Original Article

Pharmacokinetics and 48-Week Safety and Efficacy of Raltegravir for Oral Suspension in Human Immunodeficiency Virus Type-1-Infected Children 4 Weeks to 2 Years of Age

Sharon Nachman,[1] Carmelita Alvero,[2] Edward P. Acosta,[3] Hedy Teppler,[4] Brenda Homony,[4] Bobbie Graham,[5] Terence Fenton,[2] Xia Xu,[4] Matthew L. Rizk,[4] Stephen A. Spector,[6] Lisa M. Frenkel,[7] Carol Worrell,[8] Edward Handelsman,[9] and Andrew Wiznia[10]

[1]Health Sciences Center, SUNY Stony Brook, Pediatrics, New York; [2]Harvard School of Public Health, Statistical and Data Analysis Center, Boston, Massachusetts; [3]University of Alabama at Birmingham; [4]Merck & Co, West Point, Pennsylvania; [5]Frontier Science and Technology Research Foundation, Buffalo, New York; [6]University of California San Diego, Rady Children's Hospital San Diego, La Jolla, California; [7]Seattle Children's Hospital, Center for Childhood Infections, Washington; [8]Maternal and Pediatric Infectious Diseases Branch, Eunice Kennedy Shriver National Institute of Child, Health and Human Development, National Institutes of Health, Bethesda, Maryland; [9]Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; and [10]Jacobi Medical Center, Pediatrics, Bronx, New York

Corresponding Author: Sharon Nachman, MD, Department of Pediatrics, SUNY Stony Brook, Pediatrics Stony Brook, NY 11794-111. E-mail: sharon.nachman@stonybrookmedicine.edu.

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Background. IMPAACT P1066 is a Phase I/II open-label multicenter trial to evaluate safety, tolerability, pharmacokinetics (PK), and efficacy of multiple raltegravir (RAL) formulations in human immunodeficiency virus (HIV)-infected youth.

Methods. Dose selection of the oral suspension formulation for each cohort (IV: 6 months to <2 years and V: 4 weeks to <6 months) was based on review of short-term safety (4 weeks) and intensive PK evaluation. Safety data through Weeks 24 and 48 and Grade $\geq$3 or serious adverse events (AEs) were assessed. The primary virologic endpoint was achieving HIV RNA <400 copies/mL or $\geq$1 $\log_{10}$ reduction from baseline at Week 24 (Success). For Cohort IV, optimized background therapy (OBT) could have been initiated with RAL either at study entry or after intensive PK sampling was completed at Day 5–12. An OBT was started when RAL was initiated for Cohort V subjects because they were not permitted to have received direct antiretroviral therapy before enrollment.

Results. Total accrual was 27 subjects in these 2 cohorts, including 1 subject who was enrolled but never started study drug (excluded from the analyses). The targeted PK parameters (area under the curve $[AUC]_{0-12hr}$ and C_{12hr}) were achieved for each cohort allowing for dose selection. Through Week 48, there were 10 subjects with Grade 3+ AEs. Two were judged related to study drug. There was 1 discontinuation due to an AE of skin rash, 1 event of immune reconstitution syndrome, and no drug-related deaths. At Week 48, for Cohorts IV and V, 87.5% of subjects achieved virologic success and 45.5% had HIV RNA <50 copies/mL. At Week 48, gains in CD4 cells of 527.6 cells/mm^3 and 7.3% were observed.

Conclusions. A total of 6 mg/kg per dose twice daily of RAL for oral suspension was well tolerated and showed favorable virologic and immunologic responses.

Key words. pediatric HIV; raltegravir; treatment.

Raltegravir is the first US Food and Drug Administration- and European Medicines Agency-approved human immunodeficiency virus (HIV) integrase strand transfer inhibitor with demonstrated safety and efficacy in both treatment-naive and treatment-experienced HIV-1-infected adults. Raltegravir tablets (film-coated and chewable) have also been studied in treatment-experienced children over 2 years of age, and the tablets were first approved in this age group in 2011. Below 2 years of age, alternative formulations are needed, because tablet formulations used in older children are inappropriate. Neither scored tablets nor chewable tablets can be used in infants and toddlers,

because solid formulations are not appropriate due to immature chewing ability and the potential for choking.

IMPAACT P1066 (P1066) was designed to assess the safety and pharmacokinetics (PK) of raltegravir in HIV-infected children from age 4 weeks to <19 years using 3 different age-appropriate formulations with the goal of determining the appropriate raltegravir dose in age-based subgroups. After dose selection, the study provided additional data on safety, efficacy, and population PK. Data on safety, PK, and efficacy at Week 48 for cohorts over 2 years of age has been published [1]. This report describes findings up to Week 48 from subjects 4 weeks to <2 years of age who received the novel raltegravir granules for suspension formulation. The total duration of treatment in P1066 continues to 240 weeks.

METHODS

In P1066, an open-label, nonrandomized, multicenter study, subjects were enrolled into 5 age groups in 6 cohorts, with Cohorts I–III previously described [1]. Cohort IV (≥6 months to <2 years) and Cohort V (≥4 weeks to <6 months of age) were assigned to receive a novel formulation: raltegravir granules for suspension. This banana-flavored formulation was supplied as individual sachets, each containing 100 mg to be suspended in 5 mL water, yielding a final suspension concentration of 20 mg/mL.

Entry criteria included plasma HIV RNA ≥1000 copies/mL, being antiretroviral therapy (ART)-experienced but naive to integrase inhibitors (for Cohort V, failed prophylaxis to prevent mother-to-child transmission [PMTCT] was required, but no direct antiretroviral (ARV) treatment was allowed), laboratory values less than Division of AIDS (DAIDS) pediatric Grade 3 toxicity criteria[2], and absence of active opportunistic infection or concurrent cancer. The study was conducted at domestic US and international IMPAACT Network sites, after approvals were obtained from local institutional review boards and/or in-country ethics committees responsible for oversight of the study. Fifty-six sites registered, and 11 sites enrolled at least 1 subject in these 2 age cohorts.

Stage I was the dose-finding period for both Cohorts. For those Cohort IV subjects who entered the study after failing a combination ARV regimen (similar to Cohorts I–III), raltegravir was added on Day 1, and after completing the intensive PK sampling on Days 5–12, the background antiviral regimen was optimized. Cohort V subjects all entered the study with a background of failed PMTCT only but no direct ARV treatment, and they were prescribed a new background ARV regimen concurrent with initiation of raltegravir on Day 1. Stage II was designed to enroll additional subjects after dose selection to assess longer term safety and efficacy of the selected dose. For subjects enrolled in Stage II, background antiviral therapy was optimized or started with initiation of raltegravir at study entry.

The dose-finding algorithm for each cohort included a review of both Week 4 safety and intensive PK, and it required assessment of data from the first 4 subjects (termed a "mini-cohort"). Once a mini-cohort had met both the safety and PK criteria, further accrual to complete the full cohort (N = 8 subjects per cohort) could occur. Success, for safety, was defined as follows: (1) no life-threatening suspected adverse drug reaction [SADR]; (2) no Grade 4 event considered probably or definitely attributable to raltegravir; and (3) no more than 25% terminating study treatment due to a Grade 3 SADR. The PK objective was to achieve a PK profile similar to that attained in adults at the approved raltegravir dose of 400 mg twice daily. Dose selection in each full cohort occurred after all intensive PK data and at least 4 weeks of safety data were available and met the above criteria.

Long-term safety was assessed at 24 weeks (primary) and at 48 weeks in all treated subjects. All grade 3 or higher toxicity events, International Conference on Harmonization serious adverse events, and malignancies were reported to DAIDS. In assessing medication compliance at each visit, the primary care giver completed an adherence questionnaire, and site personnel collected and counted the returned used study drug sachets to determine the total number used since the last visit. An assessment of the raltegravir granules formulation palatability was conducted using a questionnaire administered to the caregivers of study subjects, either at Week 4 of treatment or at an early discontinuation visit, if applicable.

The emergence of resistant viruses was monitored by isolating viral RNA from all subjects, displaying virologic failure and determining the amino acid sequences of viral genes for integrase (IN), reverse transcriptase (RT), and protease inhibitor (PI), provided that plasma HIV RNA was >1000 copies/mL (the approximate lower limit of detection for the resistance assay) and adequate sample was available for testing. All subjects had RT and PI sequencing done at baseline. In addition, any subjects who were identified as virologic failures had resistance testing (IN, RT, and PI) performed on samples taken at or near the time of virologic failure and had IN resistance testing performed on a stored baseline sample.

Bioanalysis and Pharmacokinetics

Raltegravir plasma concentrations were measured at the University of Alabama at Birmingham using a validated, isocratic, reverse-phase high-performance liquid

chromatography/tandem mass spectrometry method consistent with those previously published [3, 4]. The linear calibration range was 10 to 10 000 ng/mL from a 200 μL plasma sample. Cohort IV blood for PK analysis was drawn at predose, 0.5, 1, 2, 4, and 12 hours postdosing. For Cohort V, blood for PK analysis was drawn at predose, 0.5, 1, 3–5, and 8–10 hours postdosing. In contrast to the older cohorts, in Cohort V, the protocol-specified PK sampling scheme did not require a collection of a 12-hour postdose sample, because this was considered a potentially excessive burden on the parent or caregiver of a young infant. However, after evaluation of the Cohort V Stage I data and given the emergence of the importance of C_{12hr} concentrations from the QDMRK study [5, 6], it was determined that these data were required. To collect PK samples at the 12-hour postdose time point, 4 additional subjects were enrolled into Stage I via protocol amendment in whom 12-hour sampling was performed. All PK assessments were on nonfasting samples.

A 2-compartment model with first-order absorption and weight-based scaling for clearance and volume was used to fit the data in NONMEM (Cohort IIB-V PopPK) [7]. The model was used to estimate C_{trough} values for 9 subjects in Cohorts IV and V, including 1 of 8 subjects enrolled in Cohort IV (6 months to <2 years of age) and 8 of 11 subjects enrolled in Cohort V (4 weeks to <6 months of age) that did not have an observed C_{12hr} sample collected.

Raltegravir pharmacokinetic parameters were calculated using standard noncompartmental analysis in Phoenix 6.4 (Certara, Inc., St. Louis, MO). The pharmacokinetic criteria used by the P1066 Protocol Team for dose selection in these cohorts (Cohorts IV and V) were modified from those used for Cohorts I–III to target a geometric mean (GM) AUC_{0-12hr} for each cohort between 14 and 45 μM × h (6.2–20 ng × h/mL) and an approximate GM raltegravir $C_{12hr} \geq 75$ nM (33.3 ng/mL). The increased upper limit for the GM AUC_{0-12hr} of 45 μM × h is based on mean exposures observed in the 800 mg multiple-dose arm of Protocol 001, the highest raltegravir multiple dose exposure data available at the time [8]. Dose adjustments for any individual subject with an $AUC_{0-12hr} \geq 63$ μM × h were considered by the team on a case-by-case basis, and a repeat intensive PK visit was required after dose adjustment.

Statistics

The primary analysis group for safety and efficacy comprised subjects treated with only the final selected dose of raltegravir, referred to as the Final Dose population, whether enrolled in Stage I or II. These results reflect the age-specific doses proposed and approved for commercial use. By the data freeze date (March 17, 2014), all subjects enrolled in Cohorts IV and V had been on study for at least 48 weeks; therefore, this report presents the safety and efficacy results of the complete 48-week data.

Efficacy responses were secondary objectives. The primary virologic outcome, virologic success, was defined as achieving either HIV RNA <400 copies/mL or ≥1 $\log_{10}$ reduction from baseline at Week 24. The secondary efficacy objectives included the proportion achieving HIV RNA <50 copies/mL, HIV RNA <400 copies/mL, and the change from baseline in CD4 cell count and percentage at Week 24 and 48 time points. An observed failure approach was used for handling missing data. For virologic endpoints, missing values were considered to be failures if missing values were due to discontinuation of study treatment for lack of efficacy or for nontreatment-related reasons, with the last available HIV RNA value not achieving virologic success. For change from baseline in CD4 cell count and percentage, baseline values were carried forward for missing data as described above. Other missing values were excluded. Virologic failure was defined as follows: (1) nonresponder—never achieved either ≥1 $\log_{10}$ drop from baseline in HIV RNA or HIV RNA <400 copies/mL through Week 24; or (2) virologic rebound at Week 24 or later confirmed HIV RNA ≥400 copies/mL after initial response with HIV RNA <400 copies/mL or confirmed >1.0 $\log_{10}$ increase in HIV RNA above nadir; confirmation required 2 consecutive measurements at least 1 week apart.

RESULTS

Enrollment and Disposition

Total accrual into Cohorts IV and V was 27 subjects, including 1 subject who was enrolled but never started study drug (excluded from the analyses). There were 15 subjects enrolled in Cohort IV and 12 in Cohort V (Table 1). Three subjects discontinued study before 48 weeks.

Demographics

Key baseline demographics for the 26 treated subjects include the following: gender, 34.6% female; race, 84.6% Black/African American; median age, 28 weeks; median baseline RNA, 5.9 $\log_{10}$ copies/mL; and median baseline CD4 cell count (%), 1400 cells/mm^3 (18.6%) (Table 2).

Intensive Pharmacokinetics and Dose Selection

All dose adjustments and decisions were based entirely on PK results, because there were no instances in which either the minicohort or full cohort dose failed the safety criteria. Weight-based dosing of approximately 6 mg/kg twice daily was selected for both cohorts. For Cohorts IV and V, the PK

Table 1. Study Enrollment and Disposition

Variable	Cohort IV (N = 15) n (%)	Cohort V (N = 12) n (%)	Total (N = 27) n (%)
Total	15 (100)	12 (100)	27 (100)
Treated	14 (93.3)	12 (100)	26 (96.3)
Nontreated	1 (6.7)	0 (0)	1 (3.7)
Subjects Completed Week 24*	14 (93.3)	11 (91.7)	25 (92.6)
Subjects Completed Week 48**	14 (93.3)	10 (83.3)	24 (88.9)
Off Study Drug	2 (13.3)	4 (33.3)	6 (22.2)
Died	1 (6.7)	0 (0)	1 (3.7)
Protocol Defined Toxicity	0 (0)	1 (8.3)	1 (3.7)
Protocol Defined Clinical Event***	0 (0)	1 (8.3)	1 (3.7)
Disallowed Medication	0 (0)	1 (8.3)	1 (3.7)
Guardian consent withdrawn	1 (6.7)	0 (0)	1 (3.7)
Not Able to Attend Clinic	0 (0)	1 (8.3)	1 (3.7)
Off Study	2 (13.3)	1 (8.3)	3 (11.1)
Death	1 (6.7)	0 (0)	1 (3.7)
Subject/parent not able to get to clinic	0 (0)	1 (8.3)	1 (3.7)
Subject/parent withdraws consent before study completion	1 (6.7)	0 (0)	1 (3.7)

Abbreviations: N, number of subjects in each cohort; n (%), number (percentage) of subjects in each subcategory.
*Subject was on study treatment to at least relative day 127.
**Subject was on study treatment to at least relative day 295.
***Subject discontinued study drug due to virologic failure.

Table 2. Demographics of Population at Study Entry

Variable	Cohort IV (N = 14) n (%)	Cohort V (N = 12) n (%)	Total (N = 26) n (%)
Gender			
Male	9 (64.3)	8 (66.7)	17 (65.4)
Female	5 (35.7)	4 (33.3)	9 (34.6)
Race			
Black or African American	10 (71.4)	12 (100)	22 (84.6)
White	2 (14.3)	0 (0)	2 (7.7)
Multiracial	1 (7.1)	0 (0)	1 (3.8)
Unknown	1 (7.1)	0 (0)	1 (3.8)
Ethnicity			
Hispanic or Latino	5 (35.7)	0 (0)	5 (19.2)
Not Hispanic or Latino	3 (21.4)	8 (66.7)	11 (42.3)
Unknown	6 (42.9)	4 (33.3)	10 (38.5)
CDC HIV Clinical Classification			
A	6 (42.9)	4 (33.3)	10 (38.5)
B	2 (14.3)	1 (8.3)	3 (11.5)
C	3 (21.4)	0 (0)	3 (11.5)
N	3 (21.4)	7 (58.3)	10 (38.5)
Viral Subtype			
Clade B	4 (28.6)	2 (16.7)	6 (23.1)
Non-Clade B*	9 (64.3)	7 (58.3)	16 (61.5)
MISSING	1 (7.1)	3 (25)	4 (15.4)
Number of ARV Classes Previously Used			
1	8 (57.1)	10 (83.3)	18 (69.2)
2	4 (28.6)	2 (16.7)	6 (23.1)
≥3	2 (14.3)	0 (0)	2 (7.7)
Subjects with prior NNRTI use	8 (57.1)	11 (91.7)	19 (73.1)
Subjects with prior PI use	5 (35.7)	0 (0)	5 (19.2)
Baseline Plasma HIV RNA (copies/mL)			
0 – ≤4000	1 (7.1)	0 (0)	1 (3.8)
>4000 – ≤50 000	1 (7.1)	2 (16.7)	3 (11.5)
>50 000 – ≤100 000	3 (21.4)	1 (8.3)	4 (15.4)
>100 000	9 (64.3)	9 (75)	18 (69.2)
Phenotypic Sensitivity Score (PSS**)			
1	0 (0)	1 (8.3)	1 (3.8)
2	2 (14.3)	4 (33.3)	6 (23.1)
≥3	9 (64.3)	4 (33.3)	13 (50)
MISSING	3 (21.4)	3 (25)	6 (23.1)
Genotypic Sensitivity Score (GSS**)			
1	0 (0)	1 (8.3)	1 (3.8)
2	3 (21.4)	4 (33.3)	7 (26.9)
≥3	10 (71.4)	3 (25)	13 (50)
MISSING	1 (7.1)	4 (33.3)	5 (19.2)

Abbreviations: ARV, antiretroviral; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; N, number of subjects in each cohort; n (%), number (percentage) of subjects in each subcategory; NNRTI, nonnucleoside reverse-transcriptase inhibitor; OBT, optimized background therapy; PI, protease inhibitor.
*Non-Clade B subtypes reported include: C, CRF12-BF, and F1.
**The GSS and PSS were defined as the total number of ARVs in OBT to which the subject's viral isolate showed genotypic/phenotypic sensitivity, based upon resistance tests performed prestudy (or at screening). If no resistance results were available for certain drugs, they will be scored as on active drug in the GSS and PSS if the subject had no prior history of use, and considered as not active if the subject had used it in the past. Scoring does not include raltegravir.

parameters used for dose selection included GM AUC_{0-12hr} and C_{12hr}, and the values were 19.8 μM × h and 22.3 μM × h and 108.2 nM and 116.6 nM, respectively (Table 3; Figure 1). Pharmacokinetics results in Cohorts IV and V were similar to the values obtained in Cohorts I–III [1].

Safety and Adverse Events

The clinical safety data consisted of diagnoses, signs and symptoms, laboratory abnormalities, and deaths. Causality of adverse events of Grade 3 or higher was assessed by consensus of the sites and the P1066 Protocol Team and Medical Officers with respect to attribution to raltegravir. Consensus (assessment as related or unrelated) was achieved for each of the events reported. By Week 48, all 26 Cohort IV and V subjects had experienced at least 1 clinical adverse event, and 92.3% had at least 1 laboratory adverse events (Table 4). By Week 48, 2 subjects experienced drug-related clinical adverse events. One adverse event, a serious erythematous rash, which occurred in a 17-week-old subject on study Day 7, was considered related to raltegravir, and it was the only event in these 2 cohorts that resulted in permanent discontinuation of study drug. The interpretation of this event is confounded by the diagnosis and treatment of *Pneumocystis jirovecii* pneumonia ([PCP] considered not related to study therapy) 1 day before the onset of the drug-related rash (ie, after 6 days on study). Concomitant treatment for this subject included other agents that are associated with rash, including benzyl penicillin, cefotaxime, vancomycin, and cotrimoxazole, as well as optimized background ART. The second drug-related adverse event was a case of immune reconstitution syndrome at the site of neonatal Bacillus Calmette-Guérin immunization in an infant 4 weeks after initiating a successful combination regimen with raltegravir; this adverse event did not limit study therapy. Four subjects

Table 3. Summary of Intensive PK Parameters

Cohort and Age	Formulation	Final Recommended Dose	N*	Mean Weight	Mean Dose in mg	Mean Dose in mg/kg	GM (CV%) AUC_{0-12hr}, μM × h	GM (CV%) C_{12hr}, nM**	GM (CV%) C_{max}, μM	GM (CV%) T_{max}, h
Cohort IV: 6 months to <2 years	Granules for suspension	~6 mg/kg twice daily	8	8.49	47.89	5.93	19.8 (34)	108.2 (52)	10.6 (64.8)	0.7 (64.7)
Cohort V: 4 weeks to <6 months	Granules for suspension	~6 mg/kg twice daily	11	5.50	30.76	5.70	22.3 (40)	116.6 (68)	8.6 (38.7)	0.8 (37.3)

Abbreviations: AUC_{12}, area under the concentration-time curve from 0 to 12 hours postdose; C_{12}, concentration at 12 hours postdose; C_{max}, maximum concentration; CV%, percent coefficient of variation; GM, geometric mean; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration.
*Number of subjects with intensive PK results at the final recommended dose.
**A population PK model was used to estimate C_{12hr} values for 1 (of 8) subject in Cohort IV and 8 (of 11) subjects in Cohort V that did not have an observed sample collected [7].

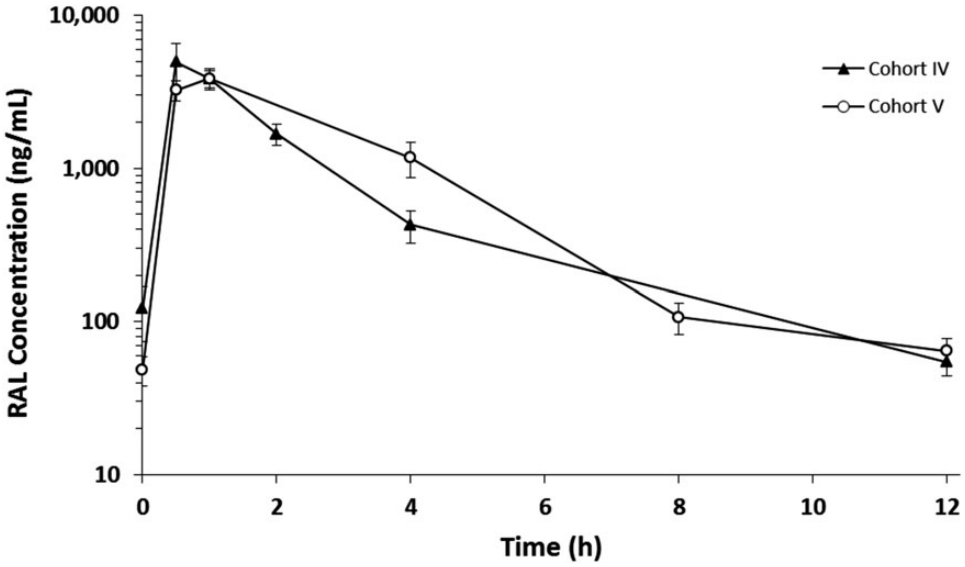

Figure 1. Oral granules for suspension concentration-time profiles for Cohorts IV and V. RAL, raltegravir.

in Cohort IV (28.6%) and 2 subjects in Cohort V (16.7%) had Grade 3 or greater laboratory adverse events during 48 weeks of exposure to raltegravir. These events included increases in bilirubin (N = 1) and lipase (N = 1) and decreases in nonfasting glucose (N = 1), potassium (N = 2), hemoglobin (N = 1), and neutrophil count (N = 3), and none were considered related to raltegravir. A Grade 4 lipase, judged not related to raltegravir, was associated with confounding proven cytomegalovirus and Epstein-Barr virus infections, and the subject resumed study raltegravir. After Week 48, 1 patient with a history of pulmonary tuberculosis with sequelae of chronic lung disease, HIV encephalopathy, and epilepsy, died of gastroenteritis (onset study Day 415), which was considered not related to raltegravir.

Virologic Efficacy

By the March 17, 2014, data cutoff, all 26 subjects enrolled in Cohorts IV and V had Week 48 data (ie, either completed the Week 48 visit, or for those who discontinued before Week 48 had the potential to experience Week 48 visits). At Week 24, 92% of subjects with evaluable data achieved virologic success, and 40.9% had HIV RNA <50 copies/mL. In addition, the mean HIV RNA decline at Week 24 was 3.2 log_{10} copies/mL, and gains in CD4 counts of 445.7 cells/mm^3 and 7.5% were observed (data not shown). At Week 48, results were generally similar to those at Week 24; 87.5% of subjects achieved virologic success, and 45.5% had HIV RNA <50 copies/mL. At Week 48, the mean HIV RNA decline was 2.8 log_{10} copies/mL, and gains in CD4 counts of 527.6 cells/mm^3 and 7.3% were observed (Table 5).

Antiretroviral Drug Resistance

In Cohort IV, no subjects experienced virologic failure by Week 24; however, 4 subjects experienced failure by Week 48. No subjects in Cohort V met virologic failure

Table 4. Clinical and Laboratory Adverse Events (Weeks 0–48)*

Variable	Cohort IV (N = 14) n (%)	Cohort V (N = 12) n (%)	Total (N = 26) n (%)
Clinical Adverse Events			
With 1 or more clinical adverse events	14 (100)	12 (100)	26 (100)
With no clinical adverse event	0 (0)	0 (0)	0 (0)
With 1 or more serious clinical adverse events	6 (42.9)	3 (25)	9 (34.6)
With 1 or more serious drug-related** clinical adverse events	0 (0)	1 (8.3)	1 (3.8)
Who died due to clinical adverse events	0 (0)	0 (0)	0 (0)
With Grade 3 or greater clinical events	5 (35.7)	4 (33.3)	9 (34.6)
With Grade 3 or greater drug-related** clinical events	0 (0)	2 (16.7)	2 (7.7)
Discontinued due to an adverse event (clinical or laboratory)	0 (0)	1 (8.3)	1 (3.8)
Laboratory Adverse Events			
With 1 or more laboratory adverse events	13 (92.9)	11 (91.7)	24 (92.3)
With no laboratory adverse event	1 (7.1)	1 (8.3)	2 (7.7)
With 1 or more serious laboratory adverse events	2 (14.3)	0 (0)	2 (7.7)
With 1 or more serious drug-related** laboratory adverse events	0 (0)	0 (0)	0 (0)
Who died due to laboratory adverse events	0 (0)	0 (0)	0 (0)
With Grade 3 or greater laboratory events	4 (28.6)	2 (16.7)	6 (23.1)
With Grade 3 or greater drug-related** laboratory events	0 (0)	0 (0)	0 (0)

Abbreviations: N, number of subjects in each cohort; n (%), number (percentage) of subjects in each subcategory.*Only events with a worse grade than baseline were included. If baseline grade was missing, then assume that the on-treatment grade was higher. Events were included if they occurred while on study drug or within 14 days after discontinuation of study drug.**Drug related adverse events were determined by the investigator to be possibly, probably or definitely related to raltegravir.

criteria by Week 24 or 48. Because of limited blood volume obtained, only 2 of the 4 Cohort IV subjects with virologic failure had genotypic data available. One subject had a mutation at IN codon 155 (without other raltegravir associated resistance mutations), and 1 subject had no known raltegravir mutations detected during study treatment.

Palatability

An assessment of taste for the raltegravir granules formulation was conducted using a questionnaire that was administered to the caregivers of Cohort IV and V subjects, either at Week 4 of treatment or at an early discontinuation visit, if applicable. The overall taste was considered average, good, or very good by 73.9%. Overall, 82.6% of caregivers reported no problems with the subject taking the granules formulation, and medication refusal was uncommon. Vomiting or spitting up medication was infrequent, being reported in 17.4% of subjects.

DISCUSSION

The recommended 6 mg/kg weight-based dosing of the raltegravir oral granules in pediatric subjects from ages ≥4 weeks to <2 years provided a similar overall exposure to raltegravir compared with that obtained in older pediatric subjects in Cohorts I–III (ages 2 to 18 years of age) and adults taking 400 mg twice daily of the adult tablet. However, peak raltegravir concentrations were slightly higher, as observed in comparative bioavailability data of these formulations in an adult Phase I study [9]. Safety evaluations, including both clinical and laboratory evaluations, demonstrate an acceptable safety profile in these young children. Data from these 2 cohorts show that raltegravir has favorable efficacy, in a combination regimen, through 48 weeks, in infants and toddlers receiving the selected dose as measured by multiple efficacy parameters. More than 87% of subjects in both cohorts combined had ≥1 $\log_{10}$ decline in HIV RNA or HIV RNA <400 copies/mL at 48 weeks, with 45.5% achieving HIV RNA <50 copies/mL. Taken together, these data suggest that raltegravir is a valuable addition to the currently available treatments of HIV in infants and children in the first 2 years of life.

Differences in the pharmacokinetic profile of the oral granules compared with the adult tablet are qualitatively similar to those observed when the chewable tablet is compared with the adult tablet. In both cases, higher $AUC_{0-\infty}$, C_{max}, and earlier T_{max} were observed, which are attributed to differences in absorption. There are considerable data from clinical studies of raltegravir at higher doses and with alternative formulations that indicate the higher peak concentrations obtained in Cohorts IV and V are not safety concerns. Doses of oral granules for pediatric subjects in Cohorts IV and V were selected such that the resulting pharmacokinetic parameters of raltegravir were similar to those attained in adults at the approved dose of 400 mg twice daily (where there exists a large amount of data demonstrating the safety and efficacy of the exposures at this dose) and in older pediatric subjects in Cohorts I–III at the approved doses. In this study, there was 1 serious Grade 3 rash attributed to raltegravir, but it occurred coincident with an event of diagnosis and treatment for PCP, suggesting a possible alternative hypothesis (including immune reconstitution syndrome) for the rash.

The rates of viral suppression continued to rise from Weeks 24 to 48, with the number of subjects having viral loads below 50 and 400 copies increasing. This is not unexpected given the high baseline viral loads in many subjects. Overall, the Week 24 and 48 efficacy data for Cohorts IV and V is generally consistent with that observed in the older cohorts (Cohorts I–III) [1] and adults [10, 11].

Table 5. Virologic and Immunologic Parameters (Observed Failure Approach) (Week 48)

Parameter	Cohort IV (N = 14)		Cohort V (N = 12)		Total (N = 26)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Proportion of subjects with ≥1 $\log_{10}$ drop from baseline in HIV RNA or HIV RNA <400 copies/mL*	13 of 14	92.9 (66.1, 99.8)	8 of 10	80 (44.4, 97.5)	21 of 24	87.5 (67.6, 97.3)
Proportion of subjects with HIV RNA <50 copies/mL*	7 of 13	53.8 (25.1, 80.8)	3 of 9	33.3 (7.5, 70.1)	10 of 22	45.5 (24.4, 67.8)
Proportion of subjects with HIV RNA <400 copies/mL*	10 of 14	71.4 (41.9, 91.6)	6 of 10	60 (26.2, 87.8)	16 of 24	66.7 (44.7, 84.4)
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Change from baseline in plasma HIV RNA ($\log_{10}$ copies/mL)**	−2.8	(−3.8, −1.7)	−2.9	(−4.3, −1.4)	−2.8	(−3.6, −2)
Change from baseline in CD4 cell count (cells/mm^3)**	278.8	(−185.6, 743.2)	876.0	(362.7, 1389.3)	527.6	(185.2, 870)
Change from baseline in CD4 percent**	6.4	(1.4, 11.3)	8.7	(2.7, 14.8)	7.3	(3.8, 10.9)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; N, number of subjects in each cohort.
*For binary endpoints: n/N with % (95% CI) was reported for each cohort, where n/N = number of responders/number of subjects.
**For continuous endpoints: mean change with (95% CI) was reported. Normal distributions were assumed for continuous endpoints.
Observed Failure Approach for handling missing data:
-For binary endpoints, missing values were considered as failures for subjects missing data due to discontinuation of study treatment for lack of efficacy or for nontreatment-related reasons with last available HIV RNA value <1 $\log_{10}$ drop from baseline and ≥400 copies/mL; otherwise, subjects with missing values were excluded.
-For continuous endpoints (eg, change from baseline in CD4 cell counts and percentage), baseline values were carried forward for subjects missing data due to discontinuation of study treatment for lack of efficacy or for nontreatment-related reasons with last available HIV RNA value <1 $\log_{10}$ drop from baseline and ≥400 copies/mL; otherwise, subjects with missing values were excluded.

A raltegravir signature mutation was documented in 1 subject with virologic failure. Virologic failure was often not associated with raltegravir signature mutations, suggesting nonadherence as a potential cause of failure. Although limited data are available, results of genotypic resistance testing in Cohorts IV and V appear generally consistent with prior experience in adults and older children.

Similar to the taste evaluation seen with the chewable tablet, where 73% reported no issues with the chewable tablets, taste did not seem to be an issue with these infants and young children as per the parent's evaluations. Few infants had infrequent gagging with most families reporting no problems with the children taking this novel formulation.

CONCLUSIONS

These results demonstrate that raltegravir, available as an oral granule formulation is safe, well tolerated, and has favorable immunologic and virologic outcomes in HIV-1-infected ARV-experienced children ages 4 weeks to <2 years of age.

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Members of the P1066 Protocol Team include: Sharon Nachman, MD, SUNY at Stony Brook, Stony Brook, NY; Nan Zheng MA, Terence Fenton Ed D, and Carmelito Alvero, MS, Statistical and Data Analysis Center, Harvard School Public Health, Boston, MA; Edward Acosta, Pharm D, University of Alabama at Birmingham, Birmingham, AL; Hedy Teppler, MD, Brenda Homony MS, Xia Xu, PhD, Larissa Wenning, PhD, Matthew Rizk, PhD, Merck & Co., West Point, PA; Bobbie Graham, BS, Frontier Science and Technology Research Foundation, Amherst, NY; Stephen A Spector, MD, University of California, San Diego and Rady Children's Hospital San Diego, La Jolla, CA; Lisa M. Frenkel, MD, University of Washington Children's Hospital, Seattle, WA; Carol Worrell, MD, Pediatric Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Development, Bethesda, MD; Ed Handelsman, MD, Paul Sato MD, Division of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD; Andrew Wiznia, MD, Jacobi Medical Center, Bronx, NY; and the IMPAACT P1066 Study Team.

Participating sites and site personnel include: 3801 Texas Children's Hospital CRS (Michelle DelRey, RN; Chivon McMullen-Jackson, RN, BSN, CCRP; Mary E. Paul, MD); 4601 University of California San Diego Maternal, Child, and Adolescent HIV CRS (Rolando M. Viani, MD, MTP; Anita, Darcey, RN; Kimberly Norris, RN, BSN); 5013 Jacobi Medical Center Bronx NICHD CRS (Marlene Burey, PNP; Jacob Abadi, MD; Michael Rosenberg, MD); 5051 University of Florida College of Medicine, Jacksonville NICHD CRS

(Mobeen Rathore, MD; Ayesha Mirza, MD; Tabetha Gayton, MS, RN, FNP; The UF CTSI is supported in part by the NIH/NCRR Clinical and Translational Science Award UL1 RR029890); 5055 South Florida CDC Ft Lauderdale NICHD CRS (Zulma Eysallenne, RN; F. Sholar Howard, ARNP; Kathleen Graham, Pharm D); 5073 SOM Federal University Minas Gerais Brazil NICHD CRS (Jorge Pinto, MD; Flavia Ferreira, MD; Fabiana Kakehasi, MD); 5075 Instituto de Infectologia Emílio Ribas Sao Paulo Brazil NICHD CRS (Marinella Della Negra, MD, PhD; Wladimir Queiroz, MD, MSc; Yu Ching Lian, MD, MSc; 5082 Hospital General de Agudos Buenos Aires Argentina NICHD CRS (Marcelo H. Losso, MD; Erica Stankievich, MD; Irene Foradori, MD); 8051 Shandukani Research CRS (Harry Moultrie, MD MSc; Angela Oosthuizen, BPharm; Gurpreet Kindra, MD PhD); 8052 Soweto IMPAACT CRS (Sylvia Dittmer, MBBCH, DCH; Hilda Ntatule Ndiweni, BC, Ed ET Admin; Amisha Patel, BPharm); 12701 Gaborone Prevention/ Treatment Trials CRS (Gaerolwe Masheto, MD; Anthony Ogwu, MD, MPH; Tebogo Kakhu, BS, RN); 20201 Durban Pediatric HIV CRS (Raziya Bobat, MD, Archary M. MD, Naidoo P. MD).

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