ODYSSEY: Design, Current Status, and Baseline Characteristics

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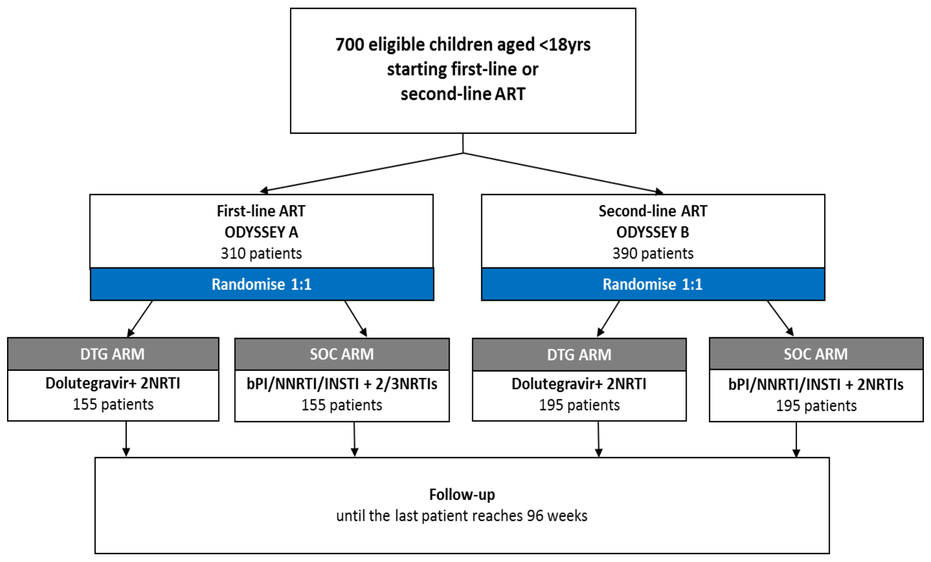
Background

- **Dolutegravir** (DTG)-based antiretroviral therapy (ART) is **highly effective and well-tolerated in adults**
- A number of sub-Saharan African countries are initiating DTG procurement, with **Clinton Health Access Initiative predicting a 59% market share by 2021**
- **DTG needs evaluating in first-line and second-line ART regimens in children.**

ODYSSEY Design

ODYSSEY (Once-daily DTG based ART in Young People vs. Standard Therapy) is a open-label, randomised, non-inferiority, basket trial evaluating the efficacy and safety of DTG plus 2 nucleos(t)ides (NRTIs) vs. standard of care (SOC) in HIV-infected children <18 years starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B) [NCT02259127]

Figure 1. ODYSSEY Trial Schema



Study hypothesis: DTG + 2 NRTIs is non-inferior to SOC (NNRTI or bPI + 2 or 3 NRTIs) in terms of efficacy and superior in terms of toxicity profile.

The **primary endpoint** is the difference in proportion with **clinical or virological failure by 96 weeks**, estimated using time to first occurrence of any of the following components:

i. Insufficient virological response defined as <1 log10 drop at week 24 and switch to second/third-line for treatment failure
ii. Viral load (VL)≥400 c/ml at or after 36 weeks confirmed by next visit
iii. Death due to any cause
iv. Any new or recurrent WHO 4 or severe WHO 3 event

700 children will provide 90% power to exclude a difference of >10% between arms; enrolling **310 children in ODYSSEY A (first-line)** and **390 in ODYSSEY B (second-line)** will provide 80% power to exclude a difference >12% between arms in both subgroups.

Secondary endpoints include

- proportion with **clinical or virological failure by 48 weeks**
- time to **WHO 4 or severe WHO 3 event**
- proportion with **VL<50c/mL** and **VL<400c/mL at 48** and **96 weeks**
- rate of **clinical events**
- change in **CD4** and **CD4/CD8 ratio**
- proportion developing **resistance**
- change in **total cholesterol, triglycerides** and **lipid fractions**
- incidence of **SAEs**, **grade 3 and 4 events** and **ART modifying events**
- **quality of life, adherence** and **acceptability**.

Protocol version 2.0 & 3.0 recruited children weighing ≥ 14kg using EMA approved doses.

Protocol version 4.0 (*current*) allows **recruitment of 60 additional children weighing ≥3kg to <14kg and aged ≥28days** using 5mg dispersible DTG tablets (with associated PK sub-studies); randomisation of children <14kg will be stratified by weight-band (3-<6, 6-<10, 10-<14kg) in addition to ODYSSEY A/B and will not delay the end of follow-up for the main trial.

Sub-studies include: **i) nested pharmacokinetic (PK) sub-studies** evaluating pragmatic dosing aligned with WHO weight-bands; results informed DTG dosing within the main cohort (*Poster#22; Oral #3*); **ii) a TB-PK sub-study**; **iii) an immunology/virology sub-study**; **iv) a qualitative sub-study** investigating how to support children on second-line treatment (*Poster #117*); and **v) a Youth Trial Board project** which aims to involve adolescent participant representatives in paediatric clinical trials.

Enrolment to 22nd of June 2018

Figure 2. Enrolment over time by A/B strata

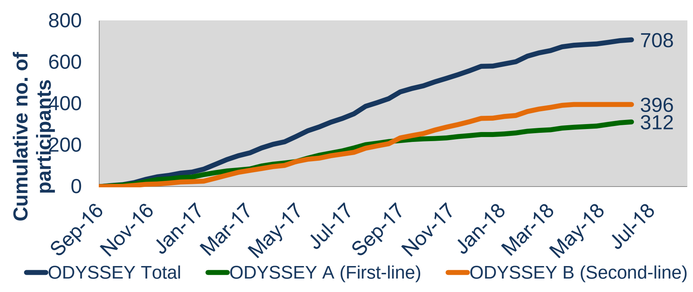
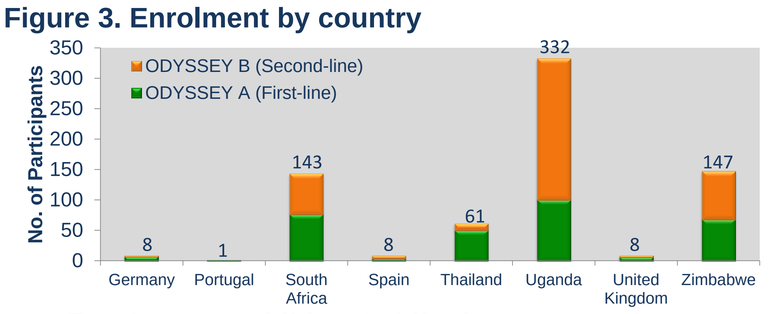


Figure 3. Enrolment by country



- **Enrolment to children ≥ 14kg is now complete**

Baseline Characteristics

Table 1. Baseline Demographics

		A (First-line)		B (Second-line)		Total	
Participants		312		396		708	
Sex, males		148	(47%)	215	(54%)	363	(51%)
Age, years		11.8	[9.1, 14.9]	12.6	[9.3, 14.6]	12.2	[9.1, 14.9]
Vertical Transmission		239	(77%)	365	(92%)	604	(86%)
CD4 (cells/ mm3)	<100	54	(18%)	54	(14%)	108	(15%)
	100-<200	19	(6%)	29	(7%)	48	(7%)
	200-<350	44	(14%)	57	(14%)	101	(14%)
	350-<1000	156	(51%)	201	(51%)	357	(51%)
	≥1000	33	(11%)	55	(14%)	88	(13%)
Log10 Viral load (copies/mL)		4.6	[3.9, 5.2]	4.3	[3.8, 4.8]	4.4	[3.9, 5.0]
WHO stage	I	121	(40%)	142	(37%)	263	(38%)
	II	112	(37%)	135	(34%)	247	(35%)
	III	47	(16%)	81	(21%)	128	(18%)
	IV	23	(8%)	37	(9%)	60	(9%)

Figures are N(%) or median [IQR]. Percentages are of non-missing data.

Table 2. Prior ART exposure in ODYSSEY B

		B (Second-line)	
Participants		396	
ART Class Exposure	NRTI/NNRTI	382	(96%)
	NRTI/NNRTI/PIs	4	(1%)
	NRTI/PI	10	(3%)
Cumulative ART exposure – all classes (years)		5.5	[0.1-15.4]

Figures are N(%) or median [IQR]. Percentages are of non-missing data.

- **42% of children were ≥35kg at enrolment**
- **Majority of children** (86%) were **vertically infected**
- ODYSSEY B participants (second-line) had median 5.5 years prior exposure to ART, **almost all (96%) NNRTI-based ART**

Figure 4. Age at Enrolment by A/B

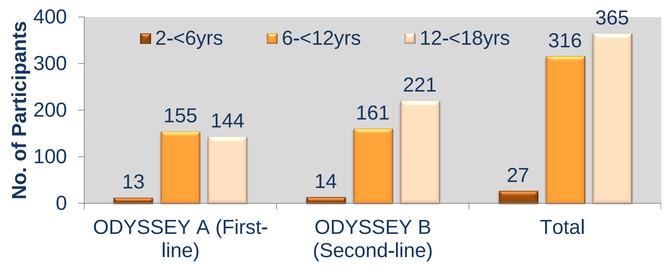


Figure 5. Weight at Enrolment by A/B

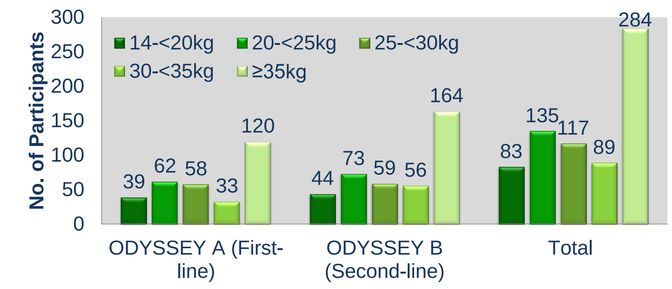
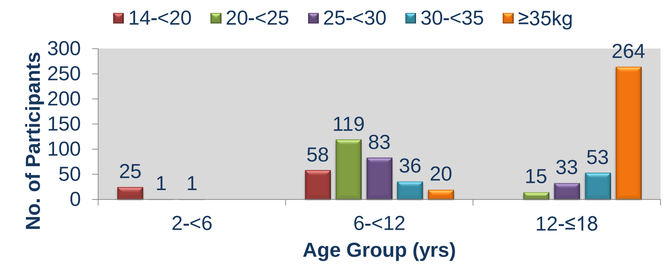


Figure 6. Weight by Age at Enrolment



Choice of Treatments

- Planned **SOC regimen + NRTIs are selected by the clinician prior to randomisation**
- **≥ 1 NRTI with presumed preserved activity** based on treatment history/any available resistance test(s) should be selected
- **Randomisation is stratified** by pre-specified NRTI backbone and SOC regimen; subgroup analyses by NRTI backbone are planned
- SOC is primarily **EFV-based ART for ART-naïve children and LPV/r -based ART for children switching to second-line with ABC+3TC or TDF+FTC/3TC**

Table 3. ART regimens at entry in SOC

	A (First-line)		B (Second-line)	
Participants	157		200	
ABC 3TC EFV	**113**	**(72%)**	3	(2%)
TDF 3TC/FTC EFV	**31**	**(20%)**	0	(0%)
ABC 3TC LPV/r	3	(2%)	**90**	**(45%)**
ZDV 3TC LPV/r	0	(0%)	**32**	**(16%)**
TDF FTC/3TC LPV/r	0	(0%)	20	(10%)
TDF 3TC ATV/r	0	(0%)	**30**	**(15%)**
ABC 3TC ATV/r	0	(0%)	16	(8%)
Other	10	(6%)	9	(5%)

Follow-up

Table 4. Follow-up to 22nd June 2018

	A (First-line)	B (Second-line)	Total
Participants	312	396	708
Median weeks from randomisation to most recent clinic visit [IQR]	48 [24-60]	36 [24-52]	37 [24-60]
Died	2 (0.6%)	1 (0.3%)	3 (0.4%)
Potentially or Confirmed LTFU**	4 (1.3%)	1 (0.3%)	5 (0.7%)

**Defined as either withdrawn consent or not seen for > 24 weeks (two consecutive study visits)

Pregnancy

- Adolescent **girls who are pregnant or planning pregnancy** within 2 years **are excluded** from ODYSSEY
- Pre-enrolment and **regular pregnancy testing** during follow-up is **done**
- In May 2018, FDA+WHO announced a **potential risk of neural tube defect** in children born to women exposed to DTG at conception and in early pregnancy
- In response, **ODYSSEY has:**
  1) **informed young people and their families**
  2) **strengthened contraceptive advice and availability and expanded our collection of information on contraceptive use**
  3) **involved the Youth Trial Board project with development of messaging around risk**
- **To date 6 pregnancies have occurred in ODYSSEY- no congenital abnormalities have been detected**

Conclusions

- **ODYSSEY has completed recruitment of children ≥ 14kg ahead of target, with excellent retention and follow-up so far.**
- **By employing a basket design (to include ART-naïve children and children starting second-line ART) and nested PK sub-studies, the ODYSSEY trial is efficiently evaluating multiple scientific questions regarding dosing and effectiveness of DTG-based ART in HIV-infected children.**