbone of interest (ABC/3TC 600/300 mg FDC) in combination with DTG (one of them was also taking maraviroc).

Outcomes

At week 48, 71% of subjects receiving DTG and 64% of subjects receiving RAL achieved the primary endpoint (HIV-1 RNA <50 c/mL). This difference in response was statistically significant with a 95% confidence interval for the adjusted difference of 0.7% to 14.2% (p=0.030). This result is supported by the PP analysis where 73% and 66% of DTG and RAL subjects, respectively, achieved plasma HIV-1 RNA <50 c/mL at Week 48 (adjusted treatment difference and 95% CI: 7.5 (0.6, 14.3)).

A separate analysis of the primary endpoint was performed on the subpopulation excluding subjects receiving DRV/r within the background regimen without evidence of primary PI mutations at baseline. Based on this population, 71% of subjects receiving DTG and 62% of subjects receiving RAL achieved

plasma HIV-1 RNA <50 c/mL at week 48 (adjusted treatment difference and 95% CI: 10.2 (3.9, 16.6)). This finding supports the results of the primary Week 48 analysis.

Regardless of the activity of the background regimen, use of recently approved ARTs in background regimen (with the noted exception for subjects receiving DRV/r without primary PI mutations described above), or current vs. historical evidence of resistance to establish study eligibility, the proportion of subjects with plasma HIV-1 RNA <50 c/mL was consistently higher in subjects receiving DTG compared to subjects receiving RAL.

Table 23. Week 24 and week 48 response by subgroups (mITT-E) (ING111762, SAILING)

	Week 24		**Week 48**	
	DTG (354) n, (%)	**RAL (361) n, (%)**	**DTG (354) n, (%)**	**RAL (361) n, (%)**
Response	281 (79)	252 (70)	251 (71)	230 (64)
Difference in proportion (95% CI)	9.6 (3.2, 15.9)		7.2 (0.3, 14.0)	
Difference in proportion (95% CI)[a]	9.7 (3.4, 15.9)		7.4 (0.7, 14.2)	
P-value[b]	0.003		0.030	
Baseline plasma HIV-1 RNA				
≤50,000 c/mL	207/249 (83)	195/254 (77)	186/249 (75)	180/254 (71)
>50,000 c/mL	74/105 (70)	57/107 (53)	65/105 (62)	50/107 (47)
Background regimen				
PSS= 2[c]	198/249 (80)	185/267 (69)	181/250 (72)	169/267 (63)
PSS< 2	83/105 (79)	67/94 (71)	70/104 (67)	61/94 (65)
DRV/r with no primary PI mutations				
Yes	57/71 (80)	63/78 (81)	50/72 (69)	54/77 (70)
No[d]	224/283 (79)	189/283 (67)	201/282 (71)	176/284 (62)

a. Difference: Proportion on DTG – RAL (unadjusted; b. One-sided p-value from weighted least square statistics; c. PSS based on full susceptibility, category '2' includes two subjects with PSS=3; d. Either no DRV/r or DRV/r use with primary PI mutations.

There were fewer virologic non-responders using the snapshot (MSDF) algorithm through week 48 in the DTG group compared to the RAL group (DTG: 20%; RAL: 28%). This result was driven by data within the window for HIV-1 RNA not being <50 c/mL (DTG: 10%; RAL: 13%) and discontinuations for lack of efficacy (DTG: 5%; RAL: 10%). At PDVF, there was also a statistically significant difference in favor of DTG for the proportion of subjects harboring virus with treatment-emergent evidence of INI resistance by Week 48 (DTG: 4/354 [1%]; RAL: 17/361 [5%]; p=0.003).

Kaplan-Meier estimates of the proportion of subjects without treatment or efficacy-related failure by Week 48 indicated statistically significant differences in favor of DTG, which was supportive of the primary analysis results.

The mean changes in CD4 count were similar between arms; around 100 cells/ mm^3 at week 24. Mean and median CD4+ cell counts further increased to week 48 in the DTG and RAL groups. The mean changes in CD4+ cell count from Baseline were +162.4 cells/mm3 in the DTG group and +153.2 cells/mm^3 in the RAL group at 48 weeks.

Other supportive clinical studies not discussed for efficacy due to low numbers contributing

ING112276 (SPRING-1) is a phase IIb dose-selection study including 205 ART-naïve subjects who received at least one dose of study medication; 17 received DTG 50 mg + ABC 600 mg/3TC 300 mg FDC. Data from ING112276 are included in the safety section.

ING116070 (CSF study) is a phase IIIb study including 13 ART-naïve subjects who received at last one dose of study medication; all 13 received DTG 50 mg + ABC/3TC 600/300 mg FDC. This study is not discussed again within the efficacy section given the low number of patients included.

2.5.3. Discussion on clinical efficacy

The combination of abacavir/lamivudine + dolutegravir) was superior to Atripla in the fully blinded SINGLE study. The response rate at week 48 was 88% *versus* 81% (+7.4% (95% CI: 2.5%, 12.3%)). The difference of 7% remained at week 96.

Abacavir/lamivudine + dolutegravir yielded similar results as abacavir/lamivudine in combination with raltegravir (SPRING-2 wk 48; 86% *versus* 87%) and darunavir/r (FLAMINGO wk 48; 90% *versus* 85%).

Also when comparing outcomes with abacavir/lamivudine+dolutegravir versus outcomes yielded with tenofovir/emtricitabine-based treatment similar response rates were observed: in comparison to tenofovir/emtricitabine + dolutegravir *or* raltegravir in SPRING-2 (wk 48; 86% *versus* 89% and 85%, respectively), and tenofovir/emtricitabine + darunavir/r in FLAMINGO (wk 48, 90% versus 81%).

Of note, similar efficacy results were obtained in patients with a baseline viral >100.000 copies/ml.

In two previous studies the abacavir/lamivudine components showed a signal for suboptimal efficacy in patients with a high baseline viral load (>100,000 copies/ml), which was not observed with tenofovir/emtricitabine. The concerned studies did not contain an integrase inhibitor-based regimen.

The studies relevant for the Triumeq application do not contain a blinded comparison between these two pairs of NRTIs in combination with dolutegravir. The only study which was fully blinded (also for the NRTI-components) was the SINGLE study, where abacavir/lamivudine + dolutegravir was compared to tenofovir/emtricitabine/efavirenz (as Atripla). Hence, it was not formally studied whether abacavir/lamivudine + dolutegravir provides the same efficacy as tenofovir/emtricitabine + dolutegravir in patients with a high baseline viral load. However, the outcomes versus various preferred regimens in the studies presented are considered reassuring. In particular as no resistance development (to the integrase inhibitor class or to the NRTIs) was observed in patients treated with dolutegravir. Therefore the CHMP considered that a cautionary statement with regards to baseline viral load is not warranted in the Triumeq SmPC.

In summary, the combination of abacavir/lamivudine + dolutegravir showed at least comparable efficacy to other preferred regimens (Atripla, 2 NRTIs + darunavir/ritonavir, 2 NRTIs + raltegravir). Importantly, with 96 weeks data SINGLE and SPRING-2 and 48 weeks data from FLAMINGO there is still not one single patients treated with dolutegravir (including in combination with abacavir/lamivudine) where a selection of relevant resistance was seen.

2.5.4. Conclusions on the clinical efficacy

Abacavir/lamivudine + dolutegravir as a combination has shown convincing efficacy in the dolutegravir development program. Similar or better response rates were seen than with recommended reference treatments. The high resistance barrier in patients naïve to the integrase inhibitor class is of clinical relevance.

2.6. Clinical safety

The DTG/ABC/3TC FDC contains the active substances DTG, ABC and 3TC at the same once daily doses as recommended for the individual components in antiretroviral therapy (ART)- naive and experienced adults (i.e., 50 mg, 600 mg and 300 mg, respectively). An assessment of the safety of each individual component taken alone as well as the safety of the components when used in combination has been provided.

Apart from bioequivalence (BE) studies, no clinical trials have been conducted with the DTG/ABC/3TC FDC. The separate medicinal products have been evaluated in numerous studies.

As the DTG component is a new chemical entity, full safety data on this single entity used in antiretroviral (ARV) combination regimens (with and without the ABC/3TC FDC) to treat INI-naive adult subjects has been provided. Clinical experience supporting the FDC has been obtained by investigating the DTG single entity and the ABC/3TC FDC in combination, to treat HIV infected Adult Subjects in Phase IIb to IIIb randomised clinical trials.

Key safety data on the ABC/3TC component that support the safety claims in the company reference safety information (RSI) and Summary of Product Characteristics (SPC) for the ABC/3TC FDC tablet have been provided with the application. Data from the Phase III studies that were submitted to register the once daily dosing applications for both ZIAGEN and EPIVIR are included to fulfil this requirement for the ABC and 3TC single entities. These studies are considered to be the most contemporary registration studies conducted for the separate preparations, because treatment options and recommendations have evolved in the time since ZIAGEN and EPIVIR were first marketed at their original twice daily dosing schedules.

Patient exposure

The description of safety data is based upon the Summary of Clinical Safety collected and analysed through 31 May 2013.

DTG / ABC / 3TC

Healthy subjects
In the phase I BA/BE study ING114580 66 subjects received the co-formulated DTG/ABC/3TC FDC tablets and the DTG single entity (SE) tablet plus the ABC/3TC FDC tablet.

DTG + ABC / 3TC

ART-naïve subjects
In total, 679 HIV-1 infected ART-naïve subjects received DTG 50 mg once daily + ABC/3TC 600/300 mg once daily in studies ING114467 (SINGLE), ING113086 (SPRING-2), ING112276 (SPRING-1), ING114915 (FLAMINGO). Furthermore, 13 HIV infected ART naïve subjects were exposed to DTG + ABC/3TC FDC in ING116070 (Study designed to determine plasma DTG concentration and evaluate the relationship between DTG concentration in plasma and Cerebral Spinal Fluid).

Summary of Extent of Exposure by Study and Overall – DTG Pivotal and Supporting Studies in ART-Naive Adults

	ING114467		ING113086		ING114915		ING112276		TOTAL
	SINGLE		SPRING-2		FLAMINGO		SPRING-1		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Exposure (Weeks)									
<12	15 (4)	34 (8)	4 (2)	4 (2)	2 (3)	2 (3)	1 (6)	3 (19)	22 (3)
12 to <24	7 (2)	18 (4)	5 (3)	8 (5)	1 (1)	0	1 (6)	0	14 (2)
24 to <48	25 (6)	27 (6)	11 (7)	7 (4)	16 (20)	17 (21)	0	0	52 (8)
48 to <96	107 (26)	112 (27)	45 (27)	39 (24)	60 (76)	61 (76)	4 (24)	3 (19)	216 (32)
>96	260 (63)	228 (54)	104 (62)	106 (65)	0	0	11 (65)	10 (63)	375 (55)
Exposure (days									
Mean (SD)	606.3 (170.63)	554.3 (221.46)	599.9 (167.77)	597.2 (178.23)	340.5 (70.77)	339.8 (74.30)	603.6 (199.41)	542.4 (263.55)	573.7 (182.77)
Median (Range)	672 (1, 760)	672 (3-699)	672 (13-685)	672 (8-700)	337 (31, 422)	337 (1-505)	672 (1-685)	672 (5-700)	672 (1-760)
Duration of dosing in Subject-years									
	687.2	635.9	277.6	268.1	73.6	74.4	28.1	23.8	1066.5

a. Sum across subjects of treatment start date – treatment stop date +1 divided by 365.25. When the IP stop date was missing, the duration was calculated up to the date of last visit or the recorded date of withdrawal/completion, whichever was earlier.

ART-experienced (INI-naïve)

A total of 18 ART-experienced (INI-naïve) subjects in study ING111762 (SAILING) received ABC/3TC; of those, 9 subjects received DTG + ABC/3TC (one subject also received maraviroc [MVC]). The mean exposure to DTG + ABC/3TC for these nine subjects during the randomized phase was 300 days.

DTG 50 mg Component

ART-naïve

As of the 31 May 2013 analysis cut-off date, a total of 1131 subjects in the four randomized, controlled trials in the ART-naïve population (ING114467, ING113086, ING114915, ING112276), and ING116070, received DTG in combination with any background therapy in the entire clinical development programme for this product.

ART-experienced (INI-naïve)

In study ING111762, 357 ART-experienced (INI-naïve) subjects have received DTG 50 mg once daily. Median duration of exposure in the randomised phase was 336 days (range 10 to 379 days).

ABC and 3TC Components

ART-naïve

In study CNA30021, 384 and 386 subjects were exposed to ABC once daily and ABC BID respectively, with a median duration of exposure of 372 and 367 days, respectively.

In study EPV20001, 272 subjects were exposed to 3TC once daily and 3TC BID respectively with a median duration of exposure of 337 days and 336 days respectively.

ART-experienced

In study CAL30001, 93 and 89 subjects were exposed to ABC/3TC FDC once daily and ABC BID+3TC once daily respectively, with a median duration of exposure of 336 days in both arms.

In study ESS30008, 130 and 130 subjects were exposed to ABC+3TC BID and ABC/3TC once daily respectively, with a median duration of exposure of 336 days in both arms.

Safety in bioequivalence study in healthy adults

Study ING114580 was a Phase I bioequivalence study of the combined formulated tablet (50 mg/600 mg/300 mg DTG/ABC/3TC FDC tablet) compared to one DTG 50 mg tablet + one ABC/3TC (600 mg/300 mg) tablet with and without food in healthy adult subjects.

Dosing with DTG+ABC/3TC fasted and the FDC fasted demonstrated similar tolerability during Part A. The most commonly-reported AEs during Part A were nausea, abdominal pain, headache, and somnolence. Tolerability was similar between the two treatments, although the incidence of nausea was higher in the separate entities group (29%) compared to the FDC (17%).

Dosing with FDC and a high fat meal was well-tolerated during Part B of the study. No AEs were reported during Part B, in healthy subjects already exposed to the FDC and DTG+ABC/3TC during Part A of the study.

No Grade 3 or 4 AEs, deaths or non-fatal SAEs were reported during the study. One subject was withdrawn from Part A of the study due to an AE (vomiting, considered related to FDC administration). No consistent, treatment related or clinically significant changes in mean or median hematology or clinical chemistry values were observed in the study. No clinically significant changes in vital signs or ECGs were observed during the study.

Adverse events

Common adverse events (≥5%)

Diarrhoea, nasopharyngitis, nausea, headache and fatigue were the most commonly reported clinical AEs occurring at similar rates within studies across the treatment groups (table S2). The AEs observed at higher frequency with DTG + ABC/3TC were insomnia, which was primarily observed in ING114467. Otherwise, AE rates between DTG +ABC/3TC and RAL +ABC/3TC were generally similar, and AEs such as dizziness, rash, nightmare and abnormal dreams occurred at higher frequencies in the EFV+ABC/3TC and/or Atripla (EFV/TDF/FTC) treatment groups.

Table 24. Frequency (%) of AEs (≥5%) DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event	376 (91)	394 (94)	138 (82)	139 (85)	69 (87)	67 (84)	16 (94)	16 (100)	599 (88)
Diarrhoea	84 (20)	83 (20)	16 (9)	12 (7)	10 (13)	23 (29)	4 (24)	1 (6)	114 (17)
Nausea	65 (16)	61 (15)	30 (18)	25 (15)	16 (20)	22 (28)	3 (18)	2 (13)	114 (17)
Nasopharyngitis	74 (18)	66 (16)	21 (12)	17 (10)	8 (10)	8 (10)	2 (12)	0	105 (15)
Headache	63 (15)	63 (15)	21 (12)	19 (12)	7 (9)	6 (8)	1 (6)	1 (6)	92 (14)
Insomnia	69 (17)	46 (11)	8 (5)	9 (5)	4 (5)	5 (6)	3 (18)	4 (25)	84 (12)
Fatigue	63 (15)	53 (13)	7 (4)	7 (4)	3 (4)	3 (4)	0	2 (13)	73 (11)
Upper respiratory tract infection	50 (12)	53 (13)	10 (6)	16 (10)	3 (4)	7 (9)	4 (24)	0	67 (10)
Dizziness	40 (10)	153 (37)	10 (6)	10 (6)	5 (6)	8 (10)	1 (6)	4 (25)	56 (8)
Cough	36 (9)	36 (9)	11 (7)	5 (3)	4 (5)	5 (6)	2 (12)	0	53 (8)
Pyrexia	26 (6)	27 (6)	10 (6)	10 (6)	5 (6)	6 (8)	1 (6)	3 (19)	42 (6)
Depression	31 (7)	34 (8)	7 (4)	6 (4)	4 (5)	2 (3)	0	0	42 (6)
Back pain	30 (7)	18 (4)	8 (5)	10 (6)	2 (3)	4 (5)	1 (6)	2 (13)	41 (6)
Bronchitis	28 (7)	26 (6)	11 (7)	7 (4)	0	4 (5)	0	2 (13)	39 (6)
Vomiting	26 (6)	24 (6)	9 (5)	8 (5)	3 (4)	7 (9)	0	0	38 (6)
Anxiety	26 (6)	30 (7)	5 (3)	11 (7)	5 (6)	3 (4)	0	0	36 (5)
Gastroenteritis	21 (5)	17 (4)	9 (5)	6 (4)	5 (6)	6 (8)	1 (6)	0	36 (5)
Oropharyngeal pain	27 (7)	16 (4)	6 (4)	5 (3)	0	2 (3)	2 (12)	0	35 (5)
Abnormal dreams	31 (7)	73 (17)	1 (<1)	2 (1)	0	0	0	1 (6)	32 (5)
Influenza	22 (5)	10 (2)	9 (5)	8 (5)	0	6 (8)	1 (6)	0	32 (5)
Sinusitis	22 (5)	15 (4)	9 (5)	9 (5)	1 (1)	3 (4)	0	2 (13)	32 (5)
Syphilis	18 (4)	25 (6)	10 (6)	6 (4)	2 (3)	3 (4)	1 (6)	1 (6)	31 (5)
Anogenital warts	21 (5)	19 (5)	8 (5)	7 (4)	1 (1)	2 (3)	0	0	30 (4)
Abdominal pain	18 (4)	15 (4)	7 (4)	8 (5)	3 (4)	3 (4)	0	0	28 (4)
Arthralgia	23 (6)	20 (5)	3 (2)	6 (4)	2 (3)	3 (4)	0	1 (6)	28 (4)
Rash	19 (5)	60 (14)	5 (3)	8 (5)	2 (3)	5 (6)	0	1 (6)	26 (4)
Pharyngitis	11 (3)	14 (3)	12 (7)	2 (1)	2 (3)	5 (6)	0	0	25 (4)
Pain in extremity	22 (5)	10 (2)	1 (<1)	6 (4)	2 (3)	2 (3)	0	0	25 (4)
Influenza like illness	10 (2)	6 (1)	9 (5)	5 (3)	2 (3)	1 (1)	1 (6)	0	22 (3)
Asthenia	14 (3)	14 (3)	5 (3)	11 (7)	1 (1)	2 (3)	0	0	20 (3)
Somnolence	9 (2)	24 (6)	2 (1)	2 (1)	0	0	1 (6)	0	12 (2)

Overall, AEs were most commonly reported from the *infections and infestations* and from the *gastrointestinal disorders* SOCs, occurring at comparable frequencies across the treatment groups within studies.

DTG +ABC/3TC had fewer AEs in the Nervous system disorders, Psychiatric disorders and Skin and subcutaneous tissue disorders SOCs, than observed for EFV+ABC/3TC and EFV/TDF/FTC treatment groups. AEs for DTG+ABC/3TC in all SOCs were comparable to RAL+ABC/3TC (Table 24), with the exception of events from the Musculoskeletal and connective tissue disorders SOC, which were more commonly reported for RAL+ABC/3TC

Nausea, diarrhoea, and headache were the most commonly reported drug-related AEs (as assessed by the reporting investigator), which in general occurred at similar or less frequently reported rates with DTG +ABC/3TC than the comparator treatment groups (Table 25).

Overall, similar drug-related AEs (type and frequency) were reported for DTG +ABC/3TC and RAL +ABC/3TC, but more drug-related AEs were reported for EFV +ABC/3TC, DRV + RTV +ABC/3TC and Atripla treatment groups (Table 25). Also, in the Phase III and IIIb studies, a higher proportion of subjects reported drug- related AEs in the DTG+ABC/3TC treatment group in ING114467 (which involved the Atripla comparator group), than were observed for the DTG+ABC/3TC treatment groups in ING113086 and ING114915. Insomnia was observed at a higher frequency with DTG +ABC/3TC than in comparator arms, which was primarily observed in ING114467. In this study there was a higher rate of certain AEs in the EFV/TDF/FTC arm.

Table 25. Possibly drug related AEs with a frequency of ≥5% in safety data base

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event	184 (44)	282 (67)	54 (32)	52 (32)	27 (34)	39 (49)	9 (53)	12 (75)	274 (40)
Gastrointestinal disorders									
Any event	92 (22)	94 (22)	33 (20)	32 (20)	21 (27)	36 (45)	4 (24)	4 (25)	150 (22)
Nausea	44 (11)	49 (12)	20 (12)	22 (13)	12 (15)	17 (21)	3 (18)	1 (6)	79 (12)
Diarrhoea	23 (6)	35 (8)	5 (3)	5 (3)	5 (6)	18 (23)	3 (18)	1 (6)	36 (5)
Psychiatric disorders									
Any event	86 (21)	125 (30)	6 (4)	7 (4)	4 (5)	1 (1)	2 (12)	5 (31)	98 (14)
Insomnia	41 (10)	25 (6)	2 (1)	1 (<1)	1 (1)	0	2 (12)	3 (19)	46 (7)
Abnormal dreams	27 (7)	66 (16)	1 (<1)	2 (1)	0	0	0	1 (6)	28 (4)
Nervous system disorders									
Any event	64 (15)	175 (42)	15 (9)	19 (12)	7 (9)	7 (9)	2 (12)	5 (31)	88 (13)
Dizziness	29 (7)	139 (33)	5 (3)	9 (5)	3 (4)	4 (5)	1 (6)	4 (25)	38 (6)
Headache	24 (6)	31 (7)	10 (6)	5 (3)	4 (5)	3 (4)	1 (6)	1 (6)	39 (6)
General disorders and administration site conditions									
Any event	41 (10)	46 (11)	5 (3)	13 (8)	2 (3)	2 (3)	0	2 (13)	48 (7)
Fatigue	29 (7)	28 (7)	2 (1)	5 (3)	2 (3)	2 (3)	0	1 (6)	33 (5)
Skin and subcutaneous tissue disorders									
Any event	29 (7)	75 (18)	7 (4)	5 (3)	2 (3)	8 (10)	0	3 (19)	38 (6)
Rash	4 (<1)	34 (8)	2 (1)	0	0	4 (5)	0	1 (6)	6 (<1)

Serious adverse event / deaths / other significant events

SAEs were most commonly reported from the infections and infestations and injury, poisoning and procedural complications SOCs, occurring at similar rates across the treatment groups. Four SAEs were

considered reasonably attributable to IP by reporting investigators across treatment groups (Table 2), including two cases of drug hypersensitivity and one case of hepatitis. In ING114467 a higher frequency of drug related events was observed with the Atripla treatment group when compared with DTG +ABC/3TC (Table27). Frequencies in all other studies were comparable across treatment groups.

Table 26. Summary of All SAEs by SOC – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		TOTAL
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event	44 (11)	51 (12)	14 (8)	21 (13)	10 (13)	6 (8)	2 (12)	4 (25)	70 (10)
Infections and infestations	17 (4)	18 (4)	5 (3)	10 (6)	1 (1)	3 (4)	0	1 (6)	23 (3)
Injury, poisoning and procedural complications	9 (2)	6 (1)	0	2 (1)	3 (4)	0	1 (6)	0	13 (2)
Psychiatric disorders	3 (<1)	12 (3)	1 (<1)	4 (2)	1 (1)	1 (1)	0	1 (6)	5 (<1)
Nervous system disorders	3 (<1)	8 (2)	0	1 (<1)	3 (4)	0	0	1 (6)	6 (<1)
Immune system disorders	1 (<1)	2 (<1)	4 (2)	1 (<1)	0	1 (1)	0	0	5 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1)	2 (<1)	0	2 (1)	1 (1)	0	1 (6)	0	4 (<1)
General disorders and administration site conditions	2 (<1)	1 (<1)	0	2 (1)	0	0	0	1 (6)	2 (<1)
Gastrointestinal disorders	1 (<1)	0	0	1 (<1)	2 (3)	1 (1)	0	0	3 (<1)
Hepatobiliary disorders	0	1 (<1)	2 (1)	2 (1)	0	0	0	0	2 (<1)
Musculoskeletal and connective tissue disorders	2 (<1)	1 (<1)	0	1 (<1)	1 (1)	0	0	0	3 (<1)
Renal and urinary disorders	1 (<1)	2 (<1)	1 (<1)	0	1 (1)	0	0	0	3 (<1)
Respiratory, thoracic and mediastinal disorders	2 (<1)	3 (<1)	0	0	0	0	0	0	2 (<1)
Blood and lymphatic system disorders	1 (<1)	2 (<1)	1 (<1)	0	0	0	0	0	2 (<1)
Cardiac disorders	1 (<1)	2 (<1)	0	0	0	0	0	0	1 (<1)
Metabolism and nutrition disorders	2 (<1)	0	1 (<1)	0	0	0	0	0	3 (<1)
Pregnancy, puerperium and perinatal conditions	1 (<1)	2 (<1)	0	0	0	0	0	0	1 (<1)
Reproductive system and breast disorders	2 (<1)	0	0	0	0	0	0	1 (6)	2 (<1)
Vascular disorders	1 (<1)	1 (<1)	0	1 (<1)	0	0	0	0	1 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	0	0	0	0	0	0	0	1 (<1)

Table 27. Summary of All Drug-Related SAEs – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event	1 (<1)	9 (2)	2 (1)	1 (<1)	1 (1)	0	0	1 (6)	4 (<1)
Drug hypersensitivity	1 (<1)	0	1 (<1)	0	0	0	0	0	2 (<1)
Suicide attempt	0	0	0	0	1 (1)	0	0	1 (6)	1 (<1)
Hepatitis	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Syncope	0	2 (<1)	0	0	0	0	0	0	0
Suicidal ideation	0	2 (<1)	0	0	0	0	0	0	0
Bipolar I disorder	0	1 (<1)	0	0	0	0	0	0	0
Depression	0	1 (<1)	0	0	0	0	0	0	0
Hallucination, visual	0	1 (<1)	0	0	0	0	0	0	0
Homicidal ideation	0	1 (<1)	0	0	0	0	0	0	0
Paranoia	0	1 (<1)	0	0	0	0	0	0	0
Hypersensitivity	0	1 (<1)	0	1 (<1)	0	0	0	0	0
Cerebrovascular accident	0	1 (<1)	0	0	0	0	0	0	0
Renal failure	0	1 (<1)	0	0	0	0	0	0	0

Deaths

DTG+ABC/3TC FDC

As of the 31 May 2013 cut-off date, there were a total of three deaths reported from DTG clinical studies in ART naïve adult subjects receiving ART regimens relevant to this application. One subject receiving DTG+ABC/3TC in supporting study ING112276 and two receiving Atripla in pivotal study ING114467 died. One of the three deaths was considered by the investigator to be possibly related to study drug TDF/FTC/EFV (renal failure).

DTG

Nine deaths were reported from the DTG development programme in INI-naïve subjects up to the 31st May 2013 data lock point.

Six involved ART-naive subjects (ING112276, ING113086, and ING114467). Three had received DTG, two received Atripla and one received RAL. Three involved ART-experienced (INI-naive) subjects (ING111762). All had received RAL.

Only one fatal case was associated with a drug related event. In addition to the deaths in studies conducted in INI naïve subjects there were four deaths in the single-armed VIKING studies in INI-resistant subjects. None were considered drug-related.

ABC and 3TC Components

There were five deaths reported across ABC and 3TC once daily registration studies. All deaths were reported in ART-naive subjects in CNA30021; two subjects in the ABC once daily group and three subjects in the ABC BID group. None of the deaths were considered by the investigator to be related to the study drug.

Laboratory findings

Liver and renal chemistry has been discussed in the previous section.

No clinically significant patterns of changes in hematology parameters were identified. No clinically significant patterns of changes in electrolytes (sodium, potassium, chloride, and bicarbonate), in metabolism indices (glucose, calcium and phosphorous) were identified.

Lipase elevations have been noted, mostly transient and asymptomatic, and none resulted in a clinical diagnosis of pancreatitis. Similar rates were observed across the treatment groups including Grade 3 and Grade 4 elevations

Four percent of subjects in the total DTG + ABC/3TC group experienced Grade 3 to 4 events which was similar to Atripla and RAL treatment groups and lower than DRV+RTV+ABC/3TC. There were no clinically significant effects on the Total cholesterol/HDL cholesterol ratio in any group.

Creatine Phosphokinase

Muscle disorders (common) and rhabdomyolysis (rare) are listed events in the ABC/3TC Company RSI. In view of the labeling for ABC/3TC and a drug (RAL) in the integrase class, the company characterized the risk of myopathy, rhabdomyolosis and Grade 3 to 4 CPK elevations with DTG + ABC/3TC.

The overall frequency of increased CPK was low and similar between treatment groups in individual studies with the exception of ING114915 where a higher frequency of CPK elevations occurred in the DTG+ABC/3TC group (15/79, 19%) compared to DRV+ABC/3TC group (11/80, 14%). In Studies ING113086 and ING114467 the rates were similar in the treatment groups. The overall rate of Grade 3 to 4 CPK elevations of 5% in the DTG + ABC/3TC ARTnaïve population was comparable to that seen with RAL, Atripla or DRV+ABC/3TC, although there were differences in the individual studies. Most CPK elevations were asymptomatic, all resolved spontaneously and no events resulted in discontinuation from study drug.

The incidence of events in the Musculoskeletal and connective tissue disorders SOC was similar across all groups in the ART-naïve population. The frequency of the individual events was low; the most frequently reported events in the total DTG+ABC/3TC group were back pain 6%, arthralgia and pain in extremities 4% each. Only 2% of subjects reported muscles spasm or myalgia and 1% musculoskeletal pain in the total DTG+ABC/3TC group. All other events were reported in <1% of subjects.

No withdrawals or treatment interruptions due to musculoskeletal events were observed in the DTG + ABC/3TC groups.

Adverse events of special interest

AESI have been determined for DTG based on pre-clinical and/or clinical safety data for DTG, labeling and/or regulatory authority interest for approved integrase inhibitors and/or the INI class, and/or regulatory authority requirements.

For the ABC/3TC FDC, AESI are based on the identified and potential ongoing risks recognized in the 2012 EU Risk Management Plan for the ABC and 3TC actives formulated as the once daily ABC/3TC

FDC tablet. These risks arose during the original non-clinical and clinical development program for ABC (i.e., carcinogenicity and hypersensitivity, respectively) or through post marketing surveillance activities (e.g., rash and ischemic cardiac disorders for ABC) and are discussed in this section.

Based on this information, several AESIs for the DTG/ABC/3TC FDC were identified. The following AESIs will be discussed in more detail:

1	Hypersensitivity Reaction	ABC and DTG
2	Rash	DTG, ABC & 3TC
3	Hepatobiliary Disorders	DTG
4	Renal disorders	DTG
5	Ischemic Cardiac Disorders	ABC
6	Gastrointestinal Disorders (incl, Pancreatitis/Lipase elevations)	DTG
7	Psychiatric disorders including Suicidality	DTG
8	Musculoskeletal, connective tissue and bone disorders	DTG
9	Immune Reconstitution Inflammatory Syndrome	All ART
10	Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)	ABC
11	Torsades de Pointe	DTG, ABC & 3TC

Hypersensitivity Reaction

The most important risk associated with ABC is a well characterized, idiosyncratic, drug-related HSR [Hetherington, 2001; Hughes, 2008; Mallal, 2008], that usually presents with multiple symptoms and involves several organ systems, as clearly described in the local product labelling for each of the marketed ABC- containing products. HLA-B*5701 has been shown to be highly associated with ABC HSR, and the practice of pre-therapy screening for HLA-B*5701 and excluding from abacavir therapy those individuals found to carry the allele, reduces the risk of HSR.

The risk of fatal or life threatening HSR is managed by ensuring that clinicians and patients are aware that, even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue ABC and not re-challenge with any ABC-containing product if a HSR cannot be ruled out on clinical grounds.

Hypersensitivity reactions have been reported with integrase inhibitors, including DTG, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. HSR is listed as an ADR for DTG, which also contains a Warning and Precaution for this reaction.

Given that hypersensitivity is a recognized risk for both the ABC and DTG constituents, further characterization of this risk when using these active moieties in combination is warranted.

The company reviewed AE preferred terms that were considered indicative of hypersensitivity reactions; these included AE PTs of hypersensitivity, drug hypersensitivity and anaphylactic reaction only and no derivatives. Cases of clinically suspected ABC HSR (as assessed by either the reporting investigator or the Sponsor) reported for the pivotal and supporting DTG studies were identified from the applicant global safety database. All subjects in the DTG clinical program who used ABC in their regimen were required by protocol to have screened negative for HLA-B*5701.

The results are presented in the table S9:

Table 28. Summary of Hypersensitivity AEs (HLA-B*5701 negative subjects) – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any 'HSR' Event[b]	4 (<1)	6 (1)	5 (3)	2 (1)	1 (1)	1 (1)	0	1 (6)	10 (1)
Any non-serious HSR Event	2 (<1)[C]	4 (<1)	2 (1)	1 (<1)	1 (1)	0	0	1 (6)	5 (<1)[C]
Any 'HSR' SAE	2 (<1)[d]	2 (<1)	3 (2)	1 (<1)	0	1 (<1)	0	0	5 (<1)[d]
Any clinically suspected ABC HSR	2 (<1)[d]	0[e]	3 (2)	1 (<1)	0	1 (<1)	0	0	5 (<1)[d]

a. ING114467 was the only study in which the dual nucleoside backbone was double-blinded, and provides reassurance for a projected low rate of HSR with both DTG and ABC.
b. Includes AE PTs hypersensitivity, drug hypersensitivity and anaphylactic reaction only and no derivatives
c. Three non- serious cases for the DTG+ABC/3TC treatment group are included in the ING114467 Week 96 CSR; however, on review, the non-serious report of drug hypersensitivity for Subject 6393 was upgraded to an SAE by the Sponsor, because it was considered to meet the MAH definition for clinically suspected ABC HSR.
d. FDC ISO data cites one SAE of drug hypersensitivity for the DTG+ABC/3TC treatment group in ING114467 and four cases of HSR for the total DTG+ABC/3TC treatment group. However, as for footnote c above, one non-serious report of drug hypersensitivity for DTG+ABC/3TC Subject 6393 in ING114467 was upgraded to an SAE by the Sponsor. See ING114467 Week 96 CSR.
e. Prior to unblinding at 48 weeks, five cases of clinically suspected ABC HSR were reported from the Atripla treatment group in ING114467.

Ten subjects receiving DTG+ABC/3TC were reported with terms indicative of HSR (hypersensitivity, drug hypersensitivity and anaphylactic reaction). Reporting rates were similar across studies and treatment groups (Table 28).

No HSR events were reported from ING116070 (CSF study) at the time of the Week 16 analysis.

With the exception of the Atripla arm in ING114467, in which 5/6 of the HSR events were considered of Grade 3 to 4 intensity, the majority of cases from each treatment group were considered of Grade 1 to 2 intensity. In the DTG+ABC/3TC treatment group two HSR events were considered of grade 3 to 4 intensity. No HSR event resulted in a fatal outcome. In the total DTG+ABC/3TC treatment group, HSR resulted in the permanent discontinuation of IP and subject withdrawal in 3 cases.

Reporting rates were consistent between DTG+ABC/3TC and comparator in ING114467 and ING114915 at <1% in each treatment group. ING114467 was the only study in which the dual nucleoside backbone was double-blinded, and provides reassurance for a projected low rate of HSR with both DTG and ABC.

There was an imbalance of reports for DTG+ABC/3TC in ING113086 compared to RAL+ABC/3TC, and more were reported as SAEs in the DTG+ABC/3TC group. In this study, for 2/3 cases symptoms resolved after switching ABC/3TC to TDF/FTC with continued DTG .

The third case involving DTG+ABC/3TC was reported as reasonably attributable to DTG by the reporting investigator. The subject developed flu like symptoms (fever and body aches), approximately ten days after commencing study treatment, which progressed over the course of four days to include symptoms of rash (profuse, purpuric and coalescing leukocytoclastic vasculitis), arthralgia, palpable liver, jaundice and atrial fibrillation. The subject's ALT peaked at >20 x ULN and his bilirubin at >4 x ULN. Clinical improvement was seen after discontinuation of DTG and ABC/3TC and start of

corticosteroid therapy. Non-drug causes of his hypersensitivity reaction were extensively investigated, but an alternative cause could not be identified including repeat HLA-B*5701 testing (negative), hepatitis A/B/C/D/E, cytomegalovirus (CMV), Epstein-Barr virus (EBV), syphilis and autoimmune disease. Due to the severity of the reaction, this subject was withdrawn from the study and not rechallenged with ABC/3TC or DTG. 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. A reaction on dolutegravir cannot be ruled out.

The frequency of cases meeting the applicant definition for suspected ABC HSR in ART-naive, HLA-B*5701 negative subjects from the phase IIb to IIIb clinical trials was <1% for the total DTG+ABC/3TC treatment group and also the RAL+ABC/3TC and DRV+RTV+ABC/3TC treatment groups. This was comparable to or lower than the incidence for ABC HSR reported in HLA-B*5701 negative subjects participating in large randomized MAH sponsored clinical trials investigating the marketed ABC containing products. Although these data are limited, they suggest that there is no additional risk from HSR in HLA-B*5701 negative subjects receiving the DTG/ABC/3TC single tablet FDC.

Rash with or without Systemic Involvement

Skin rash is associated with many antiretrovirals [NIH, 2012]. Severe skin reactions have been reported for ABC associated with hypersensitivity reactions. Rash has also been commonly reported without systemic systems (i.e., outside of the context of HSR) in post marketing follow up. Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme (EM) have been reported very rarely in patients taking ABC containing products post marketing.

Given that severe skin reactions are recognized risks for the ABC constituent, and rash is a recognized adverse drug reaction for all three components of the DTG/ABC/3TC FDC, characterization of this risk when using these active moieties in combination is addressed.

Any preferred terms related to a rash due to drug were identified from the integrated and pooled data from the pivotal and supporting clinical trials in ART- naive adult subjects. This included preferred terms such as rash, rash generalized, rash macular, rash papular, rash macula-papular, rash pruritic, and drug eruption.

Overall, mild to moderate episodes of rash were commonly reported for DTG+ABC/3TC. The rate and nature of rash with DTG+ABC/3TC FDC was no different to that observed for comparators in the Phase III/IIIb development program (with the exception of a significantly higher reporting rate observed for Atripla), or observed historically for the individual actives DTG, ABC and 3TC. Other than the case discussed above with a HSR reaction, no other instances of serious skin reaction, including SJS, TEN, or EM were reported across the studies. The majority of the reported episodes were of Grade 1 to 2 intensity. Grade 3 episodes were reported in only one subject each in the DTG+ABC/3TC and Atripla treatment groups from ING114467 and in the RAL+ABC/3TC treatment group form ING113086. No Grade 4 episodes of rash were reported across the studies. Additionally, no episodes were reported as SAEs, and none resulted in fatal outcome, across the studies.

Hepatobiliary disorders

Liver toxicity is a potential safety concern for DTG based on high dose repeat toxicity in cynomolgus monkeys, where dose related liver reactions were noted. Studies with DTG showed hepatocellular single cell necrosis and diffuse hepatocellular hypertrophy and/or vacuolation occurred in male monkeys. DTG is primarily hepatically metabolized via UGT1A1 with a minor CYP3A component. DTG

is a substrate for and an inhibitor of UGT1A1. It is likely that competition with bilirubin for a common enzymatic clearance pathway could result in an increase in unconjugated (and thus total) bilirubin during treatment with DTG.

There was one severe case of hypersensitivity with a severe liver reaction, fulfilling Hy's law criteria, which is discussed elsewhere. As such, hypersensitivity, including hepatic toxicity was the main safety concern during the DTG evaluation.

There is a Warning in the Product Information for DTG that hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. There is also a warning that patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of DTG.

ABC was associated with liver findings in nonclinical studies. All findings were reversible or showed evidence of regression except hepatocellular hypertrophy in male mice at 1000 mg (succinate)/kg/day for three months. ABC may be a weak enzyme inducer, and therefore hepatic changes may be associated with ABC-induced alterations in metabolic activity.

Synergistic or additive toxicity is not expected from the co-administration of DTG with ABC and 3TC. While both ABC and DTG caused treatment related hepatic effects, the findings in ABC treated animals were believed to be adaptive changes related to metabolic enzyme induction, and with DTG the findings were observed only at doses that exceeded the maximum tolerated dose.

Liver was not considered a target organ in nonclinical toxicity studies of 3TC.

Liver related AEs and liver chemistry in phase 3 - randomized studies

There were few AEs reported from the hepatobiliary SOC and the incidence was comparable between groups. The incidence of Grade 3/4 toxicities in Liver Chemistries was 4% or less in all arms of all Phase III studies and 2% for the total DTG treatment group

Table 29. Summary of Adverse events in Hepatobiliary SOC – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ARTNaïve Adults

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event in SOC	3 (<1)	3 (<1)	4 (2)	5 (3)	3 (4)	1 (1)	0	1 (6)	10 (1)
Cholelithiasis	3 (<1)	1 (<1)	0	0	0	0	0	0	3 (<1)
Hepatic steatosis	0	0	1 (<1)	1 (<1)	1 (1)	0	0	0	2 (<1)
Hepatitis	0	0	1 (<1)	2 (1)	0	0	0	0	1 (<1)
Hepatitis toxic	0	0	0	2 (1)	0	0	0	0	0
Autoimmune hepatitis	0	1 (<1)	0	0	0	0	0	0	0
Cholecystitis	0	1 (<1)	0	0	0	0	0	0	0
Cholestasis	0	0	0	0	0	0	0	1 (6)	0
Gallbladder cholesterolosis	0	0	0	0	1 (1)	0	0	0	1 (<1)
Hepatitis alcoholic	0	0	0	0	1 (1)	0	0	0	1 (<1)
Hepatocellular injury	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Hepatosplemomegaly	0	0	0	0	0	1 (1)	0	0	0
Hepatotoxicity	0	0	0	1 (<1)	0	0	0	0	0
Portal vein thrombosis	0	0	1 (<1)	0	0	0	0	0	1 (<1)

The occurrence of low grade elevations in total bilirubin amongst DTG +ABC/3TC recipients is likely related to competition for common enzymatic pathways (e.g., UGT1A1) for DTG and unconjugated bilirubin. Increases were not progressive, nor were they generally associated with increases in other liver enzymes (e.g., ALT). The percentage of subjects with ALT>3xULN was similar for DTG + ABC/3TC vs. RAL +ABC/3TC (ING113086) and lower for DTG +ABC/3TC compared with Atripla (ING114467). In ING114915 the percentage was greater for DTG +ABC/3TC compared with DRV+RTV + ABC/3TC but the numbers were small. There were no subjects with ALT>3xULN in either group in ING11276.

Table 30. Summary of Subjects Meeting Hepatobiliary Laboratory Abnormality Criteria - Post-Baseline Emergent – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	TOTAL DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
ALT (IU/L)									
Grades 1 to 4	54 (13)	77 (18)	27 (16)	34 (21)	9 (11)	5 (6)	0	2 (13)	90 (13)
Grades 2 to 4	12 (3)	24 (6)	12 (7)	11 (7)	4 (5)	1 (1)	0	0	28 (4)
Grades 3 to 4	2 (<1)	2 (<1)	4 (2)	4 (2)	2 (3)	1 (1)	0	0	8 (1)
Grade 1	42 (10)	53 (13)	15 (9)	23 (14)	5 (6)	4 (5)	0	2 (13)	62 (9)
Grade 2	10 (2)	22 (5)	8 (5)	7 (4)	2 (3)	0	0	0	20 (3)
Grade 3	1 (<1)	1 (<1)	3 (2)	3 (2)	1 (1)	0	0	0	5 (<1)
Grade 4	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (1)	1 (1)	0	0	3 (<1)
ALP (IU/L)									
Grades 1 to 4	14 (3)	49 (12)	2 (1)	7 (4)	4 (5)	1 (1)	1 (6)	3 (19)	21 (3)
Grades 2 to 4	0	2 (<1)	1 (<1)	1 (<1)	0	0	0	1 (6)	1 (<1)
Grades 3 to 4	0	1 (<1)	0	0	0	0	0	1 (6)	0
Grade 1	14 (3)	47 (11)	1 (<1)	6 (4)	4 (5)	1 (1)	1 (6)	2 (13)	20 (3)
Grade 2	0	1 (<1)	1 (<1)	1 (<1)	0	0	0	0	(<1)
Grade 3	0	1 (<1)	0	0	0	0	0	1 (6)	0
Grade 4	0	0	0	0	0	0	0	0	0
AST (IU/L)									
Grades 1 to 4	62 (15)	73 (17)	32 (19)	37 (23)	13 (16)	8 (10)	1 (6)	0	108 (16)
Grades 2 to 4	13 (3)	24 (6)	11 (7)	9 (5)	4 (5)	2 (3)	0	0	28 (4)
Grades 3 to 4	1 (<1)	11 (3)	5 (3)	4 (2)	2 (3)	1 (1)	0	0	8 (1)
Grade 1	49 (12)	49 (12)	21 (12)	28 (17)	9 (11)	6 (8)	1 (6)	0	80 (12)
Grade 2	12 (3)	13 (3)	6 (4)	5 (3)	2 (3)	1 (1)	0	0	20 (3)
Grade 3	1 (<1)	9 (2)	2 (1)	4 (2)	0	1 (1)	0	0	3 (<1)
Grade 4 .0 .2 (<1) .3 (2). 0 .2 (3). 0.0 0. 5 (<1).									
Total Bilirubin									
Grades 1 to 4	20 (5)	3 (<1)	9 (5)	6 (4)	3 (4)	0	2 (12)	0	34 (5)
Grades 2 to 4	3 (<1)	2 (<1)	4 (2)	0	0	0	0	0	7 (1)
Grades 3 to 4	1 (<1)	1 (<1)	2 (1)	0	0	0	0	0	3 (<1)
Grade 1	17 (4)	1 (<1)	5 (3)	6 (4)	3 (4)	0	2 (12)	0	27 (4)
Grade 2	2 (<1)	1 (<1)	2 (1)	0	0	0	0	0	4 (<1)
Grade 3	1 (<1)	1 (<1)	1 (<1)	0	0	0	0	0	2 (<1)
Grade 4	0	0	1 (<1)	0	0	0	0	0	1 (<1)

Two subjects, both from study ING113086 and both in the DTG group had a combination of ALT >3xULN with total bilirubin >2xULN and ALP <2xULN.

Liver chemistry toxicity by hepatitis co-infection status

Patients with HBV were excluded from the pivotal SINGLE study so there is limited data on use in this population (two subjects on DTG+ABC/3TC, two subjects on RAL and one subject on Atripla) and no analysis is possible.

In the ART-naïve subjects with HCV infection at Baseline had a higher incidence of post-baseline emergent Grade 2-4 liver chemistry toxicities compared with subjects who were not co-infected in groups treated with DTG, Atripla and RAL. Only six subjects co-infected with HCV were randomized to treatment with DRV+RTV and none of them had Grade 2-4 liver chemistry toxicities. For ALT and AST

the incidence of toxicities in subjects with hepatitis virus infection treated with DTG was lower than both the RAL and Atripla treated subjects, but similar to subjects treated with DRV + RTV.

The incidence of liver chemistry toxicities for subjects without hepatitis virus infection was similar in DTG, RAL and Atripla groups but lower in the DRV + RTV treated group. However, the percentage of subjects with the more severe Grade 3 to 4 elevations of ALT was low and comparable in all groups. Grade 2 to 4 elevations in bilirubin were low in all groups in both co-infected and non-infected subjects.

Table 31. Summary of Grade 2-4 Post-Baseline Emergent Clinical Chemistry Toxicities for Subjects co-infected with HCV – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	Hepatitis C infected				No hepatitis			
	Total DTG	Atripla	RAL	DRV	Total DTG	Atripla	RAL	DRV
n	59	29	20	6	616	385	141	74
ALT, n(%)	8 (14)	7 (24)	5 (25)	0	20 (3)	17 (4)	5 (4)	1 (1)
AST, n(%)	7 (12)	6 (21)	3 (15)	0	21 (3)	18 (5)	6 (4)	2 (3)
BILI, n(%)	1 (2)	0	0	0	6 (<1)	2 (<1)	0	0

Renal Function

Mild non-progressive changes in serum creatinine were seen for DTG 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.

There were no adverse treatment related renal effects of chronic administration of ABC or 3TC in nonclinical toxicity studies. In the label for ABC/3TC it is noted that laboratory abnormalities associated with hypersensitivity to abacavir in some subjects include elevated creatinine.

Renal function parameters of special interest were defined as Creatinine, calculated GFR, BUN, urine albumin/creatinine ratio and estimated CrCl. General summary outputs and statistics were created for these parameters, in addition to:

- Creatinine data was plotted to show the mean +/- standard deviation (SD) over time.
- Urinalysis test results were summarized at each assessed time point. A summary of changes in proteinuria from Baseline to maximum post-Baseline result was produced.
- A summary of Albumin/Creatinine ratio relative to ULN for subjects with Baseline values <= ULN was produced.

Adverse events

For DTG +ABC/3TC there were 3/679 subjects who reported reports of renal failure or renal impairment in total, one subject in ING114467 and two subjects in ING114915.

Creatinine and Creatinine Clearance

In ART-naïve subjects, small increases in mean and median creatinine were observed on the DTG + ABC/3TC arms. These were evident from Week 1 but plateaued with no evidence of subsequent increase.

There were 17 (3%) Grade 1 and 5 (<1%) Grade 2 post-Baseline emergent creatinine results, with no Grades 3 or 4 in subjects treated with DTG + ABC/3TC. In all of the subjects with Grade 2 levels the elevation occurred on a single occasion, but was not confirmed on repeat analyses. None of these subjects had associated increases in urinary albumin/creatinine ratio.

Urine Albumin/Creatinine ratio and Dipstick Protein Assessments

The normal range for albumin/creatinine ratios is <3.4 mg/mmoL. Albumin/creatinine ratios of 3.4 to 34 mg/mmoL are designated microalbuminuria and ratios >34 mg/mmoL macroalbuminuria. Macroalbuminuria is an indication for further investigation and consideration of referral to a nephrologist for possible institution of treatment.

Albuminuria was initially assessed by dipstick testing. However, the dipstick results appeared unreliable, particularly in the EFV controlled studies and the more accurate measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG + ABC/3TC on albumin excretion compared with EFV or RAL.

The change from Baseline in urine albumin/creatinine ratio could only be assessed in the Phase III studies, as this measurement was added to the Phase IIb studies by protocol amendments (no values were available for the Baseline). Overall, there were marginal changes in the median urine albumin/creatinine ratio in the DTG + ABC/3TC and comparator groups. Mean changes in comparator arms were occasionally skewed by large outliers, but there was no increase in the DTG + ABC/3TC treated groups. The increases were small; for the pooled DTG + ABC/3TC ART-naïve treatment group, 75% were less than 0.2 mg/mmol. Of those assessed with urine albumin creatinine ratios within the normal range at Baseline, only 3-5% of DTG + ABC/3TC and comparator treated subjects had increased to >ULN at any Week from Week 24-Week 96 in studies ING113086 and ING114467. In study ING114915 the corresponding figure was 8% of subjects in both arms (DTG + ABC/3TC and DRV+RTV) but this was a small sample and only represented four subjects in each arm.

Ischemic Cardiac Disorders

Some observational studies have suggested an association between myocardial infarction (MI) and the use of ABC. However cumulative data from observational cohorts and controlled clinical trials on the risk of MI with ABC show some inconsistency and can neither confirm nor refute a causal relationship. To date, there is no established biological mechanism to explain a potential increase in risk. As a precaution, the Company RSI and Local Country Prescribing Information for each of the ABCcontaining products recommends that Health Care Professionals should consider the underlying risk of coronary heart disease when prescribing antiretroviral therapies, including ABC, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

The company reviewed AEs relating to ischemic cardiac disorders. Any preferred terms related to ischemic cardiac disorders were identified from the integrated and pooled data from the pivotal and supporting clinical trials in ART- naïve Adult Subjects, and were included in the AESI summary tables. This included preferred terms myocardial infarction, angina pectoris and coronary artery disease. There is little evidence from the non-clinical and clinical trial program for an effect of DTG + ABC/3TC on cardiovascular disease. No subjects receiving DTG+ABC/3TC were reported with MI or any other ischemic cardiac events, after 1067 subject years of follow up in the pooled DTG+ABC/3TC treatment group. The frequency of events reported from the cardiac disorders SOC over all was generally low and comparable across studies and treatment groups. There was slight imbalance for DTG+ABC/3TC compared to DRV+RTV+ABC/3TC in ING114915 (2/79 [3%] and 0/80 subject reporting events from the cardiac disorders SOC). These were nonischemic in nature (tachycardia and cardiac failure).

Gastrointestinal disorders

The primary nonclinical finding for DTG from repeat dose toxicity studies up to 38 weeks in monkeys and 26 weeks in rats was GI intolerance.

From aggregate analyses of the Phase IIb and Phase III clinical trial data performed as part of the initial marketing applications for DTG, mild to moderate events indicative of general GI intolerance (mainly diarrhoea and nausea) are associated with DTG treatment in a small proportion of subjects, and are listed as adverse reactions in the company reference safety information for DTG. However, nonclinical findings for GI erosions did not translate into significant clinical findings.

As listed in the approved product labeling, the most commonly reported AEs for ABC and/or 3TC have been gastrointestinal in nature (nausea, vomiting, abdominal pain, and diarrhoea listed as common ADRs).

Data was medically reviewed for AE Preferred Terms that were considered indicative of general GI Intolerance, GI ulceration lesion or pancreatitis.

From the analysis of available data from the DTG development program, the risk of general GI intolerance with DTG/ABC/3TC is not expected to be greater than the risk associated with the single entities when used in CART with other ARV agents.

Overall frequency of GI events was similar between treatment groups in ING1144667 (compared to EFV) and ING113086 (compared to RAL+ABC/3TC) but higher in DRV+RTV+ABC/3TC compare to DTG+ABC/3TC in the ING114915 study.

Reporting rates for diarrhoea differed by study. Rates for DTG+ABC/3TC were either comparable to Atripla and RAL+ABC/3TC or lower than DRV+RTV+ABC/3TC. Nausea and vomiting were also commonly reported, and rates were comparable across ING114467, ING113086 and the total DTG+ABC/3TC treatment group. In ING114915 more subjects in the DRV+RTV+ABC/3TC group reported nausea and vomiting than for the DTG+ABC/3TC group in this study, and rates for the latter treatment group were comparable with DTG+ABC/3TC group overall (679 pooled subjects) and across the other studies. The majority of events indicative of general GI intolerance were of Grade 1 to Grade 2 intensity, and only few drug-related events of Grade 3 to Grade 4 were reported in the ING114467 with same frequency in both treatment groups. No events of general GI intolerance were reported as SAEs. Few GI events resulted in the permanent discontinuation of IP and subject withdrawal, with <1% (2/679, n=1 diarrhea; n=1 gastro esophageal reflux, both Grade 3) in the total DTG+ABC/3TC treatment group.

Few subjects were reported with events suggestive of GI ulcerative lesion across the studies and treatment groups. Dyspepsia and gastro esophageal reflux disease (GERD) were most commonly reported at similar rates across studies and treatment groups, with an exception of higher frequency of GERD in the DTG+ABC/3TC group and dyspepsia in the DRV+RTV+ABC/3TC group in the ING114467 and the ING114915 respectively.

In ING114467, a higher number of subjects in the DTG+ABC/3TC FDC treatment group developed GERD compared to Atripla. The majority of these GERD episodes were Grade 1 to 2 in intensity. No serious cases were reported and no subjects were permanently discontinued from IP and WD from study due to GERD.

Terms indicating potentially more severe GI complications (such as hematochezia/diarrhoea hemorrhagic/anal hemorrhage, duodenal ulcer, gastric ulcer, Crohn's disease, erosive duodenitis and erosive esophagitis) were rarely reported with no real patterns between treatment groups.

Two events of pancreatitis were reported in one subject in the DTG+ABC/3TC treatment group in ING114915. Neither event was considered drug related by the investigator who attributed both events to alcoholism.

Psychiatric Disorders Including Suicidality

From analysis of integrated Phase IIb and III clinical trial data performed for the initial marketing applications for the DTG SE, the psychiatric profile for DTG (incl. suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was favourable compared with EFV and similar to RAL.

The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared to EFV in ING114467, this was not duplicated by any other Phase IIb/III study conducted with DTG.

The appliacant further evaluated psychiatric events, including insomnia, with DTG+ABC/3TC. Psychiatric terms were identified from the integrated and pooled data from the pivotal and supporting clinical trials in ART- naive Adult Subjects, and were included in the SAS AESI summary tables in the FDC ISO.

Insomnia

Subjects in the DTG + ABC/3TC treatment group in ING114467 were significantly more likely to develop insomnia (i.e., RR values and 95% CI were >1) (p=0.021). This was not seen in any of the other Phase IIb to IIIb studies conducted with DTG.

There are several possibilities to explain the higher rate of insomnia in ING114467.

Primarily, this is possibly an artifact of the double blinded comparison with the EFVcontaining STR, Atripla, which has an ADR profile significant for psychiatric disorders. This has been seen in other double blinded clinical trials including an EFV treatment arm.

Secondly, ING114467 was the first study, and the only double blinded study, in the DTG development program that employed the ACTG SDM, which questioned subjects about specific potentially bothersome symptoms, at Day 1, Week 4, Week 24, Week 48 and Week 96. It is possible that this SDM influenced subjects reporting insomnia (difficulty falling or staying asleep, which could include abnormal dreams) to their Investigator/designee as AEs during routine study visits, particularly given the known AE profile for EFV. Additionally, the higher reporting rates for diarrhoea and fatigue for ING114467 in comparison to ING113086 (both the total safety population are possibly attributable to the use of this tool).

Suicidal ideation and behaviours

The reporting rates for AE PTs containing depression, bipolar, suicide and hypomania were low and generally comparable across studies and treatment groups. Events were generally mild to moderate intensity with few Grade 3 or 4 events and/or SAEs reported; none were fatal (i.e., there were no events of completed suicide).

In ING114915, more episodes were reported in the DTG+ABC/3TC treatment group than in the DRV+RTV+ABC/3TC treatment group (5/79 [6%] and 2/80 [3%], respectively). Rates were slightly higher for study ING114467, and reporting rates were higher for Atripla than for DTG+ABC/3TC (40/414 [10%] and 35/419 [8%], respectively.

Anxiety

Reporting rates for anxiety were low and comparable between treatment groups and across the Phase III to IIIb clinical trials, ranging from 3% to 7% for the DTG+ABC/3TC treatment groups and 4% to 7% for the comparator treatment groups. The majority of subjects developed single episodes, with few subjects from either treatment group in ING114467 and from the RAL+ABC/3TC treatment group in ING113086 reporting multiple episodes. Drug related episodes were reported only for ING114467, and were numerically higher for Atripla (11/419 [3%]) compared to DTG+ABC/3TC (4/414 [1%]).

Immune Reconstitution Inflammatory Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of ART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. A higher rate of IRIS is a potential concern with DTG due to the rapid viral load decline and CD4 cell count recovery associated with DTG based regimen.

There were few subjects with an NRTI backbone of ABC/3TC who were adjudicated as having definite or possible IRIS events. The numbers were too small to discern a pattern and the numbers were similar between the DTG + ABC/3TC groups and comparators.

Neoplasms, Benign, Malignant, and Unspecified (including Cysts and Polyps)

HIV-infected individuals have an increased risk of developing cancer – both AIDS-defining malignancies (ADM) and non-AIDS defining malignancies (NADM). In a large U.S.-based study, 10% of HIV-infected individuals developed cancer [Crum-Cianflone, 2009].

Neither ABC nor 3TC were mutagenic in bacterial tests, but consistent with other nucleoside analogues, both inhibit cellular DNA replication in in-vitro mammalian tests such as the mouse lymphoma assay. The results of an in-vivo rat micronucleus test with abacavir and 3TC in combination were negative. Lamivudine (3TC) has not shown any genotoxic activity in the in-vivo studies at doses that gave plasma concentrations up to 40-50 times higher than clinical plasma concentrations. Abacavir has a weak potential to cause chromosomal damage both in-vitro and in-vivo at high tested concentrations.

Carcinogenicity studies with orally administered ABC in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. The clinical relevance of these findings is unknown.

There were no reports of malignancies considered by Investigators to be related to ABC from the adult and paediatric clinical trial program; however it is recognized that these studies characterized the short-term safety profile, and were limited in terms of information on long-term safety.

Non-clinical studies indicated that DTG was not carcinogenic to mice at doses up to 500 mg/kg/day or rats at doses up to 50 mg/kg/day following oral administration for 104 consecutive weeks. In both species, DTG administration had no effect on survival, there were no treatment related clinical signs, and there were no neoplastic or non-neoplastic findings attributed to DTG. The NOAEL for non-neoplastic findings after chronic oral administration was the high dose of 500 mg/kg/day for mice and 50 mg/kg/day for rats.

When compared to the anticipated human exposure for a 50 mg once daily or 50 mg BID dose, the systemic exposures were ~20X or ~14X and ~17X or ~12X higher for mice and rats, respectively. On analysis of pooled Phase IIb and III clinical trial data from the DTG development program conducted

for the initial marketing applications for the DTG SE, there was no evidence for increased risk of neoplasms with DTG.

The applicant reviewed data for AE PTs that were considered indicative of benign vs malignant neoplasms.

The majority of the AEs reported from the neoplasms benign, malignant and unspecified (including cysts and polyps) SOC were non-malignant and the rate was comparable between the treatment groups. The most frequently reported AEs in this SOC were anogenital warts and benign skin papillomas, occurring at similar rates across the treatment groups. All other events were reported at a rate of <1% in the total DTG+ABC/3TC group.

Few subjects developed malignant or potentially malignant events. All were isolated and occurred in only one subject, except basal cell carcinoma in the DRV+RTV+ABC/3TC group and squamous cell carcinoma in the DTG+ABC/3TC group, which occurred in two subjects.

Table 32. Summary of all AEs from the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps) – DTG + ABC/3TC FDC Pivotal and Supporting Studies in ART-Naïve Adults

	ING114467		ING113086		ING114915		ING112276		TOTAL
	DTG 50 mg + ABC/3TC Once Daily N=414 n (%)	EFV/TDF/FTC Once Daily N=419 n (%)	DTG 50 mg + ABC/3TC Once Daily N=169 n (%)	RAL 400 mg BID + ABC/3TC Once Daily N=164 n (%)	DTG 50 mg + ABC/3TC Once Daily N=79 n (%)	DRV + RTV 800 mg/100 mg + ABC/3TC Once Daily N=80 n (%)	DTG 50 mg + ABC/3TC Once Daily N=17 n (%	EFV 600 mg + ABC/3TC Once Daily N=16 n (%)	DTG 50 mg + ABC/3TC Once Daily N=679 n (%)
Any event	38 (9)	39 (9)	17 (10)	17 (10)	4 (5)	7 (9)	2 (12)	0	61 (9)
Malignant events									
Basal cell carcinoma	1 (<1)	0	0	0	0	2 (3)	0	0	1 (<1)
Hodgkin's disease	0	1 (<1)	0	0	1 (1)	0	0	0	1 (<1)
Squamous cell carcinoma	2 (<1)	0	0	0	0	0	0	0	2 (<1)
Burkitt's lymphoma	0	0	0	0	0	0	1 (6)	0	1 (<1)
Colon cancer	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Kaposi's sarcoma	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Lung neoplasm malignant	0	0	0	1 (<1)	0	0	0	0	0
Malignant melanoma	0	1 (<1)	0	0	0	0	0	0	0
Ovarian cancer	0	1 (<1)	0	0	0	0	0	0	0
Total	5	3	1	1	1	2	1	0	7
Non-malignant events									
Anogenital warts	21 (5)	19 (5)	8 (5)	7 (4)	1 (1)	2 (3)	0	0	30 (4)
Skin papilloma	8 (2)	7 (2)	4 (2)	5 (3)	0	1 (1)	0	0	12 (2)
Lipoma	3 (<1)	3 (<1)	0	0	1 (1)	2 (3)	0	0	4 (<1)
Papilloma	0	0	0	2 (1)	1 (1)	0	1 (6)	0	2 (<1)
Melanocytic naevus	0	2 (<1)	1 (<1)	0	0	0	0	0	1 (<1)
Acrochordon	0	0	1 (<1)	1 (<1)	0	0	0	0	1 (<1)
Fibroma	0	1 (<1)	0	1 (<1)	0	0	0	0	0
Seborrhoeic keratosis	0	1 (<1)	1 (<1)	0	0	0	0	0	1 (<1)
Adenoma benign	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Anal neoplasm	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Benign breast neoplasm	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Bone neoplasm	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Chondroma	0	1 (<1)	0	0	0	0	0	0	0
Degeneration of uterine leiomyoma	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Dysplastic naevus	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Fibroadenoma of breast	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Haemangioma of liver	0	0	0	1 (<1)	0	0	0	0	0
Morton's neuroma	0	1 (<1)	0	0	0	0	0	0	0
Neoplasm	0	1 (<1)	0	0	0	0	0	0	0
Oral papilloma	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Schwannoma	0	0	1 (<1)	0	0	0	0	0	1 (<1)
Thyroid neoplasm	0	1 (<1)	0	0	0	0	0	0	0
Uterine leiomyoma	0	0	0	1 (<1)	0	0	0	0	0
Total	40	37	18	18	3	5	1	0	60

Torsades de Pointes

Non-clinical evaluation did not reveal an increased risk for cardiac conduction abnormalities with DTG.

A clinical pharmacology study has been conducted to investigate the effect of DTG on cardiac repolarization (ING111856). A single supra-therapeutic dose of DTG (250 mg) had no significant effect on cardiac repolarization in a population of 42 healthy subjects (approximately 60% female), when compared to moxifloxacin (400 mg; active control) or placebo. In this study with demonstrated ability to detect small effects, the upper bound of the two-sided 90% confidence interval for the largest placebo adjusted, QTcF was below 10 msec, the threshold for regulatory concern. The maximum

observed timematched change from Baseline in QTcF for DTG 250 mg was at 4h (mean ΔΔQTcF of 1.99 msec, 90% CI: -0.55, 4.53 msec). The maximum observed time-matched change from Baseline in QTcF for moxifloxacin was at 4h (mean ΔΔQTcF 9.58 msec, 90% CI: 7.05, 12.11 msec). Since the study had adequate sensitivity to detect a positive QT effect with moxifloxacin, it is concluded that this study was valid to assess the effects of DTG on cardiac repolarization. The dose of 250 mg using a suspension formulation yielded a maximum DTG plasma concentration of 12.4 µg/mL (range: 5.33-20.5 µg/mL), which was ~2.4 fold above mean C_{max} associated with the 50 mg once daily and 50 mg BID doses.)

All subjects in DTG treatment group with QTcF or QTcB >500msec were asymptomatic. Several subjects had clinically significant abnormalities but no trends were observed in these abnormalities. No difference in frequencies of clinically significant abnormalities were observed between arms in individual studies.

No cases of TdP or sustained ventricular tachycardia have been reported in the ARTNaïve or ART-experienced (INI Naïve) adult clinical trials. Few AEs potentially related to TdP were reported. (i.e., MedDRA AE preferred terms indicative of clinical events including, but not limited to: TdP; sudden death; ventricular tachycardia; ventricular fibrillation and flutter; syncope; seizures).

All AEs were reported at a rate of <1% or in single subjects (ING114915), except syncope (1%) in the Atripla arm in ING114467. Four convulsion-related events were reported in total, one grand mal convulsion and one epilepsy on DTG (confounded by alcohol consumption and lack of sleep, and head injury), one convulsion on Atripla (subject had recently stopped anticonvulsant treatment) and one status epilepticus on RAL. No cases of arrhythmia were reported across the treatment groups.

One case of a non-serious cardiac failure was reported with DTG + ABC/3TC in study ING114915 and was considered related to IP.

Safety in special populations

As agreed in the DTG/ABC/3TC Paediatric Investigation Plan (PIP) with the Paediatric Committee (PDCO) (EMEA-001219), there is no plan to conduct a paediatric clinical study of the DTG/ABC/3TC (50 mg/600 mg/300 mg) FDC in adolescents. This tablet formulation is intended for adults and adolescent populations (i.e., ≥12 to <18 years) who weigh at least 40 kg.

The proposed adolescent indication for DTG/ABC/3TC is supported by ING112578 (P1093), cohort I (12 to <18 years), which provides clinical data regarding DTG pharmacokinetics and long term safety and efficacy (24 week). No subjects received ABC and 3TC alongside DTG.

ABC and 3TC are approved for twice daily (BID) use in children aged 3 months to 18 years dosed individually and from 12 to 18 years when given once daily as the ABC/3TC FDC. The indication includes ART naïve and ART experienced populations. Hence the safety profile of these components in this age group has been established and monitored for several years.

Finally, the adult Phase III data in subjects receiving DTG+ABC/3TC provides long term safety and efficacy which can be extrapolated to support adolescents who have similar absorption, distribution, metabolism and elimination of the individual entities.

Use in Pregnancy and Lactation

No clinical reprotoxicity studies have been conducted with DTG+ABC/3TC.

Based on animal data, DTG is not anticipated to increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with dosing information in the product label. Findings for 3TC in the rabbit suggest a potential risk of early embryonic loss. Moreover, there is some evidence of mitochondrial toxicity following exposure to lamivudine in utero in different non-clinical studies. Evidence of early embryo lethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 32 times those in humans (based on C_{max}). Studies in humans have confirmed that 3TC crosses the placenta. Abacavir demonstrated toxicity to the developing embryo and foetus in rats at maternally toxic doses of 500 mg/kg/day and above. This dose is equivalent to 33 times human therapeutic exposure based on AUC. The findings included foetal oedema, variations and malformations, resorptions, decreased foetal body weight and an increase in still births. The dose at which there were no effects on pre or post-natal development was 160 mg/kg/day. This dose is equivalent to an exposure of about 9 times that in humans. Similar findings were not observed in rabbits.

Twenty-one pregnancies were reported across the pivotal and supporting study populations for the DTG/ABC/3TC FDC. Few cases resulted in an adverse pregnancy outcome (e.g., spontaneous abortion or ectopic pregnancy), and were comparable for DTG+ABC/3TC, RAL+ABC/3TC and Atripla, and no congenital anomalies were reported.

Pregnancy Outcomes for 20 Cumulative Cases involving ART- naive HIV infected Female Subjects[a] (DTG+ABC/3TC Data Sets)

Outcome	DTG	Atripla	RAL	DRV+ RTV	Total
Live infant, no apparent congenital anomaly	4	2	1	-	7
Elective termination, no apparent congenital anomaly	4	1	1	-	6
Spontaneous abortion, no apparent congenital anomaly	1	2	-	-	3
Ectopic pregnancy	-	1	-	-	1
Pregnancy ongoing or unknown	1	1	-	1	3
Total	**10**	**7**	**2**	**1**	**20**

a. Directly administered IP: DTG+ABC/3TC in ING114467 & ING113086; Atripla in ING114467; RAL+ABC/3TC in ING113086; and DRV+RTV+ABC/3TC in ING114915

As DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals and 3TC and ABC have been associated with findings in animal reproductive studies, administration of DTG/ABC/3TC in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus.

3TC and ABC are excreted in human milk and have some detectable exposure levels in breastfed infants. However, this exposure seems to be well below therapeutic levels. It is expected that DTG will also be secreted into human milk based on animal data, although this has not yet been confirmed in humans.

The reference safety information for DTG/ABC/3TC will recommend that, where possible, HIV infected women do not breast-feed their infants in order to avoid transmission of HIV.

Discontinuation due to adverse events

DTG +ABC/3TC

AEs leading to permanent discontinuation of IP and withdrawal (WD) from the study were more commonly reported for the Atripla and EFV treatment groups compared to DTG +ABC/3TC, which had rates comparable to RAL +ABC/3TC and DRV + RTV +ABC/3TC

With the exception of dizziness, fatigue, abnormal dreams, depression and headache in the ING114467 Atripla group, all other individually reported AE PTs resulting in withdrawal or permanent discontinuation had a reporting rate of <1% across all treatment groups or were reported in one subject in ING112276, which had small treatment populations.

2.6.1. Discussion on clinical safety

There is no experience with the co-formulated DTG/ABC/3TC FDC tablets in HIV-infected patients. In total, within the bioequivalence study (ING114580) 66 healthy subjects have received the co-formulated tablets. The short term data showed no tolerability differences between the single entities and the FDC. The tolerability and safety of DTG/ABC/3TC FDC is expected to be similar to the safety and tolerability of the single entity DTG combined with ABC/3TC FDC.

Therefore, the evidence for the safety of DTG/ABC/3TC FDC comes from studies in which HIV-infected subjects received DTG + ABC/3TC. Moreover, the safety data on the individual components is regarded as supportive. In total, 679 HIV-1 infected ART-naïve (INI naïve) subjects received DTG 50 mg once daily + ABC/3TC 600/300 mg once daily in studies, totalling exposure to 1066.5 person years. There is only limited experience with DTG+ABC/3TC in an ART-experienced (INI- naïve) patient populations. A total of 9 ART-experienced (INI-naïve) subjects received DTG + ABC/3TC. All subjects were HLA*B5701 negative.

The most common adverse events occur at a similar or lower rate in the DTC+ABC/3TC groups compared to other treatment arms. The exception is insomnia, which was reported to occur more frequently compared to EFV, but the frequency was much higher than in the studies with DTG. Notably there was a much higher number of certain AEs, including possibly drug related AEs, in the Atripla arm in this study. There was one death amongst patients receiving DTG, ABC, 3TC which was unrelated to treatment. There was no clear trend for DTG +ABC/3TC regarding the drug related SAEs.

The most important risk associated with ABC is a well characterized, idiosyncratic, drug-related hypersensitivity reaction. Appropriate risk minimisation includes pro-active screening for the presence of this allele and restricting abacavir to patients who are HLA-B*5701 negative unless no other treatment options are available. Boxed warnings are included in section 4.4 and 4.8 including detailed information describing the reactions and clinical management of hypersensitivity reactions. The potential severe hypersensitivity reaction to DTG in subject 4259 formed the main safety concern for the CHMP with implications for the RMP when assessing the dossier for dolutegravir. The detailed and adequate warning around these events has been included in section 4.4 of the SmPC. Future follow-up of such reactions are an important part of the RMP.

The MAH was requested to clarify how many patients with severe rash and HSR, that resulted in cessation of ABC, were allowed to continue DTG. Account of their follow up including time to resolution of symptoms was provided.

Liver toxicity is a potential safety concern for DTG based on high dose repeat toxicity in cynomolgus monkeys, where dose related liver reactions were noted. This was not reflected in clinical studies, where liver safety appears comparable between DTG+ ABC/3TC and control arms.

Since baseline characteristics of included subjects did not imply the inclusion of subjects with high myocardial risk and the period of observation was at most 96 weeks, not much can be said about the association of ABC and myocardial infarction. The same precautions as have been documented for ABC will apply to Triumeq.

Mild to moderate episodes of rash were commonly reported for DTG+ABC/3TC FDC. The rate and nature of rash with DTG+ABC/3TC FDC was no different to that observed for comparators in the Phase III/IIIb development program or observed historically for the individual actives DTG, ABC and 3TC.

An immediate, mild and non-progressive increase in creatinine is seen at low doses of dolutegravir. The increase of serum creatinine is not considered clinically relevant.

2.6.2. Conclusions on the clinical safety

Overall, tolerability and safety of DTG/ABC/3TC FDC is expected to be as the safety and tolerability of DTG combined with ABC/3TC FDC. The safety and tolerability of ABC/3TC is well characterized with considerable post marketing evidence, as well as a large amount of data from clinical trials.

The safety of DTG has recently been reviewed in context of the MAA for DTG. The main identified safety concern of the CHMP was hypersensitivity, including hepatic toxicity. The most important risk associated with ABC is a well characterized, idiosyncratic, drug-related hypersensitivity reaction.

Since the number of elderly subjects was limited in the pivotal SINGLE study, the FDC DTB/ABC/3TC may not be the preferred regimen especially in elderly HIV patient with additional cardiovascular risk factors. Future follow up of elderly patients should help to elucidate to contribution of ABC to increased cardiovascular risk.

All of the adverse reactions and laboratory abnormalities listed in the RSI and SmPCs for the individual active moieties (DTG, ABC and 3TC) are also presented in the RSI and SmPC for DTG/ABC/3TC FDC.

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**

Summary of safety concerns The safety profile of DTG taken in combination with ABC and 3TC is consistent with the safety profiles of the single agents, and no additional risks or safety issues due to combination therapy have been identified.	
Important identified risks	**DTG, ABC** Hypersensitivity reactions **DTG** Hepatobiliary disorders Drug Interactions
Important potential risks	**DTG, ABC and 3TC** IRIS **DTG** Serious rash (DAIDS grade 3 and 4) Renal disorders GI Intolerance and erosions Muscoskeletal events/ elevated CPK elevations Lipase elevations (grade 3 and 4) Psychiatric disorders Phototoxicity **ABC, 3TC** Carcinogenicity and long term exposure to NRTIs **ABC** Cardiac events leading to ischaemia Exposure to ABC during pregnancy Use in patients with moderate/severe hepatic impairment Drug interaction between ABC and RBV
Missing information	Use in the elderly Use in paediatrics Use in pregnancy/ breastfeeding Use of DTG in patients with severe hepatic impairment Long term safety data Affinity of DTG to melanocortin receptors

- **Pharmacovigilance plans**

On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Safety concerns addressed	Date for submission
Prospective Observational Cohort Study of Hypersensitivity in Patients Receiving DTG or DTG/ABC/3TC (category 3)	HSR Hepatotoxicity Serious rash	Final report anticipated April 2020 or 10 months after study completion
Affinity of DTG to melanocontin Receptors (category 3)	Interaction with melanocontin receptors	Q4/2014
Phototoxicity study (category 3)	Phototoxocity	Q4/2014
In vitro study to determine if DTG is a substrate of OATP1B1 and OATP1B3 (category 3)	Potential drug interaction	Q2/2014
Midazolam drug interaction study justification (category 3)	To asses the potential for an interaction with midazolam	Completed (currently under review by EMA) Submitted for DTG Jan 2014
Study ING112578 (P1093)	Use of DTG in paediatric subjects <12 years old Will provide basis for weight band DTG target exposures for future DTG/ABC/3TC FDC	Cohort 1&2a (6-18yrs) data available 2Q2014

Study / activity Type, title and category (1-3)	Safety concerns addressed	Date for submission
	paediatric formulations	Cohort 2b&3 (2-12 years) data Available 1Q2016 Cohort 4&5 (4Weeks -2 years) data available 2Q217 Final data expected 2020 (includes 3 year follow-up period).

- **Risk minimisation measures**

The PRAC considers that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

- Educational material for healthcare professionals to address the risk(s) of abacavir-associated hypersensitivity
- Patient alert card to address the risk(s) of abacavir-associated hypersensitivity

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risks – DTG and ABC		
Hypersensitivity	Information relating to HSR is included in modules 4.3, 4.4 and 4.8 of the SmPC.	Each pack of TRIUMEQ medication contains an Alert Card for patients and information on the risk of HSR with ABC in the Patient Information Leaflet. TRIUMEQ will be added to the Applicants existing ABC HSR education materials for healthcare professionals, which are used in all countries where the Applicant has marketing authorisation for any ABC- containing product.
Identified Risks – DTG		
Hepatobiliary disorders	A warning is included in module 4.4 of the SmPC with respect to management of HBV/HCV infected patients. Hepatitis is also included as an ADR in module 4.8 of the SmPC.	None
Drug Interactions	A contraindication with dofetilide is included in module 4.3 of the SmPC and further information provided in module 4.5.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential Risks DTG, ABC and 3TC		
IRIS	Information on IRIS is included in module 4.4 and 4.8 of the SmPC.	None
Potential Risks – DTG		
Serious rash (DAIDS Grade 3 or 4)	Rash is included as an ADR in module 4.8 of the SmPC. A warning and precaution around rash as part of a hypersensitivity reaction is included in module 4.4 of the SmPC.	None
Renal disorders	Information on increases in serum creatinine levels with DTG is included in module 4.8 of the SmPC.	None
Gastrointestinal erosion and intolerance	Information around GI intolerance is included in module 4.8 of the SmPC. Pre-clinical data around GI intolerance is also presented in Section 5.3 of the SmPC	None
Lipase elevations	None	None
Psychiatric disorders	Insomnia, abnormal dreams, depression, nightmare and sleep disorder are included in module 4.8 of the SmPC	None
Musculoskeletal events and CK elevations	Data on asymptomatic CPK elevations is included in module 4.8 of the SmPC	None
Phototoxicity	None	None
Potential Risks – ABC and 3TC		
Long term risk of carcinogenicity	Section 5.3 of the SmPC describes non-clinical findings in relation to mutagenicity and carcinogenicity although the clinical relevance is unknown.	None
Potential Risk ABC		
Ischaemic cardiac events	Section 4.4 advises that data relating to an association between ABC and a risk of myocardial infarction is inconsistent and no biological mechanism has been identified. Further advice is given relating to action to be taken to try to minimize all modifiable risk factors (e.g.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	smoking, hypertension and hyperlipidaemia).	
Use in pregnancy[1]	Section 4.6 of the SmPC states that TRIUMEQ should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus Section 5.3 of the SmPC describes findings in reproductive toxicology studies in rats.	None
Use in patients with moderate/severe hepatic impairment[2].	Information on the use of DTG/ABC/3TC in patients with hepatic impairment is included in module 4.2, 4.4 and 5.2 of the SmPC.	None
Interaction between ABC and Ribavirin	Section 4.4 and 4.5 of the SmPC describes that ABC and RBV may interact when coadministered. It also states that clinical findings are conflicting and that caution should be exercised when both drugs are co-administered.	None
Missing information		
Use in Elderly	Information on the use of DTG/ABC/3TC in the elderly is included in module 4.2 and 5.2 of the SmPC.	None
Use in paediatrics	Information on the use of DTG/ABC/3TC in paediatrics is included in module 4.2, 4.8 and 5.2 of the SmPC.	None
Long term safety	None	None
Affinity of DTG to melanocortin receptors	None	None

[1]. Use in pregnancy is considered a potential risk for ABC and missing information for DTG
[2]. Use in moderate/ severe hepatic impairment is considered a potential risk for ABC. Use in severe hepatic impairment is considered missing information for DTG.

The CHMP endorsed this advice without changes.

2.9. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

Triumeq is a fixed-dose combination of dolutegravir, abacavir and lamivudine (50/600/300 mg) intended as complete treatment regimen for treatment of HIV infection in adults and adolescents from 12 years of age. The MAH proposed the use in a patient population "who are treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in Triumeq."

The individual components (DTG and ABC/3TC FDC) are authorised for treatment of HIV-infection in adults and adolescents on a once-daily dosing regimen. In addition, both components, DTG 50 mg once daily and ABC/3TC FDC have been registered for use in patients experiencing virologic failure with the usual caveats on determination of resistance mutations which may preclude initiation of these ARVs in case of virologic failure on other combinations.

Bioequivalence was demonstrated between the FDC tablet and the combination of the single entities DTG plus ABC/3TC FDC (KIVEXA) (Study ING114580). Therefore, the results of efficacy and safety of the combination of the single compounds also are applicable to the FDC. Data was provided on comparative studies of the combination DTG+ABC/3TC versus EFV+TDF/FTC (Atripla) (the pivotal SINGLE study) and versus RAL+ABC/3TC and DRV/r+ABC/3TC (SPRING-2 and FLAMINGO, respectively).

Benefits

Beneficial effects

In the phase 3 program of dolutegravir, the combination found in Triumeq (abacavir/lamivudine + dolutegravir) showed superiority versus Atripla and yielded similar results as abacavir/lamivudine in combination with raltegravir or darunavir/ritonavir. Similar response rates were also seen with the "Triumeq-combination" and the other preferred NRTI-backbone, tenofovir/emtricitabine, given with an integrase inhibitor (dolutegravir or raltegravir), or darunavir/ritonavir. However, the choice of NRTI backbone in those studies where according to the discretion of the investigator.

Importantly, in the studies of interest for this application resistance development to the integrase class or the backbone NRTIs was fully lacking in those patients treated dolutegravir. Hence, the combination carries a high resistance barrier, which is of considerable clinical value.

Triumeq provides a regimen as 1 tablet taken once daily, and without regards to food intake. This increases the quality of life for patients , the compliance to the treatment, and also minimizes the risk for erroneous intake/dosing. In addition, in comparison to many other preferred HIV regimens, Triumeq has a relatively low risk for interactions with other medications often used by patients with HIV infection.

Uncertainty in the knowledge about the beneficial effects

As for all HIV products there is only llimited data available for the Triumeq combination in the females and in the elderly. This may be considered a safety issue, but likely not an efficacy issue. The same is true concerning in vivo efficacy data for HIV non-B subtypes. However, within the dolutegravir development program HIV subtypes other than B were fairly common in the SAILING study, without any signal for a lowered efficacy, which is in line with in vitro data. For abacavir/lamivudine HIV

subtype has not been considered an issue. For the specific Triumeq combination there is also limited data on efficacy in patients with severe immune suppression, taking into account the demographics in the phase 3 studies of relevance (SINGLE, SPRING-2 and FLAMINGO). However, from the dolutegravir development program as a whole there is convincing evidence that dolutegravir is highly effective in such patients. The shortcomings with regards to age groups and gender are reflected in the SmPC.

In two previous studies the abacavir/lamivudine components showed a signal for suboptimal efficacy in patients with a high baseline viral load (>100,000 copies/ml), which was not seen with tenofovir/emtricitabine. The studies relevant for the Triumeq application do not contain a blinded comparison between these two pairs of NRTIs in combination with dolutegravir. The only study which was fully blinded (also for the NRTI-components) was the SINGLE study, where abacavir/lamivudine + dolutegravir was compared to tenofovir/emtricitabine/efavirenz. Hence, it was not formally studied whether abacavir/lamivudine + dolutegravir (Triumeq) provides the same efficacy as tenofovir/emtricitabine + dolutegravirin patients with a high baseline viral load. However, the outcomes versus various preferred regimens in the studies presented are considered reassuring, in particular as no resistance development (to the integrase class or to the NRTIs) was seen in any patients who were treated with dolutegravir. The lack of a cautionary statement in Tirumeq SmPC is therefore endorsed.

Risks

Unfavourable effects

Nausea (12%), diarrhoea (5%), insomnia (7%) and headache (6%) were the most commonly reported drug-related AEs in HLA-B*5701-negative INI naïve adult subjects treated with DTG+ABC/3TC in the phase IIb and III trials. Frequencies of AEs were similar or lower for DTG+ABC/3TC arms compared to comparators EFV/TDF/FTC, or to RAL, DRV + RTV or EFV + ABC/3TC. The overall safety profile of DTG+ABC/3TC appears comparable to RAL+ABC/3TC and comparable or somewhat favourable compared to DRV+rtv + ABC/3TC and EFV/ATRIPLA.

The most important risk associated with ABC is a well-characterized, idiosyncratic, drug-related hypersensitivity reaction (HSR). HLA-B*5701 has been shown to be highly associated with ABC HSR, and the practice of pre-therapy screening for HLA-B*5701 and excluding from ABC therapy those individuals found to carry the allele, reduces the risk of HSR. Ten subjects receiving DTG+ABC/3TC reported AEs indicative of HSR, for which two were grade 3 to 4 intensity. Reporting rates were similar across studies and treatment groups. In the total DTG+ABC/3TC treatment group, HSR resulted in the permanent discontinuation of IP and subject withdrawal in 3 cases. The MAH was requested to clarify how many patients with severe rash and HSR resulting in cessation of ABC, were allowed to continue DTG. Information regarding their follow up, including time to resolution of symptoms, was provided for completeness.

One severe hypersensitivity reaction involving a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as a severe liver reaction (fulfilling Hy's law criteria) was reasonably attributable to DTG. This finding is an important safety concern and is adequately addressed in the RMP.

Severe skin reactions are recognized risks for the ABC constituent, and rash is a recognized adverse drug reaction for all three components of the DTG/ABC/3TC FDC.

Liver toxicity is a potential safety concern for DTG based on high dose repeat toxicity in cynomolgus monkeys, with whom dose related liver reactions were noted.

An immediate, mild and non-progressive increase in creatinine is seen already at low doses of dolutegravir. This is due to inhibition of OCT2 without affecting creatinine clearance. The increase of serum creatinine is not considered clinically relevant. This FDC does not result in nephrotoxicity associated with other ARVs (e.g. tenofovir).

The uncertainty around cardiovascular safety and abacavir in patients with high cardiovascular risk factors is reflected as in other abacavir containing products and is also included in the Triumeq SmPC as well.

Uncertainty in the knowledge about the unfavourable effects

The included HIV subjects were relatively young (median age 35 years), only 6 out of 833 patients in the SINGLE study were above 65 years of age. The associated cardiovascular risk of ABC may be increased in an elderly population or in younger patients with additional cardiovascular risk factors.

The frequency and causality of putative dolutegravir-related HSR, including hepatotoxicity, is not known.

There was a non-clinical signal for hepatotoxicity, however clinical studies do not indicate increased hepatotoxicity associated with the DTG/ABC/3TC regimen compared with EFV/TDF/FTC, a RAL containing regimen or a DRV+rtv containing regimen. Although the exposure with the dose used in humans compared with exposures seen at the NOAL in monkeys is substantially lower, liver toxicity will be followed up in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Benefit-risk balance

The potent antiretroviral efficacy of the combination DTG/ABC/3TC including the high barrier to resistance, the tolerability of this combination in HLA*B5701 negative subjects, the lack of CYP3A4 interactions and the simplicity of the dosing regimen make the FDC DTG/ABC/3TC a favourable addition to the antiretroviral armamentarium in HIV-infected patients. Potential DTG-related HSR has been recorded but the HSR of ABC in HLA*B5701 negative subjects is well established and sufficiently addressed in the SmPC. Future follow-up of hypersensitivity reactions are an important part of the RMP. The overall safety profile of DTG/ABC/3TC is considered comparable to RAL+ABC/3TC and somewhat favourable compared to DRV/rtv + ABC/3TC and Atripla.

Discussion on the benefit-risk balance

Single tablet regimens are known to support patient's acceptance and compliance. Two additional features make this STR of additional benefit to patients: no need to take DTG/ABC/3TC with food (in contrast to DRV) or on a empty stomach (in contrast to Atripla) and the lack of CYP3A4 interactions. The FDC DTG/ABC/3TC offers a new STR treatment option in the HLA-B*5701-negative population with a high efficacy and a high barrier to resistance. The absence of TDF might be beneficial in some patients at risk of renal insufficiency or osteopenia, although this FDC of DTG/ABC/3TC cannot be administered in patients with creatinine clearance < 50 ml/min due to dose restrictions of 3TC. A DTG-based regimen might also offer a suitable alternative for patients failing on ARVs with virus resistance to NNRTIs or protease inhibitors. Although data on the combination of DTG plus ABC/3TC in the

treatment-experienced population failing on a first line regimen that did not include an INI, is lacking, it is considered acceptable to extrapolate the efficacy in the treatment-naïve to the treatment-experienced patients, as long as existing mutations do not preclude the start of any of the three antiretroviral agents within the combination. Additional support for this extrapolation can be derived from the licensing of both compounds for patients experiencing virologic failure. This is adequately addressed in the SmPC. Furthermore in patients who are HLA*B5701 negative switch from other STRs to DTG/ABC/3TC may be possible in case of intolerability of other regimens while virus is suppressed, because of tolerability benefits.

Hence, the proposed indication by the MAH that explicitly addresses both treatment-naïve patients and patients failing on other regimens, is considered over-complete. The concise indication of the individual components ('the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age') should also apply to this FDC. Further elaboration of efficacy in patients experiencing virologic failure, the relative lack of clinical data in case of virologic failure in first line regimens and a clinical appraisal of documented resistance mutations in these patients should be addressed in section 4.4 and 5.1 to guide treatment decisions.

Two potential drawbacks of the combination of abacavir plus lamivudine are known; inferior efficacy in patients with high baseline viral load and the possible association with increased risk of myocardial infarction both in comparison with other NRTIs as backbone. Whether the benefits described above also apply to patients with high baseline viral load when ABC/3TC is used with the potent antiretroviral agent DTG is yet insufficiently substantiated in the submitted studies or cannot be refuted because of low numbers of patients with unfavourable disease characteristics. However, the outcomes versus various preferred regimens in the studies presented are considered reassuring. The same reservations about use of the FDC DTG/ABC/3TC in patients with cardiovascular risk factors apply, since few elderly patients were exposed. These precautions have been incorporated in the SmPC of the FDC DTG/ABC/3TC.

There are no quality issues which impact the safety profile and influence the benefit/risk balance.

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 Triumeq in the treatment of HIV infection 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.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe Triumeq are provided with a health care professional information pack containing the following:

- The Summary of Product Characteristics
- ABC HSR educational material for health care professionals

Key elements included in the educational material to increase understanding and awareness of ABC HSR and expand on the information already included in the SmPC:

1. Major symptoms associated with ABC HSR are fever (~80%), rash (~70%), gastrointestinal symptoms (>50%) such as nausea, abdominal pain, vomiting, and diarrhoea, generalise malaise, fatigue, and headache (~50%) and other symptoms (~30%) such as respiratory, mucosal, and musculoskeletal symptoms.

Based on the above patients are advised to contact their physician immediately to determine whether they should stop taking abacavir if:

- presence of skin rash; OR
- development of 1 or more symptom from at least 2 of the following groups:

- Fever
- Shortness of breath, sore throat or cough
- Nausea or vomiting or diarrhoea or abdominal pain
- Extreme tiredness or achiness or generally ill feeling

2. Risk factors for ABC HSR

HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an ABC HSR reaction. However, some patients with a suspected ABC hypersensitivity reaction may not have the HLA-B*5701 allele.

3. Recommendations for HLA-B*5701 screening

Before initiating abacavir therapy, clinicians should screen for HLA-B*5701(in settings where validated screening methods are available). Clinical diagnosis of suspected hypersensitivity to ABC remains the basis for clinical decision making. HLA-B*5701 screening for risk of ABC hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving ABC. If ABC hypersensitivity cannot be ruled out on clinical grounds, ABC should be permanently discontinued and should not be restarted, regardless of the results of HLA-B*5701 screening. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.

4. Information on HLA-B*5701 testing

The one-time HLA-B*5701 test identifies people at high risk for this serious allergic reaction. The gold standards for HLA-B*5701 screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide probes. Blood or saliva samples are collected and tested for genetic sequences coding for the HLA-B*5701 allele. Results of PREDICT-1 and SHAPE studies show that the presence of the HLA-B*5701 allele is associated with increased risk of ABC hypersensitivity, regardless of race, screening for HLA-B*5701 before starting treatment with ABC may identify subjects at increased risk of a HSR, avoiding treatment with ABC in subjects with the HLA-B*5701 allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity. Data from these studies do not support the use of skin patch testing in routine clinical practice. Only patients found to lack the HLA-B*5701 allele should begin therapy with ABC.

5. Management of ABC HSR reaction

Symptoms can occur at any time during treatment with ABC, but usually occur within the first 6 weeks of therapy. Symptoms are initially mild and evolve over days, becoming more severe with continued ABC therapy. Symptoms improve on cessation of ABC. Rechallenge can result in a more rapid and severe reaction, which can be fatal, therefore rechallenge is contraindicated.

6. Hypersensitivity case studies

The educational material includes 3 case studies to demonstrate different clinical scenarios and their management.

New Active Substance Status

Based on the review of data, the CHMP considered that the active substance dolutegravir was to be qualified as a new active substance at time of submission of this application. On 16 January 2014 a marketing authorisation valid throughout the European Union for dolutegravir (Tivicay) was granted.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0287/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.