Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial

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Summary

Background Islatravir (also known as ISL and MK-8591) is a unique nucleoside reverse transcriptase translocation inhibitor in clinical development for treatment of people with HIV-1 infection. In preclinical studies, intracellular islatravir-triphosphate exhibits a long half-life and prolonged virological effects. In this study, we aimed to assess islatravir safety, pharmacokinetics, and antiretroviral activity in treatment-naive adults with HIV-1 infection.

Methods This open-label, consecutive-panel, phase 1b trial was done at Charité Research Organisation (Berlin, Germany) and included men and women (aged 18–60 years, inclusive) with HIV-1 infection who were ART naive. Participants were required to have plasma HIV-1 RNA counts of at least 10 000 copies per mL within 30 days before the trial treatment phase, without evidence of resistance to nucleoside reverse transcriptase inhibitors. Participants were enrolled in one of five consecutive dosing panels, receiving a single oral dose of islatravir (0·5–30 mg). The primary outcomes were safety and tolerability of islatravir and change from baseline in HIV-1 plasma RNA; secondary outcomes were islatravir plasma and islatravir-triphosphate intracellular pharmacokinetics. We obtained descriptive safety and pharmacokinetics statistics, and estimated efficacy results from a longitudinal data analysis model. This study is registered with ClinicalTrials.gov, NCT02217904, and EudraCT, 2014-002192-28.

Findings Between Sept 17, 2015, and May 11, 2017, we enrolled 30 participants (six per panel). Islatravir was generally well tolerated. 27 (90%) participants had 60 adverse events after receipt of drug, of which 21 (35%) were deemed to be drug related. The most common (n>1) drug-related adverse events were headache (in nine [30%] participants) and diarrhoea (in two [7%]). No serious adverse events were reported, and no participants discontinued due to an adverse event. Plasma islatravir pharmacokinetics and intracellular islatravir-triphosphate pharmacokinetics were approximately dose proportional. The islatravir-triphosphate intracellular half-life was 78·5–128·0 h. Least-squares mean HIV-1 RNA at 7 days after dose decreased from 1·67 $\log_{10}$ copies per mL (95% CI 1·42–1·92) at 10 mg dose to 1·20 $\log_{10}$ copies per mL (0·95–1·46) at 0·5 mg dose. No genetic changes consistent with development of viral resistance were detected.

Interpretation Single doses of islatravir as low as 0·5 mg significantly suppressed HIV-1 RNA by more than 1·0 log at day 7 in treatment-naive adults with HIV-1 infection and were generally well tolerated, supporting the further development of islatravir as a flexible-dose treatment for individuals with HIV-1 infection.

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Introduction

Nearly 38 million people were living with HIV globally in 2018, including 1·7 million newly infected adults and children.[1] Improvements in the treatment of HIV infection have led to prolongation in life expectancy of people living with HIV who have access to treatment,[2] but effective treatment requires lifelong adherence to antiretroviral therapy (ART) because treatment failure and the selection of ART-resistant HIV are both associated with suboptimal adherence.[3] Current HIV treatments are single-tablet regimens that are taken orally once daily, but challenges remain in reaching UNAIDS goals, especially with respect to treatment adherence and viral suppression in some parts of the world.[1] HIV treatment regimens that minimise pill burden, reduce dosing frequency, and improve convenience might improve adherence[4–6] and, consequently, long-term outcomes.

Recent and potential advances in HIV therapy include simplification of oral once-daily regimens from three

Research in context

Evidence before this study

We searched the US National Library of Medicine PubMed search engine without language restrictions for research articles published between database inception and Aug 1, 2019, with the terms "MK-8591" and "EFdA". We identified further studies from the reference lists of the articles returned using these search terms and our knowledge of the literature. Previous publications have focused on in-vitro and preclinical studies of islatravir, which have shown that islatravir is a nucleoside reverse transcriptase translocation inhibitor with potent activity in vitro against HIV-1 replication. In preclinical assessment, islatravir suppressed HIV-1 viraemia in mice and rhesus macaques, and demonstrated pharmacokinetics amenable to extended-duration dosing.

Added value of this study

We report safety, pharmacokinetic, and pharmacodynamic data for islatravir following single-dose administration to treatment-naive adults with HIV-1 infection, which show that a single oral dose of islatravir as low as 0·5 mg can significantly suppress plasma HIV-1 RNA for at least 7 days, demonstrating clinical antiretroviral activity.

Implications of all the available evidence

Collective data support the further development of islatravir as a novel treatment for HIV-1 infection. The high single-dose potency, unique mechanism of action, and long half-life support islatravir as a component of regimens featuring daily oral dosing with substantial forgiveness to more extended durations, which would be an important milestone in the evolving treatment of people living with HIV.

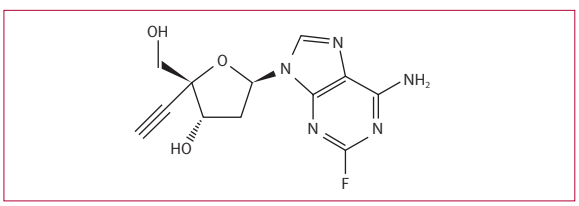

Figure 1: **Islatravir structure**

to two drugs, injectable formulations that facilitate infrequent dosing, and new classes of medication with differentiated mechanisms of action. Two-drug regimens, such as dolutegravir plus rilpivirine and dolutegravir plus lamivudine, have demonstrated non-inferiority to standard three-drug regimens in specific populations,[7,8] and intramuscular cabotegravir plus rilpivirine is being assessed as a potential regimen that is administered every 2 months.[9] Several new classes of molecules, including a subcutaneously injected HIV capsid inhibitor[10] and parenterally administered broadly neutralising antibodies,[11] might also have the potential to be administered less frequently than current regimens. Islatravir (also known as ISL, MK-8591, and 4′-ethynyl-2-fluoro-2′-deoxyadenosine; previously known as EFdA) has characteristics that potentially allow it to manifest all of these potential advances.

Islatravir is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI), with structural and mechanistic features that distinguish it from currently marketed antiretroviral drugs. Islatravir has three chemical structure components that contribute to its unique profile: a 3′-OH group, also found in naturally occurring nucleotides (and not in nucleoside reverse transcriptase inhibitors [NRTIs]), which is associated with the very high binding affinity for the reverse transcriptase; a 4′-ethynyl group, responsible for the ability of islatravir to block primer translocation and cause immediate chain termination; and a 2-fluoro group, which inhibits islatravir metabolism and contributes to its long half-life (figure 1).[12,13] If translocation does occur, islatravir also acts as a delayed chain terminator.[12–14] The active form of islatravir, islatravir-triphosphate, is efficiently incorporated onto the end of the viral DNA chain but leads to mismatched primers that are difficult to extend.[12] The multiple mechanisms of action, coupled with the high binding affinity to reverse transcriptase, translate to robust antiviral efficacy. In vitro, islatravir inhibits the replication of multiple strains of HIV-1[13,15,16] and has a potency up to several orders of magnitude higher than that of NRTIs.[13]

Islatravir is at least ten times more potent towards wild-type HIV-1 in human peripheral blood mononuclear cells (PBMCs) than other marketed antiretroviral drugs. It is also more potent against resistant variants than tenofovir alafenamide and more potent against common NRTI-resistant HIV-1 isolates than any approved NRTI is against wild-type HIV-1.[17,18] Emergence of resistance to islatravir in selection experiments in vitro is through Met184Ile and Met184Val substitutions in reverse transcriptase, which confer 3·9 times and five times reduced susceptibility to islatravir in clinical isolates containing these mutations, respectively, compared with wild-type virus.[18] Islatravir exhibits high potency across a broad panel of NRTI resistant HIV-1 clinical isolates.[17] As monotherapy, islatravir has demonstrated the ability to suppress viraemia in macaques infected with simian immunodeficiency virus (SIV) for up to 6 months without recrudescence with resistant virus while on treatment

and emergence of Met184 mutations only upon cessation of drug treatment.[19] Because of the high potency of islatravir, systemic concentrations of islatravir achieved at projected clinical doses in people are expected to suppress viruses that contain common NRTI resistance mutations fully, including those with Met184Ile/Val.

Islatravir has shown robust antiviral efficacy in preclinical animal models of HIV-1 infection, including humanised mice infected with HIV-1[16] and rhesus macaques infected with SIV.[16,20] In rhesus macaques, islatravir administered orally was rapidly absorbed, with peak plasma concentration occurring approximately 90 min after dose.[16] The potential for extended-duration dosing of islatravir for treatment was shown in SIV-infected macaques, in which once-weekly oral dosing led to rapid and robust declines in SIV RNA and maintained viral suppression for at least 7 days.[20] Weekly dosing with oral islatravir protected male macaques against intrarectal SIV challenge.[21]

The preclinical evaluation of islatravir has shown high antiviral potency and pharmacokinetics supportive of daily and extended-duration low-dose administration in humans. Pharmacokinetic data from clinical trials in healthy participants further support the potential for extended-duration dosing.[20] We therefore aimed to investigate the safety, tolerability, pharmacokinetics, and antiretroviral activity of islatravir in treatment-naive adults with HIV-1.

Methods

Study design and participants

This single-dose, open-label, consecutive-panel, phase 1b trial in treatment-naive adults with HIV-1 infection (protocol MK-8591-003), was done at Charité Research Organisation (Berlin, Germany).

Men and women (aged 18–60 years, inclusive) infected with HIV-1 and who were ART naive were eligible for enrolment in the trial. Participants were required to have plasma HIV-1 RNA of at least 10 000 copies per mL within 30 days before the trial treatment phase, without evidence of resistance to NRTIs. Details of additional key inclusion and exclusion criteria are given in the appendix (p 1). Participants had to be willing to receive no other ART during the treatment phase of the trial. Ethik-Kommission des Landes Berlin, Berlin, Germany, approved the trial, which was done in accordance with the Good Clinical Practice guidelines. All participants provided written informed consent (in German).

Procedures

Investigators assigned participants to one of five consecutive panels, in the order participants became available and fulfilled the enrolment criteria. After enrolment, participants received a single dose of islatravir (10 mg in panel A, 2 mg in panel B, 30 mg in panel C, 1 mg in panel D, and 0·5 mg in panel E). Once a panel was filled (ie, six participants had been dosed), new eligible participants were enrolled in the next panel and dosed accordingly. We initially planned two additional panels, but these were not done because the study objectives were satisfied after completion of the first five panels. No masking was required because the trial was open label.

Preclinical studies in rhesus macaques have shown that antiviral efficacy of islatravir is related to the trough concentration of islatravir-triphosphate in PBMCs.[20,21] As such, we assessed a range of doses in the clinical trial to cover projected efficacious intracellular islatravir-triphosphate concentration at 168 h after dose (C_{168}; trough at 7 days after dose). We selected doses on the basis of pharmacokinetic data obtained from trials in healthy participants and included a 30 mg dose to explore the upper end of the islatravir dose–response curve.

We administered a single oral dose (0·5 mg, 1 mg, 2 mg, 10 mg, or 30 mg) of islatravir to participants in the fasted state (participants fasted ≥8 h before dose administration and 4 h after). Blood samples were collected for plasma islatravir analysis (before dose and at 0·25 h, 0·5 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 96 h after dose), islatravir-triphosphate PBMC analysis (4 h, 12 h, 24 h, 96 h, 120 h, 144 h, 168 h, 240 h, and 336 h after dose, and at the post-trial visit), and HIV-1 RNA and viral resistance analysis (before dose, at selected timepoints after dose, and at the post-trial visit).

After islatravir administration, participants were recommended to start standard tenofovir-based ART on completion of the treatment phase of the trial (7 days after dosing with 0·5 mg, 1 mg, or 2 mg islatravir, or 10 days after dosing with 10 mg or 30 mg islatravir). The intervals were selected on the basis of a conservative projection of islatravir-triphosphate concentration decay to a level below that of expected sufficient activity according to analysis of preclinical data.

We did safety assessments, including adverse event monitoring, vital signs, electrocardiograms (ECGs), and laboratory tests, throughout the trial.

We analysed islatravir in human plasma by protein precipitation followed by reversed-phase chromatographic separation coupled with tandem mass spectrometric detection. The liquid chromatography-tandem mass spectrometry system consisted of a Waters ACQUITY Ultra Performance Liquid Chromatography system (Waters Corporation, Milford, MA, USA) coupled with an AB Sciex API 5500 triple quadrupole mass spectrometer (AB Sciex, Framingham, MA, USA) with an electrospray ionisation source. The lower limit of quantitation was 0·1 ng/mL with a linear calibration range from 0·1 ng/mL to 100 ng/mL, using 150 µL of plasma. Assay accuracy was between 99·1% and 102%, and precision was between 1·8% and 8·7%.

See Online for appendix

We analysed islatravir-triphosphate in human PBMC lysate using protein precipitation, followed by ion exchange chromatography coupled with tandem mass spectrometry, as described previously. The lower limit of

quantitation was 0·1 ng/mL with a linear curve range from 0·1 ng/mL to 40 ng/mL. Assay accuracy was between 102·0% and 108·3%, and precision was between 5·4% and 9·6% (n=26).

We calculated values of the following islatravir plasma pharmacokinetic parameters: area under the curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), apparent terminal half-life ($t_{1/2}$), apparent total clearance of drug after oral administration (CL/F), and apparent volume of distribution during terminal phase after oral drug administration (Vz/F). For islatravir-triphosphate PBMC pharmacokinetic parameters, we calculated the following: $AUC_{0-\infty}$, C_{max}, C_{168}, T_{max}, and apparent terminal $t_{1/2}$. We calculated values of all pharmacokinetic parameters with non-compartmental anaylsis methods, obtaining C_{max} and T_{max} values directly from concentration–time data using Phoenix WinNonlin, version 6.3 or higher (Certara, Princeton, NJ, USA), and $AUC_{0-\infty}$ and AUC_{0-168} using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. Islatravir CL/F was calculated as dose/AUC_{0-168} and Vz/F as (CL/F)/λ_z, where λ_z is the terminal elimination rate constant.

We analysed blood samples to determine HIV-1 plasma RNA and detect emergence of viral resistance to islatravir. We used the dual-target COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (version 2.0; Roche Molecular Diagnostics, Pleasanton, CA, USA) for the quantitation of HIV-1 RNA in human plasma samples. The test quantitates HIV-1 RNA over the range of 20–10 000 000 copies per mL (33–$1·67\times10^7$ IU/mL) in individuals with HIV-1 group M and O infection. We did resistance testing on plasma samples with at least 1000 copies per mL using the ViroSeq HIV-1 Genotyping System (version 2.0) according to the manufacturer's instructions (Celera, Alameda, CA, USA). Briefly, after extraction, we reversed transcribed and amplified RNA to generate a fragment of 1800 base pairs, which we purified and sequenced on an ABI 3100-PRISM using Big Dye Terminator (version 3.1; Applied Biosystems, Courtaboeuf, France). The entire protease gene and about a third of the reverse transcriptase gene were covered. The raw dataset was processed with the Geneious 9.0.5 software package (Biomatters, Auckland, New Zealand). Consensus sequences were analysed with the HIV-DB database, and confirmed by HIV-GRADE and Geno2Pheno.

For the **HIV-DB database** see http://hivdb.stanford.edu

For **HIV-GRADE** see http://www.hiv-grade.de

For **Geno2Pheno** see www.geno2pheno.org

Outcomes

The primary outcome measures were the safety and tolerability of islatravir, as measured by the number of participants with one or more adverse events, and the change from baseline in plasma HIV-1 RNA copies per mL. Secondary outcomes were to assess the intracellular pharmacokinetic profile of islatravir-triphosphate in PBMCs, the plasma pharmacokinetic profile of islatravir, and the pharmacokinetic–pharmacodynamic association of islatravir and islatravir-triphosphate with plasma HIV-1 RNA reduction.

Statistical analysis

We summarised adverse events descriptively. We pooled, log-transformed, and analysed $AUC_{0-\infty}$ and C_{max} of islatravir in plasma and $AUC_{0-\infty}$, C_{168}, and C_{max} of intracellular islatravir-triphosphate from participants in all panels. Non-model-based descriptive statistics are provided.

The log_{10} plasma HIV-1 RNA (copies per mL) measurements from participants were assumed to be normally distributed and linear in terms of dose level and time. We pooled and analysed individual measurements from participants in all panels on the basis of a longitudinal data analysis model containing fixed effects for dose level, time (before dose and 168 h after dose) and dose level by time interaction, and a random effect for participant. The response vector consisted of the baseline and 168 h after baseline values. Time was treated as a categorical variable so that no restriction was imposed on the trajectory of means over time. We estimated the least-squares mean change from baseline and 95% CI for each dose level at 168 h after baseline from this model. Descriptive statistics for change from baseline at 168 h are also provided. We did the statistical analysis of HIV-1 RNA reduction using SAS, version 9.4.

This study is registered with ClinicalTrials.gov, NCT02217904, and EudraCT, 2014-002192-28.

Role of the funding source

DJR, SZ, IDL, JAG, EF, SAS, MI, MR, and RPM are current or former employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co Inc, Kenilworth, NJ, USA, and were involved in trial design [DJR, SZ, IDL, JAG, MR, EF, SAS, MI, and RPM], data analysis [DJR, SZ, EF, and RPM], data collection [EF and SAS], data interpretation [DJR, SZ, IDL, MI, MR, EF, and RPM], writing or reviewing of the report [DJR, SZ, IDL, MR, EF, JAG, SAS, MI, and RPM], and the decision to submit the paper for publication [DJR, SZ, IDL, MR, EF, JAG, SAS, MI, and RPM]. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

30 participants (six per panel) enrolled and completed the trial between Sept 17, 2015, and May 11, 2017 (table 1, figure 2). Consistent with the inclusion and exclusion criteria (appendix p 1), no individuals with opportunistic infections were enrolled in the trial.

27 (90%) of 30 participants had a total of 60 adverse events post-dose, of which 21 (35%) were considered to be related to islatravir. The most common (more than one) drug-related adverse events were headache (in nine [30%]) and diarrhoea (in two [7%]; table 2). No serious

	Islatravir 0·5 mg (n=6)	Islatravir 1 mg (n=6)	Islatravir 2 mg (n=6)	Islatravir 10 mg (n=6)	Islatravir 30 mg (n=6)	Total (n=30)
Sex						
Male	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	30 (100·0)
Age (years)	29·5 (26–51)	27·0 (23–55)	42·5 (31–56)	28·0 (24–49)	32·5 (26–49)	31·5 (23–56)
Race						
Asian	0	1 (17%)	0	0	0	1 (3%)
White	6 (100%)	5 (83%)	6 (100%)	6 (100%)	6 (100%)	29 (97%)
Ethnicity						
Hispanic or Latino	0	1 (17%)	0	2 (33%)	0	3 (10%)
Not Hispanic or Latino	6 (100%)	5 (83%)	6 (100%)	4 (67%)	6 (100%)	27 (90%)
Baseline plasma HIV-1 RNA (log_{10} copies per mL)	4·59 (0·50)	4·66 (0·20)	4·70 (0·35)	4·68 (0·39)	4·17 (0·41)	4·56 (0·40)
Baseline CD4 count (cells per μL)	563 (211)	442 (159)	516 (126)	582 (186)	681 (181)	557 (181)
Time since diagnosis (months)	53 (46)	52 (52)*	32 (17)*	24 (28)	44 (54)	41 (41)†

Data are n (%), median (range), or mean (SD). *n=5. †n=28.

Table 1: **Participant demographics and baseline clinical characteristics**

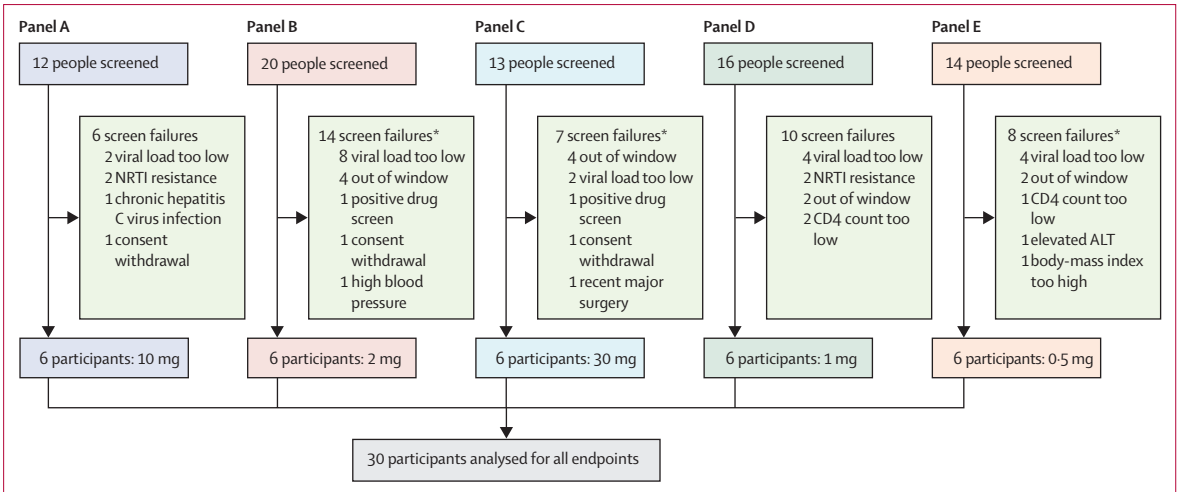

Figure 2: **Trial profile**

ALT=alanine aminotransferase. NRTI=nucleotide reverse transcriptase inhibitor. *Some individuals had screening failure for more than one reason.

adverse events or laboratory adverse events were reported, and no participants discontinued treatment because of adverse events. All adverse events were mild to moderate and resolved by the end of the trial. We observed no clinically meaningful changes in clinical laboratory values, vital signs, or ECGs. Although the number of participants was too low for formal statistical analysis, the examination of incidence and severity of adverse events did not suggest any association with dose level.

The islatravir plasma concentration–time profiles showed that islatravir undergoes biphasic elimination (table 3). Islatravir-triphosphate half-life was in the range of 78·5–128·0 h, and mean intracellular islatravir-triphosphate C_{168} values were 0·1–4·8 pmol per 10^6 cells (table 4). Plasma islatravir and islatravir-triphosphate pharmacokinetics seem to be approximately dose proportional across the studied dose range (0·5–30 mg; tables 3, 4). HIV-1 plasma RNA decreased after dosing (figure 3, table 5). We did not detect any NRTI resistance-associated genotypes[22] in the virus population of any participant before the trial (appendix pp 2–16). In 17 (57%) of 30 participants, after monotherapy HIV-1 plasma RNA was sufficient for genotypic resistance testing (appendix p 17). No resistance mutations emerged over the course of the trial.

Discussion

To our knowledge, islatravir is the first NRTTI in development for the treatment of HIV-1 infection. Our trial showed that single oral doses of islatravir of 0·5–30 mg administered to treatment-naive adults with HIV-1 infection demonstrated potent antiretroviral activity and was generally well tolerated, with a single dose as low as 0·5 mg significantly suppressing HIV-1 plasma RNA by more than 1·0 log for at least 7 days. The results also

	Screening (n=30)	Islatravir 0·5 mg (n=6)	Islatravir 1 mg (n=6)	Islatravir 2 mg (n=6)	Islatravir 10 mg (n=6)	Islatravir 30 mg (n=6)	Post study (n=30)	Total (n=30)
Participants with one or more adverse events	0	3 (50%)	2 (33%)	2 (33%)	5 (83%)	1 (17%)	0	13 (43%)
Participants with no adverse events	30 (100%)	3 (50%)	4 (67%)	4 (67%)	1 (17%)	5 (83%)	30 (100%)	17 (57%)
Gastrointestinal disorders	0	0	1 (17%)	1 (17%)	1 (17%)	1 (17%)	0	4 (13%)
Abdominal pain upper	0	0	0	0	1 (17%)	0	0	1 (3%)
Diarrhoea	0	0	0	1 (17%)	0	1 (17%)	0	2 (7%)
Nausea	0	0	1 (17%)	0	0	0	0	1 (3%)
Vomiting	0	0	1 (17%)	0	0	0	0	1 (3%)
Infections and infestations	0	1 (17%)	0	0	0	0	0	1 (3%)
Rash pustular	0	1 (17%)	0	0	0	0	0	1 (3%)
Nervous system disorders	0	2 (33%)	2 (33%)	0	5 (83%)	0	0	9 (30%)
Dizziness	0	0	0	0	1 (17%)	0	0	1 (3%)
Headache	0	2 (33%)	2 (33%)	0	5 (83%)	0	0	9 (30%)
Psychiatric disorders	0	0	0	0	1 (17%)	0	0	1 (3%)
Apathy	0	0	0	0	1 (17%)	0	0	1 (3%)
Skin and subcutaneous tissue disorders	0	0	0	1 (17%)	0	0	0	1 (3%)
Eczema	0	0	0	1 (17%)	0	0	0	1 (3%)
Hyperhidrosis	0	0	0	1 (17%)	0	0	0	1 (3%)

Every participant is counted a single time for each applicable row and column; a system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Individuals could have reported more than one adverse event within each category.

Table 2: **Drug-related adverse events (incidence >0% in one or more treatment groups)**

	Islatravir 0·5 mg (n=6)	Islatravir 1 mg (n=6)	Islatravir 2 mg (n=6)	Islatravir 10 mg (n=6)	Islatravir 30 mg (n=6)
$AUC_{0-\infty}$ (nM h)	38·2 (23·6)	88·7 (35·1)	157 (41·1)	1100 (17·4)	3220 (24·7)
C_{max} (nM)	20·3 (36·4)	38·8 (31·3)	43·8 (51·2)	235 (32·1)	678 (29·6)
T_{max}* (h)	0·50 (0·25–0·50)	0·50 (0·50–1·00)	0·50 (0·50–1·00)	1·00 (0·50–1·00)	0·75 (0·50–1·00)
Apparent terminal $t_{1/2}$ (h)	2·3 (16·7)	10·4 (144)	47·4 (74·6)	59·7 (15·4)	56·8 (11·2)
CL/F (L/h)	44·6 (23·6)	38·5 (35·1)	43·4 (41·1)	31·0 (17·4)	31·8 (24·7)
Vz/F (L)	149 (16·4)	575 (102)	2960 (38·8)	2670 (20·7)	2600 (25·5)

Data are geometric mean (geometric mean percent coefficient of variation) unless otherwise stated. Islatravir $t_{1/2}$ at 0·5 and 1 mg doses is low or variable because of some concentrations at timepoints being lower than the limit of quantification. ART=antiretroviral therapy. $AUC_{0-\infty}$=area under the curve from time zero to infinity. CL/F=clearance of drug after oral administration. C_{max}=maximum plasma concentration. HIV-1=human immunodeficiency virus type 1. $t_{1/2}$=half-life. T_{max}=time to reach C_{max}. Vz/F=volume of distribution during terminal phase oral after drug administration. *Median (range).

Table 3: **Summary pharmacokinetics of plasma islatravir following administration of islatravir to ART-naive adults with HIV-1 infection in the fasted state**

	Islatravir 0·5 mg (n=6)	Islatravir 1 mg (n=6)	Islatravir 2 mg (n=6)	Islatravir 10 mg (n=6)	Islatravir 30 mg (n=6)
$AUC_{0-\infty}$ (pmol per 10^6 cells × h)	35·3 (68·3)	60·0 (33·9)	76·2 (33·0)	445* (31·9)	1380 (40·3)
C_{max} (pmol per 10^6 cells)	0·3 (54·5)	0·4 (49·3)	0·5 (62·9)	2·8 (49·9)	8·9 (60·3)
C_{168} (pmol per 10^6 cells)	0·1 (85·6)	0·2 (31·4)	0·2 (39·2)	1·0 (26)	4·8 (85·9)
T_{max}† (h)	12 (4–24)	8 (4–24)	8 (4–144)	12 (12–240)	24 (4–96)
Apparent terminal $t_{1/2}$ (h)	95·3 (38·2)	118 (16·1)	120 (14·7)	128* (42·2)	78·5 (31·4)

Data are geometric mean (geometric mean percent coefficient of variation) unless otherwise stated. ART=antiretroviral therapy. $AUC_{0-\infty}$=area under the curve from time zero to infinity. C_{168}=concentration at 168 hours post-dose. C_{max}=maximum plasma concentration. HIV-1=human immunodeficiency virus type 1. PBMCs=peripheral blood mononuclear cells. $t_{1/2}$=half-life. T_{max}=time to reach Cmax. *n=5. †Median (range).

Table 4: **Summary pharmacokinetics of islatravir-triphosphate in PBMCs following administration of single oral doses of islatravir to ART-naive adults with HIV-1 infection in the fasted state**

suggest that higher doses of islatravir, of up to 30 mg, could extend the period of viral suppression achieved by a single dose to beyond 7 days. The unique structural features of islatravir (ie, the 3′-OH group, 4′-ethynyl group, and 2-fluoro group) result in properties that distinguish it from all other marketed antiretrovirals.[12,13] The potency of

islatravir was demonstrated by its antiretroviral activity across a range of doses, in terms of both the absolute decrease in HIV-1 RNA counts and the prolonged effect on HIV-1 RNA counts. The observed reduction in plasma HIV-1 RNA was sustained for at least 7 days following single-dose administration of islatravir across the tested dose range, including the lowest dose of 0·5 mg, with a dose–response plateau at about 10 mg.

The pharmacokinetic data are consistent with the pharmacodynamic data, and showed an extended islatravir-triphosphate half-life (78·5–128 h) and mean intracellular islatravir-triphosphate C_{168} values of 0·1–4·8 pmol per 10^6 cells. These findings are also consistent with preclinical studies in rhesus macaques, which showed that once-weekly dosing of islatravir resulting in PBMC islatravir-triphosphate concentrations of ≥0·53 pmol per 10^6 cells was sufficient to maintain HIV-1 viral suppression.[20] The lowest doses (0·5–2 mg) used in the current trial resulted in decreased plasma HIV-1 RNA despite having PBMC islatravir-triphosphate C_{168} values of <0·53 pmol per 10^6 cells.

No emergent viral resistance was observed after a single dose of islatravir in any of the participants in the trial. Previous in-vitro and preclinical studies[17,19] also suggested that islatravir has a high barrier to resistance. In addition, islatravir is effective against several NRTI-resistant HIV-1 variants in vitro and was more effective against certain NRTI-resistant strains than against wild-type HIV-1.[17] No single amino-acid substitution was shown to significantly reduce its potency,[17] and the presence of reverse transcriptase Met184Ile and Met184Val substitutions, which confer resistance against some NRTIs,[23] were shown to be susceptible to islatravir in preclinical studies despite having 3·9-fold and 5-fold decrease in potency, respectively.[16,18,19] The high barrier to resistance shown by islatravir has been proposed to be due to its unique mechanisms of action that are each distinct from the mechanisms used by currently marketed antiretroviral drugs.[12]

The long intracellular half-life of islatravir-triphosphate offers various potential dosing options for islatravir, from daily to more extended dosing. Daily dosing with an agent effective for substantially longer than the dosing interval would provide a high margin of forgiveness for that particular agent, and could continue to provide effective treatment as part of a complete regimen that would include other long-acting agents, even in the event of missed doses. Boosted protease inhibitors with a high barrier of resistance appear to protect co-administered ART components,[6] suggesting that an NRTTI with a high barrier of resistance could also act as a central component of a complete regimen.

With the high potency and long half-life of islatravir-triphosphate, sufficient concentrations should be maintained for a prolonged period, which could allow for extended dosing periods to weekly or beyond.[24] The long half-life of orally dosed islatravir-triphosphate provides a distinct route to extended dosing, especially when compared with formulation-based approaches such as cabotegravir and rilpivirine,[9] because there is no tissue depot that might persist for a long time. In addition, low-concentration, long-lasting doses also offer the potential for prophylaxis approaches. For example, the prevention of SIV infection demonstrated in rhesus macaques down to weekly doses as low as 0·1 mg/kg[21] supports a potential role for islatravir as a single agent for pre-exposure prophylaxis.

The major limitation of the current study is that, as a small, phase 1 trial in a limited population, further studies will be needed to establish islatravir efficacy in a broader and more diverse population of people living with HIV. Specifically, it is difficult to assess the barrier to the development of resistance in such a study, and the assessment of safety and general tolerability is also

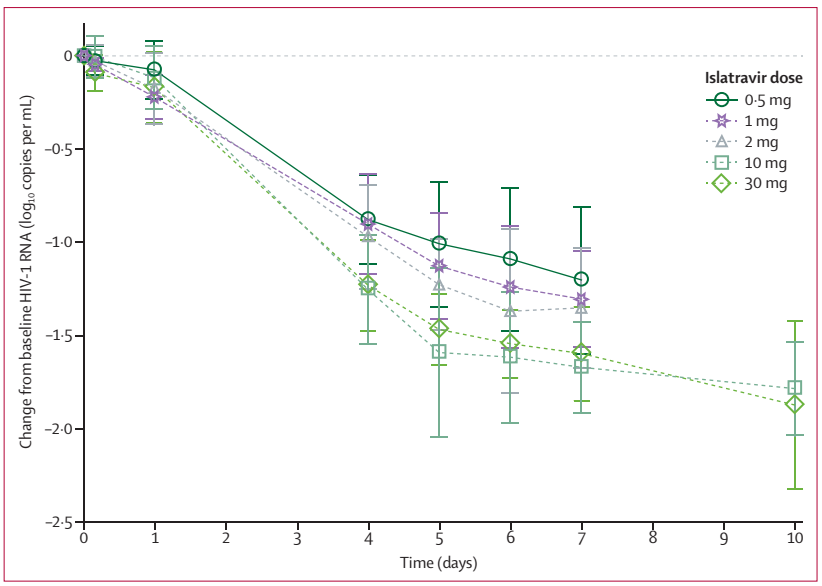

Figure 3: **Mean (SD) plasma HIV-1 RNA change from baseline after administration of single doses of islatravir to ART-naive adults with HIV-1 infection (n=6 per panel)**
Error bars indicate 95% CI. ART=antiretroviral therapy.

	Islatravir 0·5 mg (n=6)	Islatravir 1 mg (n=6)	Islatravir 2 mg (n=6)	Islatravir 10 mg (n=6)	Islatravir 30 mg (n=6)
Minimum change	−0·60	−0·95	−0·83	−1·31	−1·28
Median change	−1·26	−1·29	−1·39	−1·63	−1·57
Maximum change	−1·62	−1·73	−1·68	−1·97	−2·04
SD	0·39	0·26	0·32	0·24	0·25
Least squares mean change (95% CI)	−1·20 (−1·46 to −0·95)	−1·30 (−1·55 to −1·05)	−1·35 (−1·60 to −1·10)	−1·67 (−1·92 to −1·42)	−1·60 (−1·85 to −1·34)

Data are in $\log_{10}$ copies per mL. ART=antiretroviral therapy. HIV-1=human immunodeficiency virus type 1.

Table 5: **Summary statistics for change from baseline in plasma HIV-1 RNA at 168 h (7 days) after single oral islatravir to ART-naive adults with HIV-1 infection in the fasted state**

hampered by the relatively small set of participants exposed to islatravir for a relatively short period of time. Further studies can address these safety issues, particularly assessing sequelae, such as the bone and renal issues associated with regimens containing tenofovir disoproxil fumarate;[25] in addition, these studies can examine multiple dosing regimens of islatravir in combination with other agents.

The results of this phase 1b, single-dose trial in adults infected with HIV-1, along with the results of previous preclinical studies, show that the antiviral potency, pharmacokinetics, physical properties, and promising resistance profile of islatravir have the potential to fulfil the requirements of a new class of ART that can provide extended-duration HIV-1 treatment and prophylaxis. The features of islatravir, as well as recent advances and promises in HIV-1 treatment regimens and agents, suggest that islatravir could be paired with several potential partners for treatment, and as monotherapy for prevention.

As such, islatravir is currently being assessed in a phase 2b trial with doravirine and lamivudine as a daily medication for treatment (NCT03272347; EudraCT 2017-000437-32; protocol MK-8591-011), and will be assessed shortly in a phase 2 trial examining the potential for oral monthly dosing for prophylaxis (NCT04003103; protocol MK-8591-016).

Contributors

DS, DJR, SZ, IDL, MR, EF, AH, JAG, SAS, MI, and RPM were involved in designing the trial. DS, CK, EF, SAS, and JH contributed towards the collection of trial data. DS, DJR, SZ, EF, JH, and RPM were involved in study data analysis. Contributions towards data interpretation were provided by DS, DJR, SZ, IDL, MR, EF, CK, JH, SAS, MI, and RPM. All authors contributed to drafting the manuscript or reviewing it critically, and approved the final version for publication.

Declaration of interests

DJR, SZ, EF, JAG, SAS, MI, and RPM are current or former employees of Merck Sharp & Dohme (MSD) Corp, a subsidiary of Merck & Co Inc, Kenilworth, NJ, USA, and may own stock, hold stock options, or both in Merck & Co Inc, Kenilworth, NJ, USA. IDL and MR are current or former employees of MSD (Europe) Inc and may own stock, hold stock options, or both in Merck & Co Inc, Kenilworth, NJ, USA. All other authors declare no competing interests.

Data sharing

Merck Sharp & Dohme Corp, a subsidiary of Merck & Co Inc, Kenilworth, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymised patient-level data and clinical study reports from the company's clinical trials for the purpose of legitimate scientific research. The company is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data sharing website (http://engagezone.msd.com/ds_documentation.php). Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that might prevent MSD from sharing the requested data.

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