Clinical Infectious Diseases Advance Access published June 18, 2014

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

Scott L. Letendre[1], Anthony M. Mills[2], Karen T. Tashima[3], Deborah A. Thomas[4], Sherene S. Min[4], Shuguang Chen[4], Ivy H. Song[4], Stephen C. Piscitelli[4], on behalf of the extended ING116070 study team

[1]University of California, San Diego, San Diego, California, USA

[2]Anthony Mills, MD, Inc, Los Angeles, California, USA

[3]The Miriam Hospital, Providence, Rhode Island, USA

[4]GlaxoSmithKline, Research Triangle Park, North Carolina, USA

Corresponding author: Stephen Piscitelli, PharmD, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709; (919) 483-2523; stephen.c.piscitelli@gsk.com

Alternate corresponding author: Deborah Thomas, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709; (919) 483-9959; debbie.a.thomas@gsk.com

Summary of main point (40-word summary of article's main point): Median dolutegravir concentrations in cerebrospinal fluid were similar to unbound dolutegravir concentrations in plasma and in all subjects exceeded the in vitro 50% inhibitory concentration for wild-type viruses (0.2 ng/mL) by ≥ 66-fold, suggesting that dolutegravir achieves therapeutic concentrations in cerebrospinal fluid.

ABSTRACT

Background: Dolutegravir (DTG), a once-daily, 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 + abacavir/lamivudine 600/300 mg once daily. CSF and plasma (total and unbound) DTG concentrations were measured at Weeks 2 and 16. HIV-1 RNA was 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 males enrolled; 2 withdrew prematurely, 1 for a non–drug-related serious adverse event (pharyngitis) and 1 for lack of efficacy. 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 $\log_{10}$ c/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA below 50 c/mL and 10/11 subjects (91%) had CSF HIV-1 RNA below 2 c/mL at Week 16.

Conclusions: 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 DTG achieves therapeutic concentrations in the CNS. HIV-1 RNA reductions were similar in CSF and plasma.

INTRODUCTION

Despite the advent of modern, potent antiretroviral therapy (ART), 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, as 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].

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]. 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. Efficacy and safety of DTG in large, phase III trials have been previously reported [19, 20]. DTG is approximately 99% bound to plasma proteins and is primarily metabolized via UDP-glucuronosyltransferase 1A1, with cytochrome P450 3A4 as a minor pathway. DTG 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, due 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 (no more than 10 days of prior therapy), HIV-1–infected adults (at least 18 years old). Eligible participants had a screening plasma HIV-1 RNA of at least 5000 copies/mL (c/mL), CD4+ cell count of at least 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 (CDC) category C disease (except Kaposi's 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 prior to undergoing study procedures. This study is registered on ClinicalTrials.gov: NCT01499199.

Eligible subjects received DTG 50 mg plus the dual nucleoside reverse transcriptase inhibitor (NRTI) combination tablet abacavir 600 mg/lamivudine 300 mg (ABC/3TC; Kivexa®/Epzicom®, ViiV Healthcare, Research Triangle Park, North Carolina), all taken once daily. The intention-to-

treat exposed (ITT-E) and safety populations both comprised all randomized subjects who received at least one dose of study medication.

Study Endpoints

The primary study analyses occurred at Week 16; additional analyses were pre-planned for Weeks 2 and 96. The primary endpoint was the DTG concentration in CSF at Week 16. Secondary endpoints 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 below 50 c/mL and below 400 c/mL; change from Baseline in plasma and CSF HIV-1 RNA; the relationship between DTG concentration in CSF and HIV-1 RNA in CSF; the relationship between plasma and CSF HIV-1 RNA suppression, and HIV disease progression and safety parameters (i.e., adverse events 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 occur at Weeks 24, 36 and 48, and every 12 weeks thereafter to Week 96. Plasma was collected at each visit to evaluate HIV-1 RNA (all visits) and plasma DTG concentration (Weeks 2 and 16; plasma PK samples were collected 2-6 hours post-dose). 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 post-dose and within 1 hour of the plasma PK sample). CD4+ cell counts were determined at each visit (except Week 2).

Central laboratory facilities (Quest Diagnostics, Valencia, California) provided hematology, clinical chemistry and HIV-1 RNA testing. CSF HIV-1 RNA was determined using an HIV-1 RNA SuperLow assay (testing provided by bioMONTR® Labs, Research Triangle Park, North Carolina) with a lower limit of detection of 2 c/mL. Two mL plasma was lysed and extracted on the EasyMAG platform (bioMérieux SA, Durham, North Carolina). 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 utilized 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 SA). Plasma HIV-1 RNA levels were determined using the RealTime HIV-1 PCR assay (Abbott Molecular Inc, Des Plaines, Illinois); the plasma lower limit of detection was 40 c/mL.

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

Safety was assessed throughout the study period, and included monitoring and recording of all AEs, serious AEs (SAEs), vital signs and laboratory parameters (e.g., hematology, fasting lipid profile and chemistries). AEs were assessed and graded according to the Division of AIDS toxicity scales [22]. Liver chemistry threshold stopping criteria were implemented to assure subject safety and to evaluate liver inflammation etiology.

PDVF was defined as 2 consecutive plasma HIV-1 RNA values above 200 c/mL on or after Week 16, with cases of PDVF triggering virologic resistance testing. Resistance testing was performed by Monogram Biosciences, Inc. (San Francisco, California).

Statistical Analyses

ING116070 was a single-arm study to assess the distribution of DTG into the CSF compartment. As such, there was 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 ITT-E population. Subjects' responses (e.g., <50 c/mL) for plasma HIV-1 RNA were calculated and summarized according to a missing, switch or discontinuation = failure (MSDF) algorithm, as codified by the US Food and Drug Administration's (FDA's) Snapshot algorithm [23], wherein all subjects without plasma HIV-1 RNA data at the visit of interest (e.g., due to missing data or early discontinuation) or who substituted their concomitant ART (except switches to permitted NRTIs prior to Week 2) were treated as non-responders. Otherwise, virologic success or failure was determined by the last available HIV-1 RNA assessment while the subject was on treatment for the visit of interest. Descriptive summaries were provided for the following: absolute values and change from Baseline in HIV-1 RNA (plasma and CSF), 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 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.

RESULTS

Of 17 subjects screened, 13 subjects enrolled and received study medication. All subjects were white males, 23% (n=3) were of Hispanic ethnicity, and the 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 prior to Week 2 for a non–drug-related SAE of pharyngitis, 1 for lack of efficacy [i.e., never suppressed plasma HIV-1 RNA to <200 c/mL by Week 16]). No subjects had switched background NRTI therapy.

Evaluable, paired CSF and plasma PK samples were available from 12 subjects at Week 16; 1 subject at Week 2 had PK samples collected outside the required 2 to 6 hour post-dose sampling window, resulting in 11 evaluable subjects at week 2. DTG concentrations in CSF and plasma are shown in Table 2. The median DTG concentration in CSF was 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 to 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. DTG 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 fraction of DTG in plasma; these appeared to stay constant over 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 [*P* value] = 0.65 [0.023] and 0.73 [0.007], respectively).

CSF HIV-1 RNA levels decreased rapidly, with a median decrease of -2.19 $\log_{10}$ c/mL by Week 2; 7 of 12 (58%) and 11 of 12 (92%) subjects had CSF HIV-1 RNA below either 50 or 400

c/mL, respectively, at Week 2. By Week 16, the median change from Baseline in CSF HIV-1 RNA was -3.42 $\log_{10}$ c/mL, which was similar to that observed in plasma (-3.04 $\log_{10}$ c/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.

At Week 16, 10 of 13 (77%) and 12 of 13 (92%) subjects had plasma HIV-1 RNA below either 50 c/mL or 400 c/mL, respectively, using the FDA Snapshot MSDF algorithm, and 11 of 11 (100%) subjects had CSF HIV-1 RNA below both 50 c/mL and 400 c/mL using all available data. One additional subject had a late (Day 141) assessment for Week 16 CSF HIV-1 RNA, which was below 50 c/mL. Overall, at week 16, all subjects had HIV RNA levels in the CSF below 2 c/mL except one subject with a value of 5 c/mL. There were 11 subjects with both plasma and CSF HIV-1 RNA data available at Week 16. Nine (82%) of these subjects had HIV-1 RNA below 50 c/mL in both plasma and CSF.

One subject met the definition of PDVF. This subject entered the study with plasma HIV-1 RNA at 6.57 $\log_{10}$ c/mL, which rapidly declined to 743 c/mL by Week 2, but never decreased below 200 c/mL through Week 16 (viral load was 236 c/mL at Week 16). No INI or major NRTI, non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) mutations were detected at the time of PDVF. Additionally, phenotypic analyses showed susceptibility to all tested NRTIs, NNRTIs and PIs, and no fold-change in susceptibility to either DTG or raltegravir (RAL, the first INI approved for HIV treatment); fold-change to both DTG and RAL was below 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 CDC Class B or Class C condition.

DTG was generally well tolerated. Most AEs were Grade 1 or Grade 2 in intensity. Headache was the only AE reported by more than 2 subjects (7/13 [54%]), with 2 of the headaches reported as being related to study drug. Of note, headache is a known AE associated with lumbar punctures, with the majority of headaches reported temporally with the lumbar puncture.

Table 3 summarizes drug-related AEs reported in more than 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 on study. No deaths occurred. One subject prematurely withdrew from the study prior to Week 2; this was due to a Grade 4, non–drug-related SAE of pharyngitis and 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. Additionally, no clinically significant trends in post-dose laboratory abnormalities were observed.

DISCUSSION

Many consider that distribution of antiretroviral drugs into “sanctuary” sites in therapeutic concentrations favors suppression of HIV replication there. One “sanctuary” site, the CNS, may be especially important since drug-resistant viruses that are not present in blood have been found there (i.e., 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 to 6 hours after dosing and exceeded the IC_{50} against wild-type virus (0.51 nM = 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 c/mL) at Week 16 in the CSF in all evaluable subjects and in plasma in 10 of 12 (83%) evaluable subjects, demonstrating the potent antiviral activity of this regimen in multiple compartments.

DTG is highly protein bound in plasma, and only total DTG was measured in the CSF due to assay limits. However, the impact of protein binding for unbound DTG concentration in the CSF is likely small as the concentration of binding proteins (e.g., albumin and alpha-1 acid glycoprotein) in CSF is much lower than in plasma (100- to 1000-fold lower) [31, 32]. This is supported by previous studies with other highly bound antiretrovirals that demonstrated nearly all of 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 likely mainly governed 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 this class attractive for patients with high viral loads or those with significant issues such as neurocognitive impairment. The distribution of RAL into CSF was evaluated in HIV-infected patients [28]. While RAL demonstrates 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 over IC_{50}). RAL 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- to 90-fold. While 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 [35].

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 [36]. In this current study, no correlation was identified between DTG concentration in CSF and HIV-1 RNA reduction in CSF, primarily since CSF concentrations were well in excess of the IC_{50} and most subjects in the study had good responses to therapy both in the plasma and CSF. The uniformity of response did not allow for the description of a concentration-effect relationship.

DTG was generally 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 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 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/3TC may be an effective regimen in subjects with neurocognitive complications of HIV disease.

Funding

This work was supported by ViiV Healthcare.

Disclaimer

The contents are the responsibility of the author(s) and do not necessarily reflect the views of the funders.

Potential Conflicts of Interest

D. A. T., S. S. M., S. C., I. H. S., and S. C. P. are employees of GlaxoSmithKline and own stock in the company. S. L. L. and K. T. T. received grant support from ViiV Healthcare that supported their work on this study. S. L. L. has grant support pending through institutions including the National Institutes of Health, AbbVie, Merck, and Gilead, has acted as a consultant for Merck, and developed educational presentations for which he has received payment for ViiV Healthcare and AbbVie. K. T. T. has received grant support and has grant support pending through institutions including Merck, Bristol-Myers Squibb, and Gilead Sciences. A. M. M. has received grant support and honoraria from ViiV Healthcare, has grant support pending through institutions including Gilead Sciences, Bristol-Myers Squibb, and AbbVie, and has received fees for lectures including service on speakers bureaus from Gilead.

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.

Acknowledgments

The authors wish to thank the ING116070 study participants and their families and caregivers for participation in the study. The authors wish to acknowledge the staff at each ING116070 investigator site.

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. The authors also wish to acknowledge the following individuals for editorial assistance during the development of this manuscript: Katrina Oie Rodenberger, Gina Uhlenbrauck.

REFERENCES

1. Heaton RK, Clifford DB, Franklin DR Jr, et al, for the CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology **2010;** 75:2087–96.

2. Heaton RK, Franklin DR, Ellis RJ, et al, for the CHARTER and HNRC Groups. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol **2011;** 17:3–16.

3. Spudich S, González-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. Cold Spring Harb Perspect Med **2012;** 2:a007120.

4. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis **2010;** 50:773–8.

5. Edén A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. J Infect Dis **2010;** 202:1819–25.

6. Letendre S, Capparelli E, Best B, et al. Better antiretroviral penetration into the central nervous system is associated with lower CSF viral load. In: 13th Conference on Retroviruses and Opportunistic Infections, Denver, Colorado, 5–8 February 2006.

7. Letendre S, Marquie-Beck J, Capparelli E, et al, for the CHARTER Group. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol **2008;** 65:65–70.

8. Cusini A, Vernazza PL, Yerly S, et al; the Swiss HIV Cohort Study. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with

better HIV-1 viral suppression in cerebrospinal fluid. J Acquir Immune Defic Syndr **2013;** 62:28–35.

9. Price RW, Spudich S. Antiretroviral therapy and central nervous system HIV type 1 infection. J Infect Dis **2008;** 197(suppl 3):S294–306.

10. Gisslen M, Hagberg L, Rosengren L, et al. Defining and evaluating HIV-related neurodegenerative disease and its treatment targets: a combinatorial approach to use of cerebrospinal fluid molecular biomarkers. J Neuroimmune Pharmacol **2007;** 2:112–9.

11. Sinclair E, Ronquillo R, Lollo N, et al. Antiretroviral treatment effect on immune activation reduces cerebrospinal fluid HIV-1 infection. J Acquir Immune Defic Syndr **2008;** 47:544–52.

12. Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological disorders: I. Establishment of reference values. Scand J Clin Lab Invest **1977;** 37:385–90.

13. Power C, Kong PA, Crawford TO, et al. Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood-brain barrier. Ann Neurol **1993;** 34:339–50.

14. Reichel A. The role of blood-brain barrier studies in the pharmaceutical industry. Curr Drug Metab **2006;** 7:183–203.

15. Isaac A, Taylor S, Cane P, et al. Lopinavir/ritonavir combined with twice-daily 400 mg indinavir: pharmacokinetics and pharmacodynamics in blood, CSF and semen. J Antimicrob Chemother **2004;** 54:498–502.

16. Yilmaz A, Izadkhashti A, Price RW, et al. Darunavir concentrations in cerebrospinal fluid and blood in HIV-1–infected individuals. AIDS Res Hum Retroviruses **2009;** 25:457–61.

17. Best BM, Koopmans PP, Letendre SL, et al, for the CHARTER Group. Efavirenz concentrations in CSF exceed IC_{50} for wild-type HIV. J Antimicrob Chemother **2011;** 66:354–57.

18. Yilmaz A, Gisslén M, Sudich S, et al. Raltegravir cerebrospinal fluid concentrations in HIV-1 infection. PLoS One **2009;** 4:e6877.

19. Raffi F, Jaeger H, Quiros-Roldan E, et al; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis **2013;** 13:927-35.

20. Walmsley SL, Antela AA, Clumeck N, et al, for the SINGLE Investigators. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. N Engl J Med **2013;** 369:1807–18.

21. Bennetto-Hood C, Tabolt G, Savina P, Acosta EA. A sensitive HPLC-MS/MS method for the determination of dolutegravir in human plasma. J Chromatog B Analyt Technol Biomed Life Sci **2014;** 945-946:225-32.

22. Division of AIDS, National Institute of Allergy and Infectious Diseases. Division of AIDS table for grading the severity of adult and pediatric adverse events: version 1.0, December 2004; clarification August 2009. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf. Accessed 11 April 2014.

23. Smith F, Hammerstrom T, Soon G, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. Drug Inf J **2011;** 45:291–300.

24. Antinori A, Perno CF, Giancola ML, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: different patterns of phenotypic resistance in CSF and plasma. Clin Infect Dis **2005;** 41:1787–93.

25. Kobayashi M, Yoshinaga T, Seki T, et al. In vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother **2011;** 55:813–21.

26. Letendre SL, Capparelli EV, Ellis RJ, McCutchan JA, and the HIV Neurobehavioral Research Center Group. Indinavir population pharmacokinetics in plasma and cerebrospinal fluid. Antimicrob Agents Chemother **2000;** 44:2173–5.

27. Croteau D, Letendre S, Best BM, et al, for the CHARTER Group. Therapeutic amprenavir concentrations in cerebrospinal fluid. Antimicrob Agents Chemother **2012;** 56:1985–9.

28. Croteau D, Letendre S, Best BM, et al, for the CHARTER Group. Total raltegravir concentrations in cerebrospinal fluid exceed the 50-percent inhibitory concentration for wild-type HIV-1. Antimicrob Agents Chemother **2010;** 54:5156–60.

29. Capparelli EV, Letendre SL, Ellis RJ, Patel P, Holland D, McCutchan JA. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. Antimicrob Agents Chemother **2005;** 49:2504–6.

30. Foudraine NA, Hoetelmans RMW, Lange JMA, et al. Cerebrospinal-fluid HIV-1 RNA and drug concentrations after treatment with lamivudine plus zidovudine or stavudine. Lancet **1998;** 351:1547–51.

31. Adam P, Sobek O, Táborský L, Hildebrand T, Tutterová O, Zácek P. CSF and serum orosomucoid (α-1-acid glycoprotein) in patients with multiple sclerosis: a comparison among particular subgroups of MS patients. Clin Chim Acta **2003;** 334:107–10.

32. Haas DW, Johnson B, Nicotera J, et al. Effects of ritonavir on indinavir pharmacokinetics in cerebrospinal fluid and plasma. Antimicrob Agents Chemother **2003;** 47:2131–7.

33. Croteau D, Rossi SS, Best BM, et al; CHARTER Group. Darunavir is predominantly unbound to protein in cerebrospinal fluid and concentrations exceed the wild-type HIV-1 median 90% inhibitory concentration. J Antimicrob Chemother **2013;** 68:684–9.

34. van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis **2012;** 12:111–8.

35. Kobayashi M, Yoshinaga T, Seki T, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother **2011;** 55:813–21.

36. Min S, Sloan L, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS **2011;** 25:1737–45.

TABLES

Table 1. Summary of Baseline Characteristics (ITT-E Population)

Baseline Characteristic	N=13
Baseline plasma HIV-1 RNA	
≤100,000 c/mL, n (%)	8 (62)
>100,000 c/mL, n (%)	5 (38)
Mean, $\log_{10}$ c/mL (SD)	4.93 (0.86)
Median, $\log_{10}$ c/mL (range)	4.73 (3.60, 6.57)
Baseline CSF HIV-1 RNA	
Mean, $\log_{10}$ c/mL (SD)	3.59 (1.21)
Median, $\log_{10}$ c/mL (range)	3.64 (1.46, 5.60)
Baseline CD4+ cell count	
<350 cells/mm^3, n (%)	6 (46)
≥350 cells/mm^3, n (%)	7 (54)
Mean, cells/mm^3 (SD)	409 (188)
Median, cells/mm^3 (range)	360 (152, 863)
Hepatitis B and C test results, n (%)	
Non-reactive (neither B nor C)	13 (100)
CDC category, n (%)	
A: Asymptomatic or lymphadenopathy or acute HIV	7 (54)
B: Symptomatic, not AIDS	3 (23)
C: AIDS	3 (23)

CDC, US Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; ITT-E, intention-to-treat exposed; SD, standard deviation.

Table 2. Summary of Dolutegravir Concentrations in Plasma and CSF

	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)

CSF, cerebrospinal fluid.

[a] n=11; excludes 1 subject with pharmacokinetic samples collected outside the 2 to 6 hour post-dose window.

Table 3. Summary of the Most Common Drug-Related Adverse Events (Reported for >1 Subject in the Safety Population)

Preferred term	N=13
Any event, n (%)	**8 (62)**
Fatigue	2 (15)
Headache	2 (15)
Nausea	2 (15)