DOLUTEGRAVIR PHARMACOKINETICS, SAFETY AND EFFICACY IN HIV+ CHILDREN 2 TO <6 YEARS OLD

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Background

- New drugs are needed to treat HIV-1 infected children globally
- Dolutegravir (DTG; S/GSK1349572) is a first-line agent for HIV-1 infected adults due to its potency, high barrier to resistance, and tolerability
- IMPAACT P1093 (NCT01302847) is an ongoing phase 1/2 open-label pharmacokinetic (PK) and dose finding study of DTG in age-defined pediatric cohorts (4 wks to <18 yrs old).
- Results from the cohorts of 12 to <18[1]and to <12[2] year olds have lead to FDA-approved dosing for children of weight ≥ 30 kg.
- Here we present the week 4 results used for dose determination among children aged 2 to <6 years

Methods

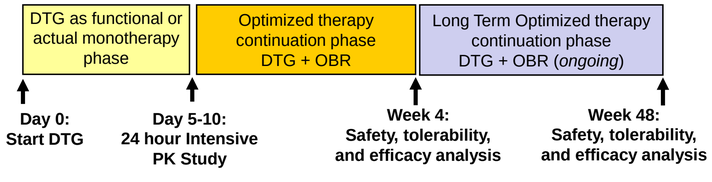
Study Participants

- HIV-1 infected children aged ≥2 and <6 years
- ART experienced but Integrase Strand Transfer Inhibitor Naïve
- Plasma HIV-1 RNA >1,000 copies/mL
- On failing regimen for ≥12 weeks or off ART treatment for ≥ 4 weeks
- Not taking other agent with known interactions with DTG metabolism
- Genotype and history suggest at least one fully active drug for optimized background regimen (OBR)

Design

- Intensive PK performed on cohort of 10 Participants used to establish dose
- DTG granules-in-suspension was tested at dose of ~0.8 mg/kg once daily, based on data from the older cohorts in P1093
- PK targets were geometric means of AUC_{24h} between of 37-67 mg*hour/L (primary) and C_{24h} between 0.77-2.26 mg/L (secondary), based on adult data.

Intensive PK Studies



DTG Granule Dosing Table

Weight Band (kg)	Dose (mg)	Granule Suspension (ml)	Dose (mg/kg) for edges of weight range	
			Lower Weight	Upper Weight
<8	4.8	3	>0.60	0.60
8 - <15	8.0	5	1.0	0.53
15 - <20	16.0	10	1.07	0.80
20 - <30	22.4	14	1.12	0.75
≥30	32.0	20	1.07	<1.07

Results:

Participant Characteristics (n=10*)

Characteristic	Median (IQR)
Age (years)	4.3 (3.6, 4.6)
Weight (kg)	15.5 (13.8, 15.9)
CD4 Cell Count (cells/mm3)	1,323 (763, 2441)
CD4 Percent	28 (22.0, 31.4)
Plasma HIV RNA (log_{10} c/mL)	4.8 (4.7, 5.3)

* One participant had to be replaced due to specimen transport errors, so 11 were ultimately enrolled to yield these 10 evaluable participants. Study sites: Brazil (n=3) United States (n=3), South Africa (n=3), Thailand (n=1).

Participant Dosing

Participant	Age (yr)	Sex	Weight (kg)	Dose (mg)	Dose (mg/kg)
1	2.1	F	10.5	8	0.76
2	3.5	M	12.2	8	0.66
3	3.6	F	13.8	8	0.58
4	4.2	M	13.7	8	0.58
5	4.2	M	17.0	16	0.94
6	4.4	F	15.2	16	1.05
7	4.99	F	15.5	16	1.03
8	4.6	M	16.1	16	0.99
9	5.0	F	15.1	16	1.06
10	5.7	M	16.0	16	1.00

Virologic Outcomes (HIV RNA copies/ml)

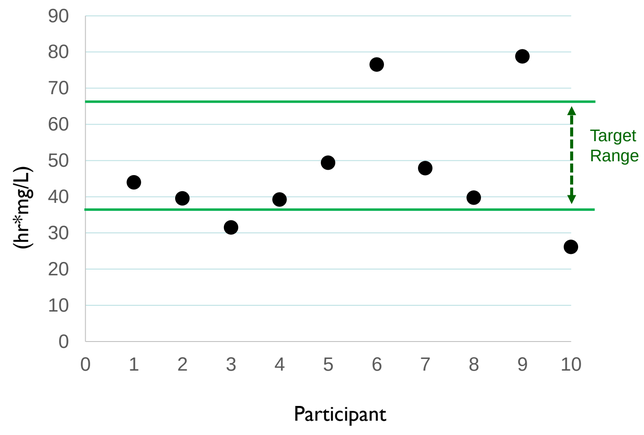
Participant	OBR	Baseline	Week 4
1	TDF, 3TC, LPV/r	185,000	100
2	AZT, 3TC, EFV	49,391	41
3	AZT, 3TC	94,224	39
4	TDF, FTC	50,466	39
5	ZDV, 3TC	50,517	39
6	TDF, FTC	5,683	39
7	ABC, 3TC, DRV, RTV	4,381	39
8	TDF, DRV, RTV	1,000,000	621
9	3TC, DRV, RTV	187,000	230
10	AZT, 3TC	2,270,000	1,665

PK Outcomes*

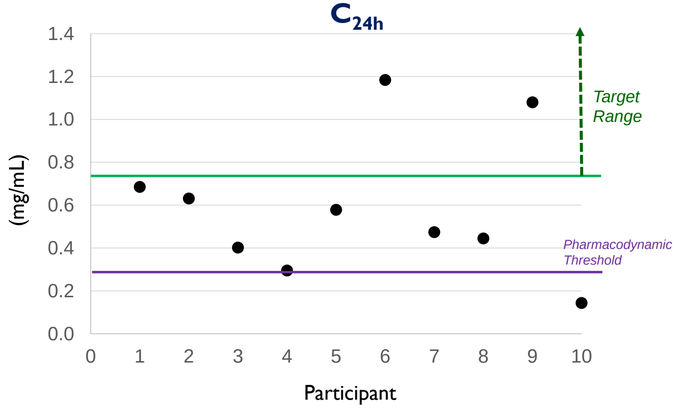
AUC_{24h} : 44.7 (36%) mg*h/L (√)
C_{24h} : 0.51 (68%) mg/L (↓)

Geometric means (CV%)

AUC_{24h}



C_{24h}



Safety and tolerability at 4 weeks

- No Grade 3 or Grade 4 adverse events attributed to study drug
- No discontinuations due to adverse events

Conclusions

- DTG granules-in-suspension administered at ~0.8 mg/kg once daily in this cohort of children ≥2 to <6 years old achieved the target AUC24h;
- C24h was below the target but above the pharmacodynamic threshold reported in adults of EC90 = ~0.3mg/mL.
- DTG was virologically potent and well tolerated through week 4.
- These novel data will form the basis for dosing of DTG as dispersible tablets to be studied in this and younger age cohorts.

References

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2) Wiznia A, Alvero C, Fenton T, George K, Townley E, Hazra R, Graham B, Buchanan A; Vavro C, Viani. R IMPAACT 1093: Dolutegravir in 6- to 12-Year-Old HIV-Infected Children: 48-Week Results, Conference on Retroviruses and Opportunistic Infections (CROI), 2016 (Boston, MA), Abstract #816.

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