Pharmacokinetics and safety of coformulated bictegravir, emtricitabine, and tenofovir alafenamide in children aged 2 years and older with virologically suppressed HIV: a phase 2/3, open-label, single-arm study

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Summary

Background Coformulated bictegravir, emtricitabine, and tenofovir alafenamide is a single-tablet regimen and was efficacious and well tolerated in children and adolescents with HIV (aged 6 years to <18 years) in a 48-week phase 2/3 trial. In this study, we report data from children aged at least 2 years and weighing 14 kg to less than 25 kg.

Methods We conducted this open-label, multicentre, multicohort, single-arm study in South Africa, Thailand, Uganda, and the USA. Participants were virologically suppressed children with HIV, aged at least 2 years, weighing 14 kg to less than 25 kg. Participants received bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg) once daily, switching to bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) upon attaining a bodyweight of at least 25 kg. The study included pharmacokinetic evaluation at week 2 to confirm the dose of coformulated bictegravir, emtricitabine, and tenofovir alafenamide for this weight band by comparing with previous adult data. Primary outcomes were bictegravir area under the curve over the dosing interval (AUC_{tau}) and concentration at the end of the dosing interval (C_{tau}) at week 2, and incidence of treatment-emergent adverse events and laboratory abnormalities until the end of week 24 in all participants who received at least one dose of bictegravir, emtricitabine, and tenofovir alafenamide. This study is registered with ClinicalTrials.gov, NCT02881320.

Findings Overall, 22 participants were screened (from Nov 14, 2018, to Jan 11, 2020), completed treatment with bictegravir, emtricitabine, and tenofovir alafenamide (until week 48), and entered an extension phase. The geometric least squares mean (GLSM) ratio for AUC_{tau} for bictegravir was 7·6% higher than adults (GLSM ratio 107·6%, 90% CI 96·7–119·7); C_{tau} was 34·6% lower than adults (65·4%, 49·1–87·2). Both parameters were within the target exposure range previously found in adults, children, or both". Grade 3–4 laboratory abnormalities occurred in four (18%) participants by the end week 24 and six (27%) by the end of week 48. Drug-related adverse events occurred in three participants (14%) by the end of week 24 and week 48; none were severe. No Grade 3–4 adverse events, serious adverse events, or adverse events leading to discontinuation occurred by the end of week 24 and week 48.

Interpretation Data support the use of single-tablet coformulated bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg) for treatment of HIV in children aged at least 2 years and weighing 14 kg to less than 25 kg.

Funding Gilead Sciences.

Introduction

An estimated 1·7 million children, aged up to 14 years, live with HIV worldwide. 74% of adults and adolescents with HIV receive treatment, compared with only 54% of children aged 0–14 years.[1] Children who receive antiretroviral therapy (ART) generally have poorer outcomes than adults, partly because of late diagnoses, inadequate formulation of HIV medicines for children, and problems retaining children in care. Only an estimated 40% of children with HIV are virally suppressed, compared with 67% of adults.[1]

Single-tablet, fixed-dose combinations (FDCs) of ART have simplified the management of HIV. Such regimens are associated with improved adherence, which is important for maintaining long-term viral suppression and is particularly pertinent to paediatric populations.[2] However, many FDCs are not formulated for once-daily administration,[3] and most single-tablet FDCs are unavailable to young children because of age or weight limitations.[4]

Coformulated bictegravir, emtricitabine, and tenofovir alafenamide is a once-daily, single-tablet FDC of an

Research in context

Evidence before this study

Fixed-dose drug combinations, taken as single-tablet regimens, have simplified the management of HIV infection and improved adherence to treatment. However, most fixed-dose combinations are not available for young children.

Coformulated bictegravir, emtricitabine, and tenofovir alafenamide is a single-tablet, fixed-dose combination of an integrase strand transfer inhibitor (ie, bictegravir) and two nucleoside reverse transcriptase inhibitors (ie, emtricitabine and tenofovir alafenamide). In the USA and Europe, bictegravir, emtricitabine, and tenofovir alafenamide is approved with two doses: full-dose bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) is recommended for adults and children weighing at least 25 kg, and low-dose bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg) for children weighing 14 kg to less than 25 kg (and aged ≥2 years in Europe). We previously showed that full-dose bictegravir, emtricitabine, and tenofovir alafenamide is efficacious and well tolerated in children and adolescents aged 6 years to younger than 18 years in a 48-week phase 2/3 trial. The data reported herein are from a cohort of children using low-dose bictegravir, emtricitabine, and tenofovir alafenamide within the same study (children aged ≥2 years and weighing 14 kg to <25 kg).

We also searched PubMed for articles published between Jan 1, 1997, and Jan 1, 2023, with broad search terms of "single-tablet regimen", "fixed-dose combination", "children", and "HIV" and found only four clinical study articles investigating single-tablet regimens in children. This search result included two articles on coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (in children aged 6 to <12 years and adolescents aged 12 to <18 years). One article was on rilpivirine–emtricitabine and tenofovir disoproxil fumarate (in children and adolescents aged 11 years to <18 years). An article on the use of full-dose bictegravir, emtricitabine, and tenofovir alafenamide for children aged 6 years to younger than 18 years and weighing at least 25 kg came from the same study reported herein. No articles were identified on single-tablet regimens in children aged 2 years, weighing 14 kg to less than 25 kg.

Added value of this study

To our knowledge, this analysis is the first report from a trial evaluating the pharmacokinetics, safety, and efficacy of bictegravir, emtricitabine, and tenofovir alafenamide in children with HIV aged at least 2 years, weighing 14 kg to less than 25 kg. The acceptability or palatability of, and adherence to, the low-dose tablet were also evaluated. In this study, we administered coformulated bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg) to young children once daily for 48 weeks. Pharmacokinetic measurements of area under the curve at the end of the dosing interval, maximum plasma concentration, and concentration at the end of the dosing interval for bictegravir showed exposure within the range previously found in adults, children, or both. All participants with HIV RNA data available maintained virological suppression at week 48, and CD4 cell counts remained largely stable. There were no confirmed virological failures prompting resistance testing. Bictegravir, emtricitabine, and tenofovir alafenamide was well tolerated. Acceptability and palatability ratings for bictegravir, emtricitabine, and tenofovir alafenamide were high, as was adherence to treatment.

Implications of all the available evidence

The findings of this study support the use of low-dose single-tablet bictegravir, emtricitabine, and tenofovir alafenamide for the treatment of HIV in children aged at least 2 years and weighing 14 kg to less than 25 kg. These data supported the approval of bictegravir, emtricitabine, and tenofovir alafenamide and the low-dose tablet for children weighing 14 kg to less than 25 kg by the US Food and Drug Administration and the European Medicines Agency, as well as the recommendation for bictegravir, emtricitabine, and tenofovir alafenamide use in this population in guidelines issued by the US Department of Health and Human Services.

integrase strand transfer inhibitor, bictegravir, and two nucleoside reverse transcriptase inhibitors, emtricitabine and tenofovir alafenamide. Integrase strand transfer inhibitors have become widely adopted because of their effectiveness and safety profiles and can be particularly suitable for use in children. The integrase strand transfer inhibitor dolutegravir is now part of WHO's recommended first-line regimen for children with HIV.[5] Bictegravir has a high barrier to resistance, an important feature for a drug that will be taken for a long period of time,[6] and tenofovir alafenamide has suitable renal and bone safety profiles that compare favourably with tenofovir disoproxil fumarate.[7,8] Clinical trial results show that coformulated bictegravir, emtricitabine, and tenofovir alafenamide is highly effective and well tolerated in adults.[8–10]

Full-dose bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) is approved in many countries for adults. There is also growing supportive evidence from real-world studies of this FDC in routine clinical practice in adults.[11,12] We previously showed that coformulated bictegravir, emtricitabine, and tenofovir alafenamide is efficacious and well tolerated in children and adolescents (aged 6 years to <18 years) weighing 25 kg or more in a 48-week phase 2/3 trial.[13] In the USA, full-dose coformulated bictegravir, emtricitabine, and tenofovir alafenamide is a recommended treatment option for adults and children weighing at least 25 kg, and the low-dose tablet (ie, bictegravir 30 mg, emtricitabine 120 mg, and tenofovir alafenamide 15 mg) has been approved for children weighing 14 kg to less

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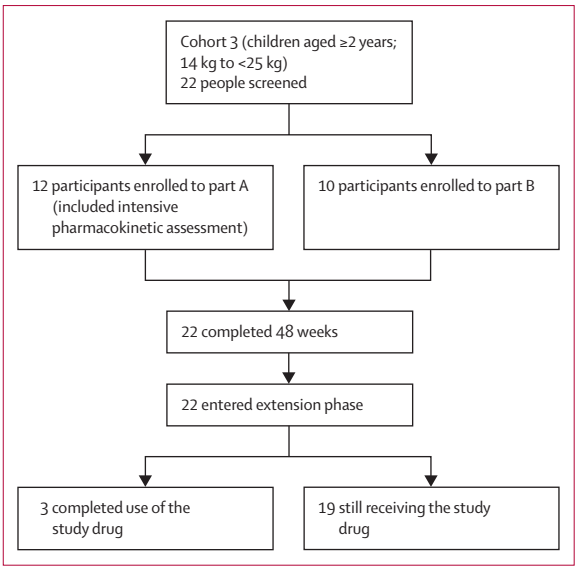

Figure 1: **Trial profile**

than 25 kg.[14] This approval has resulted in the recommendation for coformulated bictegravir, emtricitabine, and tenofovir alafenamide by the US Department of Health and Human Services as a preferred regimen for children aged 2 years or older and weighing at least 14 kg.[15] In Europe, the bictegravir, emtricitabine, and tenofovir alafenamide label was extended to include children and adolescents aged 2 years or older, with the low-dose tablet recommended for children weighing 14 kg to less than 25 kg.[16] Currently, approval has not been granted for this population in other countries, although it is under review in some countries.

We aimed to study the pharmacokinetics, efficacy, and safety of low-dose coformulated bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed children with HIV aged 2 years or older and weighing between 14 kg and less than 25 kg at enrolment.

Methods

Study design and participants

We did this phase 2/3, open-label, multicentre, multicohort, single-arm study at 24 study centres in South Africa (n=9), Thailand (n=4), Uganda (n=1), and the USA (n=10). Results from cohort 1 (participants aged 12 years to <18 years and ≥35 kg) and cohort 2 (participants aged 6 years to <12 years and ≥25 kg) of this study were reported previously.[13] Here, we present results from cohort 3 after the last participant completed the main study phase of 48 weeks.

See Online for appendix

Participants in cohort 3 were virologically suppressed children with HIV, aged at least 2 years and weighing between 14 kg and less than 25 kg. Virological suppression was defined as plasma HIV RNA of less than 50 copies per mL (or undetectable, if the limit of detection of the local assay used was ≥50 copies per mL) for at least 6 months before screening. Participants had adequate haematological function, CD4 cell counts of at least 200 cells per µL, normal liver function, and normal renal function. Eligible participants were receiving a stable ART regimen of two nucleoside reverse transcriptase inhibitors plus a third agent for at least 6 months before screening and had no documented or suspected resistance to emtricitabine, tenofovir, or integrase strand transfer inhibitors (including, but not limited to, the reverse transcriptase resistance mutations K65R and M184V/I). We excluded children with active pulmonary or extrapulmonary tuberculosis; those positive for hepatitis B virus surface antigen; and those positive for hepatitis C virus antibodies with detectable RNA loads (appendix pp 2–3).

Study enrolment occurred in two parts (figure 1; appendix p 7). Part A evaluated intensive pharmacokinetic data at week 2 to confirm the dose of bictegravir, emtricitabine, and tenofovir alafenamide for evaluation in this age and weight band. After dose confirmation, additional participants were enrolled in part B to complete the cohort. Participants who completed 48 weeks of study treatment were given the option to receive bictegravir, emtricitabine, and tenofovir alafenamide in an open-label extension phase with visits scheduled every 12 weeks, until this treatment becomes commercially available (according to the age and weight of the participant) or becomes available through an access programme.

The study was approved by institutional review boards or independent ethics committees at each site and done in accordance with Good Clinical Practice requirements and the Declaration of Helsinki. Written informed consent was provided by the parent or guardian of all participants and written assent was provided by participants, when possible.

Procedures

Participants received a low-dose oral FDC tablet of bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg), administered once daily with or without food, and were switched to full-dose bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) upon attaining a weight of at least 25 kg. Tablets were film-coated and could be split into two pieces to aid administration, if required. Investigators carried out clinical visits at screening; day 1 (baseline); and weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48. Procedures were done at these visits as outlined in the appendix (p 7). Laboratory tests included haematological analyses, serum chemistry tests, fasting lipid parameters, CD4 cell counts, estimated glomerular filtration rate (calculated with the Schwartz formula; $eGFR_{Schwartz}$), and measurement of plasma HIV RNA (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Anthropometric measures were evaluated with Z scores (ie, the number of SDs from the mean value of the reference population). We assessed safety through physical

examinations, Tanner stage assessments for participants aged at least 6 years, laboratory tests, concomitant drugs, and recording of adverse events, which we coded using the Medical Dictionary for Regulatory Activities (version 22.0). Adverse events and laboratory abnormalities were graded according to a modified version of the Division of AIDS guidelines (version 2.1). Safety data were collected on a cumulative basis on or after the date the study drug was first administered up until the date of the last dose plus 30 days. Serial blood samples for intensive pharmacokinetics assessment in part A of this trial were collected at the week 2 visit. We assessed the acceptability and palatability of coformulated bictegravir, emtricitabine, and tenofovir alafenamide at day 1 and weeks 4, 24, and 48. Investigators asked participants, or their parent or guardian, about ease of swallowing, the shape and size of study drug, and the study drug taste through facial scale or age-appropriate labels (or both). Treatment adherence, assessed by pill count, was reviewed with participants, their parent or guardian, or both at each visit from week 1.

Outcomes

Primary endpoints were steady-state pharmacokinetics for bictegravir at week 2, measured by area under the curve at the end of dosing interval (AUC_{tau}) and observed drug concentration at the end of the dosing interval (C_{tau}), and the safety and tolerability of coformulated bictegravir, emtricitabine, and tenofovir alafenamide, measured by the incidence of adverse events and laboratory abnormalities on or after the first bictegravir, emtricitabine, and tenofovir alafenamide dose until the last participant's week 24 visit.

Secondary endpoints were the proportion of participants with less than 50 copies of HIV RNA per mL, as defined by the US Food and Drug Administration (FDA) snapshot algorithm,[17] at weeks 24 and 48; changes from baseline in CD4 cell count and percentage at weeks 24 and 48; additional pharmacokinetics parameters of maximum plasma concentration (C_{max}) for bictegravir; AUC_{tau}, C_{max}, and C_{tau} for emtricitabine; area under the curve up to last measurable concentration; C_{max} for tenofovir alafenamide; incidence of adverse events and laboratory abnormalities until the last participant's week 48 visit; and acceptability and palatability of bictegravir, emtricitabine, and tenofovir alafenamide. Pharmacokinetic parameters of C_{max}, AUC_{tau}, and C_{tau} for tenofovir were analysed post hoc.

Statistical analysis

Sample size calculations showed that a minimum of ten evaluable participants from part A would provide at least 90% power for bictegravir AUC_{tau} and C_{tau} to conclude exposure equivalence between children and adults. We assumed that the expected geometric least squares mean (GLSM) ratio between children and adults was 1, with an equivalency boundary of 50–200%. The equivalency boundary was proposed on the basis that higher variability of bictegravir exposures was observed in cohort 1 and cohort 2 participants[13] than in adults (while being within with the drug exposure ranges for which there are existing safety data in adults), and a favourable exposure–response was observed for bictegravir, emtricitabine, and tenofovir alafenamide in adults (according to safety and efficacy data). Additionally, previous studies with children, adolescents, or both have allowed for an equivalency boundary of 50–200% to account for the high variability in these populations.[18–21] Two one-sided tests were done at an α level of 0·05 and the interparticipant SD (natural log scale) was 0·63.

We determined exposures for bictegravir, emtricitabine, tenofovir alafenamide, and tenofovir through non-compartmental analysis (Phoenix WinNonlin v8.2.2.227). Pharmacokinetic parameters were summarised and compared with historical adult reference data.[14,22,23] Pharmacokinetic data for bictegravir, emtricitabine, tenofovir alafenamide, and tenofovir for all cohorts were summarised with descriptive statistics. We fitted an ANOVA with a mixed-effects model appropriate for parallel group design to natural-logarithm transformed AUC_{tau} and C_{tau} for bictegravir.

We summarised the proportion of participants with less than 50 copies of HIV RNA per mL at weeks 24 and 48 as defined by the FDA snapshot algorithm;[17] we did missing=excluded analyses at weeks 24, 48, and 96.

For more on **Phoenix WinNonlin software** see https://www.certara.com/software/phoenix-winnonlin

	Children aged ≥2 years and weighing 14 kg to <25 kg (N=22)
Median age, years	6 (3 to 7)
Female at birth*	11 (50%)
Race	
Black	16 (73%)
Asian	5 (23%)
Other	1 (5%)
Country	
South Africa	11 (50%)
Thailand	5 (23%)
Uganda	2 (9%)
USA	4 (18%)
Median weight, kg	18·7 (15·2 to 21·7)
Median weight Z score	−0·35 (−1·47 to 0·10)
Median height Z score	−0·53 (−1·74 to 0·00)
Median BMI Z score	−0·11 (−1·48 to 0·60)
HIV RNA <50 copies per mL	22 (100%)
Median CD4 cells per μL	962 (748 to 1419)
Median CD4, %	32·0 (29·3 to 37·2)
Vertical transmission	22 (100%)
Median $eGFR_{Schwartz}$, mL/min per 1·73 m²	160·5 (145·0 to 168·0)

Data are n (IQR) or n (%). eGFR=estimated glomerular filtration rate. *Sex was self-reported or reported by the caregiver to the question "Sex at birth—male or female?"

Table 1: **Demographics and HIV baseline characteristics (full analysis set)**

	Cohort 3 (children)—part A		Reference (adults)		Ratio (%; cohort GLSM/reference GLSM; 90% CI)	Model rMSE
	n	GLSM	n	GLSM		
Bictegravir*						
AUC_{tau} (h × ng/mL)	12	105892·0	1193	98430·0	107·6 (96·7–119·7)	0·269
C_{max} (ng/mL)	12	9856·7	1193	5986·1	164·7 (149·5–181·4)	0·232
C_{tau} (ng/mL)	11†	1604·8	1193	2453·0	65·4 (49·1–87·2)	0·578
Emtricitabine‡						
AUC_{tau} (h × ng/mL)	12	14708·4	77	11789·5	124·8 (111·8–139·2)	0·293
C_{max} (ng/mL)	12	3629·6	77	2004·0	181·1 (150·1–218·5)	0·366
C_{tau} (ng/mL)	11†	74·3	74	89·9	82·6 (47·7–143·1)	1·086
Tenofovir alafenamide‡						
AUC_{tau} (h × ng/mL)	12	281·7	77	194·6	144·7 (114·9–182·2)	0·587
AUC_{last} (h × ng/mL)	12	279·7	77	192·5	145·3 (115·3–183·1)	0·594
C_{max} (ng/mL)	12	392·8	77	227·2	172·9 (139·8–213·8)	0·663
Tenofovir§						
AUC_{tau} (h × ng/mL)	12	317·7	841	283·9	111·9 (99·3–126·2)	0·250
C_{max} (ng/mL)	12	21·1	841	14·8	142·8 (124·9–163·3)	0·281
C_{tau} (ng/mL)	11†	9·9	841	10·3	96·0 (81·7–112·8)	0·324

AUC_{last}=area under the curve up to the last measurable concentration. AUC_{tau}=area under the curve at the end of dosing interval. C_{max}=maximum observed concentration. C_{tau}=observed drug concentration at the end of the dosing interval. GLSM=geometric least square means. rMSE=maximum square root of mean square error for the test and reference groups. *Reference range derived from a population pharmacokinetic analysis and includes exposures from participants in phase 3 studies on bictegravir, emtricitabine, and tenofovir alafenamide (GS-US-380–1489, GS-US-380–1490, GS-US-380–1844, and GS-US-380–1878) who underwent sparse and intensive pharmacokinetic sampling.[16] †One participant had missing pharmacokinetic values. ‡Reference range derived from a non-compartmental analysis and includes participants in the phase 3 studies on bictegravir, emtricitabine, and tenofovir alafenamide (GS-US-380–1489, GS-US-380–1490, GS-US-380–1844, and GS-US-380–1878) who underwent intensive pharmacokinetic sampling.[16] §Reference range derived from a population pharmacokinetic analysis and includes participants in the phase 3 studies on elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (GS-US-292–0104 and GS-US-292–0111) who underwent intensive pharmacokinetic sampling.[24,25]

Table 2: **Intensive pharmacokinetics summary (pharmacokinetics analysis set)**

Participants with confirmed virological rebound and 200 or more copies of HIV-1 RNA per mL were subject to resistance testing. We summarised the changes from baseline in CD4 cell counts and percentages, safety data, acceptability and palatability, and adherence with descriptive statistics.

An Independent Data Monitoring Committee reviewed study progress and did an interim data review. This trial was registered with ClinicalTrials.gov (NCT02881320), EudraCT (2016–002345–39), and the FDA (GS-US-380–1474).

Role of the funding source

The study funder had the lead role in study design, data collection, data analysis, data interpretation, and writing of the manuscript.

Results

Enrolment took place between Nov 14, 2018, and Jan 11, 2020, and the last participant in cohort 3 completed their week 48 visit on May 3, 2021. Data from case report forms and virology assessments were collected up to May 3, 2021; laboratory data were collected up to Oct 20, 2021.

Investigators screened 22 participants and all were enrolled. The first 12 participants were enrolled in part A and the subsequent ten in part B. All participants received the study drug, completed treatment to week 48, and entered the extension phase (figure 1). Median exposure was 99·5 weeks (IQR 73·9–108·1 weeks).

At data cutoff, 19 participants continued to receive the study drug and three had completed the study. 11 participants switched from low-dose bictegravir, emtricitabine, and tenofovir alafenamide to the full-dose tablet upon attaining a weight of 25 kg or more; five participants switched before week 48. All participants were receiving the low-dose bictegravir, emtricitabine, and tenofovir alafenamide tablet during the intensive pharmacokinetics visit at week 2. At baseline, the median age was 6 years (IQR 3–7 years). Half (11/22) of the participants were female and most (16/22, 73%) were Black. All participants had acquired HIV via vertical transmission and were fully suppressed on a stable ART regimen (table 1).

Intensive pharmacokinetic measurements of exposure for bictegravir at week 2 showed that the 90% CIs for the GLSM ratios for AUC_{tau} and C_{max} were within the predefined pharmacokinetics equivalence boundaries of 50–200% compared with adults (table 2). Specifically, bictegravir AUC_{tau} was similar to adults, and C_{max} was 64·7% higher and C_{tau} was 34·6% lower than in adults (table 2).

Intensive pharmacokinetic measurements of exposure at week 2 for emtricitabine, tenofovir alafenamide, and tenofovir were similar to adults. The 90% CIs of the GLSM ratios for some of the pharmacokinetic parameters exceeded the equivalence boundary (lower boundary of the 90% CI for emtricitabine C_{tau} [47·7%] and upper boundaries of the 90% CIs for emtricitabine C_{max} [218·5%] and tenofovir alafenamide C_{max} [213·8%]).

20 (91%) of 22 participants at week 24 and 21 (95%) participants at week 48 had less than 50 HIV RNA copies per mL according to the FDA snapshot algorithm, which includes missing sample collections (figure 2A). In missing=excluded analyses, the proportion of participants with less than 50 HIV RNA copies per mL was 100% at weeks 24 (n=20), 48 (n=21), and 96 (n=17). As no children had confirmed virological failure, no one qualified for virological resistance testing.

Changes in CD4 cell counts until 48 and week 96 are shown in figure 2B. There was a slight decline in absolute CD4 cell counts over this period; the median change from baseline in CD4 cell count was –123 (IQR –219 to 11) cells per µL at week 48 and –137 (–373 to –28) cells per µL at week 96. Analysis of CD4 cell count by age indicated a larger fluctuation in participants younger than 5 years than those aged 5 years or older, with a trend for a greater decrease in the younger subgroup (appendix p 8). Nevertheless, the percentage of CD4 cells remained stable in the overall population, with a median change from baseline of 1·1% (–0·9 to 3·9) at week 48 and –0·8% (–2·6 to 5·7) at week 96 (figure 2B).

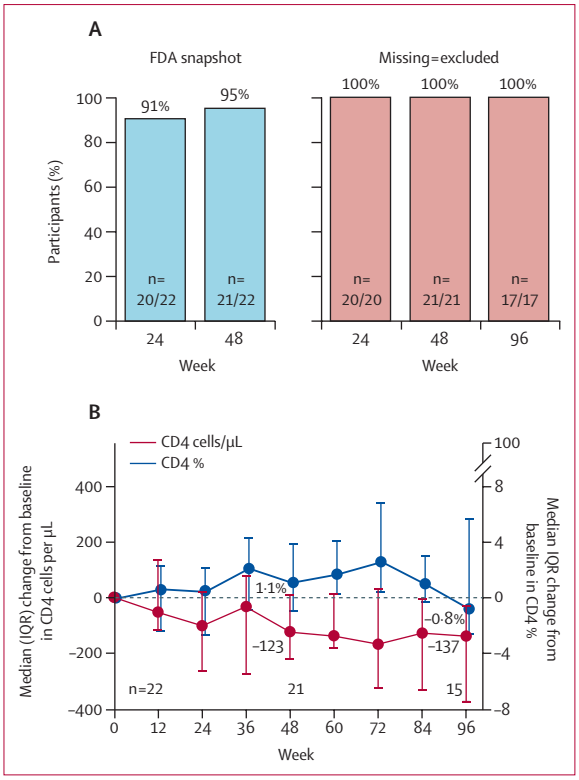

Figure 2: **Proportion of participants with less than 50 copies of plasma HIV RNA per mL (FDA snapshot algorithm; A) and change from baseline in CD4 cell counts and percentages (B) in the full analysis set**
FDA=US Food and Drug Administration.

Safety was reported on a cumulative basis and the safety analysis set included 11 participants who switched to full-dose bictegravir, emtricitabine, and tenofovir alafenamide. No distinction was made between low-dose and full-dose coformulated bictegravir, emtricitabine, and tenofovir alafenamide in calculating duration of exposure. At the data cutoff date, median exposure to bictegravir, emtricitabine, and tenofovir alafenamide was 99·5 (IQR 73·9–108·1) weeks.

Overall, 18 (82%) of 22 participants had one or more adverse event (table 3). The most commonly reported adverse events were upper respiratory tract infection (n=7, 32%), cough (n=5, 23%), nasopharyngitis (n=3, 14%), vomiting (n=3, 14%), and diarrhoea (n=3, 14%; table 1; appendix p 4). No participant had a grade 3 or 4 adverse event, a serious adverse event, or an adverse event leading to premature study drug discontinuation. Adverse events determined as related to the study drug by the investigator occurred in three participants (14%; table 3). All adverse events related to the study drug were self-limited grade 1 or 2 and did not result in study drug discontinuation.

Grade 3 or 4 laboratory abnormalities were reported for six (27%) participants (table 3). Decreases from baseline in median values for $eGFR_{Schwartz}$ were observed at week 1 and stabilised after week 16 (appendix p 9).

	Until end of week 24 (N=22)	Until end of week 48 (N=22)
Any AE	17 (77%)	18 (82%)
Grade 3–4 AE	0	0
Serious AE	0	0
AE leading to study drug discontinuation	0	0
Grade 3–4 laboratory abnormalities‡	4 (18%)	6 (27%)
AE related to study drug§	3 (14%)	3 (14%)
Neutropenia (grade 2)	1 (5%)	1 (5%)
Abdominal pain (grade 1 and 2)	1 (5%)	1 (5%)
Constipation (grade 2)	1 (5%)	1 (5%)
Nausea (grade 1)	1 (5%)	1 (5%)
Irritability (grade 1)	1 (5%)	1 (5%)
Social avoidant behaviour (grade 1)	1 (5%)	1 (5%)
Weight increased (grade 1)	0	1 (5%)
Grade 3–4 AE related to study drug	0	0

Data are n (%). Data in the two columns are not mutually exclusive but display cumulative data at two study points. AE=adverse event. *At the data cutoff date; all safety data were collected on or after the date the study drug was first administered up until the date of the last dose plus 30 days and until the end of week 24 (ie, the last participant completing their week 24 visit; cumulative data); median exposure to bictegravir, emtricitabine, and tenofovir alafenamide was 54·9 (IQR 29·3–66·4) weeks. †At the data cutoff date; all safety data were collected on or after the date the study drug was first administered up until the date of the last dose plus 30 days and until the end of week 48 (ie, the last participant completing their week 48 visit; cumulative data); median exposure to bictegravir, emtricitabine, and tenofovir alafenamide was 99·5 (73·9–108·1) weeks. ‡Decreased neutrophils was the only grade 3–4 laboratory abnormality reported in more than one participant (18% [4 of 22]; grade 3 [n=3]; grade 4 [n=1]). In total, eight participants had grade 2–4 decreased neutrophils and only one of these was considered to be an AE related to the study drug. Decreased neutrophils were transient in all participants and returned to baseline grade or lower. §Participants could have more than one AE related to study drug: neutropenia (one participant); abdominal pain, constipation, and nausea (one participant); and irritability, social avoidant behaviour (onset at week 8 and resolution by week 11), and increased weight (one participant).

Table 3: **Safety summary until the end of week 24 (primary endpoint)* and week 48 (secondary endpoint and end of the main study phase)† for children aged ≥2 years, weighing 14 kg to <25 kg (safety analysis set)**

Bodyweight Z scores increased during the study. The median change from baseline score at week 48 was 0·27 (IQR –0·08 to 0·54). BMI Z scores remained stable, with a median change at week 48 of 0·04 (–0·38 to 0·86). There were no clinically relevant changes in height Z scores. Median fasting values for triglycerides, total cholesterol, direct LDL cholesterol, and HDL cholesterol remained stable or decreased slightly from baseline (appendix p 6).

At week 48, most (18/22, 82%) participants swallowed bictegravir, emtricitabine, and tenofovir alafenamide tablets whole (figure 3). Among those who took the tablet whole, 79–89% at each assessment reported it was easy or super easy to swallow regardless of whether they took the low-dose or full-dose tablet (figure 3). Six participants younger than 6 years split the tablet in half on one or more occasions during the study. Three participants who split the tablet in half at baseline swallowed it whole at

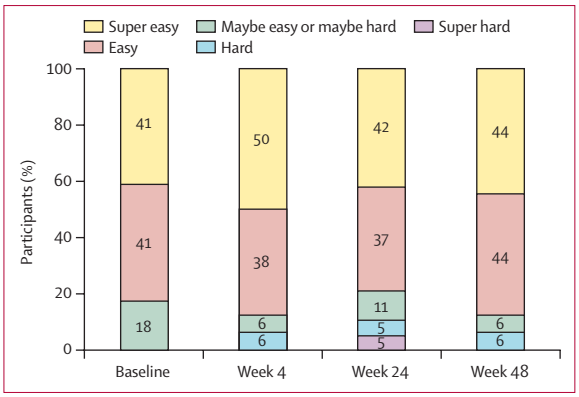

Figure 3: **Ease of swallowing coformulated bictegravir, emtricitabine, and tenofovir alafenamide whole in the safety analysis set**
The number of participants who swallowed the tablet whole was 17 of 22 at baseline, 16 of 22 at week 4, 19 of 22 at week 24, and 18 of 22 at week 48.

week 48 (all three were taking the low-dose tablet until week 48).

Most participants had a neutral (including those who did not taste anything) or positive palatability assessment of study drug (20 [91%] of 22 at baseline, 20 [95%] of 21 at week 4, 20 [91%] of 22 at week 24, and 21 [100%] of 21 at week 48). Median adherence to bictegravir, emtricitabine, and tenofovir alafenamide by pill count was 99% up to week 48. 19 (86%) of 22 participants had at least 95% adherence, one (5%) had 90–94% adherence, two (9%) had 80–89% adherence, and none had less than 80% adherence.

Discussion

In this analysis of single-tablet, low-dose bictegravir, emtricitabine, and tenofovir alafenamide in children with HIV aged at least 2 years and weighing between 14 kg and less than 25 kg at enrolment, we found that bictegravir pharmacokinetic parameters were within the range previously found in adults, children, or both, implying similar exposure. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide showed high levels of effectiveness and was well tolerated, with good adherence and palatability in this population.

Pharmacokinetic parameters for low-dose bictegravir, emtricitabine, and tenofovir alafenamide in this paediatric population were compared with historical data from adults receiving the full-dose version. Bictegravir AUC_{tau} and C_{max} were within the predefined equivalence boundaries of 50–200%. Although the lower boundary of the 90% CI of the GLSM ratio for bictegravir C_{tau} (49·1%) fell slightly outside the equivalence boundary, it was previously shown that bictegravir exposures of less than 48% of the mean still maintained virological suppression in adults.[24] Furthermore, bictegravir C_{tau} remained approximately 12-times above the protein-adjusted 95% effective concentration (162 ng/mL) for wild-type virus.[14] All bictegravir parameters were within the range previously found to be safe and efficacious in adults,[25] children,[13] or both. Although upper or lower boundaries of the 90% CI GLSM ratio for emtricitabine C_{tau}, emtricitabine C_{max}, and tenofovir alafenamide C_{max} were outside of the predefined equivalence boundaries, all parameters were within a range previously found to be safe and efficacious in adults,[25] children,[13] or both.

No participant had confirmed virological failure throughout the 48 weeks. CD4 cell counts and percentages remained stable. The slight decline in absolute CD4 cell counts from baseline to week 48 is not considered clinically relevant and is physiologically expected in children of this age, particularly those younger than 5 years,[26] in line with our observations for this population.

Overall, no safety concerns were identified. Adverse events related to the study drug occurred in three participants and none were severe or resulted in discontinuation of the study drug. Bodyweight Z scores increased modestly whereas BMI Z scores remained stable; there were no clinically relevant changes in height Z scores, indicating no effect on growth. These findings accord with studies on regimens containing tenofovir alafenamide in older children and adolescents (6 years to <18 years)[27] and adults[28] that indicate that weight gain in participants taking tenofovir alafenamide is generally similar to expected yearly weight gain in the general population (ie, tenofovir alafenamide is weight neutral) when other factors, such as any weight-suppressive ART drugs taken before switching to tenofovir alafenamide, are taken into consideration. No clinically relevant differences in metabolic parameters were observed. Overall, the safety profile of bictegravir, emtricitabine, and tenofovir alafenamide in this study was similar to that previously reported for adult populations. Exposure-related adverse events have not been identified in adults receiving bictegravir, emtricitabine, and tenofovir alafenamide.[13]

No renal or bone safety signals were noted, with no bone-related adverse events reported. Bone mineralisation was not directly evaluated in this study, but tenofovir alafenamide is known to have a favourable bone safety profile in adults compared with tenofovir disoproxil fumarate.[29] The effect of other products containing tenofovir alafenamide on bone mineralisation in paediatric populations is under investigation in ongoing studies (NCT02016924 and NCT01854775). Changes in $eGFR_{Schwartz}$ in this study were consistent with the known effect of bictegravir on the renal creatinine transporter and were not considered clinically significant.[30]

Acceptability and palatability of the low-dose bictegravir, emtricitabine, and tenofovir alafenamide tablets was high in this cohort. The potential benefit of a small pill size, reduced pill burden with single-tablet FDC formulation, and a palatable medication option for ART adherence is important. The approved tablets for coformulated bictegravir, emtricitabine, and tenofovir alafenamide are small: the full-dose tablet is

approximately 15 mm by 8 mm,[13] which, to the best of our knowledge, is the smallest full-dose single-tablet FDC regimen currently available. The low-dose tablet is approximately 14 mm by 6 mm. A subset of study participants at some point in the study required the tablet to be split before ingestion. As not all children can swallow tablets, another cohort enrolled in this study is evaluating bictegravir, emtricitabine, and tenofovir alafenamide as FDC tablets for oral suspension (ie, dispersible tablets) in infants and toddlers aged 1 month or older (weighing 3 kg to <25 kg) who are unable to swallow tablets. It should be noted that crushing bictegravir, emtricitabine, and tenofovir alafenamide tablets to aid swallowing is not recommended, as it could lead to suboptimal exposure to bictegravir and tenofovir alafenamide.[31]

This study is subject to limitations inherent to small sample size, open-label paediatric studies, which can miss rare adverse events specific to paediatric populations. Given that the effect on disease progression and the mechanism of action of antiretrovirals is the same in adults and children, efficacy and partial safety data can be extrapolated from adult studies when comparable pharmacokinetic exposures can be achieved (as was achieved in this study).[32–33]

Currently, across all three cohorts, this study has evaluated bictegravir, emtricitabine, and tenofovir alafenamide in 122 children and adolescents aged at least 2 years to younger than 18 years and weighing at least 14 kg.[13] The study did not generate data on co-infections, such as tuberculosis and hepatitis B virus.

In conclusion, pharmacokinetics, efficacy, safety, and acceptability or palatability data from this study support the use of single-tablet bictegravir, emtricitabine, and tenofovir alafenamide for children weighing at least 14 kg and the use of the low-dose bictegravir (30 mg), emtricitabine (120 mg), and tenofovir alafenamide (15 mg) tablets for the treatment of HIV in children weighing between 14 kg and less than 25 kg. These findings supported the approval of bictegravir, emtricitabine, and tenofovir alafenamide and the low-dose tablet in the USA and Europe for children weighing 14 kg to less than 25 kg (and aged at least 2 years in Europe) and the ongoing evaluation of FDC tablets for oral suspension in infants aged at least 1 month and children aged at least 2 years who are unable to swallow tablets. In a population that has barriers to treatment access, and in whom adherence is of particular importance, an effective, single-tablet regimen for children with HIV is anticipated to be of clinical benefit.

Contributors

CAR, EN, RS, ELV, SR, CKC, UL, PK, EH, AL, EJM, MFC, NR, and AHG acquired the study data. MK, RL, JTH, VAV, KK, and AHG verified and analysed the data. CAR, EN, EJM, MFC, and NR analysed the data. All authors had full access to all the study data, interpreted the data, were involved with drafting or critical revisions of the manuscript, provided approval of the final manuscript for submission, and agree to be accountable for all aspects of the work.

Declaration of interests

CAR received grant support to their institution from Gilead, GSK, and ViiV Healthcare during the study and outside the submitted work; and support for meeting travel from Gilead outside the submitted work. RS reports grant support to their institution from Gilead, GSK, Merck, and Penta outside the submitted work; and support for meeting travel from Gilead outside the submitted work. CKC and PK report grant support to their institution from Gilead for the conduct of this study. MK, RL, JTH, VAV, and KK are employed by Gilead and hold stocks in Gilead. MFC reports grant support to their institution from Gilead for the conduct of this study. AHG reports clinical trial agreement to their institution from Gilead for the conduct of this study; and is Chair of the Data Safety and Monitoring Board for a study sponsored by the National Institute of Dental and Craniofacial Research. All other authors declare no competing interests.

Data sharing

Gilead Sciences shares anonymised individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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