IMPORTANT SAFETY INFORMATION

Indication

TROGARZO® (ibalizumab-uiyk), in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

Use in Specific Populations

- **Pregnancy:** No adequate human data are available to establish whether or not TROGARZO® poses a risk to pregnancy outcomes. Monoclonal antibodies, such as ibalizumab-uiyk, are transported across the placenta as pregnancy progresses; therefore, ibalizumab-uiyk has the potential to be transmitted from the mother to the developing fetus.
- **Lactation:** No data are available regarding the presence of TROGARZO® in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for HIV-1 transmission, instruct mothers not to breastfeed if they are receiving TROGARZO®.

Contraindications

- TROGARZO® is contraindicated in patients with a prior hypersensitivity reaction to TROGARZO® or any components of the product.

Warnings and Precautions

Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

- Hypersensitivity reactions including infusion-related reactions and anaphylactic reactions have been reported following infusion of TROGARZO® during post-approval use. Symptoms may include dyspnea, angioedema, wheezing, chest pain, chest tightness, cough, hot flush, nausea, and vomiting. If signs and symptoms of an anaphylactic or other clinically significant hypersensitivity reaction occur, immediately discontinue administration of TROGARZO® and initiate appropriate treatment.

Immune Reconstitution Inflammatory Syndrome

- Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in one patient treated with TROGARZO® in combination with other antiretrovirals. During the initial phase of combination antiretroviral therapies, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

Embryo-Fetal Toxicity

- Based on animal data, TROGARZO® may cause reversible immunosuppression (CD4+ T cell and B cell lymphocytopenia) in infants born to mothers exposed to TROGARZO® during pregnancy. Immune phenotyping of the peripheral blood and expert consultation are recommended to provide guidance regarding monitoring and management of exposed infants based on the degree of immunosuppression observed. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Adverse Reactions

- The most common adverse reactions (all Grades) seen in clinical trial experience, reported in at least 5% of subjects receiving TROGARZO® were diarrhea (8%), dizziness (8%), nausea (5%) and rash (5%).
- Most (90%) of the adverse reactions reported were mild or moderate in severity. Two subjects experienced severe adverse reactions: one subject had a severe rash and one subject developed IRIS manifested as an exacerbation of progressive multifocal leukoencephalopathy.

For more information, please refer to the full Prescribing Information for TROGARZO® online at www.trogarzo.com.

THERA technologies

Trogarzo®
(ibalizumab-uiyk)
Injection
200 mg/1.33 mL (150 mg/mL)

Virologic effectiveness of ibalizumab clinical trial experience compared to real-world clinical care without ibalizumab in the OPERA® Cohort

An indirect treatment comparison

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Please see IMPORTANT SAFETY INFORMATION on the back of this document. This can also be found in the accompanying full Prescribing Information or online at www.trogarzo.com.

Trogarzo®
(ibalizumab-uiyk)
Injection
200 mg/1.33 mL (150 mg/mL)

Virologic effectiveness of ibalizumab clinical trial experience compared to real-world clinical care without ibalizumab in the OPERA® Cohort

Contact Information:
Laurence Brunet
919-827-0010
laurence.brunet@epividian.com

Laurence Brunet,[1] Michele L. Jonsson Funk,[2] R Brandon Cash,[3] Jennifer S. Fusco,[1] Lydia Walder,[4] Andrew Laws,[4] Michael Wohlfeiler,[5] Michael Sension,[6] Gregory P. Fusco[1]

[1] Epividian, Raleigh, NC, USA; [2] University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3] Theratechnologies, Inc., Montreal, QC, Canada; [4] FIECON Ltd, St Albans, United Kingdom; [5] AIDS Healthcare Foundation, Miami, FL, USA; [6] CAN Community Health, Sarasota, FL, USA

Background

- Heavily treatment experienced (HTE) people with HIV are individuals who require highly tailored ART regimens with less common ARV combinations due to viral resistance, tolerability, toxicity, or drug-drug interactions
- HTE individuals may have an increased risk of viral rebound, AIDS, and mortality
- Ibalizumab (IBA) is an 800mg intravenous (IV) infusion or IV push given every 2 weeks, in addition to an optimized background regimen (OBR)
- IBA may be considered for individuals with ongoing detectable viremia and lacking sufficient options to build a fully suppressive regimen
- The efficacy of IBA compared to other regimens is currently unknown because ethical considerations prevented the inclusion of comparison arms in IBA clinical trials
  - TMB-202: 48-week randomized dose-response trial amended to 24-week, 2008-2010 (Arm 1: n=59 on IBA 800mg every 2 weeks + OBR; Arm 2: n=54 on IBA 2000mg every 4 weeks + OBR)
  - TMB-301/311: 24-week single arm trial with optional extension to 96 weeks, 2015-2018 (n=40 on IBA 2000mg loading dose followed by IBA 800mg every 2 weeks + OBR)
- External controls can help interpret the results of clinical trials when randomization to a control arm cannot be performed

Objective

To assess the virologic effectiveness of IBA-containing regimens received by HTE individuals in clinical trials, compared to non-IBA-containing regimens prescribed to HTE individuals in routine clinical care in the OPERA® cohort

Methods

Clinical trial population (IBA regimen)

- Received IBA treatment corresponding to the FDA-approved dosing schedule
  - TMB-202: Arm 1 only (IBA 800mg every 2 weeks + OBR)
  - TMB-301/311: all
- Resistance profile available
- Viral load (VL) available at either week 24, 48, 60 and/or 96

External control population (non-IBA regimen)

- OPERA® cohort: prospectively captured, routine clinical data from electronic health records in the US; ~14% of people with HIV in care in the United States
- Inclusion criteria (based on clinical trial inclusion)
  - ≥18 years old
  - Documented 3- or 4-class resistance
  - Switch to a new non-IBA containing regimen between 01Jan2008 and 31Dec2020
  - Last VL >1000 copies/mL (c/mL) at switch
  - No pregnancy, AIDS-defining event, or cancer
  - Follow-up VL available
- Censoring events: (a) initiation of new anchor agent, (b) >45 days without ART, (c) lost to follow-up, (d) death, or (e) study end (30Jun2022)

Outcomes

- Achievement of undetectability (first VL <50 c/mL) or suppression (first VL <200 c/mL)
- Loss of undetectability (first VL ≥50 c/mL) or suppression (first VL ≥200 c/mL), after their respective achievement; undetectability or suppression assumed to be maintained in the absence of VL

Analyses

- Standardized mortality rate (SMR)-weighting: external control (non-IBA) group is weighted to look like the trial group (IBA)
  - IBA group: weight =1
  - Non-IBA group: weight derived from probability of receiving IBA based on baseline characteristics (age, CD4 cell count, VL, overall susceptibility score to ARVs [Fig 1])
- Time to undetectability or suppression over first 24 weeks of follow-up
  - Multiple imputation with chained equations for missing VL
  - SMR-weighted Cox proportional hazards models with bootstrapped confidence intervals (CI)
- Time to loss of undetectability or suppression over all follow-up
  - SMR-weighted Cox proportional hazards models

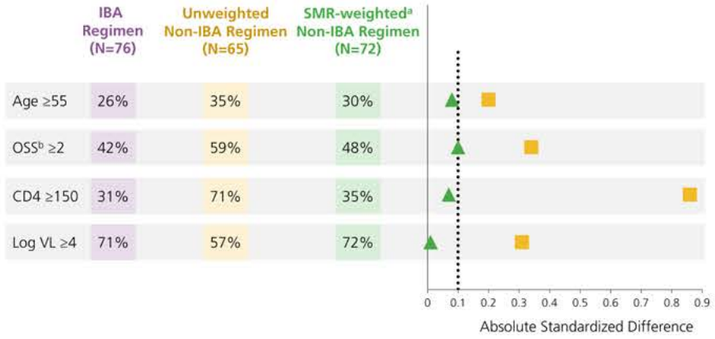
Results

Table 1. Study population and duration of follow-up

	IBA Regimen in Trials	Non-IBA Regimens in OPERA®
N	**76**	**65**
TMB-202, n (%)	45 (59)	NA
TMB-301/311, n (%)	31 (41)	NA
Weeks of follow-up, median (IQR)[a]	24 (24, 96)	138 (64, 237)
≤24 weeks of follow-up, n (%)	41 (54)	8 (12)

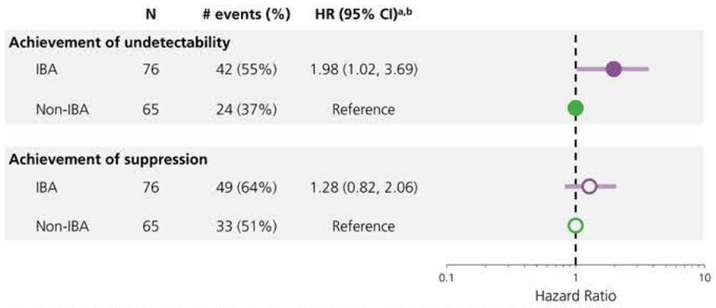
IBA, ibalizumab; IQR, interquartile range; N, number; NA, not applicable
[a] TMB-202: 11 (24%) individuals had 48 weeks of follow-up; TMB-301/311: 24 (77%) individuals had extended follow-up >24 weeks

Figure 1. Distribution of baseline characteristics and balance between IBA-containing and non-IBA-containing regimens before and after SMR-weighting[a]



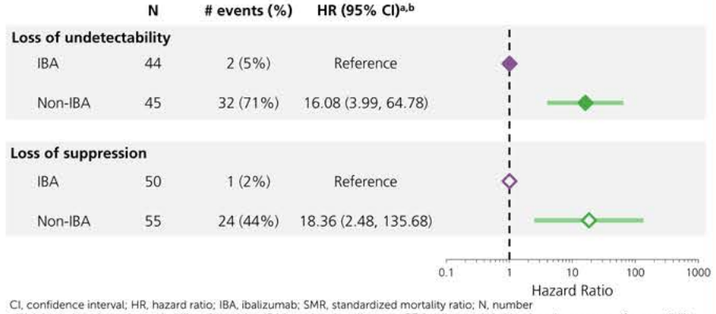
IBA, ibalizumab; SMR, standardized mortality ratio; N, number; OSS, overall susceptibility score; VL, viral load
[a] Weight derived from the probability of receiving IBA based on baseline age, CD4 cell count, viral load, and overall susceptibility score to specific antiretrovirals in their regimen
[b] The overall susceptibility score provides a measure of the number of potent antiretrovirals in the regimen, where the influence of each is scaled by relative resistance to that drug class. Antiretrovirals included in the derivation of the score are darunavir, dolutegravir, emtricitabine, etravirine, lamivudine, tenofovir disoproxil fumarate, and tenofovir alafenamide.

Figure 2. Achievement of viral undetectability or suppression over the first 24 weeks of follow-up



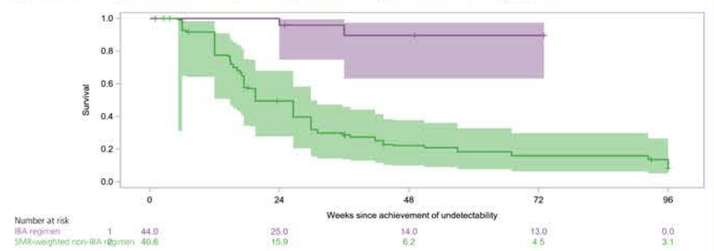
CI, confidence interval; HR, hazard ratio; IBA, ibalizumab; SMR, standardized mortality ratio; N, number
[a] Weight derived from the probability of receiving IBA based on baseline age, CD4 cell count, viral load, and overall susceptibility score to specific antiretrovirals in their regimen
[b] SMR-weighted Cox proportional hazards models; bootstrapped confidence intervals; missing viral loads imputed with multiple imputation with chained equations

Figure 3. Loss of virologic control among individuals who had previously achieved control over the entire follow-up



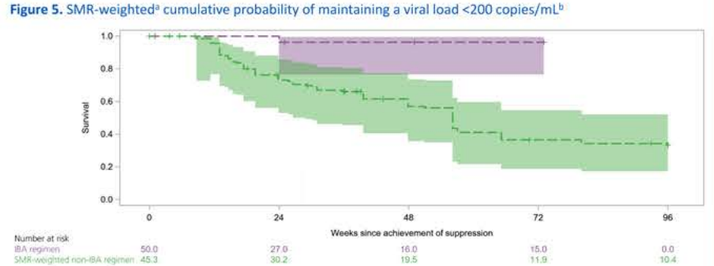
CI, confidence interval; HR, hazard ratio; IBA, ibalizumab; SMR, standardized mortality ratio; N, number
[a] Weight derived from the probability of receiving IBA based on baseline age, CD4 cell count, viral load, and a measure of susceptibility to specific antiretrovirals in their regimen
[b] SMR-weighted Cox proportional hazards models

Figure 4. SMR-weighted[a] cumulative probability of maintaining a viral load <50 copies/mL[b]



IBA, ibalizumab; SMR, standardized mortality ratio
[a] Weight derived from the probability of receiving IBA based on baseline age, CD4 cell count, viral load, and overall susceptibility score to specific antiretrovirals in their regimen
[b] The first 96 weeks after achieving suppression are presented

Figure 5. SMR-weighted[a] cumulative probability of maintaining a viral load <200 copies/mL[b]



IBA, ibalizumab; SMR, standardized mortality ratio
[a] Weight derived from the probability of receiving IBA based on baseline age, CD4 cell count, viral load, and overall susceptibility score to specific antiretrovirals in their regimen
[b] The first 96 weeks after achieving suppression are presented

Discussion

- This is the first study comparing IBA-containing regimens in clinical trials to non-IBA-containing regimens in routine care
  - 76 trial participants on IBA were compared to 65 HTE individuals on non-IBA regimens in OPERA® (external control) [Table 1]
- While trial participants had more severe disease than non-IBA controls [Fig 1], IBA was associated with favorable virologic outcomes:
  - Covariate balance was achieved with SMR-weighting [Fig 1]
  - At 24 weeks, a statistically significant doubling of the likelihood of viral undetectability was observed with IBA compared to non-IBA regimen (HR: 1.98, 95% CI: 1.02, 3.69) [Fig 2]
  - Achievement of viral suppression was also more likely but did not reach statistical significance [Fig 2]
  - Once achieved, undetectability was maintained through the end of follow-up by 95% of those on IBA and 27% of those on non-IBA regimens [Fig 3]
  - The likelihood of losing undetectability or suppression was 16 to 18 times higher for on non-IBA regimens compared to IBA; confidence intervals were wide but statistically significant [Fig 3]
- Limitations
  - Small sample size [Table 1]
  - Limited duration of follow-up in the trials (median 24 weeks) compared to the OPERA® cohort (median 138 weeks) [Table 1]
  - Covariates available from the trials were limited; residual confounding cannot be ruled out
  - IBA infusions every 2 weeks created more opportunities for interaction with healthcare providers than oral regimens
  - More variability in the timing of VL monitoring in routine care
- Ongoing viremia increases the risk of treatment failure, comorbidity, death, and HIV transmission
  - For HTE individuals, receiving IBA every 2 weeks has the potential for important clinical and public health benefits, given the higher likelihood of achieving and maintaining undetectability.

Key Findings

- Use of IBA in trials was associated with favorable virologic outcomes compared to non-IBA regimens in routine care among HTE individuals
  - Shorter time to virologic undetectability
  - Longer durability of undetectability and suppression
- With more individuals achieving and maintaining undetectability, IBA could have important clinical and public health benefits for HTE individuals

Acknowledgements

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