Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dolutegravir sodium/Abacavir sulfate/Lamivudine

Proprietary Product Name: Triumeq

Sponsor: ViiV Healthcare Pty Ltd

May 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
λx	Terminal phase elimination rate constant
3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
ALT	Alanine aminotransferase
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC (0 - ∞)	Area under the concentration-time curve from time zero to infinity
AUC (0 – 24)	Area under the concentration-time curve from time zero to 24 hours
AUC (0 – τ)	Area under the concentration-time curve over the dosing interval
%AUCex	Percentage of AUC(0 - ∞) obtained by extrapolation
BD	Twice daily
BID	Twice daily
BCRP	Breast cancer resistance protein
BilT	Total bilirubin
BMI	Body mass index
BP	Blood pressure
C24	Concentration at 24 hours
CDC	Centres for Disease Control
CER	Clinical evaluation report
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent clearance after oral administration

Abbreviation	Meaning
Cmax	Maximum observed concentration
c/mL	Copies per millilitre
CPK	Creatine phosphokinase
CSF	Cerebrospinal fluid
CSR	Clinical study report
C	Concentration
CV	Coefficient of variation
CVw	Within subject coefficient of variation
dL	Decilitre
DNA	Deoxyribonucleic acid
DRV	Darunavir
DRVr	Darunavir plus ritonavir
DRV + RTV	Darunavir plus ritonavir
DTG	Dolutegravir
ECG	Electrocardiogram
EFV	Emtricitabine
ABC/3TC	Epzicom
ERDF	Efficacy related discontinuation = failure
ETR	Etravirine
EU	European Union
FC	Fold change
FDA	Food and Drug administration
FDC	Fixed dose combination
FTC	Emtricitabine
GCP	Good clinical practice
GI	Gastrointestinal
GSK	GlaxoSmithKline

Abbreviation	Meaning
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency Virus
HLA	Human leukocyte antigen
Hr	Hour
HR	Heart rate
HSR	Hypersensitivity reaction
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IN	Integrase
INI	Integrase inhibitor
IP	Investigational product
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intent to treat
ITT-E	Intent to treat exposed
kg	Kilogram
LDL	Low density lipoprotein
LFT	Liver function test
LOCF	Last observation carried forward
µg	Microgram
mITT	Modified intent to treat
mITT-E	Modified intent to treat exposed
mL	Millilitre
mm	Millimetre
MSDF	Missing , switch discontinuation = failure (Snapshot algorithm)
N	Number of participants planned

Abbreviation	Meaning
n	Number of individuals participating
ng	Nanogram
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitor
PDVF	Protocol defined virologic failure
P-gp	P glycoprotein
PK	Pharmacokinetic
PP	Per protocol
PRO	Protease
PR/RT	Protease/reverse transcriptase
QTcB	Heart rate corrected QT interval using Bazett's formula
QTcF	Heart rate corrected QT interval using Fridericia's method
RAL	Raltegravir
RAP	Reporting analysis plan
RNA	Ribonucleic acid
RR	Relative risk
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SOC	System organ class
τ	Dosing interval, time between consecutive doses
TDF	Tenofovir
TdP	Torsade de pointes
tlag	Lag time before observation of drug concentrations in sampled matrix
tmax	Time of occurrence of Cmax
$t_{½}$	Terminal half life
TRDF	Treatment related discontinuation = failure

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
USA	United States of America
VF	Virologic failure
ViiV	ViiV Healthcare Pty Ltd
Vz/F	Apparent volume of distribution after oral administration

I. Introduction to product submission

Submission details

Type of submission:	New fixed dose combination tablet of previously registered active ingredients
Decision:	Approved
Date of decision:	8 January 2015
Active ingredients:	Dolutegravir sodium/Abacavir sulfate/Lamivudine
Product name:	Triumeq
Sponsor's name and address:	ViiV Healthcare Pty Ltd PO Box 18079 Melbourne VIC 8003
Dose form:	Tablets
Strength:	50 mg dolutegravir (as sodium)/ 600 mg abacavir (as sulfate)/300 mg lamivudine
Container:	Bottle
Pack size:	30
Approved therapeutic use:	*Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age who are antiretroviral treatment-naive or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents (dolutegravir, abacavir or lainivudine) in Triumeq.*
Route of administration:	Oral (PO)
Dosage:	Therapy should be initiated by a physician experienced in the management of HIV infection. The recommended dose of Triumeq in adults and adolescents weighing at least 40 kg is one tablet once daily, taken with or without food.
ARTG number :	218644

Product background

This AusPAR describes the application by the sponsor, ViiV Healthcare, to register a new combination tablet for the following indication:

> *Triumeq 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.*

This indication was modified during the TGA's evaluation process to:

> *Triumeq is indicated 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 (dolutegravir, abacavir or lamivudine) in Triumeq.*

The new combination tablet consists of three anti-retroviral drugs (abacavir sulphate (ABC), lamivudine (3TC) and dolutegravir sodium (DTG)) all of which are contained in currently registered ViiV Healthcare products as single agents.

DTG is a low nanomolar inhibitor of HIV integrase which requires once-daily dosing. ABC and 3TC are established nucleoside reverse transcriptase inhibitors.

The approved indications for DTG and ABC stipulate that they should be used as part of antiretroviral combination therapy. Abacavir and 3TC are already available as a fixed dose combination therapy at the same dose levels as are being proposed in the current application (Kivexa) and as triple combination therapy with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (Trizivir). Thus, the proposed daily dosages and the use of the three individual agents in combination are consistent with their current registered use.

The proposed dosing regimen involves oral administration of one tablet once daily, providing a maximum recommended daily dose of 50 mg of DTG, 600 mg ABC and 300 mg 3TC. Because Triumeq is a fixed dose tablet, it should not be prescribed for patients requiring dose adjustment, that is:

- Adults or adolescents who weighing <40 kg
- Children < 12 years of age
- Patients with creatinine clearance <50 mL/min
- Patients with mild hepatic impairment
- Patients resistant to integrase inhibitors

Regulatory status

This active ingredient combination has not been registered in Australia previously. Trizivir has been registered in Australia since April 2001, Kivexa since March 2005 and 3TC lamivudine since February 1996.

At the time the TGA considered this application, a similar application had been approved in the USA, European Union (EU) and Canada (see Table 1).

Table 1: International regulatory status

Country	Date of approval	Approved indications
USA	22 August 2014	Triumeq is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. **Limitations of Use**: Triumeq alone is not recommended for use in patients with current or past history of resistance to any components of Triumeq [see Microbiology (12.4)]. Triumeq alone is not recommended in patients with

Country	Date of approval	Approved indications
		resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in Triumeq is insufficient in these subpopulations. See full prescribing information for dolutegravir.
EU	2 September 2014	Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age weighing at least 40 kg (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 (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.
Canada	9 October 2014	Triumeq™ (dolutegravir/abacavir/lamivudine) is indicated for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults. **Pediatrics (<18 years of age)**: The safety and effectiveness of Triumeq™ in pediatric patients has not been established. **Geriatrics (> 65 years of age)**: Clinical studies of Triumeq™ did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of Triumeq™ in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

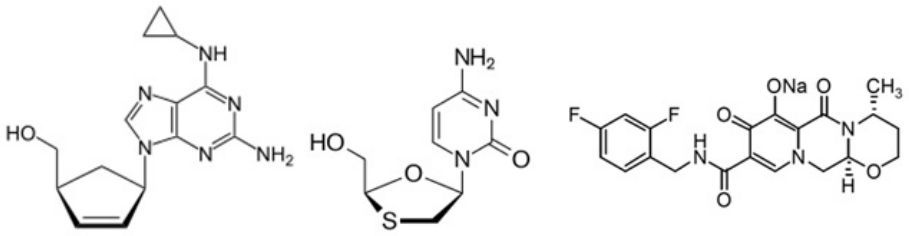
II. Quality findings

Drug substances (active ingredients)

Dolutegravir 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. Abacavir and lamivudine are nucleoside analogue

reverse transcriptase inhibitors, inhibiting the formation of viral DNA. The structures of the three drugs are shown below.

Figure 1: Chemical structure of the active ingredients



abacavir lamivudine dolutegravir

The active raw materials are stated to be identical to the actives used in the currently registered ViiV Healthcare products.

Drug product

Dolutegravir/abacavir/lamivudine tablets are purple, biconvex, film coated oval tablets debossed with '572 Tri' on one face. They are formulated as immediate release tablets. The tablet size is approximately 22 x 11 mm, with a total tablet weight of 1720.8 mg.

The strengths are the same as those approved for registration for the respective single active tablets.

The proposed finished product specifications adequately control identity, potency and other physical, chemical and microbiological properties relevant to the clinical use of the product.

Satisfactory data was provided to support a shelf life of 15 months when stored at 30°C with the additional storage conditions '*Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant.*'

Biopharmaceutics

Study No: ING114580: Relative bioavailability of the commercial formulation against co-administered single active 50 mg dolutegravir tablet and 300 mg lamivudine/600 mg abacavir tablet.

Bioequivalence was demonstrated between the proposed 50 mg dolutegravir/600 mg abacavir/300 mg lamivudine fixed dose combination tablet and co-administered 50 mg dolutegravir tablet and 600 mg abacavir/300 mg lamivudine tablet in healthy fasting subjects (Part A of the study).

The effect of food on bioavailability of the combined formulation was also investigated (Part B of the study).

Administration of the proposed fixed dose combination tablet with a high fat meal resulted in a 37% increase in the peak plasma concentration (C_{max}) and a 48% increase in the area under the plasma concentration versus time curve (AUC) for dolutegravir. This was consistent with the findings of the fed/fasted study provided in support of the registration of the single active 50 mg dolutegravir tablet (Study ING113574). The company considers this not clinically significant based on the accumulated safety data on Phase IIb and Phase III studies which permitted dolutegravir dosing without restriction to food or food content.

Administration of the proposed fixed dose combination tablet with a high fat meal did not affect the AUC of abacavir. The Abacavir C_{max} decreased by about 23% when administered with a high fat meal. This was consistent with previous finding of the fed/fasted study provided in support of the registration of the abacavir/lamivudine fixed dose combination tablet.

Lamivudine AUC and C_{max} were not affected by the administration with a high fat meal.

The sponsor considers the results support the recommendation that the proposed fixed dose combination tablet can be given without regard to food.

Quality summary and conclusions

There are no objections on chemistry and quality control grounds to registration of Triumeq tablets.

III. Nonclinical findings

Introduction

The nonclinical submission comprised two new pharmacokinetic studies investigating potential pharmacokinetic interactions between DTG and substrates of a range of membrane transporters. No new studies have been submitted assessing potential pharmacodynamic, pharmacokinetic and toxicological interactions of DTG in combination with ABC and 3TC, although the potential for pharmacodynamic and pharmacokinetic interactions was addressed in the original evaluation of DTG. The applicant cites the ICH guideline[1] as justification for lack of new nonclinical data, which states that pharmaceuticals under development for indications in life-threatening or serious diseases (such as advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without current effective therapy warrant a case-by case approach to toxicological evaluation.

Pharmacology

The sponsor claims that in vitro checkerboard experiments have shown that DTG, ABC and 3TC are additive to synergistic in their activity. This statement presumably refers to data previously submitted to support the registration of DTG. In this study, DTG was additive to synergistic with maraviroc, adefovir, raltegravir, stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir and enfuvirtide, the antihepatitis B agent adefovir and ribavirin. The combination of DTG and 3TC was not investigated in this study but a lack of antagonism has previously been demonstrated between DTG and two different members of the NRTI class (ABC and stavudine). This is acceptable.

Pharmacokinetics

In order to provide further information on potential pharmacokinetic interactions, new in vitro studies were submitted to investigate the effects of DTG on various membrane transporters. Based on these results, DTG may potentially interact with co-administered agents that are substrates for the organic anion transporters 1 and 3 (OAT1 and OAT3) (50% inhibitory values (IC_{50}) values of 2.12 and 1.97 µM, respectively), as well as

[1] ICH Topic M3 (R2). Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. CPMP/ICH/286/95.

substrates of the multidrug and toxin extrusion transporter 1 (MATE1) (IC_{50} = 6.34 µM). Interactions with substrates of the MATE2-K transporter are less likely, since DTG concentrations an order of magnitude higher were associated with its inhibition (IC_{50} = 4.8 µM). Interactions with substrates for the multidrug resistance protein 4 (MRP4) and the hepatic cannilicular transporter bile salt export pump (BSEP) are considered to be unlikely based on the data provided.

Tenofovir is eliminated by a combination of glomerular filtration and proximal tubular secretion[2] involving the organic anion transporters OAT1 (and to a lesser extent, OAT3), and so based on the data described above, co-administration of tenofovir with DTG may result in increased plasma concentrations of the former. Tenofovir-associated kidney toxicity in humans is believed to be influenced by the exposure of tenofovir within the proximal tubule cells of the kidney. This might be expected to be increased by concomitant administration of DTG through the latter agent's inhibition of renal OAT 1, OAT 3 and MRP4. However, this was not anticipated based on newly submitted pharmacokinetic modelling data using the SimCYP population based simulator. The PI statement for DTG reports that there were no clinically relevant interactions between DTG and tenofovir, which is in agreement with the predicted lack of interaction.

From previously submitted data to support the registration of DTG it was found that this agent inhibited the basolateral renal organic cation transporter 2 (OCT2; IC_{50} = 1.93 µM) and the renal apical multidrug and toxin extrusion transporters MATE 1 (IC_{50} = 6.34 µM) and MATE2-K (IC_{50} = 24.8 µM). This action provided a mechanistic basis for mild increases in serum concentrations of creatinine in clinical studies. A potential for interaction between lamivudine and other agents whose elimination is predominantly renal is referred to in the approved PI documents for lamivudine and Kivexa. Inhibition of OCT2 mediated transport by dolutegravir is likely to reduce the plasma clearance of lamivudine, and hence lead to increases in plasma concentrations of this agent. While the sponsor did submit a plasma kinetic study with the combination, there are no data comparing the effects of DTG on the plasma kinetics of 3TC. In addition, the submitted kinetic study measured plasma concentrations of DTG, ABC and 3TC after administration of a single dose, and did not provide data on the steady state plasma kinetics of the three agents. The observation that DTG administration was associated with increases in serum concentrations of creatinine confirms that the in vitro inhibition of OCT2 and MATE 1 is clinically relevant, and hence the sponsor was asked to comment on the safety implications of the proposed combination with respect to the possible increase of plasma concentrations of 3TC. This effect may be exacerbated in patients who are renally impaired. DTG is contraindicated for co-administration with the OCT2 substrates dofetilide and pilsicainide as these agents have narrow therapeutic indices.

To address the potential for DTG to reduce the clearance of 3TC by inhibition of active tubular secretion, the sponsor estimated the active tubular secretion (CL_{ATS}) of 3TC to be190 mL/min which is 47.5% of the total plasma clearance (399 mL/min). Based on the sponsor's calculations, the maximum increase in 3TC exposure due to complete inhibition of active renal secretion is predicted to be 1.9 times. Using a worst case scenario, drug interaction calculations were made assuming that DTG inhibited OCT2 with an IC_{50} = 0.1 µM, (that is, approximately ten times lower than the value determined experimentally), which indicated that 3TC exposure would increase by 28% as a result of DTG inhibition of OCT2. To put this in a clinical context, the same theoretical considerations applied to the combination of 3TC and the MATE2-K, MATE1 and OCT2 inhibitor trimethoprim[3] predict that 3TC exposure would be increased by 70% when co-administered with trimethoprim.

[2] Fernandez-Fernandez, B. *et al* (2011). *AIDS Research and Treatment* **2011** http://dx.doi.org/10.1155/2011/354908

[3] IC_{50} values = 0.66 µM for MATE2-K, 6.2 µM for MATE1 and 13 µM for OCT2.

In a clinical interaction study, the reported increase in 3TC AUC was 35%.[4] The approved PI statement for 3TC states the following:

> *'Administration of trimethoprim, as trimethoprim/sulfamethoxazole 160 mg/800 mg increased lamivudine exposure by about 40%. However, unless the patient already has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim/sulfamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully.'*

The sponsor's arguments are accepted, and it is noted that the proposed PI statement states that Triumeq is not suitable for patients with renal impairment (creatinine clearance < 50 mL/min), since they require a 3TC dose adjustment.

Toxicology

The sponsor did not submit any toxicity studies with the proposed combination. The justification for the absence of such studies was based on the relevant ICH guidance document[5] which states:

> *'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).'*

In addition, Question 9 of the 'Questions and Answers' section of this guideline states that combination toxicity studies are not generally warranted for HIV products unless there is a specific cause for concern under clinically relevant conditions.

The sponsor submitted a plasma kinetic study in healthy human subjects given a single dose of the proposed fixed dose combination (FDC) formulation of DTG, ABC and 3TC (Triumeq). These data have been used to determine relative levels of systemic exposure in previously submitted toxicity studies with the individual components, as shown below.

Relative exposure

The following tables (Table 2) show the relative exposure in repeat dose toxicity and carcinogenicity studies with DTG, ABC and 3TC.

Table 2: Relative exposure (combined sexes) in repeat-dose toxicity and carcinogenicity studies with DTG

Species	Study duration	Dose mg/kg /day	Dose mg/ $m^{2\dagger}$	Day	AUC_{0-24h} µg·h/mL	Expo-sure ratio#	Expo-sure ratio†
Mouse (CD-1)	2 years [carcinog-enicity]	7.5	22.5	182	153	3.7	0.7
		25	75		411	10	2
		500	1500		1082	27	45
Rat (SD)	26 weeks	5	30	180	203	5	0.9

[4] Moore *et al* (1996).
[5] ICH Topic M3 (R2): Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. CPMP/ICH/286/95, June 2009.

Species	Study duration	Dose mg/kg /day	Dose mg/ m²†	Day	AUC_{0-24h} µg·h/mL	Expo-sure ratio#	Expo-sure ratio†
		50	300		764	13	9
		500	3000		1557	38	91
Rat (SD)	2 years [carcinog-enicity]	2	12	182	190	4.6	0.36
		10	60		536	13	2
		50	300		927	23	9
Monkey (Cynomo lgus)	9 months	3	36	270	17	0.4	1
		10	120		35	0.9	4
		15	180		39	1.0	6
		30	360		62	1.5	11
Human‡	Single dose	50 mg/day	33	-	40.9	–	-

[a]Animals received the sodium salt (correction factor = 1.07); # = animal: human plasma AUC_{0-24h}; †animal to human mg/m² dose ratio, based on conversion factors (from mg/kg) of 3, 6, 12 and 33 for mouse, rat, monkey and human, respectively, or using A = KW2/3 for juvenile rats, based on mean body weight data from the study; ‡50 kg body weight; AUC_{0-t} taken from Study ING114580, bioequivalence of Triumeq tablet compared to DTG plus Epzicom (combined 600 mg/300 mg ABC/3TC); t= last quantifiable concentration.

Table 3: Relative exposure in carcinogenicity studies with ABC

Species (Duration)	Dose (mg/kg/day)		Sex	C_{max} (µg/mL)		AUC_{0-24} (µg.h/mL)		Animal to Human AUC Ratio (600 mg)[a]
	Salt	Base		First Sample	Final Sample	First Sample	Final Sample	
Rat (carcinogenicity)	NA	30	M F	4.2 3.8	3.8 4.6	18.4 16.1	17.0 19.5	1.2 1.4
	NA	120	M F	9.6 10.0	9.4 15.1	96.3 71.3	24.1 97.5	1.7 7.0
	NA	600	M F	22.1 19.5	ND 39.6	442 350	ND 390	31.8[d] 28.1
Mouse (carcinogenicity)	NA	55	M F	4.3 6.5	5.8 4.0	25.4 37.7	27.2 44.3	2.0 3.2
	NA	110	M F	8.9 14.6	8.9 7.3	46.7 86.2	62.9 80.5	4.5 5.8
	NA	330	M F	22.1 27.8	27.3 30.7	231 278	260 311	18.7 22.3
Human[e]	600 mg		M/F	4.03		13.9		NA

Key:
a = Calculated for AUC based on end of treatment values.
b = Animals received 420 mg/kg/day (210 mg(base)/kg/day) from Week 1 through Week 5 of the study. The dose was reduced to 300 mg/kg/day at Week 6.
c = First sample taken on lactation day/post-natal Day 10; last sample taken on lactation day/post-natal Day 63.
d = Based on first sample exposure.
e = Based on exposure (C_{max} and AUC_{0-t}) achieved in the single dose pivotal bioequivalence study of DTG/ABC/3TC, Study ING114580.

Table 4: Relative exposure in carcinogenicity studies with 3TC

Species	Study Duration	Dose mg/kg	C_{max} µg/L[a]	AUC_{0-t} µg.h/mL	Exposure ratio[#]
Mouse	carcinogenicity	180	1.1	16.4	1.3
		600	3.4	47.6	3.9
		2000	9.7	151	12.3
Rat	carcinogenicity	200	4.5	75	6
		1000	15	242	20
		2000	28	533	43
		3000	38	880	72
[b]Human	single dose	300 mg	2.1	12.3	-

[a]Approximate C_{max} values either 1 or 2 h post dose in Week 5; bAUC_{0-t} taken from Study ING114580, bioequivalence of Triumeq tablet compared to DTG plus EPZICOM (combined 600 mg/300 mg ABC/3TC); t= last quantifiable concentration; # = animal:human plasma $AUC_{0-24\ h}$.

The major target organs for toxicity in the repeat dose toxicity studies with DTG were the gastrointestinal tract (in rodents and monkeys), liver, (mouse and monkey) and renal and bone marrow toxicity in monkeys. The No observable adverse effect level (NOAEL) and Lowest observable adverse effect level (LOAEL) for gastrointestinal toxicity in the rat (50 and 500 mg/kg, respectively) correspond to relative exposures of 13 and 38, respectively, based on AUC, or 9 and 91, respectively, based on body surface area (BSA; mg/m^2). In the monkey, the NOAEL of 15 mg/kg/day corresponds to a relative exposure of 1 based on AUC and 6 based on mg/m^2. The LOAEL for gastrointestinal toxicity in the monkey corresponds to a relative exposure of 2 based on AUC and 11 based BSA.

Data submitted to support the registration of abacavir showed that the liver was a target organ for this compound in mice, rats and monkeys. However, the sponsor claims that these effects represent hepatic adaptive responses to metabolic enzyme induction rather than overt toxicity is in agreement with the nonclinical evaluator and the potential for additive or synergistic toxicity at clinically relevant concentrations is considered to be low.

In conclusion, the sponsor's justification for not conducting combination toxicity studies is accepted.

Genotoxicity

The clastogenicity of ABC in combination with 3TC was examined in a rat micronucleus assay in vivo, which was Good Laboratory Practice (GLP) compliant and in accordance with the relevant EU guideline[6]. This study was originally conducted to support the registration of Kivexa but had not previously been evaluated by the TGA. Oral administration of ABC and 3TC to male SD rats at doses of up to 2000 mg/kg/day for two days, either alone or in combination, did not provide any evidence of a clastogenic effect in the bone marrow. The systemic exposures for ABC and 3TC achieved in this study were,

[6] ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. EMA/CHMP/ICH/126642/2008

respectively, 86 and 31 times the clinical exposure level (using the human plasma kinetic data presented above).

Reproductive toxicity

No new reproductive toxicity studies were submitted either for the combination or for the individual components. However, new estimates of relative systemic exposure have been calculated from previously evaluated reproductive toxicity studies with the individual components of Triumeq based on new plasma kinetic data with the proposed fixed dose combination Triumeq.

Table 5: Relative exposure in reproductive toxicity studies with DTG

Species	Study	Dose mg/kg/day	Day	$AUC_{0-24\,h}$ µg·h/mL	Exposure ratio#
Rat (SD)	†Fertility & early embryonic development	100	N/A	751	18
		300		-	-
		1000		1787	44
	Embryofetal development	100	GD 17	1251.8	31
		300		1409.2	34
		1000		2031.8	50
	‡Pre- & Postnatal toxicity	5	N/A	-	-
		50		-	-
		1000		2031.8	50
Rabbit (Japanese white)	Embryofetal development	40	GD 18	2.6	0.06
		200		14.5	0.35
		1000		30.1	0.74
Human	Single dose	50 mg		*40.9	–

= animal:human plasma $AUC_{0-24\,h}$; †Toxicokinetic data taken from 4-week repeat dose study in rats; ‡Toxicokinetic data from the high dose (HD) level in the embryofetal development study in this species; *AUC_{0-t} taken from Study ING114580, bioequivalence of Triumeq tablet compared to DTG plus Epzicom (combined 600 mg/300 mg ABC/3TC); t= last quantifiable concentration.

Table 6: Relative exposure in reproductive toxicity studies with ABC succinate

Species	Study	Dose mg/kg/day		Day	AUC_{0-24h} µg·h/mL	Exposure ratio#
		salt	base			
Rat (SD)	†Fertility & early embryonic development	60	51	N/A	44	3
		150	137		121	9
		500	427		414	30
	Embryofetal development	100	65	GD 17	42	3
		300	194		159	11
		1000	648		427	31
	‡Pre- & Postnatal toxicity	60	51	N/A	51	4
		150	137		137	10
		500	427		427	31
Rabbit	Embryofetal development	125	81	GD 18	15	1.1
		350	227		33	2.4
		700	453		102	7
Human	Single dose	600 mg		N/A	13.9	–

= animal:human plasma AUC_{0-24h}; †Toxicokinetic data taken from 4-week repeat dose study in rats; ‡Toxicokinetic data from the HD level in the embryofetal development study in this species; *AUC_{0-t} taken from Study ING114580, bioequivalence of Triumeq tablet compared to DTG plus EPZICOM (combined 600 mg/300 mg ABC/3TC); t= last quantifiable concentration.

Table 7: Relative exposure in reproductive toxicity studies with 3TC

Species	Study	Dose mg/kg BID	Day	C_{max} µg/mL	AUC_{0-24h} µg·h/mL	Exposure ratio	
						‡	#
Rat	Embryofetal development	45	GDs 7, 16	3.1	-	1.0	-
		300		23.8	-	11	-
		2000		66.9	-	32	-
Rabbit	Embryofetal development	7.5		0.45	*2.3	0.2	0.37
		20		1.05	*5.9	0.5	1.0

Species	Study	Dose mg/kg BID	Day	C_{max} µg/mL	$AUC_{0\text{-}24h}$ µg·h/mL	Exposure ratio	
		45		2.55	*14.8	1.2	2.4
		150		8.0	-	3.8	-
		500		68.4	-	33	-
Human	Single dose	300 mg	1	2.1	12.3		

*$AUC_{0\text{-}24h}$ calculated from $AUC_{0\text{-}12h}$ data (dosing was BID); ǂanimal: human plasma $C_{max;}$ # = animal:human plasma $AUC_{0\text{-}24h}$; Human plasma kinetic data taken from Study ING114580, bioequivalence of Triumeq tablet compared to DTG plus EPZICOM (combined 600 mg/300 mg ABC/3TC); t= last quantifiable concentration.

Pregnancy classification

The sponsor proposes Pregnancy Category B3[7], which is appropriate based on the Pregnancy categories of the individual agents (B1, B3 and B3 for DTG, ABC and 3TC, respectively).

Nonclinical summary and conclusions

- The nonclinical submission comprised two new pharmacokinetic studies investigating potential pharmacokinetic interactions between DTG and substrates of a range of membrane transporters and an in vivo clastogenicity assay with ABC and 3TC. No new studies have been conducted with the proposed combination, which the sponsor justified based on the proposed use in a life threatening or serious disease.[8]
- Dolutegravir was previously shown to be additive to synergistic with a range of antiretroviral agents including ABC but not 3TC. The latter two agents are already approved in combination. A lack of antagonism has previously been demonstrated between DTG and two different members of the nucleoside reverse transcriptase inhibitor (NRTI) class (ABC and stavudine). This is acceptable.
- Newly submitted in vitro membrane transporter studies with DTG suggests that this agent may potentially interact with co-administered agents that are substrates for the organic anion transporters OAT1 and OAT3 (IC_{50} values of 2.12 and 1.97 µM, respectively) as well as substrates of the multidrug and toxin extrusion transporter MATE1 (IC_{50} = 6.34 µM). Interactions with substrates of the MATE2-K transporter are less likely. The plasma kinetics of substrates for the multidrug resistance protein 4 (MRP4) and the hepatic cannilicular transporter bile salt export pump (BSEP) are considered to be unlikely to be changed by co-administration with DTG.
- Dolutegravir inhibits the basolateral renal organic cation transporter in vitro, which appears to be clinically relevant based on mild increases in serum concentrations of creatinine in clinical studies. As 3TC is predominantly eliminated by OCT2, MATE1 co-administration with DTG may lead to increases in plasma concentrations of this agent.

[7] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[8] ICH Topic M3 (R2). Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. CPMP/ICH/286/95.

The human kinetic data was based on a single dose of the three components rather than steady state data, and also did not enable any potential effects of DTG on 3TC kinetics to be examined. Triumeq is not recommended for use in patients who are renally impaired (creatinine clearance < 50 mL/min), since these patients require a dose adjustment for 3TC.

- A new pharmacokinetic modelling study using the SimCYP population based simulator supported a lack of clinically relevant interaction between DTG and the renally excreted OAT1 and OAT3 substrate tenofovir. Thus, DTG is not anticipated to exacerbate tenofovir-mediated renal toxicity.
- The sponsor did not submit any toxicity studies with the proposed combination. The justification for the absence of such data is based on a lack of concordance for target organ toxicity between the three individual components. Although the liver was a target organ for both DTG and ABC, the effects of the latter appear to represent hepatic adaptive responses to metabolic enzyme induction rather than overt toxicity, and the potential for additive or synergistic toxicity at clinically relevant concentrations is considered to be low. Therefore the sponsor's justification for not conducting combination toxicity studies is accepted.
- Data from the plasma kinetic study in healthy human subjects given a single dose of the proposed fixed dose combination (FDC) formulation of DTG, ABC and 3TC were used to recalculate relative exposure levels in the previously submitted repeat dose toxicity studies with the individual components.
- A newly submitted rat in vivo micronucleus assay found no evidence of clastogenicity for ABC in combination with 3TC when both agents were administered at oral doses up to 2000 mg/kg/day for two days (corresponding to respective systemic exposures 86 and 31 times the clinical exposure level). ABC was previously found to be clastogenic in an in vivo micronucleus assay in mice.
- There are no nonclinical objections to the proposed new fixed dose combination.
- A large number of changes to the PI were recommended based on differences between the proposed PI document and the approved PI documents for the individual components. Most of these recommendations have been incorporated into the sponsor's updated PI provided on 9 September 2014. However, some issues remain to be resolved.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor has cited the following potential clinical benefits for the DTG/ABC/3TC FDC:

- Activity against drug resistant HIV; less toxicity and greater tolerability; durability and higher barrier to developing resistance; fewer drug interactions; a convenient dosing schedule.
- Regimens that include integrase inhibitors (INIs) can provide most, if not all such improvements over existing regimens, particularly when combined with other antiretrovirals in a single tablet regimen.

- There is substantial evidence in the literature (references included) that supports the benefit of streamlined treatment regimens (STR), including those with once daily administration and a minimised pill burden. Due to a reduction in the number of individual dose units to be taken by patients, this single tablet regimen is expected to improve patient compliance and therefore maximise antiviral efficacy and reduce the incidence of resistance.
- Another potential treatment advantage for the DTG/ABC/3TC FDC versus most other available single-tablet regimens (STRs) include a lack of significant cytochrome P450 (CYP) 3A enzyme interactions and the ability to dose without regard to food.

Contents of the clinical dossier

In support of their application to register the new fixed dose product, ViiV Healthcare provided a pivotal bioequivalence Study ING114580 and a pivotal safety and efficacy Study ING114467. Also included in the data package are supportive safety and efficacy studies ING113086, ING114915 and ING111762, and drug interaction Study ING116898 and pharmacodynamic Study ING116070. The studies are summarised below.

The strategy for the development of Triumeq takes into account data available from clinical studies conducted under different development programs for dolutegravir, abacavir, lamivudine and the ABC/3TC fixed-dose combination.

For the Triumeq development program, one pivotal study and five supportive studies provide safety and efficacy data in support of this combination product. These studies were conducted in the populations intended for registration and provide data from participants taking all three FDC components concomitantly and/or DTG plus 2 nucleoside reverse transcriptase inhibitors (NRTIs), or at least 1 fully active agent in the case of the antiretroviral therapy (ART)-experienced, integrase inhibitor (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 as a regimen once-daily DTG 50 mg + ABC/3TC 600/300 mg FDC was evaluated as one of two randomised study treatments.
- ING113086 (SPRING-2), ING114915 (FLAMINGO), ING112276 (SPRING-1) clinical studies within the DTG single entity development program include participants 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), also clinical studies within the DTG single entity development program, were considered supportive in demonstrating the safety and efficacy of the DTG 50 mg tablet in combination with ABC/3TC or other active antiretroviral drugs.

Paediatric data

Not submitted.

Good clinical practice

ViiV Healthcare has given the assurance that all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. The assurance was given that all studies were conducted with the approval of Ethics Committees or Institutional Review Boards, that informed consent was obtained for all participants, and that the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the

time the studies were conducted and that where required, regulatory approval was obtained from the relevant health authority.

Pharmacokinetics/pharmacodynamics

Evaluator's conclusions on pharmacokinetics/pharmacodynamics

ING114580 Bioequivalence pivotal

ING114580 was a crossover study of 66 healthy adults evaluating the single-dose pharmacokinetics of an oral DTG/ABC/3TC50/600/300 mg combination tablet formulation proposed for commercial use, compared to co-administration of the separate tablet formulations of DTG 50 mg and Epzicom (ABC/3TC 600/300 mg).

The primary objective was to evaluate bioequivalence in the fasted state between a single FDC tablet formulation of DTG/ABC/3TC 50/600/300 mg versus co-administration of the separate tablet formulations of DTG plus FDC ABC/3TC. The primary outcome was plasma DTG, ABC and 3TC AUC from time zero to infinity ($AUC_{(0-\infty)}$), AUC from time zero until plasma concentration versus time curve, from time zero to 't' (where t = the final time of positive detection; $AUC_{(0-t)}$), and C_{max}. Bioequivalence was determined if the 90% confidence interval (CI) of the ratio of geometric least squares means FDC/DTG + ABC/3TC was within the range 0.8 to 1.25.

Secondary Objectives were to evaluate the effect of food on the bioavailability of the FDC tablet formulation and to assess the safety and tolerability of the combination of DTG, ABC and 3TC.

For each of DTG, ABC and 3TC, the 90% CIs for the geometric least-squares mean ratios for each of the bioequivalence parameters are within the bioequivalence criteria range of 0.8 to 1.25.

Plasma DTG 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, 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.

ING116898 Interaction – Calcium carbonate and ferrous fumarate

ING116898 was a Phase I, open-label, randomised, four-period crossover study to evaluate the effects of calcium carbonate 1200 mg and ferrous fumarate 324 mg on pharmacokinetics of DTG 50 mg in 12 healthy adults.

Participants were randomised to receive DTG co-administered with calcium carbonate in Cohort 1 and with ferrous fumarate in Cohort 2, and received each of four treatments as follows. Each dosing session was separated by wash-out of at least 7 days.

1. A single dose of DTG 50 mg administered under fasted conditions
2. A single dose of DTG 50 mg co-administered with a single dose of calcium carbonate or ferrous fumarate under fasted conditions
3. A single dose of DTG 50 mg co-administered with a single dose of calcium carbonate or ferrous fumarate with a moderate-fat meal (approximately 30% fat)

4. A single dose of DTG 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate or ferrous fumarate.

The primary objectives were to compare:

- Single dose plasma DTG PK following co-administration of DTG and calcium carbonate or ferrous fumarate in the fasted state, to DTG alone in the fasting state
- Single dose plasma DTG PK following co-administration of DTG 50 and calcium carbonate or ferrous fumarate with a moderate-fat meal, to DTG alone in the fasting state
- Single dose plasma DTG PK following administration of DTG in the fasted state 2 hour prior to administration of calcium carbonate or ferrous fumarate to DTG alone on the fasting state
- Single dose plasma DTG PK following co-administration of DTG and calcium carbonate or ferrous fumarate in a fed state to DTG and calcium carbonate or ferrous fumarate in a fasted state.

Primary endpoints were the DTG PK parameters: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and the plasma concentration at 24 hours (C24). Interactions of DTG with calcium carbonate or ferrous fumarate were considered not clinically significant if the observed decrease in dolutegravir AUC or C_{max} was less than 70%.

Co-administration of DTG with either calcium carbonate or ferrous fumarate under fasted condition resulted in reduction in plasma DTG exposures; plasma DTG $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and C24 by approximately 37 to 39% with calcium carbonate and 54 to 57% with ferrous fumerate.

Co-administration of DTG with calcium carbonate or ferrous fumarate under fed condition counteracted the interaction and provided plasma exposures comparable to DTG alone under fasted conditions. Similarly, DTG administered under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate or ferrous fumarate resulted in plasma exposures comparable to DTG alone.

ING116070 Pharmacodynamic CSF

ING116070 is an ongoing Phase IIIb single-arm, open-label, multicentre study of HIV-1 infected ART-naïve patients to determine the potential for dolutegravir to enter the cerebrospinal fluid compartment. Participants were HIV-1 infected treatment naïve adults ≥ 18 years of age, with screening plasma HIV-1 RNA ≥ 5000 copies/mL(c/mL); CD4+ cell[9] count ≥ 200 cells/mm3 and negative for HLA-B*5701[10]. All 13 enrolled subjects were White and male. Study medication was DTG 50 mg with background FDC ABC/3TC 600/300 mg taken once daily with or without food. The Week 16 results were presented.

The primary objective was to determine total and unbound plasma DTG concentration and evaluate the relationship between DTG concentration in plasma and cerebrospinal fluid (CSF) at Week 16. Primary outcomes were CSF DTG concentration and total and unbound plasma DTG PK concentration of samples drawn within 2 to 6 hours post-dose and within

[9] CD4 cells or T-cells are a type of white blood cells that play a major role in protecting your body from infection. They send signals to activate your body's immune response when they detect 'intruders,' like viruses or bacteria.

[10] The HLA-B gene has many different normal variations, allowing each person's immune system to react to a wide range of foreign invaders. Hundreds of versions (alleles) of HLA-B are known, each of which is given a particular number (such as HLA-B5701). Among people with HIV infection, a version of HLA-B designated HLA-B*5701 is associated with an extreme sensitivity to abacavir. This drug is a treatment for HIV-1 that slows the spread of the virus in the body. People with abacavir hypersensitivity often develop a fever, chills, rash, upset stomach, and other symptoms when treated with this drug.

1 hour of CSF sample collection at Week 16; the relationship between DTG concentration in plasma and CSF was evaluated using an estimation approach.

Secondary Objectives were to assess:

- The effect of DTG + ABC/3TC on CSF and plasma HIV-1 viral load; tolerability and safety
- The relationship between CSF DTG concentration and HIV-1RNA in CSF at Weeks 2 and 16
- The relationship between HIV-1 RNA suppression in plasma and CSF at Weeks 2 and 16
- The development of viral resistance in participants experiencing virologic failure.

At Week 16, the correlation between CSF and total plasma DTG concentrations was: (Pearson Correlation Coefficient [P-value] = 0.647 [0.023]. There was also a correlation between CSF and unbound plasma DTG concentrations (Pearson Correlation Coefficient [P-value] = 0.728 [0.007]. However, this finding contradicted findings at Week 2 and for the combined results.

Although there appeared to be a correlation between CSF DTG concentration and absolute CSF HIV-1 RNA levels, the direction of correlations at Week 2 and Week 16 were opposite. There was a significant overlap in CSF DTG concentrations between participants with CSF HIV-1 RNA < 50 c/mL and ≥ 50 c/mL at Week 2.

1. At Week 16, two participants had withdrawn prematurely, 11 had CSF HIV-1 RNA < 50 c/mL using an Observed Dataset. The median change from Baseline to Week 16 in CSF HIV-1 ribonucleic acid (RNA) was -3.42 log10 c/mL and was similar to that observed in plasma (-3.04 log10 c/mL). Eleven participants had both plasma and CSF HIV-1 RNA data available and nine (82%) of these had both plasma and CSF HIV-1 RNA < 50 c/mL.

The most common drug related adverse events were fatigue, headache and nausea, each reported by 2/13 participants. The majority of adverse events were Grade 1 or Grade 2. There were no investigational product (IP) related serious adverse events (SAEs) reported and no deaths. Small median increases in serum creatinine and small decreases in the calculated creatinine clearance were noted beginning at Week 2 and remaining stable to Week 16.

Efficacy/safety and virology

Evaluator's conclusions on efficacy/safety and virology

ING114467 (single) Treatment-naive pivotal efficacy and safety

ING114467 is an ongoing, Phase III, parallel group, randomised, double-blind, active-controlled multinational study of DTG plus fixed dose ABC/3TC compared with EFV/TDF/FTC in treatment of HIV-1 infected ART naïve adult patients with plasma HIV-1 RNA ≥1000 c/mL; and negative HLA-B*5701 allele. Week 96 results were presented.

The primary objective was to demonstrate the antiviral activity of DTG + ABC/3TC FDC once daily therapy compared to emtricitabine (EFV)/ tenofovir (TDF)/ emtricitabine (FTC). The primary endpoint was the proportion of participants with plasma HIV-1 RNA < 50 copies/mL up until Week 48 using the Snapshot algorithm, Missing, Switch, or Discontinuation = Failure (MSDF). The primary efficacy analyses were performed on the ITT-E population (all randomised patients who received at least one dose of study drug) at Week 48. Non-inferiority was concluded if the lower bound of a two-sided 95% confidence

interval for the difference in response rates between the two treatment arms was greater than - 10%. A similar assessment at Week 96 was a secondary objective. The Week 96 results were presented.

Participant withdrawals by Week 96 were 17% versus 26% for DTG+ABC/3TC and for EFV/TDF/FTC respectively. Adverse events were the most common reason for withdrawal. Withdrawals due to AEs for the DTG + ABC/3TC and EFV/TDF/FTC groups were 3% and 11% respectively. Withdrawals due to lack efficacy were reported for 18 (4%) of the DTG+ABC/3TC group and 14 (3%) of the EFV/TDF/FTC arm. Seventeen (4%) in the DTG+ABC/3TC arm and 18 (4%) in the EFV/TDF/FTC arm were lost to follow up.

At Week 96, the adjusted difference, DTG minus EFV/TDF/FTC was 8.0% (+2.3%, +13.8%) protocol defined virologic failure (PDVF) was two consecutive HIV-1 RNA values ≥ 50 c/mL HIV-1 RNA from Week 24 onwards. Genotypic and phenotypic integrase (IN) resistance results were available for 13/25 (52%) of the DTG group versus 10/25 (40%) of the EFV/TDF/FTC group. Genotypic and phenotypic NNRTI resistance results were available for 17/25 (68%) in the DTG versus 12/25 (48%) of the EFV/TDF/FTC group. No treatment emergent primary IN inhibitor (INI) or NRTI resistance mutations were observed through 96 weeks for those participants on DTG plus ABC/3TC FDC with PDVF. Six participants in the EFV/TDF/FTC treatment group had treatment emergent non NRTI (NNRTI) resistance mutations. Phenotypic changes to EFV were observed in five of these participants.

Regarding safety, dizziness, diarrhoea, nasopharyngitis, headache, nausea and fatigue were most commonly reported AEs and occurred at similar rates across both treatment groups. Treatment related events were more common in the EFV/TDF/FTC group. The most common drug related adverse events were dizziness, abnormal dreams, nausea, insomnia, diarrhoea, fatigue, headache and rash. Most events in both groups were considered Grade 1 or 2. The incidence of Grade 3 and 4 events combined was DTG+ABC/3TC 57/414 [14%] versus EFV/TDF/FTC 83/419 [20%].

One individual in the DTG/ABC/3TC group reported an SAE considered related to IP (drug hypersensitivity). Nine in the EFV/TDF/FTC group had SAEs considered related to study treatment: syncope, reported by two individuals; depression, homicidal ideation and suicidal ideation; paranoia and suicidal ideation; drug hypersensitivity; cerebrovascular accident; hallucination, visual; and bipolar 1 disorder each reported by one individual. One death in the EFV/TDF/FTC group was considered possibly related (renal failure).

For EFV/TDF/FTC versus DTG/ABC/3TC respectively, rash was considered study treatment related for 34/419 (8%) versus 4/414 (<1%), and rash leading to permanent discontinuation for 9/419 (2%) versus 2/414 (<1%). All but one episode of rash were Graded 1 or 2; one was considered Grade 3.

Relative risk and 95% CI < 1 favouring DTG/ABC/3TC were noted for dizziness, abnormal dreams, rash and somnolence; favouring EFV/TDF/FTC insomnia, influenza and pain in extremity.

Comparable rates for participants with any gastrointestinal event were reported in both treatment groups. The higher number of discontinuations for gastrointestinal (GI) events in the EFV/TDF/FTC treatment group did not appear to be related to higher event toxicity/intensity grades.

There was a low rate of elevated liver chemistries in both arms. The mean changes in low density lipoprotein (LDL) and total cholesterol were small and not considered statistically significant.

Twelve participants became pregnant (DTG+ABC/3TC 5/414, EFV/TDF/FTC 7/419). Four normal neonates have been delivered (2 in each group). Three participants in the DTG/ABC/3TC group and 1 in the EFV/TDF/FTC group had elective terminations. A

further elective termination was carried out due to an ectopic pregnancy (EFV/TDF/FTC). Three spontaneous abortions were reported; 1 in the DTG/ABC/3TC group and 2 in the EFV/TDF/FTC group; none were considered related to IP. No congenital anomalies were reported. One pregnancy in the EFV/TDF/FTC group was ongoing at data cut off. The partner of a male participant in the DTG/ABC/3TC group delivered a normal infant.

ING113086 (Spring-2) treatment-naïve supportive efficacy and safety

ING113086 is an ongoing Phase III randomised, double-blind, active-controlled, multicentre, non-inferiority study including treatment-naïve adult patients. The study was designed to assess safety and efficacy of DTG 50 mg once daily versus RAL 400 mg twice daily, each administered with either ABC/3TC or TDF/FTC. Approximately 40% of each group were treated with ABC/3TC background. Week 96 results were presented.

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 in HIV-1 infected therapy-naive subjects. Antiviral activity was assessed as the proportion of participants with plasma HIV-1 RNA < 50 c/mL determined by the Snapshot algorithm. Non-inferiority of DTG 50 mg was concluded if the lower bound of a two-sided 95% confidence interval for the difference in proportions (DTG minus RAL) was greater than -10%. The adjusted difference in the proportions was based on a stratified analysis using Cochran-Mantel-Haenszel weights. A key secondary objective was to demonstrate the antiviral activity of DTG versus RAL over 96 weeks.

In total, 681 patients completed Week 96: DTG 349 (85%); RAL 332 (81%). Fifteen patients (DTG 8, RAL 7) discontinued due to an AE; twenty-nine withdrew due to protocol deviations (DTG 13, RAL 16); five discontinued upon reaching protocol-defined liver stopping criteria (DTG 2, RAL 3).

At Week 96, the efficacy outcome was achieved by 81% of the DTG group and 76% of RAL group. The difference in proportions (95% CI) was 4.4% (-1.2, 10.0).

For the Kaplan-Meier sub analysis of proportions treated with ABC/3TC background, without treatment failure using the treatment related discontinuation = failure approach, the point estimates (95% CI) for DTG was 92.5% (87.1, 95.6) and for RAL 91.7% (89.1, 93.1).

As for ING114467, PDVF was two consecutive HIV-1 RNA values ≥ 50 c/mL HIV-1 RNA from Week 24 onwards. Ten of the 22 participants with PDVF in the DTG arm had IN genotype assessed at both baseline and at PDVF versus 20 of 29 in the RAL arm. In the DTG arm 0/10 had emergent INI resistance mutations (versus 1/20 in the RAL group).

Fourteen of the 22 individuals with PDVF in the DTG treatment group had PR/RT genotype assessment at both Baseline and at PDVF, while 20 of the 29 with PDVF in the RAL treatment group had PR/RT genotype at both Baseline and PDVF. NRTI primary resistance mutations (4/20) were observed in subjects on RAL. No treatment emergent NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.

With respect to safety, the most commonly reported clinical AEs among participants receiving dolutegravir (DTG) and raltegravir (RAL) were nausea, nasopharyngitis, diarrhoea and headache, with no appreciable difference between treatment groups. Most events in both treatment groups were considered Grade 1 or 2. There were 18 Grade 4 events reported in the DTG group, 2 of which were reported as SAEs and considered IP related: drug hypersensitivity and hepatitis. Seven participants randomised to RAL reported Grade 4 AEs; all reported as serious and none related to IP.

Reporting rates for IP related AEs were: DTG 124/411 (30%); RAL 121/411 (29%). The only drug-related AE reported in ≥ 5% of subjects in each treatment group was nausea: DTG 40/411 (10%); RAL 45/411 (11%). Grade 3/4 events considered possibly or

probably related to IP in each group were reported for 4 in the DTG 4 group, 5 in the RAL group. For DTG, the events were: Grade 3: headache, dizziness, feeling abnormal, arrhythmia; Grade 4: Drug hypersensitivity with associated ALT/AST/ALP/total bilirubin/LFT and, hepatitis (one participant each). For RAL, the events reported for the five participants with Grade 3 events assessed as possibly/probably related were: Grade 3: nausea, abdominal pain, aphasia, drug eruption, fatigue, alanine aminotransferase (ALT) increased, creatine phosphokinase (CPK) increased, lipase increased and decreased appetite.

There were no deaths related to IP. At least one SAE was reported by 10% for DTG and 12% for RAL. Drug related events were reported by < 1% of those taking DTG and 1% for RAL. All individually reported SAE preferred terms had an incidence of ≤ 1% in either treatment group. The SAEs considered to be related to DTG (N = 3) were: Arrhythmia leading to withdrawal; hypersensitivity considered by the investigator to be related to DTG (the sponsor also implicated co-suspect ABC/3TC) and hepatitis considered possibly drug induced.

There were 4 reports of hypersensitivity in the DTG group, none in the RAL group. The hypersensitivity AEs were considered reasonably attributable to abacavir.

Diarrhoea and nausea were two of the most commonly reported GI AEs. For those considered IP related the incidences were DTG 18% and RAL 17%. Less than 1% of each group reported GI events in either treatment group resulting in the permanent discontinuation of IP and withdrawal. GI events considered SAEs were reported by: DTG <1%, RAL 2%).

There was a similar overall pattern in graded treatment emergent clinical chemistry toxicities for DTG and RAL. The numbers in each treatment group with ALT ≥ 3times the upper limit of normal (xULN) were: DTG 21 (5%); RAL 19 (5%). Two patients on DTG had a combination ALT > 3xULN with total bilirubin ≥ 2xULN and alkaline phosphatase (ALP) < 2xULN. A total of 11 patients [DTG 7, 2%; RAL 4, < 1%] met at least one of the criteria for stopping. Seven participants (DTG 5, RAL 2) had maximum treatment emergent ALT values ≥ 10xULN: all met criteria for stopping IP. Of the five participants in each group with ALT elevations ≥5xULN but <10xULN, four met liver criteria for stopping IP. Eleven in each group recorded ALT ≥ 3xULN but <5xULN; one in the RAL group met liver stopping criteria.

Treatment emergent Grade 1 creatinine toxicities were reported for DTG 14, RAL 8; one (DTG) had Grade 2 toxicity. The incidence of AEs related to the Renal and Urinary disorders system organ class (SOC) was (DTG 24/411 (6%); RAL 16/411 (4%).

Grade 4 elevations of CK were recorded by 18 (4%) in the DTG group and 8 (2%) in the RAL group. For all those in the DTG group and seven in the RAL group, the changes were transient without associated AEs. High degrees of physical activity preceded the CPK elevations in the majority of cases (13/18 for DTG and 4/8 for RAL) and by a seizure in 1 participant in the RAL arm.

The incidence of AEs related to the Musculoskeletal and Connective Tissue Disorders SOC was: DTG 74/411 (18%); RAL 86/411 (21%). Arthralgia was reported by: DTG 10/411 (2%); RAL 14/411 (3%); myalgia by: DTG 11/411 (3%); RAL 8/411 (2%).

There was no clinically significant change in Total/high density lipoprotein (HDL) cholesterol or triglycerides.

ING114915 (Flamingo) treatment-naive supportive efficacy and safety

Study ING114915 is an ongoing Phase IIIb randomised, open-label, active-controlled, multicentre, parallel group, non-inferiority study of treatment-naïve adults. Participants 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 ABC/3TC or TDF/FTC.

Approximately one third of each group were treated with ABC/3TC backbone. Week 48 results were presented.

The primary objective was to demonstrate non-inferiority of antiviral activity of DTG compared to DRV/RTV over 48 weeks, assessed as the proportion of participants with plasma HIV-1 RNA < 50 c/mL determined by the FDA 'Snapshot' algorithm. The primary comparison was made at a one-sided 2.5% level of significance. Treatment with DTG was declared non-inferior to treatment with DRV/r if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 was above - 12%. The adjusted difference in the proportions was based on a stratified analysis using Cochran-Mantel-Haenszel weights. Superiority was declared if the lower limit of the 95% CI calculated in the mITT-E analysis was above 0%.

If the primary comparison of interest demonstrated non-inferiority for the modified Intent-to-Treat Exposed (mITT-E) population of DTG compared to DRV/r, then the following comparisons were tested according to the gatekeeping procedure described below:

1. Superiority of DTG to darunavir plus ritonavir (DRV/r) with respect to change from baseline in LDL cholesterol at Week 48 on the modified safety population
2. Superiority of DTG to DRV/r with respect to the incidence of Grade 2 or higher in LDL cholesterol lab abnormalities at Week 48 on the modified safety population
3. Superiority of DTG to DRV/r with respect to time to viral suppression (< 50 copies/mL) to 48 Weeks on the mITT-E population

Of 488 patents randomly assigned, 484 received at least 1 dose of study medication. The rates of premature withdrawals were: DTG 7%; DRV+RTV 12%. The proportions withdrawing due to AEs were: DTG 1%, DRV+RTV 4%, and lost to follow-up: DTG 2%, DRV+RTV 4%.

At Week 48, 90% of the DTG group versus 83% of the DRV+RTV group achieved the primary endpoint. The difference (95% CI) = 7.1% (0.9, 13.2). Superiority of DTG was concluded.

Differences in virologic response rate were primarily driven by discontinuations due to AEs (DTG 1%, DRV+RTV 4%) and other reasons (DTG 2%, DRV+RTV 5%). The 'Other' reasons for discontinuation among the subjects with no virologic data at Week 48 included protocol deviation, lost to follow-up, and withdrawal of consent.

The median time to suppression was 28 days for subjects in the DTG treatment group compared to 85 days in the DRV+RTV treatment group. The difference was statistically significant against the pre-specified threshold of 0.05 (2-sided) ($p < 0.001$). This was the third step in the pre-specified multiple-testing strategy.

PDVF definition was 2 consecutive HIV-1 RNA values > 200 c/mL HIV-1 RNA on or after Week 24. Two participants (<1%) in each treatment group met PDVF. Each had genotype and phenotype results at baseline and time of PDVF. Neither had treatment-emergent resistance INI mutations or phenotypic resistance to DTG or treatment-emergent resistance mutations in reverse transcriptase or protease. One patient in the DTG treatment arm with tenofovir (TDF)/FTC as the NRTI backbone, had phenotypic resistance to nelfinavir (4.12 fold change (FC)), in spite of having no treatment emergent protease resistance mutations.

With respect to safety the most commonly reported AEs in both treatment groups were diarrhoea, nausea, headache, and nasopharyngitis. Diarrhoea and upper respiratory tract infection were more frequently reported among those in the DRV+RTV group and headache was more frequently reported in the DTG group. The majority of events reported in both groups were considered to be of Grade 1 or Grade 2.

The incidences of drug-related events were similar except for diarrhoea which was reported more frequently in the DRV+RTV group. The discrepancy in incidence was largely due to higher numbers in the DRV+RTV group with Grade 1 events.

No deaths were reported. One patient in the DTG treatment group reported an SAE considered by the investigator to be related to IP; a suicide attempt. SAEs were individually reported by < 1% of participants. One SAE report of hypersensitivity reaction Grade 2, disseminated maculopapular rash and erythema without associated symptoms, was suspected by the investigator to be due to ABC; however, the sponsor did not consider the event to be a convincing case of ABC hypersensitivity reaction due to lack of multisystem involvement and considered DRV+RTV to be the likely cause.

The incidence of psychiatric disorders was 19% for the DGT group and 14% for the DRV+RTV group. Insomnia, depression, and anxiety were the most commonly reported. The frequencies were: insomnia DTG 18 (7%); DRV+RTV 15 (6%); anxiety: DTG 10 (4%); DRV+RTV 7 (3%) and depression DTG 11 (5%); DRV+RTV 6 (2%). All other events in this SOC were reported in ≤ 1%. Insomnia was considered drug related for 2% of the DTG group and 1% of the DRV+RTV group. The majority of events in either treatment group were considered of Grade 1 intensity and/or not reasonably drug-related.

ING111762 (Sailing) treatment-experienced

ING11762 was a Phase III randomised 1:1, double-blind study of the safety and efficacy of DTG 50 mg once daily versus RAL 400 mg twice daily, both administered with an investigator selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy- experienced adults with HIV-1 RNA > 400 c/mL and documented resistance to two or more different classes of antiretroviral agents but no prior exposure to any integrase inhibitor. In total, 354 were included in the DTG group and 364 in the active control group. As far as could be ascertained, 7 DTG treated patients took ABC/3TC as background. The Week 48 results were reported. The Week 24 results were evaluated for registration of DTG. Week 48 results were presented.

The primary objective was to demonstrate the antiviral efficacy of DTG 50 mg once daily compared to RAL 400 mg twice daily each with a background regimen consisting of one to two fully active single agents The primary endpoint was the proportion of subjects with HIV-1 RNA < 50 c/mL to Week 48 using a Missing, Switch, or Discontinuation = Failure (MSDF) Snapshot' algorithm. Non-inferiority of DTG 50 mg and RAL was concluded if the lower bound of a two-sided 95% CI for the difference in proportions (DTG - RAL) was greater than -12%. Superiority was declared if the lower bound of the 95% confidence interval calculated in the mITT-E analysis was above 0%.

At Week 48, 71% of subjects receiving DTG and 64% of subjects receiving RAL achieved the primary endpoint at Week 48. The difference, DTG – RAL, (95% CI) was 7.2 (0.3, 14.0). The pre-specified basis for concluding non-inferiority and superiority were met.

PDVF was defined as follows.

- Virologic Non-response
  - A decrease in plasma HIV-1 RNA of less than 1 log10 c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 c/mL.
  - Confirmed plasma HIV-1 RNA levels ≥ 400 c/mL on or after Week 24.
- Virologic Rebound
  - Confirmed rebound in plasma HIV-1 RNA levels to ≥ 400 c/mL after prior confirmed suppression to < 400 c/mL.
  - Confirmed plasma HIV-1 RNA levels >1 log10 c/mL above the nadir value where nadir is the lowest HIV-1 RNA value ≥ 400 c/mL.

Cumulative PDVF at Week 48 was reported for 21 (6%) of the DTG group and 45 (12%) of the RAL group: 1% receiving DTG and 5% receiving RAL had evidence of treatment emergent genotypic or phenotypic INI resistance at the time of PDVF by Week 48 p = 0.003, based on a pre-specified analysis of this secondary endpoint.

At Week 48, 17 participants experiencing PDVF in the DTG arm had matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at the RAL associated T97, E138, and polymorphic V151 positions, and at R263. In the RAL arm 38 patients who experienced PDVF had matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at positions commonly observed during RAL therapy including primary resistance mutations at Y134, Q148, and N155 as well as associated secondary mutations.

A unique IN substitution (R263K or R263R/K mixture) conferring little change in susceptibility to DTG and RAL was observed in 2 patients with treatment emergent resistance on DTG. No DTG subjects had treatment-emergent INI phenotypic resistance at PDVF. Thirteen patients receiving RAL had evidence of treatment-emergent INI phenotypic resistance to RAL at PDVF.

With respect to safety, the most common AES were diarrhoea, upper respiratory tract infection, headache, nausea, cough, vomiting, rash. The most common Grade 2 to 4 drug related AEs were diarrhoea, nausea, headache, and abdominal pain. AEs leading to discontinuation of treatment occurred in less than one percent of patients in each group.

Six participants in the DTG group were identified as having IRIS or possible IRIS. Five of these six were considered to have hepatitis B and/or hepatitis C Immune reconstitution inflammatory syndrome (IRIS).

Clinical questions

1. The FDC is a large, 22 mm x 11 mm, film coated tablet. The depth and circumference have not been stated in the clinical component of the dossier. The sponsor is requested to supply the depth and circumference measurements.
    a. What are the dimensions of Kivexa tablets and Tivicay tablets?
    b. Does the Triumeq tablet swell in the presence of water?
    c. The only submitted study in which the FDC was administered was ING114580, in which 54 healthy adults were administered 1 tablets and 12 were administered 2 tablets.

In general, many people find it hard to swallow big pills[11], and as HIV infected patients are prone to dysphagia which may be due to a number of factors such as candida, HSV and CMV infections, aphthous ulceration, gastroesophageal reflux, HIV associated altered oesophageal motility and function, it is possible that the benefits of once daily dosing may be countered by lack of compliance due to difficulty in swallowing the large tablets. Acknowledging the literature references on the benefits of reduced tablet loads included in the dossier, is there direct evidence to support the contention that the FDC DTG/ABC/3TC tablet is readily swallowed by patients with HIV-1 infection, with resultant increase in compliance?

[11] FDA Guidance for Industry Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules. DRAFT GUIDANCE
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf

Pivotal pharmacokinetic study ING114580

2. With respect to Table 7 (see Attachment 2), please confirm that the values in the column headed ABC/3TC are for either ABC or 3TC administered as single entities.

   Assuming this is so, and taking into consideration problems inherent in use of historical comparisons, ABC and 3TC AUC values appear similar but it is likely that Cmax for both ABC and 3TC would not meet bioequivalence limits had the comparison been done contemporaneously.

   As DTG has the theoretical capacity to increase 3TC levels based on *in vitro* inhibition of OCT2, it is surprising that the FDC Cmax level of 3TC shown in Table 7 is approximately 75% of the single active point estimate. Please comment.

   No Cmin data has been supplied. Please submit Cmin data for Study InG114580 if available.

3. It appears possible that a clinically relevant drug-drug interaction between DTG and 3TC may exist based on renal transporter OCT2 and possibly other renal transporters such as OAT1, MATE1 and MATE2-K based on *in vitro* studies. It is considered unproven that such an interaction is unlikely. A formal interaction study between DTG and 3TC, including assessment of intracellular levels of lamivudine is recommended.

Pharmacodynamic study ING116070

4. The sponsor is requested to supply details of the protocol deviations which the evaluator could not locate in the clinical study report (CSR).

Pivotal study ING114469 treatment-naïve - efficacy

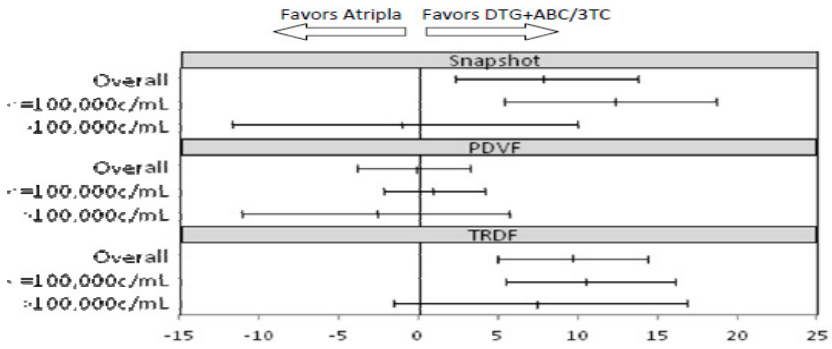
5. Justification is required for the 95% confidence interval and p-value used in assessment of virologic suppression at Week 96. The proposed text includes the statement that the difference between treatment groups was significant; however, multiplicity was not accounted for after Week 48.

6. The applicant is requested to comment on the notion that the Snapshot analysis includes a composite endpoint. The surrogate endpoint of HIV-1 RNA < 50 c/mL is accepted as an important efficacy endpoint. The decision to discontinue treatment due to adverse event may be subjective and open to bias, particularly when the study is unblinded (for example ING114915), or when the nature of the adverse events lead to identification of the treatment in a blinded study. Discontinuation criteria are not all clinically relevant and neither is a missing laboratory value at a specified time point. The inclusion of results of the Snapshot analysis in the Product Information, qualified as HIV-1 RNA < 50 c/mL, is not considered accurate. The result based in < 50 c/mL is considered more appropriately that of the Kaplan Meier ERDF analysis (Table 26).

7. Figure 3 Study Accountability page 50 of ING114467 Report [in CSR] is illegible. Please provide a legible copy.

8. With regard to Figure 5 of the CSR (Figure 2 below) the y-axis labelling is partially illegible. The figure purports to show that results favour DTG + ABC/3TC, however these results are considered exploratory. Overlapping of confidence intervals is not accepted as proof of similarity, especially in the presence of very wide confidence intervals. Sub-analyses are considered the basis for further specific investigation.

Figure 2: Difference in Proportion of Responders and 95% CI by Baseline Viral Load Strata (DTG + ABC/3TC - EFV/TDF/FTC)



Pivotal study ING113086 treatment-naive – efficacy

9. How many patients were enrolled in the Russian site, the site at which 3 participants became pregnant? Were there concerns about investigator oversight at this site?
10. How many participants were enrolled in each treatment group in Russia? What proportion of participants in Russia was treated with ABC/3TC? What proportion of the overall study numbers treated with ABC/3TC were enrolled in Russian sites? If TDF/FTC cannot be used in Russia, it seems likely that ABC/3TC was used exclusively and this may have had the potential to bias the results due to differing treatment protocols.
11. Please provide a legible copy of the study schematic.

Supportive study ING114615 treatment-naïve - efficacy

12. The Kaplan Meier Figure is missing the numbers assessed at each time point. Please provide a figure with numbers of participants contributing.

Study ING111768 treatment-experienced - efficacy

13. The sponsor is requested to justify inclusion of this study in the Triumeq Product information when so few participants were treated with the active components of Triumeq.

Pivotal study ING114476 – treatment –naïve - virology

14. The draft PI states that there were no INI-resistant mutations reported in ING114467. However, the treatment emergent substitution E157Q/P was noted Week 24 albeit without accompanying DTG phenotypic resistance and with replicative capacity which could not be determined. The University of California HIV InSite [12] includes this substitution amongst the list of resistance mutations in patients with no previous exposure to integrase inhibitors, again with the qualification that no phenotypic decrease in susceptivity to dolutegravir or raltegravir was reported.

Supportive study InG114915 treatment –naïve - virology

15. Does the sponsor consider that different definitions of viral failure and different methods of assessment of mutations impact the resistance findings of the studies? Justification is requested for not including definitions of PDVF in in the draft PI.

[12]HIV InSite: http://hivinsite.ucsf.edu/InSite?page=ar-07-03

Study ING111762 treatment-experienced - virology

16. The report states that the cumulative numbers with PDVF at Week 48 were 21 in the DTG group and 45 in the RAL group. Table 57 reports the numbers for DTG and RAL as 19 and 44 respectively. Which is correct? Has the evaluator not understood correctly?

17. As there were 4 participants in the DTG group without paired samples for the integrase assessments and 7 in the RAL group, the percent in the DTG group with paired samples, it could be argued, should have been (17/21) 81% rather than the 89% shown in Table 58. Similarly for RAL, using 45 as denominator 84% of participants had paired samples rather than 88%. The number of drop-outs from analysis is considered to have the potential to alter the results of subsequent analyses. Comment is requested.

18. The draft PI mentions R263K (2 patients) and V151V/I. The applicant is requested to discuss the reason for not including more detailed information on participant 9402 in the Product Information[13]. Table 59 also includes R236R/K, E138T/A, T97A and T79T/A in the patient with baseline RAL associated resistance associated mutations. The draft PI only mentions that this patient existed and the possible reason why this patient had pre-existing integrase mutations but leaves out the what is considered the most important information, that is, the emergence of further mutations with increasing fold changes to > maximum.

Supportive study ING114915 treatment-naïve - safety

19. The statement in Module 5 CSR page 77, '*any of these grade 4 events were assessed as related to DTG by the investigator*' requires clarification. Were these events IP related?

20. With respect to changes in triglyceride levels, please provide the denominators for each result. Is the bracketed number a percent?

21. It appears that not all participants provided fasting blood samples. The sponsor is requested to supply the numbers of individuals with fasting low density lipoprotein (LDL) results and the drop-out percentages for the step-wise pre-specified multiple testing strategy.

Second round benefit-risk assessment

The indication is a well-recognised disease state. The proposed combination is based on valid therapeutic principles. Each component has a documented therapeutic contribution. The choice of each substance is considered justified based on modes of action and the dosage frequencies. Each of the individual components can be taken with and without food. The doses used in the fixed combination are identical to the doses used in the broad clinical setting and there is safety data generated with these doses are available.

The choice of each substance is considered justified based on treatment recommendations included in Australasian Society for HIV Medicine (ASHM) and the US Department of Health and Human Services (DHHS guidelines) in which it is stated that the optimal antiretroviral regimen for a treatment-naive patient consists of two NRTIs in combination with a third active ARV drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir or an integrase inhibitor.

[13]At Baseline, one subject (Subject [information redacted]) in the DTG arm (with ATV/r + TDF) harboured virus with RAL associated resistance mutations at Q148H, E138A, G140S, and elevated DTG FC of 12 at Baseline and RAL FC >Max measureable. At PDVF integrase substitutions E138T/A and T97A emerged and DTG and RAL FCs both increased to >Max measureable.

It is noted that DTG + ABC/3TC has recently been added to the AIDSinfo Guidelines[14] for the use of Antiretroviral Agents in HIV-Infected Adults and Adolescent section: Regimens for ART-naïve patients regardless of baseline viral load or CD4 cell count.

Bioequivalence was shown for each component of the FDC compared to DTG and the FDC ABC/3TC. The FDC was not tested against each component separately. However it is most likely that patients in clinical practice who are treated with ABC and 3TC would take the fixed dose product ABC/3TC.

The pivotal efficacy study documented superior efficacy of DTG + ABC/3TC versus EFV/TDF/FTC, the difference being largely driven by a larger proportion in the comparator arm discontinuing due to AEs. No treatment emergent primary INI or NRTI resistance mutations were observed through 96 weeks for those subjects on DTG plus ABC/3TC FDC with PDVF. The study did not use the FDC proposed for registration.

There may be an improvement in risk benefit balance due to possible increased treatment compliance due to decreased number of tablets required. Increased compliance in turn may reduce the risk of development of resistance mutations. However, it remains to be determined whether the relatively large tablet (22 x 11 x 7.6 mm with maximum circumference 54.6 mm) will be a problem for some patients.

Second round evaluation of clinical data submitted in response to questions

See Attachment 2 for the sponsor's responses to the *Clinical questions* and the evaluator's comments on the sponsor's responses.

Second round assessment of benefits

The DTG/ABC/3TC fixed dose combination has been shown to be bioequivalent to DTG + ABC/3TC. The latter combination has been shown to be effective in maintaining viral suppression as shown in ING114467. There were no unexpected safety concerns detected in ING114467. There was a high barrier to resistance reported in the study. The FDC may increase treatment compliance although this remains hypothetical.

Second round assessment of risks

The safety profiles of lamivudine and abacavir have been established since first registration in the US of lamivudine in 1995 and abacavir in 1998. The safety profile of the recently registered dolutegravir is not so well established. For individual patients, there is the potential for development of significant adverse events consistent with the known safety profiles.

The large dimensions of the tablet (22 x 11 x 7.6 mm with circumference 54.6 mm) may preclude use, or result in misuse of the product for some patients.

Second round assessment of benefit-risk balance

The balance is considered to lie on the side of benefit.

[14] AIDSinfo is a service of the US Department of Health and Human Services (HHS), offering access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information for health care providers, researchers, people affected by HIV/AIDS and the general public.

Second round recommendation regarding authorisation

Registration of the fixed dose combination, dolutegravir/abacavir/lamivudine is recommended.

The recommended condition of registration is that product information is presented to the Therapeutic Goods Administration, to the Australian medical fraternity and the general public as clearly as is possible, in accordance with the recommendations by this evaluator The details of these are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Triumeq EU-RMP version 1.0 dated 3 October 2013 (data lock point 31 May 2013) and an Australian-specific Annex (ASA) version 1.0 which were reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8: Summary of ongoing safety concerns

Important identified risks	Hypersensitivity reactions Hepatobiliary disorders Drug interaction between dolutegravir and dofetilide
Important potential risks	IRIS Serious rash Renal disorders Gastrointestinal (GI) intolerance and erosions Muscoskeletal events/elevated CPK elevations Lipase elevations Psychiatric disorders Carcinogenicity and long-term exposure to NRTIs Cardiac events leading to ischaemia Exposure to abacavir during pregnancy Drug interaction between abacavir and ribavirin
Missing information	Use in the elderly Use in paediatrics Use in pregnancy/breastfeeding Use in hepatic impairment Long-term safety data

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance for all safety concerns except the following (Table 9).

Table 9: Additional pharmacovigilance measures

Important identified risks	Proposed pharmacovigilance
Hypersensitivity reactions	Routine pharmacovigilance EuroSIDA cohort study Aggregate review of clinical trial and spontaneous cases of suspected hypersensitivity reaction
Hepatobiliary disorders	Routine pharmacovigilance EuroSIDA cohort study
Serious rash	Routine pharmacovigilance EuroSIDA cohort study
Carcinogenicity and long-term exposure to NRTIs	Routine pharmacovigilance Review outputs from the sponsor supported data collection on adverse events of anti-HIV drugs from AIDS associated malignancy and non AIDS associated malignancy
Cardiac events leading to ischaemia	Routine pharmacovigilance Review outputs from ongoing HAART-OC collaboration and ongoing studies: COL110408, COL112372 and COL112779
Exposure to abacavir during pregnancy	Routine pharmacovigilance Review of the Antiretroviral Pregnancy Registry
Drug interaction between abacavir and ribavirin	Routine pharmacovigilance Review final outputs from ongoing study COL112055
Missing information	Proposed pharmacovigilance
Use in paediatrics	Routine pharmacovigilance Ongoing dolutegravir paediatric Study ING112578
Use in pregnancy/breastfeeding	Routine pharmacovigilance Review of the Antiretroviral Pregnancy Registry

Risk minimisation activities

In addition to routine risk minimisation activities via the PI and Consumer Medicine Information (CMI), the sponsor proposes a patient alert card and HLA-B*5701 screening for the risk of hypersensitivity. The training provided by the Australasian Society for HIV Medicine to prescribers is also included as a risk minimisation measure.

Reconciliation of issues outlined in the RMP report

Table 10 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 10: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*Information provided in responses to safety considerations raised by the non-clinical and clinical evaluators include a consideration of the relevance for the Risk Management Plan. No changes to the Risk Management Plan are proposed on the basis of these responses.*	The sponsor's response is satisfactory.
In the sponsor's email response to the TGA dated 03 February 2014, the contact details of the contact person for the RMP in Australia were provided as. This information should be included in the ASA.	*The person responsible for the implementation of the RMP activities within Australia is the nominated qualified person responsible for pharmacovigilance at ViiV Healthcare Pty Limited.* *The TGA have previously been advised of the nominated person responsible for pharmacovigilance. Per correspondence from ViiV Healthcare Pty Ltd to the TGA, dated 1 February 2012 and 3 February 2014. GSK Australia provides Pharmacovigilance services to ViiV Healthcare Pty Ltd as set out in the Australian Specific Annex to the EU RMP.*	The sponsor's response is noted. The TGA is developing guidance for the content and format of ASA.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	Per the Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines v1.3, June 2014, the sponsor commits to update the TGA with any changes to the responsible person within 15 calendar days in accordance with the requirements.	
The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	*ViiV notes the evaluator's suggestion. ViiV refers the evaluator to Part III.4 of the EU RMP (Table 29 and Table 30) and Annex 4 of the EU RMP (Synopsis of on-going and completed clinical trial programme). The anticipated timings of all the relevant clinical studies are included in these sections of the EU-RMP. The Australian Specific Annex to the EU-RMP notes in Section 2.4 that all additional pharmacovigilance activities are relevant to Australian patients. The results of these studies will be summarised in future RMPs and Periodic benefit-risk evaluation reports (PBRERs), as appropriate. Further, according to TGA requirements and corresponding standard internal ViiV/GSK process, any safety signals identified in these studies may result in an update to the Core Safety Information and/or other appropriate actions, which would trigger submissions to the TGA for assessment of additional safety information for inclusion in the PI and for implementation of other risk minimisation activities.* *Any efficacy data generated from these studies may be used to support future submissions to the TGA; however, while all relevant safety data must be notified to the TGA, ViiV understands that the decision to submit applications to update efficacy data in the product information is at the discretion of the sponsor unless it impacts the product benefit/risk. As a result,*	The sponsor's response is noted. The TGA is developing guidance for the content and format of ASA.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	ViiV does not propose to outline a submission plan for efficacy data at this time. *Therefore, ViiV believes that sufficient information is already included in the EU RMP to address the evaluator's question.*	
The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.	*The safety specification and pharmacovigilance plan identified in the EU-RMP are relevant for patients in Australia. Therefore all of the planned pharmacovigilance actions proposed in the EU-RMP will be implemented in Australia. Section 2.3 and 2.4 of the ASA confirms that all planned/ongoing studies are relevant to Australian patients. Relevant study findings will be reported to the TGA via Periodic Benefit Risk Evaluation Reports and future RMP updates.* *Risk minimisation measures described in the EU-RMP will be implemented in Australia. Differences in such measures between the EU and Australia are clearly described in Section 3.1 and 3.2 of the ASA.* *Consequently, ViiV does not believe it necessary to provide a separate table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in a revised ASA. This is also in keeping with other approved ASAs for ViiV and GSK products.*	The sponsor's response is noted. The TGA is developing guidance for the content and format of ASA.
The sponsor has advised that the following advice (refer to the EU Summary of Product Characteristics (SmPC)) on patients with liver disease and patients with chronic hepatitis B or C is currently missing in the proposed Australian PI. The evaluator considers that	*The advice described was added to the SmPCs of Ziagen and Kivexa during variations Ziagen EMEA/H/C/252/II/62 and Kivexa EMEA/H/C/II/35, which were approved on the 24 October 2011.* *The advice was reluctantly added to the SmPCs at the request of the EMA, and at the time the company did not consider that updates to the*	The recommendations on the draft Product Information remain, awaiting consideration by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
these advices are relevant and important. It is recommended to the Delegate that they are added to the PI.	*Ziagen or Kivexa Global Datasheet were warranted, and did not believe that the enforced additional text impacted the benefit risk assessment of Ziagen or Kivexa.* *COL112055: (Pharmacokinetic Interactions Of Ribavirin And Abacavir In HCV Mono-Infected Subjects Who Previously Successfully Completed Or Failed RBV-Based Treatment For HCV) is an ongoing US study which is due to report out this year. The sponsor is awaiting results from this study before further considering a position in the Ziagen and Kivexa GDSs.* *Of note, the European medicines Agency (EMA) made certain requests during the Kivexa Renewal;* *(OPR evaluator: table not included)* *The sponsor is awaiting the availability of COL112055 in order to satisfy the PAM.* *With this in mind the sponsor does not believe it is necessary to add details of the potential abacavir/ribavirin to the Triumeq PI at this time. Additionally it is noted that the local Australian PI's of Ziagen and Kivexa do not include this information.*	
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that where changes to the PI are required, the content of the proposed CMI be updated accordingly to provide adequate information to patients and carers.	*ViiV commits to ensuring that CMI is aligned with the PI. Based on changes made to the PI, ViiV has updated the CMI and included the new version.*	Refer to Recommendation 5.

Summary of recommendations

Issues in relation to the RMP

Details on the following outstanding issues are in section 5. 'Reconciliation of issues outlined in the RMP report'.

Recommendation 5: The recommendation(s) on the draft Product Information remain, awaiting consideration by the Delegate.

Additional recommendations

The following safety concerns identified in the clinical evaluation report should be added to the safety concern list in the Australian Specific Annex:

'Identified risk

Rebound hepatitis following discontinuation of lamivudine.

Potential risks

Mitochondrial dysfunction for ABC and/or 3TC

Bone disorders

Overdose

Patient misuse of antacids and iron containing medications risking loss of efficacy for dolutegravir

Missing information

Long term follow-up of individuals exposed in utero should be considered separately from the 'Long term safety data' included in.

The large size of the tablet is a potential problem, especially for patients with oral and oesophageal problems

Interaction study between DTG and lamivudine has not been done'

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

Triumeq EU-RMP version 1.0, dated 3 October 2013 (data lock point 31 May 2013) and Australian-specific Annex to be revised to the satisfaction of the TGA, should be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The sponsor is required to provide an update of the GMP status of all overseas manufacturing sites prior to registration.

There are no other objections regarding registration of dolutegravir/ abacavir/ lamivudine tablets from a pharmaceutical chemistry perspective.

A shelf life of 15 months when stored below 30 °C is currently supported.

Nonclinical

The nonclinical submission comprised two new pharmacokinetic studies investigating potential pharmacokinetic interactions between DTG and substrates of a range of membrane transporters and an in vivo clastogenicity assay with ABC and 3TC. No toxicity studies have been conducted with the proposed combination. The evaluator considered the potential for additive or synergistic toxicity at clinically relevant concentrations to be low.

There are no nonclinical objections to the proposed new fixed dose combination.

Clinical

To support this application to register the new fixed dose product including dolutegravir, abacavir and lamivudine, a pivotal bioequivalence Study ING114580 and a pivotal safety and efficacy Study ING114467 have been submitted.

Also included in the data package are supportive safety and efficacy Studies ING113086, ING114915 and ING111762, and drug interaction Study ING116898 and pharmacodynamic Study ING116070.

A summary of submitted clinical studies and the evaluator's overall conclusions are provided in Attachment 2.

Pharmacology

ING114580 was a single-centre, randomised, two-part, open-label, crossover to evaluate the single-dose pharmacokinetics of an oral DTG 50 mg/ABC 600 mg/3TC 300 mg combination tablet formulation proposed for commercial use, compared to co-administration of the separate tablet formulations of DTG 50 mg and the US registered fixed dose combination of ABC/3TC, in the fasted state. For each of DTG, ABC, and 3TC, the 90% CIs for the geometric least-squares mean ratios for each of the bioequivalence parameters were within the bioequivalence criteria range of 0.8 to 1.25. Part B of this study involved a subset who had completed the two doses in the fasted state, who were administered oral DTG 50 mg/ABC 600 mg/3TC 300 mg combination tablet with a high fat meal. The results for DTG for the FDC tablet following the high fat meal were approximately 48% higher for AUC and 37% higher for C_{max} than in the fasted condition but the applicant did not consider these increases were clinically significant. For both ABC and 3TC the results indicate that plasma exposures from the FDC tablet administered with a high fat meal were similar to those in the fasted state, although the C_{max} for ABC was approximately 23% lower when the FDC tablet was taken with food. These results are presented in Attachment 2.

ING116898 was an interaction study to evaluate effects of calcium carbonate 1200 mg and ferrous fumarate 324 mg on pharmacokinetics of DTG 50 mg in healthy adults. Co-administration of DTG with either calcium carbonate or ferrous fumarate under fasted condition resulted in reduction in plasma DTG exposures; plasma DTG $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, C_{max} and C24 by approximately 37 to 39% with calcium carbonate and 54 to 57% with ferrous fumerate. Co-administration of DTG with calcium carbonate or ferrous fumarate under fed condition counteracted the interaction and provided plasma exposures comparable to DTG alone under fasted conditions. Similarly, DTG administered under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate or ferrous fumarate resulted in plasma exposures comparable to DTG alone.

Pharmacodynamics

ING116070 is an ongoing Phase IIIb single-arm, open-label, multicentre study of HIV-1 infected ART-naïve patients to determine the potential for dolutegravir to enter the cerebrospinal fluid (CSF) compartment. Week 16 results were submitted for 11 participants. DTG concentrations observed in CSF at both Week 2 and Week 16 exceed the in vitro IC_{50} against wild-type viruses (0.2 ng/mL) for all subjects suggesting that DTG is able to achieve therapeutic concentrations in the CSF. A regimen of DTG + ABC/3TC was effective in decreasing CSF HIV-1 RNA levels.

Efficacy study ING114467

This is a single ongoing pivotal study in treatment-naïve adult patients. The study involves a Phase III, parallel group, randomised, double-blind design and compares DTG + ABC/3TC (Epzicom) with emtricitabine/tenofovir/efavirenz (EFV/TDF/FTC). The study commenced in 2011 and this submission provides a Week 96 analysis report with last observation dated May 2013. The 48 week data from this study were included in initial dolutegravir submission (SINGLE).

At Week 48 (previously evaluated), the adjusted difference (DTG- EFV) was 7.4 % (95% CI: 2.5-12.3) (p=0.003) consistent with conclusion of superiority of DTG + ABC/3TC. The primary efficacy endpoint was reassessed as a secondary objective at Week 96. The adjusted difference, DTG minus EFV/TDF/FTC was 7.3% (95% CI: +1.4%, +13.3%). The result supported the Week 48 finding.

Virologic response rate differences between DTG+ABC/3TC and EFV/TDF/FTC were due to a lower rate of discontinuations due to AEs on the DTG+ABC/3TC arm (13/414, 3% on DTG+ABC/3TC versus 48/419, 11% on EFV/TDF/FTC). Eight percent (8%) of EFV/TDF/FTC participants were virologic non responders compared with 7% in the DTG+ABC/3TC group. Twenty percent (20%) of participants in the EFV/TDF/FTC group and 12% in the DTG + ABC/3TC group were considered non responders because of lack of virologic data at Week 96.

Study ING113086 (spring-2)

This is an ongoing supportive study in treatment naïve patients. The study involves a Phase III, parallel group, randomised double-blind design and compares DTG versus raltegravir each administered with either ABC/3TC or TDF/FTC. The study commenced in October 2010. This submission provides a Week 96 analysis report.

The key secondary objective was to demonstrate the antiviral activity of DTG versus RAL over 96 weeks. At Week 96, 81% of the DTG group and 76% of the RAL group achieved < 50 c/mL plasma HIV-1 RNA in ITT-E population. The per-protocol results were 83% and 80% respectively. The difference in proportions (95% CI) for the ITT-E population was 4.4% (-1.2, 10.0). Kaplan-Meier estimates of the proportion of subjects without treatment/efficacy related failure by Week 96 were similar for DTG and RAL. DTG administered once daily with two NRTIs demonstrated non-inferiority to RAL at Week 96. The proportion of subjects with HIV RNA <50 c/mL (81%) compares favourably with RAL (76%) through 96 weeks.

Study ING114915 (flamingo)

This is an ongoing supportive study in treatment naïve patients. The study involves a Phase IIIb, parallel group, randomised, open-label design and compares DTG versus darunavir+ritonavir, each in combination with ABC/3TC or TDF/FTC. The study commenced in October 2010

The primary objective was to demonstrate the non-inferior antiviral activity of DTG compared to DRV+RTV over 48 weeks of treatment. Antiviral activity was assessed as the proportion of participants with plasma HIV-1 RNA < 50 c/mL determined by the FDA

Snapshot algorithm. Non-inferior criteria were if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 was above - 12%. The primary population used in analysis was the mITT-E population, defined as all randomised subjects who received at least 1 dose of IP.

Of 488 patents randomly assigned, 484 received at least 1 dose of study medication. The rates of premature withdrawals were: DTG 7%; DRV+RTV 12%. The proportions withdrawing due to AEs were: DTG 1%, DRV+RTV 4%, and lost to follow-up: DTG 2%, DRV+RTV 4%.

Most participants were White (72%) and male (85%) with median age of 34 years. Most had negative screening test for hepatitis B and HCV (90%), were in CDC Class A (84%), and identified homosexual activity as an HIV risk factor (70%).

Initially 33% of subjects were prescribed ABC/3TC as background NRTI, the remainder receiving TDF/FTC.

The primary analysis demonstrated non-inferiority of DTG compared to DRV+RTV; superiority was also concluded. At Week 48, 90% of the DTG group versus 83% of the DRV+RTV group achieved the primary endpoint. The difference (95% CI) = 7.1% (0.9, 13.2). The results for the Per Protocol (PP) analysis supported the mITT-E analysis: 91% and 84% of DTG and DRV+RTV subjects, respectively, achieved <50 c/mL plasma HIV-1 RNA at Week 48 and the lower end of the 95% CI for the adjusted treatment difference was 1.4%.

Differences in virologic response rate were primarily driven by discontinuations due to AEs (DTG 1%, DRV+RTV 4%) and other reasons (DTG 2%, DRV+RTV 5%).

Treatment differences for DTG compared to DRV+RTV across the baseline stratification factors were supportive of the primary analysis. Treatment differences for DTG compared to DRV+RTV across demographic subgroups were generally supportive of the primary analysis. The median time to suppression was 28 days for subjects in the DTG treatment group compared to 85 days in the DRV+RTV treatment group. The CER comments that relevance of this study to Triumeq is limited as the numbers treated with DTG/ABC/3TC were relatively small.

Study ING111762 (sailing) - treatment-experienced

This is an ongoing supportive study in treatment experienced patients.. The study involves a Phase III, randomised, double-blind design comparing DTG 50 mg once daily versus RAL 400 mg twice daily, both administered with an investigator selected background regimen to HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy- experienced adults with documented resistance to 2 or more different classes of antiretroviral agents. The study commenced in October 2010. The Week 48 results are reported in this submission, the Week 24 week results having been previously evaluated for registration of dolutegravir.

The primary objective was to demonstrate the antiviral efficacy of DTG 50 mg once daily compared to RAL 400 mg twice daily each with a background regimen consisting of one to two fully active single agents. The primary endpoint was the proportion of participants with HIV-1 RNA < 50 c/mL to Week 48 using the Snapshot algorithm.

At Week 48, 71% of patients receiving DTG and 64% receiving RAL achieved HIV-1 RNA < 50 c/mL. The difference, DTG - RAL, (95% CI) was 7.2 (0.3, 14.0). The pre-specified basis for concluding non-inferiority and superiority were met.

Within subgroups defined by the baseline randomization strata, treatment differences were generally supportive of the overall treatment difference; however, DTG and RAL response rates were similar for subjects receiving DRV/r without primary PI mutations. Other subgroup analyses were generally supportive of the overall result. The CER

comments that this study included very few participants with background therapy of ABC/3TC.

Virology

In ING114467, the pivotal study in treatment naïve patients, the protocol defines virologic failure (PDVF) as two consecutive HIV-1 RNA values ≥ 50 c/mL on or after Week 24. PDVF mandated testing for resistance and withdrawal from the trial. Virologic failure occurred in 25/414 (6%) in the DTG + ABC/3TC group and 25/419 (6%) in the EFV/TDF/FTC group. The majority with confirmed PDVF had low-level viraemia. Thirteen participants in the DTG + ABC/3TC group and 10 in the EFV/TDF/FTC group arm had IN genotype and phenotype at both Baseline and PDVF. No INI resistance mutations were found. One participant in the DTG + ABC/3TC group had a treatment emergent substitution E157Q/P at Week 24, without accompanying DTG phenotypic resistance.

In ING113086 (Spring -2), a supportive study in treatment naïve patients, PDVF was met by 22 (5%) in the DTG group versus 29 (7%) in the RAL group. Three participants had PDVF after Week 48 (2 DTG patients and 1 RAL patient). No treatment emergent IN or NRTI resistance mutations were detected. Overall, there was a low rate of discontinuation due to virologic failure in both treatment arms, with only three additional subjects with PDVF identified after Week 48. The durability of the virologic response in the DTG and RAL groups was maintained through Week 96. Both INI (RAL) and NRTI primary resistance mutations were observed in subjects on RAL with PDVF up to Week 48. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.

In ING114915 (Flamingo) in treatment naïve patients, two participants (<1%) in DTG treatment group and 2 patients in DRV+RTV group met PDVF up to Week 48. No treatment-emergent primary IN or NRTI resistance mutations were observed in either treatment group.

In ING11762 (Sailing), a supportive study in treatment experienced patients, at Week 48 21 (6%) and 45 (12%) PDVFs were reported for DTG and RAL respectively. At Week 48, 17 participants with PDVF in the DTG arm had matched Baseline and PDVF INI genotypic resistance testing results available. Four patients in the DTG arm had emergent integrase-defined substitutions: 3 out of 4 experienced virologic rebound; 1 experienced non-response. Integrase substitutions emerged at the RAL associated T97, E138, and polymorphic V151 positions and at R263. At Week 48, 38 participants with PDVF in the RAL arm had matched Baseline and PDVF INI genotypic resistance testing results available. Integrase substitutions emerged at positions commonly observed during RAL therapy including primary resistance mutations at Y134, Q148, and N155 as well as associated secondary mutations. No DTG subjects had treatment-emergent INI phenotypic resistance at PDVF. Thirteen subjects receiving RAL had evidence of treatment-emergent INI phenotypic resistance to RAL at PDVF.

The study design presented a risk that many subjects would have resistance to only two classes of ART (most likely to NRTIs and NNRTIs but not PIs).

Safety

ING114580 was the pivotal study in healthy adults evaluating the single-dose pharmacokinetics of an oral DTG ABC/3TC combination tablet formulation proposed for commercial use, compared to co-administration of the separate tablet formulations of DTG 50 + ABC/3TC. Sixty-six participants received at least one dose of study medication. Adverse events were reported by 38 to 40% of participants, with nausea and headache most frequent events. There was no Grade 3 or 4 adverse events and no SAEs reported.

ING114467 is the pivotal ongoing, Phase III, parallel group, randomised, double-blind, active-controlled, multinational study of DTG + ABC/3TC compared with EFV/TDF/FTC in treatment of HIV-1 infected ART naïve adult patients. Safety results are presented in Attachment 2. A total of 843 patients were included in the safety population. Treatment related events were more common in the EFV/TDF/FTC group. The most common drug related adverse events were dizziness (67% versus 44%) and abnormal dreams (33% versus 7%), both of which were reported more commonly in the EFV/TDF/FTC group. The incidence of Grade 3 and 4 events combined was 57/414 (14%) for the DTG+ABC/3TC group versus 83/419 (20%) for the EFV/TDF/FTC group. In the DTG/ABC/3TC group, Grade 4 events (also reported as SAEs and considered unrelated) were subdural haematoma, priapism, homicidal and suicidal ideation and intentional overdose/ suicide attempt. Five participants reported non-serious Grade 4 events in the EFV/TDF/FTC group: muscle injury, creatinine phosphokinase (CPK) increase (2 participants) and hyperglyceridaemia (considered IP related).

Two participants treated with EFV/TDF/FTC reported at least one drug related Grade 4 event, also reported as an SAE: one with cerebrovascular accident, one with paranoia and suicidal ideation. In the DTG + ABC/3TC group, one SAE was considered related to IP (drug hypersensitivity). Nine in the EFV/TDF/FTC group had SAEs considered related to study treatment: syncope (2); depression, homicidal ideation and suicidal ideation; paranoia and suicidal ideation; drug hypersensitivity; cerebrovascular accident; hallucination, visual; and bipolar (1 each).There were two deaths to Week 96, both in the EFV/TDF/FTC treatment group and included in the Week 48 analysis. One event, renal failure, was considered possibly related to study drug.

Any AE leading to permanent discontinuation and withdrawal was reported in 3% of DTG +ABC/3TC and 12% of EFV/TDF/FTC group.

Four participants in the DTG group and 6 in the EFV/TDF/FTC group reported hypersensitivity.

The distribution and number of graded treatment emergent clinical chemistry toxicities was similar between the DTG + ABC/3TC and EFV/TDF/FTC treatment groups.

There was a low rate of elevated liver chemistries in both arms. For ALT > 3xULN reported numbers were 7 (2%) for the DTG+ABC/3TC group and 17 (4%) for the EFV/TDF/FTCgroup. Reports for elevated ALP were 14 (3%) for the DTG/ABC/3TCgroup; 47, (11%) for the EFV/TDF/FTCgroup. No one in either group reported combined ALT >3xULN, total bilirubin >2xULN and ALP <2xULN.

Rhabdomyolysis and myositis were not reported for DTG/ABC/3TC group. One case of myositis was reported for EFV/TDF/FTC group. The incidence of musculoskeletal and connective tissue disorders was comparable between treatment groups (DTG/ABC/3TC 109/414 (26%), versus EFV/TDF/FTC 93/419 (22%). The incidence of arthragia was, DTG+ABC/3TC 23/414 (6%), versus EFV/TDF/FTC 20/419 (5%). Myalgia was reported by 16 of 419 (4%) in the EFV/TDF/FTC group versus 7 of 414 (2%) the DTG/ABC/3TC group.

The most commonly reported treatment emergent haematology abnormality was decreased absolute neutrophils. No clinically significant differences were reported between the two treatment arms with respect to haematology abnormalities.

The mean changes in LDL and total cholesterol were small.

Twelve participants became pregnant (DTG+ABC/3TC 5/414, EFV/TDF/FTC 7/419). Four normal neonates have been delivered (2 in each group). Three participants in the DTG/ABC/3TC group and 1 in the EFV/TDF/FTC group had elective terminations. A further elective termination was carried out due to an ectopic pregnancy (EFV/TDF/FTC). Three spontaneous abortions were reported; 1 in the DTG/ABC/3TC group 2 in the

EFV/TDF/FTC group; none were considered related to IP. No congenital anomalies were reported. One pregnancy in the EFV/TDF/FTC group was ongoing at data cut off. The partner of a male participant in the DTG/ABC/3TC group delivered a normal infant.

Safety conclusions for the DTG/ABC/3TC group of patients demonstrated a safety and tolerability profile that was generally favourable to that of EFV/TDF/FTC group over the period of the study.

- Based on Week 96 data, there appears to be no increased risk of either hepatic or renal toxicity for patients treated with DTG/ABC/3TC compared to those treated with EFV/TDF/FTC
- Nervous system and psychiatric disorders were more frequent in patients treated with EFV/TDF/FTC, with the exception of insomnia, which was more frequent in the DTG/ABC/3TC group
- The superiority of the efficacy response rate in the DTG/ABC/3TC group was due to a higher rate of participants on EFV/TDF/FTC reporting events leading to withdrawal from the study; specifically from the psychiatric disorders, nervous system disorders, gastrointestinal disorders and general disorders and administration site conditions events SOCs
- There is no evidence from this study for increased risk of rash with or without systemic symptoms in patients treated with DTG/ABC/3TC. There was no increase in suspected abacavir HSR for DTG/ABC/3TC in this HLA-B*5701 pre-screened population.

ING113086 (Spring-2) was a supporting study comparing DTG and RAL in treatment naïve patients, in which around 40% of patients received ABC/3TC as backbone NRTI. A total of 822 patients received at least 1 dose of study medication. With respect to safety, the most commonly reported clinical AEs among participants receiving DTG and RAL were nausea, nasopharyngitis, diarrhoea and headache with no appreciable difference between treatment groups. Most events in both treatment groups were considered Grade 1 or 2. There were 18 Grade 4 events reported in the DTG group, 2 of which were reported as SAEs and considered IP related: drug hypersensitivity and hepatitis. Seven participants randomised to RAL reported Grade 4 AEs, all reported as serious and none related to IP.

Reporting rates for IP related AEs were: DTG 124/411 (30%); RAL 121/411 (29%). The only drug-related AE reported in ≥ 5% of subjects in each treatment group was nausea: DTG 40/411 (10%); RAL 45/411 (11%). Grade 3/4 events considered possibly or probably related to IP in each group were reported for 4 in the DTG 4 group, 4 in the RAL group. For DTG, the events were: Grade 3: headache, dizziness, feeling abnormal, arrhythmia; Grade 4: Drug hypersensitivity with associated ALT/AST/ALP/total bilirubin/LFT and hepatitis (one participant each). For RAL, the events reported for the five participants with Grade 3 events assessed as possibly/probably related were: Grade 3: nausea, abdominal pain, aphasia, drug eruption, fatigue, ALT increased, CPK increased, lipase increased and decreased appetite.

There were no deaths related to IP. At least one SAE was reported by 10% for DTG and 12% for RAL. Drug related events were reported by < 1% of those taking DTG and 1% for RAL. All individually reported SAE preferred terms had an incidence of ≤ 1% in either treatment group. The SAEs considered to be related to DTG (N = 3) were: Arrhythmia leading to withdrawal; hypersensitivity considered by the investigator to be related to DTG (the sponsor also implicated co-suspect ABC/3TC) and hepatitis considered possibly drug induced.

DTG demonstrated a safety and tolerability profile that was similar to that of RAL over the period of the study. No new DTG safety concern was uncovered between Weeks 48 and 96. The conditions labelled for RAL including serious rash and myopathy and rhabdomyolysis

were not reported for DTG. Numbers studied may preclude identification of rare events. Serious hypersensitivity events were rare and there was no increased risk for DTG compared to RAL.

ING114915 (Flamingo) is a supporting study comparing DTG and DRV+RTV , with either ABC/3TC (33%) or TDF/FTC (67%), in treatment naïve patients. 484 patients received at least 1 dose of study medication. The most commonly reported AEs in both treatment groups were diarrhoea, nausea, headache and nasopharyngitis. Diarrhoea and upper respiratory tract infection were more frequently reported among those in the DRV+RTV group and headache was more frequently reported in the DTG group. The majority of events reported in both groups were considered to be of Grade 1 or Grade 2. The incidences of drug-related events were similar except for diarrhoea which was reported more frequently in the DRV+RTV group. The discrepancy in incidence was largely due to higher numbers in the DRV+RTV group with Grade 1 events.

No deaths were reported. One patient in the DTG treatment group reported an SAE considered by the investigator to be related to IP; a suicide attempt. SAEs were individually reported by < 1% of participants. One SAE report of hypersensitivity reaction Grade 2, disseminated maculopapular rash and erythema without associated symptoms, was suspected by the investigator to be due to ABC; however, the sponsor did not consider the event to be a convincing case of ABC hypersensitivity reaction due to lack of multisystem involvement and considered DRV+RTV to be the likely cause.

The incidence of psychiatric disorders was 19% for the DGT group and 14% for the DRV+RTV group. Insomnia, depression, and anxiety were the most commonly reported. The frequencies were: insomnia DTG 18 (7%); DRV+RTV 15 (6%); anxiety: DTG 10 (4%); DRV+RTV 7 (3%) and depression DTG 11 (5%); DRV+RTV 6 (2%). All other events in this SOC were reported in ≤ 1%. Insomnia was considered drug related for 2% of the DTG group and 1% of the DRV+RTV group.

ING11762 (Sailing) is a supporting study comparing DTG 50 mg once daily versus RAL 400 mg twice daily, with an investigator selected background regimen, in treatment experienced adults. Week 48 results are presented. The numbers included in the safety populations were DTG 357 and RAL 362 with 7 or 9 participants treated with DTG+ABC/3TC. The most common Grade 2 to 4 drug related AEs were diarrhoea, nausea, headache, and abdominal pain. AEs leading to discontinuation of treatment occurred in less than one percent of patients in each group. Six participants in the DTG group were identified as having IRIS or possible IRIS. Five of these six were considered to have hepatitis B and/or hepatitis C IRIS There was a signal of HCV IRIS with DTG. The clinical evaluator considered it was not possible to make generalisation regarding the similarity of safety compared to studies enrolling treatment-naïve patients.

Clinical evaluator's conclusions and recommendation

Benefits: The DTG/ABC/3TC fixed dose combination has been shown to be bioequivalent to DTG + ABC/3TC. The latter combination has been shown to be effective in maintaining viral suppression as shown in ING114467. There were no unexpected safety concerns detected in ING114467. There was a high barrier to resistance reported in the study. The FDC may increase treatment compliance although this remains hypothetical.

Risk: The safety profiles of lamivudine and abacavir have been established since first registration in the US of lamivudine in 1995 and abacavir in 1998. The safety profile of the recently registered dolutegravir is not so well established. For individual patients, there is the potential for development of significant adverse events consistent with the known safety profiles.

The large dimensions of the tablet (22 x 11x7.6 mm with circumference 54.6 mm) may preclude use, or result in misuse of the product for some patients.

Registration of the fixed dose combination, dolutegravir/abacavir/lamivudine was recommended.

Risk management plan

Outstanding issues in relation to the RMP were the safety concerns identified in the clinical evaluation report should be added to the safety concern list in the Australian Specific Annex.

ACSOM advice was not sought for this submission.

Risk-benefit analysis

Delegate's considerations

The Delegate agrees with the clinical assessment of the benefits and risk of this fixed dose combination tablet. The Delegate concurs with the recommendation for registration.

The clinical evaluator comments on the large dimensions of the tablet. The sponsor has noted that Kivexa and Atripla are other fixed dose combination tablets with similar dimensions. The sponsor has also commented that difficulty swallowing has been reported in only 2 cases with no adverse effect on medication adherence in DTG/ABC/3TC FDC development studies.

The clinical evaluator recommends deletion of references in the *Clinical Trials* section of this product to studies ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) as a minority of participants received the DTG+ABC/3TC combination, and the results for subgroup analyses were considered insufficiently rigorous for inclusion in PI. The Delegate supports this recommendation.

Summary of issues

The clinical evaluation report concludes the DTG/ABC/3TC fixed dose combination has been shown to be bioequivalent to DTG + ABC/3TC. The latter combination has been shown to be effective in maintaining viral suppression as shown in ING114467. There were no unexpected safety concerns detected in ING114467. There was a high barrier to resistance reported in the study. The clinical evaluation supports registration of the fixed dose combination tablet.

The clinical evaluation report considers the large dimensions of the tablet may preclude use, or result in misuse of the product for some patients. The Delegate accepts the sponsor comment that other registered fixed dose combination tablets, such as Kivexa, have similar dimensions.

The Delegate supports the clinical evalautor's recommendation in relation to inclusion of the Studies ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) in the Triumeq PI (see *Delegate's considerations* above).

Proposed action

The Delegate had no reason to say, at this time, that the application for Triumeq should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACPM consider it is appropriate to include clinical Studies ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) in the Clinical Trials Section of PI for Triumeq?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

Triumeq is a once-daily FDC that combines the novel integrase inhibitor (INI) dolutegravir (DTG) with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir sulfate (abacavir, ABC) and lamivudine (3TC). Triumeq has been developed as a single treatment regimen (STR) for the treatment of HIV infection and has recently been approved by the US and the EMA on 22 Aug 2014 and 2 Sep 2014, respectively.

ViiV welcomes the TGA Delegate's assessment that there are no reasons that the application for Triumeq should not be approved for registration. This recommendation is also supported by the clinical evaluator who has stated that '*The balance is considered to lie on the side of benefit*' and '*Registration of the fixed dose combination, dolutegravir/abacavir/lamivudine is recommended*'.

The proposed indication, as amended, is as follows:

> *Triumeq 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 (dolutegravir, abacavir or lamivudine) in Triumeq.*

The sponsor believes that Triumeq will be a valuable new therapeutic option for patients and prescribers, as it allows the benefits of a maximally simplified daily treatment (that is, a once-daily single tablet regimen). Triumeq offers improved tolerability and treatment outcomes versus Atripla, and DTG's high barrier to resistance versus other non-nucleoside reverse-transcriptase inhibitor (NNRTI) or INI-based STRs.

The only advice sought by the TGA Delegate from ACPM is regarding the recommendation to remove discussion of the ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) studies from the Clinical Trials section of the PI. ViiV agrees to this recommendation.

Triumeq is also being assessed for reimbursement at the November 2014 Pharmaceutical Benefits Advisory Committee (PBAC) meeting under the parallel processing arrangement. ViiV would like to thank and acknowledge the TGA for providing the Delegate's Overview in time for this PBAC meeting.

Efficacy

For the Triumeq development program, one pivotal study and five supportive studies provide safety and efficacy data in support of this combination 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).

The pivotal Triumeq study is ING114467 (SINGLE). This study evaluated a regimen of once-daily DTG 50 mg + ABC/3TC 600/300 mg FDC as one of two randomised study treatments. Superiority of DTG + ABC/3TC combination over EFV/TDF/FTC (Atripla), a recommended first-line therapy in US Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS), World Health Organization (WHO), and other

treatment guidelines for HIV-1-infected, antiretroviral therapy (ART)-naïve subjects, was demonstrated at both Week 48 and 96.

- Differences in efficacy were primarily driven by a lower rate of discontinuation due to AEs on the DTG + ABC/3TC arm
- Week 48 (the time point for the primary endpoint analysis) treatment differences between DTG + ABC/3TC combination and EFV/TDF/FTC were consistent across the Baseline stratification factors
- The results from the pivotal Study ING114467 demonstrate that a treatment regimen with DTG/ABC/3TC is at least as effective as treatment regimens with EFV/TDF/FTC combination, including subjects with a Baseline viral load >100,000 c/mL.

Underpinning all the clinical efficacy studies was the bioequivalence (BE) Study ING114580, establishing that Triumeq is bioequivalent to DTG+ABC/3TC administered concomitantly. The broad experience with the constituent antiretroviral agents combined with confirmatory BE data establishes the safety.

The clinical evaluator has concluded that '*there were no unexpected safety concerns detected in ING114467*'. The safety and tolerability profile of Triumeq has been shown to be favourable:

- The risk of toxicity with DTG+ABC/3TC combination appears to be no different to that observed with either DTG alone or the ABC/3TC FDC when used with other ARV-agents in combination ART (cART)
- The safety profile for DTG + ABC/3TC was generally favourable compared with Atripla and comparable to RAL+ABC/3TC and DRV+RTV + ABC/3TC combinations in ART-naïve HIV- infected patients
- Cases of hypersensitivity reaction have been uncommon with DTG+ABC/3TC, with rates comparable to Atripla, RAL+ABC/3TC and DRV+RTV+ABC/3TC combinations
- Cumulative data suggest a hepatic safety profile for DTG + ABC/3TC that is comparable to Atripla, RAL + ABC/3TC and DRV +RTV + ABC/3TC combinations
- The incidence of rash in patients treated with DTG+ABC/3TC FDC was lower than with Atripla but comparable to RAL+ABC/3TC and DRV+RTV+ABC/3TC.

The safety profile of ABC and 3TC is well defined and supported by years of postmarketing experience and extensive clinical trial data. The safety and efficacy profile of the component drug DTG has been established from the DTG clinical program although it is recognised that DTG is a newer agent which was approved by the TGA in January 2014. The safety of DTG and Triumeq will be continually monitored via further clinical development and postmarketing monitoring. Reporting of safety data and any changes in benefit-risk profile will be captured in periodic benefit risk evaluation reports and updates to the risk management plan.

Identified risks for Triumeq include hypersensitivity reactions, hepatitis and a potentially serious drug interaction with dofetilide/pilsicainide. The sponsor believes that appropriate labelling and risk management activities have been assigned to mitigate these risks.

The sponsor's comments on delegate's request for ACPM advice

1. *Does the ACPM consider it is appropriate to include clinical studies ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) in the Clinical Trials section of the PI for Triumeq?*

The effectiveness of Triumeq for the treatment of HIV-1 infection is demonstrated with results from clinical studies conducted over many years under the development programs for DTG, ABC, 3TC, and the ABC/3TC FDC.

The efficacy of Triumeq in ART-naïve subjects is primarily demonstrated in the pivotal Study ING114467 (SINGLE), but also in the supportive Studies ING113086 (SPRING-2) and ING114915 (FLAMINGO). ART-experienced subjects were included in supportive Study ING111762 (SAILING).

The sponsor accepts the position of the TGA Delegate and the clinical evaluator that a relatively small proportion of the patients included in these supportive studies received all three components of Triumeq. The sponsor believes that these studies are of value in the additional demonstration of the efficacy and safety of Triumeq. ViiV is prepared to accept the position of the TGA Delegate that discussion of these studies therefore should be removed from the Triumeq PI and replaced by a cross reference to the Tivicay PI.

Accordingly, ViiV therefore proposes to remove the detail of these studies from the Clinical Trials section of the Australian PI and add a statement based of the US PI instead.

Dimensions of tablet

Since the early days of cART, where patients struggled with many pills, two or three times daily, to contemporary years, patients and health care providers have advocated the development of as simple as possible of regimens. Triumeq is a once daily tablet without food requirements.

The Triumeq tablet is very close in size to the other single table regimens, especially Atripla, as well as the Kivexa formulation. The fact that Triumeq has a very similar size to these already marketed formulations would predict that adherence should not be negatively affected. This is especially true when taking into account the Kivexa formulation, since that product has been in use in Australia since its listing on the Pharmaceutical Benefits Scheme in 2005.

Two clinical trials provide insight on any patient impact regarding tablet size: the pivotal BE trial, ING 114580, which was conducted in adult subjects, and a large, ongoing multi-center, international Phase IIIB-study, ING117172, which has randomised over 300 women to date to Triumeq or tenofovir/emtricitabine plus atazanavir/ritonavir. As of October 2014, the sponsor is aware of only three cases regarding an issue with the formulation from subjects in the development studies: in one case the subject had some difficulty swallowing the Kivexa tablet (commercial) in the BE trial (PK sampling was discontinued) and the patient remained in the trial; one subject in the ongoing ING117172 study has mentioned difficulty in swallowing the Triumeq tablet but has remained in the trial for over 6 months and is still participating; and one subject in Thailand (September 2014) who was recovering from tonsillitis/tonsillectomy reported having difficulty swallowing the Triumeq tablet but is also continuing to participate in the study.

Additionally the sponsor has initiated a large multi-center, Phase IIIB, randomised, open-label, non-inferiority study, 201147 (STRiiVING), comparing Triumeq versus current ART regimen in treatment-experienced adults using the Triumeq clinical tablets, which are the same size as the commercial tablets. As of 29 October 2014, there are 276 subjects randomised to Triumeq and the sponsor is not aware of any AEs/SAEs reported for 'difficulty swallowing' or 'dysphagia'.

The impact of the tablet size for particular patient populations which could potentially be more likely to experience problems swallowing a large tablet, such as paediatric patients or those with oesophageal infections, is not expected to be of significance. The indication for Triumeq is for children from 12 years of age which is also the indication for Kivexa. Therefore difficulty in swallowing is unlikely to be an issue in this older population. Additionally, HIV-infected patients are starting care earlier in their disease process based

on current treatment guidelines. Complications related to opportunistic infections such as oesophageal issues like candidal and HSV oesophagitis tend to be now less common in current care. Based on these facts, the sponsor holds the view that tablet size will not adversely affect medication adherence or result in misuse of the product.

If there are questions or concerns, health care providers or patients are encouraged to contact ViiV Healthcare consumer lines. If a patient develops a candida infection or other temporary medical condition that affects swallowing (such as herpes simplex virus, HSV) this probably would not be specific to Triumeq. However, a clinical advantage of fixed dose combination (FDC) is that there is no opportunity for patients to become only partly compliant, by holding the larger pills, and taking smaller ones. This would be a condition that could lead to essential monotherapy and drive resistance development. As most of these are temporary conditions, especially in the era of highly effective HIV therapy, the tablet could be resumed when the patient's swallowing improves – akin to any other large tablets. Further, if the swallowing condition becomes long term or permanent, the health care provider could change the patient's regimen to separate tablets or select medicines that are taken as liquids or can be crushed and suspended or are merely smaller pills. Importantly, with earlier initiation of therapy with respect to CD4 cell count and highly effective therapy, opportunistic infections such as candidal esophagitis are less frequent in the HIV-infected population.[15]

Addition of safety concerns to the Australian specific annex of the EU-risk management plan

The TGA Delegate has noted an outstanding issue from the clinical evaluator in which some specific safety concerns should be added to the Australian Specific Annex (ASA) of the EU-Risk Management Plan (RMP). ViiV agrees to add four further requested identified and potential risks to the ASA. ViiV also agrees that long term follow-up of individuals exposed in utero should be considered separately from the 'Long term safety data'. However, the sponsor does not believe that the tablet size, overdose or an interaction study between DTG and lamivudine should be included, justifications for which are included in the table below.

Table 11: Addition of Safety concerns to the ASA

Identified Risks	Sponsor's comment
Rebound hepatitis following discontinuation of lamivudine.	This risk is described in the PI and the sponsor agrees to including it as an identified risk in the ASA
Potential Risks	
Mitochondrial dysfunction for ABC and/or 3TC	Mitochondrial dysfunction is included in the EU RMP as a Pharmacogical class effect for the NRTI class and this information is also included in the Australian PI. The sponsor therefore agrees to add this to the ASA as a potential risk.

[15]Coelho L, Cardoso SW, Amancio RT, Moreira RI, Campos DP, et al. (2014) Trends in AIDS-Defining Opportunistic Illnesses Incidence over 25 Years in Rio de Janeiro, Brazil. PLoS ONE 9(6): e98666. doi:10.1371/journal.pone.0098666

Identified Risks	Sponsor's comment
Bone disorders	Bone disorders are included in the EU RMP as a Pharmacological class effect for CART. Although the aetiology is considered to be multifactorial (including corticosteroid use, biphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV-disease and/or long-term exposure to CART. The sponsor agrees to add this to the ASA as a potential risk.
Overdose	There is currently limited experience with overdosage in dolutegravir. Limited experience of single higher doses (up to 250 mg in healthy patients) revealed no specific symptoms or signs, apart from those listed as adverse reactions. No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as adverse reactions. On the basis that Triumeq is not expected to have an increased likelihood for overdose in clinical practice nor does it have a narrow therapeutic margin, the sponsor does not agree to add this to the ASA as a potential risk.
Patient misuse of antacids and iron containing medications risking loss of efficacy for dolutegravir	The PI states that the absorption of dolutegravir is reduced by certain antacids. The sponsor therefore agrees to include it in the ASA as a potential risk.
Missing Information	
Long term follow-up of individuals exposed in utero should be considered separately from the 'Long term safety data'	The sponsor agrees to separate these two types of missing information.
The large size of the tablet is a potential problem, especially for patients with oral and oesophageal problems	Please refer to the discussion above. The sponsor continues to hold the view that tablet size will not adversely affect medication adherence or result in misuse of the product and therefore does not agree that this should be added to the ASA.
Interaction study between DTG and lamivudine has not been done	The sponsor acknowledges that DTG has the potential to increase lamivudine (3TC) exposure via inhibition of OCT2 which may be involved in 3TC renal excretion, however, based on the accumulated clinical PK and safety data and predicted effect of DTG on 3TC exposure using various static models, no interaction between DTG and 3TC is

Identified Risks	Sponsor's comment
	observed or expected (details provided below). Therefore, the sponsor does not agree that it is necessary to conduct an interaction study between DTG and 3TC and therefore would not include this in the ASA. Summary of evidences of no interaction between DTG and 3TC: Firstly, PK data from Study ING114580 and comparisons to historical data (Study CAL10001) indicated that 3TC PK parameters were similar with and without co-administration with DTG, implying that there is no significant drug interaction between DTG and 3TC in vivo. Additionally, based on in vitro transporter data, it is not predicted that DTG would have a significant impact on 3TC plasma concentrations. 3TC is predominantly cleared by the kidney via both glomerular filtration and active tubular secretion which represents about 47.5% of total clearance of 3TC. Based on modelling using IC50 of DTG on OCT2 transporter, the increase in 3TC exposure by DTG through OCT2 inhibition is expected to be less than 28%. Finally, DTG has been co-administered with 3TC in multiple Phase II/III clinical studies (ING112276, ING113086, and ING114467) and no significant safety issues have been identified due to co-administration with DTG and 3TC.

Benefit-risk assessment and conclusion

The TGA Delegate has stated that he agrees with the clinical assessment of the benefits and risk and that he concurs with the recommendation for registration.

Triumeq is the first STR with once-daily dosing that contains the benefits of the new INI drug DTG, with the long-established clinical benefits of ABC/3TC.

DTG co-administered with ABC/3TC, contained in Triumeq, have demonstrated improved efficacy and tolerability versus Atripla, with substantial reduction of treatment-limiting adverse drug reactions that translate to improved treatment outcomes through 96 weeks of therapy. Furthermore, Triumeq offers a high barrier to resistance, with no INI or NRTI emergent resistance seen through 96 weeks in ART-naïve subjects on DTG plus ABC/3TC regimens. Triumeq also offers the advantages of DTG in a treatment-experienced patient population, with significantly lower emergent resistance in ART-experienced subjects when compared to RAL through 48 weeks and dosing convenience for patients without NRTI resistance who might benefit from ABC/3TC. Triumeq provides convenient once-daily dosing (for ART-naïve and ART-experienced, INI naïve individuals), without the need for a pharmacokinetic booster or induction effects on the metabolism of other drugs, which decreases possible drug interactions with concomitant drugs. Triumeq also provides an STR option for patients for whom tenofovir is not considered appropriate due to resistance or safety concerns. From a safety perspective, clinical studies showed that the safety/tolerability of the dosing regimen of DTG 50 mg plus ABC/ 3TC 600/300 mg was consistent with the established safety/tolerability profile of the three individual components.

Therefore, Triumeq offers an important option for patients with HIV infection who would be optimally treated with a DTG-based regimen and who would benefit from the

adherence advantages associated with STRs. The advantages of this DTG-based regimen include improved efficacy and tolerability over Atripla, a better drug interaction profile without the effects on the metabolism of other drugs (that is, induction or inhibition of CYP450 enzymes) and the lack of NRTI or INI resistance over 96 weeks of therapy.

Consistent with TGA Delegate and clinical evaluator, ViiV believes that the benefit-risk assessment for Triumeq (dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg) tablets is positive and supports approval for the following indication:

> *Triumeq is indicated 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 (dolutegravir, abacavir or lamivudine) in Triumeq.*

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Triumeq tablet containing dolutegravir (as sodium) 50 mg/abacavir (as sulfate) 600 mg/lamivudine 300 mg to have an overall positive benefit–risk profile for the indication;

> *Triumeq is indicated as a 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 (dolutegravir, abacavir or lamivudine) in Triumeq.*

In making this recommendation the ACPM advised that the risk of use in patients carrying resistant virus was a critical risk and should be diligently avoided. PI warnings and advice on resistance testing should be prominent.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Statements in the *Precautions* section against use in presence of resistance or previous exposure to integrase inhibitors if there was evidence of virological failure
- The need for use of the generic descriptors for the active substances is required due to the importance of immediate identification in terms of identification for class resistance
- A statement highlighting that the dose of dolutegravir should be increased if integrase resistance mutations are present and therefore a fixed dose combination may be inappropriate
- A statement in the *Clinical Trials* section highlighting the issue that studies were conducted only in treatment naïve patients

- The statement in the *Precautions* section on *Transmission of Infection* is no longer valid and should be amended to better reflect current observations.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the ACPM consider it is appropriate to include clinical studies ING113086 (Spring-2), ING114915 (Flamingo) and ING111762 (Sailing) in the CLINICAL TRIALS Section of PI for Triumeq?*

The ACPM noted that the sponsor has agreed to remove references to these studies. The *Clinical Trials* section should include a description of the FDC and components.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Triumeq containing dolutegravir (as sodium) 50 mg/abacavir (as sulfate) 600 mg/lamivudine 300 mg tablet bottles, indicated for:

> *Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age who are antiretroviral treatment-naive or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents (dolutegravir, abacavir or lainivudine) in Triumeq.*

Specific conditions of registration applying to these goods

The Risk Management Plan (RMP) for Triumeq containing dolutegravir (as sodium) 50 mg/abacavir (as sulfate) 600 mg/lamivudine 300 mg tablet: EU-RMP version 1.0, dated 3 October 2013 (data lock point 31 May 2013) included with submission (PM- 2013-04112-1-2) with Australian-specific Annex version 2.0 dated 7 January 2015; and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Triumeq at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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