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TITLE PAGE

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Information Type: ViiV Healthcare Epidemiology Final Study Report

Control: Non-Interventional.

Title:	Dolutegravir Use and Predictors of CNS events: Meta-analysis of Data from Phase III/IIIb Clinical Trials
Phase:	IV
Compound Number:	GSK1349572
Effective Date:	27-June-2018

Subject: Safety, Dolutegravir, CNS, HIV

Author(s): PPD

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

Sponsor Signatory Signature Page

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study 207953 (eTrack Project # 207953).

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Date: 20/8/18

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ABSTRACT

TITLE

DOLUTEGRAVIR USE AND CNS EVENTS: META-ANALYSIS OF DATA FROM PHASE III/IIIB CLINICAL TRIALS

KEYWORDS

Safety, Dolutegravir, CNS, HIV

Background: In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, CNS AE rates were low, and most CNS AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. A couple of observational HIV cohorts (see references) suggest that Neuropsychiatric Symptoms (NPs) may result in somewhat higher rates of discontinuation in clinical practice than documented in clinical trials, and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use. Therefore, we are proposing to re-examine data from the phase III adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any variables associated with (from a pre-specified list) development of a Neuropsychiatric Symptom (NP) during the course of the trials which could explain what is observed in the cohorts.

Methods: The primary objective was to assess if there are any variables associated with the development of a NP during the course of the trials. This meta-analysis will include data that were previously collected for VH-sponsored clinical trials in adult Phase III/IIIb of drug development for dolutegravir. Studies included in the meta-analysis are Spring 2, Single, Flamingo, Aria and Sailing. The incidence of NP events was calculated from frequencies of reported adverse events (AEs) in the included clinical trials; 95% CIs are based on exact binomial 2-sided CIs. To assess the effect of pre-specified variables associated with the exposure adjusted incidence rate and relative rate of NP events in human immunodeficiency virus (HIV) patients treated with DTG containing versus non DTG containing regimens as well as DTG + ABC exposure vs DTG + other regimens Poisson mixed effects meta-regression models was used. 95% CIs were calculated for rates and relative rates.

Results: Overall for the Poisson model at patient level, adjusted estimates [SE] for NPs rates per 1,000 person years were 5.26 [0.068] with DTG versus 5.21 [0.07] with nonDTG (aRR 1.05 [95%CI 0.9, 1.21, p=0.55]), and 5.4 [0.079] with DTG+ABC versus 5.3 [0.085] with DTG+nonABC (aRR 1.1 [95%CI 0.89, 1.37, p=0.37]). Descriptive analyses of first insomnia events and subsequent non-insomnia events are in Tables 15 and 16. First insomnia events with subsequent non-insomnia NPs occurred infrequently (2.2%), with higher rates of patients reporting a NP event without a preceding insomnia event (23.0%). At the event level in the DTG vs non-DTG psychiatric history, region, sex and race were found to be significant. In the DTG+ABC vs DTG+non-ABC analysis treatment, HIV RNA, psychiatric history, region, age, race and CD4 count were found to be significant.

Conclusion:

In this meta-analysis including 3,353 participants, the rate of NPs was similar between DTG and non-DTG treated patients. Variables associated with increased NPs in the DTG vs nonDTG patient level analysis were past psychiatric history, non-EU residence and, in contrast with previous findings, younger age. Within the DTG vs DTG+ABC analysis, past psychiatric history and country of residence showed significant

association. Concomitant ABC use was not a variable associated with NPs at the patient level. At the event level in the DTG vs non-DTG psychiatric history, region, sex and race were found to be significant. In the DTG+ABC vs DTG+non-ABC analysis treatment, HIV RNA, psychiatric history, region, age, race and CD4 count were found to be significant. The treatment effect of DTG + ABC vs DTG + non-ABC is likely driven by the Single study due to the significant treatment by study interaction. There was no indication that insomnia was associated with subsequent NP events.

LIST OF ABBREVIATIONS

ABC	Abacavir
AE	Adverse Event
ATV	Atazanavir
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CNS	Central Nervous System
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
RAL	Raltegravir
RCT	Randomized Controlled Trial
US	United States
VH	ViiV Healthcare

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N/A

Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	02 Jun 2017	02 Jun 2017	Data was already collected as part of clinical trials. Data consolidation started on 2 Jun after registry posting
Final report of study results	30 Jul 2018		

Rationale and background

Background

In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, NP AE rates were low, and most NP AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. Evolving observational HIV cohort data (1,2,4,5,6,7,8) suggest that NP AEs may result in somewhat higher rates of DTG discontinuation in clinical practice than documented in clinical trials and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use.

Rationale

Therefore, we re-examined patient level data from the phase III/IIIb adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any variables associated with development of a NP AE during the course of the trials which could explain what is observed in the cohorts. These are the same studies as were included in the Fettiplace et al manuscript (2017).

Research question and objectives

The primary objective was to identify if there are any variables associated with the development of a NP AE during the course of the trials.

Research methods

Study design

This meta-analysis included individual patient level data that were previously collected for VH-sponsored randomized clinical trials in adult Phase III/IIIb of drug development for dolutegravir.

Subjects

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included is 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

Table 1. Overview of GSK/VH-sponsored clinical trials included in the meta-analysis.

Study name	Study identifier	Study duration included in meta-analysis	Primary objective	DTG exposed	DTG unexposed
ARIA[1]	ING117172	48	A Phase IIIb study to demonstrate the non-inferior antiviral activity, safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV and TDF/FTC FDC in HIV-1 infected, ART-naïve women.	248	247
FLAMINGO	ING114915	96	A Phase IIIb study to demonstrate the non-inferior antiviral activity of DTG 50mg administered once daily compared to DRV+RTV 800mg + 100mg once daily both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve subjects.	242	242
SINGLE[1]	ING114467	144	A Phase III study to demonstrate the non-inferior antiviral activity of DTG + ABC/3TC once daily therapy compared to EFV/TDF/FTC in HIV-1 infected ART-naïve subjects.	414	419
SPRING-2	ING113086	96	A Phase III study to demonstrate the antiviral activity of DTG 50 mg administered once daily compared	411	411

Study name	Study identifier	Study duration included in meta-analysis	Primary objective	DTG exposed	DTG unexposed
			to RAL 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects.		
SAILING	ING111762	48	A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults	357	362

[1]Randomized with respect to ABC therapy (i.e. an experimental control for ABC)

Variables

Exposure definitions

Two sets of analyses were carried out reflecting the different exposures of interest – DTG and DTG + ABC. For the first set of analyses the exposed group was treated with DTG as part of cART. The comparator group was exposed to non-DTG-containing cART regimen. A single subject may only contribute to one of the exposure categories. For the second set of analyses we considered DTG + ABC exposure vs DTG + Other exposure.

The mean exposure in days was calculated from patient level data available for each study. Exposure categories were constructed according to exposure to DTG or not in the cART as well as DTG + ABC vs not. The total exposure time in person-years was obtained by taking the sum of each subjects' exposure time from start to end of treatment and dividing it by 365.25.

Outcome definitions

For the 5 VH-sponsored clinical trials, outcomes were identified on the basis of reported AEs listed in an aggregated clinical trials database maintained by VH.

The same definitions as described in the Fettiplace et al. JAIDS paper (2017) was used to select the events of interest based on selected psychiatric symptoms occurring in HIV-positive patients during dolutegravir treatment as classified by company physicians. The following specific preferred terms were used to define a NP event in this analysis:

- Insomnia
- Anxiety
- Depression
- Suicidality
- Nightmares/abnormal dreams
- Headache

As described in Fettiplace et al the category insomnia includes the terms insomnia, initial insomnia, terminal insomnia, and middle insomnia. The category anxiety includes the terms anxiety and anxiety disorder. The category depression includes the terms depression, major depression, depressed mood, depressive symptom, and bipolar disorder. The category suicidality includes suicide attempt, suicidal ideation, completed suicide, intentional self-injury, and self-injurious behavior. The category headache includes the terms headache and migraine.

The analysis was carried out for both all AEs and all drug related AEs during the course of the trials for the summary tables at the patient and event level. The Poisson model was conducted for all AEs at the patient level and event level for both levels of exposure.

Baseline Variables The following set of variables were hypothesized based on the cohort data to be variables potentially associated with the development of a NP AE during the course of the trials and were therefore included and tested for in the analysis:

- Gender (M vs F)
- Age (< and ≥ 50)
- Race (White vs Other)
- Region
- Country
- Previous psychiatric history (Y vs N)
- Any chronic co-morbidity, including HCV, Diabetes, Hypertension (Y vs N)

- HIV acquisition risk factor
- History of drug use (Y vs N)
- Baseline viral load (< and ≥ 100,000 copies/ml)
- CD4 nadir (< and ≥ 200)
- BMI

Study size

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included will be 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

Statistical methods

Data analysis

This analysis looked at studies with a follow-up of ≥48 weeks. This analysis calculated incidence of a NP AE as defined by the psychiatric symptoms described for both definitions of exposure and evaluated if there are any variables associated with described. Since this was an exploratory analysis we used a p-value of 0.10 for significance testing of those variables associated with an NP AE for inclusion in the statistical models. Prior to inclusion in the analysis the incidence of a NP AE was tabulated by variables associated with and any variables associated with zero counts in categories were excluded from the Poisson regression model.

1. Essential analysis

Incidence of NP events by variables associated with

Percentages are based on the frequency of AEs collected during the conduct of clinical trials and presented by levels of a variables associated with and study as well as aggregate. 95% CIs are based on exact binomial 2-sided confidence intervals (CIs).

Relationship between exposure to DTG, variables associated with and development of outcome

Exposure adjusted incidence rates per 1,000 person-years were calculated. The Poisson regression models used to calculate relative rates, adjusted for variables associated with the endpoint; the offset was the natural log of person years of exposure to treatment. Study was fitted as a random effect within the pooled model. 95% CIs are presented for rates and relative rates. P-values were calculated for variables associated with an NP AE. A stepwise approach was used to identify significant variables associated with a significance level of 10%. In the event level analysis "OM by level" options were in the model to address observed convergence issues. Without this option, SAS assumes same weights across categorical variables and this assumption was made in the patient level analysis. Adding this options in the event level analysis allows SAS to estimate LSmeans using different weights across the categorical levels. Results are presented in a forest plot (by study and aggregate).

Insomnia analysis

To consider whether insomnia is a pre cursor to other NP AEs, a tabular display showing NP preceded and not preceded by insomnia split by NP subcategory was created.

Study Management

Ethical approval and subject consent

N/A, ethical approval was obtained for primary data collection as part of the clinical trials. This meta-analysis used clinical trial data used for individual study reporting.

Subject confidentiality

This meta-analysis used previously collected, clinical trial data and no identifying information was provided.

Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	02 Jun 2017	02 Jun 2017	Data was already collected as part of clinical trials. Data consolidation started on 2 Jun after registry posting
Final report of study results	27 June 2018		

RESULTS

Patient characteristics

The patient characteristics and number of NP events of patients contributing from each of the studies are displayed in table 2.

Table 2: Patient characteristics and number of NP events

		DTG (N=1672)		Non-DTG (N=1681)	
Baseline variables		n (%)[1]	# patients with NP event(%)[2]	n (%)[1]	# patients with NP event(%)[2]
Sex	Male	1155 (69)	309 (27)	1150 (68)	301 (26)
	Female	517(31)	121 (23)	531 (32)	107 (20)
Age (years)	<50	1429 (85)	379 (27)	1436 (85)	356 (25)
	>=50	243 (15)	51 (21)	245 (15)	52 (21)
Race	White	1099 (66)	298 (27)	1095 (65)	266 (24)
	Other	571 (34)	132 (23)	584 (35)	141 (24)
HIV-1 RNA(c/mL)	<100,000	1225 (73)	310 (25)	1234 (73)	302 (24)
	>=100,000	447 (27)	120 (27)	447 (27)	106 (24)
CD4+ (c/mm^3)	<200	374 (22)	74 (20)	370 (22)	75 (20)

		DTG (N=1672)		Non-DTG (N=1681)	
Baseline variables		n (%)[1]	# patients with NP event(%)[2]	n (%)[1]	# patients with NP event(%)[2]
	>=200	1298 (78)	356 (27)	1311 (78)	333 (25)
BMI (kg/m^2)	<18.5	61 (4)	16 (26)	67 (4)	14 (21)
	18.5 to 24.9	908(54)	226 (25)	856 (51)	216 (25)
	>=25	701 (42)	188 (27)	754 (45)	175 (23)
Psychiatric history	Yes	577 (35)	214 (37)	589 (35)	199 (34)
	No	1095 (65)	216 (20)	1092 (65)	209 (19)
Any Co-morbidity	Yes	371 (22)	97 (26)	404 (24)	85 (21)
	No	1301 (78)	333 (26)	1277 (76)	323 (25)
HIV Risk Factor	Yes	1669 (>99)	429 (26)	1676 (>99)	406 (24)
	No	3 (<1)	1 (33)	5 (<1)	2 (40)
Drug Use	Yes	12 (1)	2 (17)	8 (<1)	1 (13)
	No	1660 (99)	428 (26)	1673 (>99)	407 (24)
Country	Argentina	51 (3)	13 (25)	40 (2)	7 (18)
	Australia	29 (2)	12 (41)	30 (2)	13 (43)
	Belgium	11 (1)	7 (64)	16 (1)	4 (25)
	Brazil	62 (4)	7 (11)	63 (4)	11 (17)
	Canada	73 (4)	31 (42)	70 (4)	29 (41)
	Chile	13 (8)	3 (23)	12 (1)	3 (25)
	Denmark	2 (<1)	0	3 (<1)	0
	France	106 (6)	38 (36)	99 (6)	30 (30)
	Germany	82 (5)	16 (20)	104 (6)	24 (23)
	Greece	2 (<1)	0	1 (<1)	0
	Hungary	0 (0)	0	1 (<1)	0
	Italy	85 (5)	14 (16)	82 (5)	10 (12)

		DTG (N=1672)		Non-DTG (N=1681)	
Baseline variables		n (%)[1]	# patients with NP event(%)[2]	n (%)[1]	# patients with NP event(%)[2]
	Mexico	27 (2)	1 (4)	25 (1)	0
	Netherlands	8 (<1)	3 (38)	3 (<1)	1 (33)
	Portugal	4 (<1)	1 (25)	5 (<1)	1 (20)
	Puerto Rico	6 (<1)	1 (17)	8 (<1)	1 (13)
	Romania	27 (2)	2 (7)	29 (2)	0
	Russia	94 (6)	6 (6)	100 (59)	5 (5)
	South Africa	85 (5)	17 (20)	81 (5)	11 (14)
	Spain	323 (19)	77 (24)	324 (19)	81 (25)
	Switzerland	7 (<1)	2 (29)	6 (<1)	2 (33)
	Taiwan	7 (<1)	2 (29)	4 (<1)	1 (25)
	Thailand	19 (1)	3 (16)	21 (1)	3 (14)
	United Kingdom	42 (3)	13 (31)	30 (2)	13 (43)
	United States	507 (3)	161 (32)	524 (31)	158 (30)
Region	Europe	793 (5)	179 (23)	803 (48)	171 (21)
	North-America	607 (4)	193 (32)	619 (37)	187 (30)
	Rest of the World	272 (16)	58 (21)	259 (15)	50 (19)
Study	ING117172	248 (15)	52 (21)	247 (15)	49 (20)
	ING114915	242 (15)	71 (29)	242 (14)	57 (24)
	ING114467	414 (25)	146 (35)	419 (25)	151 (36)
	ING113086	411 (25)	107 (26)	411 (25)	102 (25)
	ING111762	357 (21)	54 (15)	362 (22)	49 (14)
Abacavir Exposure	Yes	943 (44)	265 (28)	279 (17)	61 (22)
	No	729 (44)	165 (23)	1402 (83)	347 (25)

[1]Denominators based on number of subjects in each treatment group.
[2] Denominators are based on number of subjects in each baseline variable category

Crude and adjusted incidence rates

Tables 3, 4, 5, 6, 7 and 8 give the crude and exposure adjusted incidence rates by variables associated with at the patient and event analysis levels for the exposures of DTG vs nonDTG and DTG+ABC vs DTG+Other. For the latter grouping the analysis was re-run excluding Single.

These tables show that psychiatric history consistently has a big numerical difference in incidence rates (adjusted and unadjusted) in all exposure groups. For example, for DTG vs non DTG exposure, the psychiatric history = "yes" exposure adjusted incidence is 268 events per 1,000 person-years (95% CI:235, 307) and "no" is 143 events per 1,000 person-years (95%CI:125, 164). Similarly in the nonDTG group history = "yes" has an exposure adjusted incidence of 258 events per 1,000 person-years (95%CI:225, 297) with "no" 146 events per 1,000 person-years (95%CI:127, 167). It should be noted that no statistical testing was conducted on this data

Tables 3.11 and 3.12 in the Appendix show a summary of the incidence of NP events by number of event groupings for both exposure categories.

Table 3: Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables DTG vs Non-DTG - Patient with NP event analysis level

		DTG		Non-DTG	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.26(0.24, 0.28)	186(170, 205)	0.24(0.22, 0.26)	185(168, 204)
Sex	Male	0.27(0.24, 0.29)	177(158, 198)	0.26(0.24, 0.29)	179(160, 201)
	Female	0.23(0.20, 0.27)	216(181, 258)	0.20(0.17, 0.24)	203(168, 245)
Age (years)	<50	0.27(0.24, 0.29)	190(172, 210)	0.25(0.23, 0.27)	188(169, 208)
	>=50	0.21(0.16, 0.27)	163(124, 214)	0.21(0.16, 0.27)	167(128, 220)
Race	White	0.27(0.25, 0.30)	185(165, 207)	0.24(0.22, 0.27)	172(152, 194)
	Other	0.23(0.20, 0.27)	191(161, 227)	0.24(0.21, 0.28)	216(183, 255)
HIV-1 RNA(c/mL)	<100,000	0.25(0.23, 0.28)	184(165, 206)	0.24(0.22, 0.27)	186(166, 208)
	>=100,000	0.27(0.23, 0.31)	191(160, 229)	0.24(0.20, 0.28)	183(151, 222)
CD4+ (c/mm^3)	<200	0.20(0.16, 0.24)	179(142, 225)	0.20(0.16, 0.25)	192(153, 241)
	>=200	0.27(0.25, 0.30)	188(169, 209)	0.25(0.23, 0.28)	183(165, 204)
BMI (kg/m^2)	<18.5	0.26(0.16, 0.39)	215(132, 351)	0.21(0.12, 0.33)	192(114, 324)
	18.5 to 24.9	0.25(0.22, 0.28)	177(155, 201)	0.25(0.22, 0.28)	187(164, 214)
	>=25	0.27(0.24, 0.30)	198(171, 228)	0.23(0.20, 0.26)	180(155, 209)
Psychiatric	Yes	0.37(0.33, 0.41)	268(235, 307)	0.34(0.30, 0.38)	258(225, 297)
	No	0.20(0.17, 0.22)	143(125, 164)	0.19(0.17, 0.22)	146(127, 167)
Any Co-morbidity	Yes	0.26(0.22, 0.31)	195(160, 239)	0.21(0.17, 0.25)	177(143, 218)
	No	0.26(0.23, 0.28)	184(165, 205)	0.25(0.23, 0.28)	187(168, 209)
HIV Risk Factor	Yes	0.26(0.24, 0.28)	186(169, 205)	0.24(0.22, 0.26)	184(167, 203)
	No	0.33(0.01, 0.91)	398(56, 2825)	0.40(0.05, 0.85)	399(100, 1596)
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0.13(0.00, 0.53)	182(26, 1293)
	No	0.26(0.24, 0.28)	186(169, 205)	0.24(0.22, 0.26)	185(168, 204)
Country	Argentina	0.25(0.14, 0.40)	284(165, 489)	0.18(0.07, 0.33)	189(90, 397)
	Australia	0.41(0.24, 0.61)	241(137, 424)	0.43(0.25, 0.63)	279(162, 480)
	Belgium	0.64(0.31, 0.89)	403(192, 845)	0.25(0.07, 0.52)	196(73, 521)
	Brazil	0.11(0.05, 0.22)	128(61, 268)	0.17(0.09, 0.29)	207(114, 373)
	Canada	0.42(0.31, 0.55)	256(180, 364)	0.41(0.30, 0.54)	283(197, 408)
	Chile	0.23(0.05, 0.54)	303(98, 939)	0.25(0.05, 0.57)	312(101, 968)
	Denmark	0	0(0,)	0	0(0,)
	France	0.36(0.27, 0.46)	220(160, 303)	0.30(0.21, 0.40)	208(146, 298)
	Germany	0.20(0.12, 0.30)	110(67, 179)	0.23(0.15, 0.32)	136(91, 203)
	Greece	0	0(0,)	0	0(0,)
	Hungary	0	0	0	0(0,)

		DTG		Non-DTG	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Italy	0.16(0.09, 0.26)	111(66, 188)	0.12(0.06, 0.21)	84(45, 156)
	Mexico	0.04(0.00, 0.19)	43(6, 302)	0	0(0,)
	Netherlands	0.38(0.09, 0.76)	238(77, 738)	0.33(0.01, 0.91)	212(30, 1508)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0.20(0.01, 0.72)	272(38, 1928)
	Puerto Rico	0.17(0.00, 0.64)	90(13, 639)	0.13(0.00, 0.53)	77(11, 550)
	Romania	0.07(0.01, 0.24)	54(13, 214)	0	0(0,)
	Russia	0.06(0.02, 0.13)	54(24, 121)	0.05(0.02, 0.11)	42(18, 101)
	South Africa	0.20(0.12, 0.30)	254(158, 408)	0.14(0.07, 0.23)	169(94, 305)
	Spain	0.24(0.19, 0.29)	149(119, 186)	0.25(0.20, 0.30)	169(136, 211)
	Switzerland	0.29(0.04, 0.71)	173(43, 691)	0.33(0.04, 0.78)	182(45, 726)
	Taiwan	0.29(0.04, 0.71)	362(90, 1447)	0.25(0.01, 0.81)	276(39, 1958)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0.14(0.03, 0.36)	190(61, 588)
	United Kingdom	0.31(0.18, 0.47)	235(137, 405)	0.43(0.25, 0.63)	356(207, 613)
	United States	0.32(0.28, 0.36)	235(201, 274)	0.30(0.26, 0.34)	230(197, 269)
Region	Europe	0.23(0.20, 0.26)	147(127, 171)	0.21(0.19, 0.24)	148(127, 172)
	North-America	0.32(0.28, 0.36)	232(202, 268)	0.30(0.27, 0.34)	232(201, 267)
	Rest of the World	0.21(0.17, 0.27)	222(171, 287)	0.19(0.15, 0.25)	205(155, 271)
Study	ING117172	0.21(0.16, 0.27)	246(188, 323)	0.20(0.15, 0.25)	247(187, 327)
	ING114915	0.29(0.24, 0.36)	170(134, 214)	0.24(0.18, 0.29)	143(110, 185)
	ING114467	0.35(0.31, 0.40)	212(181, 250)	0.36(0.31, 0.41)	237(202, 279)
	ING113086	0.26(0.22, 0.31)	155(128, 188)	0.25(0.21, 0.29)	152(125, 184)
	ING111762	0.15(0.12, 0.19)	179(137, 234)	0.14(0.10, 0.17)	163(123, 216)
Abacavir Exposure	Yes	0.28(0.25, 0.31)	198(176, 224)	0.22(0.17, 0.27)	143(111, 183)
	No	0.23(0.20, 0.26)	170(146, 198)	0.25(0.23, 0.27)	195(176, 217)

Note: a: NP adverse events is counted as number of patients.
Note: b: Crude estimate defined as NP/N.
Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, NP= Neuropsychiatric Symptom, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

Table 4:
Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables
DTG vs Non-DTG - NP Events Analysis Level

		DTG		Non-DTG	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.38(0.36, 0.40)	276(255, 298)	0.35(0.33, 0.38)	270(249, 292)
Sex	Male	0.39(0.37, 0.42)	261(238, 286)	0.38(0.35, 0.41)	258(235, 284)
	Female	0.35(0.31, 0.39)	321(278, 372)	0.31(0.27, 0.35)	307(263, 358)
Age (years)	<50	0.39(0.36, 0.41)	278(256, 303)	0.35(0.33, 0.38)	266(244, 290)
	>=50	0.33(0.27, 0.40)	258(208, 321)	0.37(0.31, 0.44)	293(238, 360)
Race	White	0.41(0.38, 0.44)	279(254, 306)	0.36(0.33, 0.39)	254(230, 281)
	Other	0.33(0.29, 0.37)	270(234, 311)	0.34(0.30, 0.38)	306(267, 352)
HIV-1 RNA(c/mL)	<100,000	0.38(0.35, 0.41)	276(252, 302)	0.36(0.33, 0.38)	270(246, 296)
	>=100,000	0.38(0.34, 0.43)	274(236, 319)	0.35(0.30, 0.40)	270(230, 315)
CD4+ (c/mm^3)	<200	0.33(0.28, 0.38)	295(247, 352)	0.29(0.24, 0.34)	274(227, 331)
	>=200	0.40(0.37, 0.42)	271(249, 296)	0.37(0.35, 0.40)	269(246, 294)
BMI (kg/m^2)	<18.5	0.44(0.32, 0.58)	362(249, 528)	0.34(0.23, 0.47)	315(210, 475)
	18.5 to 24.9	0.36(0.33, 0.39)	257(230, 286)	0.36(0.33, 0.39)	267(239, 299)
	>=25	0.40(0.36, 0.44)	296(263, 332)	0.34(0.31, 0.38)	265(235, 300)
Psychiatric	Yes	0.60(0.55, 0.64)	431(388, 479)	0.54(0.50, 0.58)	416(372, 464)
	No	0.27(0.24, 0.29)	193(173, 217)	0.25(0.23, 0.28)	192(170, 216)
Any Co-morbidity	Yes	0.43(0.38, 0.48)	322(276, 377)	0.32(0.27, 0.36)	266(224, 316)
	No	0.37(0.34, 0.39)	263(240, 288)	0.37(0.34, 0.39)	271(247, 297)
HIV Risk Factor	Yes	0.38(0.36, 0.40)	276(255, 298)	0.35(0.33, 0.38)	269(248, 291)
	No	0.33(0.01, 0.91)	398(56, 2825)	0.80(0.28, 0.99)	798(300, 2127)
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0.13(0.00, 0.53)	182(26, 1293)
	No	0.38(0.36, 0.41)	276(255, 298)	0.36(0.33, 0.38)	270(249, 293)
Country	Argentina	0.33(0.21, 0.48)	371(231, 597)	0.18(0.07, 0.33)	189(90, 397)
	Australia	0.52(0.33, 0.71)	301(182, 500)	0.63(0.44, 0.80)	408(260, 639)
	Belgium	0.91(0.59, 1.00)	575(310, 1069)	0.31(0.11, 0.59)	245(102, 588)
	Brazil	0.15(0.07, 0.26)	164(86, 316)	0.19(0.10, 0.31)	226(128, 397)
	Canada	0.68(0.57, 0.79)	413(313, 544)	0.60(0.48, 0.72)	410(303, 555)

		DTG		Non-DTG	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Chile	0.31(0.09, 0.61)	404(152, 1076)	0.42(0.15, 0.72)	520(217, 1250)
	Denmark	0	0(0,)	0	0(0,)
	France	0.52(0.42, 0.62)	319(245, 416)	0.55(0.44, 0.65)	375(287, 489)
	Germany	0.23(0.15, 0.34)	130(83, 204)	0.35(0.26, 0.45)	204(147, 283)
	Greece	0	0(0,)	0	0(0,)
	Hungary	0	0	0	0(0,)
	Italy	0.26(0.17, 0.37)	175(115, 266)	0.16(0.09, 0.26)	109(63, 188)
	Mexico	0.04(0.00, 0.19)	43(6, 302)	0	0(0,)
	Netherlands	0.38(0.09, 0.76)	238(77, 738)	0.33(0.01, 0.91)	212(30, 1508)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0.20(0.01, 0.72)	272(38, 1928)
	Puerto Rico	0.50(0.12, 0.88)	270(87, 838)	0.13(0.00, 0.53)	77(11, 550)
	Romania	0.07(0.01, 0.24)	54(13, 214)	0	0(0,)
	Russia	0.06(0.02, 0.13)	54(24, 121)	0.06(0.02, 0.13)	51(23, 113)
	South Africa	0.25(0.16, 0.35)	313(204, 481)	0.16(0.09, 0.26)	200(116, 344)
	Spain	0.34(0.29, 0.39)	211(175, 254)	0.38(0.32, 0.43)	255(214, 305)
	Switzerland	0.29(0.04, 0.71)	173(43, 691)	0.33(0.04, 0.78)	182(45, 726)
	Taiwan	0.29(0.04, 0.71)	362(90, 1447)	0.25(0.01, 0.81)	276(39, 1958)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0.14(0.03, 0.36)	190(61, 588)
	United Kingdom	0.38(0.24, 0.54)	290(178, 473)	0.53(0.34, 0.72)	438(269, 715)
	United States	0.52(0.48, 0.57)	388(344, 437)	0.45(0.41, 0.49)	344(303, 391)
Region	Europe	0.31(0.28, 0.34)	202(178, 229)	0.32(0.29, 0.35)	222(196, 251)
	North-America	0.52(0.48, 0.56)	382(342, 426)	0.45(0.41, 0.49)	344(306, 387)
	Rest of the World	0.27(0.22, 0.33)	283(225, 355)	0.24(0.19, 0.29)	250(195, 321)
Abacavir Exposure	Yes	0.43(0.39, 0.46)	301(273, 332)	0.31(0.26, 0.37)	203(165, 251)
	No	0.32(0.29, 0.36)	241(212, 274)	0.36(0.34, 0.39)	286(262, 312)

Note: a: NP adverse events is counted as number of events.

Note: b: Crude estimate defined as NP/N.

Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.

Note: 95% Confidence intervals based on Exact Binomial 2-sided.

Note: N=Number of patients, Pyrs=Person years, NP= Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir.

Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

Table 5:
Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables
DTG+ABC vs DTG+Non-ABC - Patient with NP Events Analysis Level Including 5 Studies

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.28(0.25, 0.31)	198(176, 224)	0.23(0.20, 0.26)	170(146, 198)
Sex	Male	0.30(0.26, 0.34)	184(158, 214)	0.24(0.20, 0.27)	169(143, 200)
	Female	0.25(0.21, 0.30)	231(189, 282)	0.19(0.13, 0.26)	175(119, 257)
Age (years)	<50	0.28(0.25, 0.31)	197(173, 224)	0.24(0.21, 0.28)	180(153, 211)
	>=50	0.29(0.21, 0.38)	206(146, 290)	0.14(0.09, 0.21)	117(74, 186)
Race	White	0.29(0.26, 0.33)	198(171, 229)	0.24(0.20, 0.28)	167(139, 200)
	Other	0.26(0.21, 0.31)	199(160, 246)	0.20(0.15, 0.25)	180(136, 239)
HIV-1 RNA(c/mL)	<100,000	0.29(0.26, 0.33)	206(179, 236)	0.20(0.17, 0.24)	155(128, 187)
	>=100,000	0.25(0.20, 0.30)	178(139, 227)	0.30(0.23, 0.37)	210(161, 272)
CD4+ (c/mm^3)	<200	0.20(0.15, 0.27)	166(119, 231)	0.19(0.14, 0.25)	193(141, 264)
	>=200	0.30(0.27, 0.33)	204(180, 233)	0.24(0.20, 0.28)	164(138, 195)
BMI (kg/m^2)	<18.5	0.30(0.15, 0.49)	229(119, 440)	0.23(0.10, 0.41)	199(95, 418)
	18.5 to 24.9	0.28(0.24, 0.32)	192(163, 226)	0.21(0.17, 0.25)	155(125, 193)
	>=25	0.28(0.24, 0.33)	204(170, 246)	0.25(0.20, 0.30)	189(150, 236)
Psychiatric	Yes	0.41(0.36, 0.47)	284(239, 338)	0.32(0.27, 0.38)	248(201, 306)
	No	0.22(0.19, 0.25)	155(131, 183)	0.17(0.14, 0.21)	126(101, 157)
Any Co-morbidity	Yes	0.29(0.23, 0.35)	206(161, 265)	0.22(0.16, 0.30)	179(128, 249)
	No	0.28(0.25, 0.31)	196(171, 225)	0.23(0.19, 0.26)	168(141, 199)
HIV Risk Factor	Yes	0.28(0.25, 0.31)	198(175, 223)	0.23(0.20, 0.26)	170(146, 198)
	No	0.33(0.01, 0.91)	398(56, 2825)	0	0
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0	0
	No	0.28(0.25, 0.31)	198(176, 224)	0.23(0.20, 0.26)	170(146, 198)
Country	Argentina	0.29(0.13, 0.51)	329(157, 690)	0.22(0.09, 0.42)	245(110, 545)
	Australia	0.53(0.28, 0.77)	305(159, 586)	0.25(0.05, 0.57)	148(48, 458)
	Belgium	0.63(0.24, 0.91)	341(142, 819)	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	0.33(0.01, 0.91)	363(51, 2580)	0.10(0.04, 0.21)	115(52, 257)
	Canada	0.40(0.28, 0.54)	247(164, 372)	0.50(0.25, 0.75)	285(142, 569)

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Chile	0	0(0,)	0.33(0.07, 0.70)	399(129, 1236)
	Denmark	0	0(0,)	0	0
	France	0.43(0.28, 0.59)	265(167, 421)	0.31(0.20, 0.44)	191(124, 297)
	Germany	0.18(0.09, 0.31)	101(53, 194)	0.22(0.09, 0.40)	124(59, 259)
	Greece	0	0	0	0(0,)
	Italy	0.20(0.09, 0.35)	145(73, 290)	0.14(0.05, 0.27)	85(38, 189)
	Mexico	0.17(0.00, 0.64)	181(25, 1282)	0	0(0,)
	Netherlands	0.29(0.04, 0.71)	171(43, 684)	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0	0
	Puerto Rico	0.25(0.01, 0.81)	135(19, 961)	0	0(0,)
	Romania	0.17(0.02, 0.48)	105(26, 420)	0	0(0,)
	Russia	0.06(0.02, 0.13)	47(20, 113)	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	0.24(0.11, 0.42)	322(161, 643)	0.17(0.08, 0.30)	214(111, 411)
	Spain	0.28(0.22, 0.34)	174(134, 227)	0.17(0.11, 0.25)	107(70, 164)
	Switzerland	0	0(0,)	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	0	0(0,)	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0	0
	United Kingdom	0.24(0.10, 0.44)	209(100, 438)	0.46(0.19, 0.75)	277(124, 616)
	United States	0.34(0.29, 0.40)	245(201, 299)	0.28(0.22, 0.35)	219(171, 281)
Region	Europe	0.23(0.20, 0.27)	155(129, 187)	0.22(0.17, 0.27)	136(106, 172)
	North-America	0.35(0.30, 0.40)	245(205, 292)	0.27(0.22, 0.33)	213(169, 269)
	Rest of the World	0.27(0.19, 0.37)	271(189, 390)	0.17(0.12, 0.24)	187(130, 270)
Study	ING117172	0.21(0.16, 0.27)	246(188, 323)	0	0
	ING114915	0.27(0.17, 0.38)	156(102, 239)	0.31(0.24, 0.38)	176(134, 233)
	ING114467	0.35(0.31, 0.40)	212(181, 250)	0	0
	ING113086	0.25(0.19, 0.32)	151(112, 205)	0.27(0.21, 0.33)	158(124, 201)
	ING111762	0.12(0.03, 0.28)	153(57, 407)	0.15(0.12, 0.20)	182(138, 240)

Note: a: NP adverse events is counted as number of patients.

Note: b: Crude estimate defined as NP/N.

Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.

Note: 95% Confidence intervals based on Exact Binomial 2-sided.

Note: N=Number of patients, Pyrs=Person years, NP= Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir.

Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SPRING-2(ING113086), SINGLE(ING114467), and SAILING(ING111762).

Table 6:
Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables
DTG+ABC vs DTG+Non-ABC - Patient with NP Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.22(0.19, 0.26)	183(153, 219)	0.23(0.20, 0.26)	170(146, 198)
Sex	Male	0.23(0.18, 0.29)	145(110, 191)	0.24(0.20, 0.27)	169(143, 200)
	Female	0.22(0.18, 0.27)	227(179, 287)	0.19(0.13, 0.26)	175(119, 257)
Age (years)	<50	0.22(0.18, 0.26)	177(145, 214)	0.24(0.21, 0.28)	180(153, 211)
	>=50	0.27(0.17, 0.40)	237(147, 381)	0.14(0.09, 0.21)	117(74, 186)
Race	White	0.23(0.19, 0.28)	173(138, 217)	0.24(0.20, 0.28)	167(139, 200)
	Other	0.22(0.16, 0.28)	204(152, 276)	0.20(0.15, 0.25)	180(136, 239)
HIV-1 RNA(c/mL)	<100,000	0.24(0.20, 0.28)	193(158, 235)	0.20(0.17, 0.24)	155(128, 187)
	>=100,000	0.18(0.11, 0.25)	151(99, 229)	0.30(0.23, 0.37)	210(161, 272)
CD4+ (c/mm^3)	<200	0.14(0.08, 0.22)	129(79, 210)	0.19(0.14, 0.25)	193(141, 264)
	>=200	0.25(0.21, 0.29)	196(162, 238)	0.24(0.20, 0.28)	164(138, 195)
BMI (kg/m^2)	<18.5	0.32(0.14, 0.55)	263(126, 552)	0.23(0.10, 0.41)	199(95, 418)
	18.5 to 24.9	0.20(0.16, 0.25)	159(123, 206)	0.21(0.17, 0.25)	155(125, 193)
	>=25	0.25(0.19, 0.31)	208(160, 272)	0.25(0.20, 0.30)	189(150, 236)
Psychiatric	Yes	0.30(0.22, 0.38)	242(181, 324)	0.32(0.27, 0.38)	248(201, 306)
	No	0.20(0.16, 0.24)	160(127, 200)	0.17(0.14, 0.21)	126(101, 157)
Any Co-morbidity	Yes	0.23(0.16, 0.31)	187(129, 271)	0.22(0.16, 0.30)	179(128, 249)
	No	0.22(0.18, 0.27)	182(148, 223)	0.23(0.19, 0.26)	168(141, 199)
HIV Risk Factor	Yes	0.22(0.19, 0.26)	182(152, 218)	0.23(0.20, 0.26)	170(146, 198)
	No	0.33(0.01, 0.91)	398(56, 2825)	0	0
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0	0
	No	0.23(0.19, 0.26)	183(153, 219)	0.23(0.20, 0.26)	170(146, 198)
Country	Argentina	0.29(0.13, 0.51)	329(157, 690)	0.22(0.09, 0.42)	245(110, 545)
	Australia	0.38(0.09, 0.76)	231(75, 717)	0.25(0.05, 0.57)	148(48, 458)
	Belgium	0	0	0.67(0.09, 0.99)	738(185, 2950)

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Brazil	0.33(0.01, 0.91)	363(51, 2580)	0.10(0.04, 0.21)	115(52, 257)
	Canada	0.24(0.10, 0.44)	168(80, 352)	0.50(0.25, 0.75)	285(142, 569)
	Chile	0	0(0,)	0.33(0.07, 0.70)	399(129, 1236)
	France	0.50(0.32, 0.68)	314(193, 513)	0.31(0.20, 0.44)	191(124, 297)
	Germany	0.29(0.10, 0.56)	164(68, 394)	0.22(0.09, 0.40)	124(59, 259)
	Greece	0	0	0	0(0,)
	Hungary	0	0	0	0
	Italy	0.19(0.07, 0.39)	172(72, 414)	0.14(0.05, 0.27)	85(38, 189)
	Mexico	0.17(0.00, 0.64)	181(25, 1282)	0	0(0,)
	Netherlands	0	0	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0	0
	Puerto Rico	0.25(0.01, 0.81)	135(19, 961)	0	0(0,)

	Romania	0	0(0,)	0	0(0,)
	Russia	0.06(0.02, 0.13)	47(20, 113)	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	0.24(0.11, 0.42)	322(161, 643)	0.17(0.08, 0.30)	214(111, 411)
	Spain	0.20(0.13, 0.30)	136(86, 216)	0.17(0.11, 0.25)	107(70, 164)
	Switzerland	0	0(0,)	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	0	0(0,)	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0	0
	United Kingdom	0.43(0.18, 0.71)	492(221, 1095)	0.46(0.19, 0.75)	277(124, 616)
	United States	0.26(0.18, 0.34)	226(160, 320)	0.28(0.22, 0.35)	219(171, 281)
Region	Europe	0.21(0.16, 0.26)	151(116, 196)	0.22(0.17, 0.27)	136(106, 172)
	North-America	0.25(0.19, 0.33)	212(155, 289)	0.27(0.22, 0.33)	213(169, 269)
	Rest of the World	0.24(0.16, 0.33)	255(169, 383)	0.17(0.12, 0.24)	187(130, 270)
Study	ING117172	0.21(0.16, 0.27)	246(188, 323)	0	0
	ING114915	0.27(0.17, 0.38)	156(102, 239)	0.31(0.24, 0.38)	176(134, 233)
	ING113086	0.25(0.19, 0.32)	151(112, 205)	0.27(0.21, 0.33)	158(124, 201)
	ING111762	0.12(0.03, 0.28)	153(57, 407)	0.15(0.12, 0.20)	182(138, 240)

Note: a: NP adverse events is counted as number of patients.

Note: b: Crude estimate defined as NP/N.

Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.

Note: 95% Confidence intervals based on Exact Binomial 2-sided.

Note: N=Number of patients, Pyrs=Person years, NP= Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir.

Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915), SPRING-2(ING113086), and SAILING(ING111762).

Table 7:
Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables
DTG+ABC vs DTG+Non-ABC - NP Events Analysis Level DTG+ABC vs DTG+Non-ABC Including 5 Studies

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.43(0.39, 0.46)	301(273, 332)	0.32(0.29, 0.36)	241(212, 274)
Sex	Male	0.45(0.41, 0.49)	276(244, 312)	0.34(0.30, 0.38)	245(213, 281)
	Female	0.39(0.34, 0.44)	357(304, 419)	0.24(0.17, 0.32)	222(158, 312)
Age (years)	<50	0.41(0.38, 0.45)	292(262, 324)	0.35(0.31, 0.39)	259(227, 297)
	>=50	0.51(0.42, 0.61)	368(285, 475)	0.17(0.11, 0.25)	143(94, 218)
Race	White	0.46(0.42, 0.50)	310(276, 348)	0.35(0.30, 0.39)	238(205, 277)
	Other	0.36(0.31, 0.42)	281(235, 337)	0.28(0.22, 0.34)	251(198, 319)
HIV-1 RNA(c/mL)	<100,000	0.44(0.41, 0.48)	310(277, 347)	0.30(0.26, 0.34)	229(196, 267)
	>=100,000	0.38(0.32, 0.44)	275(226, 335)	0.39(0.32, 0.46)	273(217, 344)
CD4+ (c/mm^3)	<200	0.44(0.37, 0.52)	359(287, 450)	0.23(0.17, 0.29)	227(170, 304)
	>=200	0.42(0.39, 0.46)	290(260, 323)	0.36(0.32, 0.40)	245(212, 282)
BMI (kg/m^2)	<18.5	0.60(0.41, 0.77)	457(288, 726)	0.29(0.14, 0.48)	256(133, 492)
	18.5 to 24.9	0.41(0.37, 0.46)	285(249, 326)	0.30(0.25, 0.34)	217(181, 261)
	>=25	0.43(0.38, 0.48)	311(268, 361)	0.36(0.31, 0.42)	274(227, 331)
Psychiatric	Yes	0.66(0.61, 0.72)	459(400, 526)	0.52(0.46, 0.58)	396(335, 468)
	No	0.31(0.27, 0.35)	221(193, 255)	0.21(0.17, 0.25)	153(125, 188)
Any Co-morbidity	Yes	0.51(0.44, 0.58)	366(304, 442)	0.32(0.25, 0.40)	255(193, 337)
	No	0.40(0.37, 0.44)	282(251, 316)	0.32(0.28, 0.36)	238(206, 274)
HIV Risk Factor	Yes	0.43(0.39, 0.46)	301(273, 331)	0.32(0.29, 0.36)	241(212, 274)
	No	0.33(0.01, 0.91)	398(56, 2825)	0	0
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0	0
	No	0.43(0.40, 0.46)	302(273, 333)	0.32(0.29, 0.36)	241(212, 274)
Country	Argentina	0.42(0.22, 0.63)	470(253, 873)	0.26(0.11, 0.46)	285(136, 599)
	Australia	0.59(0.33, 0.82)	339(182, 630)	0.42(0.15, 0.72)	246(103, 592)
	Belgium	1.00(0.63, 1.00)	545(273, 1090)	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	0.33(0.01, 0.91)	363(51, 2580)	0.14(0.06, 0.25)	154(77, 308)
	Canada	0.68(0.55, 0.80)	419(306, 574)	0.69(0.41, 0.89)	391(217, 707)
	Chile	0	0(0,)	0.44(0.14, 0.79)	531(199, 1416)
	Denmark	0	0(0,)	0	0
	France	0.52(0.36, 0.68)	324(213, 492)	0.52(0.39, 0.64)	316(225, 444)
	Germany	0.20(0.10, 0.34)	112(60, 209)	0.28(0.14, 0.47)	159(83, 306)
	Greece	0	0	0	0(0,)

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Italy	0.32(0.18, 0.48)	236(137, 406)	0.20(0.10, 0.35)	127(66, 245)
	Mexico	0.17(0.00, 0.64)	181(25, 1282)	0	0(0,)
	Netherlands	0.29(0.04, 0.71)	171(43, 684)	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0	0
	Puerto Rico	0.75(0.19, 0.99)	406(131, 1260)	0	0(0,)
	Romania	0.17(0.02, 0.48)	105(26, 420)	0	0(0,)
	Russia	0.06(0.02, 0.13)	47(20, 113)	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	0.33(0.18, 0.52)	442(245, 799)	0.19(0.10, 0.33)	237(128, 441)
	Spain	0.41(0.34, 0.48)	258(208, 321)	0.21(0.15, 0.30)	132(90, 195)
	Switzerland	0	0(0,)	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	0	0(0,)	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0	0
	United Kingdom	0.28(0.13, 0.47)	239(119, 477)	0.62(0.32, 0.86)	369(185, 738)
	United States	0.59(0.53, 0.65)	421(363, 490)	0.44(0.37, 0.50)	340(278, 415)
Region	Europe	0.32(0.28, 0.36)	212(181, 248)	0.30(0.25, 0.35)	187(152, 229)
	North-America	0.60(0.55, 0.65)	418(365, 479)	0.42(0.36, 0.48)	326(269, 393)
	Rest of the World	0.36(0.27, 0.46)	356(259, 489)	0.22(0.16, 0.29)	233(168, 323)
Study	ING117172	0.33(0.27, 0.39)	389(313, 483)	0	0
	ING114915	0.37(0.26, 0.48)	215(149, 310)	0.45(0.38, 0.53)	261(208, 328)
	ING114467	0.55(0.50, 0.60)	333(293, 379)	0	0
	ING113086	0.32(0.25, 0.40)	195(149, 254)	0.38(0.31, 0.44)	221(180, 271)
	ING111762	0.24(0.11, 0.42)	305(153, 611)	0.21(0.17, 0.26)	251(198, 318)

Note: a: NP adverse events is counted as number of events.
Note: b: Crude estimate defined as NP/N.
Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, NP=Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir.
Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915), SPRING-2(ING113086), SINGLE(ING114467) and SAILING(ING111762).

Table 8:
Summary of Crude and Exposure Adjusted Incidence Rates of NP Adverse Events by Baseline Variables
DTG+ABC vs DTG+Non-ABC - NP Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	0.33(0.29, 0.37)	266(229, 309)	0.32(0.29, 0.36)	241(212, 274)
Sex	Male	0.29(0.23, 0.35)	183(143, 234)	0.34(0.30, 0.38)	245(213, 281)
	Female	0.35(0.30, 0.41)	361(300, 436)	0.24(0.17, 0.32)	222(158, 312)
Age (years)	<50	0.29(0.25, 0.33)	234(197, 277)	0.35(0.31, 0.39)	259(227, 297)
	>=50	0.61(0.48, 0.73)	530(385, 728)	0.17(0.11, 0.25)	143(94, 218)
Race	White	0.36(0.30, 0.41)	269(224, 322)	0.35(0.30, 0.39)	238(205, 277)
	Other	0.28(0.22, 0.35)	261(201, 341)	0.28(0.22, 0.34)	251(198, 319)
HIV-1 RNA(c/mL)	<100,000	0.35(0.30, 0.40)	282(239, 332)	0.30(0.26, 0.34)	229(196, 267)
	>=100,000	0.25(0.18, 0.33)	212(149, 302)	0.39(0.32, 0.46)	273(217, 344)
CD4+ (c/mm^3)	<200	0.37(0.28, 0.46)	338(250, 458)	0.23(0.17, 0.29)	227(170, 304)
	>=200	0.32(0.27, 0.36)	249(210, 296)	0.36(0.32, 0.40)	245(212, 282)
BMI (kg/m^2)	<18.5	0.68(0.45, 0.86)	564(340, 936)	0.29(0.14, 0.48)	256(133, 492)
	18.5 to 24.9	0.25(0.20, 0.31)	198(157, 249)	0.30(0.25, 0.34)	217(181, 261)
	>=25	0.39(0.33, 0.46)	332(269, 410)	0.36(0.31, 0.42)	274(227, 331)
Psychiatric	Yes	0.43(0.35, 0.52)	355(279, 452)	0.52(0.46, 0.58)	396(335, 468)
	No	0.28(0.24, 0.33)	231(191, 279)	0.21(0.17, 0.25)	153(125, 188)
Any Co-morbidity	Yes	0.48(0.39, 0.58)	395(306, 509)	0.32(0.25, 0.40)	255(193, 337)
	No	0.28(0.24, 0.33)	228(190, 274)	0.32(0.28, 0.36)	238(206, 274)
HIV Risk Factor	Yes	0.33(0.29, 0.37)	266(229, 309)	0.32(0.29, 0.36)	241(212, 274)
	No	0.33(0.01, 0.91)	398(56, 2825)	0	0
Drug Use	Yes	0.17(0.02, 0.48)	194(49, 777)	0	0
	No	0.33(0.29, 0.37)	267(230, 311)	0.32(0.29, 0.36)	241(212, 274)
Country	Argentina	0.42(0.22, 0.63)	470(253, 873)	0.26(0.11, 0.46)	285(136, 599)
	Australia	0.50(0.16, 0.84)	308(116, 822)	0.42(0.15, 0.72)	246(103, 592)
	Belgium	0	0	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	0.33(0.01, 0.91)	363(51, 2580)	0.14(0.06, 0.25)	154(77, 308)
	Canada	0.31(0.15, 0.51)	215(112, 414)	0.69(0.41, 0.89)	391(217, 707)
	Chile	0	0(0,)	0.44(0.14, 0.79)	531(199, 1416)
	France	0.63(0.44, 0.79)	393(254, 609)	0.52(0.39, 0.64)	316(225, 444)
	Germany	0.35(0.14, 0.62)	197(88, 438)	0.28(0.14, 0.47)	159(83, 306)
	Greece	0	0	0	0(0,)
	Hungary	0	0	0	0

		DTG+ABC		DTG+Non-ABC	
Baseline Variables		Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Italy	0.35(0.17, 0.56)	310(161, 596)	0.20(0.10, 0.35)	127(66, 245)
	Mexico	0.17(0.00, 0.64)	181(25, 1282)	0	0(0,)
	Netherlands	0	0	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	0.25(0.01, 0.81)	291(41, 2066)	0	0
	Puerto Rico	0.75(0.19, 0.99)	406(131, 1260)	0	0(0,)
	Romania	0	0(0,)	0	0(0,)
	Russia	0.06(0.02, 0.13)	47(20, 113)	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	0.33(0.18, 0.52)	442(245, 799)	0.19(0.10, 0.33)	237(128, 441)
	Spain	0.24(0.15, 0.34)	159(104, 244)	0.21(0.15, 0.30)	132(90, 195)
	Switzerland	0	0(0,)	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	0	0(0,)	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	0.16(0.03, 0.40)	169(55, 524)	0	0
	United Kingdom	0.43(0.18, 0.71)	492(221, 1095)	0.62(0.32, 0.86)	369(185, 738)
	United States	0.51(0.42, 0.60)	445(348, 570)	0.44(0.37, 0.50)	340(278, 415)
Region	Europe	0.25(0.20, 0.30)	184(145, 233)	0.30(0.25, 0.35)	187(152, 229)
	North-America	0.46(0.38, 0.54)	387(307, 486)	0.42(0.36, 0.48)	326(269, 393)
	Rest of the World	0.33(0.24, 0.43)	354(251, 501)	0.22(0.16, 0.29)	233(168, 323)
Study	ING117172	0.33(0.27, 0.39)	389(313, 483)	0	0
	ING114915	0.37(0.26, 0.48)	215(149, 310)	0.45(0.38, 0.53)	261(208, 328)
	ING113086	0.32(0.25, 0.40)	195(149, 254)	0.38(0.31, 0.44)	221(180, 271)
	ING111762	0.24(0.11, 0.42)	305(153, 611)	0.21(0.17, 0.26)	251(198, 318)

Note: a: NP adverse events is counted as number of events.
Note: b: Crude estimate defined as NP/N.
Note: c: Exposure adjusted incidence rates per 1,000 person-years defined as NP/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, NP=Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir.
Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915), SPRING-2(ING113086), and SAILING(ING111762).

Poisson analysis results

Tables 9, 10 and figure 1 display the Poisson model results for the patient level analysis in both the DTG vs nonDTG and DTG+ABC vs DTG+Other exposure groups.

Overall for the Poisson model at patient level, adjusted estimates [SE] for NPs rates per 1,000 person years were 5.26 [0.068] with DTG versus 5.21 [0.07] with nonDTG (aRR 1.05 [95%CI 0.9, 1.21, p=0.55]), and 5.4 [0.079] with DTG+ABC versus 5.3 [0.085] with DTG+nonABC (aRR 1.1 [95%CI 0.89, 1.37, p=0.37]).

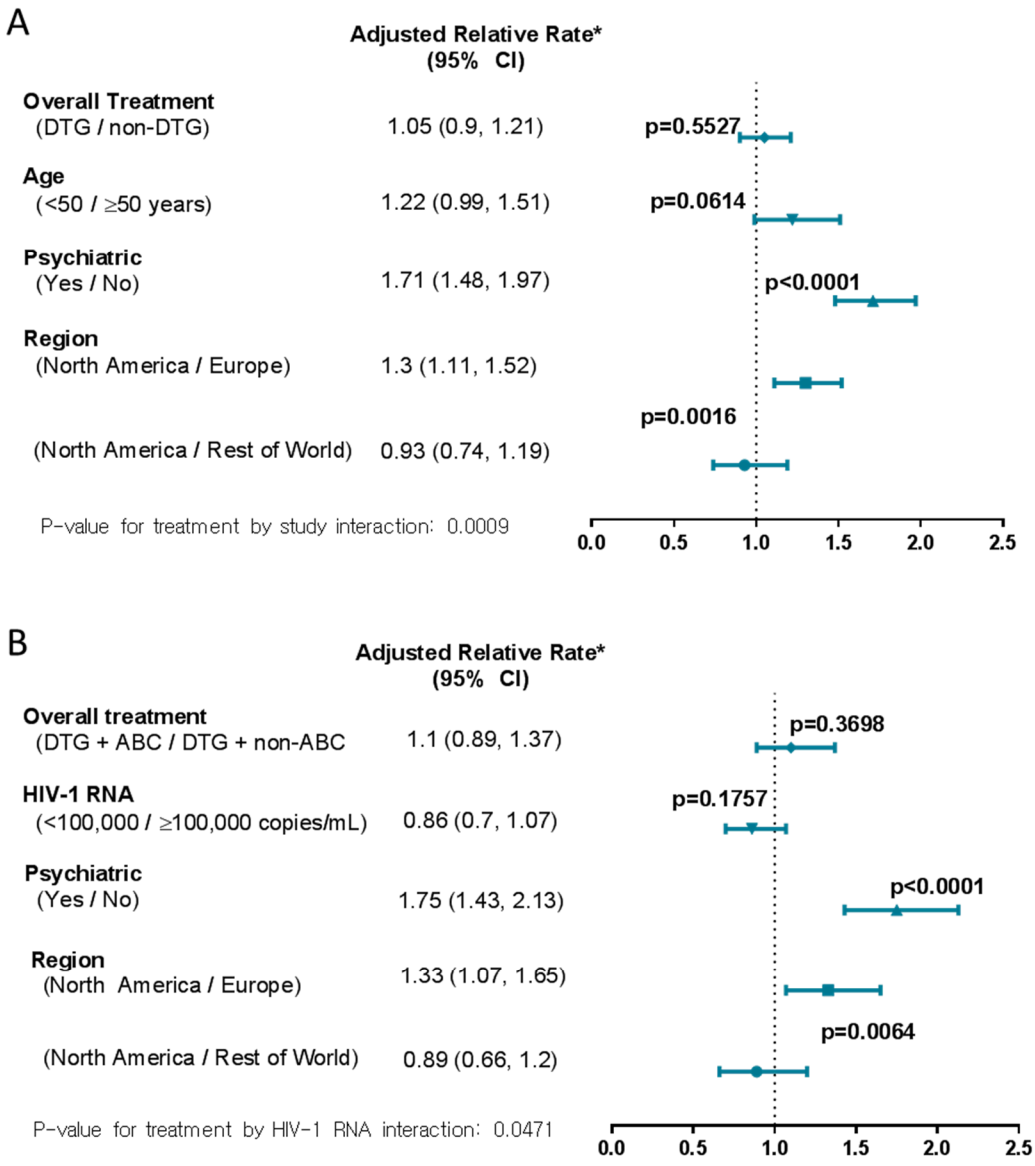
For the DTG vs nonDTG analysis, age, psychiatric history and region were found to be significant variables associated with, with a significant treatment by study interaction. This is illustrated in Figure 1.

For the DTG+ABC vs DTG+Other patient level analysis, HIV RNA, psychiatric history and region were found to be significant variables associated with a significant treatment by HIV RNA level interaction.

The analysis was repeated at the event level and the results are shown in tables 11 and 12. Table 13 illustrates the difference in results in terms of variables associated with. At the event level in the DTG vs non-DTG psychiatric history, region, sex and race were found to be significant. In the DTG+ABC vs DTG+non-ABC analysis treatment, HIV RNA, psychiatric history, region, age, race and CD4 count were found to be significant. The treatment effect is likely driven by the Single study due to the significant treatment by study interaction.

Figure 1:

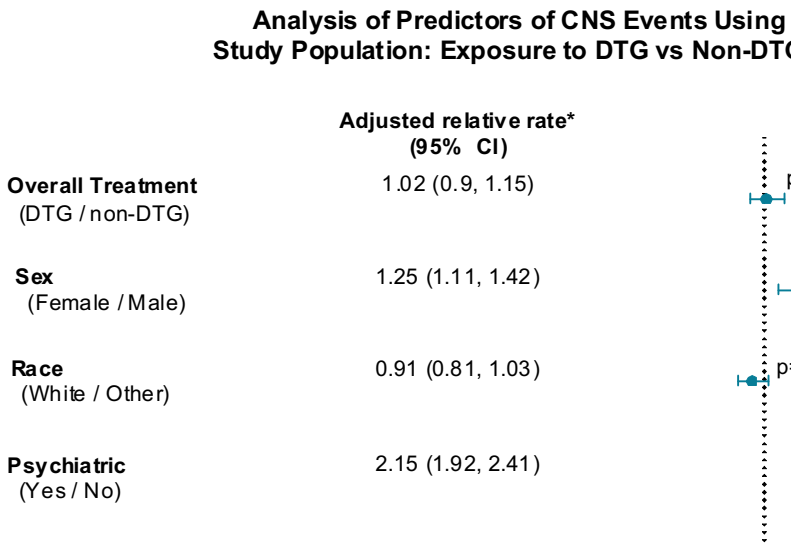
Results from analysis of predictors of NPs using Poisson regression for (A) exposure to DTG vs non-DTG and (B) exposure to DTG + ABC vs DTG + non-ABC



*Adjusted estimate rate is per 1,000 person-years
Pre-specified variables included in the Poisson model were gender, age, race, region, country, previous psychiatric history, any chronic co-morbidity, HIV acquisition risk factor, history of drug use, baseline viral load, CD4 nadir, and BMI

Figure 2:

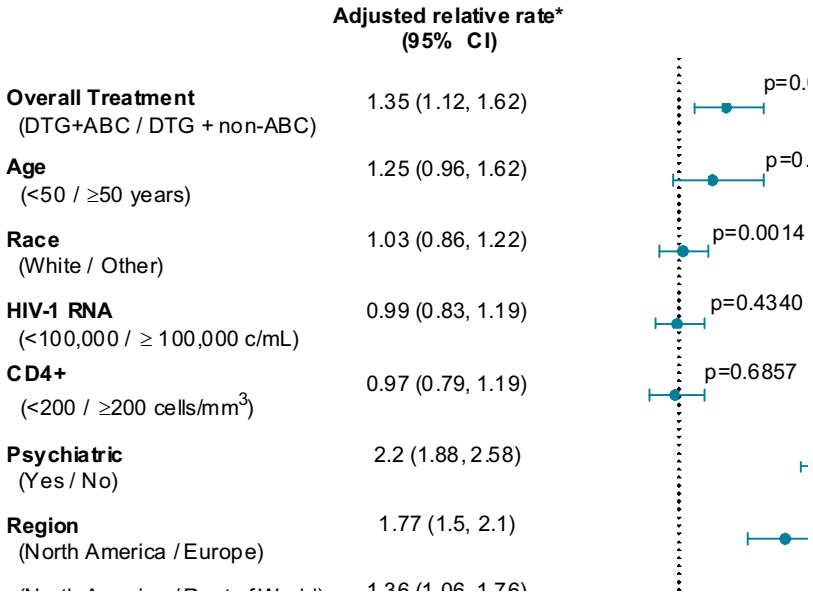
A



P-value for treatment by race, region and study interactions: 0.0031, 0.0469 and <.0001 respectively

B

Analysis of predictors of CNS events using Poi
Study population: Exposure to DTG + ABC vs DTG + n



P-value for treatment by age, psychiatric, HIV-1 RNA, CD4+ and study interaction: 0.0045, 0.0664, 0.0205, 0.0119 and 0.0079 respectively

Table 9:
Analysis of variables associated with NP Events using Poisson Regression
Study Population: Exposure to DTG vs Non-DTG - Patient with NP Events Analysis Level

Variables		Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG	5.26 (0.068)		
	Non-DTG*	5.21 (0.07)	1.05 (0.9, 1.21)	0.5527
Age (years)	<50	5.34 (0.044)		
	>=50	5.14 (0.102)	1.22 (0.99, 1.51)	0.0614
Psychiatric	Yes	5.5 (0.069)		
	No	4.97 (0.068)	1.71 (1.48, 1.97)	<.0001
Region	North-America	5.3 (0.067)		
	Europe	5.04 (0.074)	1.3 (1.11, 1.52)	0.0016
	Rest of the World	5.37 (0.112)	0.93 (0.74, 1.19)	

Note: a: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model
Note: Adjusting for variables associated with in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model
Note: Person-years (Pyrs) defined as exposure duration/365.25
* Non-DTG is the reference group so the adjusted relative rate of DTG: Non-DTG. Adjusted rates are relative to Age <50 years, Psychiatric History of "Yes" and the North American Region.
Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
SE=Standard Error, CI=Confidence Interval.

P-value for treatment by study interaction: 0.0009

Table 10:
Analysis of variables associated with NP Events using Poisson Regression Study Population: Exposure to DTG+ABC vs DTG+Non-ABC - Patient with NP Events Analysis Level

Variables		Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG+ABC	5.4 (0.079)		
	DTG+Non-ABC*	5.3 (0.085)	1.1 (0.89, 1.37)	0.3698
HIV-1 RNA(c/mL)	<100,000	5.27 (0.065)		
	>=100,000	5.42 (0.096)	0.86 (0.7, 1.07)	0.1757
Psychiatric	Yes	5.63 (0.081)		
	No	5.07 (0.078)	1.75 (1.43, 2.13)	<.0001
Region	North-America	5.4 (0.08)		
	Europe	5.12 (0.08)	1.33 (1.07, 1.65)	0.0064
	Rest of the World	5.52 (0.134)	0.89 (0.66, 1.2)	

Note: a: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for variables associated with in this table and study is included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

* DTG+ABC is the reference group so the adjusted relative rate of DTG+ABC: DTG+Non-ABC. Adjusted rates are relative to Baseline HIV-1 RNA <100,000, Psychiatric History of "Yes" and the North American Region.

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by HIV-1 RNA interaction: 0.0471

Table 11:
Analysis of variables associated with NP Events using Poisson Regression
Study Population: Exposure to DTG vs Non-DTG – Event Level Analysis

Variables		Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG	5.52 (0.044)		
	Non-DTG*	5.5 (0.046)	1.02 (0.9, 1.15)	0.6313
Sex	Female	5.67 (0.056)		
	Male	5.44 (0.037)	1.25 (1.11, 1.42)	0.0969
Race	White	5.48 (0.038)		
	Other	5.57 (0.054)	0.91 (0.81, 1.03)	0.0917
Psychiatric	Yes	6.01 (0.041)		
	No	5.25 (0.043)	2.15 (1.92, 2.41)	<.0001
Region	North-America	5.8 (0.045)		
	Europe	5.3 (0.046)	1.65 (1.46, 1.86)	<.0001
	Rest of the World	5.5 (0.088)	1.35 (1.12, 1.63)	

Note: a: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model
Note: Adjusting for variables associated with in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model
Note: Person-years (Pyrs) defined as exposure duration/365.25
* Non-DTG is the reference group so the adjusted relative rate of DTG: Non-DTG. Adjusted rates are relative to Sex of Female, Race of White, Psychiatric History of "Yes" and the North American Region.
Number of events is the unit of analysis so multiple events per subjects is allowed
Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
SE=Standard Error, CI=Confidence Interval.
P-value for treatment by race, region and study interactions: 0.0031, 0.0469 and <.0001 respectively

Table 12:
Analysis of variables associated with NP Events using Poisson Regression Study Population: Exposure to DTG+ABC vs DTG+Non-ABC – Event Level Analysis

Variables		Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG+ABC	5.63 (0.055)		
	DTG+Non-ABC*	5.33 (0.078)	1.35 (1.12, 1.62)	0.0015
Age (years)	<50	5.53 (0.048)		
	>=50	5.31 (0.131)	1.25 (0.96, 1.62)	0.0215
Race	White	5.51 (0.053)		
	Other	5.48 (0.078)	1.03 (0.86, 1.22)	0.0014
HIV-1 RNA(c/mL)	<100,000	5.5 (0.053)		
	>=100,000	5.5 (0.08)	0.99 (0.83, 1.19)	0.4340
CD4+ (c/mm^3)	<200	5.52 (0.099)	0.97 (0.79, 1.19)	
	>=200	5.49 (0.05)		0.6857
Psychiatric	Yes	6.02 (0.058)		
	No	5.23 (0.062)	2.2 (1.88, 2.58)	<.0001
Region	North-America	5.82 (0.062)		
	Europe	5.25 (0.066)	1.77 (1.5, 2.1)	<.0001
	Rest of the World	5.51 (0.121)	1.36 (1.06, 1.76)	

Note: a: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for variables associated with in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

* DTG+ABC is the reference group so the adjusted relative rate of DTG+ABC: DTG+Non-ABC. Adjusted rates are relative to Age <50 years, Race of White, Baseline HIV-1 RNA <100,000, Baseline CD4+ count <200 and Psychiatric History of "Yes" and the North American Region.

Number of events is the unit of analysis so multiple events per subject is allowed

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by age, psychiatric, HIV-1 RNA, CD4+ and study interaction: 0.0045, 0.0664, 0.0205, 0.0119 and 0.0079 respectively

Table 13:
Comparison of significant variables associated with in Poisson models at Patient and Event level analyses

	Variables selected	
	Patient-level analysis	**NP Events-level analysis**
Exposure to DTG vs non DTG	Age (years)	
	Psychiatric	Psychiatric
	Region	Region
		Sex
		Race
Exposure to DTG+ABC vs DTG+Non-ABC		Overall treatment (DTG+ABC vs DTG+Non-ABC)
	HIV-1 RNA(c/mL)	HIV-1 RNA(c/mL)
	Psychiatric	Psychiatric
	Region	Region
		Age (years)
		Race
		CD4+ (c/mm^3)

Green cells are variables selected in both patient level and NP event level analysis
Yellow cells are variables not selected in both patient level and NP event level analysis

Insomnia analyses

Descriptive analyses and proportion of subjects with first insomnia events and subsequent non-insomnia events are in tables 14, 15, 16 and 17.

For the broader analysis of DTG vs non-DTG first insomnia events with subsequent non-insomnia NPs occurred infrequently (2.2%), with higher rates of patients reporting a NP event without a preceding insomnia event (23.0%).

Table 14:
Analysis of First Insomnia Events and Subsequent NP Events

	DTG (N=1672)	Non-DTG (N=1681)	Difference, % (95%CI) [a]
Patients without NP events	1242 (74.3%)	1273 (75.7%)	-1.45 (-4.38, 1.48)
Patients reporting first insomnia event with subsequent NP event	37 (2.2%)	25 (1.5%)	0.73 (-0.19, 1.64)
Insomnia	7 (0.4%)	8 (0.5%)	-0.06 (-0.51, 0.39)
Anxiety	13 (0.8%)	7 (0.4%)	0.36 (-0.16, 0.88)
Bipolar	0 (0.0%)	1 (0.1%)	-0.06 (-0.18, 0.06)
Headache	22 (1.3%)	10 (0.6%)	0.72 (0.06, 1.38)
Suicidal	2 (0.1%)	0 (0.0%)	0.12 (-0.05, 0.29)
Patients reporting NP event without preceding insomnia event	384 (23.0%)	378 (22.5%)	0.48 (-2.36, 3.32)
Insomnia	92 (5.5%)	78 (4.6%)	0.86 (-0.62, 2.35)
Anxiety	54 (3.2%)	66 (3.9%)	-0.70 (-1.95, 0.56)
Bipolar	3 (0.2%)	0 (0.0%)	0.18 (-0.02, 0.38)
Headache	202 (12.1%)	204 (12.1%)	-0.05 (-2.26, 2.15)
Suicidal	17 (1.0%)	17 (1.0%)	0.01 (-0.67, 0.68)
Patients reporting only one NP event	310 (18.5%)	278 (16.5%)	2.00 (-0.57, 4.58)
Insomnia	77 (4.6%)	59 (3.5%)	1.10 (-0.24, 2.43)
Anxiety	30 (1.8%)	29 (1.7%)	0.07 (-0.82, 0.96)
Bipolar	1 (0.1%)	0 (0.0%)	0.06 (-0.06, 0.18)
Headache	146 (8.7%)	143 (8.5%)	0.23 (-1.67, 2.13)
Suicidal	11 (0.7%)	6 (0.4%)	0.30 (-0.18, 0.78)

Note: a: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG - Non-DTG
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
Note: NP= Neuro Psychiatric Symptom, DTG= Dolutegravir

Table 15:
Analysis of First Insomnia Events and Subsequent NP Events

	DTG (N=1672)		
	n(%)	95% CI of %	Difference, % (95%CI) [a]
Patients reporting first insomnia event with subsequent NP event	37 (2.2%)	(1.51, 2.92)	
Patients reporting NP event without preceding insomnia event	384 (23.0%)	(22.34, 23.59)	-20.8 (-22.9, -18.6)
Patients reporting only one NP event	310 (18.5%)	(17.90, 19.18)	-16.3 (-18.3, -14.3)

Note: a: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG - Non-DTG
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
Note: NP=Neuro Psychiatric Symptom, DTG= Dolutegravir

Table 16:
Analysis of First Insomnia Events and Subsequent NP Events

	DTG+ABC (N= 943)	DTG+Non-ABC (N= 729)	Difference, % (95%CI) [a]
Patients without NP events	678 (71.9%)	564 (77.4%)	-5.47 (-9.65, -1.29)
Patients reporting first insomnia event with subsequent NP event	26 (2.8%)	11 (1.5%)	1.25 (-0.12, 2.62)
Insomnia	2 (0.2%)	5 (0.7%)	-0.47 (-1.14, 0.19)
Anxiety	2 (0.2%)	11 (1.5%)	-1.30 (-2.23, -0.36)
Bipolar	0 (0.0%)	0 (0.0%)	0.00 (0.00, 0.00)
Headache	3 (0.3%)	19 (2.6%)	-2.29 (-3.50, -1.08)
Suicidal	0 (0.0%)	2 (0.3%)	-0.27 (-0.65, 0.11)
Patients reporting NP event without preceding insomnia event	233 (24.7%)	151 (20.7%)	4.00 (-0.03, 8.02)
Insomnia	64 (6.8%)	28 (3.8%)	2.95 (0.82, 5.07)
Anxiety	37 (3.9%)	17 (2.3%)	1.59 (-0.06, 3.25)
Bipolar	2 (0.2%)	1 (0.1%)	0.07 (-0.32, 0.47)
Headache	113 (12.0%)	89 (12.2%)	-0.23 (-3.38, 2.93)
Suicidal	8 (0.8%)	9 (1.2%)	-0.39 (-1.38, 0.61)
Patients reporting only one NP event	193 (20.5%)	117 (16.0%)	4.42 (0.71, 8.12)
Insomnia	56 (5.9%)	21 (2.9%)	3.06 (1.12, 4.99)
Anxiety	20 (2.1%)	10 (1.4%)	0.75 (-0.50, 2.00)
Bipolar	1 (0.1%)	0 (0.0%)	0.11 (-0.10, 0.31)
Headache	83 (8.8%)	63 (8.6%)	0.16 (-2.57, 2.89)
Suicidal	5 (0.5%)	6 (0.8%)	-0.29 (-1.10, 0.51)

Note: a: 95% confidence intervals based on The Wald test

Note: Difference Calculated as DTG+ABC - DTG+Non-ABC

Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

Note: NP=Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir

Table 17:
Analysis of First Insomnia Events and Subsequent NP Events

	DTG+ABC (N= 943)		
	n(%)	95% CI of %	Difference, % (95%CI) [a]
Patients reporting first insomnia event with subsequent NP event	26 (2.8%)	(1.71, 3.80)	
Patients reporting NP event without preceding insomnia event	233 (24.7%)	(23.79, 25.63)	-22.0 (-24.9, -19.0)
Patients reporting only one NP event	193 (20.5%)	(19.52, 21.41)	-17.7 (-20.5, -14.9)

Note: a: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG+ABC - DTG+Non-ABC
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
Note: NP=Neuro Psychiatric Symptom, DTG= Dolutegravir, ABC=Abacavir

Discussion

Overall, the analysis has shown that psychiatric history and region are associated with NP events at both the patient and event level at both exposure levels. In the DTG vs non DTG exposure analysis age was additionally found to be associated at the patient level and sex and race at the event level. In the DTG+ABC vs DTG+non-ABC exposure analysis HIV RNA was found to be associated at both the patient and event level while age, race and CD4+ were found to be associated at the event level only.

The event level analysis can be viewed as a sensitivity analysis which was employed to increase the power to detect variables associated with NPs. This was pre specified due to the relatively low event rate of NPs in the trials. However, the patient level analysis is the most meaningful in terms of clinical relevance.

It was hypothesized whether insomnia would be a pre cursor to the development of NPs. However, in our analysis this was not shown to be the case.

Limitations

Only a review of the GSK/VH clinical trial database was performed to identify studies for inclusion. It is possible that more data has been published from non- VH-sponsored clinical trials that were not included in this analysis. The clinical trial databases used different versions of MedDRA coding, though the search terms used in the definitions are expected to have captured all possible events recorded.

As the clinical trials were not specifically designed to evaluate NP outcomes, the collection of additional variables associated with NP events may not have been incorporated in the original study protocols. Additionally, there will be no additional adjudication for NP events for the current meta-analysis. Based on these limitations of the available data, the current meta-analysis will mainly be explorative in nature.

The included studies were generally designed as efficacy studies, and the primary endpoint was not NP outcomes, thus the total drug exposure in person-years will be defined as an average time exposed to the treatment rather than calculated until time to event or end of study, whichever occurred first. Due to the small number of events, the post-NP event follow-up time will have a very limited effect on the overall exposure.

Absence of any effect may be due to size and therefore power of the study and not because there is no relationship between variables associated with NP events and outcome. The results will therefore need to be treated as exploratory and interpreted with caution. No adjustments have been made for multiple testing within this analysis adding to caution required in interpretation.

Conclusions

In this meta-analysis including 3,353 participants, the rate of NPs was similar between DTG and non-DTG treated patients. Variables associated with increased NPs in the DTG vs nonDTG patient level analysis were past psychiatric history, non-EU residence and, in contrast with previous findings, younger age. Within the DTG vs DTG+ABC analysis, past psychiatric history and country of residence showed significant association. Concomitant ABC use was not a variable associated with NPs at the patient level. At the event level in the DTG vs non-DTG psychiatric history, region, sex and race were found to be significant. In the DTG+ABC vs DTG+non-ABC analysis treatment, HIV RNA, psychiatric history, region, age, race and CD4 count were found to be significant. The treatment effect is likely driven by the Single study due to the significant treatment by study interaction. There was no indication that insomnia was associated with subsequent NP events.

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Appendix 1 – SAS tables

Table 3.01
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG – Patient with CNS event analysis level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	1672	2307	430	0.26(0.24, 0.28)	186(170, 205)	1681	2206	408	0.24(0.22, 0.26)	185(168, 204)
Sex	Male	1155	1747	309	0.27(0.24, 0.29)	177(158, 198)	1150	1678	301	0.26(0.24, 0.29)	179(160, 201)
	Female	517	560	121	0.23(0.20, 0.27)	216(181, 258)	531	528	107	0.20(0.17, 0.24)	203(168, 245)
Age (years)	<50	1429	1994	379	0.27(0.24, 0.29)	190(172, 210)	1436	1895	356	0.25(0.23, 0.27)	188(169, 208)
	>=50	243	314	51	0.21(0.16, 0.27)	163(124, 214)	245	311	52	0.21(0.16, 0.27)	167(128, 220)
Race	White	1099	1615	298	0.27(0.25, 0.30)	185(165, 207)	1095	1550	266	0.24(0.22, 0.27)	172(152, 194)
	Other	571	689	132	0.23(0.20, 0.27)	191(161, 227)	584	653	141	0.24(0.21, 0.28)	216(183, 255)
HIV-1 RNA(c/mL)	<100,000	1225	1680	310	0.25(0.23, 0.28)	184(165, 206)	1234	1627	302	0.24(0.22, 0.27)	186(166, 208)
	>=100,000	447	627	120	0.27(0.23, 0.31)	191(160, 229)	447	579	106	0.24(0.20, 0.28)	183(151, 222)
CD4+ (c/mm^3)	<200	374	414	74	0.20(0.16, 0.24)	179(142, 225)	370	390	75	0.20(0.16, 0.25)	192(153, 241)
	>=200	1298	1893	356	0.27(0.25, 0.30)	188(169, 209)	1311	1816	333	0.25(0.23, 0.28)	183(165, 204)
BMI (kg/m^2)	<18.5	61	75	16	0.26(0.16, 0.39)	215(132, 351)	67	73	14	0.21(0.12, 0.33)	192(114, 324)
	18.5 to 24.9	908	1278	226	0.25(0.22, 0.28)	177(155, 201)	856	1156	216	0.25(0.22, 0.28)	187(164, 214)
	>=25	701	951	188	0.27(0.24, 0.30)	198(171, 228)	754	973	175	0.23(0.20, 0.26)	180(155, 209)
Psychiatric	Yes	577	798	214	0.37(0.33, 0.41)	268(235, 307)	589	770	199	0.34(0.30, 0.38)	258(225, 297)
	No	1095	1509	216	0.20(0.17, 0.22)	143(125, 164)	1092	1436	209	0.19(0.17, 0.22)	146(127, 167)

Any Co-morbidity	Yes	371	496	97	0.26(0.22, 0.31)	195(160, 239)	404	482	85	0.21(0.17, 0.25)	177(143, 218)
	No	1301	1811	333	0.26(0.23, 0.28)	184(165, 205)	1277	1725	323	0.25(0.23, 0.28)	187(168, 209)
HIV Risk Factor	Yes	1669	2305	429	0.26(0.24, 0.28)	186(169, 205)	1676	2201	406	0.24(0.22, 0.26)	184(167, 203)

Table 3.01
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG - Patient with CNS event analysis level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	5	5	2	0.40(0.05, 0.85)	399(100, 1596)
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	8	5	1	0.13(0.00, 0.53)	182(26, 1293)
	No	1660	2297	428	0.26(0.24, 0.28)	186(169, 205)	1673	2201	407	0.24(0.22, 0.26)	185(168, 204)
Country	Argentina	51	46	13	0.25(0.14, 0.40)	284(165, 489)	40	37	7	0.18(0.07, 0.33)	189(90, 397)
	Australia	29	50	12	0.41(0.24, 0.61)	241(137, 424)	30	47	13	0.43(0.25, 0.63)	279(162, 480)
	Belgium	11	17	7	0.64(0.31, 0.89)	403(192, 845)	16	20	4	0.25(0.07, 0.52)	196(73, 521)
	Brazil	62	55	7	0.11(0.05, 0.22)	128(61, 268)	63	53	11	0.17(0.09, 0.29)	207(114, 373)
	Canada	73	121	31	0.42(0.31, 0.55)	256(180, 364)	70	102	29	0.41(0.30, 0.54)	283(197, 408)
	Chile	13	10	3	0.23(0.05, 0.54)	303(98, 939)	12	10	3	0.25(0.05, 0.57)	312(101, 968)
	Denmark	2	4	0	0	0(0,)	3	4	0	0	0(0,)

	France	106	172	38	0.36(0.27, 0.46)	220(160, 303)	99	144	30	0.30(0.21, 0.40)	208(146, 298)
	Germany	82	146	16	0.20(0.12, 0.30)	110(67, 179)	104	177	24	0.23(0.15, 0.32)	136(91, 203)
	Greece	2	2	0	0	0(0,)	1	1	0	0	0(0,)
	Hungary	0	0	0	0	0	1	1	0	0	0(0,)
	Italy	85	126	14	0.16(0.09, 0.26)	111(66, 188)	82	119	10	0.12(0.06, 0.21)	84(45, 156)
	Mexico	27	23	1	0.04(0.00, 0.19)	43(6, 302)	25	18	0	0	0(0,)
	Netherlands	8	13	3	0.38(0.09, 0.76)	238(77, 738)	3	5	1	0.33(0.01, 0.91)	212(30, 1508)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	5	4	1	0.20(0.01, 0.72)	272(38, 1928)

Table 3.01
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG - Patient with CNS event analysis level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Puerto Rico	6	11	1	0.17(0.00, 0.64)	90(13, 639)	8	13	1	0.13(0.00, 0.53)	77(11, 550)
	Romania	27	37	2	0.07(0.01, 0.24)	54(13, 214)	29	37	0	0	0(0,)
	Russia	94	111	6	0.06(0.02, 0.13)	54(24, 121)	100	119	5	0.05(0.02, 0.11)	42(18, 101)
	South Africa	85	67	17	0.20(0.12, 0.30)	254(158, 408)	81	65	11	0.14(0.07, 0.23)	169(94, 305)
	Spain	323	517	77	0.24(0.19, 0.29)	149(119, 186)	324	478	81	0.25(0.20, 0.30)	169(136, 211)

	Switzerland	7	12	2	0.29(0.04, 0.71)	173(43, 691)	6	11	2	0.33(0.04, 0.78)	182(45, 726)
	Taiwan	7	6	2	0.29(0.04, 0.71)	362(90, 1447)	4	4	1	0.25(0.01, 0.81)	276(39, 1958)
	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	21	16	3	0.14(0.03, 0.36)	190(61, 588)
	United Kingdom	42	55	13	0.31(0.18, 0.47)	235(137, 405)	30	37	13	0.43(0.25, 0.63)	356(207, 613)
	United States	507	686	161	0.32(0.28, 0.36)	235(201, 274)	524	687	158	0.30(0.26, 0.34)	230(197, 269)
Region	Europe	793	1215	179	0.23(0.20, 0.26)	147(127, 171)	803	1155	171	0.21(0.19, 0.24)	148(127, 172)
	North-America	607	831	193	0.32(0.28, 0.36)	232(202, 268)	619	807	187	0.30(0.27, 0.34)	232(201, 267)
	Rest of the World	272	262	58	0.21(0.17, 0.27)	222(171, 287)	259	244	50	0.19(0.15, 0.25)	205(155, 271)
Study	ING117172	248	211	52	0.21(0.16, 0.27)	246(188, 323)	247	198	49	0.20(0.15, 0.25)	247(187, 327)
	ING114915	242	418	71	0.29(0.24, 0.36)	170(134, 214)	242	398	57	0.24(0.18, 0.29)	143(110, 185)

Table 3.01

Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors

DTG vs Non-DTG - Patient with CNS event analysis level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	ING114467	414	687	146	0.35(0.31, 0.40)	212(181, 250)	419	636	151	0.36(0.31, 0.41)	237(202, 279)

	ING113086	411	689	107	0.26(0.22, 0.31)	155(128, 188)	411	673	102	0.25(0.21, 0.29)	152(125, 184)
	ING111762	357	301	54	0.15(0.12, 0.19)	179(137, 234)	362	300	49	0.14(0.10, 0.17)	163(123, 216)
Abacavir Exposure	Yes	943	1337	265	0.28(0.25, 0.31)	198(176, 224)	279	428	61	0.22(0.17, 0.27)	143(111, 183)
	No	729	970	165	0.23(0.20, 0.26)	170(146, 198)	1402	1778	347	0.25(0.23, 0.27)	195(176, 217)

Note: [a]: CNS adverse events is counted as number of patients.
Note: [b]: Crude estimate defined as CNS/N.
Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),
SPRING-2(ING113086), and SAILING(ING111762).

Table 3.05
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG - CNS Events Analysis Level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	1672	2307	636	0.38(0.36, 0.40)	276(255, 298)	1681	2206	595	0.35(0.33, 0.38)	270(249, 292)
Sex	Male	1155	1747	456	0.39(0.37, 0.42)	261(238, 286)	1150	1678	433	0.38(0.35, 0.41)	258(235, 284)
	Female	517	560	180	0.35(0.31, 0.39)	321(278, 372)	531	528	162	0.31(0.27, 0.35)	307(263, 358)
Age (years)	<50	1429	1994	555	0.39(0.36, 0.41)	278(256, 303)	1436	1895	504	0.35(0.33, 0.38)	266(244, 290)
	>=50	243	314	81	0.33(0.27, 0.40)	258(208, 321)	245	311	91	0.37(0.31, 0.44)	293(238, 360)
Race	White	1099	1615	450	0.41(0.38, 0.44)	279(254, 306)	1095	1550	394	0.36(0.33, 0.39)	254(230, 281)
	Other	571	689	186	0.33(0.29, 0.37)	270(234, 311)	584	653	200	0.34(0.30, 0.38)	306(267, 352)
HIV-1 RNA(c/mL)	<100,000	1225	1680	464	0.38(0.35, 0.41)	276(252, 302)	1234	1627	439	0.36(0.33, 0.38)	270(246, 296)
	>=100,000	447	627	172	0.38(0.34, 0.43)	274(236, 319)	447	579	156	0.35(0.30, 0.40)	270(230, 315)
CD4+ (c/mm^3)	<200	374	414	122	0.33(0.28, 0.38)	295(247, 352)	370	390	107	0.29(0.24, 0.34)	274(227, 331)
	>=200	1298	1893	514	0.40(0.37, 0.42)	271(249, 296)	1311	1816	488	0.37(0.35, 0.40)	269(246, 294)
BMI (kg/m^2)	<18.5	61	75	27	0.44(0.32, 0.58)	362(249, 528)	67	73	23	0.34(0.23, 0.47)	315(210, 475)
	18.5 to 24.9	908	1278	328	0.36(0.33, 0.39)	257(230, 286)	856	1156	309	0.36(0.33, 0.39)	267(239, 299)
	>=25	701	951	281	0.40(0.36, 0.44)	296(263, 332)	754	973	258	0.34(0.31, 0.38)	265(235, 300)
Psychiatric	Yes	577	798	344	0.60(0.55, 0.64)	431(388, 479)	589	770	320	0.54(0.50, 0.58)	416(372, 464)
	No	1095	1509	292	0.27(0.24, 0.29)	193(173, 217)	1092	1436	275	0.25(0.23, 0.28)	192(170, 216)
Any Co-morbidity	Yes	371	496	160	0.43(0.38, 0.48)	322(276, 377)	404	482	128	0.32(0.27, 0.36)	266(224, 316)
	No	1301	1811	476	0.37(0.34, 0.39)	263(240, 288)	1277	1725	467	0.37(0.34, 0.39)	271(247, 297)
HIV Risk Factor	Yes	1669	2305	635	0.38(0.36, 0.40)	276(255, 298)	1676	2201	591	0.35(0.33, 0.38)	269(248, 291)

Table 3.05
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG - CNS Events Analysis Level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	5	5	4	0.80(0.28, 0.99)	798(300, 2127)
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	8	5	1	0.13(0.00, 0.53)	182(26, 1293)
	No	1660	2297	634	0.38(0.36, 0.41)	276(255, 298)	1673	2201	594	0.36(0.33, 0.38)	270(249, 293)
Country	Argentina	51	46	17	0.33(0.21, 0.48)	371(231, 597)	40	37	7	0.18(0.07, 0.33)	189(90, 397)
	Australia	29	50	15	0.52(0.33, 0.71)	301(182, 500)	30	47	19	0.63(0.44, 0.80)	408(260, 639)
	Belgium	11	17	10	0.91(0.59, 1.00)	575(310, 1069)	16	20	5	0.31(0.11, 0.59)	245(102, 588)
	Brazil	62	55	9	0.15(0.07, 0.26)	164(86, 316)	63	53	12	0.19(0.10, 0.31)	226(128, 397)
	Canada	73	121	50	0.68(0.57, 0.79)	413(313, 544)	70	102	42	0.60(0.48, 0.72)	410(303, 555)
	Chile	13	10	4	0.31(0.09, 0.61)	404(152, 1076)	12	10	5	0.42(0.15, 0.72)	520(217, 1250)
	Denmark	2	4	0	0	0(0,)	3	4	0	0	0(0,)
	France	106	172	55	0.52(0.42, 0.62)	319(245, 416)	99	144	54	0.55(0.44, 0.65)	375(287, 489)
	Germany	82	146	19	0.23(0.15, 0.34)	130(83, 204)	104	177	36	0.35(0.26, 0.45)	204(147, 283)
	Greece	2	2	0	0	0(0,)	1	1	0	0	0(0,)
	Hungary	0	0	0	0	0	1	1	0	0	0(0,)

	Italy	85	126	22	0.26(0.17, 0.37)	175(115, 266)	82	119	13	0.16(0.09, 0.26)	109(63, 188)
	Mexico	27	23	1	0.04(0.00, 0.19)	43(6, 302)	25	18	0	0	0(0,)
	Netherlands	8	13	3	0.38(0.09, 0.76)	238(77, 738)	3	5	1	0.33(0.01, 0.91)	212(30, 1508)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	5	4	1	0.20(0.01, 0.72)	272(38, 1928)

Table 3.05

Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors

DTG vs Non-DTG - CNS Events Analysis Level

		DTG (N=1672)					Non-DTG (N=1681)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Puerto Rico	6	11	3	0.50(0.12, 0.88)	270(87, 838)	8	13	1	0.13(0.00, 0.53)	77(11, 550)
	Romania	27	37	2	0.07(0.01, 0.24)	54(13, 214)	29	37	0	0	0(0,)
	Russia	94	111	6	0.06(0.02, 0.13)	54(24, 121)	100	119	6	0.06(0.02, 0.13)	51(23, 113)
	South Africa	85	67	21	0.25(0.16, 0.35)	313(204, 481)	81	65	13	0.16(0.09, 0.26)	200(116, 344)
	Spain	323	517	109	0.34(0.29, 0.39)	211(175, 254)	324	478	122	0.38(0.32, 0.43)	255(214, 305)
	Switzerland	7	12	2	0.29(0.04, 0.71)	173(43, 691)	6	11	2	0.33(0.04, 0.78)	182(45, 726)
	Taiwan	7	6	2	0.29(0.04, 0.71)	362(90, 1447)	4	4	1	0.25(0.01, 0.81)	276(39, 1958)

	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	21	16	3	0.14(0.03, 0.36)	190(61, 588)
	United Kingdom	42	55	16	0.38(0.24, 0.54)	290(178, 473)	30	37	16	0.53(0.34, 0.72)	438(269, 715)
	United States	507	686	266	0.52(0.48, 0.57)	388(344, 437)	524	687	236	0.45(0.41, 0.49)	344(303, 391)
Region	Europe	793	1215	245	0.31(0.28, 0.34)	202(178, 229)	803	1155	256	0.32(0.29, 0.35)	222(196, 251)
	North-America	607	831	317	0.52(0.48, 0.56)	382(342, 426)	619	807	278	0.45(0.41, 0.49)	344(306, 387)
	Rest of the World	272	262	74	0.27(0.22, 0.33)	283(225, 355)	259	244	61	0.24(0.19, 0.29)	250(195, 321)
Abacavir Exposure	Yes	943	1337	402	0.43(0.39, 0.46)	301(273, 332)	279	428	87	0.31(0.26, 0.37)	203(165, 251)
	No	729	970	234	0.32(0.29, 0.36)	241(212, 274)	1402	1778	508	0.36(0.34, 0.39)	286(262, 312)

Note: [a]: CNS adverse events is counted as number of events.
Note: [b]: Crude estimate defined as CNS/N.
Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

Table 3.030
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	943	1337	265	0.28(0.25, 0.31)	198(176, 224)	729	970	165	0.23(0.20, 0.26)	170(146, 198)
Sex	Male	565	925	170	0.30(0.26, 0.34)	184(158, 214)	590	822	139	0.24(0.20, 0.27)	169(143, 200)
	Female	378	412	95	0.25(0.21, 0.30)	231(189, 282)	139	149	26	0.19(0.13, 0.26)	175(119, 257)

Age (years)	<50	828	1176	232	0.28(0.25, 0.31)	197(173, 224)	601	817	147	0.24(0.21, 0.28)	180(153, 211)
	>=50	115	160	33	0.29(0.21, 0.38)	206(146, 290)	128	153	18	0.14(0.09, 0.21)	117(74, 186)
Race	White	615	914	181	0.29(0.26, 0.33)	198(171, 229)	484	701	117	0.24(0.20, 0.28)	167(139, 200)
	Other	328	423	84	0.26(0.21, 0.31)	199(160, 246)	243	266	48	0.20(0.15, 0.25)	180(136, 239)
HIV-1 RNA(c/mL)	<100,000	684	977	201	0.29(0.26, 0.33)	206(179, 236)	541	703	109	0.20(0.17, 0.24)	155(128, 187)
	>=100,000	259	360	64	0.25(0.20, 0.30)	178(139, 227)	188	267	56	0.30(0.23, 0.37)	210(161, 272)
CD4+ (c/mm^3)	<200	171	211	35	0.20(0.15, 0.27)	166(119, 231)	203	202	39	0.19(0.14, 0.25)	193(141, 264)
	>=200	772	1125	230	0.30(0.27, 0.33)	204(180, 233)	526	768	126	0.24(0.20, 0.28)	164(138, 195)
BMI (kg/m^2)	<18.5	30	39	9	0.30(0.15, 0.49)	229(119, 440)	31	35	7	0.23(0.10, 0.41)	199(95, 418)
	18.5 to 24.9	515	745	143	0.28(0.24, 0.32)	192(163, 226)	393	534	83	0.21(0.17, 0.25)	155(125, 193)
	>=25	398	553	113	0.28(0.24, 0.33)	204(170, 246)	303	398	75	0.25(0.20, 0.30)	189(150, 236)
Psychiatric	Yes	309	447	127	0.41(0.36, 0.47)	284(239, 338)	268	351	87	0.32(0.27, 0.38)	248(201, 306)
	No	634	890	138	0.22(0.19, 0.25)	155(131, 183)	461	619	78	0.17(0.14, 0.21)	126(101, 157)
Any Co-morbidity	Yes	215	300	62	0.29(0.23, 0.35)	206(161, 265)	156	196	35	0.22(0.16, 0.30)	179(128, 249)
	No	728	1036	203	0.28(0.25, 0.31)	196(171, 225)	573	775	130	0.23(0.19, 0.26)	168(141, 199)
HIV Risk Factor	Yes	940	1334	264	0.28(0.25, 0.31)	198(175, 223)	729	970	165	0.23(0.20, 0.26)	170(146, 198)

Table 3.030
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	0	0	0	0	0
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	0	0	0	0	0
	No	931	1326	263	0.28(0.25, 0.31)	198(176, 224)	729	970	165	0.23(0.20, 0.26)	170(146, 198)
Country	Argentina	24	21	7	0.29(0.13, 0.51)	329(157, 690)	27	25	6	0.22(0.09, 0.42)	245(110, 545)
	Australia	17	30	9	0.53(0.28, 0.77)	305(159, 586)	12	20	3	0.25(0.05, 0.57)	148(48, 458)
	Belgium	8	15	5	0.63(0.24, 0.91)	341(142, 819)	3	3	2	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	3	3	1	0.33(0.01, 0.91)	363(51, 2580)	59	52	6	0.10(0.04, 0.21)	115(52, 257)
	Canada	57	93	23	0.40(0.28, 0.54)	247(164, 372)	16	28	8	0.50(0.25, 0.75)	285(142, 569)
	Chile	4	2	0	0	0(0,)	9	8	3	0.33(0.07, 0.70)	399(129, 1236)
	Denmark	2	4	0	0	0(0,)	0	0	0	0	0
	France	42	68	18	0.43(0.28, 0.59)	265(167, 421)	64	104	20	0.31(0.20, 0.44)	191(124, 297)
	Germany	50	89	9	0.18(0.09, 0.31)	101(53, 194)	32	57	7	0.22(0.09, 0.40)	124(59, 259)
	Greece	0	0	0	0	0	2	2	0	0	0(0,)
	Italy	41	55	8	0.20(0.09, 0.35)	145(73, 290)	44	71	6	0.14(0.05, 0.27)	85(38, 189)
	Mexico	6	6	1	0.17(0.00, 0.64)	181(25, 1282)	21	18	0	0	0(0,)
	Netherlands	7	12	2	0.29(0.04, 0.71)	171(43, 684)	1	1	1	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	0	0	0	0	0
	Puerto Rico	4	7	1	0.25(0.01, 0.81)	135(19, 961)	2	4	0	0	0(0,)

Table 3.030
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Romania	12	19	2	0.17(0.02, 0.48)	105(26, 420)	15	18	0	0	0(0,)
	Russia	88	106	5	0.06(0.02, 0.13)	47(20, 113)	6	4	1	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	33	25	8	0.24(0.11, 0.42)	322(161, 643)	52	42	9	0.17(0.08, 0.30)	214(111, 411)
	Spain	202	321	56	0.28(0.22, 0.34)	174(134, 227)	121	196	21	0.17(0.11, 0.25)	107(70, 164)
	Switzerland	2	2	0	0	0(0,)	5	9	2	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	2	1	0	0	0(0,)	5	5	2	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	0	0	0	0	0
	United Kingdom	29	34	7	0.24(0.10, 0.44)	209(100, 438)	13	22	6	0.46(0.19, 0.75)	277(124, 616)
	United States	287	403	99	0.34(0.29, 0.40)	245(201, 299)	220	283	62	0.28(0.22, 0.35)	219(171, 281)
Region	Europe	487	728	113	0.23(0.20, 0.27)	155(129, 187)	306	487	66	0.22(0.17, 0.27)	136(106, 172)
	North-America	350	502	123	0.35(0.30, 0.40)	245(205, 292)	257	329	70	0.27(0.22, 0.33)	213(169, 269)
	Rest of the World	106	107	29	0.27(0.19, 0.37)	271(189, 390)	166	155	29	0.17(0.12, 0.24)	187(130, 270)
Study	ING117172	248	211	52	0.21(0.16, 0.27)	246(188, 323)	0	0	0	0	0
	ING114915	79	135	21	0.27(0.17, 0.38)	156(102, 239)	163	284	50	0.31(0.24, 0.38)	176(134, 233)

	ING114467	414	687	146	0.35(0.31, 0.40)	212(181, 250)	0	0	0	0	0
	ING113086	169	278	42	0.25(0.19, 0.32)	151(112, 205)	242	412	65	0.27(0.21, 0.33)	158(124, 201)

Table 3.030

Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors

DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	ING111762	33	26	4	0.12(0.03, 0.28)	153(57, 407)	324	275	50	0.15(0.12, 0.20)	182(138, 240)

Note: [a]: CNS adverse events is counted as number of patients.
Note: [b]: Crude estimate defined as CNS/N.
Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915),
SPRING-2(ING113086), SINGLE(ING114467), and SAILING(ING111762).

Table 3.031
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	529	650	119	0.22(0.19, 0.26)	183(153, 219)	729	970	165	0.23(0.20, 0.26)	170(146, 198)
Sex	Male	218	345	50	0.23(0.18, 0.29)	145(110, 191)	590	822	139	0.24(0.20, 0.27)	169(143, 200)
	Female	311	304	69	0.22(0.18, 0.27)	227(179, 287)	139	149	26	0.19(0.13, 0.26)	175(119, 257)
Age (years)	<50	467	578	102	0.22(0.18, 0.26)	177(145, 214)	601	817	147	0.24(0.21, 0.28)	180(153, 211)
	>=50	62	72	17	0.27(0.17, 0.40)	237(147, 381)	128	153	18	0.14(0.09, 0.21)	117(74, 186)
Race	White	331	439	76	0.23(0.19, 0.28)	173(138, 217)	484	701	117	0.24(0.20, 0.28)	167(139, 200)
	Other	198	210	43	0.22(0.16, 0.28)	204(152, 276)	243	266	48	0.20(0.15, 0.25)	180(136, 239)
HIV-1 RNA(c/mL)	<100,000	404	504	97	0.24(0.20, 0.28)	193(158, 235)	541	703	109	0.20(0.17, 0.24)	155(128, 187)
	>=100,000	125	146	22	0.18(0.11, 0.25)	151(99, 229)	188	267	56	0.30(0.23, 0.37)	210(161, 272)
CD4+ (c/mm^3)	<200	114	124	16	0.14(0.08, 0.22)	129(79, 210)	203	202	39	0.19(0.14, 0.25)	193(141, 264)
	>=200	415	525	103	0.25(0.21, 0.29)	196(162, 238)	526	768	126	0.24(0.20, 0.28)	164(138, 195)
BMI (kg/m^2)	<18.5	22	27	7	0.32(0.14, 0.55)	263(126, 552)	31	35	7	0.23(0.10, 0.41)	199(95, 418)
	18.5 to 24.9	287	364	58	0.20(0.16, 0.25)	159(123, 206)	393	534	83	0.21(0.17, 0.25)	155(125, 193)
	>=25	220	259	54	0.25(0.19, 0.31)	208(160, 272)	303	398	75	0.25(0.20, 0.30)	189(150, 236)
Psychiatric	Yes	152	186	45	0.30(0.22, 0.38)	242(181, 324)	268	351	87	0.32(0.27, 0.38)	248(201, 306)
	No	377	464	74	0.20(0.16, 0.24)	160(127, 200)	461	619	78	0.17(0.14, 0.21)	126(101, 157)
Any Co-morbidity	Yes	122	150	28	0.23(0.16, 0.31)	187(129, 271)	156	196	35	0.22(0.16, 0.30)	179(128, 249)
	No	407	500	91	0.22(0.18, 0.27)	182(148, 223)	573	775	130	0.23(0.19, 0.26)	168(141, 199)
HIV Risk Factor	Yes	526	647	118	0.22(0.19, 0.26)	182(152, 218)	729	970	165	0.23(0.20, 0.26)	170(146, 198)

Table 3.031
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	0	0	0	0	0
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	0	0	0	0	0
	No	517	639	117	0.23(0.19, 0.26)	183(153, 219)	729	970	165	0.23(0.20, 0.26)	170(146, 198)
Country	Argentina	24	21	7	0.29(0.13, 0.51)	329(157, 690)	27	25	6	0.22(0.09, 0.42)	245(110, 545)
	Australia	8	13	3	0.38(0.09, 0.76)	231(75, 717)	12	20	3	0.25(0.05, 0.57)	148(48, 458)
	Belgium	0	0	0	0	0	3	3	2	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	3	3	1	0.33(0.01, 0.91)	363(51, 2580)	59	52	6	0.10(0.04, 0.21)	115(52, 257)
	Canada	29	42	7	0.24(0.10, 0.44)	168(80, 352)	16	28	8	0.50(0.25, 0.75)	285(142, 569)
	Chile	4	2	0	0	0(0,)	9	8	3	0.33(0.07, 0.70)	399(129, 1236)
	France	32	51	16	0.50(0.32, 0.68)	314(193, 513)	64	104	20	0.31(0.20, 0.44)	191(124, 297)
	Germany	17	30	5	0.29(0.10, 0.56)	164(68, 394)	32	57	7	0.22(0.09, 0.40)	124(59, 259)
	Greece	0	0	0	0	0	2	2	0	0	0(0,)
	Hungary	0	0	0	0	0	0	0	0	0	0
	Italy	26	29	5	0.19(0.07, 0.39)	172(72, 414)	44	71	6	0.14(0.05, 0.27)	85(38, 189)

	Mexico	6	6	1	0.17(0.00, 0.64)	181(25, 1282)	21	18	0	0	0(0,)
	Netherlands	0	0	0	0	0	1	1	1	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	0	0	0	0	0
	Puerto Rico	4	7	1	0.25(0.01, 0.81)	135(19, 961)	2	4	0	0	0(0,)

Table 3.031
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Romania	2	4	0	0	0(0,)	15	18	0	0	0(0,)
	Russia	88	106	5	0.06(0.02, 0.13)	47(20, 113)	6	4	1	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	33	25	8	0.24(0.11, 0.42)	322(161, 643)	52	42	9	0.17(0.08, 0.30)	214(111, 411)
	Spain	88	132	18	0.20(0.13, 0.30)	136(86, 216)	121	196	21	0.17(0.11, 0.25)	107(70, 164)
	Switzerland	2	2	0	0	0(0,)	5	9	2	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	2	1	0	0	0(0,)	5	5	2	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	0	0	0	0	0
	United Kingdom	14	12	6	0.43(0.18, 0.71)	492(221, 1095)	13	22	6	0.46(0.19, 0.75)	277(124, 616)
	United States	124	141	32	0.26(0.18, 0.34)	226(160, 320)	220	283	62	0.28(0.22, 0.35)	219(171, 281)
Region	Europe	273	370	56	0.21(0.16, 0.26)	151(116, 196)	306	487	66	0.22(0.17, 0.27)	136(106, 172)
	North-America	159	189	40	0.25(0.19, 0.33)	212(155, 289)	257	329	70	0.27(0.22, 0.33)	213(169, 269)
	Rest of the World	97	90	23	0.24(0.16, 0.33)	255(169, 383)	166	155	29	0.17(0.12, 0.24)	187(130, 270)
Study	ING117172	248	211	52	0.21(0.16, 0.27)	246(188, 323)	0	0	0	0	0
	ING114915	79	135	21	0.27(0.17, 0.38)	156(102, 239)	163	284	50	0.31(0.24, 0.38)	176(134, 233)
	ING113086	169	278	42	0.25(0.19, 0.32)	151(112, 205)	242	412	65	0.27(0.21, 0.33)	158(124, 201)
	ING111762	33	26	4	0.12(0.03, 0.28)	153(57, 407)	324	275	50	0.15(0.12, 0.20)	182(138, 240)

Note: [a]: CNS adverse events is counted as number of patients.
Note: [b]: Crude estimate defined as CNS/N.
Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915),
SPRING-2(ING113086), and SAILING(ING111762).

Table 3.070
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level DTG+ABC vs DTG+Non-ABC Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	943	1337	402	0.43(0.39, 0.46)	301(273, 332)	729	970	234	0.32(0.29, 0.36)	241(212, 274)
Sex	Male	565	925	255	0.45(0.41, 0.49)	276(244, 312)	590	822	201	0.34(0.30, 0.38)	245(213, 281)
	Female	378	412	147	0.39(0.34, 0.44)	357(304, 419)	139	149	33	0.24(0.17, 0.32)	222(158, 312)
Age (years)	<50	828	1176	343	0.41(0.38, 0.45)	292(262, 324)	601	817	212	0.35(0.31, 0.39)	259(227, 297)
	>=50	115	160	59	0.51(0.42, 0.61)	368(285, 475)	128	153	22	0.17(0.11, 0.25)	143(94, 218)
Race	White	615	914	283	0.46(0.42, 0.50)	310(276, 348)	484	701	167	0.35(0.30, 0.39)	238(205, 277)
	Other	328	423	119	0.36(0.31, 0.42)	281(235, 337)	243	266	67	0.28(0.22, 0.34)	251(198, 319)
HIV-1 RNA(c/mL)	<100,000	684	977	303	0.44(0.41, 0.48)	310(277, 347)	541	703	161	0.30(0.26, 0.34)	229(196, 267)
	>=100,000	259	360	99	0.38(0.32, 0.44)	275(226, 335)	188	267	73	0.39(0.32, 0.46)	273(217, 344)
CD4+ (c/mm^3)	<200	171	211	76	0.44(0.37, 0.52)	359(287, 450)	203	202	46	0.23(0.17, 0.29)	227(170, 304)
	>=200	772	1125	326	0.42(0.39, 0.46)	290(260, 323)	526	768	188	0.36(0.32, 0.40)	245(212, 282)
BMI (kg/m^2)	<18.5	30	39	18	0.60(0.41, 0.77)	457(288, 726)	31	35	9	0.29(0.14, 0.48)	256(133, 492)
	18.5 to 24.9	515	745	212	0.41(0.37, 0.46)	285(249, 326)	393	534	116	0.30(0.25, 0.34)	217(181, 261)
	>=25	398	553	172	0.43(0.38, 0.48)	311(268, 361)	303	398	109	0.36(0.31, 0.42)	274(227, 331)
Psychiatric	Yes	309	447	205	0.66(0.61, 0.72)	459(400, 526)	268	351	139	0.52(0.46, 0.58)	396(335, 468)
	No	634	890	197	0.31(0.27, 0.35)	221(193, 255)	461	619	95	0.21(0.17, 0.25)	153(125, 188)
Any Co-morbidity	Yes	215	300	110	0.51(0.44, 0.58)	366(304, 442)	156	196	50	0.32(0.25, 0.40)	255(193, 337)
	No	728	1036	292	0.40(0.37, 0.44)	282(251, 316)	573	775	184	0.32(0.28, 0.36)	238(206, 274)
HIV Risk Factor	Yes	940	1334	401	0.43(0.39, 0.46)	301(273, 331)	729	970	234	0.32(0.29, 0.36)	241(212, 274)

Table 3.070
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level DTG+ABC vs DTG+Non-ABC Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	0	0	0	0	0
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	0	0	0	0	0
	No	931	1326	400	0.43(0.40, 0.46)	302(273, 333)	729	970	234	0.32(0.29, 0.36)	241(212, 274)
Country	Argentina	24	21	10	0.42(0.22, 0.63)	470(253, 873)	27	25	7	0.26(0.11, 0.46)	285(136, 599)
	Australia	17	30	10	0.59(0.33, 0.82)	339(182, 630)	12	20	5	0.42(0.15, 0.72)	246(103, 592)
	Belgium	8	15	8	1.00(0.63, 1.00)	545(273, 1090)	3	3	2	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	3	3	1	0.33(0.01, 0.91)	363(51, 2580)	59	52	8	0.14(0.06, 0.25)	154(77, 308)
	Canada	57	93	39	0.68(0.55, 0.80)	419(306, 574)	16	28	11	0.69(0.41, 0.89)	391(217, 707)
	Chile	4	2	0	0	0(0,)	9	8	4	0.44(0.14, 0.79)	531(199, 1416)
	Denmark	2	4	0	0	0(0,)	0	0	0	0	0
	France	42	68	22	0.52(0.36, 0.68)	324(213, 492)	64	104	33	0.52(0.39, 0.64)	316(225, 444)
	Germany	50	89	10	0.20(0.10, 0.34)	112(60, 209)	32	57	9	0.28(0.14, 0.47)	159(83, 306)
	Greece	0	0	0	0	0	2	2	0	0	0(0,)
	Italy	41	55	13	0.32(0.18, 0.48)	236(137, 406)	44	71	9	0.20(0.10, 0.35)	127(66, 245)

	Mexico	6	6	1	0.17(0.00, 0.64)	181(25, 1282)	21	18	0	0	0(0,)
	Netherlands	7	12	2	0.29(0.04, 0.71)	171(43, 684)	1	1	1	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	0	0	0	0	0
	Puerto Rico	4	7	3	0.75(0.19, 0.99)	406(131, 1260)	2	4	0	0	0(0,)

Table 3.070
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level DTG+ABC vs DTG+Non-ABC Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Romania	12	19	2	0.17(0.02, 0.48)	105(26, 420)	15	18	0	0	0(0,)
	Russia	88	106	5	0.06(0.02, 0.13)	47(20, 113)	6	4	1	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	33	25	11	0.33(0.18, 0.52)	442(245, 799)	52	42	10	0.19(0.10, 0.33)	237(128, 441)
	Spain	202	321	83	0.41(0.34, 0.48)	258(208, 321)	121	196	26	0.21(0.15, 0.30)	132(90, 195)
	Switzerland	2	2	0	0	0(0,)	5	9	2	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	2	1	0	0	0(0,)	5	5	2	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	0	0	0	0	0

	United Kingdom	29	34	8	0.28(0.13, 0.47)	239(119, 477)	13	22	8	0.62(0.32, 0.86)	369(185, 738)
	United States	287	403	170	0.59(0.53, 0.65)	421(363, 490)	220	283	96	0.44(0.37, 0.50)	340(278, 415)
Region	Europe	487	728	154	0.32(0.28, 0.36)	212(181, 248)	306	487	91	0.30(0.25, 0.35)	187(152, 229)
	North-America	350	502	210	0.60(0.55, 0.65)	418(365, 479)	257	329	107	0.42(0.36, 0.48)	326(269, 393)
	Rest of the World	106	107	38	0.36(0.27, 0.46)	356(259, 489)	166	155	36	0.22(0.16, 0.29)	233(168, 323)
Study	ING117172	248	211	82	0.33(0.27, 0.39)	389(313, 483)	0	0	0	0	0
	ING114915	79	135	29	0.37(0.26, 0.48)	215(149, 310)	163	284	74	0.45(0.38, 0.53)	261(208, 328)
	ING114467	414	687	229	0.55(0.50, 0.60)	333(293, 379)	0	0	0	0	0
	ING113086	169	278	54	0.32(0.25, 0.40)	195(149, 254)	242	412	91	0.38(0.31, 0.44)	221(180, 271)

Table 3.070

Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors

DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level DTG+ABC vs DTG+Non-ABC Including 5 Studies

		DTG+ABC (N= 943)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	ING111762	33	26	8	0.24(0.11, 0.42)	305(153, 611)	324	275	69	0.21(0.17, 0.26)	251(198, 318)

Note: [a]: CNS adverse events is counted as number of events.

Note: [b]: Crude estimate defined as CNS/N.

Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915),
SPRING-2(ING113086), SINGLE(ING114467) and SAILING(ING111762).

Table 3.071
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
Overall	Yes	529	650	173	0.33(0.29, 0.37)	266(229, 309)	729	970	234	0.32(0.29, 0.36)	241(212, 274)
Sex	Male	218	345	63	0.29(0.23, 0.35)	183(143, 234)	590	822	201	0.34(0.30, 0.38)	245(213, 281)
	Female	311	304	110	0.35(0.30, 0.41)	361(300, 436)	139	149	33	0.24(0.17, 0.32)	222(158, 312)
Age (years)	<50	467	578	135	0.29(0.25, 0.33)	234(197, 277)	601	817	212	0.35(0.31, 0.39)	259(227, 297)
	>=50	62	72	38	0.61(0.48, 0.73)	530(385, 728)	128	153	22	0.17(0.11, 0.25)	143(94, 218)
Race	White	331	439	118	0.36(0.30, 0.41)	269(224, 322)	484	701	167	0.35(0.30, 0.39)	238(205, 277)
	Other	198	210	55	0.28(0.22, 0.35)	261(201, 341)	243	266	67	0.28(0.22, 0.34)	251(198, 319)
HIV-1 RNA(c/mL)	<100,000	404	504	142	0.35(0.30, 0.40)	282(239, 332)	541	703	161	0.30(0.26, 0.34)	229(196, 267)
	>=100,000	125	146	31	0.25(0.18, 0.33)	212(149, 302)	188	267	73	0.39(0.32, 0.46)	273(217, 344)
CD4+ (c/mm^3)	<200	114	124	42	0.37(0.28, 0.46)	338(250, 458)	203	202	46	0.23(0.17, 0.29)	227(170, 304)
	>=200	415	525	131	0.32(0.27, 0.36)	249(210, 296)	526	768	188	0.36(0.32, 0.40)	245(212, 282)
BMI (kg/m^2)	<18.5	22	27	15	0.68(0.45, 0.86)	564(340, 936)	31	35	9	0.29(0.14, 0.48)	256(133, 492)
	18.5 to 24.9	287	364	72	0.25(0.20, 0.31)	198(157, 249)	393	534	116	0.30(0.25, 0.34)	217(181, 261)
	>=25	220	259	86	0.39(0.33, 0.46)	332(269, 410)	303	398	109	0.36(0.31, 0.42)	274(227, 331)
Psychiatric	Yes	152	186	66	0.43(0.35, 0.52)	355(279, 452)	268	351	139	0.52(0.46, 0.58)	396(335, 468)
	No	377	464	107	0.28(0.24, 0.33)	231(191, 279)	461	619	95	0.21(0.17, 0.25)	153(125, 188)
Any Co-morbidity	Yes	122	150	59	0.48(0.39, 0.58)	395(306, 509)	156	196	50	0.32(0.25, 0.40)	255(193, 337)
	No	407	500	114	0.28(0.24, 0.33)	228(190, 274)	573	775	184	0.32(0.28, 0.36)	238(206, 274)
HIV Risk Factor	Yes	526	647	172	0.33(0.29, 0.37)	266(229, 309)	729	970	234	0.32(0.29, 0.36)	241(212, 274)

Table 3.071
Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	No	3	3	1	0.33(0.01, 0.91)	398(56, 2825)	0	0	0	0	0
Drug Use	Yes	12	10	2	0.17(0.02, 0.48)	194(49, 777)	0	0	0	0	0
	No	517	639	171	0.33(0.29, 0.37)	267(230, 311)	729	970	234	0.32(0.29, 0.36)	241(212, 274)
Country	Argentina	24	21	10	0.42(0.22, 0.63)	470(253, 873)	27	25	7	0.26(0.11, 0.46)	285(136, 599)
	Australia	8	13	4	0.50(0.16, 0.84)	308(116, 822)	12	20	5	0.42(0.15, 0.72)	246(103, 592)
	Belgium	0	0	0	0	0	3	3	2	0.67(0.09, 0.99)	738(185, 2950)
	Brazil	3	3	1	0.33(0.01, 0.91)	363(51, 2580)	59	52	8	0.14(0.06, 0.25)	154(77, 308)
	Canada	29	42	9	0.31(0.15, 0.51)	215(112, 414)	16	28	11	0.69(0.41, 0.89)	391(217, 707)
	Chile	4	2	0	0	0(0,)	9	8	4	0.44(0.14, 0.79)	531(199, 1416)
	France	32	51	20	0.63(0.44, 0.79)	393(254, 609)	64	104	33	0.52(0.39, 0.64)	316(225, 444)
	Germany	17	30	6	0.35(0.14, 0.62)	197(88, 438)	32	57	9	0.28(0.14, 0.47)	159(83, 306)
	Greece	0	0	0	0	0	2	2	0	0	0(0,)
	Hungary	0	0	0	0	0	0	0	0	0	0
	Italy	26	29	9	0.35(0.17, 0.56)	310(161, 596)	44	71	9	0.20(0.10, 0.35)	127(66, 245)

	Mexico	6	6	1	0.17(0.00, 0.64)	181(25, 1282)	21	18	0	0	0(0,)
	Netherlands	0	0	0	0	0	1	1	1	1.00(0.03, 1.00)	1087(153, 7717)
	Portugal	4	3	1	0.25(0.01, 0.81)	291(41, 2066)	0	0	0	0	0
	Puerto Rico	4	7	3	0.75(0.19, 0.99)	406(131, 1260)	2	4	0	0	0(0,)

Table 3.071

Summary of Crude and Exposure Adjusted Incidence Rates of CNS Adverse Events by Baseline Predictors

DTG+ABC vs DTG+Non-ABC - CNS Events Analysis Level Excluding SINGLE(ING114467)

		DTG+ABC (N= 529)					DTG+Non_ABC (N= 729)				
Baseline Predictors		N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]	N	Pyrs	CNS[a]	Crude estimate (95%CI)[b]	Exposure adjusted estimate (95%CI)[c]
	Romania	2	4	0	0	0(0,)	15	18	0	0	0(0,)
	Russia	88	106	5	0.06(0.02, 0.13)	47(20, 113)	6	4	1	0.17(0.00, 0.64)	224(32, 1594)
	South Africa	33	25	11	0.33(0.18, 0.52)	442(245, 799)	52	42	10	0.19(0.10, 0.33)	237(128, 441)
	Spain	88	132	21	0.24(0.15, 0.34)	159(104, 244)	121	196	26	0.21(0.15, 0.30)	132(90, 195)
	Switzerland	2	2	0	0	0(0,)	5	9	2	0.40(0.05, 0.85)	217(54, 867)
	Taiwan	2	1	0	0	0(0,)	5	5	2	0.40(0.05, 0.85)	437(109, 1747)
	Thailand	19	18	3	0.16(0.03, 0.40)	169(55, 524)	0	0	0	0	0
	United Kingdom	14	12	6	0.43(0.18, 0.71)	492(221, 1095)	13	22	8	0.62(0.32, 0.86)	369(185, 738)

	United States	124	141	63	0.51(0.42, 0.60)	445(348, 570)	220	283	96	0.44(0.37, 0.50)	340(278, 415)
Region	Europe	273	370	68	0.25(0.20, 0.30)	184(145, 233)	306	487	91	0.30(0.25, 0.35)	187(152, 229)
	North-America	159	189	73	0.46(0.38, 0.54)	387(307, 486)	257	329	107	0.42(0.36, 0.48)	326(269, 393)
	Rest of the World	97	90	32	0.33(0.24, 0.43)	354(251, 501)	166	155	36	0.22(0.16, 0.29)	233(168, 323)
Study	ING117172	248	211	82	0.33(0.27, 0.39)	389(313, 483)	0	0	0	0	0
	ING114915	79	135	29	0.37(0.26, 0.48)	215(149, 310)	163	284	74	0.45(0.38, 0.53)	261(208, 328)
	ING113086	169	278	54	0.32(0.25, 0.40)	195(149, 254)	242	412	91	0.38(0.31, 0.44)	221(180, 271)
	ING111762	33	26	8	0.24(0.11, 0.42)	305(153, 611)	324	275	69	0.21(0.17, 0.26)	251(198, 318)

Note: [a]: CNS adverse events is counted as number of events.
Note: [b]: Crude estimate defined as CNS/N.
Note: [c]: Exposure adjusted incidence rates per 1,000 person-years defined as CNS/Pyrs.
Note: 95% Confidence intervals based on Exact Binomial 2-sided.
Note: N=Number of patients, Pyrs=Person years, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 4 studies: ARIA(ING117172), FLAMINGO(ING114915),
SPRING-2(ING113086), and SAILING(ING111762).

Table 3.11
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG

		DTG (N=1672)				Non-DTG (N=1681)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
Overall	Yes	1672	1242(74.3%)	310(18.5%)	120(7.2%)	1681	1273(75.7%)	278(16.5%)	130(7.7%)
Sex	Male	1155	846(50.6%)	214(12.8%)	95(5.7%)	1150	849(50.5%)	210(12.5%)	91(5.4%)
	Female	517	396(23.7%)	96(5.7%)	25(1.5%)	531	424(25.2%)	68(4.0%)	39(2.3%)
Age (years)	<50	1429	1050(62.8%)	268(16.0%)	111(6.6%)	1436	1080(64.2%)	247(14.7%)	109(6.5%)

	>=50	243	192(11.5%)	42(2.5%)	9(0.5%)	245	193(11.5%)	31(1.8%)	21(1.2%)
Race	White	1099	801(47.9%)	216(12.9%)	82(4.9%)	1095	829(49.3%)	179(10.6%)	87(5.2%)
	Other	571	439(26.3%)	94(5.6%)	38(2.3%)	584	443(26.4%)	98(5.8%)	43(2.6%)
HIV-1 RNA(c/mL)	<100,000	1225	915(54.7%)	225(13.5%)	85(5.1%)	1234	932(55.4%)	206(12.3%)	96(5.7%)
	>=100,000	447	327(19.6%)	85(5.1%)	35(2.1%)	447	341(20.3%)	72(4.3%)	34(2.0%)
CD4+ (c/mm^3)	<200	374	300(17.9%)	55(3.3%)	19(1.1%)	370	295(17.5%)	53(3.2%)	22(1.3%)
	>=200	1298	942(56.3%)	255(15.3%)	101(6.0%)	1311	978(58.2%)	225(13.4%)	108(6.4%)
BMI (kg/m^2)	<18.5	61	45(2.7%)	11(0.7%)	5(0.3%)	67	53(3.2%)	9(0.5%)	5(0.3%)
	18.5 to 24.9	908	682(40.8%)	164(9.8%)	62(3.7%)	856	640(38.1%)	153(9.1%)	63(3.7%)
	>=25	701	513(30.7%)	135(8.1%)	53(3.2%)	754	579(34.4%)	115(6.8%)	60(3.6%)
Psychiatric	Yes	577	363(21.7%)	142(8.5%)	72(4.3%)	589	390(23.2%)	118(7.0%)	81(4.8%)
	No	1095	879(52.6%)	168(10.0%)	48(2.9%)	1092	883(52.5%)	160(9.5%)	49(2.9%)
Any Co-morbidity	Yes	371	274(16.4%)	67(4.0%)	30(1.8%)	404	319(19.0%)	56(3.3%)	29(1.7%)
	No	1301	968(57.9%)	243(14.5%)	90(5.4%)	1277	954(56.8%)	222(13.2%)	101(6.0%)
HIV Risk Factor	Yes	1669	1240(74.2%)	309(18.5%)	120(7.2%)	1676	1270(75.6%)	278(16.5%)	128(7.6%)
	No	3	2(0.1%)	1(0.1%)	0	5	3(0.2%)	0	2(0.1%)
Drug Use	Yes	12	10(0.6%)	2(0.1%)	0	8	7(0.4%)	1(0.1%)	0

Table 3.11
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG

		DTG (N=1672)				Non-DTG (N=1681)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
	No	1660	1232(73.7%)	308(18.4%)	120(7.2%)	1673	1266(75.3%)	277(16.5%)	130(7.7%)
Country	Argentina	51	38(2.3%)	10(0.6%)	3(0.2%)	40	33(2.0%)	7(0.4%)	0
	Australia	29	17(1.0%)	10(0.6%)	2(0.1%)	30	17(1.0%)	8(0.5%)	5(0.3%)
	Belgium	11	4(0.2%)	5(0.3%)	2(0.1%)	16	12(0.7%)	3(0.2%)	1(0.1%)
	Brazil	62	55(3.3%)	5(0.3%)	2(0.1%)	63	52(3.1%)	10(0.6%)	1(0.1%)
	Canada	73	42(2.5%)	18(1.1%)	13(0.8%)	70	41(2.4%)	19(1.1%)	10(0.6%)
	Chile	13	10(0.6%)	2(0.1%)	1(0.1%)	12	9(0.5%)	2(0.1%)	1(0.1%)
	Denmark	2	2(0.1%)	0	0	3	3(0.2%)	0	0
	France	106	68(4.1%)	25(1.5%)	13(0.8%)	99	69(4.1%)	19(1.1%)	11(0.7%)
	Germany	82	66(3.9%)	13(0.8%)	3(0.2%)	104	80(4.8%)	17(1.0%)	7(0.4%)
	Greece	2	2(0.1%)	0	0	1	1(0.1%)	0	0
	Hungary	0	0	0	0	1	1(0.1%)	0	0
	Italy	85	71(4.2%)	10(0.6%)	4(0.2%)	82	72(4.3%)	8(0.5%)	2(0.1%)
	Mexico	27	26(1.6%)	1(0.1%)	0	25	25(1.5%)	0	0
	Netherlands	8	5(0.3%)	3(0.2%)	0	3	2(0.1%)	1(0.1%)	0
	Portugal	4	3(0.2%)	1(0.1%)	0	5	4(0.2%)	1(0.1%)	0
	Puerto Rico	6	5(0.3%)	0	1(0.1%)	8	7(0.4%)	1(0.1%)	0
	Romania	27	25(1.5%)	2(0.1%)	0	29	29(1.7%)	0	0
	Russia	94	88(5.3%)	6(0.4%)	0	100	95(5.7%)	4(0.2%)	1(0.1%)
	South Africa	85	68(4.1%)	14(0.8%)	3(0.2%)	81	70(4.2%)	9(0.5%)	2(0.1%)
	Spain	323	246(14.7%)	56(3.3%)	21(1.3%)	324	243(14.5%)	56(3.3%)	25(1.5%)

Table 3.11
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG vs Non-DTG

		DTG (N=1672)				Non-DTG (N=1681)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
	Switzerland	7	5(0.3%)	2(0.1%)	0	6	4(0.2%)	2(0.1%)	0
	Taiwan	7	5(0.3%)	2(0.1%)	0	4	3(0.2%)	1(0.1%)	0
	Thailand	19	16(1.0%)	3(0.2%)	0	21	18(1.1%)	3(0.2%)	0
	United Kingdom	42	29(1.7%)	10(0.6%)	3(0.2%)	30	17(1.0%)	10(0.6%)	3(0.2%)
	United States	507	346(20.7%)	112(6.7%)	49(2.9%)	524	366(21.8%)	97(5.8%)	61(3.6%)
Region	Europe	793	614(36.7%)	133(8.0%)	46(2.8%)	803	632(37.6%)	121(7.2%)	50(3.0%)
	North-America	607	414(24.8%)	131(7.8%)	62(3.7%)	619	432(25.7%)	116(6.9%)	71(4.2%)
	Rest of the World	272	214(12.8%)	46(2.8%)	12(0.7%)	259	209(12.4%)	41(2.4%)	9(0.5%)
Study	ING117172	248	196(11.7%)	44(2.6%)	8(0.5%)	247	198(11.8%)	32(1.9%)	17(1.0%)
	ING114915	242	171(10.2%)	49(2.9%)	22(1.3%)	242	185(11.0%)	44(2.6%)	13(0.8%)
	ING114467	414	268(16.0%)	97(5.8%)	49(2.9%)	419	268(15.9%)	96(5.7%)	55(3.3%)
	ING113086	411	304(18.2%)	80(4.8%)	27(1.6%)	411	309(18.4%)	71(4.2%)	31(1.8%)
	ING111762	357	303(18.1%)	40(2.4%)	14(0.8%)	362	313(18.6%)	35(2.1%)	14(0.8%)
Abacavir Exposure	Yes	943	678(40.6%)	193(11.5%)	72(4.3%)	279	218(13.0%)	45(2.7%)	16(1.0%)
	No	729	564(33.7%)	117(7.0%)	48(2.9%)	1402	1055(62.8%)	233(13.9%)	114(6.8%)

Note: [a]: CNS adverse events is counted as number of patients.
Note: N=Number of patients, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),
SPRING-2(ING113086), and SAILING(ING111762).

Table 3.012
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC

		DTG+ABC (N= 943)				DTG+Non_ABC (N= 729)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
Overall	Yes	943	678(71.9%)	193(20.5%)	72(7.6%)	729	564(77.4%)	117(16.0%)	48(6.6%)
Sex	Male	565	395(41.9%)	119(12.6%)	51(5.4%)	590	451(61.9%)	95(13.0%)	44(6.0%)
	Female	378	283(30.0%)	74(7.8%)	21(2.2%)	139	113(15.5%)	22(3.0%)	4(0.5%)
Age (years)	<50	828	596(63.2%)	166(17.6%)	66(7.0%)	601	454(62.3%)	102(14.0%)	45(6.2%)
	>=50	115	82(8.7%)	27(2.9%)	6(0.6%)	128	110(15.1%)	15(2.1%)	3(0.4%)
Race	White	615	434(46.0%)	133(14.1%)	48(5.1%)	484	367(50.3%)	83(11.4%)	34(4.7%)
	Other	328	244(25.9%)	60(6.4%)	24(2.5%)	243	195(26.7%)	34(4.7%)	14(1.9%)
HIV-1 RNA(c/mL)	<100,000	684	483(51.2%)	149(15.8%)	52(5.5%)	541	432(59.3%)	76(10.4%)	33(4.5%)
	>=100,000	259	195(20.7%)	44(4.7%)	20(2.1%)	188	132(18.1%)	41(5.6%)	15(2.1%)
CD4+ (c/mm^3)	<200	171	136(14.4%)	22(2.3%)	13(1.4%)	203	164(22.5%)	33(4.5%)	6(0.8%)
	>=200	772	542(57.5%)	171(18.1%)	59(6.3%)	526	400(54.9%)	84(11.5%)	42(5.8%)
BMI (kg/m^2)	<18.5	30	21(2.2%)	5(0.5%)	4(0.4%)	31	24(3.3%)	6(0.8%)	1(0.1%)
	18.5 to 24.9	515	372(39.4%)	104(11.0%)	39(4.1%)	393	310(42.5%)	60(8.2%)	23(3.2%)
	>=25	398	285(30.2%)	84(8.9%)	29(3.1%)	303	228(31.3%)	51(7.0%)	24(3.3%)
Psychiatric	Yes	309	182(19.3%)	87(9.2%)	40(4.2%)	268	181(24.8%)	55(7.5%)	32(4.4%)
	No	634	496(52.6%)	106(11.2%)	32(3.4%)	461	383(52.5%)	62(8.5%)	16(2.2%)
Any Co-morbidity	Yes	215	153(16.2%)	42(4.5%)	20(2.1%)	156	121(16.6%)	25(3.4%)	10(1.4%)
	No	728	525(55.7%)	151(16.0%)	52(5.5%)	573	443(60.8%)	92(12.6%)	38(5.2%)
HIV Risk Factor	Yes	940	676(71.7%)	192(20.4%)	72(7.6%)	729	564(77.4%)	117(16.0%)	48(6.6%)
	No	3	2(0.2%)	1(0.1%)	0	0	0	0	0

Drug Use	Yes	12	10(1.1%)	2(0.2%)	0	0	0	0	0

Table 3.012
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC

		DTG+ABC (N= 943)				DTG+Non_ABC (N= 729)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
	No	931	668(70.8%)	191(20.3%)	72(7.6%)	729	564(77.4%)	117(16.0%)	48(6.6%)
Country	Argentina	24	17(1.8%)	5(0.5%)	2(0.2%)	27	21(2.9%)	5(0.7%)	1(0.1%)
	Australia	17	8(0.8%)	8(0.8%)	1(0.1%)	12	9(1.2%)	2(0.3%)	1(0.1%)
	Belgium	8	3(0.3%)	3(0.3%)	2(0.2%)	3	1(0.1%)	2(0.3%)	0
	Brazil	3	2(0.2%)	1(0.1%)	0	59	53(7.3%)	4(0.5%)	2(0.3%)
	Canada	57	34(3.6%)	12(1.3%)	11(1.2%)	16	8(1.1%)	6(0.8%)	2(0.3%)
	Chile	4	4(0.4%)	0	0	9	6(0.8%)	2(0.3%)	1(0.1%)
	Denmark	2	2(0.2%)	0	0	0	0	0	0
	France	42	24(2.5%)	15(1.6%)	3(0.3%)	64	44(6.0%)	10(1.4%)	10(1.4%)
	Germany	50	41(4.3%)	8(0.8%)	1(0.1%)	32	25(3.4%)	5(0.7%)	2(0.3%)
	Greece	0	0	0	0	2	2(0.3%)	0	0
	Italy	41	33(3.5%)	6(0.6%)	2(0.2%)	44	38(5.2%)	4(0.5%)	2(0.3%)
	Mexico	6	5(0.5%)	1(0.1%)	0	21	21(2.9%)	0	0
	Netherlands	7	5(0.5%)	2(0.2%)	0	1	0	1(0.1%)	0
	Portugal	4	3(0.3%)	1(0.1%)	0	0	0	0	0
	Puerto Rico	4	3(0.3%)	0	1(0.1%)	2	2(0.3%)	0	0
	Romania	12	10(1.1%)	2(0.2%)	0	15	15(2.1%)	0	0
	Russia	88	83(8.8%)	5(0.5%)	0	6	5(0.7%)	1(0.1%)	0
	South Africa	33	25(2.7%)	6(0.6%)	2(0.2%)	52	43(5.9%)	8(1.1%)	1(0.1%)
	Spain	202	146(15.5%)	40(4.2%)	16(1.7%)	121	100(13.7%)	16(2.2%)	5(0.7%)

	Switzerland	2	2(0.2%)	0	0	5	3(0.4%)	2(0.3%)	0

Table 3.012
Summary of Incidence of CNS Adverse Events by Baseline Predictors
DTG+ABC vs DTG+Non-ABC

		DTG+ABC (N= 943)				DTG+Non_ABC (N= 729)			
			CNS Events				CNS Events		
Baseline Predictors		N	0	1	2+	N	0	1	2+
	Taiwan	2	2(0.2%)	0	0	5	3(0.4%)	2(0.3%)	0
	Thailand	19	16(1.7%)	3(0.3%)	0	0	0	0	0
	United Kingdom	29	22(2.3%)	6(0.6%)	1(0.1%)	13	7(1.0%)	4(0.5%)	2(0.3%)
	United States	287	188(19.9%)	69(7.3%)	30(3.2%)	220	158(21.7%)	43(5.9%)	19(2.6%)
Region	Europe	487	374(39.7%)	88(9.3%)	25(2.7%)	306	240(32.9%)	45(6.2%)	21(2.9%)
	North-America	350	227(24.1%)	82(8.7%)	41(4.3%)	257	187(25.7%)	49(6.7%)	21(2.9%)
	Rest of the World	106	77(8.2%)	23(2.4%)	6(0.6%)	166	137(18.8%)	23(3.2%)	6(0.8%)
Study	ING117172	248	196(20.8%)	44(4.7%)	8(0.8%)	0	0	0	0
	ING114915	79	58(6.2%)	16(1.7%)	5(0.5%)	163	113(15.5%)	33(4.5%)	17(2.3%)
	ING114467	414	268(28.4%)	97(10.3%)	49(5.2%)	0	0	0	0
	ING113086	169	127(13.5%)	34(3.6%)	8(0.8%)	242	177(24.3%)	46(6.3%)	19(2.6%)
	ING111762	33	29(3.1%)	2(0.2%)	2(0.2%)	324	274(37.6%)	38(5.2%)	12(1.6%)
Abacavir Exposure	Yes	943	678(71.9%)	193(20.5%)	72(7.6%)	0	0	0	0
	No	0	0	0	0	729	564(77.4%)	117(16.0%)	48(6.6%)

Note: [a]: CNS adverse events is counted as number of patients.
Note: N=Number of patients, CNS= Central Nervous System, DTG= Dolutegravir,ABC=Abacavir.
Note: Data presented is from 5 studies: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

Table 1.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG vs Non-DTG - Patient with CNS Events Analysis Level

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG	430/ 1672	5.26 (0.068)		
	Non-DTG	408/ 1681	5.21 (0.07)	1.05 (0.9, 1.21)	0.5527
Age (years)	<50	735/ 2865	5.34 (0.044)		
	>=50	103/ 488	5.14 (0.102)	1.22 (0.99, 1.51)	0.0614
Psychiatric	Yes	413/ 1166	5.5 (0.069)		
	No	425/ 2187	4.97 (0.068)	1.71 (1.48, 1.97)	<.0001
Region	North-America	380/ 1226	5.3 (0.067)		
	Europe	350/ 1596	5.04 (0.074)	1.3 (1.11, 1.52)	0.0016
	Rest of the World	108/ 531	5.37 (0.112)	0.93 (0.74, 1.19)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by study interaction: 0.0009

Table 2.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG+ABC	265/ 943	5.4 (0.079)		
	DTG+Non-ABC	165/ 729	5.3 (0.085)	1.1 (0.89, 1.37)	0.3698
HIV-1 RNA(c/mL)	<100,000	310/ 1225	5.27 (0.065)		
	>=100,000	120/ 447	5.42 (0.096)	0.86 (0.7, 1.07)	0.1757
Psychiatric	Yes	214/ 577	5.63 (0.081)		
	No	216/ 1095	5.07 (0.078)	1.75 (1.43, 2.13)	<.0001
Region	North-America	193/ 607	5.4 (0.08)		
	Europe	179/ 793	5.12 (0.08)	1.33 (1.07, 1.65)	0.0064
	Rest of the World	58/ 272	5.52 (0.134)	0.89 (0.66, 1.2)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study is included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by HIV-1 RNA interaction: 0.0471

Table 3.903:Analysis of First Insomnia Events and Subsequent CNS Events

	DTG (N=1672)	Non-DTG (N=1681)	Difference, % (95%CI) [a]
Patients without CNS events	1242 (74.3%)	1273 (75.7%)	-1.45 (-4.38, 1.48)
Patients reporting first insomnia event with subsequent CNS event	37 (2.2%)	25 (1.5%)	0.73 (-0.19, 1.64)
Insomnia	7 (0.4%)	8 (0.5%)	-0.06 (-0.51, 0.39)
Anxiety	13 (0.8%)	7 (0.4%)	0.36 (-0.16, 0.88)
Bipolar	0 (0.0%)	1 (0.1%)	-0.06 (-0.18, 0.06)
Headache	22 (1.3%)	10 (0.6%)	0.72 (0.06, 1.38)
Suicidal	2 (0.1%)	0 (0.0%)	0.12 (-0.05, 0.29)
Patients reporting CNS event without preceding insomnia event	384 (23.0%)	378 (22.5%)	0.48 (-2.36, 3.32)
Insomnia	92 (5.5%)	78 (4.6%)	0.86 (-0.62, 2.35)
Anxiety	54 (3.2%)	66 (3.9%)	-0.70 (-1.95, 0.56)
Bipolar	3 (0.2%)	0 (0.0%)	0.18 (-0.02, 0.38)
Headache	202 (12.1%)	204 (12.1%)	-0.05 (-2.26, 2.15)
Suicidal	17 (1.0%)	17 (1.0%)	0.01 (-0.67, 0.68)
Patients reporting only one CNS event	310 (18.5%)	278 (16.5%)	2.00 (-0.57, 4.58)
Insomnia	77 (4.6%)	59 (3.5%)	1.10 (-0.24, 2.43)
Anxiety	30 (1.8%)	29 (1.7%)	0.07 (-0.82, 0.96)
Bipolar	1 (0.1%)	0 (0.0%)	0.06 (-0.06, 0.18)
Headache	146 (8.7%)	143 (8.5%)	0.23 (-1.67, 2.13)
Suicidal	11 (0.7%)	6 (0.4%)	0.30 (-0.18, 0.78)

Note: [a]: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG - Non-DTG
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),

SPRING-2(ING113086), and SAILING(ING111762).
Note: CNS= Central Nervous System, DTG= Dolutegravir

Table 3.903: Analysis of First Insomnia Events and Subsequent CNS Events

	DTG (N=1672)		
	n(%)	95% CI of %	Difference, % (95%CI) [a]
Patients reporting first insomnia event with subsequent CNS event	37 (2.2%)	(1.51, 2.92)	
Patients reporting CNS event without preceding insomnia event	384 (23.0%)	(22.34, 23.59)	-20.8 (-22.9, -18.6)
Patients reporting only one CNS event	310 (18.5%)	(17.90, 19.18)	-16.3 (-18.3, -14.3)

Note: [a]: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG - Non-DTG
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).
Note: CNS= Central Nervous System, DTG= Dolutegravir

Table 3.103:Analysis of First Insomnia Events and Subsequent CNS Events

	DTG+ABC (N= 943)	DTG+Non-ABC (N= 729)	Difference, % (95%CI) [a]
Patients without CNS events	678 (71.9%)	564 (77.4%)	-5.47 (-9.65, -1.29)
Patients reporting first insomnia event with subsequent CNS event	26 (2.8%)	11 (1.5%)	1.25 (-0.12, 2.62)
Insomnia	2 (0.2%)	5 (0.7%)	-0.47 (-1.14, 0.19)
Anxiety	2 (0.2%)	11 (1.5%)	-1.30 (-2.23, -0.36)
Bipolar	0 (0.0%)	0 (0.0%)	0.00 (0.00, 0.00)
Headache	3 (0.3%)	19 (2.6%)	-2.29 (-3.50, -1.08)
Suicidal	0 (0.0%)	2 (0.3%)	-0.27 (-0.65, 0.11)
Patients reporting CNS event without preceding insomnia event	233 (24.7%)	151 (20.7%)	4.00 (-0.03, 8.02)
Insomnia	64 (6.8%)	28 (3.8%)	2.95 (0.82, 5.07)
Anxiety	37 (3.9%)	17 (2.3%)	1.59 (-0.06, 3.25)
Bipolar	2 (0.2%)	1 (0.1%)	0.07 (-0.32, 0.47)
Headache	113 (12.0%)	89 (12.2%)	-0.23 (-3.38, 2.93)
Suicidal	8 (0.8%)	9 (1.2%)	-0.39 (-1.38, 0.61)
Patients reporting only one CNS event	193 (20.5%)	117 (16.0%)	4.42 (0.71, 8.12)
Insomnia	56 (5.9%)	21 (2.9%)	3.06 (1.12, 4.99)
Anxiety	20 (2.1%)	10 (1.4%)	0.75 (-0.50, 2.00)
Bipolar	1 (0.1%)	0 (0.0%)	0.11 (-0.10, 0.31)
Headache	83 (8.8%)	63 (8.6%)	0.16 (-2.57, 2.89)
Suicidal	5 (0.5%)	6 (0.8%)	-0.29 (-1.10, 0.51)

Note: [a]: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG+ABC - DTG+Non-ABC
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),

SPRING-2(ING113086), and SAILING(ING111762).
Note: CNS= Central Nervous System, DTG= Dolutegravir, ABC=Abacavir

Table 3.104:Analysis of First Insomnia Events and Subsequent CNS Events

	DTG+ABC (N= 943)		
	n(%)	95% CI of %	Difference, % (95%CI) [a]
Patients reporting first insomnia event with subsequent CNS event	26 (2.8%)	(1.71, 3.80)	
Patients reporting CNS event without preceding insomnia event	233 (24.7%)	(23.79, 25.63)	-22.0 (-24.9, -19.0)
Patients reporting only one CNS event	193 (20.5%)	(19.52, 21.41)	-17.7 (-20.5, -14.9)

Note: [a]: 95% confidence intervals based on The Wald test
Note: Difference Calculated as DTG+ABC - DTG+Non-ABC
Note: Data presented is from: ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),
SPRING-2(ING113086), and SAILING(ING111762).
Note: CNS= Central Nervous System, DTG= Dolutegravir, ABC=Abacavir

Table 1.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG vs Non-DTG - Patient with CNS Events Analysis Level

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG	430/ 1672	5.26 (0.068)		
	Non-DTG	408/ 1681	5.21 (0.07)	1.05 (0.9, 1.21)	0.5527
Age (years)	<50	735/ 2865	5.34 (0.044)		
	>=50	103/ 488	5.14 (0.102)	1.22 (0.99, 1.51)	0.0614
Psychiatric	Yes	413/ 1166	5.5 (0.069)		
	No	425/ 2187	4.97 (0.068)	1.71 (1.48, 1.97)	<.0001
Region	North-America	380/ 1226	5.3 (0.067)		
	Europe	350/ 1596	5.04 (0.074)	1.3 (1.11, 1.52)	0.0016
	Rest of the World	108/ 531	5.37 (0.112)	0.93 (0.74, 1.19)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by study interaction: 0.0009

Table 2.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG+ABC vs DTG+Non-ABC - Patient with CNS Events Analysis Level

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG+ABC	265/ 943	5.4 (0.079)		
	DTG+Non-ABC	165/ 729	5.3 (0.085)	1.1 (0.89, 1.37)	0.3698
HIV-1 RNA(c/mL)	<100,000	310/ 1225	5.27 (0.065)		
	>=100,000	120/ 447	5.42 (0.096)	0.86 (0.7, 1.07)	0.1757
Psychiatric	Yes	214/ 577	5.63 (0.081)		
	No	216/ 1095	5.07 (0.078)	1.75 (1.43, 2.13)	<.0001
Region	North-America	193/ 607	5.4 (0.08)		
	Europe	179/ 793	5.12 (0.08)	1.33 (1.07, 1.65)	0.0064
	Rest of the World	58/ 272	5.52 (0.134)	0.89 (0.66, 1.2)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study is included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467), SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by HIV-1 RNA interaction: 0.0471

Table 3.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG vs Non-DTG

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG	636/ 1672	5.52 (0.044)		
	Non-DTG	595/ 1681	5.5 (0.046)	1.02 (0.9, 1.15)	0.6313
Sex	Female	342/ 1048	5.67 (0.056)		
	Male	889/ 2305	5.44 (0.037)	1.25 (1.11, 1.42)	0.0969
Race	White	844/ 2194	5.48 (0.038)		
	Other	386/ 1155	5.57 (0.054)	0.91 (0.81, 1.03)	0.0917
Psychiatric	Yes	664/ 1166	6.01 (0.041)		
	No	567/ 2187	5.25 (0.043)	2.15 (1.92, 2.41)	<.0001
Region	North-America	595/ 1226	5.8 (0.045)		
	Europe	501/ 1596	5.3 (0.046)	1.65 (1.46, 1.86)	<.0001
	Rest of the World	135/ 531	5.5 (0.088)	1.35 (1.12, 1.63)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model

Note: Person-years (Pyrs) defined as exposure duration/365.25

Number of events is the unit of analysis so multiple events per subjects is allowed

Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),

SPRING-2(ING113086), and SAILING(ING111762).

SE=Standard Error, CI=Confidence Interval.

P-value for treatment by race, region and study interactions: 0.0031, 0.0469 and <.0001 respectively

Table 4.6:Analysis of Predictors of CNS Events using Poisson Regression

Study Population

Exposure to DTG+ABC vs DTG+Non-ABC

Predictors		Events/patients	Adjusted estimate (SE) [a]	Adjusted Relative Rate (95%CI) [a]	P-value
Overall treatment	DTG+ABC	402/ 943	5.63 (0.055)		
	DTG+Non-ABC	234/ 729	5.33 (0.078)	1.35 (1.12, 1.62)	0.0015
Age (years)	<50	555/ 1429	5.53 (0.048)		
	>=50	81/ 243	5.31 (0.131)	1.25 (0.96, 1.62)	0.0215
Race	White	450/ 1099	5.51 (0.053)		
	Other	186/ 571	5.48 (0.078)	1.03 (0.86, 1.22)	0.0014
HIV-1 RNA(c/mL)	<100,000	464/ 1225	5.5 (0.053)		
	>=100,000	172/ 447	5.5 (0.08)	0.99 (0.83, 1.19)	0.4340
CD4+ (c/mm^3)	<200	122/ 374	5.52 (0.099)	0.97 (0.79, 1.19)	
	>=200	514/ 1298	5.49 (0.05)		0.6857
Psychiatric	Yes	344/ 577	6.02 (0.058)		
	No	292/ 1095	5.23 (0.062)	2.2 (1.88, 2.58)	<.0001
Region	North-America	317/ 607	5.82 (0.062)		
	Europe	245/ 793	5.25 (0.066)	1.77 (1.5, 2.1)	<.0001
	Rest of the World	74/ 272	5.51 (0.121)	1.36 (1.06, 1.76)	

Note: [a]: Estimates for LSMeans rates are per 100,000 persons years and adjusted Relative Rates are from Poisson model

Note: Adjusting for predictors in this table and study included as a random effect. 95% Confidence intervals are also derived from the same model
Note: Person-years (Pyrs) defined as exposure duration/365.25
Number of events is the unit of analysis so multiple events per subject is allowed
Note: Data presented is from : ARIA(ING117172), FLAMINGO(ING114915), SINGLE(ING114467),
SPRING-2(ING113086), and SAILING(ING111762).
SE=Standard Error, CI=Confidence Interval.
P-value for treatment by age, psychiatric, HIV-1 RNA, CD4+ and study interaction: 0.0045,
0.0664, 0.0205, 0.0119 and 0.0079 respectively

TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Dolutegravir Use and Predictors of CNS events: Meta-analysis of Data from Phase III/IIIb Clinical Trials

Compound Number: GSK1349572

Development Phase

Effective Date: [DD-MM-YYYY]

Subject: Safety, Dolutegravir, CNS, HIV

Author(s):

PPD

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1. LIST OF ABBREVIATIONS

ABC	Abacavir
AE	Adverse Event
ATV	Atazanavir
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CNS	Central Nervous System
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
RAL	Raltegravir
RCT	Randomized Controlled Trial
US	United States
VH	ViiV Healthcare

2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

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Primary Author/ Project officer	**Date**
VP, Global Medical Sciences	**Date**
VP, Safety and Pharmacovigilance	**Date**

3. ABSTRACT

Title: Dolutegravir Use and CNS events: Meta-analysis of Data from Phase III/IIIb Clinical Trials

Rationale and background: In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, CNS AE rates were low, and most CNS AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. A couple of observational HIV cohorts (see references) suggest that CNS AEs may result in somewhat higher rates of discontinuation in clinical practice than documented in clinical trials, and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use. Therefore, we are proposing to re-examine data from the phase III adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any predictors (from a pre-specified list) of development of a CNS AE during the course of the trials which could explain what is observed in the cohorts.

Research question and objectives:

The primary objective is to assess if there are any predictors for the development of a CNS AE during the course of the trials.

Study design: This meta-analysis will include data that were previously collected for VH-sponsored clinical trials in adult Phase III/IIIb of drug development for dolutegravir.

Study size: Studies included in the meta-analysis will be Spring 2, Single, Flamingo, Aria and Sailing

Data analysis: The incidence of CNS events will be calculated from frequencies of reported adverse events (AEs) in the included clinical trials; 95% CIs will be based on exact binomial 2-sided CIs. To assess the effect of pre-specified predictors on the exposure adjusted incidence rate and relative rate of CNS events in human immunodeficiency virus (HIV) patients treated with DTG containing versus non DTG containing regimens as well as DTG + ABC exposure vs DTG + other regimens Poisson mixed effects meta-regression models will be used. 95% CIs will be calculated for rates and relative rates.

4. AMENDMENTS AND UPDATES

N/A

5. MILESTONES

Milestone	Planned date
Start of data analysis	01 May 2017
Draft report	30 JUN 2017
Final report of study results	30 JUL 2017

6. BACKGROUND AND RATIONALE

6.1. Background

In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, CNS AE rates were low, and most CNS AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. Evolving observational HIV cohort data (1,2,4,5,6,7,8) suggest that CNS AEs may result in somewhat higher rates of DTG discontinuation in clinical practice than documented in clinical trials and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use.

6.2. Rationale

Therefore, we are proposing to re-examine patient level data from the phase III/IIIb adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any predictors of development of a CNS AE during the course of the trials which could explain what is observed in the cohorts. These are the same studies as were included in the Fettiplace et al manuscript (2017).

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective is to identify if there are any predictors of the development of a CNS AE during the course of the trials.

8. RESEARCH METHODS

8.1. Study Design

This meta-analysis will include individual patient level data that were previously collected for VH-sponsored randomized clinical trials in adult Phase III/IIIb of drug development for dolutegravir.

8.2. Study Population and Setting

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included will be 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

Table 1. Overview of GSK/VH-sponsored clinical trials included in the meta-analysis.

Study name	Study identifier	Study duration included in meta-analysis	Primary objective	DTG exposed	DTG unexposed
ARIA[1]	ING117172	48	A Phase IIIb study to demonstrate the non-inferior antiviral activity, safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV and TDF/FTC FDC in HIV-1 infected, ART-naïve women.	248	247
FLAMINGO	ING114915	96	A Phase IIIb study to demonstrate the non-inferior antiviral activity of DTG 50mg administered once daily compared to DRV+RTV 800mg + 100mg once daily both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve subjects.	242	242
SINGLE[1]	ING114467	144	A Phase III study to demonstrate the non-inferior antiviral activity of DTG + ABC/3TC once daily therapy compared to EFV/TDF/FTC in HIV-1 infected ART-naïve subjects.	414	419
SPRING-2	ING113086	96	A Phase III study to demonstrate the antiviral activity of DTG 50 mg administered once daily compared to RAL 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects.	411	411
SAILING	ING111762	48	A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults	357	362

[1]Randomized with respect to ABC therapy (i.e. an experimental control for ABC).

8.3. Variables

8.3.1. Exposure definitions

Two sets of analyses will be carried out reflecting the different exposures of interest – DTG and DTG + ABC. For the first set of analyses the exposed group was treated with DTG as part of cART. The comparator group was exposed to non-DTG-containing cART regimen. A single subject may only contribute to one of the exposure categories. For the second set of analyses we will consider DTG + ABC exposure vs DTG + Other exposure.

The mean exposure in days will be calculated from patient level data available for each study. Exposure categories will be constructed according to exposure to DTG or not in the cART as well as DTG + ABC vs not. The total exposure time in person-years will be obtained by taking the sum of each subjects' exposure time from start to end of treatment and dividing it by 365.25.

8.3.2. Outcome definitions

For the 5 VH-sponsored clinical trials, outcomes were identified on the basis of reported AEs listed in an aggregated clinical trials database maintained by VH.

The same definitions as described in the Fettiplace et al. JAIDS paper (2017) will be used to select the events of interest based on selected psychiatric symptoms occurring in HIV-positive patients during dolutegravir treatment as classified by company physicians. The following specific preferred terms will be used to define a CNS event in this analysis:

- Insomnia
- Anxiety
- Depression
- Suicidality
- Nightmares/abnormal dreams
- Headache

As described in Fettiplace et al the category *insomnia* includes the terms *insomnia*, *initial insomnia, terminal insomnia*, and *middle insomnia*. The category *anxiety* includes the terms *anxiety* and *anxiety disorder*. The category *depression* includes the terms *depression*, *major depression*, *depressed mood*, *depressive symptom*, and *bipolar disorder*. The category *suicidality* includes *suicide attempt*, *suicidal ideation*, *completed suicide*, *intentional self-injury*, and *self-injurious behavior*. The category headache includes the terms *headache* and *migraine*.

The analysis will be carried out for both all AEs and all drug related AEs during the course of the trials and will model both events and patients with an event as an outcome. Treatment of recurrent events will depend on how many re-occurring events are found to be present in the data. If there are 15% or more re-occurring events a sensitivity analysis will be carried out taking these into account. If fewer recurrent events are present in the data then only the first event for each patient will be included.

8.3.3. Predictors

The following set of variables are hypothesized based on the cohort data to be predictors of the development of a CNS AE during the course of the trials and will therefore be included and tested for in the analysis:

- Gender (M vs F)
- Age (< and ≥ 50)
- Race (White vs Other)
- Region
- Country
- Previous psychiatric history (Y vs N)
- Any chronic co-morbidity, including HCV, Diabetes, Hypertension (Y vs N)
- HIV acquisition risk factor
- History of drug use (Y vs N)
- Baseline viral load (< and ≥ 100,000 copies/ml)
- CD4 nadir (< and ≥ 200)
- BMI

8.4. Data sources

The studies that will be included in the meta-analysis were initially identified in the VH clinical-trial repository that includes prospectively collected data from VH-sponsored trials and contains clinical studies from phases III/IIIb of drug development shown in table 1.

8.5. Study size

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included will be 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

8.6. Data analysis

This analysis will look at studies with a follow-up of ≥48 weeks. This analysis will calculate incidence of a CNS AE as defined by the psychiatric symptoms described in section 8.3.2 for both definitions of exposure and evaluate if there are any predictors described in section 8.3.3. Since this is an exploratory analysis we will use a p-value of 0.10 for significance testing of those predictors. Prior to inclusion in the analysis the incidence of a CNS AE will be tabulated by predictor and any predictors with zero counts in categories will be excluded from the Poisson regression model.

8.6.1. Essential analysis

Incidence of CNS events by predictor

Percentages will be based on the frequency of AEs collected during the conduct of clinical trials and presented by levels of a predictor and study as well as aggregate. 95% CIs will be based on exact binomial 2-sided confidence intervals (CIs).

Relationship between exposure to DTG, predictors and development of outcome

Exposure adjusted incidence rates per 1,000 person-years will be calculated, and Poisson regression models will used to calculate relative rates, adjusted for predictors described in section 8.3.3. Study will be fitted as an indicator within the pooled model. 95% CIs will be calculated for rates and relative rates. P-values will be calculated for predictors. A stepwise approach will be used to identify significant predictors with a significance level of 10%. Results will be presented in a forest plot (by study and aggregate). The characteristics of those subjects at highest risk of a CNS event will be identified and the difference versus the remainder of the subjects quoted.

Sensitivity analyses

If there are 15% or more recurrent events a sensitivity analysis will be carried out taking these into account.

To consider whether insomnia is a pre cursor to other CNS AEs events, a tabular display of insomnia followed by other CNS AE yes/no will be created.

8.6.2. General considerations for data analyses

The possibility of multiple events in one patient may need to be taken into account. Therefore, the analysis of AE incidence is carried out both at the event and patient level.

8.7. Quality control and Quality Assurance

Quality control and quality assurance processes have been performed as part of the clinical trial protocols. Two statisticians will independently program for this analysis to ensure quality control of highest level.

Additionally, the analyses will be performed per European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (2010).

8.8. Limitations of the research methods

Only a review of the GSK/VH clinical trial database was performed to identify studies for inclusion. It is possible that more data has been published from non- VH-sponsored clinical trials that were not included in this analysis.

As the clinical trials were not specifically designed to evaluate CNS outcomes, the collection of additional predictors for CNS events may not have been incorporated in the original study protocols. Additionally, there will be no additional adjudication for CNS events for the current meta-analysis. Based on these limitations of the available data, the current meta-analysis will mainly be explorative in nature.

The included studies were generally designed as efficacy studies, and the primary endpoint was not CNS outcomes, thus the total drug exposure in person-years will be defined as an average time exposed to the treatment rather than calculated until time to event or end of study, whichever occurred first. Due to the small number of events, the post-CNS event follow-up time will have a very limited effect on the overall exposure.

Absence of any effect may be due to size and therefore power of the study and not because there is no relationship between predictors and outcome. The results will therefore need to be treated as exploratory.

8.8.1. Study closure/uninterpretability of results

N/A

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

N/A, ethical approval was obtained for primary data collection as part of the clinical trials. This meta-analysis will use previously collected, anonymized clinical trial data.

9.2. Subject confidentiality

This meta-analysis will use previously collected, anonymized clinical trial data. No identifying information will be provided.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves secondary use of anonymized data from RCTs. All serious and non-serious AEs, pregnancy exposures and incidents related to any VH product during the conduct of the RCTs have already been reported to the case management and regulatory authorities per the RCT protocols. There is no potential for identification of any additional AEs or SAEs. Hence there will not be a study specific pharmacovigilance plan developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience includes healthcare providers, regulatory and health authorities. The study results will be made available externally through conference presentation.

11.2. Study reporting and publications

Study results will be included in safety and regulatory reports as appropriate. Results will also be submitted for publication at a relevant conference.

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