FINDINGS from:

IMPAACT 2019 - Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Pat Flynn, MD
IMPAACT Annual Meeting, June 2022

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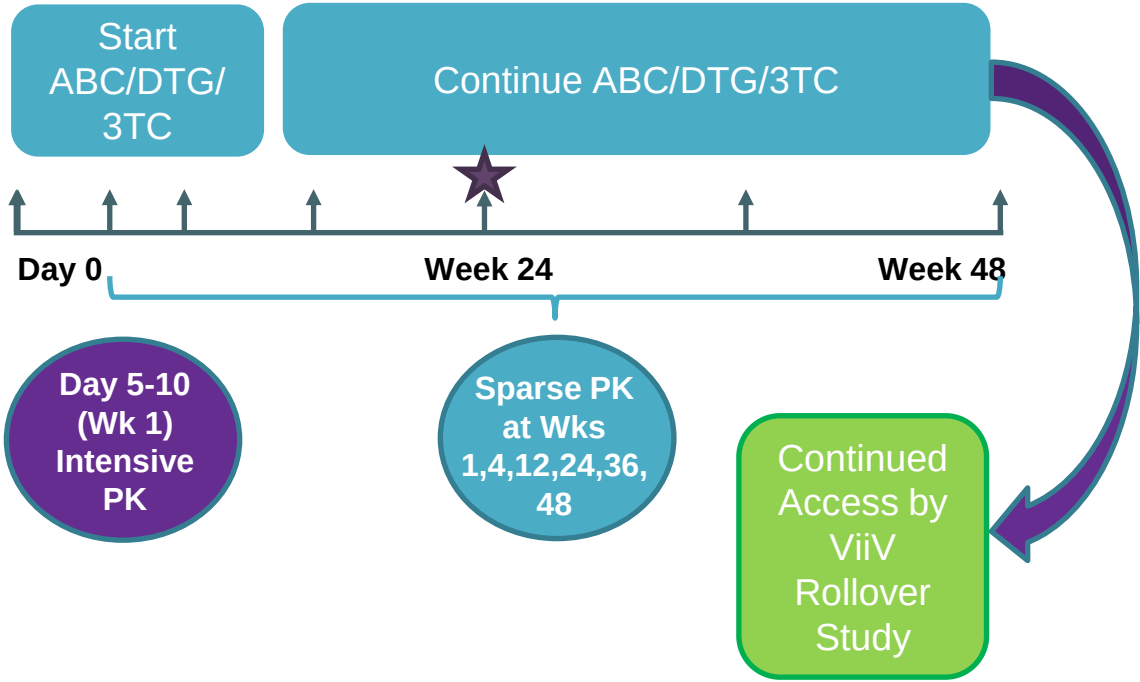
IMPAACT 2019 - Phase I/II, Multi-site, Open-label, Non-comparative Dose Confirmation Study

- Primary Objectives:
  - Confirm proposed dosing of ABC/DTG/3TC dispersible tablets and immediate release tablets using intensive PKs
  - Evaluate safety over 24 weeks of administration
- Ultimate goal of licensure for children ≥ 6 kg
- Dosing recommendations for IMPAACT 2019 based on DTG PK (P1093, Odyssey) and established dosing recommendations for ABC and 3TC



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Study Overview

- Study sites in Botswana, South Africa, Thailand and the United States

Key Eligibility Criteria:

- Children <12 years of age
- Treatment-naïve **or**
- Treatment-experienced with HIV VL <200 copies/mL on a stable non-NNRTI-containing ARV regimen for ≥6 months
- At least 50 participants, 25 < 6 years and 25 ≥ 6 years to < than 12 years of age

WB1 (6 to <10 kg)	ABC 180mg/DTG 15mg/3TC 90mg •3 DT dispersed in 15 mL water
WB2 (10 to <14kg)	ABC 240mg/DTG 20mg/3TC 120mg •4 DT dispersed in 20 mL water
WB3 (14 to <20 kg)	ABC 300mg/DTG 25mg/3TC 150mg •5 DT dispersed in 20 mL water
WB4 (20 to <25kg)	ABC 360mg/DTG 30mg/3TC 180mg •6 DT dispersed in 20 mL water
WB5 (≥25 kg)	ABC 600mg/DTG 50mg/3TC 300mg •1 IR tablet swallowed whole

DT: dispersible tablets; IR: immediate-release tablet; NNRTI: non-nucleoside reverse transcriptase inhibitor; VL: viral load; WB: weight band.

Dose Confirmation Approach

Both PK and safety criteria had to be met for dose confirmation within each weight band

Drug	PK Parameter	Individual Target	Weight Band Target[a]
DTG	$AUC_{0\text{-}24h}$ (µg·h/mL)	25.0-134	35.1-134
	C_{24h} (µg/mL)	≥0.5	0.67-2.97
ABC	$AUC_{0\text{-}24h}$ (µg·h/mL)	--	6.3-50.4
3TC	$AUC_{0\text{-}24h}$ (µg·h/mL)	--	6.3-26.5

[a]Geometric mean contained within each target range

Entry
(Day 0)

Directly Observed Therapy
(≥4 days)

- Confirmed dosing ≥4 days prior to intensive PK
- In-person, real-time video or timestamp video

Intensive PK Assessment
(Days 5-10)

- Weight band assessment of DTG, ABC, and 3TC (n=5-7)

Safety Assessment
(Week 4)

Acceptable safety criteria:

- No deaths/life-threatening adverse events (AEs) related to study drug, and
- Drug-related grade 3+ AEs or drug-related permanent d/c in <2 participants

Continue Study Medication through Wk 48

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Key Milestones

- IMPAACT approval for protocol development – September 2017
- First participant enrolled – September 2020
- Study Monitoring Committee (SMC) Review of weight band (WB) 5 – February 2021
- SMC Review of WBs 3 and 4 – March 2021
- SMC Review of WB 2 – July 2021
- SMC Review of WB 1 – September 2021
- Last participant enrolled - June 2021
- Last participant, last visit – May 2022

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Accrual by Weight Band, Age and Country

Weight Band	Intensive PK	Sparse PK	ART-Naïve?
WB1 (6 to <10 kg)	7*	1	3
WB2 (10 to <14kg)	7*	4	0
WB3 (14 to <20 kg)	7	8	0
WB4 (20 to <25kg)	7	3	0
WB5 (≥25 kg)	7*	4	0
Available Data	35	20	3

Country

- Total enrollment – 57
- US – 10†
- Thailand - 17
- Botswana - 13
- South Africa - 17

Age

- Less than 6 years – 28
- 6 years and older - 29

*One participant in WB 1 and one participant in WB2 withdrew within one week of enrollment due to palatability issues; one participant relocated and was off study drug prior to week 24 but after intensive PK studies

† US sites enrolled 2 participants in WB2, 2 in WB 3, 1 in WB4 and 5 in WB 5

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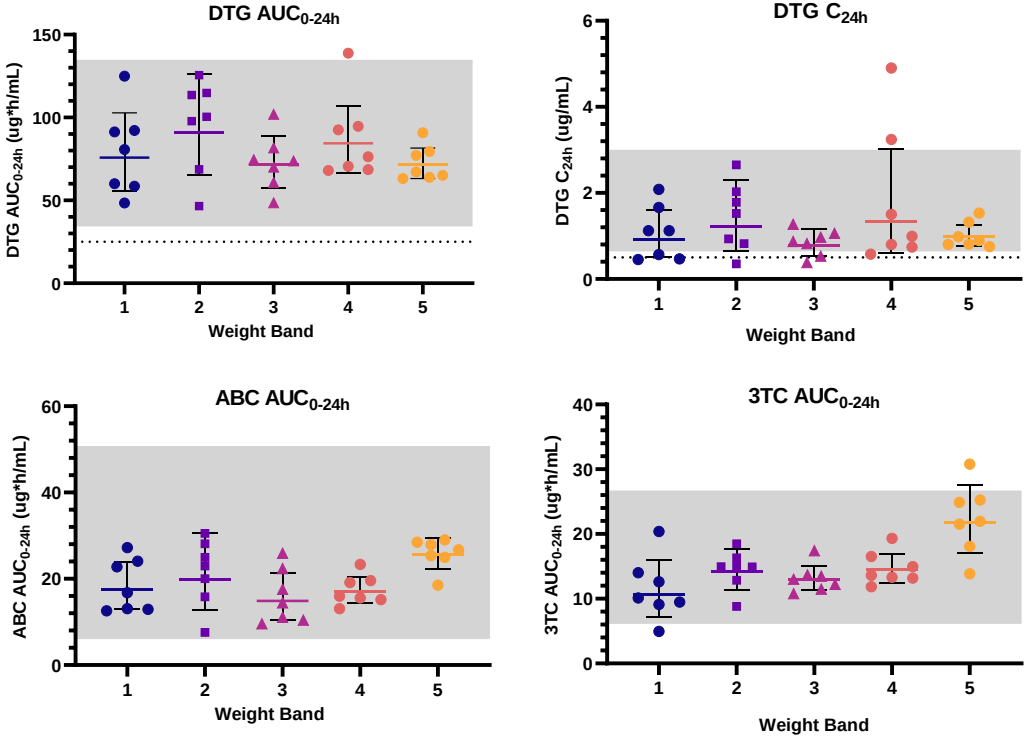
Analysis

- ***Dose Confirmation Population*** – first 5-7 participants in each weight band who underwent intensive PK studies, day 5-10, and exclusively received study drug through week 4 or experienced a study drug-related grade 3 or higher AE or any AE resulting in study drug discontinuation
  - N= 35
  - **PK analysis**
- ***All Treated Population*** – participants who received at least one dose of the study drug
  - N=57
  - **Acceptability, adherence, palatability**
- ***Primary Safety Population*** – participants who received study drug at the final confirmed dose through week 24, including those that had WB adjustments due to growth or who discontinued treatment due to toxicity
  - N=54
  - 2 participants withdrew within one week of enrollment due to palatability issues
  - 1 participant relocated and was off study drug prior to week 24 but after intensive PK studies
  - **Safety and virologic efficacy**

Dose Confirmation Population - PK Targets Met in All Weight Bands



Data presented as geometric mean (95% CI).
Dotted lines (•••) indicate individual DTG minimum target. Gray shading (▒) indicates WB target ranges.

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Safety in *Dose Confirmation Population*

- Safety criteria met at Wk 4 (no deaths/life-threatening AEs related to study drug nor ≥ 2 Grade 3+ AEs related to study drug or resulting in permanent d/c) –

- **DOSING CONFIRMED IN ALL WEIGHT BANDS**

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Safety

- *Primary Safety Population* participants (n=54) over **24** weeks of study

	Weight Band					
	1 (N=8)	2 (N=11)	3 (N=15)	4 (N=10)	5 (N=10)	Total (N=54)
Any Grade 3+ event	2	2	4	0	0	8
Any Grade 3+ drug-related AE	0	0	0	0	0	0
Any serious drug-related AE	0	0	0	0	0	0
Any life-threatening drug-related AE	0	0	0	0	0	0
Any drug-related AE causing death	0	0	0	0	0	0
Any drug-related AE causing permanent treatment discontinuation	0	0	0	0	0	0

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Safety – Preliminary Data after Week 24

- All participants, 24 - 48 weeks of study
  - Study drug was held, and then permanently discontinued, in one participant after hepatic dysfunction was identified at the Week 36 visit. Participant remained on study and has had a complete recovery
  - Participant with Grade 3 drug-related increase in creatinine and eGFR, ABC/DTG/3TC continued

Safety – *Primary Safety Population*

Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m² OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m² OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m² OR ≥ 50% decrease from participant's baseline or dialysis needed

- DAIDS criteria based on actual value or change from baseline value

Creatinine

	Grade by Absolute Value					
Reported Grade	Normal	1	2	3	4	Total
Normal	30	0	0	0	0	30
1	0	3	0	0	0	3
2	15	3	1	0	0	19
3	3	0	0	0	0	3
4	1	0	0	0	0	1
Total	49	6	1	0	0	56

eGFR

	Grade by Absolute Value					
Reported Grade	Normal	1	2	3	4	Total
Normal	17	0	0	0	0	17
1	0	0	0	0	0	0
2	22	0	10	0	0	32
3	4	0	2	0	0	6
4	1	0	0	0	0	1
Total	44	0	12	0	0	56

Virology

- 51 of 51 (100%) ART – experienced participants in the *Primary Safety Population* maintained viral suppression (< 200 copies/mL) through Wk 24
- Of the 3 ARV-naïve participants, 2 of 3 (67%) were virologically suppressed (< 200 copies/mL) at Wk 24
  - 2 achieved viral suppression at Wk 12 and Wk 24, respectively
  - 1 participant had a viral load of > 3 million/mL at entry
    - 2,246 copies/mL at Wk 12
    - 419 copies/mL at Wk 24 with confirmation value of 358 copies/mL.
    - Participant remained on study drug and was suppressed at Wks 36 and 48

Tolerability

- *All Treated Population* (n=57) through Wk 24
- Preparation - > 90% acceptable of dispersible tablets (volume of water, number of tablets)
- Adherence – On average, < 1 % of doses missed (caregiver report)
- Palatability – 89% children's facial expressions very good, good or average
- Well tolerated; only 2 participants withdrew from the study for palatability reasons
  - One in weight band 1, switched from lopinavir/r- based ART
  - One in weight band 2, switched from raltegravir – based ART

Conclusions

- PK targets were met in all weight bands for ABC/DTG/3TC *Dispersible* and *Immediate Release Tablets* in children living with HIV less than 12 years of age
- Safety and tolerability of administration were demonstrated

ViiV Healthcare announces US FDA approval of Triumeq PD, the first dispersible single tablet regimen containing dolutegravir, a once-daily treatment for children living with HIV

March 30, 2022 – NOTE: Data from IMPAACT 2019 was not included as part of the submission

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Acknowledgments

IMPAACT 2019 Protocol Team

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Study Sites

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St. Jude Children's Research Hospital CRS, Memphis, TN, USA (6501)
Wits RHI Shanukani Research Center CRS, Johannesburg, South Africa (8051)
Soweto IMPAACT CRS, Johannesburg, South Africa (8052)
FAM_CRU CRS, Tygerburg Hospital, Tygerburg, South Africa (8950)
Gaborone CRS, Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana (12701)
Molepolole CRS, Botswana Harvard AIDS Institute Partnership, Molepolole, Botswana (12702)
Umlazi CRS, Prince Mshiyeni Memorial Hospital, Umlazi, South Africa (30300)
CMU HIV Treatment CRS, Chiang Mai University, Chiang Mai, Thailand (31784)

Study Participants & Caregivers!

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