2. STUDY SUMMARY

Study title:	**A Phase II, Multicenter, Single-Arm, Open-Label Clinical Trial to Evaluate the Safety and Efficacy of Triple Therapy with Dolutegravir plus 2 NRTIs, in Treatment-Naïve HIV-2 Infected Subjects.**
Study code:	DTG-01-01
Sponsor:	BlueClinical, Ltd. (grant from ViiV Healthcare).
Study type:	Interventional.
Phase:	Phase II (therapeutic exploratory).
Clinical indication:	Treatment of HIV-2 infection.
Coordinating Investigator:	Patrícia Pacheco, MD Hospital Professor Doutor Fernando Fonseca, E.P.E. IC 19, 2720-276 Amadora, Portugal Phone: +351 – 214 348 200; Fax: +351 – 214 345 566 patriciacorreiapacheco@gmail.com
Dates of Clinical Part:	17MAY2017 (first screening) to 02JUL2019 (last completion).
Investigational medicinal products:	**Test Product**: Dolutegravir (DTG), was provided either as Triumeq® or as Tivicay®. Dolutegravir was used in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs). The NRTIs used in combination with DTG were abacavir (ABC) plus lamivudine (3TC) or tenofovir (TDF) plus emtricitabine (FTC), which is in line with the current standard of care. The combination ABC/3TC/DTG was preferential except in case of hepatitis B co-infection, in case the subject had a positive HLA-B*5701 allele screening assessment or in cases where the treatment with Triumeq® was not indicated (e.g., in subjects with high cardiovascular risk). When the combination ABC/3TC/DTG was used, DTG was provided as single-tablet regimen (STR) – Triumeq®. When the combination ABC/3TC/DTG could not be used, combination of TDF/FTC+DTG was used instead and DTG was provided as Tivicay®.
Objectives:	***Primary:*** – To evaluate the efficacy of DTG in combination with two NRTIs in the treatment of HIV-2 treatment-naïve subjects, as measured by the proportion of subjects achieving a plasma viral load of <40 copies/mL and/or by the change from baseline in CD4 cell count and in CD4/CD8 ratio at Week 48. ***Secondary:*** – To evaluate the study treatment immunological effect, as measured by the change from baseline in CD4 cell count and the CD4/CD8 ratio at Week 48. – To evaluate the study treatment safety and tolerability, as assessed by review of the accumulated safety data.

	Exploratory: To evaluate the study treatment antiretroviral activity, as measured by the Time to Virologic Response (TVR) and the Time to Loss Of Virologic Response (TLOVR).
Methodology:	Multicenter, single-arm, open-label clinical trial to evaluate the efficacy, the safety and the tolerability of 50 mg dolutegravir once daily (q.d.) given in combination with 2 NRTIs backbone in HIV-2 positive, treatment-naïve subjects.
Number of Subjects (Planned and Analyzed):	Planned: To enroll 30 subjects. Actual: Enrolled = 30 subjects (22 women and 8 men); Safety Analysis Population = 30 subjects; Intend-to-treat population = 30 subjects; Per-protocol population = 27 subjects.
Diagnosis and Main Selection Criteria:	Inclusion criteria: 1. Able to understand and willing to comply with all the requirements of the study, as confirmed by giving voluntary written informed consent for participation. 2. Male or female gender. 3. Age ≥ 18 years on the day of signing the informed consent. 4. HIV-2 positive as determined by a positive result in the respective assay. 5. CD4 count ≤500 cells/mm^3 (in case of undetectable baseline HIV-2 viral load); and/or classified as B- or C-stage, by the HIV disease staging and classification system of Centers for Disease Control and Prevention (CDC); and/or had detectable viral load irrespective of CD4 count; and/or had other medical conditions / co-morbidities in which treatment is considered, according to European AIDS Clinical Society (EACS) and national guidelines; 6. Naïve to ART including investigational antiretroviral agents. 7. Considered clinically stable with no signs or symptoms of active infection, at the time of entry into the study (i.e., clinical status and all chronic medications should be unchanged for at least 2 weeks prior to the start of treatment in this study), in the opinion of the investigator. 8. If woman or man with reproductive potential, agreed to adopt an effective contraceptive method throughout the study. Exclusion criteria: 1. History or presence of allergy to the study drugs or their components. 2. HIV-1 infection or HIV1/HIV2 dual infection.

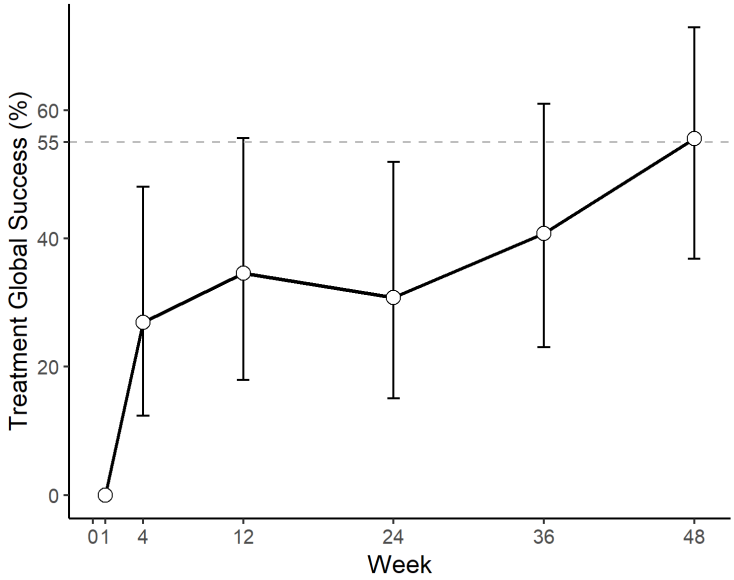
	3. History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the subject's participation for the full duration of the study, such that it is not in the best interest of the subject to participate. 4. Documented or known resistance to DTG and/or NRTIs. 5. Treatment with systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study or is anticipated to need them during the course of the study. 6. Requiring or is anticipated to require any of the prohibited medications while in the study (dofetilide, inducers of CYP3A4, including phenobarbital, phenytoin, carbamazepine and rifampicin). 7. Current (active) diagnosis of tuberculosis. 8. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin). 9. Moderate to severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification. 10. If subject eligible to receive Tivicay®: Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 11. Estimated creatinine clearance <50 mL/min at time of screening, based on Cockcroft-Gault equation. 12. Current (active) diagnosis of acute hepatitis due to any cause. 13. Under treatment for a viral infection other than HIV-2, such as hepatitis B, with an agent that might be active against HIV-2, including but not limited to 3TC, TDF or entecavir, unless the treatment with these agents occurred prior to the diagnosis of HIV. 14. Anticipated need for Hepatitis C virus (HCV) therapy with interferon and/or ribavirin during the study. 15. Positive HLA-B*5701 allele screening assessment and was also not eligible for treatment with the other acceptable NRTIs (TDF/FTC). 16. Significant suicidality risk, according to the investigator's judgment. 17. Participation in a study with an investigational compound/device within 30 days of signing informed consent or anticipates participating in such a study involving an investigational compound/device during the course of this study.

	18. If woman, she was pregnant, breastfeeding, or expecting to conceive at any time during the study. 19. If woman, she was expecting to donate eggs at any time during the study. 20. If man, expecting to donate sperm at any time during the study.
Duration of Treatment:	The estimated study duration for each subject was approximately 57 weeks and consisted of 8 visits.
Criteria for Evaluation	
Safety:	Safety/tolerability was evaluated through the assessment of adverse events, chest X-ray, vital signs and clinical laboratory tests. A chest X-ray was performed at screening visit. Adverse events were monitored throughout the study. Full physical examination was performed at screening visit, and a directed physical examination was performed at each subsequent visit until visit 8 (Post- 14-day Follow-up or Early Discontinuation visit). Safety Laboratory tests were performed at screening and at every scheduled visit from Visit 3 to Visit 8.
Statistical Methods:	The primary efficacy analysis evaluated the study treatment efficacy, as measured by the "overall treatment success", defined as the proportion of patients with "global success" at Week 48. "Global success" is a composite variable defined as a plasma HIV-2 RNA viral load <40 copies/mL and a delta of CD4 depending on the initial CD4 count (CD4 delta >+100 cells/mm^3 for initial CD4s ≤ 500 cells/mm^3; or CD4delta > +50 cells/mm^3 for initial CD4s > 500 cells/mm^3). The statistical methods for the analysis of the primary endpoint using a per-protocol set was based on the one-sample proportion test (one sided test) and its correspondent interval 95% confidence interval (CI). The overall treatment success was to be considered superior to 55% if the lower bound of the 95% CI was higher than 55%. The secondary efficacy analysis evaluated the change from baseline in CD4 cell count and CD4/CD8 ratio, based on paired-sample T-test or the non-parametric test (Wilcoxon signed-rank test or sign test). For the safety analysis, only descriptive statistics were reported. The time to event variables (TVR and TLOVR) were estimated by using Kaplan-Meier models.

Summary – Conclusions

Efficacy Results:

The overall treatment success defined as the proportion of patients with "global success" are displayed below.

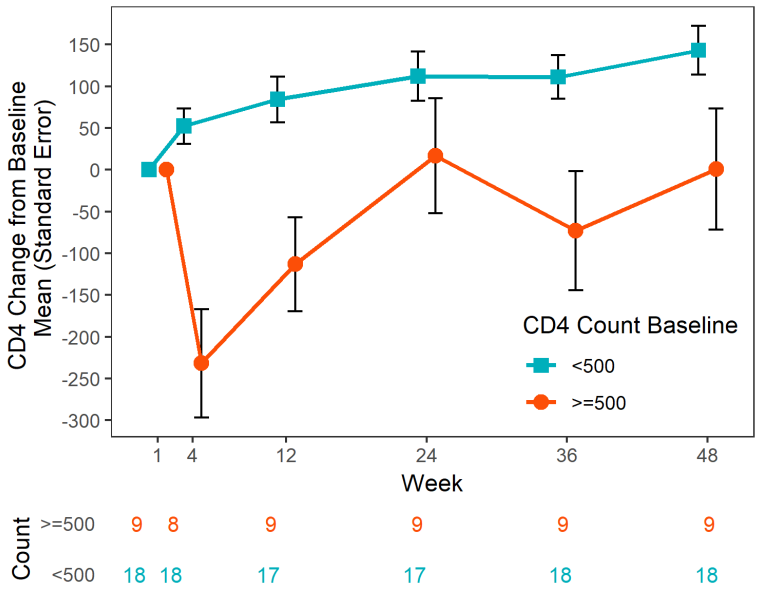


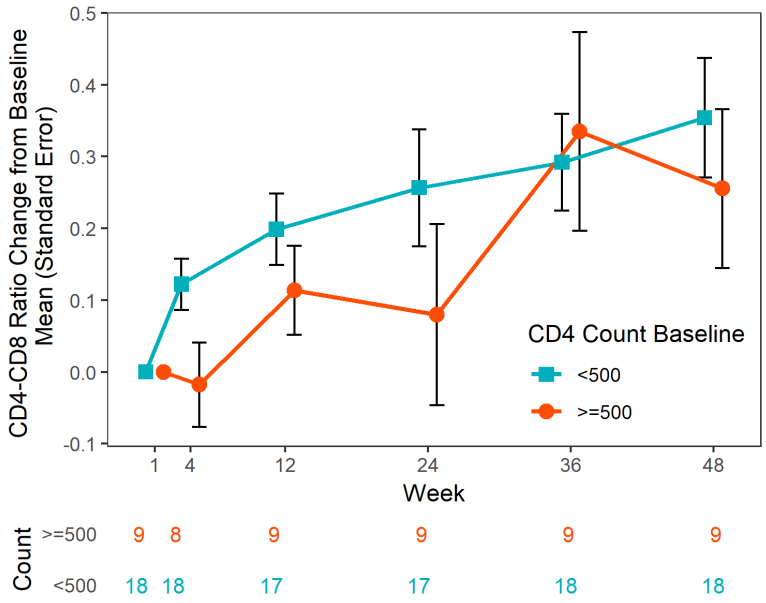
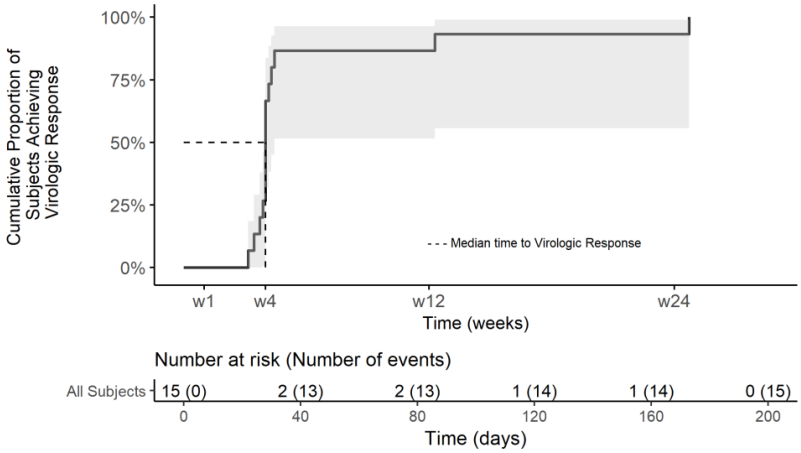
The proportion of subjects with "global success" at week 48 was as follows:

	n/N	Proportion	95% CI	Statistic Test	p-value
Global Success at Week 48	15/27	55.56%	36.81% - 72.88%	0.000	0.5000

n - Number of Subjects that Achieved Success
N - Total Number of Subjects with Evaluable Data
CI - Confidence Interval

Changes from baseline in CD4 cell count and CD4/CD8 ratio were as follows:



	
Safety Results:	Twenty-four (24) subjects out of 30 subjects who received the study treatment reported a total of 118 TEAEs, of which 42 were considered drug-related. The most common TEAE was "headache" reported by 7 subjects (23.33%). All TEAEs were classified with grade 1-3 in severity. Seventy-two (72) TEAEs were classified with grade 1 in severity. The remaining TEAEs were of grade 2 (44 TEAEs) or grade 3 (2 TEAEs). Subject 01_02 was discontinued from the study due to TEAEs ("anxiety", "insomnia" and "memory impairment"). These TEAEs were considered drug-related. There were no SAEs.
Exploratory Results:	The time to virologic response is displayed below:  The median time subjects achieve virological response was 28 days. No virological failures were observed.

Conclusion:	At baseline, 15 subjects out of 27 were viremic with mean pVL≥40 copies/mL. Mean change from baseline of CD4 count and CD4/CD8 ratio at week 48 were 95.6 (95% CI 28.0-163.1) cells/μL and 0.26 (95% CI 0.17-0.43) respectively. At week 24, all viremic subjects at baseline, achieved virological response (median time=28 days), having two consecutive values of pVL<40 copies/mL. No virological failures were observed. The results suggest that DTG+2NRTIS are a safe and effective first-line treatment, with CD4 cell recovery comparable to other regimens already tested in HIV-2 infection.
Date of Report:	23JUN2020