BACKGROUND and METHODS

IMPACT P1093 is an ongoing phase III, multicenter, open-label pharmacokinetics (PK), safety, dose-finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in 5 age-defined cohorts. Cohort I (≥12–19 years), Cohort IA (6–12 years), Cohort IB (≥6–12 years), Cohort III (≥2–6 years), Cohort IV (≥6–18 years), and Cohort V (≥4 weeks <18 years). All participants were treated with FTC/TDF as part of their background regimen. The primary endpoint was virologic suppression (<0.5 log10 copies/mL) through week 48. Secondary endpoints were the achievement of virologic suppression in all age groups, safety, and tolerability.

RESULTS

Emergence of resistance in HIV-1 Integrase following dolutegravir (DTG) treatment in 6 to <18 year olds was evaluated in the P1093 study.

Subject 1, a 12 year old adolescent was enrolled to Cohort IA with extensive prior ART. This participant received DTG with an OBR of EFV/FTC/TDF. Adequate DTG exposure was observed through Week 24. Virologic failure was reported at Week 12 after reports of non-compliance. The clonal analysis showed IN substitutions, A49G and M50I, were observed at Week 16, and remained at 46% for Week 24. This participant completed the study at Week 52.

Subject 2, a 16 year old adolescent enrolled to Cohort I with 14 years of prior ART. This participant received DTG with an OBR of FTC/TDF. Adequate DTG exposure was observed through Week 24. Virologic failure was reported at Week 12 after reports of non-compliance, but remained on study through Week 192 with continued viremia and reports of non-compliance. (Vavro, 2021). Additional table and figures.

Subject 3, a 7 year old enrolled to Cohort IB received granule formulation of DTG with an OBR of 3TC/FTC. Adequate DTG exposure was observed through Week 24. At Week 24 the participant switched to DTG tablet dosing due to oral refusal. The patient met virologic failure at Week 48 after continued non-compliance.

PHYLGENETIC ANALYSIS SUMMARY

- A common ancestor for each of the clonal clusters/subset is displayed by colored circles.
- More diversity at Baseline versus virologic failure was consistent with under drug pressure. The clonal analysis showed IN substitutions, A49G and M50I, were observed at Week 136 and Week 160 but their specific impact on DTG is not well understood.
- The impact of the rarely occurring G118R on both DTG FC and decreased integrase RC was modulated by forming strong hydrogen bonds with E92 but allows space for substrate binding resulting in reduced IN RC.
- The clonal analysis showed IN substitutions, A49G and M50I, were observed at Week 136 and Week 160 but their specific impact on DTG is not well understood.
- Additional IN substitutions were observed, such as L74I, G118R, and R263K, which were not observed at Baseline.
- The clonal analysis showed IN substitutions, A49G and M50I, were observed at Week 136 and Week 160 but their specific impact on DTG is not well understood.

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REFERENCES