DolPHIN-2 Study : Review of Safety of Dolutegravir in Pregnancy

Preliminary data from Botswana have reported an incidence of 4 neural tube defects (NTDs) amongst infants born to 426 women who received dolutegravir (DTG) *at the time of becoming pregnant or early on in the first trimester* (up to 14w of pregnancy), giving an overall rate of 0.9% for NTDs (this compares with 0.1% NTDs observed with other anti-retrovirals). On 18th May 2018 the WHO issued the following advice:

In the interim, WHO[1] advises that countries and ministries follow the existing 2016 WHO Consolidated ARV Guidelines, and consider the following:

- *Pregnant women who are taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance.*
- *Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women should be based on drugs for which adequate efficacy and safety data are available; an efavirenz–based regimen is a safe and effective first-line regimen.*
- *If other first-line ARVs cannot be used in women of childbearing age, DTG may be considered in cases where consistent contraception can be assured.*
- *Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes*

Similar advice has been issued by the US (FDA)[2] and European (EMEA)[3] Regulatory Agencies.

The DolPHIN-1 (NCT02245022) pilot, and DolPHIN-2 (D2; NCT03249181) Study are two clinical trials sponsored by the University of Liverpool, and conducted in partnership with the University of Cape Town, the Infectious Diseases Institute (Kampala), Radboud University Medical Centre and the Liverpool School of Tropical Medicine. DolPHIN-1 and DolPHIN-2 assess DTG versus standard of care in pregnant women initiating HIV treatment in the third trimester (after 28w of pregnancy); both specifically exclude women at earlier stages of pregnancy.

The DolPHIN-2 investigators have considered this new evidence, and have undertaken a detailed review of all 55 live infants born to DolPHIN-2 (D2) participants thus far, and all live births from the 60 participants in DolPHIN-1. To date, we have observed no incidences of NTDs in mothers randomised either to efavirenz (the comparator arm) or DTG. This finding is supported by the Botswana study, which reported no NTDs in women starting DTG after the first trimester. Neural tube defects are developmental malformations that result in failure to close the neural tube during fetal development- this process is complete by 4 weeks of gestation, and any risk factors predisposing to NTD (eg folate deficiency, or drug exposure) exert their effects around the time of conception or in early pregnancy only.

The decision to undertake a clinical trial is continually reviewed in the light of emerging evidence. Late treatment initiation in DolPHIN mothers is associated with a seven-fold risk of infant HIV transmission, and a doubling of infant mortality in the first year of life. The final results of the DolPHIN-1 pilot are not yet published, but have been submitted as a late breaker to the AIDS 2018 Conference, and demonstrate significantly superior virological suppression with DTG compared to standard treatment in these high risk mothers. This could potentially lead to reduced transmission of HIV to infants.

In view of the very limited incremental risk of NTDs in D2 mothers, and the potentially significant benefits for reduced infant transmissions, the DolPHIN-2 Trial Management Group, in consultation with the University of Liverpool (the Study Sponsor), the D2 Trial Steering Committee and the Independent Data & Safety Monitoring Board have taken the view that the DolPHIN-2 study should continue. However the following additional precautions will be taken:

- Revision of the Participant Information Leaflet to incorporate recent data, with all participants to be informed, counselled, and reconsented if they wish to continue.
- Ensure contraception is offered to all women post-delivery, and switch treatment for participants randomised to DTG who decline contraception (who will still be followed-up for safety evaluation)
- Check folate status or offer folate supplementation to all pregnant women
- Close monitoring of all serious adverse events and congenital malformations in D2

The DOlPHIN-2 team, and the University of Liverpool remain fully committed to the safety and wellbeing of all our study participants, and their infants.

Notes for Health Professionals:

1 The Botswana study is an observational surveillance cohort involving 8 treatment facilities covering approximately 45% of all births nationally. Safety data have previously been reported suggesting DTG was safe in pregnancy[4] although the majority of women initiated DTG in the second and third trimesters.

2 Safety data for DTG in 1200 pregnancies (mostly deriving from 6 large databases, including Botswana and the Antiviral Pregnancy Registry) have recently been reviewed[5]. The rate of adverse birth outcomes and congenital abnormalities was similar to historical control studies of HIV-positive women.

3 No clear mechanism has been implicated for this putative toxicity. No embryotoxicity was observed for DTG in any preclinical toxicology studies.

Professor S.H. Khoo MD, FRCP
DolPHIN-2 Chief Investigator

21st May 2018

on behalf of the DolPHIN-2 consortium, the DolPHIN-2 Trial Steering Committee and Independent Data & Safety Monitoring Group, and the University of Liverpool.

References

1 World Health Organisation. Potential safety issue affecting women living with HIV using dolutegravir at the time of Conception. 18th May 2018

2 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1

3 https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm

4 Zash R et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. IAS 2017. 23–26 July 2017. Paris. Oral abstract MOAX0202LB.

5 Hill, et al. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr; 4(2): 66–71.