ING116070: A Study of the Pharmacokinetics and Antiviral Activity of Dolutegravir in Cerebrospinal Fluid in HIV-1–Infected, Antiretroviral Therapy–Naive Subjects

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Background. Dolutegravir (DTG), a once-daily, human immunodeficiency virus type 1 (HIV-1) integrase inhibitor, was evaluated for distribution and antiviral activity in cerebrospinal fluid (CSF).

Methods. ING116070 is an ongoing, single-arm, open-label, multicenter study in antiretroviral therapy–naive, HIV-1–infected adults. Subjects received DTG (50 mg) plus abacavir/lamivudine (600/300 mg) once daily. The CSF and plasma (total and unbound) DTG concentrations were measured at weeks 2 and 16. The HIV-1 RNA levels were measured in CSF at baseline and weeks 2 and 16 and in plasma at baseline and weeks 2, 4, 8, 12, and 16.

Results. Thirteen white men enrolled in the study; 2 withdrew prematurely, 1 because of a non–drug-related serious adverse event (pharyngitis) and 1 because of lack of treatment efficacy. The median DTG concentrations in CSF were 18 ng/mL (range, 4–23 ng/mL) at week 2 and 13 ng/mL (4–18 ng/mL) at week 16. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma. Median changes from baseline in CSF (n = 11) and plasma (n = 12) HIV-1 RNA were −3.42 and −3.04 $\log_{10}$ copies/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA levels <50 copies/mL and 10 of 11 (91%) had CSF HIV-1 RNA levels <2 copies/mL at week 16.

Conclusions. The DTG concentrations in CSF were similar to unbound plasma concentrations and exceeded the in vitro 50% inhibitory concentration for wild-type HIV (0.2 ng/mL), suggesting that DTG achieves therapeutic concentrations in the central nervous system. The HIV-1 RNA reductions were similar in CSF and plasma.

Clinical Trials Registration. NCT01499199.

Keywords. cerebrospinal fluid; dolutegravir; HIV.

Despite the advent of modern, potent antiretroviral therapy (ART), human immunodeficiency virus (HIV)–associated neurocognitive impairment continues to be clinically significant [1–3]. In HIV-infected patients receiving therapy, HIV has been found in the cerebrospinal fluid (CSF) of individuals who have an undetectable plasma viral load, both for patients with neurologic symptoms [4] and for those who are neurologically asymptomatic [5]. Such discordant findings between plasma and CSF may be influenced by choice of therapy, because treatment with ART that has better estimated distribution into the central nervous system (CNS) has been associated with better viral suppression in CSF [6–8]. Thus, it has become increasingly important to understand to what degree components of ART can exert activity within the brain, a long-considered "sanctuary" site [6, 9–11].

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Although the CSF space is not equivalent to the brain extracellular or intracellular environment, drug distribution into the CSF is a practical way to gain some understanding of the potential for CNS tissue distribution. Therefore, CSF provides a valuable surrogate to estimate drug distribution and antiviral effects across the blood-brain barrier and blood-CSF barrier [12–14]. The CSF distribution of many antiretrovirals, including lopinavir, darunavir, efavirenz and raltegravir, has been assessed [15–18].

Dolutegravir (DTG; Tivicay, ViiV Healthcare, Research Triangle Park, North Carolina) is a novel HIV integrase inhibitor (INI) with a pharmacokinetic profile that allows once-daily administration in INI-naive subjects. The efficacy and safety of DTG in large, phase III trials have been reported elsewhere [19, 20]. Dolutegravir is approximately 99% bound to plasma proteins and is primarily metabolized via uridine 5′-diphosphoglucuronosyltransferase 1A1, with cytochrome P450 3A4 as a minor pathway. It is also a substrate of P-glycoprotein and breast cancer resistance protein. These attributes indicate that distribution across the blood-brain barrier and blood-CSF barrier will be limited. However, owing to the potency of DTG, even modest distribution into the CNS may result in concentrations that provide antiviral activity.

Study ING116070 was designed to assess the extent of DTG entry into the CSF compartment, and to evaluate virologic responses in CSF and plasma. Results from the planned week 16 primary analysis are presented.

METHODS

Design and Study Population

ING116070 is an ongoing, 96-week, phase IIIb, single-arm, open-label, multicenter (3 US sites) study in ART-naive (≤10 days of prior therapy), HIV-1–infected adults (≥18 years old). Eligible participants had a screening plasma HIV-1 RNA level ≥5000 copies/mL and a $CD4^+$ cell count ≥200 cells/mm^3 and were negative for the *HLA-B*5701* allele. Exclusions included contraindication to lumbar puncture, moderate or severe cognitive impairment, evidence of primary viral resistance, active US Centers for Disease Control and Prevention category C disease (except Kaposi sarcoma), defined laboratory values, pregnancy, breastfeeding, moderate or severe hepatic impairment, hepatitis B virus infection, anticipated need for hepatitis C virus therapy during the study period, malignancy, or recent treatment with HIV-1 vaccines or immunomodulators. Ethics committee approval was obtained at all participating centers in accordance with the principles of the 2008 Declaration of Helsinki. Each patient provided written informed consent before undergoing study procedures. This study is registered at ClinicalTrials.gov (NCT01499199).

Eligible subjects received (DTG 50 mg) along with the dual nucleoside reverse-transcriptase inhibitor (NRTI) combination tablet abacavir/lamivudine (ABC/3TC [Kivexa/Epzicom, ViiV Healthcare]; 600/300 mg), all taken once daily. The intention-to-treat exposed and safety populations both comprised all randomized subjects who received ≥1 dose of study medication.

Study End Points

The primary study analyses occurred at week 16; additional analyses were preplanned for weeks 2 and 96. The primary end point was the DTG concentration in CSF at week 16. Secondary end points included DTG concentrations in plasma (total and unbound) and CSF (total), the relationship between DTG concentrations in plasma and CSF, the proportion of subjects with plasma HIV-1 RNA <50 or <400 copies/mL, change from baseline in plasma and CSF HIV-1 RNA, the relationship between DTG concentration in CSF and HIV-1 RNA in CSF, and the relationship between plasma and CSF HIV-1 RNA suppression and HIV disease progression and safety parameters (ie, adverse events [AEs] and laboratory abnormalities). Additionally, the incidence of treatment-emergent genotypic and phenotypic resistance to DTG and other on-study ART was assessed for any subject with protocol-defined virologic failure (PDVF).

Procedures and Assessments

Study visits occurred at baseline and weeks 2, 4, 8, 12, and 16; additional visits for this ongoing study were scheduled for weeks 24, 36, and 48, and every 12 weeks thereafter until week 96. Plasma samples were collected at each visit to evaluate HIV-1 RNA levels (all visits) and plasma DTG concentrations (weeks 2 and 16; plasma pharmacokinetic samples were collected 2–6 hours after the dose). The CSF samples were obtained by lumbar puncture at baseline and weeks 2 and 16 for evaluation of HIV-1 RNA levels and at weeks 2 and 16 for evaluation of CSF DTG concentrations (collected 2–6 hours after the dose and within 1 hour of the plasma pharmacokinetic sample). The $CD4^+$ cell counts were determined at each visit (except week 2).

Central laboratory facilities (Quest Diagnostics) provided hematologic, clinical chemistry, and HIV-1 RNA testing. The CSF HIV-1 RNA levels were determined using an HIV-1 RNA SuperLow assay (testing provided by bioMONTR Labs) with a lower limit of detection of 2 copies/mL. First, 2 mL of plasma was lysed and extracted on the EasyMAG platform (bioMérieux). Eluates containing HIV-1 RNA were aliquoted and amplified by 3 enzymes: T7 RNA polymerase, *Avian myeloblastosis* virus reverse transcriptase, and RNase H. Primers and molecular beacons targeting the *pol*/*gag* region of HIV-1 RNA were used for amplification and detection by isothermal reactions at 41°C. Quantitation of HIV-1 RNA was determined by a proprietary reduction algorithm in conjunction with the NucliSENS EasyQ HIV-1 v2.0 Director software (bioMérieux). Plasma HIV-1 RNA levels were determined using the RealTime HIV-1

PCR assay (Abbott Molecular); the plasma lower limit of detection was 40 copies/mL.

Measurements of DTG concentrations were performed using validated analytic methods based on protein precipitation, followed by high-performance liquid chromatography tandem mass spectrometry analysis [21]. The DTG concentrations in plasma were analyzed by GlaxoSmithKline, and the CSF samples were analyzed by QPS (Newark, Delaware). For total plasma concentration, the DTG lower limit of quantification was 20 ng/mL, and the upper limit was 20 000 ng/mL. Unbound plasma DTG concentration and total CSF DTG concentrations both had a lower limit of quantification of 1 ng/mL and an upper limit of 1000 ng/mL.

Safety was assessed throughout the study period, with monitoring and recording of all AEs, serious AEs (SAEs), vital signs, and laboratory parameters (eg, hematologic, fasting lipid profile, and chemistry results). The AEs were assessed and graded according to the Division of AIDS toxicity scales [22]. Liver chemistry threshold stopping criteria were implemented to ensure subject safety and to evaluate causes of liver inflammation.

Protocol-defined virologic failure was defined as 2 consecutive plasma HIV-1 RNA values >200 copies/mL on or after week 16, with cases triggering virologic resistance testing. Resistance testing was performed by Monogram Biosciences.

Statistical Analyses

ING116070 was a single-arm study to assess the distribution of DTG into the CSF compartment. As such, it included no formal hypothesis test. Pearson correlations between DTG concentrations in plasma (total and unbound) and CSF at weeks 2 and 16 were calculated. Efficacy analyses were based on the intention-to-treat exposed population. Subjects' responses (eg, <50 copies/mL) for plasma HIV-1 RNA were calculated and summarized according to a missing, switch, or discontinuation equals failure (MSDF) algorithm, as codified by the US Food and Drug Administration Snapshot algorithm [23], wherein all subjects without plasma HIV-1 RNA data at the visit of interest (eg, owing to missing data or early discontinuation) or who changed their concomitant ART (except for switches to permitted NRTIs before week 2) were treated as nonresponders. Otherwise, virologic success or failure for the visit of interest was determined by the last available HIV-1 RNA assessment while the subject was receiving treatment. Descriptive summaries were provided for the following: absolute values and change from baseline in HIV-1 RNA (plasma and CSF) and $CD4^+$ cell counts; the incidence and severity of all AEs, treatment-related AEs, AEs leading to withdrawal, SAEs, and graded laboratory abnormalities; plasma (total and unbound) and CSF (total) DTG concentrations; and the incidence of PDVF or treatment-emergent genotypic and phenotypic resistance to DTG and other on-study ART. The assessments of DTG concentrations in plasma and CSF, and of CSF HIV-1 RNA responses, were based on all available data.

Table 1. Baseline Characteristics in the Intention-to-Treat Exposed Population (N = 13)

Characteristic	Results
Baseline plasma HIV-1 RNA	
≤100 000 copies/mL, No. (%)	8 (62)
>100 000 copies/mL, No. (%)	5 (38)
Mean (SD), log_{10} copies/mL	4.93 (0.86)
Median (range), log_{10} copies/mL)	4.73 (3.60, 6.57)
Baseline CSF HIV-1 RNA	
Mean (SD), log_{10} copies/mL	3.59 (1.21)
Median (range), log_{10} copies/mL	3.64 (1.46, 5.60)
Baseline $CD4^+$ cell count	
<350 cells/mm^3, No. (%)	6 (46)
≥350 cells/mm^3, No. (%)	7 (54)
Mean (SD), cells/mm^3	409 (188)
Median (range), cells/mm^3	360 (152, 863)
Nonreactive hepatitis B and C test results, No. (%)[a]	13 (100)
CDC category, No. (%)[b]	
A	7 (54)
B	3 (23)
C	3 (23)

Abbreviations: CDC, US Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HIV-1, human immunodeficiency virus type 1; SD, standard deviation.

[a] Nonreactive results showed neither hepatitis B nor hepatitis C.

[b] CDC category A is defined as asymptomatic, lymphadenopathy, or acute HIV infection; category B, symptomatic, not AIDS; and category C, AIDS.

RESULTS

Of 17 subjects screened, 13 subjects enrolled and received study medication. All subjects were white men, 3 (23%) were of Hispanic ethnicity, and their median age was 42 years (range, 28–52 years). Baseline characteristics are summarized in Table 1. At the week 16 analysis, 2 subjects had prematurely withdrawn (1 before week 2 owing to a non–drug-related SAE of pharyngitis and 1 owing to lack of treatment efficacy [ie, plasma HIV-1 RNA never suppressed to <200 copies/mL by week 16]). No subjects had switched background NRTI therapy.

Evaluable, paired CSF and plasma pharmacokinetic samples were available from 12 subjects at week 16; 1 subject at week 2 had pharmacokinetic samples collected outside the required 2–6 hour postdose sampling window, resulting in 11 evaluable subjects at week 2. The DTG concentrations in CSF and plasma are shown in Table 2. The median DTG concentrations in CSF were 18 ng/mL (range, 4–23 ng/mL) at week 2 and 13 ng/mL (4–18 ng/mL) at week 16, both of which exceeded the in vitro 50% inhibitory concentration (IC_{50}) of 0.2 ng/mL. Concentrations of DTG in CSF were low compared with plasma with median CSF-plasma ratios of 0.52% (range, 0.12%–0.66%) at week 2 and 0.41% (range, 0.30%–2.04%) at week 16. The DTG

Table 2. Dolutegravir Concentrations in Plasma and Cerebrospinal Fluid

	Week 2 (n = 12)		Week 16 (n = 12)	
Dolutegravir Concentration	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Plasma total, ng/mL	3420 (831)	3360 (2090–5280)	3030 (1350)	3210 (640–4920)
Plasma unbound, ng/mL	16.8 (4.10)	17.1 (10.3–24.0)	23.0 (8.24)	23.9 (3.81–32.1)
Unbound fraction in plasma, %	0.495 (0.082)	0.488 (0.333–0.655)	0.995 (1.05)	0.701 (0.488–4.30)
CSF total, ng/mL	16.2 (5.84)[a]	18.2 (4.0–23.2)[a]	12.6 (3.64)	13.2 (3.7–18.3)
CSF–total plasma ratio, %	0.467 (0.178)[a]	0.516 (0.115–0.658)[a]	0.546 (0.480)	0.412 (0.299–2.04)

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation.

[a] n = 11 (excluding 1 subject with pharmacokinetic samples collected outside the 2–6-hour postdose window).

concentrations in CSF were similar to unbound plasma concentrations (Table 2). Ratios of DTG CSF total concentration to plasma total concentration were similar to the unbound fractions of DTG in plasma; these seemed to stay constant during the sampling window and were similar between weeks 2 and 16.

At week 16, there was a significant correlation between total DTG concentrations in CSF and plasma, as well as between total DTG concentrations in CSF and unbound DTG concentrations in plasma (Pearson correlation coefficient, 0.65 [$P = .023$] and 0.73 [$P = .007$], respectively).

CSF HIV-1 RNA levels decreased rapidly, with a median change of -2.19 $\log_{10}$ copies/mL by week 2; 7 of 12 (58%) and 11 of 12 (92%) subjects had CSF HIV-1 RNA levels <50 or <400 copies/mL, respectively, at week 2. By week 16, the median change from baseline in CSF HIV-1 RNA was -3.42 $\log_{10}$ copies/mL, which was similar to that observed in plasma (-3.04 $\log_{10}$ copies/mL) at the same time point, although there was no statistically significant correlation between the two. In addition, DTG concentrations in CSF did not correlate with changes from baseline in CSF HIV-1 RNA at week 16.

Results at week 16 showed that 10 (77%) and 12 (92%) of 13 subjects had plasma HIV-1 RNA levels <50 copies/mL or <400 copies/mL, respectively, using the US Food and Drug Administration Snapshot MSDF algorithm, and all 11 subjects (100%) had CSF HIV-1 RNA levels below 50 copies/mL, using all available data. Another subject had a late (day 141) assessment for week 16 CSF HIV-1 RNA, which was <50 copies/mL. Overall, at week 16, all subjects had CSF HIV RNA levels <2 copies/mL, except 1 subject with a value of 5 copies/mL. Eleven subjects had both plasma and CSF HIV-1 RNA data available at week 16. Nine (82%) of them had HIV-1 RNA levels <50 copies/mL in both plasma and CSF.

One subject met the definition of PDVF. This subject entered the study with a plasma HIV-1 RNA level of 6.57 $\log_{10}$ copies/mL, which rapidly declined to 743 copies/mL by week 2, but never decreased to <200 copies/mL through week 16 (viral load, 236 copies/mL at week 16). No INI or major NRTI, nonnucleoside reverse-transcriptase inhibitor or protease inhibitor mutations were detected at the time of PDVF. Additionally, phenotypic analyses showed susceptibility to all tested NRTIs, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitor and no fold change in susceptibility to either DTG or raltegravir (the first INI approved for HIV treatment); the fold change in response to both DTG and raltegravir was <1 at baseline.

At week 16, the median increase in $CD4^+$ cell count was 226 cells/mm^3 (interquartile range, 136–337 cells/mm^3). Through the week 16 analysis, no subject reported a new or recurrent Centers for Disease Control and Prevention category B or C condition.

In general, DTG was well tolerated. Most AEs were grade 1 or 2 in intensity. Headache was the only AE reported by >2 subjects (7 of 13 [54%]), with 2 headaches reported as being related to the study drug. Headache is a known AE associated with lumbar punctures, with the majority of such headaches reported following the lumbar puncture.

Table 3 summarizes drug-related AEs reported in >1 subject; all were considered grade 1 in intensity with the exception of a single grade 2 worsening of depression that the investigator thought might be related to the investigational product. The subject had an extensive personal and family history of depression and was maintained in the study. No deaths occurred. One subject prematurely withdrew from the study before week 2; this was because of a grade 4, non–drug-related SAE of pharyngitis and a grade 2 AE of syphilis. The only other SAE reported during the study, in a different subject, was a non–drug-related SAE of cholecystitis. No clinically significant trends in postdose laboratory abnormalities were observed.

Table 3. Most Common Drug-Related Adverse Events[a]

Type of Event	Adverse Events, No. (%)
Any event	8 (62)
Fatigue	2 (15)
Headache	2 (15)
Nausea	2 (15)

[a] Adverse events reported for >1 subject in the safety population (N = 13).

DISCUSSION

Many consider that distribution of antiretroviral drugs into "sanctuary" sites in therapeutic concentrations favors suppression of HIV replication there. One such site, the CNS, may be especially important because drug-resistant viruses that are not present in blood have been found there (ie, the viruses can have a different fold change in IC_{50} compared with those found in the plasma [24]). In this study, DTG was measurable in all CSF samples collected 2–6 hours after dosing and exceeded the IC_{50} against wild-type virus (0.51 nmol/L = 0.2 ng/mL) [25]. Median DTG CSF concentrations were 90-fold and 66-fold above the IC_{50} at weeks 2 and 16, respectively, suggesting that DTG achieves therapeutic concentrations in the CSF. The planned narrow sampling window does not allow us to demonstrate persistence of drug in the CSF over the entire dosing interval, especially at the end of the interval when CSF concentrations might be lowest. However, DTG likely has slow clearance of drug and flat concentration-time profiles in the CSF, similar to what has been observed with other antiretrovirals [26–28]. In addition, ABC and 3TC both distribute well into the CNS [29, 30], indicating that a combination regimen of ABC/3TC with DTG might be effective in rapidly clearing HIV from the CSF. In parallel with these pharmacokinetic data, HIV-1 RNA rapidly declined in both plasma and CSF, and was undetectable (<50 copies/mL) at week 16 in the CSF in all evaluable subjects and in plasma in 10 of 12 evaluable subjects (83%), demonstrating the potent antiviral activity of this regimen in multiple compartments.

Dolutegravir is highly protein bound in plasma, and only total DTG was measured in the CSF owing to assay limits. However, the impact of protein binding for unbound DTG concentration in the CSF is probably small because the concentration of binding proteins (eg, albumin and α-1 acid glycoprotein) in CSF is much lower than in plasma (100- to 1000-fold lower) [31, 32]. This is supported by findings of other studies with other highly bound antiretrovirals demonstrating that nearly all the drug in the CSF was unbound [33]. The similarity of the concentration of DTG in CSF and the unbound concentration in plasma implies that the distribution of DTG into CSF is probably governed mainly by passive diffusion with a low possibility of active transporter involvement.

The more rapid decline in plasma HIV-1 RNA for an INI-based versus an efavirenz-based regimen [34] makes the INI class attractive for patients with high viral loads or with significant issues, such as neurocognitive impairment. The distribution of raltegravir into CSF was evaluated in HIV-infected patients [28]. Although raltegravir has a higher CSF-to-plasma ratio of approximately 6% versus 0.5% for DTG, the greater potency of DTG results in a much higher CSF inhibitory quotient (ratio of drug concentration to IC_{50}). The raltegravir concentrations in CSF exceeded the IC_{50} for wild-type HIV (3.2 ng/mL) in all specimens by a median of 4.5-fold, whereas in this study DTG exceeded the IC_{50} by 66–90-fold. Although the clinical relevance of these values is unknown, they suggest the potential for a greater effect, especially if INI resistance is present. Furthermore, DTG has demonstrated wild-type activity against most INI single-mutant HIV-1 and thus provides a greater barrier to the development of resistance in the CNS [25].

A previous phase IIa study (ING111521) has demonstrated good correlation between DTG plasma concentration and reduction in HIV-1 RNA in plasma after 10-day monotherapy [35]. In this current study, no correlation was identified between DTG concentration in CSF and HIV-1 RNA reduction in CSF, primarily because CSF concentrations were well in excess of the IC_{50} and most subjects in the study had good responses to therapy in both plasma and CSF. The uniformity of response did not allow for the description of a concentration-effect relationship.

In general, DTG was well tolerated in the ART-naive, HIV-1–infected subjects in this study. The most common AE was headache, which was often temporally related to lumbar puncture and not deemed related to study drug by the investigator in most cases. Overall, the safety profile of DTG plus ABC/3TC in this limited number of patients is consistent with findings of larger phase III studies administering the same regimen [19, 20].

In 1 subject with PDVF, integrase genotypic or phenotypic results did not show development of resistance to INIs or NRTIs. Other studies of DTG (50 mg once daily) in ART-naive patients have demonstrated a lack of NRTI or INI resistance in participants with PDVF for up to 96 weeks of study, despite the development of resistance in the comparator treatment arm [19, 20]. Given the pharmacokinetic and efficacy data in this study, the combination of DTG, ABC, and 3TC may be an effective regimen in subjects with neurocognitive complications of HIV disease.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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