25 July 2019
EMA/469134/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Trogarzo

International non-proprietary name: ibalizumab

Procedure No. EMEA/H/C/004961/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area under the time-concentration curve
cART	Combination antiretroviral therapy
CCR5	Chemokine coreceptor 5
CD4+	Cluster of differentiation 4 positive
CD4	Cluster of differentiation 4 (glycoprotein on the surface of T-helper cells)
CDC	Complement dependent cytotoxicity
CEX	Cation Exchange Chromatography
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
C_{max}	Maximum observed concentration
C_{peak}	Peak plasma concentration
CPP	critical process parameters
CQA	critical quality attributes
C_{trough}	Trough plasma concentration
CRF	Case Report Form
CSR	Clinical Study Report
CXCR4	C-X-C chemokine receptor type 4
DAIDS	Division of AIDS
DSMB	Data Safety Monitoring Board
EC85	Equiactive concentration supported 85%
ECL	Electrochemiluminescence
EI	Entry inhibitor
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study

EOPCB	End of Production Cell Bank
ePPND	enhanced pre- and post-natal development
FAHI	Functional Assessment of HIV Infection
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HTE	Heavily treatment experienced
Hu5A8	Humanized version of antibody 5A8 (ibalizumab)
IC50	50% inhibitory concentration
ICH	International Council for Harmonisation
ICHalfmax	Concentration required to achieve half-maximum percent inhibition
ICHM FC	ICHalfmax fold change
IGG	Immunoglobulin G
ID	Identification
IM	Intramuscular
IND	Investigational New Drug Application
INI	Integrase inhibitor
ITT	Intent-to-treat
IRB	Institutional Review Board
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
KPP	key process parameters
LOCF	Last observation carried forward
LLOQ	Lower limit of quantitation
mAb	Monoclonal antibody
MCB	Master Cell Bank
MDR	Multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Missing equals failure
mITT	Modified intent-to-treat
MOR	maximum operating range

MPI	Maximum percent inhibition
MRHD	Maximum recommended human dose
Mu5A8	Murine version of 5A8
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOR	normal operating range
NRTI	Nucleoside reverse transcriptase inhibitor
OBR	Optimized background regimen
OSS	Overall sensitivity score; sum of active drugs in OBR based on a net assessment of information from genotypic and phenotypic testing results
PC	Protocol correct
PD	Pharmacodynamic(s)
PDL	Population Doubling Level
PI	Protease inhibitor
PK	Pharmacokinetic(s)
PNGS	Potential N-linked glycosylation site
PP	Per Protocol
PPQ	Process Performance Qualification
PRO	Patient-reported outcome
PT	Preferred term
QC	Quality check
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RD	Receptor density
RNA	Ribonucleic acid
RO	Receptor occupancy
ROD21-W25	Receptor occupancy value over the course of the entire study (Day 21 to Week 25)
ROW5-W25	Receptor occupancy value from Week 5 to Week 25 (including only values after administration of bi-weekly 800-mg maintenance doses)
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error

SmPC	Summary of Product Characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLOVR	Time to loss of virologic response
ULOQ	Upper limit of quantification
USP	United States Pharmacopoeia
VF	Virologic failure
WCB	Working Cell Bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Theratechnologies International Limited submitted on 27 August 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Trogarzo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "Treatment of adults infected with HIV-1 resistant to at least 1 agent in 3 different classes, in combination with other antiretroviral medicinal products".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that ibalizumab was considered a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0271/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP with Decision P/0271/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance ibalizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Daniela Melchiorri

The application was received by the EMA on	27 August 2018
Accelerated Assessment procedure was agreed-upon by CHMP on	26 July 2018
The procedure started on	13 September 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 November 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	14 November 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 November 2018
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	20 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 December 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 January 2019
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
- A GMP inspection at on site responsible for manufacture of the active substance, and one site responsible for manufacture of the active substance and finished product, located in China between 17-18 January 2019 and 21-25 January 2019, respectively.	18 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	14 February 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 February 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 April 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 May 2019
The List of outstanding issues were sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2019
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	11 April 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trogarzo on	25 July 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The sought indication is in patients infected with multidrug resistant (MDR) HIV-1. MDR HIV-1 is defined as those patients with HIV-1 who have phenotypic or genotypic resistance to the standard antiretroviral therapy drug classes: nucleoside or nucleotide reverse transcriptase inhibitors (NRTI) or non-NRTIs (NNRTI), protease inhibitors (PI), and integrase strand transfer inhibitors (INSTI). MDR HIV-1 is usually established by at least one major resistance mutation within each drug class present in genotypic resistance testing, but in these patients often many resistance mutations are seen simultaneously. Upon virologic failure to their current antiretroviral regimen, these patients often have limited (or no) treatment options remaining.

The agreed indication for Ibalizumab is its use in combination with other antiretrovirals for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

2.1.2. Epidemiology

The applicant provided the following assessment of the epidemiology of multidrug resistant HIV-1 in Europe:

According to the United Nations Programme on HIV/AIDS (UNAIDS 2016), there were 2.1 million people living with HIV in 2016 in Western/Central Europe and North America, translating to a prevalence of 0.3% of adults in this region or 30/10,000. According to UNAIDS estimates from 2013, where the same region was used to report prevalence of HIV infection, 56% of this prevalence comes from North America and 4% comes from Canada (UNAIDS 2016). Excluding these two populations from the prevalence calculation yields 840,000 people living with HIV in Western/Central Europe. The total population in this area is 460,614,900 people. This means the prevalence rate of HIV in this area is 18.24 per 10,000 people, while the prevalence of MDR HIV-1 infection was estimated to be 1.131 per 10,000 people. More specifically, an overall prevalence of about 52,000 people with MDR HIV-1 was found out of 840,000 people living with HIV in the EU (6.2%).

Out of the 52,000 people living with MDR HIV-1, Theratechnologies estimate that approximatively 5 to 10% of these patients have limited treatment options and have immediate need for a new treatment.

2.1.3. Aetiology and pathogenesis

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress, and subsequently maintain, the HIV-1 viral load to levels that are at least below the limit of detection of most commonly used assays. A detection limit of 50 copies/ml of blood has long been the standard.

HIV-1 replication occurs at a high rate and this, in combination with the absence of proofreading capacity of the viral reverse transcriptase, results in an estimated mutation rate of approximately one nucleotide mutation per replicative cycle. Hence, many HIV variants are simultaneously present in each infected individual, which is also described as "quasispecies". Upon antiviral drug pressure, the circulating HIV-1

variants most fit under this selection pressure will be able to replicate, resulting in selection of a viral population with reduced susceptibility to this treatment. Often, resistance to drugs in a certain ARV class results in cross-resistance to other drugs in that same class.

2.1.4. Clinical presentation, diagnosis prognosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis therefore most often occurs during chronic infection. Recent estimates suggest that even in high income settings; about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/mm^3. In some settings, up to half of people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 disease. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and Pneumocystis jirovecii pneumonia.

Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

Initial laboratory testing should include assessment of HIV staging parameters (CD4 cell count, HIV RNA) as well as a HIV genotype test for detection of drug resistance. The spectrum of drug resistance in an individual patient can range from minimal resistance that affects the activity of one or two drugs, to multidrug resistance that includes resistance to several drug classes. However, the risk of developing multidrug-resistant virus is much lower than in the past due to simpler regimens that are well tolerated. These regimens are therefore less likely to induce drug resistance mutations.

2.1.5. Management

Standard treatment for HIV-1 infection consists of a combination of 3 antiretroviral agents (ARV), from at least 2 different classes, and typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. This treatment works well to suppress HIV-1 viral load to undetectable levels, in the far majority of patients. However, viral resistance to any regimen can develop, due to e.g. poor adherence, too low exposure due to drug interactions, or low potency of the drug.

Patients with MDR HIV-1 have very few treatment options due to high viral resistance. When viral replication is not suppressed to an undetectable level, patients are at increased risk for disease progression, AIDS, and ultimately death. Treatment regimens in these patients typically include drugs at higher than standard dosages and drugs from less frequently used classes such as Fusion inhibitors and CCR5 antagonists. It is recommended in HIV-1 treatment guidelines that, in case of MDR HIV-1, to use at least 2 and preferably 3 active drugs in the new regimen and to also consider investigational agents for patients for whom it is not possible to construct a sustainable suppressive regimen using approved treatment options.

The main goal in any HIV-1 infected patient is full virologic suppression, i.e. having HIV-1 RNA load below the limit of detection of most commonly used assays (often <50 copies/mL blood). If virologic suppression cannot be achieved, the next best is preserving immunologic function, preventing clinical progression, and minimizing the increasing resistance to drug classes that could potentially include newly developed drugs.

2.1.6 About the product

Ibalizumab (formerly known as Hu5A8, TNX-355, and TMB-355) is a CD4 domain 2-directed humanized monoclonal antibody, which has been developed for the treatment of human immunodeficiency virus (HIV) infection. Ibalizumab binds to a conformational epitope located primarily on domain 2 of the CD4 receptor, inhibiting HIV entry into target cells.

The following indication and posology is agreed for ibalizumab:

"Trogarzo, in combination with other antiretroviral(s), is indicated for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen"

The recommended dose of ibalizumab is a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks. If a maintenance dose (800 mg) of ibalizumab is missed by 3 days or longer beyond the scheduled dosing day, a loading dose (2,000 mg) should be administered as early as possible. Resume maintenance dosing (800 mg) every 2 weeks thereafter.

Early epitope mapping studies suggested that ibalizumab binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. Recent fine mapping studies have identified at least 5 amino acid residues on CD4 domain 2 and 2 residues within the C-terminus of domain 1 that are critical to ibalizumab binding. Based on the known 3-dimensional structures of CD4, this epitope would be positioned on the surface of CD4 opposite the site in domain 1 that is required for CD4 binding of the major histocompatibility complex II receptor and also for gp120 attachment. This is consistent with previous findings suggesting that ibalizumab does not interfere with CD4-mediated immune functions. The unique binding specificity of ibalizumab to domain 2 of CD4 allows the antibody to inhibit viral entry and fusion without causing immunosuppression. The precise mechanism by which ibalizumab inhibits HIV has not been completely elucidated, but it appears to interfere specifically with post-attachment steps required for entry of HIV-1 virus particles into host cells, as well as gp120-mediated syncytium formation (cell fusion).

Of note, ibalizumab is a parenterally administered antiretroviral medication with infrequent dosing administrations (every other week).

2.1.7 Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the conclusion that there is an unmet medical need for patients with multidrug resistant HIV-1. Ibalizumab may be able to address (some of) this unmet medical need. It has a novel mechanism of action compared to currently available ARVs and has activity against both CCR5 and CXCR4 tropic viruses, seemingly regardless of existing resistance towards other ARVs. Therefore, it was agreed that ibalizumab may be considered a significant therapeutic innovation.

However, during the CHMP meeting on 28 February 2019, the CHMP concluded that it was no longer appropriate to pursue accelerated assessment as clinical major objections still remained that could not be resolved within accelerated assessment timeframe and agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile solution containing 200 mg of ibalizumab as active substance. The excipients are: sucrose, sodium chloride, polysorbate 80, histidine, hydrochloric acid and water for injections.

The product is supplied in 2 ml Type I borosilicate glass vials sealed with a butyl rubber stopper and an aluminium cap.

2.2.2. Active Substance

General information

Ibalizumab is a humanized immunoglobulin G (IgG) isotype 4 monoclonal antibody (mAb) for the treatment of human immunodeficiency virus (HIV) disease. Ibalizumab binds to a conformational epitope on domain 2 of CD4, a glycoprotein receptor expressed on the surface of T-helper cells (CD4), inhibiting HIV-1 entry into target cells.

The humanised monoclonal antibody ibalizumab has a molecular weight of about 150 kDa. The molecule has a constant region that is composed of two heavy chains of the gamma 4 subclass and two kappa light chains. The four chains are stabilised by multiple disulfide bonds.

Ibalizumab is a glycoprotein and the constant region of each heavy chain has a single N-linked oligosaccharide chain.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The active substance upstream and downstream manufacturing processes are typical for a therapeutic monoclonal antibody preparation.

The upstream manufacturing process consists of thawing a vial of the cell bank, cell culture, harvest, purification, and formulation. The production stage of the cell culture process is in bioreactors. The clarified supernatant is collected.

The downstream purification process consists of multiple types of chromatography, low pH virus inactivation step and neutralisation step, followed by nano-filtration (virus removal step), and ultrafiltration and diafiltration (UF/DF).

Excipients are added to the concentrated product to generate formulated bulk drug substance. The formulated bulk drug substance is filled after filtration into the container after excipient addition.

Sufficient information about the transfer and storage of the active substance between unit operations has been provided.

Overall, detailed information has been provided on each active substance production step, including the pooling strategy, process parameters and in-process controls and in-process testing (IPC/IPT).

Production scale and batch definition as well as the lot numbering system have been sufficiently described.

Control of materials

Ibalizumab is produced in the mouse myeloma cell line NS0. The origin, source and history of the NS0 host cell have been described. Summaries of adventitious safety information for biologically-sourced materials have been provided.

Details of the preparation and characterisation of the expression construct have been described. The DNA sequence of the whole expression plasmid, including coding regions for VL and the kappa chain, was confirmed by DNA sequencing. Transfection of the NS0 host cell line with the ibalizumab genes, selection and cloning procedures have been described.

The two-tiered cell bank system was characterised based on the Guidance "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" and ICH Q5A and Q5D. No identifiable virus-like particles other than endogenous murine retrovirus which are not unexpected in NS0 host cells such as intracisternal A-type retrovirus-like particles and both budding and extracellular C-type particles could be detected in the MCB.

During one of the three process performance qualification (PPQ) lots, cell culture was extended for additional cell passages during the cell expansion stage in order to define any potential need for longer seed train expansion in future manufacturing. End of production cells (EOPC) testing was carried out on this lot in compliance with ICH Q5A. Stability of the working cell bank (WCB) and MCB will be evaluated throughout the lifetime of the ibalizumab product.

Culture media are defined, and media compositions and manufacturing process have been provided.

Control of critical steps and intermediates

Tests and acceptance criteria for process control outputs (in-process controls and in-process testing) performed at critical steps identified in the manufacturing process to ensure that the process is controlled have been provided.

Data demonstrated that product purity is under control during downstream processing. Controls for product purity by various types of chromatography are included.

Impurity clearance by the downstream process was assessed during PPQ. Data demonstrated that the process-related impurities are robustly cleared, and no in-process controls are required.

The bioburden and endotoxin sampling points, locations of filters, and hold points for the harvest and purification processes of the commercial ibalizumab manufacturing process were provided. Overall microbial contamination control of the ibalizumab manufacturing process is through a comprehensive control strategy which includes process control, facility control and analytical testing control.

Product hold times were employed during PPQ. The proposed hold times for the ibalizumab active substance process intermediates to be used for the commercial process and any risks have been adequately discussed.

An extensive list of PPs and IPC/IPT has been provided which overall demonstrate sufficient control of the upstream and downstream production process steps of active substance.

Process validation and/or evaluation

Extensive information has been provided about the process performance qualification (PPQ) studies. The lifecycle approach is based on:

- Process design, process development, and Process Characterization (PC) (Stage 1);
- Process qualification of the commercial manufacturing processes (Stage 2); and
- Ongoing process verification and maintenance of the commercial production (Stage 3).

The performance qualification of the ibalizumab manufacturing process is designed to provide documented evidence that the manufacturing process, when operated within defined process control ranges, can consistently produce product meeting pre-determined acceptance criterion. Three consecutive batches of GMP production PPQ runs were executed to support active substance process validation.

Upstream process
The upstream process consists of five main process steps: vial thaw, subculture, adaptation stage, production stage and harvest. The detailed process was described in the upstream process performance qualification protocol and the validation documentation. All the manufacturing processes are controlled by maintaining the cell culture process parameters within defined ranges.

Downstream process
The active substance release testing results for active substance purity and quality are comparable to the reference standard or acceptance criteria. The levels of bioburden and endotoxin were less than the acceptance criteria. Appearance of the active substance for the three PPQ runs is colourless and slightly opalescent liquid.

The process related residual impurities of the active substance are below the quantitation limits. At the active substance storage temperature, the ibalizumab active substance is free from microbial contamination after being stored in glass bottles for the PPQ runs.

Additional studies evaluating the media hold time, and the capability of the process to remove endotoxins from the buffer, have been described. The potential for leachables from the materials used in manufacture was also studied. The short-term stability of in-process intermediates was assessed after storage at different temperatures.

Protocols for chromatography resins and UF/DF membrane at-scale lifetime studies have been provided. The protocols for the lifetime studies / re-use for chromatography resins and UF/DF membrane, including the data monitoring/recording (lot number, cycle number, output) are considered appropriate.

The in-process product purity of multiple runs was monitored. Results of several GMP active substance PPQ batches demonstrate consistent production when the process is run within normal operating ranges.

The PPQ data (in addition to the process characterization/design data) support the control strategy for process related impurities. The active substance is routinely tested for process related impurities whilst process validation data show adequate clearance to acceptable low levels during the purification process.

Manufacturing process development

The overview of the ibalizumab manufacturing process history, manufacture process development has been provided. Several manufacturing changes were made throughout process development.

A summary of the quality attributes of the finished product used in Phase 1, Phase 2, and Phase 3 has been provided. It shows that scale up resulted in minimal changes in the attributes.

In summary, the data demonstrated that ibalizumab finished product produced from active substance manufactured at a larger scale had no differences from materials produced at smaller scales.

In order to develop a formulation for further clinical use, the ibalizumab finished product was concentrated to 100mg/ml as three prototypes for stability testing and formulation screening. After the stability assessment for 100mg/ml ibalizumab prototype formulation, GMP lots of 120mg/ml ibalizumab finished product were successfully reformulated.

Overall, the presented data show that the active substance from Process 1 and Process 2 are comparable. All Process 2 results from multiple GMP runs met lot release criteria and pre-determined comparability acceptance criteria. Statistical analysis of the applicable quantitative lot release data between multiple Process 1 GMP runs and multiple Process 2 GMP runs shows that there are no significant differences. All applicable compendial, qualitative and quantitative results for general properties, identity, impurities and adventitious agents (microbial testing) are comparable between the two processes. Characterization results show that the primary and higher order structures are highly consistent between the 2 processes. The stability profile and trending data are also comparable between the two processes based on available data.

Characterisation

Extensive characterisation data has been provided. The primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, and purity were assessed. Characterisation studies were also done on materials under forced degradation conditions. The glycan profile of ibalizumab was also analysed. The biological activity of major charge isoforms was evaluated. Results indicate that all charge isoforms have very similar activity.

No studies of the Fc-mediated effector functions of ibalizumab were performed. The absence of evidence for cellular toxicity *in vivo* in monkeys and humans administered ibalizumab is consistent with the expected behaviour of this IgG4 molecule.

Forced degradation studies investigated potential degradation pathways of finished product under severe storage conditions: Thermal, pH, oxidation, photolysis, freeze/thaw test, agitation. Degradation was examined using the techniques of SEC-HPLC, CEX, CE-SDS and SDS-PAGE and compared to potency outcomes. Ibalizumab remains stable after agitation, oxidation and several freeze-thaw cycles. Under high pH and light stress conditions, impurities% was increased and potency decreased. The increases in the impurities% may be due to some fragmentation and aggregation. UV and thermal stress only caused slight changes in the analytical results. Ibalizumab can remain stable after days of agitation and several freeze-thaw cycles.

Information on process-related impurities was also provided. The purity tests were conducted to determine host cell residual DNA, residual host cell protein, and process-related impurities. All released active substance lots met these specifications. The removal of process-related impurities during processing is supported by process validation studies.

In conclusion, complete and satisfactory characterisation data on ibalizumab active substance has been presented.

Specification

The proposed panel of release tests cover physicochemical tests (appearance, pH, osmolality), identification, quantity, purity and impurities, potency and microbial quality. In general, the panel of tests are in line with ICH Q6B.

For the quantitative specifications, the release and stability data from multiple lots of active substance were analysed, and the 95% confidence and prediction intervals were calculated. Upon request, more detailed information has been provided on the statistical tools have been applied for calculation of the release and shelf life specifications and some acceptance criteria were either amended or better justified. The Applicant is recommended to re-evaluate the specifications after more manufacturing experience and testing data (30 batches) is obtained.

Analytical procedures
Summaries of method descriptions have been provided. Representative chromatograms and electropherograms have been provided. As per request, additional details were provided on sample preparation and reportable result calculations.

Validation of analytical procedures
Analytical procedures were validated in accordance to ICH Q2(R). It has been sufficiently demonstrated that the final method for the detection of HCPs is suitable.

Batch analyses
Comprehensive batch analysis has been provided on multiple active substance batches. The active substance release testing results are very consistent between the batches.

Reference standards of materials

Overall, sufficiently detailed information has been provided about the qualification/characterisation of the reference standards. The complete qualification of the reference standard is documented.

A new primary reference standard was recently manufactured. An active substance Lot has been used to prepare a finished product clinical lot that has been used in the Phase 3 clinical study. A set of vials has been allocated as the primary reference material and part of the vials will be used as the secondary/working reference standard. The primary reference standard will be used to qualify the working reference standard and future primary reference materials. The working reference standard will be used for routine release and stability testing of commercial lots. Data showed that the Primary Reference Standard was comparable to the Analytical Reference Standard.

The approach for using a two-tiered reference standard system comprising primary and secondary/working reference standards is considered good practice if well monitored/qualified. High level information has been provided about the trend monitoring and review of data to identify any significant change in primary/secondary reference standard quality. An appropriate re-qualification protocol, including acceptance criteria for all testing parameters, of the reference materials has been presented upon request.

Stability

Multiple GMP substance lots were manufactured and placed on stability testing. The stability studies (protocols) are carried out in accordance with the relevant ICH guidelines. GMP substance batches produced according to the proposed commercial production process have been put into stability studies. Appropriate QAs have been tested at regular intervals in accordance with the relevant ICH guidelines.

Overall, stability-indicating tests have been chosen which are expected to detect changes in the quality of the product. In general, no significant trends, if any, are discerned for all QAs tested during the storage period when stored under long term storage conditions. The presented data sufficiently support a maximum storage time at the recommended storage conditions.

It has been substantiated that the containers used in the stability studies are representative of those proposed for use in commercial manufacture.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Ibalizumab finished product is a sterile, preservative-free, colourless to slightly yellow, clear to slightly opalescent aqueous solution, with no visible particles, supplied as 200 mg of ibalizumab as active substance, hydrochloric acid (for pH adjustment), L-histidine (as buffering agent), polysorbate 80 (surfactant), sodium chloride (as tonicity agent), sucrose (as stabilizer), and water for injection (solvent). The product is available in a 2 ml single-dose type I glass vial with rubber stopper and an aluminium overseal. Each ibalizumab vial contains an overfill to ensure 200 mg of product can be withdrawn.

Pharmaceutical development

Formulation development

The formulation of the finished product is the same as the active substance. The development of the sterile intravenous formulation (concentrate for solution for infusion to be diluted with sodium chloride 0.9% before administration) began at a small scale. These lots were used in Phase 1 and 2a clinical trials. The process was later scaled up and multiple GMP lots were used in a Phase 2b trial and in expanded access patients. TaiMed continued the development of a more concentrated 150 mg/mL product. Excipients used in the Phase 3 formulation are already present in Phase 1 and Phase 2 formulations. Concentration of excipients were optimized to increase the solubility and to stabilise the highly concentrated ibalizumab at 150 mg/ml, as well as to adjust for tonicity.

Manufacturing process development

The finished product process includes substance pooling, mixing, sterile filtration, aseptic filling, stoppering and capping. Differences in the finished product manufacturing process between the phase I and phase II material processes and the phase III material, proposed commercial process include the filling process.

Three comparative studies were performed to evaluate the product quality attributes of ibalizumab finished product generated from different stage of manufacturing process and the results showed the materials generated form each stage process is not markedly different. All these materials are comparable and stable.

Relevant information on the process development and has been provided. The rationale for this classification and strategy for classification of in-process controls and process parameters has been described.

Manufacture of the product and process controls

The finished product fill/finish process is a standard process and includes bulk substance mixing, sterile filtration, aseptic filling, stoppering and capping. The filled finished product vials go through 100% visual inspection for any defects, and those vials that pass the visual inspection are then tested for release, labelled, packed, stored at 2-8°C and distributed. The fill/finish process consistency and quality are monitored by in-process control sampling of bioburden, endotoxin, periodical fill weight check and release testing. The process parameters and corresponding target values/ranges have been presented and classification of the process parameters, as well as information on how the target values/ranges have been set.

Process controls

Process parameters and in-process controls for all manufacturing steps (active substance pooling and mixing, pre-sterile filtration, sterile filtration, aseptic filling and stoppering, capping, and visual inspection) and the operational ranges/criteria have been presented.

The classification of process parameters and in-process controls has been adequately discussed.

Process validation / verification

Process validation was performed on three finished product PPQ lots. The process consistency and quality is monitored by in-process control sampling of bioburden, endotoxin and periodical fill weight check.

In-process samples were taken to validate the mixing efficiency and impact on finished product quality. Results indicated that the active substance was stable during the hold time. After holding, the product was sterile filtered. Bubble point testing for filter integrity was performed and all results met the criteria. Results for the fill weight check and parameters for filling, stoppering and capping were at target value or within the target range.

Filter validation was performed with a bacterial filter retention study, leachable study and filter bubble point determination study.

Three consecutive media fills were performed when the aseptic filling line was first qualified and periodically thereafter for various container closure configurations. All media fills passed the predefined criteria and growth promotion testing results met all requirements.

A shipping validation study was performed, indicating that ibalizumab finished product can be transported for routine commercial shipping.

Product specification

The proposed panel of release tests cover physicochemical tests (appearance, pH), identity, purity and impurities, potency, quantity, microbial quality and other general tests. In general the panel of tests is in line with ICH Q6B.

Upon request, the statistical approach has been further clarified and additional finished product lots have been included in the analyses to set the release and shelf life specifications. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

Analytical procedures
Summaries of method descriptions specific for the finished product have been provided. Methods also used for active substance are described in the active substance section.

Validation of analytical procedures
Verifications of all compendial methods were performed to demonstrate suitability of use, and the validation has been described.

Batch analyses
Comprehensive batch analysis has been provided on multiple finished product batches.
As discussed for active substance specifications, also for finished product specifications the Applicant is recommended to re-evaluate the active substance and finished product specifications after more manufacturing experience (30 batches) and testing data is obtained.

The information on references standards used for testing of the finished product is provided in the active substance section.

Container closure

The ibalizumab finished product is packaged for commercial distribution in 2mL type I glass vials sealed with a rubber stopper and an aluminium cap. The product contact materials have been tested to USP/EP requirements and shown to be suitable for parenteral pharmaceutical use. Specifications for glass vial, stopper and aluminium seal have been provided. Sufficient information on the container closure has been presented.

Stability of the product

Data from the ongoing long-term stability study of multiple ibalizumab injection finished product batches, including real time stability data at 2-8°C has been provided. Based on the presented data, a shelf life claim for the finished product of 3 years is acceptable when stored under the recommended storage conditions (2°C to 8°C, protected from light).

The stability studies also include storage at accelerated and stressed conditions, where some degradation is observed.

The stability protocols for ongoing studies and a protocol for post-approval annual stability batches have been provided. The stability protocols are acceptable.

Additional stability studies such as temperature cycling (freeze-thaw study, cold-stress study), a study with vials in inverted position, and an in-use study have been presented.

A microbiological challenge study and a compatibility study performed on post-diluted product in 0.9% normal saline solution support the proposed storage periods of the post-diluted solution of up to 24 hours at 2-8 °C and up to 4 hours at 25±2 °C.

If refrigerated, allow the diluted ibalizumab solution to stand at room temperature (20°C to 25°C) for at least 30 minutes but no more than 4 hours prior to administration.

Adventitious agents

A comprehensive strategy, including raw material sourcing and testing and viral clearance process validation, is used to ensure that the ibalizumab active substance and the resulting finished product are free of adventitious agents. The strategy is designed in accordance to the ICH Guideline Q5A.

Non-viral Adventitious Agents

Raw materials of animal origin were used in establishment of the production cell line. Human derived materials were also used in the establishment of the production cell line.

There are no components directly derived from animal or human materials utilized in the master and working cell banks, nor in the subsequent active substance or finished product manufacturing processes.

FBS from approved and inspected slaughter establishments has been used in the generation of the cell line. The provided information indicates the risk of TSE transmission via the administration of ibalizumab is remote.

Viral Adventitious Agents

Viral safety testing on the MCB and WCB that originate from the NS0 cell line was performed in accordance with FDA guidance "Points to Consider in the Characterization of Cell lines Used to Produce Biologicals" and is also in line with relevant ICH guidelines. The MCB and WCB were analysed and confirm to be free of adventitious agents.

The unprocessed bulk substance produced from the NS0 cell line for three PPQ runs was tested for sterility, mycoplasma, virus (adventitious and species specific) and retrovirus.

The ibalizumab substance manufacturing process uses a NS0 cell line that is known to contain rodent retrovirus-like particles (RVLP). In order to generate data for the viral safety assessment the amount of RVLPs in the unprocessed bulk was estimated.

A panel of model viruses was chosen for use in viral clearance studies in qualified scale-down models to demonstrate the ability of the downstream process to clear retrovirus, as well as to clear viruses in general. The purification steps investigated in the clearance validation studies included various types of chromatography, low pH viral inactivation, and viral filtration.

The full study report is provided which contains details of the qualified scale down model used.

The to-be-marketed clinical intravenous administration of ibalizumab is as a single 2000 mg i.v. loading dose followed by every other week administration of 800 mg i.v. ibalizumab as the chronic maintenance dose. The mean viral clearance factors and the manufacturing data from 3 PPQ batches were used to estimate the adequacy of viral clearance for both the single dose at 2000 mg and the chronic dose at 800 mg. The viral safety of the substance was assessed based on the safety factor between the calculated RVLP per dose and the overall cumulative viral clearance and inactivation capacity of the downstream process.

In summary, viral clearance studies have been performed in accordance with relevant ICH guidelines. The applied model-viruses are sufficiently justified. As expected, the NS0 cell line contains rodent retro-virus like particles. The applicant's calculation of the estimated retrovirus particles per dose indicate an acceptable safety factor in terms of potential presence of retro-virus like particles in human doses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the Module 3 Quality dossier presented in support of this marketing authorisation application for Trogarzo (ibalizumab) is of acceptable standard, with the descriptions of the manufacture and control of the active substance and finished product in sufficient and adequate detail.

Active substance

The active substance upstream and downstream manufacturing processes are typical for a therapeutic monoclonal antibody preparation and overall sufficiently detailed information has been provided on each active substance production step, including process parameters and IPC/IPT. An extensive list of PPs and IPC/IPT has been provided which overall demonstrates tight control of the upstream and downstream production process steps of the active substance. Overall, the proposed settings for PPs MOR/NOR ranges and IPC/IPT ranges are sufficiently supported by the process characterisation/design studies and process performance qualification (PPQ) runs. As per request, it has been clarified in more detail what action will be taken in case a pre-defined acceptance criterion for IPC is not met.

In principle, a change to PPs should follow the current Commission Regulation (EC) No 1234/2008 ('the variations Regulation') and EU Guidelines on the details of the various categories of variations (2013/C 223/01) as appropriate.

In support of process validation/evaluation, there have been multiple runs in total where the in-process product purity was monitored. Some IPC/IPT testing is part of the ongoing process verification program and might be reduced or removed after completion of the ongoing process verification protocol.

The descriptions of the analytical procedures used for release and stability testing of active substance (and finished product) are suitably detailed.

For the quantitative specifications, the release and stability data from multiple lots of active substance were analysed, and the 95% confidence and prediction intervals were calculated. Upon request, more detailed information has been provided on the statistical tools have been applied for calculation of the release and shelf life specifications and some acceptance criteria were either amended or better justified. The Applicant is recommended to re-evaluate the specifications after more manufacturing experience and testing data (30 batches) is obtained.

Finished product

The finished product manufacturing process is a standard process for sterile pharmaceuticals and includes substance pooling, mixing, sterile filtration, aseptic filling, stoppering and capping.

As discussed for active substance specifications, also for finished product specifications the Applicant is recommended to re-evaluate the active substance and finished product specifications after more manufacturing experience (30 batches) and testing data is obtained.

In general, batch release test results provided show consistency between the batches manufactured.

The stability of the finished product is considered acceptable for 3 years when stored at 2-8°C.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended one point for further investigation.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Ibalizumab binds to CD4 on CD4+ cells, most likely to the BC-loop (aa121-125) between the first and the second domains (junction D1 and D2) on a surface opposite to the site on D1 where HIV-1 gp120 and human MHC class II bind. It has high affinity to CD4 with a Kd in the picomolar range of 82.2 pM.

HIV can still bind to CD4 cells, but in the presence of ibalizumab entry into the cell is inhibited. This could be due to the blocking of conformational changes induced by HIV on the cell surface that are necessary for virus-cell fusion.

In vitro pharmacodynamics

In early pharmacodynamic studies, a number of HIV laboratory strains and primary isolates of patients were used to determine the concentration ibalizumab needed to block infection of target cells. Data from several studies and investigations are provided. Inhibitory action of ibalizumab against laboratory strains IIIB, MN, C08 and C17 show high potency with ID100 values of ≤1.0 µg/ml. The IC90 could not be determined for all patient primary isolates tested, in particular some Clade B isolates with macrophage tropic phenotype. However, IC50 was determined for most isolates, which includes strains from Clades A, B, C, D, E, and O which were in general very low (≤0.152 µg/ml). Ibalizumab is also active against a HIV-2 strain and a SIV strain. The data described so far are taken from an FDA IND filing document. This can therefore only be considered as supportive data. Further data is available from a study performed in 2004, in which 6 primary isolates representing Clades B, C and D with either tropism for CCR5 or CXCR4, were used to determine inhibitory activity of ibalizumab. IC50 values were in the range of 0.03 – 0.07 µg/ml.

In vitro data from clinical trials

Ibalizumab activity was tested against 78 Clade B clinical isolates from a phase 2a study performed in 2006, before patients were treated. All isolates were susceptible to ibalizumab independent of co-receptor tropism. EC50 values ranged from 0.01 µg/ml to 0.23 µg/ml. This is well below the lowest serum concentrations in humans at predose of >30 µg/mL. In an earlier phase Ib study, 17 clinical isolates were tested for susceptibility to ibalizumab. Although the IC50 values before treatment were low, ranging from 0.02 to 0.16 µg/ml, after 9 weeks of treatment susceptibility reduced and the maximum percent inhibition (MPI) reached ranged from 32% to 79%, indicating induction of resistance. This is further discussed in the clinical section. Later clinical studies, performed from 2008 to 2011 (phase 2b) and 2015 to 2016 (phase 3), showed decreases in MPI in patients with viral failure or rebound. In the phase 3 study 71% of patients reaching 90-100% MPI, 16% of patients reaching an MPI of 80-90%, and 13% reaching an MPI of <80% at Baseline. Overall, it can be concluded that ibalizumab has potent antiviral activity against diverse strains of HIV regardless of tropism for CCR5 or CXCR4 co-receptors.

Ibalizumab is able to block infection of target cells by free virus and by cell-cell transmission.

In vivo pharmacodynamics

In vivo studies have been performed in rhesus monkeys and SIV. Since it was shown *in vitro* that ibalizumab is also active against SIV, this is considered an appropriate animal model. The murine

progenitor of ibalizumab, Mu5A8, induced a reduction in viral load and increase in $CD4^+$ cells of rhesus monkeys infected with SIV_{mac}, when given 4 times at 3 mg/kg every 3 days. The humanized form of ibalizumab was also tested in SIV-infected rhesus monkeys. Anti-ibalizumab antibodies were produced in the treated monkeys, which neutralized ibalizumab, reduced exposure and inhibited efficacy. Nevertheless, reductions in SIV viral load were seen in the monkeys up to day 10 of treatment.

Initial data on resistance to ibalizumab was generated in rhesus monkeys using SIV as infective agent. These data indicate that resistant strains of SIV readily emerge after treatment in vivo or exposure in vitro to ibalizumab. A similar effect is likely to occur with HIV. Further data on resistance to HIV and possible mechanisms are discussed in section 2.4.3.

Secondary pharmacodynamics

Binding of ibalizumab or Mu5A8 on domain 2 of CD4 did not have an effect on the function of CD4 in vitro. In vivo, there was an expected pharmacological effect on $CD4^+$ cell increase in monkeys treated with Mu5A8. No negative effect on immune function was observed in monkeys, as coating of $CD4^+$ lymphocytes with Mu5A8 as a result of treatment did not cause any measurable abnormality in either primary or secondary immune responses. These data demonstrated that coating of $CD4^+$ T-cells with Mu5A8 is not associated with loss of T-cells or with immunosuppression.

No other secondary pharmacology studies were performed with ibalizumab. Considering the nature of the product and its specificity, this is agreed.

Safety pharmacology endpoints were assessed as part of the repeated dose toxicity studies in rhesus and cynomolgus monkeys. This is acceptable.

Pharmacodynamic interactions

In vitro data in PBMC's shows that ibalizumab has the potential to have a synergistic effect with other anti-retroviral agents when tested in combination in a low passage clinical isolate, namely enfuvirtide, abacavir, and atazanavir. Anti-viral activity was measured as reverse transcriptase activity. In line with this result, a second experiment using 5 clinical isolates and measuring anti-viral activity by HIV p24 production, showed synergy between ibalizumab and enfuvirtide. The effect of the combination ibalizumab and maraviroc on activity was measured in MAGI-CCR5 cells and PBMC's, with β-galactosidase levels and reverse transcriptase activity as measures of antiviral activity respectively. Results show that the combination of ibalizumab and maraviroc is slightly synergistic, with positive synergy results for the HIV_{Bal} strain, but additive results for HIV_{ADA}. Patient serum also had a synergistic effect on ibalizumab activity. This is likely due to anti-pg120 antibodies naturally present in the serum of patients. This indicates that IC50 values of ibalizumab might be even lower *in vivo* than those determined in vitro.

2.3.2. Pharmacokinetics

All pharmacokinetic evaluations of intravenous ibalizumab are based on the results of one pharmacokinetic study, a published pharmacology study, early pharmacology studies which included serum levels of ibalizumab and five GLP toxicity studies of ibalizumab in monkeys (rhesus and cynomolgus). In addition, one study using the subcutaneous dosing route was submitted. Since this is not a relevant dosing route, the study is not assessed. No specific drug disposition studies have been conducted with Hu5A8 in any species.

Methods of analysis

In the early studies in Rhesus monkeys, the concentration of hu5A8/BG9169 in plasma or serum was determined by (different) ELISAs. Methods are described only shortly in the study reports and no

validation results/reports are provided. The LLOQ and ULOQ of the first method are unknown. The LLOQ in the second method (detection of BG9169) is 124 ng/ml (ULOQ unknown).

For the detection of ibalizumab in the 9 month repeated dose study in Cynomolgus monkey an ELISA is used which measures the CD4 binding activity of ibalizumab, irrespective of whether the ibalizumab molecules are in the bivalent or monovalent form. The LLOQ and ULOQ are reported to be 20 and 1000 ng/ml. Pre-study validation results are reported to be conform with acceptance criteria, however, no validation reports are provided.

Also in the EPPND study in Cynomolgus monkeys, ibalizumab serum concentrations were analysed using a validated ELISA, with an LLOQ of 10 ng/ml. Some of the validation results (calibration curve, precision and accuracy, incurred sample reanalysis) are provided, however, no details on for example selectivity, dilution and stability were included. In addition, no information on interference due to anti-ibalizumab antibodies is provided.

In many of the ELISAs used to determine the concentration of ibalizumab, CD4 is used to capture or detect ibalizumab. However, it has been shown that anti-ibalizumab antibodies result in an abrupt loss of CD4 binding activity and in samples with ADA's, the concentration of ibalizumab will probably be underestimated. Indeed, in many of the studies it is therefore concluded that there is significant interference from anti-ibalizumab antibodies and that the method is only suitable to determine the concentrations of ibalizumab in samples without anti-drug antibodies, i.e. only in samples <10 days after first dosing. This means that kinetics after repeated dosing cannot be adequately investigated with these assays.

In addition, it is unclear whether the results of the different analytical methods are comparable and how this relates to the difference in PK results obtained in the different studies. The presence of antibodies to hu5A8/BG9169 in plasma or serum was in the early studies in Rhesus monkeys determined by (different) ELISAs. Only a short description of the methods is given and no validation reports are provided. The validity of these assays could therefore not be assessed.

For the detection of anti-ibalizumab in the 9 month repeated dose study in Cynomolgus monkeys, two ELISAs are used; a bridging ELISA, in which all classes of immunoglobulins can be detected, and a sandwich ELISA, which detects only IgG antibodies. Animals were considered positive if they had at least 1 post-dose sample which met all criteria by either ELISA and had a sample with a reportable anti-ibalizumab concentration at any dilution. As indicated by the applicant, both ELISA's had limitations in detection of anti-ibalizumab antibodies due to the presence of endogenous ibalizumab.

In the EPPND study, a qualitative ECL method was used for the detection of anti-ibalizumab antibodies. According to the report, established LPC and HPC were 169 and 5000 ng/ml in neat serum. No matrix interference was observed in cynomolgus monkey serum. Drug tolerance in the screening assay was observed at ≤ 60 µg/mL at the HPC and at ≤ 10 µg/ml for the LPC and PC 250 ng/ml. Drug tolerance evaluated using the PC was highly dependent on the affinity of the PC and may not have been representative for all study samples.

It should be kept in mind that the presence of anti-ibalizumab antibodies may be underestimated due to the drug tolerance limitations of the assays.

Absorption

Pharmacokinetic and toxicokinetic studies with ibalizumab were only performed in monkeys (Rhesus and Cynomolgus), because CD4 in other animal models is not recognized by Hu5A8. The pharmacokinetic results of day 1 following IV administration of ibalizumab are summarized in the following Table 1.

Table 1 Pharmacokinetic results of day 1 following IV administration of ibalizumab in monkeys

Dose	Sex	$AUC_{0-\infty}$ (h*µg/mL)	C_{max} (µg/mL)	$T_{1/2}$ (h)	Vd (mL/kg)	Cl (mL*kg/day)	Study
Rhesus							
3 mg/kg	N/A (n=3)			124.8			TMB-RD-R2017003
5 mg/kg	Male (n=4)	3218	109	28.82			Inveresk 575384
5 mg/kg	Female (n=5)	2467	117	35.96			Inveresk 575384
25 mg/kg	Male (n=5)	34537	426	70.58			Inveresk 575384
25 mg/kg	Female (n=5)	32332	439	75.26			Inveresk 575384
30 mg/kg	N/A (n=4)			134.4			TMB-RD-R2017003
30 mg/kg	Male (n=2)	106202		143.7			TSI Mason 2-N98
30 mg/kg	Female (n=2)	121137		126.2			TSI Mason 2-N98
Cynomolgus							
10 mg/kg	Male (n=4)	23743	261	59.9/24*	28.1		S-020 1652-181
10 mg/kg	Male (n=4)	30606	380	75.4/31*	44.8		S-020 1652-181
25 mg/kg	6/sex	50250	763	115	52.4	8.37	MNA0001
50 mg/kg	6/sex	125237	1678	135	47.7	6.93	MNA0001

Ibalizumab showed a biphasic decline, with a rapid initial distribution phase, followed by a slow elimination phase. Systemic exposure of ibalizumab (AUC) increased in a supraproportional manner over the dose range of 5 to 25 mg/kg after a single dose (10-13x, first dose 8 week study), but more dose proportional over the dose range of 25 to 50 mg/kg (2.4x, first dose 9 month study). Cmax increased dose-proportionally over a dose range from 5-50 mg/kg. In humans, Cmax and AUC were dose-dependent and increased disproportionately to dose.

Following repeated dosing in the 9 month study in cynomolgus monkeys, the total exposure (Cmax and AUC) was dose-dependent and AUC was increased disproportionally to dose. Accumulation ratios were low to moderate (2.4-3.2 for AUC for once weekly IV) and the accumulation index of trough concentrations was greater than that of peak concentrations. Nevertheless, due to the interference from ADA's in many of the ELISA's used to detect ibalizumab, the concentrations of ibalizumab after repeated dosing may be underestimated in samples with presence of ADA's. Therefore, dose and time dependency could not be accurately estimated.

Although there were some indications for a gender differences in exposure in the 8 week study in Rhesus monkeys (slightly higher AUC in males and slightly higher Cmax and t1/2 in females), all differences were <2 and no gender differences were observed in the 9 month study in Cynomolgus monkeys.

Distribution

Formal tissue distribution and protein binding studies were not conducted with ibalizumab, which is agreed. Consistent with the known distribution of monoclonal antibodies, ibalizumab has a low volume of

distribution (47-52 ml/kg), approximately the plasma volume of the monkeys, suggesting that the drug was largely restricted to the vasculature.

In studies on cross reactivity, ibalizumab was shown to bind to CD4 surface molecules on lymphocytes. There was no evidence of inappropriate staining (cross-reactivity) of rhesus monkey tissues.

In the EPPND study, it was shown that ibalizumab serum concentrations were comparable in postnatal adult females and infants, consistent with the fact that IgG4 can cross the placenta in monkeys and humans and is approximately 100% at full term. The data suggest that the elimination rates of ibalizumab in adults and infants may be similar. Ibalizumab was detectable in infant serum from BD 14 (first point of analysis) until BD 91.

Excretion to milk has not been investigated. It is known that in human, IgG monoclonal antibodies are transferred to colostrum and milk, but only in small amounts (Hurley et al., 2013).

Metabolism

No metabolism studies with ibalizumab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1). Ibalizumab is an IgG monoclonal antibody and monoclonal antibodies are metabolised to peptides and amino acids (Keizer et al., 2010). Metabolism of endogenous IgG occurs in plasma and in various body tissues (e.g. skin, muscle, and liver). Metabolism is via proteolysis by the reticuloendothelial system and by the liver, target-mediated elimination and non specific endocytosis. It is agreed that no metabolism studies are warranted for ibalizumab.

Excretion

Monoclonal antibodies are not directly excreted due to their molecular size, but are metabolised to peptides and amino acids that can be re-used in the body for de novo synthesis of proteins or are excreted by the kidney (Keizer et al., 2010). Ibalizumab will be excreted as peptides and amino acids via urine or the peptides and amino acids are re-used for the synthesis of proteins. The absence of excretion studies is in accordance with ICH S6(R1).

Plasma clearance of ibalizumab was low (6.93-8.37 ml•kg/day at d1). Terminal elimination half life (t1/2) increased with the dose (4.8-5.6 days at 25 and 50 mg/kg after a single dose, respectively) and also increased after repeated dosing (up to 8.2-10.7 days after 260 days). Overall, the t1/2 was similar in rhesus and cynomolgus monkeys.

Altogether, the increase of t1/2 with the dose, the accumulation of drug after repeated dosing and the decrease in clearance with increased dosing indicate that clearance mechanisms may become saturated at high doses, which is a common characteristic of monoclonal antibodies targeting cell surface molecules, such as CD4.

Pharmacokinetic drug interactions

Ibalizumab is a monoclonal antibody and is therefore degraded as other monoclonal antibodies and not via CYPs and Phase II enzymes, nor is a substrate for drug transporters. Therefore, no pharmacokinetic drug-drug interactions are expected.

Immunogenicity

Antibodies against ibalizumab were observed in several of the rhesus and cynomolgus monkey studies, starting approximately 10 day after dosing, which can be expected since ibalizumab is a humanized antibody. It is noted that no ADA's were observed in a chimpanzee study, a species closer to humans.

In several of the studies, there appeared to be an inverse relationship between the anti-ibalizumab antibody titre and the ibalizumab concentration in serum. Also in the antigenicity study, measurable serum ibalizumab concentration in animals that received a 10 mg/kg initial dose, in addition to two

challenge doses, were much lower than in animals that did not receive an initial dose. Although this might indicate the presence of clearing antibodies, more and more ibalizumab was recovered after sample dilution (apparently due to the dissociation of antibody-drug complexes). This shows that the ADA's are not clearing, but that they limit the adequate detection of ibalizumab in ADA positive samples. According to Reimann et al (1997 and 2002), anti-ibalizumab antibodies in monkeys appear to be capable of neutralizing binding to CD4. Since many of the ibalizumab detection assays make use of binding to CD4, the interference is predictable.

Furthermore, it is noted that in the EPPND study, plasma drug levels in several animals (tested negative for ADA's) were greater than assay drug tolerance (60 µg/ml at the high positive control (HPC) and 10 µg/ml for the LPC) and therefore, the number of positive animals can be an underestimation.

2.3.3. Toxicology

Single and repeat dose toxicity

Male and female rhesus monkeys treated with 30 mg/kg ibalizumab once, showed an enlarged spleen eight days after treatment, which was not observed at 15 days after treatment. No further changes effects were noted.

Repeated intravenous exposure to ibalizumab was studied up to 2 months in rhesus monkeys and up to 9 months in cynomolgus monkeys.

In rhesus monkeys, peripheral blood mononuclear cells proliferation was decreased at the highest dose tested (25 mg/kg), in reaction to the mitogens Concanavalin A and pokeweed. However, after 10-week recovery, stimulation indices were similar or greater than baseline level responses. Germinal centres of secondary follicles in lymph nodes and the spleen were similar to control. In addition, as expected in an immunologically responsive lymph node, positive staining with IgM and IgD was observed in the marginal and mantle zones, showing a pattern reflecting central B-cell proliferation surrounded by resting B-cells. The observation of secondary follicles is suggestive of the presence of activated CD4+ T cells expressing the T-cell activation marker CD40L at those locations. Additional, flow cytometric data did not show any significant decrease in T- or B-cell populations. Also, extensive coating of CD4-bearing cells with complexes of ibalizumab and anti-ibalizumab antibodies may have interfered with mitogen binding, resulting in a transient suppression of *ex vivo* mitogen responses at the high dose (25 mg/kg). As recovery was observed of stimulation indices and other related histological clinical pathology parameters were not indicative of adverse changes, it's relevance for humans is limited.

In the 9-month study with cynomolgus monkeys, no adverse effects were observed in animals without a strong antibody response against ibalizumab. However, throughout the study, antibodies against ibalizumab were observed in 83% (10/12) and 58% (7/12) of the animals at the low and high dose (25 and 50 mg/kg), respectively. In total, 7 animals at the low dose and 1 animal at the high dose developed a severe anti-drug-antibody response, resulting in lack of exposure, after which these animals were euthanized and necropsied around 6.5 months. Some of these animals showed clinical signs, including drowsiness, reduced coordination and hypersalivation. Furthermore, glomerulopathy with hyperplasia and hypertrophy of cells in the mesangium and increased mesangial matrix in the renal glomeruli was observed in these animals. Multifocal glomerulopathy was observed together with reduced albumin levels, which can be an indication for protein loss through the kidney. As these effects were observed only in animals with a strong antibody response against ibalizumab, its relevance for humans is limited.

At the NOAEL ibalizumab exposure in cynomolgus monkeys without an anti-ibalizumab response was approximately 4 fold exposure at the MRHD.

A risk assessment of the carcinogenic potential of ibalizumab using a weight of evidence approach indicates that ibalizumab is not expected to be carcinogenic in adult patients infected with HIV-1. However, considering that ibalizumab is intended to be used in combination with other antiretroviral medicinal products in a population with underlying immunodeficiency, the potential risks associated with human oncoviruses should be addressed through clinical monitoring and post-marketing surveillance.

Genotoxicity

As ibalizumab is a biotechnology-derived protein product made of natural amino acids, and as per ICH S6(R1), genotoxicity studies are not applicable and therefore have not been conducted.

Carcinogenicity

A risk assessment of the carcinogenic potential of ibalizumab was done using a weight of evidence approach as a US FDA post-approval commitment. The conclusion of this report made by the applicant was that given the weight of evidence, ibalizumab is not expected to be carcinogenic. Standard 2-year carcinogenicity studies in rodents or 6-month studies in transgenic mice were not possible, because ibalizumab does not bind rodent CD4. In addition, performing a monkey toxicology study longer than 9 months in duration would not further inform the carcinogenicity risk assessment of ibalizumab, and thus, use of non-human primate cells for such a study was not warranted. Therefore, the most clinically meaningful approach to address the potential human carcinogenicity risk of ibalizumab, including risks associated with human oncoviruses, was through clinical monitoring and post-marketing surveillance of human patients chronically administered ibalizumab.

Reproductive and developmental toxicity

No reproductive, no early embryonic or embryo-fetal developmental studies were performed. According to ICH 6 guideline, the potential maternal and developmental effects of ibalizumab in pregnant cynomolgus monkeys and their offspring were evaluated.

The objectives of the pre-postnatal toxicity study, were to assess potential maternal and developmental effects of Ibalizumab in pregnant cynomolgus monkeys and their offspring. In pregnant females, ibalizumab administration resulted in statistically significant increases in CD3+/CD8+ T-cytotoxic lymphocyte absolute counts on GD133; with corollary changes observed in percent of cells gated. Increases in this cell population were not present after parturition. During the postpartum period (on PPD28), CD3+ T-lymphocyte absolute counts and percent of cells gated were statistically significantly increased in the ibalizumab-treated adult females. These increases generally recovered to within control ranges at PPD91. There were no ibalizumab-related alterations in absolute counts or percent of cells gated observed for CD3+/CD4+ T-helper lymphocyte or CD3-/CD20+ B-lymphocyte populations. In infants of mothers exposed to ibalizumab, statistically significant decreases were observed in infant CD3+ total T-lymphocytes, CD3+/CD4+ T-helper lymphocytes, and CD3-/CD20+ B lymphocytes on at least 1 of the measured time points (BD14 and BD28). Additionally, statistically significant increases were observed in infant CD3+/CD8+ T-cytotoxic lymphocytes. These values generally trended toward control ranges at BD28 or BD91.

Toxicokinetics

After repeated exposure, systemic exposure of ibalizumab increased in an approximately dose proportional manner over the dose range of 10 to 50 mg/kg in monkeys. Adequate exposure was maintained to evaluate safety in the toxicological studies. Exposure multiples (based on SS Cmax) varied from 4.9-19.6 for i.v. administrations. Anti-ibalizumab antibodies were measured in all studies (see pharmacokinetics chapter 3.7) and interfered with the ibalizumab detection assay, thereby probably causing an underestimation of the ibalizumab concentrations after 10 days after first exposure. E.g., in

the 9 month study, ADA's were observed in eight animals. These animals had extremely low serum concentration levels of test article within hours of dosing.

Interspecies comparison

The pharmacokinetics of ibalizumab was studied only in monkeys (Cynomolgus and Rhesus).

In both humans and monkeys, ibalizumab shows nonlinear pharmacokinetics, characteristic of saturable (capacity-limited) elimination kinetics. Following a single dose, systemic exposure of ibalizumab (AUC) increased in a supra-proportional manner in humans and monkeys. However, after repeated exposure, ibalizumab AUC increased approximately dose proportionally in monkeys. Following a single dose, plasma clearance was low, and decreased as the dose increased (in humans from 229 to 8.6 mL•kg/day at a dose of 0.3 to 25 mg/kg; in monkeys from 8.37-6.93mL•kg/day at a dose of 25-50 mg/kg). Similarly, terminal elimination half-life (T1/2) increased with the dose and also increased after repeated dosing. It is noted that terminal half-life in monkeys is much longer than in humans (in humans, terminal elimination half-life was increased from 1.58 (single dose) to 3.27 days (multiple doses) and from 2.67 (single dose) to 3.11 days (multiple doses) for 10 mg/kg once weekly and 25 mg/kg every 2 weeks (Q2W), respectively; in monkeys, terminal elimination half-life was increased from 4.8 (SD) to 8.2 days (MD) and from 5.6 (SD) to 10.7 days (MD) for 25 mg/kg and 50 mg/kg, respectively). No relevant gender differences were observed in the pharmacokinetics of ibalizumab.

Enhanced ePPND

An enhanced pre- and post-natal development study was performed with cynomolgus monkeys. Observed effects included significant increase in CD3+ total T-lymphocytes and CD3+/CD8+ T-cytotoxic lymphocytes in adult females. In infants CD3+/CD8+ T-cytotoxic lymphocytes were also increased, with a decrease in CD3+ total T-lymphocytes, CD3+/CD4+ T-Helper lymphocytes and CD3-/CD20+ B-lymphocytes. In general, values were going back towards control ranges at 28 or 91 days after birth. However, in infants the CD3+/CD4+ T-Helper lymphocytes were significantly decreased up to 91 days, with values comparable to control at 180 days. The NOAEL in this study for effects on development was 110 mg/kg ibalizumab. The relevance of the decrease of CD3+/CD4+ T-Helper lymphocytes for human is unknown. Exposure at end of pregnancy was 8 fold exposure at the MRHD.

Local tolerance

Local tolerance was studied in a subcutaneous 3-week study in cynomolgus monkeys. Lymphoid hyperplasia in the inguinal lymph nodes was observed, which was reversible. This is consistent with a normal monkey immune response to an injected humanized foreign protein. Therefore, this effect is probably not relevant for humans.

Tissue cross-reactivity

No cross-reactivity to ibalizumab was observed in any human or rhesus monkey tissue tested, as only staining of target CD4 cells occurred. Ibalizumab stained the same rhesus monkey tissues as human tissues, indicating that the rhesus monkey is a relevant species for safety and tolerability evaluations.

2.3.4. Ecotoxicity/environmental risk assessment

Ibalizumab is a monoclonal antibody consisting of naturally occurring amino acids. As such it is not expected to have any impact on the environment.

2.3.5. Discussion on non-clinical aspects

The decrease of CD4+ T-cells in cynomolgus monkeys from BD14-91 in the ePPND study was further discussed. The main argument is that, although CD4+ cells in infants of treated females was temporarily suppressed compared to control, there was no further impact on immunocompetence of the infants. The relevance of this effect for human pregnancy and lactation remains unknown but as ibalizumab is a later line treatment option, the number of pregnant women to be treated with ibalizumab is expected to be very limited. In addition, the effect on CD4+ cells is transient and no functional effects on immunocompetence were observed. Because of this, further screening in human infants for this effect is not considered necessary.

2.3.6. Conclusion on non-clinical aspects

There are no non-clinical major objections that would prevent granting of a marketing authorization.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Main studies. (Table 2)

Table 2 Tabular overview of clinical studies

Type of Study	Study Identifier	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment	PK Sampling Schedule
Phase 1a	Hu5A8.01	Single dose IV , 0.3, 1, 3, 10, 25 mg/kg	30: 5/group	HIV-1 Subjects with uncontrolled viral replication	Single dose	Day 0: predose, 0.5 h (for 0.3-3 mg/kg), 1 h (for 0.3-10 mg/kg), 3, 6, 12 h Day 1, 2, 3, 4, 7, 14, 21 (only 25 mg/kg), 28

Type of Study	Study Identifier	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment	PK Sampling Schedule
						and 90
Phase 1b	TNX 355.02	Multi-dose IV, Arm A: 10 mg/kg q wk for 10 doses; Arm B: 10 mg/kg single dose, then 6 mg/kg q 2 wks for 5 doses; Arm C: 25 mg/kg q 2 wks for 5 doses	22: Arm A: 9; Arm B: 10; Arm C: 3	HIV-1 Subjects with triple-class treatment experience	Multi-dose, 10 weeks	Arm A: prior and after infusion on Day 1, Wk 1, 2, 3, 5, 7 and 9; Wk 10, 10.5, 11, 11.5, 12, 13, 14, 15 and 16 Arm B: prior and after infusion on Day 1, Wk 1, 2, 3, 5, 7 and 9; Wk 10, 10.5, 11, 11.5, 12, 13, 14, 15 and 16 Arm C: prior and after infusion on Day 1, Wk 1, 2, 4, 6 and 8; Wk 9, 10, 10.5, 11, 11.5, 12, 13, 14, 15 and 16
Phase 2a	TNX 355.03	Multi-dose IV and placebo Arm A: 15 mg/kg + OBR q 2 wks for 48 wks; Arm B:10 mg/kg + OBR q wk (for 9 wks), then 10 mg/kg + OBR q 2wks (for additional 39 wks);	Arm A: 28; Arm B: 27; Arm C:27 (23 cross over)	HIV-1 Subjects with triple-class treatment experience	48 wks double blind phase, total up to 216 wks	Prior and after infusion on Day 1, Wk 1, 2, 3, 4, 8, 12, 16, 24, 32, 40 and 48

Type of Study	Study Identifier	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment	PK Sampling Schedule
		Arm C: placebo, cross over to 15 mg/kg when viral load failed				
Phase 2b	TMB-202	Multiple fixed doses IV, 800 mg q 2 wks, or 2000 mg q 4 wks	59 (800 mg q2 wks) 54 (2000 mg q4 wks)	HIV-1 Subjects with triple-class treatment experience resistant to NRTI, NNRTI and PI	24 weeks,	All patients: 10 min, 1 and 6 h after Day 1 infusion; prior and after infusion on Wk 2, 4, 8, 12, 24 PK substudy: Day 1, 7, 8, 9, 10, 11, 14, 21, 22, 23, 24, 25 and 28 after Wk 8 dosing
Phase 3	TMB-301	Fixed dose IV, 2000 mg loading dose followed by 800 mg maintenance dose q2 wks + OBR up to 23 weeks	40	HIV-1 Subjects with heavily treatment-experience and with multidrug resistance to at least one agent in three classes	24 weeks,	Prior infusion: Wk 1, 2, 3, 5, 9, 13, 17, 21 and 25 After infusion: Wk 1, 3, 13 and 21
Expanded Access Study	TMB-311	Cohort 1: Fixed dose IV, 800 mg q2 wks + OBR or 2000 mg q4 wks + OBR Cohort 2: Fixed dose IV, 2000 mg loading dose followed by 800 mg maintenance dose q2 wks + OBR	Cohort 1: 41 Cohort 2: 38	HIV-1 Subjects with heavily treatment-experience and with multidrug resistance to at least one agent in three classes	48 weeks	Not applicable

2.4.2. Pharmacokinetics

All pharmacokinetic studies for ibalizumab have been conducted in patients with HIV. Ibalizumab is proposed to be administered intravenously with a loading dose of 2000 mg and followed by a 800 mg dose every two weeks as maintenance.

Absorption The Tmax was dose-dependent, with later Tmax at higher doses.

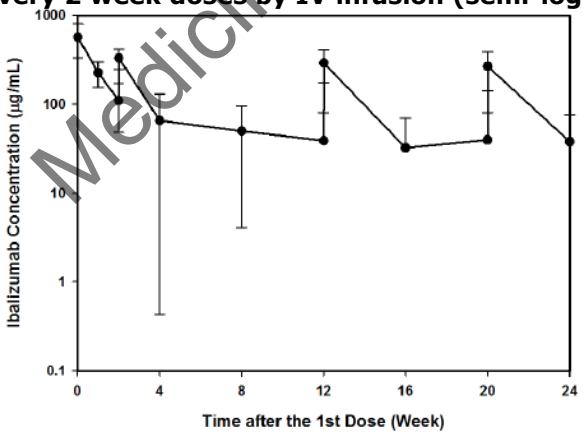
Distribution The volume of distribution is about 30-50 ml/kg (i.e. 2.1 – 3.5 L), which is comparable with vascular space, indicating no extravascular distribution. Pooled data in a population PK analysis indicated a Vd of 4.8 L.

Elimination As an IgG4 antibody, ibalizumab is expected to be cleared by catabolism and also target-mediated clearance (by CD4+ T cells). In the single dose study (Hu5A8.01), the elimination half-life increased with increasing dose (0.3 mg/kg – 25 mg/kg), from 2.7 to 64 hours (0.11 – 2.7 days). Overall, the elimination half-life with the proposed 10 mg/kg and 25 mg/kg dose is 1-3 days.

Dose proportionality The pharmacokinetics of ibalizumab is nonlinear, likely due to binding to the target. Mean estimates of AUC increased more than proportionally with dose over the dose range of 0.3 to 25 mg/kg. In the lower dose range (0.3 – 3 mg/kg), Cmax is also increased more than dose proportional, whereas in the higher dose range (10 – 25 mg/kg), Cmax increase is proportional to the dose. Clearance is decreased when dose is increased. The decrease in total clearance is expected to be predominantly influenced by the saturation of target-mediated elimination of ibalizumab in lower doses. Only a dose of 800 mg (with a single 2000 mg loading dose) is proposed for ibalizumab, therefore dose proportionality is not considered relevant for efficacy and safety.

Time dependency Ibalizumab steady-state/single dose Cmax accumulation ratio was estimated to be 1.4 with 15 mg/kg every two weeks, this is in line with the elimination half-life (1-3 days) and every two weeks dose scheme. With the final dosing scheme of the single 2000 mg loading dose and 800 mg every two weeks no accumulation for Cmax was observed. The serum trough concentration of ibalizumab decreased and reached steady state after 2-3 doses of 800 mg (Figure 1). The estimated effective half-life of ibalizumab is 5- 8 days.

Figure 1 Mean ibalizumab serum concentrations following 2000 mg loading dose and 800 mg every 2 week doses by IV infusion (semi-log scale, TMB301)



Variability Inter-individual variability of Cmax, AUC, and CL of ibalizumab is moderate to high (20 - 50%). The intersubject variability of the serum trough concentrations in study TMB301 is about 100%.

PK in target population All the PK studies were conducted in HIV patients. The dose of 800 mg was selected to achieve at least 85% CD4 occupancy. The loading dose of 2000 mg was added because in case of starting with a 800 mg dose, only 50% of patients achieved >85% occupancy in the 2 weeks after the first dose. In study TMB301, after the 2000 mg loading dose the mean Ctrough of ibalizumab was above 30 µg/ml at steady state, and in the first 2 weeks 77% of patients had >85% occupancy, and. The 85% occupancy was supported by Ctrough >0.13 µg/ml.

Special population No direct effect of hepatic or renal function on the pharmacokinetics of ibalizumab is expected because antibodies are in principle cleared by catabolism. No studies or analyses were conducted for investigating the impact in patients with renal or hepatic impairment.

No study in children has been conducted. A population pharmacokinetics analysis was conducted to estimate the dose in adolescent (18-12) and children (6-11). The results suggested that the adults dose can be given to adolescent, whereas the dose should be reduced for children (i.e. a loading dose of 1500 mg and biweekly maintenance dose of 600 mg). The small observed differences in exposure of ibalizumab in terms of gender and race can be explained by body weight. No specific study was conducted in elderly patients. PopPK analysis indicated that body weight was the only statistically significant covariate and ibalizumab concentrations decreased as body weight increased. Response rate data at the 800 mg q2wk dose however indicate no clear effect on the % observed for a body weight of <70 kg, 70 - 85 kg and >85 kg. Immunogenicity is very low and only observed in the early phase of the treatment transiently. Therefore, immunogenicity is not expected to have a significant effect on PK of ibalizumab.

Pharmacokinetic interaction studies

Ibalizumab is a monoclonal antibody and is therefore degraded as other monoclonal antibodies and not via CYPs and Phase II enzymes, nor is a substrate for drug transporters. Therefore no pharmacokinetic drug-drug interactions are expected.

2.4.3. Pharmacodynamics

To induce antiviral activity, ibalizumab needs to bind to domain 2 of the CD4 receptor on human target cells. Through this binding, viral entry into the cell is inhibited via blockage of the essential post-attachment conformational changes in gp120 and/or the CD4 receptor, without interfering with major histocompatibility complex (MHC) class II-mediated immune functions, which requires access to CD4 domain 1. As binding to the CD4 receptor is the desired mechanism of action, the applicant studied CD4 receptor occupancy as their main pharmacodynamic target. Additionally, potential effects of ibalizumab binding on CD4 receptor density (i.e. the number of CD4 molecules on the cell surface) was studied, as well as potential viral resistance mechanisms to circumvent ibalizumab's antiviral activity.

CD4 receptor occupancy (RO)

Serum CD4 receptor occupancy (RO, i.e. the proportion of total CD4 molecules on patient blood cells that are occupied by bound ibalizumab) and the mean percentage change from baseline in CD4 receptor

density (RD, which will be discussed in the following section) were measured in samples from clinical trials to determine if an association exists between these measures and virologic outcome.

For the Phase 1a, 1b and 2a trials, CD4+ T-cell coating by ibalizumab was determined. For the Phase 2b and 3 trials, receptor occupancy by ibalizumab was determined using a more sensitive assay. However, no true validation report could be provided by the applicant. Due to the change in assays during the clinical development program, and given that the earlier studies investigated mg/kg doses of ibalizumab whereas the later studies used a fixed concentration, with actual tested concentrations varying across the different studies, results of the individual studies cannot be pooled and their comparability is reduced.

From the early studies (Hu5A8.01, TNX 355.02, and TNX 355.03) it was concluded that CD4 cell coating was dose dependent, and that at least 3.0 mg/kg was necessary to have full coating in all patients after a single infusion in Hu5A8.01. In the multiple-dose study TNX 355.02, either a 10 mg/kg weekly dose (Arm A), or a 25 mg/kg biweekly dose (Arm C) resulted in fully coated CD4 cells, whereas a lower biweekly dose of 6 mg/kg (Arm B) was not enough to achieve complete coating in all patients.

In later studies with ibalizumab provided as fixed dose regardless of weight (TMB-202 and TMB-301), RO was no longer dose dependent. Table 3 shows RO levels in pre-dose samples collected while on treatment (excluding Baseline samples) for Study TMB-202. Pre-dose samples collected at Baseline, when no ibalizumab was present in serum, yielded average receptor occupancy measurements of 7.7 ± 7.7% (range, 0 to 31%). For samples collected immediately post-dose on Day 1, when super-saturating concentrations of ibalizumab were present in serum (regardless of dose), the average receptor occupancy measurement was 97.1 ± 4.7% (range, 86 to 100%). For the purposes of this study, these data ranges define values for low (0 to 31%), intermediate (32 to 82%), or high (83 to 100%) levels of receptor occupancy.

Table 3 CD4 Receptor Occupancy at Pre-Dose Trough (ITT Population, TMB-202)

Pre-dose time point (unless otherwise noted)	Number (%) of Patients							
	Ibalizumab + OBR							
	800 mg q2wk				2000 mg q4wk			
		Level of receptor occupancy				Level of receptor occupancy		
	n	Low (0-31%)	Int (32-82%)	High (83-100%)	n	Low (0-31%)	Int (32-82%)	High (83-100%)
Day 1 (Baseline)	38	38 (100)	0	0	27	27 (100)	0	0
Day 1, post-dose	10	0	0	10 (100)	17	0	0	17 (100)
Week 2	43	10 (23)	15 (35)	18 (42)	33	0	1 (3)	32 (97)
Week 4	48	13 (27)	14 (29)	21 (44)	37	22 (60)	5 (14)	10 (27)
Week 8	42	8 (19)	11 (26)	23 (55)	35	15 (43)	8 (23)	12 (34)
Week 12	43	8 (19)	10 (23)	25 (58)	31	13 (42)	8 (26)	10 (32)
Week 24	35	3 (9)	6 (17)	26 (74)	28	7 (25)	4 (14)	17 (61)

Source: Table 14.2.7.1.5

Int=intermediate; OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks

Both the 800 mg biweekly dose and the 2000 mg Q4W dose did not result in complete RO, in contrast to the 25 mg/kg biweekly dose found to result in complete coating in study TNX 355.02. Of note, the 25 mg/kg Q2W dose in TNX-355.02 corresponds to a 2000 mg biweekly dose in an 80 kg patient, which may explain the higher RO levels in the earlier study. It is however not known what level of RO is needed for

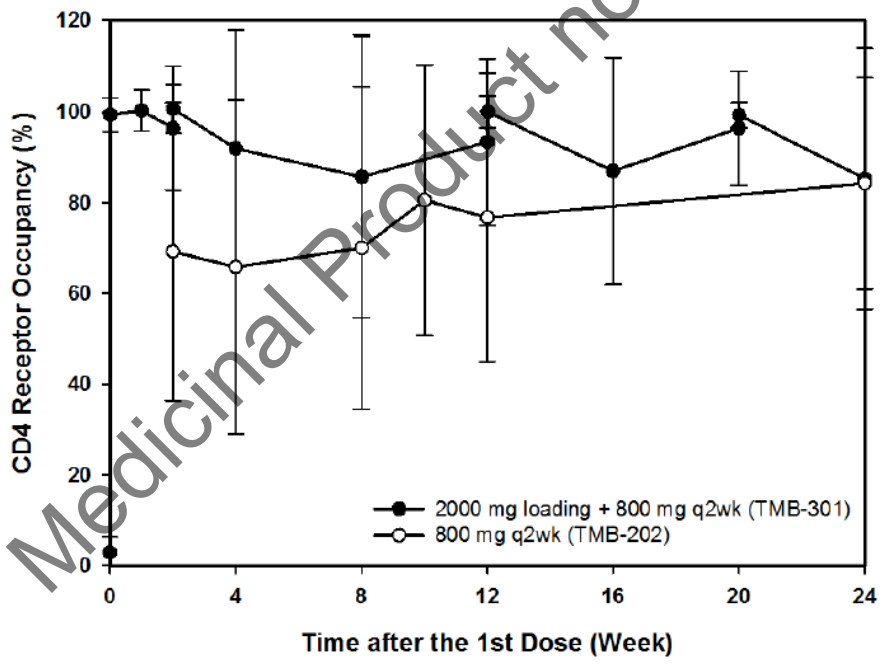
optimal viral load reduction (see further below, section *Relationship between plasma concentration and effect*), and hence the implications of the observed non-complete coating, if any, are unknown.

The number of patients with data included in table above is substantially lower than the total number of patients treated in this study (which was n=59 in the 800 mg q2wk group and n=54 in the 2000 mg q4wk group). Due to the high number of missing data points for TMB-202 and lack of a validation report, it cannot be excluded that the reported RO values may be biased.

In Study TMB-301, RO levels were measured immediately following infusion at Day 7 (Baseline), Day 21, Week 13, and Week 21. Additional samples were collected at Day 14, and after administration of 800-mg doses starting at Day 21, trough RO measurements were performed on samples collected immediately before dose administration at Week 5 and then every 4 weeks through Week 25. The population mean RO for these measurements were relatively stable throughout the study, ranging between 85%-96% through Week 25.

Comparing between TMB-202 and TMB-301 studies, with the addition of the loading dose, the mean RO increased from 67% to 96% and percentage of subjects with RO <85% decreased from 50% to 23% at week 2 after the 1st dose (Figure 2 and Figure 3). This indicates that the 2000 mg loading dose helped to reach 85% RO at the initial dose and to maintain high levels of receptor occupancy throughout the dosing period. At week 24 after the 1st dose, the RO was comparable between these two dosing regimens.

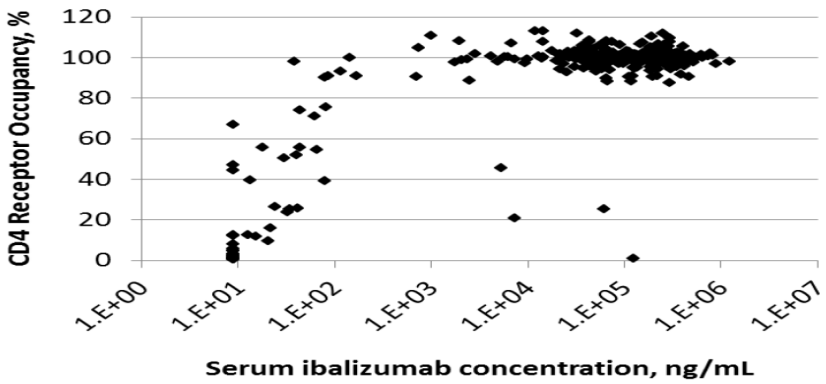
Figure 2 Mean (± SD) CD4 receptor occupancy in TMB-301 and TMB-202



Relationship Between Serum Concentration and CD4 Receptor Occupancy

In both Study TMB-202 and TMB-301 there was a correlation between serum ibalizumab concentrations and receptor occupancy levels. This was however not the case in the previous study (TNX 355.03), due to non-quantitative and unreliable results of the assay used at that time.

Figure 3 Dose-Response of CD4 Receptor Occupancy to Ibalizumab Concentrations (TMB-301)



Source: Appendix 16.2.6, Listing 16.2.6.9.
CD4=cluster of differentiation 4.

Curve fitting of the above depicted data produced an EC85=130 ng/mL for ibalizumab binding to CD4 on CD4+ T cells in patient blood. The results also indicate a general correlation between lower ibalizumab concentrations (i.e., <100 ng/mL) and reduced RO. The 4 outliers are, according to the applicant, due to unexplained technical or operational issues, but no root-cause analysis is provided. Given that RO analyses will not be performed in clinical practice this is accepted. However, it is advised that if RO analyses are envisioned to be helpful for further development in e.g. children, root-cause analysis of the technical or operational issues may be important.

Relationship between plasma concentration and effect

The question then rises to what extent RO values and/or serum ibalizumab concentrations correlate with virologic outcome. In study TNX 355.02 a correlation between cell coating (RO) and viral load decrease was observed. Although the sample size of the study is small and no firm conclusions should be drawn, the results suggested that already partial coating of CD4 cells with ibalizumab could induce a decrease in HIV viral load. Of note, in study TNX 355.02, ibalizumab was given without concomitant OBR. As such, the (temporary, see clinical efficacy section) decrease in HIV-1 viral load seen in this study, can be fully attributed to ibalizumab.

In Study TMB-202, virologic outcomes were analysed according to each patient's average level of CD4 receptor occupancy measured pre-dose at Weeks 2 through 24 (Table 4).

Table 4 Virologic Outcomes by CD4 Receptor Occupancy (Study TMB-202)

Population Statistic	Ibalizumab + OBR								
	800 mg q2wk (N=59)			2000 mg q4wk (N=54)			Total (N=113)		
	Level of CD4 Receptor Occupancy at Trough								
	Low	Int	High	Low	Int	High	Low	Int	High
n	9	18	23	13	21	11	22	39	34
ITT-MEF population									
Mean change from baseline to Week 24, log_{10} copies/mL	-1.1	-1.6	-1.9	-1.2	-1.9	-1.6	-1.2	-1.8	-1.8
Viral load <50 copies/mL, %	25	47	52	15	38	27	19	42	44
Viral load <400 copies/mL, %	38	59	70	31	57	55	33	58	65
ITT-LOCF population									
Mean change from baseline to Week 24, log_{10} copies/mL	-1.8	-2.0	-2.1	-1.7	-2.0	-2.0	-1.7	-2.0	-2.1
Viral load <50 copies/mL, %	25	53	52	15	38	27	19	45	44
Viral load <400 copies/mL, %	63	65	74	54	57	64	57	61	71

Source: Table 14.2.8.1.1, Table 14.2.8.1.2, Table 14.2.8.3.1, Table 14.2.8.3.2, Table 14.2.8.6.1, Table 14.2.8.6.2

Int=intermediate; OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks

The results suggest a somewhat worse outcome for patients in the low RO category vs patients in the intermediate or high RO category, although no notable differences can be observed between the last two categories (intermediate and high).

Also for Study TMB-301, virologic outcomes were analysed in relation to each patient's average level of CD4 receptor occupancy (Table 5)

Table 5 CD4 Mean Trough RO and Virologic Responses at Week 25 (ITT-MEF, Study TMB-301)

	Mean Trough $RO_{D21\text{-}W25}$	
	<80%	>80%
N	6	34
<50 HIV-1 RNA copies/mL, n (%)	1 (17)	16 (47)
<400 HIV-1 RNA copies/mL, n (%)	2 (33)	19 (56)
Mean ± SD change from BL in HIV-1 RNA, log_{10} copies/mL	-1.1 ± 1.4	-1.7 ± 1.5
	Mean Trough $RO_{W5\text{-}W25}$	
	<80%	>80%
N	8	32
<50 HIV-1 RNA copies/mL, n (%)	3 (38)	14 (44)
<400 HIV-1 RNA copies/mL, n (%)	6 (50)	17 (53)
Mean ± SD change from BL in HIV-1 RNA, log_{10} copies/mL	-1.5 ± 1.7	-1.7 ± 1.5

Source: Appendix 16.2.6, Listing 16.2.6.9.

BL=baseline; CD4=cluster of differentiation 4; HIV-1=human immunodeficiency virus Type 1; ITT=intent-to-treat; MEF=missing equals failure; NA=not applicable; $RO_{D21\text{-}W25}$=receptor occupancy value over the course of the entire study (Day 21 to Week 25); $RO_{W5\text{-}W25}$=receptor occupancy value from Week 5 to Week 25 (including only values after administration of bi-weekly 800-mg maintenance doses); SD=standard deviation.

There seems to be a numerical difference in outcome (VL<50 copies/mL) between patients with a mean RO between Day 21 and Week 25 of <80% (1/6 (17%)) or >80% (16/34 (47%)), but not between Week 5 and Week 25 (38% vs 44%, respectively). This seems to be due to two patients who, when including the RO values during the whole study, had a mean RO>80%, which subsequently decreased to <80% when

only the maintenance dose RO values were taken into account. Both patients achieved a viral load <50 copies/ml.

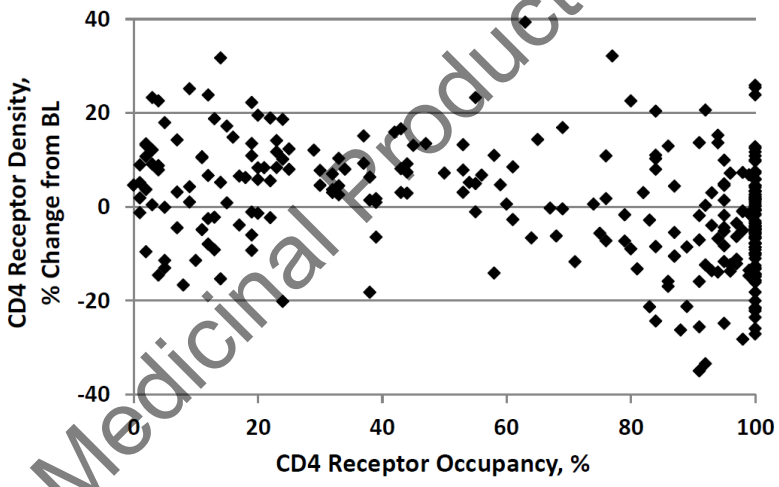
A caveat of the above analyses is that there is high inter-individual variability of viral load reduction. Overall, it can be concluded that there is no data to support a clear relationship between RO levels and virologic response. This, together with the inability to use the earlier studies due to the lack of a quantitative assay at the time those studies were running, the high number of missing data points for TMB-202, and the lack of a true validation report for the assay used in the main studies, results in the conclusion that RO values are not very useful for decision making.

Absolute CD4+ T cell count and receptor density (RD)

There was considerable inter-patient variability in absolute CD4+ T cell counts during each study. In all studies, absolute CD4+ T cell counts increased during the first days to weeks after ibalizumab infusions, which was most likely due to redistribution of cells. At day 28, absolute CD4+ T cell counts in all groups in Hu5A8.01 (single infusion study) returned back to baseline values. Also, in TNX 355.02, the increase in absolute CD4+ T cell counts was not sustained, as highest values were reached at Week 1 or 2. In TNX 355.03, changes from Baseline in CD4+ T cell counts were modest in all treatment arms and differences between arms were small.

In Studies TMB-202 and TMB-301, receptor density (RD) was measured. RD is defined as the amount of CD4 molecules on patient blood cells. To determine the potential effects of CD4 binding by ibalizumab on CD4 receptor density during Study TMB-202, the results of receptor density measurements were paired with the corresponding receptor occupancy results for core pharmacokinetic samples from Weeks 2 through 24. (Figure 4).

Figure 4 CD4 Receptor Density at Weeks 2 Through 24 (Pre-dose Samples, Study TMB-202)

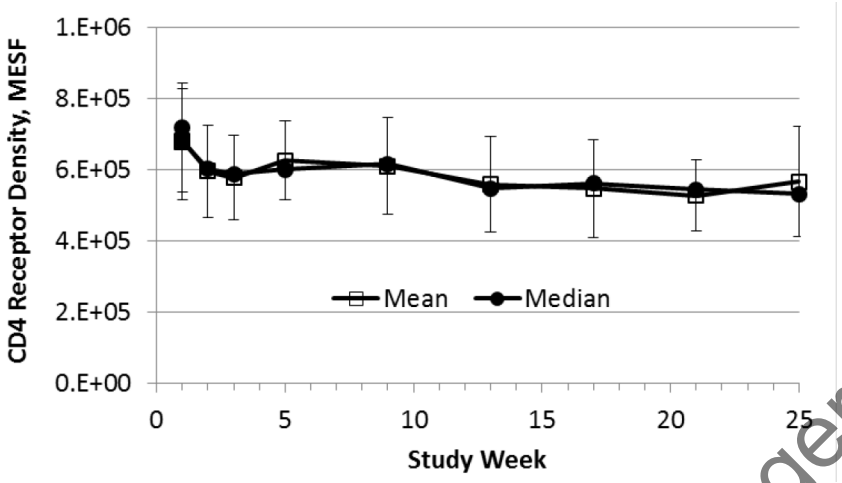


Source: Figure 14.2.8.1

The majority of samples with high receptor occupancy exhibited slightly reduced receptor density relative to Baseline (median change in receptor density = -4.1%), whereas the majority of samples with low or intermediate receptor occupancy exhibited no change or slightly elevated receptor density (median change in receptor density = 0 and 4.9%, respectively). As such, there seems to be a (weak) relation between CD4 receptor density and CD4 receptor occupancy, suggesting that there is some downregulation of CD4 molecules when the receptor is occupied.

Also in Study TMB-301, RD was measured over the course of the study to monitor CD4 receptor levels in response to ibalizumab treatment. The mean RD across all patients was 10%–23% below baseline levels from Day 14 through Week 25 (Figure 5). Longer-term data are unfortunately not available.

Figure 5 Mean Trough CD4 Receptor Density



Source: Appendix 16.2.6, Listing 16.2.6.9.
CD4=cluster of differentiation 4; MESF=molecules of equivalent soluble fluorescence.

HIV-1 Viral Resistance

Phenotypic and genotypic assessments have been conducted throughout the ibalizumab development program to identify potential correlates with ibalizumab treatment outcomes. The program has relied almost exclusively on susceptibility testing performed at Monogram Biosciences. The primary indicators of ibalizumab susceptibility are maximum percent inhibition (MPI), which reflects the upper plateau in dose-response curves observed at high drug concentrations *in vitro*, the inhibitor concentration at the midpoint of the dose-response curve ($IC_{HalfMax}$), and to some extent the 50% inhibitory concentration (IC_{50}).

There were no virologic assessments conducted as part of the Phase 1a study (Hu5A8.01). In the Phase 1b study TNX 355.02, samples were collected for viral resistance testing at Baseline and Week 9. Analysis of baseline and virologic failure viruses unambiguously showed reduced ibalizumab susceptibility at virologic failure. This reduced susceptibility seemed to be linked to the amount of potential N-linked glycosylation sites (PNGS) in variable region 5 (V5) of the Envelop protein of HIV-1. The most conserved positions were at amino acids 460-462 (site 1) and 464-466 (site 2), relative to the HXB2 sequence. Removal of site 1 PNGS clearly reduced ibalizumab susceptibility, i.e. resulted in HIV-1 clones that can still (to some extent) infect CD4+ cells despite ibalizumab binding to the CD4 receptor. Additional removal of site 2 PNGS even further reduced ibalizumab susceptibility. Site-directed mutagenesis confirmed the association between V5 glycosylation and ibalizumab susceptibility.

The applicant concluded that the most probable explanation for ibalizumab escape is the ability of ibalizumab resistant HIV-1 variants to facilitate CD4 induced conformational changes in the CD4-gp120 complex, which enables co-receptor engagement despite bound ibalizumab. The re-establishment of requisite conformational changes in the presence of ibalizumab may be enabled by elimination of steric hindrances imposed by one or more V5 glycosylation moieties.

A clinical virology report was provided for Study TMB-202, dated 29 March 2016. Twenty-five (25) patients experienced protocol-defined virologic failure while on blinded study medication due to non-response (two consecutive viral load measurements with <1 log10 reduction from Baseline). There was no difference between the two ibalizumab regimens, with 12/59 (20.3%) and 13/54 (24.1%) patients experiencing virologic failure in the 800 mg Q2W and 2000 mg Q4W groups, respectively. Five (5) additional patients experienced virologic rebound or breakthrough with HIV RNA ≥200 copies/ml after virologic suppression. Results presented in the provided report are in line with the results from the phase I study TNX 355.02, indicating reduced ibalizumab susceptibility at virologic failure (baseline MPI 95±7% (median, 97%), failure MPI 65±15% (median, 61%). The mean IC Half Max increased from 26±13 ng/ml (median, 23 ng/ml) at baseline to 58±32 ng/ml (median, 60 ng/ml) at virologic failure. It was again concluded that loss of PNGS is the primary pathway for development of ibalizumab resistance. Overall, 8 of 12 analysed virologic failure samples lost susceptibility to one or more OBR agents that were fully active at Baseline. The remaining 4 of 12 virologic failure samples lost susceptibility to ibalizumab only.

In Study TMB-301, 10 of the 40 patients (25%) experienced virologic failure or viral load rebound. One additional patient classified as an early discontinuation but experienced an unconfirmed viral load rebound after initial response. This percentage of patients with virologic failure is in line with earlier studies (TMB-202) and is considered significant in this rather short time frame of 25 weeks. Phenotypic and genotypic analyses were performed on baseline and virologic failure samples for the 10 patients. MPI values for the baseline isolate in each pair ranged from 55% to 99% with a mean = 87 ± 16% (median=95%). Individual MPI values for the 10 virologic failure isolates ranged from 43% to 72% with a mean = 58±9% (median = 58%). All 10 MPI values recorded at virologic failure were numerically lower than the paired baseline value, except for one patient who had the same MPI value, 55, at both baseline and virologic failure. The phenotypic results, in general, suggest that there was a reduction in ibalizumab susceptibility during the course of treatment on TMB-301. Changes in HIV susceptibility to OBR agents were also monitored at virologic failure. Six of the 10 patients who experienced virologic failure or viral load rebound were administered fostemsavir as a component of their OBR. OSS calculations were incomplete for these patients because samples could not be tested for fostemsavir susceptibility at treatment failure. Excluding fostemsavir from the OSS calculation, a total of 3 patients had a lower OSS value at virologic failure. For the patients administered fostemsavir, none appeared to lose susceptibility to any other OBR agents between baseline and virologic failure/rebound. The other 4 patients all responded initially and failed after developing resistance to ibalizumab but without developing resistance to any other agents in their OBR, with the possible exception of fostemsavir for which susceptibility testing was unavailable. (Table 6)

Overall, it should be concluded that based on all resistance data provided, there is no evidence for a beneficial effect of continuation of ibalizumab treatment upon virologic failure. A such, it is included in section 4.2 of the SmPC that "If the treating physician determines there is no additional clinical benefit for the patient in terms of viral load reduction, discontinuation of ibalizumab treatment should be considered."

Table 6 OSS Scores at Baseline and Virologic Failure (Study TMB-301)

PID	OBR[b]	BL OSS	VF OSS	Change
01-001	DTG, DRV, FTC, TFV	4	3	-1
04-001	DRV, DTG, ENF, FTC, TFV, fostemsavir	3[b]	3[b]	0
08-001	FTC, TFV, TPV, fostemsavir	1[b]	1[b]	0
09-002	DTG, FTC, TFV	3	nd[c]	nd[c]
17-001	DRV, DTG, FTC, TFV, fostemsavir	0[b]	0[b]	0
18-002	ABC, DRV, FTC, TFV, fostemsavir	2[b]	3[b]	1
21-001	DRV, FTC, MVC, TFV	1	0	-1
22-001	DRV, FTC, TFV	3	3	0
27-002	DRV, DTG, FTC, TFV, fostemsavir	0[b]	0[b]	0
29-002	3TC, DRV, RAL, TFV	2	1	-1
32-001	FTC, TFV, fostemsavir	0[b]	0[b]	0

[a] 3TC, lamivudine; ABC, abacavir; DRV, darunavir; DTG, dolutegravir, ENF, enfuvirtide, TFV, tenofovir; FTC, emtricitibine, MVC, maraviroc; RAL, raltegravir; TPV, tipranavir
[b] Fostemsavir was excluded for OSS calculations due to unavailability of drug for testing at virologic failure
[c] Not determined due to failed PSGT test at virologic failure
Source: Appendix C

Genetic differences in PD response

Analysis of gender, race (Black, White or Others, no Asian samples were analysed) and ethnicity did not reveal major differences in PD responses. However, the subgroups are too small to draw firm conclusions.

Mechanism of action

Ibalizumab binds to the CD4 receptor and is believed to inhibit viral entry by blocking post-attachment conformational changes in gp120 and/or the CD4 receptor. CD4 is a glycoprotein receptor expressed on the surface of T-helper cells, and is the primary site of attachment for HIV-1. By preventing the requisite conformational changes, ibalizumab may, in turn, block the engagement of chemokine co-receptors, thereby interrupting the viral entry process. As ibalizumab binds to domain 2 of CD4, it does not interfere with major histocompatibility complex (MHC) class II-mediated immune functions, which requires access to CD4 domain 1.

2.4.4. Discussion on clinical pharmacology

Analytical assays were in general sufficiently validated. All pharmacokinetic studies for ibalizumab have been conducted in HIV patients. Ibalizumab is proposed to be administered intravenously with a loading dose of 2000 mg and followed by 800 mg every two weeks as maintenance dose. As ibalizumab is an intravenously infusion, Cmax is reached after the end infusion, with some fluctuation due to monoclonal antibodies adsorption to the endothelium and subsequently release into circulation.

As expected for a large Mab, the volume of distribution is similar to vascular space (i.e. 3-6 L). It seems that the elimination is dose dependent due to saturable CD4 mediated clearance. For the clinically relevant doses, 2000 mg and 800 mg, the elimination half-life is around 1-3 days. Dose proportionality

has been shown for Cmax, whereas AUC increased more than dose proportional in the dose range of 10 mg/kg – 25 mg/kg at both single and multiple dose level. Based on PK and PD data, CD4 in T cells is expected to be saturated with the dose of 10 mg/kg and higher. The effective half-life of ibalizumab is around 5 – 8 days.

In the phase III efficacy and safety study, ibalizumab was administrated 800 mg every two weeks after a 2000 mg loading dose. No accumulation is observed under these conditions. The dose was selected to achieve at least 85% CD4 occupancy, i.e. mean Ctrough of 126 ng/ml, in phase III study (TMB301) (details in PD). The loading dose of 2000 mg was added because with the loading dose 50% of the patients can achieve 85% occupancy in the first 2 weeks. However, considering that the method used to calculate the receptor occupancy is considerate not reliable and the results may be biased due to many missing values; conclusions on RO cannot be drawn.

Regarding the special patient populations, the small differences in exposure of ibalizumab in terms of gender and race can be explained by body weight. Only 5 elderly subjects were included in the studies. Although there is an indication of lower trough concentrations in elderly, the lower number of patients prevents to draw a conclusion. PopPK analysis indicated that body weight was the only statistically significant covariate and ibalizumab concentrations decreased as body weight increased. Response rate data at the 800 mg q2wk dose however indicate no clear effect on the % observed for a body weight of <70 kg, 70 - 85 kg and >85 kg. The dose of ibalizumab was estimated for adolescent (18-12) and children (6-11) based on adult pop-PK model adjusted by CD4 count and bodyweight. However the model is not considered qualified for its purposes, and without paediatric data the estimated dose regimen in paediatric population cannot be verified. Paediatric indication is not requested in this application, thus no questions are raised. The immunogenicity is very low and only observed in the early phase of the treatment transiently. Therefore, immunogenicity is not expected to have a significant effect on PK of ibalizumab.

The mechanism of action of ibalizumab relies on binding to domain 2 of the CD4 receptor on human target cells, thereby inhibiting HIV-1 entry into the cell via blockage of essential post-attachment conformational changes in gp120 and/or the CD4 receptor. Binding of ibalizumab to domain 2 of the CD4 receptor does not interfere with major histocompatibility complex (MHC) class II-mediated immune functions, which requires access to CD4 domain 1.

The applicant considers CD4 receptor occupancy (RO, i.e. the proportion of total CD4 molecules on patient blood cells that are occupied by bound ibalizumab) as their main pharmacodynamic target. However, it should be concluded that there is no data to support a clear relationship between RO levels and virologic response. As such, it remains unclear how much CD4 coating (RO) is needed for an antiviral effect. The final dose regimen that was tested in the Phase III study TMB-301 was selected based on, among others, a target trough level of >0.3 µg/mL in order to achieve high RO levels (>80%). The PK/PD analysis showed that an ibalizumab serum concentration of >~100 ng/mL was sufficient to achieve RO levels of >80%. Significant virologic responses were however also observed for patients with mean RO levels <80%. As patients concomitantly received an individualised OBR in the main studies, which in itself has an effect on virologic outcome which differs per patient, this may explain the absence of a clear relation between ibalizumab receptor occupancy and virologic outcome. This however severely hampers the usability of any RO-based target for extrapolation to e.g. children.

Analysis of baseline and virologic failure viruses unambiguously showed reduced ibalizumab susceptibility at virologic failure. This reduced susceptibility seems to be linked to the amount of potential N-linked glycosylation sites (PNGS) in variable region 5 (V5) of the Envelop protein of the virus. Site-directed mutagenesis confirmed the association between V5 glycosylation and ibalizumab susceptibility. The most probable explanation for ibalizumab escape is the ability of ibalizumab resistant HIV-1 variants to facilitate CD4 induced conformational changes in the CD4-gp120 complex, which enable co-receptor

engagement despite bound ibalizumab. The re-establishment of requisite conformational changes in the presence of ibalizumab may be enabled by elimination of steric hindrances imposed by one or more V5 glycosylation moieties.

A significant number of patients developed virologic failure in the clinical studies, 10/40 (25%) in TMB-301 and 25/113 (22%) in TMB-202. Viral load rebound occurred in 6 additional patients, 1 in TMB-301 and 5 in TMB-202, respectively. Analyses of paired samples collected at Baseline and at the time of virologic failure from TMB-202 and TMB- 301, showed that approximately half of the observed amino acid mutations represented the acquisition of new resistance-associated mutations at virologic failure. The far majority of patients with virologic failure lost susceptibility to one or more of the previously fully active OBR agents, and a clearly reduced susceptibility to ibalizumab was observed in the virologic failure vs. baseline samples. A statement has been included in the SmPC to alert physicians to reconsider treatment with ibalizumab in case there is no additional clinical benefit for the patient in terms of viral load reduction and/or CD4 T-cell count preservation.

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of ibalizumab has been investigated to a reasonable extent. However, as the dose selection was recommended based on the target of 80% CD4 occupancy, considering there is no correlation between the % occupancy and the level of viral load reduction, it is difficult to assess whether the proposed doses and dose regimen of ibalizumab are optimal.

No clear relation was observed between the proposed PD target (RO levels) and virologic response in the Phase 2b or Phase 3 studies.

2.5. Clinical efficacy

The clinical development program consists of six clinical studies. Five clinical studies (2 Phase 1, 2 Phase 2, and 1 Phase 3) were conducted in only de novo ibalizumab patients with HIV infection. In addition, an extension study (Study TMB-311) is ongoing. The applicant considers both TMB-301 and TMB-202 to be pivotal to this application. (Table 7)

Table 7 Overview of studies in clinical development program

Study	Study Design	Numbers by Treatment Regimen	Primary (or main) endpoint
Pivotal Study			
TMB-301 HIV-1 Subjects with heavily treatment-experience and with multidrug resistance to at least one agent in three classes	24-week, Phase III, multi-center, open label, single arm study	N=40 2000 mg loading dose, 800 mg q 2 wks + OBR	proportion of patients achieving a ≥ 0.5 log10 decrease from Day 7 (Baseline) in viral load at Day 14, along with a 95% confidence interval (CI) around the observed rate
TMB-202 HIV-1 Subjects with triple-class treatment experience resistant to NRTI, NNRTI and PI	24-week, Phase II, double-blind, randomized, dose-finding, multi-center trial	Arm A (N=59) 800 mg q 2 wks + OBR Arm B (N=54) 2000 mg q 4 wks + OBR	proportion of patients with HIV-1 RNA levels below the assay limit (<50 copies/mL) at Week 24
Additional Studies			
TMB-311 HIV-1 Subjects with heavily treatment-experience and with multidrug resistance to at least one agent in three classes	Expanded Access Study, open label, 2 cohorts	Cohort 1 (N=41) 800 mg q2 wks + OBR or 2000 mg q4 wks + OBR Cohort 2 (N=38) 2000 mg loading dose followed by 800 mg maintenance dose q2 wks + OBR	Expanded Access Study, no primary efficacy endpoint defined

Study	Study Design	Numbers by Treatment Regimen	Primary (or main) endpoint
TNX 355.03 HIV-1 Subjects with triple-class treatment experience	48-week, Phase II, double-blind, randomized, placebo controlled, dose-finding, multi-center trial	Arm A (N=28) 15 mg/kg + OBR q 2 wks for 48 wks; Arm B (N=27) 10 mg/kg + OBR q wk (for 9 wks), then 10 mg/kg + OBR q 2wks (for additional 39 wks); Arm C (N=27, with 23 cross-over) placebo, cross over to 15 mg/kg when viral load failed	mean change in viral load at Week 24 between either of the 2 active arms of ibalizumab and the placebo plus OBR (Arm C)
TNX 355.02 HIV-1 Subjects with stable HIV-1 RNA plasma level of ≥5,000 copies/mL	10-week, Phase Ib, open label, multi-dose trial	Arm A (N=9) 10 mg/kg q wk for 10 doses; Arm B (N=10) 10 mg/kg single dose, then 6 mg/kg q 2 wks for 5 doses; Arm C (N=3) 25 mg/kg q 2 wks for 5 doses	change from baseline in HIV viral load (log10 HIV-1 RNA copies/mL)
Hu5A8.01 HIV-1 Subjects With uncontrolled Viral replication	Phase Ia, open label, single dose-ranging study	Single dose IV, 0.3, 1.0, 3.0, 10, 25 mg/kg, N=5 per group	change from Baseline in HIV viral load

2.5.1. Dose response studies

Dose response has been investigated in 4 clinical studies (Hu5A8.01, TNX-355.02, TNX-355.03, and TMB-202). The initial studies were based on weight-based dosing of ibalizumab, and included:

- a single-dose study (Hu5A8.01) investigating 5 different doses (0.3, 1, 3, 10, and 25 mg/kg, respectively),

- a double-blind study (TNX-355.02) that compared 2 dosage regimens (Arm A received 10 mg/kg administered weekly for 10 total doses, Arm B received a single loading dose of 10 mg/kg, followed 1 week later by 6 mg/kg Q2W for a total of 5 maintenance doses). After these 2 cohorts had received all doses of ibalizumab, another 3 patients were enrolled in Arm C and each received 25 mg/kg of intravenous ibalizumab Q2W for 5 doses, and

- a placebo-controlled, 3-arm study (TNX-355.03) that evaluated safety, pharmacokinetics, and antiviral activity in two ibalizumab arms (Arm A – 15 mg/kg Q2W, Arm B – 10 mg/kg weekly for 9 doses followed by 10 mg/kg Q2W) both in combination with a personalised OBR versus placebo plus OBR.

From these studies, it was evident that monotherapy induced selection of viral variants with reduced ibalizumab susceptibility, resulting in rapid viral rebound (TNX-355.02). It also was found that ibalizumab, together with OBR, significantly reduced HIV-1 viral load, with no notable differences in

virologic response between the 15 mg/kg Q2W arm and the 10 mg/kg Q1W for 9 weeks, followed by 10 mg/kg Q2W arm (TNX-355.03).

During the procedure, more focus was put on study TNX-355.03 as it was considered that this study provides an unbiased estimate of the initial viral response to ibalizumab doses of 10 and 15 mg/kg compared to placebo, albeit on top of an optimized background regimen. Hence, some more information on this study is provided below.

In TNX-355.03, patients were randomized to one of three arms:

• Arm A: Alternating IV infusions of 15 mg/kg ibalizumab and placebo, weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 15 mg/kg ibalizumab every 2 weeks; or

• Arm B: 10 mg/kg ibalizumab IV infusions weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 10 mg/kg ibalizumab every 2 weeks; or

• Placebo Arm: Placebo, weekly IV infusions for the first 9 doses (through the Week 8 visit), then IV infusions of placebo every 2 weeks Arm A.

Patients in all three arms also received an Optimized Background Regimen (OBR). As of Week 16, patients in Placebo arm who experienced virologic failure had the option of receiving 15 mg/kg open-label ibalizumab every 2 weeks and/or switching to a new OBR. Patients in Arm A and B arm who experienced virologic failure had the option of switching to a new OBR. Note that OBT in the TNX-355.03 study documentation refers to Optimized Background Treatment, which is the same as OBR.

A summary of patient disposition and main results of Study TNX-355.03 is provided in table below.

(Table 8)

Table 8 Summary of patient disposition and main results of study TMX-355.03

	Arm A (15 mg/kg)	Arm B (10 mg/kg)	Arm C (Placebo)
Data from CSR TNX-355.03			
Total no. patients randomised	28	27	27
No. patients that completed Week 16	27	24	24
No. patients that completed Week 48	15	17	11
No. patients that completed Week 48 without change in original OBT	13	12	6
No. of patients that switched to ibalizumab 15 mg/kg after Week 16	--	--	19
No. of patients that switched to OBT2 after Week 16	10	10	11
Median Baseline VL $\log_{10}$ copies/mL	5.16	4.76	4.81
Median VL $\log_{10}$ copies/mL at Week 48 for patients without change in original OBT	3.41	2.72	4.14
Mean VL $\log_{10}$ reduction at Week 2	0.87	1.15	0.38
Mean VL $\log_{10}$ reduction at Week 16	1.07	1.33	0.26
Mean VL $\log_{10}$ reduction at Week 48 for patients without change in original OBT	1.16	1.74	0.99
Revised Analysis			
Median VL $\log_{10}$ copies/mL at Week 48	4.86	4.52	4.69
No. patients that achieved ≥ 0.5 $\log_{10}$ reduction at Week 48	10	12	3

Based on all information provided, it should be concluded that Study TNX-355.03 provides evidence of an add-on effect of ibalizumab over OBR. By Week 16, i.e. prior to the possible switching of patients in the Placebo arm to the 15 mg/kg dose of ibalizumab every 2 weeks and/or to change in OBR for all patients, mean viral load decrease was 1.07 log10 copies/ml in Arm A, 1.33 log10 copies/ml in Arm B and only 0.26 log10 copies/ml in the Placebo arm (p=0.002 vs. Arm A, p <0.001 vs. Arm B).

The observation that twice as many patients completed the study at Week 48 without changing their OBR in the ibalizumab treatment arms than in the Placebo arm (13 patients in Arm A, 12 patients in Arm B and 6 patients in Placebo) also adds to this conclusion.

In study TMB-202, two fixed-dose regimens were tested next. Patients were randomized to receive either 800 mg Q2W (corresponding to ~10 mg/kg in an 80 kg patient) or 2000 mg Q4W (corresponding to ~25 mg/kg in an 80 kg patient). All patients received a personalised OBR next to the ibalizumab infusions.

The final selected regimen to be tested in the Phase III study TMB-301 was selected based on all earlier studies and a target trough level of >0.3 µg/mL in order to achieve high RO levels (≥80%). Please refer to the Pharmacodynamics section for more information as to why the appropriateness of this target is questionable.

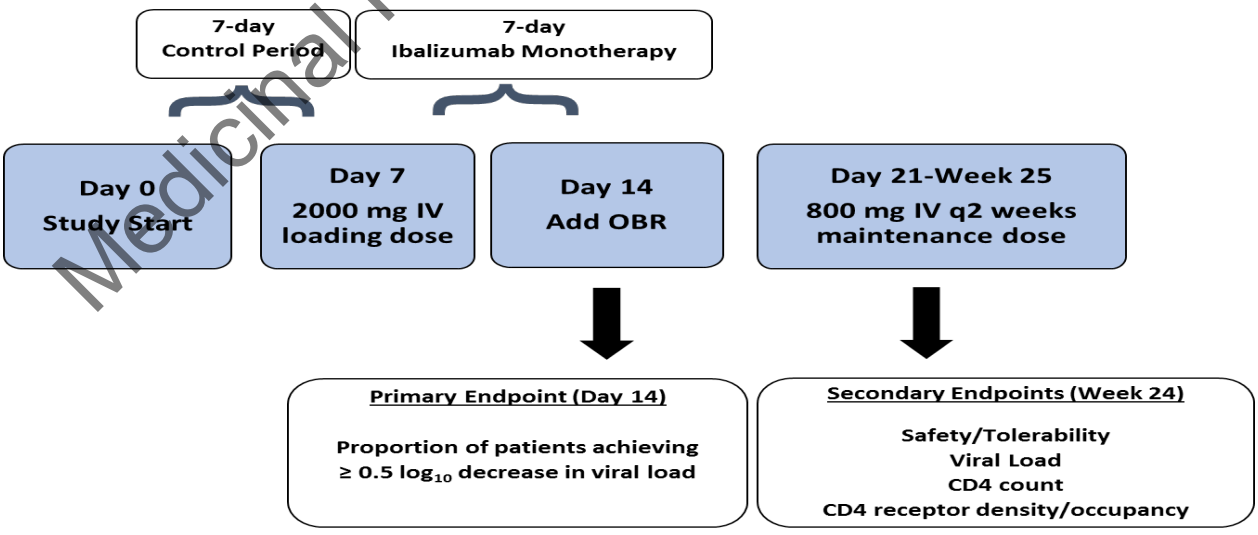
2.5.2. Main studies

Study TMB-301: A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant HIV-1

Methods

The study consisted of three periods: a control period (Days 0−6), a functional monotherapy period (Days 7−13), and a maintenance period (Day 14−Week 25). See Figure below for a graphical representation of the study design. The primary evaluation of efficacy was performed at Day 14. Additional secondary evaluations were conducted at Week 25 (EOS).(Figure 6)

Figure 6 Design of TMB-301



The design of this study has not been discussed with EU regulators. The applicant has had several discussions with FDA regarding the development program and clinical trial designs. The design of this pivotal study is considered fit for the purpose of showing an early effect of ibalizumab monotherapy on viral load, but it is not an ideal setup to determine the longer-term additional effect of ibalizumab over OBR alone. For this, a comparator arm receiving active OBR without ibalizumab would have been preferred. However, given the patient population and difficulties in selecting an OBR with enough active drugs, and given the results from prior studies showing that ibalizumab has antiviral activity, the chosen design is accepted.

Study Participants

The main inclusion criteria were:

1) no AIDS-defining events in the 3 months before Screening, other than cutaneous Kaposi's sarcoma or wasting syndrome because of HIV;

2) a viral load > 1000 copies/mL and documented resistance to at least one ARV medication from each of three classes of ARV medications as measured by resistance testing;

3) receiving a stable highly active ARV regimen for at least 8 weeks before Screening and willing to continue that regimen until Day 14, OR (in the past 8 weeks) had failed and was off therapy and willing to stay off therapy until Day 14; and

4) full viral sensitivity/susceptibility to at least one ARV agent, other than ibalizumab, as determined by the Screening resistance tests (overall sensitivity score [OSS] criteria) and willing and able to be treated with at least one agent to which the patient's viral isolate was fully sensitive/susceptible according to the Screening resistance tests as a component of OBR.

Main exclusion criteria were: any active AIDS-defining illness per Category C conditions (other than cutaneous Kaposi's sarcoma and wasting syndrome because of HIV); any significant diseases, acute illness, active infection secondary to HIV requiring acute therapy, or immunomodulating therapy.

Treatments

Ibalizumab was administered via IV infusion. For the 2000-mg doses, 10 vials were to be used, for the 800-mg doses, 4 vials were to be used. The applicant is working on the development of a larger vial size of ibalizumab which is much appreciated.

In addition to the study drug (ibalizumab), all patients received an OBR, which was a standard–of-care regimen selected by the Investigator on the basis of treatment history and the results of recent viral resistance testing.

Objectives

The primary objective of this study was to demonstrate the antiviral activity of ibalizumab at Day 14 and at Week 25 (end of study [EOS]).

The secondary objectives of this study were to:

- Assess the safety and tolerability of ibalizumab assessed through Week 25 (EOS)
- Assess the mean change from Day 7 (Baseline) in CD4+ cell count at Week 25 (EOS)
- Characterize HIV-1 sensitivity/susceptibility changes associated with protocol-defined virologic failure (VF) after ibalizumab administration in combination with OBR

- Determine the presence and significance of anti-ibalizumab antibodies, if any (immunogenicity of ibalizumab)
- Assess CD4 receptor density and occupancy
- Determine the impact of ibalizumab on quality of life (QoL) as assessed by patient-reported outcomes (PROs)

No formal statistical hypotheses were tested.

Because the objective was based on both Day 14 and Week 25, for this assessment report these endpoints will be considered as two co-primary endpoints. The interpretation of the results will unfortunately be hampered due to the lack of a control arm to which the observed antiviral activity could be related. Secondary objectives are considered relevant and accepted. CD4 receptor density and occupancy, and sensitivity/susceptibility changes associated with virologic failure have been described in the PD section of this report.

Outcomes/endpoints

The primary efficacy endpoint was:

- The proportion of patients achieving a ≥ 0.5 log10 decrease from Day 7 (Baseline) in viral load at Day 14.

Secondary efficacy endpoints were:

- Proportion of patients achieving a ≥ 0.5 log10 and 1.0 log10 decrease from Baseline (Day 7) in viral load at Week 25 (EOS)
- Proportion of patients with HIV-1 RNA levels <50 copies/mL and <400 copies/mL at Week 25 (EOS)
- Mean change from Day 7 (Baseline) in viral load at Day 14 and Week 25 (EOS)
- Mean change from Day 7 (Baseline) in CD4+ cell count at Week 25 (EOS)

Relevant additional endpoints included RO and RD exploratory endpoints, changes in HIV-1 sensitivity/susceptibility, and genotypic changes in HIV-1 envelope associated with ibalizumab administration in combination with OBR.

The primary endpoint of proportion of patients achieving a ≥0.5 log 10 decrease in viral load after 7 days of treatment (at day 14), is considered relevant. The chosen strategy circumvents the interference of other ARVs while enabling a direct comparison with no treatment for each patient individually. As ibalizumab monotherapy was shown to result in viral rebound and decreased viral susceptibility rapidly (see study TNX 355.02), a longer than 7 days functional monotherapy period would not have been appropriate. A ≥0.5 log 10 decrease in 7 days can be considered proof of antiviral activity and hence the strategy of the applicant to compare the proportion of patients who achieve this goal during the control period (day 0-7) and ibalizumab monotherapy (day 7-14) is relevant.

Statistical methods

The two co-primary variables were analysed for the intent-to-treat (ITT) population, which is defined as all patients enrolled in the study. For the primary endpoint an estimation of the considered proportion of patients and a belonging 95% confidence interval was calculated. The "Snapshot Approach" with regard to imputation of virologic failures was used and for missing data the missing equals failure (MEF) approach was included in the primary analyses of the two co-primary variables.

No multiplicity correction is needed, because both co-primary endpoints should show statistically significant proportions.

The PC analysis could be regarded as a sensitivity analysis of the primary estimand. The PC population is defined as all patients who have a non-missing viral load assessment at Day 7, Day 14, and at EOS (Week 25 or whenever the patient completed treatment).

The McNemar test was used to compare the proportion of patients achieving a ≥ 0.5 log10 decrease in the ibalizumab monotherapy period (Day 7- Day 13) compared to the control period (Day 0- Day 6).

Study TMB-202: A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab Plus an Optimized Background Regimen in Treatment-Experienced Patients Infected With HIV-1 (Amended to 24-Week Study)

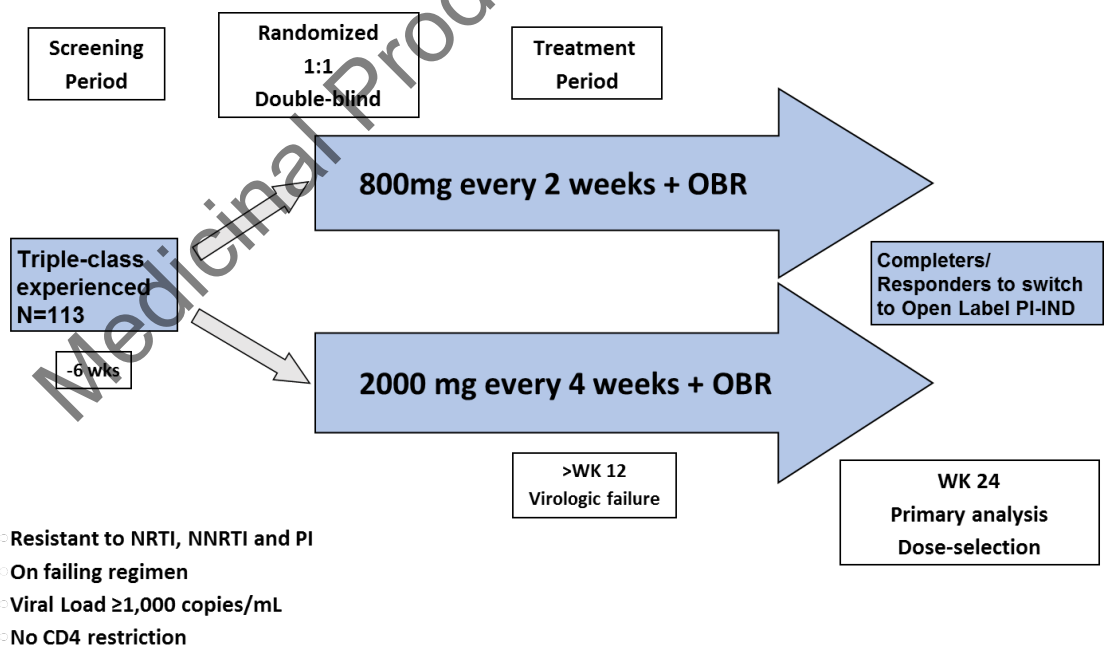
Methods

Patients were randomly allocated to one of the following two dose regimens:

1. 800 mg of ibalizumab every 2 weeks (q2wk) plus OBR
2. 2000 mg of ibalizumab every 4 weeks (q4wk) and placebo on the intervening 2-week period visit, plus OBR

During the study, all patients received an investigator-selected OBR. The selection of the OBR was aided by results of a screening resistance test and review of the patient's prior antiretroviral therapy. The random assignment was stratified by (a) use or non-use of a viral entry inhibitor, and (b) use or non-use of an integrase inhibitor in OBR. (Figure 7)

Figure 7 Design of TMB-202



Study Participants

The main difference between the inclusion criteria for TMB-301 and TMB-202 is related to the virus sequence. While in TMB-301 patients needed to be infected with virus with documented resistance to at least one ARV medication from each of three classes (not further defined) of ARV medications, in TMB-202 patients needed to be infected with virus with documented decreased susceptibility to at least one agent in each of the NRTI, NNRTI and PI class. Notwithstanding the notable differences as compared to the envisioned target population, the population enrolled in TMB-202 is considered to provide relevant information.

Exclusion criteria were comparable to those listed for TMB-301.

Treatments

Blinded kits of ibalizumab parenteral formulation or placebo were administered via intravenous infusion at dose levels of 800 mg q2wk or 2000 mg q4wk for 24 weeks. As in Study TMB-301, all patients received an OBR, which was a standard-of-care regimen selected by the investigator prior to randomization.

Objectives

The primary objectives of this study were to:

- Evaluate the dose-response effectiveness of antiviral activity of the ibalizumab dose regimens at Week 24 in order to determine the optimal dose and regimen. The primary evaluation of effectiveness was based on the proportion of patients achieving undetectable viral loads at Week 24.
- Evaluate the safety and tolerability of two dose regimens of ibalizumab for dose selection

The secondary objectives of this study were to:

- Evaluate changes from Baseline in viral load, CD4+ T-cell counts, and time to loss of virologic response (TLOVR)
- Characterize HIV-1 sensitivity/susceptibility changes associated with ibalizumab administration in combination with an optimized background regimen (OBR)
- Determine the presence and significance of anti-ibalizumab antibodies, if any (immunogenicity of ibalizumab)
- Assess CD4 receptor density and occupancy
- Determine the impact of ibalizumab on quality of life as assessed by patient-reported outcomes on questionnaires
- Evaluate the pharmacokinetic profile of two dose regimens of ibalizumab at steady state

No formal statistical hypotheses were tested.

Outcomes/endpoints

The key primary efficacy endpoint is the proportion of patients with HIV-1 RNA levels below the assay limit (<50 copies/mL) at Week 24.

Secondary Efficacy Endpoints included: Mean change from Baseline in CD4+ T-cell count at Week 24/EOS; The time to loss of virologic response (TLOVR) through Week 24; Changes in HIV-1 sensitivity/susceptibility associated with ibalizumab administration in combination with selected OBR; CD4 receptor occupancy and mean percentage change from Baseline in CD4 receptor density. The later endpoints have been discussed in the PD section of this report.

Randomisation and blinding

The randomisation was stratified based on the use or non-use of entry inhibitor and/or integrase inhibitors and was not stratified by site.

The study was set-up as a double blind study.

Statistical methods

No formal hypotheses were tested.

The key primary variable was analysed for the intent-to-treat (ITT) population, which is defined as all patients enrolled in the study. For the key primary endpoint an estimation of the considered proportion of patients and a corresponding 95% confidence interval was calculated.

The comparison of the two doses for the key primary efficacy endpoint was performed using Fisher exact test. To ascertain the dose level responses, a 95% confidence interval of the difference between the two doses was generated. The primary efficacy analysis was performed at Week 24 with missing data equals failure (MEF).

The PP analysis could be regarded as a sensitivity analysis of the primary estimand. The PP population is a subset of the ITT population. The PP population includes all randomized patients through the last observed visit without major protocol violation who are considered to be sufficiently compliant (i.e. receiving at least 80% of the required dosage regimen and OBR per protocol, no violations of study entry eligibility criteria, no excluded concomitant treatment, treatment remained blinded and patient completed the 24 weeks treatment).

Results Study TMB-301

Participant flow

Table 9 Patient Disposition Study TMB-301 (All Patients)

	All Patients (N=40)
Number of patients screened	63
Number of patients enrolled	40
Virologic responses at Day 14, n (%)[a]	
Complete virologic response[b]	1 (2.5)
Per protocol endpoint[c]	33 (82.5)
Virologic failure[d]	0 (0.0)
Virologic responses at EOS, n (%)	
Complete virologic response[b]	17 (42.5)
Suboptimal response[e]	7 (17.5)
Virologic failure[d]	7 (17.5)
Did not reach EOS	9 (22.5)
Number (%) of patients who completed treatment (per protocol)[f]	32 (80.0)
Number (%) of patients who did not complete treatment[g]	8 (20.0)
Adverse event	4 (10.0)
Death	3 (7.5)
Physician decision	1 (2.5)
Withdrawal by patient	1 (2.5)
Patient noncompliant	1 (2.5)
Lost to follow-up	1 (2.5)
Number (%) of patients who completed study (per protocol)[h]	31 (77.5)
Number (%) of patients who did not complete study[g]	9 (22.5)
Adverse event	5 (12.5)
Death	4 (10.0)
Physician decision	1 (2.5)
Withdrawal by patient	1 (2.5)
Patient noncompliant	1 (2.5)
Lost to follow-up	1 (2.5)

Source: Appendix 14.1, Tables 14.1.1 and 14.12 and Appendix 16.2.6, Listings 16.2.6.5 and 16.2.6.6.

EOS=end of study; HIV=human immunodeficiency virus; OBR=optimized background regimen.

[a] Day 14 patients received a 2000-mg ibalizumab loading dose at Day 7 and no OBR.

[b] Complete virologic response was defined as having an HIV RNA viral load of <50 copies/mL.

[c] Protocol endpoint was ≥0.5 $\log_{10}$ decrease in viral load from Baseline at Day 14.

[d] Virologic failure was defined as two consecutive viral load measurements of <0.5 $\log_{10}$ decline from the Baseline viral load beginning at Day 14.

[e] Suboptimal response was defined as patients at EOS with an HIV RNA viral load of >50 copies/mL who did not experience virologic failure.

[f] Treatment completion defined as receiving all doses of ibalizumab through Week 25.

[g] Denominator is the total number of patients enrolled (N=40).

[h] Study completion defined as receiving all doses of ibalizumab and completing the Week 25 or Week 29 follow-up visit.

Study Initiation Date: 6 Jul 2015

Study Completion Date: 20 Oct 2016

Out of the 63 patients screened, 23 were not enrolled. The main reasons for excluding patients from participation were due to either 1) viral load <1000 copies/ml, 2) no resistance to at least 1 drug from 3 different ARV classes, or 3) not having at least one fully active agent.

Baseline data

The majority of patients in the study were white (55%), male (85%), and between 23 and 65 years of age (mean [SD] age: 50.5 [10.99] years). Baseline characteristics are depicted in Table 10 and Table 11.

Table 10 Baseline Disease Characteristics Study TMB-301 (ITT Population)

Statistic	All Patients N=40
Years since HIV diagnosis[a]	
N	40
Mean (SD)	20.3 (7.76)
Median	23.0
Min–Max	2–30
Total number of ARV medications per patient[b]	
N	40
Mean (SD)	11.0 (5.02)
Median	10.0
Min–Max	3–22
Viral load (log_{10} copies/mL)	
N	40
Mean (SD)	4.47 (0.782)
Median	4.55
Min–Max	2.5–5.9
$CD4^+$ cell counts (cells/mm^3)	
N	40
Mean (SD)	150.2 (181.85)
Median	73.0
Min–Max	0–676
HIV-1 RNA (copies/mL)	
N	40
Mean (SD)	100287.1 (171843.65)
Median	35350.0
Min–Max	304–743000
Proportion with $CD4^+$ cell count <200 cells/mm^3 at Baseline, n (%)	27 (67.5)
Proportion requiring investigational agent, n (%)[c]	17 (42.5)

Source: Appendix 14.1, Table 14.1.4; Appendix 16.2.4, Listing 16.2.4.2; Appendix 16.2.5, Listing 16.2.5.2, 16.2.5.3, and 16.2.5.5; and Appendix 16.2.6, Listing 16.2.6.2.

ARV=antiretroviral; $CD4^+$=cluster of differentiation 4 positive (glycoprotein expressed on the surface of T-helper cells); HIV=human immunodeficiency virus; ITT=intent-to-treat; Max=maximum; Min=minimum; OBR=optimized background regimen; SD=standard deviation.

[a] Where HIV diagnosis date is available.

[b] Each ART medication is counted once for each patient, no matter how many times the patient may have re-started the medication.

[c] Patients were counted once if they received fostemsavir on study. Note that 1 patient (01-001) was not included in Listing 16.2.5.5 as having received fostemsavir because of an error in reporting by the site. The patient received fostemsavir as part of their OBR, but the source documentation in the study file did not include this information. Thus the total number of patients who received fostemsavir as part of the OBR is 18, but the data listing was not updated since the error was discovered after database lock.

Examination of all resistance test results for patients enrolled in the study revealed extensive ARV resistance. Historical resistance test results were obtained for 31 of 40 enrolled patients. Resistance to at least one NRTI, NNRTI, PI, or integrase inhibitor (INI) was documented for 93%, 93%, 90%, and 68% of patients, respectively (Table 11). Resistance to all drugs in the NRTI, NNRTI, PI, or INI classes was documented for 65%, 65%, 63%, and 48% of patients, respectively. For these four non-EI classes of ARVs, overall, 85% of patients had documented resistance to all drugs from at least one class, 73% had resistance to all drugs from at least two classes, 50% had resistance to all drugs from at least three classes, and 33% had resistance to all drugs from all four classes. Five patients (13%) had documented

resistance to all approved ARVs including EIs. On average, patients were resistant to 6 of 7 NRTIs, 4 of 5 NNRTIs, 6 of 8 PIs, 2 of 3 INIs, and 1 of 2 EIs.

Table 11 Documented Resistance at Baseline (Study TMB-301)

ARV Class	NRTI	NNRTI	PI	INI	EI
# of patients records	40	40	40	40	38
Known resistance to ≥1 drug in class, n (%)	37 (93)	37 (93)	36 (90)	27 (68)	35 (92)
Known resistance to all drugs in class, n (%)	26 (65)	26 (65)	25 (63)	19 (48)	8 (21)
# of drugs in class with known resistance					
Mean ± SD	5.6 ± 2.3	4.1 ± 1.6	6.2 ± 2.9	1.8 ± 1.3	1.1 ± 0.5
Median	7.0	5.0	8.0	2.0	1.1

Source: Appendix 16.7, TMB-301 Clinical Virology Report.

ARV=antiretroviral; EI=entry inhibitor; INI=integrase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; SD=standard deviation.

For each patient, an OBR consisting of at least one fully active ARV agent was selected by the Investigator. An overview of these OBRs is provided in the table below.(Table 12)

Table 12 Overview of OBR per patient(Study TMB-301)

	OBR					
Screen ID	**OBR1**	**OBR2**	**OBR3**	**OBR4**	**OBR5**	**OBR6**
01-001	DTG	DRV	FTC	TFV		
01-002	FSV	DRV	DTG	FTC	TFV	
01-005	FTC	TFV	DRV	DTG	FSV	
01-006	ATV	FTC	TFV	DTG	FSV	
02-001	FTC	TFV	DTG	FSV		
02-002	DTG	FSV	DRV	FTC	TFV	
04-001	DRV	FTC	TFV	DTG	FSV	ENF
04-002	DTG	DRV	FTC	TFV	FSV	
05-001	ABC	DTG	3TC			
05-003	DTG	DRV				
05-004	ABC	DTG	3TC	DRV		
05-005	DRV	DTG	MVC			
08-001	TPV	FTC	TFV	FSV		
09-002	DTG	FTC	TFV			
13-001	DTG	DRV	FTC	TFV	LPV	
13-002	DTG	DRV	FTC	TFV	MVC	
17-001	FSV	DTG	DRV	FTC	TFV	
17-002	DRV	DTG	ETR	FSV	TFV	FTC
17-003	DRV	DTG	FSV	FTC	TFV	
18-002	ABC	FSV	DRV	FTC	TFV	TFV
19-001	ETR	TFV	MVC	ABC	3TC	
19-002	ETR	DTG				
21-001	DRV	MVC	FTC	TFV		
21-002	DTG	DRV	FTC	TFV		
22-001	FTC	TFV	DRV			
22-002	DTG	DRV	ETR			
22-003	fAPV	FTC	TFV			
23-002	DTG	FTC	TFV			
25-001	TFV	DRV				
25-002	RPV	DRV				
26-001	FTC	TFV	DRV	FSV		
27-001	DTG	FSV	FTC	TFV		
27-002	DRV	DTG	FTC	TFV	FSV	
29-001	FTC	TFV	LPV	RAL		
29-002	DRV	3TC	RAL	TFV		
30-001	ATV	RPV	FTC	TFV		
30-004	LPV	3TC	AZT			
32-001	FTC	TFV	FSV			
32-002	TFV	DRV	DTG	FSV		
32-003	ETR	DTG	FTC	TFV	DRV	

In order to estimate the activity of OBR in each patient, the combined results of susceptibility testing performed at Screening and patients' historical resistance tests, where available, were used to calculate the OSS at Baseline. Table 13 below presents an outline of this calculation.

Table 13 Overall Susceptibility Score (OSS) Calculations

Description		How it is Calculated
OSS	Sum of active drugs in OBR based on combined information, or Assessments, from genotypic and phenotypic testing.	Protease inhibitors, reverse transcriptase inhibitors, and integrase inhibitors Score '1' if virus from patient is 'Sensitive' to drug in both Phenosense and Geneseq assessments. Score '0' if virus from patient is 'Partially Sensitive' or 'Resistant' or 'reduced susceptibility' to drug in either Phenosense or Geneseq assessment. Entry inhibitors Score '1' for enfuvirtide if virus from patient is 'Sensitive' in HIV Entry report Enfuvirtide Assessment; score '0' for enfuvirtide if virus from patient has 'Reduced Susceptibility in HIV Entry report Enfuvirtide Assessment. Score'1' for maraviroc if virus from patient is CCR5-tropic ('R5') in HIV Trofile report); score '0' for maraviroc if virus from patient is CXCR4-tropic or dual-mixed tropic (R5 and X4) in Trofile report. Investigational agent - fostemsavir Score'1' for fostemsavir if no prior experience. Score '0' for fostemsavir if historical resistance testing reveals an IC50 ≥10 nM (partially sensitive) or >100 nM (resistant) in HIV Entry report from Monogram Biosciences.

Baseline overall susceptibility scores (OSSs) were 0, 1, or ≥2, for 12.5%, 30%, and 57.5% of patients, respectively.

The mean ibalizumab mean percentage inhibition (MPI) at Baseline was 91 ± 14%, with a median value of 97%. Twenty-seven samples (71%) had MPI values of 90%–100%, 6 (16%) had MPI values of 80%–90%, and 5 (13%) had MPI values <80%. The mean ICHalfMax Fold Change was 1.2 ± 0.9, with a median of 0.9.

Numbers analysed

The ITT population included all 40 patients enrolled in the study. The PC population included all patients who had a non-missing viral load assessment at Day 7, Day 14, and Week 25 (EOS) and included 26 patients (65%),(Table 14)

Table 14 Data Sets Analysed (Study TMB-301)

Study Populations	All Patients N=40 n (%)
Screened	63
Enrolled	40
Intent-to-treat (ITT)[a]	40 (100)
Modified intent-to-treat (mITT)[b]	40 (100)
Safety (SAF)[c]	40 (100)
Protocol correct (PC)[d]	26 (65.0)

Source: Appendix 14.1, Table 14.1.1.

[a] ITT population consists of all patients enrolled into the study.

[b] mITT population consists of all ITT patients receiving at least one dose of study drug.

[c] SAF population consists of patients receiving at least one partial dose of study drug.

[d] PC population consists of patients with non-missing viral load at Day 7, Day 14, and EOS (End of Study visit; conducted at Week 25).

Fourteen subjects (35%) were not included in the Protocol correct population as they had viral load data missing at Day 7, Day 14, or EOS (Week 25). For 9 of the 14 this was because they did not complete the study and therefore had no viral load value at Week 25/EOS. The remaining 5 subjects experienced virologic failure and were therefore excluded from the Protocol correct population, even though they did have viral load data reported at the requested timepoints and it was not pre-specified that these subjects should be excluded from the PC.

Of note, the main conclusions will be based on the outcomes of all 40 enrolled subjects.

Outcomes and estimation

Primary Efficacy Analyses

Proportion of Patients Achieving a ≥0.5 log10 Decrease in Viral Load from Day 7 (Baseline) to Day 14 & Proportion of Patients Achieving a ≥0.5 log10 Decrease in Viral Load from Day 7 (Baseline) to Week 25/EOS

The primary endpoint (i.e. proportion of patients achieving a ≥ 0.5 log10 decrease from baseline at day 14) was found statistically significantly different from Control period (Day 0 to Day 6) [82.5% with 95% CI (67.2%, 92.7%) at Day 14 and are considered clinically relevant. For the PC population these results were 84.6% with 95% CI (65.1%, 95.6%) at Day 14 (Table 15))

Table 15 Proportion of Patients Achieving a ≥0.5 log10 Decrease in Viral Load from Day 7 (Baseline) to Day 14 & Proportion of Patients Achieving a ≥0.5 log10 Decrease in Viral Load from Day 7 (Baseline) to Week 25/EOS (ITT-MEF population, Study TMB-301)

	All Patients N=40
Patients achieving a ≥0.5 log10 decrease from	
Day 0 to Day 7 (Baseline), n	1
Proportion (%)	2.5%
95% CI	(0.06, 13.16)%
Day 7 (Baseline) to Day 14, n	33
Proportion (%)	82.5%
95% CI	(67.22, 92.66)%
Day 7 (Baseline) to Week 25/EOS, n	25
Proportion (%)	62.5%
95% CI	(45.80, 77.27)%

The observed ≥0.5 log10 decrease in viral load after the first ibalizumab infusion in 33/40 (82.5%) of patients, compared to 1/40 (2.5%) with a spontaneous ≥0.5 log10 decrease in viral load in the week prior to infusion, can be considered proof of an antiviral effect of ibalizumab. The seven patients without a ≥0.5 log10 decrease in viral load do not seem to differ from the 33 patients with a ≥0.5 log10 decrease in viral load in baseline characteristics such as viral load or CD4+ T cell counts. The applicant states that there was no relation with susceptibility to ibalizumab or receptor occupancy/density levels that may explain this outcome, which can also be seen in the table below (Table 16)

Table 16 Ibalizumab Susceptibility for Primary Endpoint Responders and Non-responders

	Primary Endpoint Met (N=31)			Primary Endpoint Not Met (N=7)		
Ibalizumab	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max
$IC_{HalfMax}$ FC	1.2±1.0	0.9	0.6-6	1.3±0.7	1.1	0.5-3
MPI	90±14	96	41-100	90±16	98	55-99

All patients had high serum concentrations and CD4 receptor occupancy at Day 14, so drug exposure was also not a factor in nonresponse.

Secondary Efficacy Analyses

Mean Change from Baseline (Day 7) in Viral Load at Day 14 and Week 25 (EOS)

Mean HIV-1 RNA in the ITT-MEF population was 100,287.1 copies/mL at Baseline, decreasing to 24,076.1 copies/ml at Day 14 (change of -76,211.0 copies/ml), reaching a nadir of 13,230.5 copies/ml at Day 21

(change of -87,056.7 copies/ml). Levels increased only slightly at Week 5, remaining low (mean ≤24,000 copies/ml) throughout the study. The mean HIV-1 RNA value at Week 25 (EOS) was 32,935.6 copies/ml.

The proportion of patients achieving a ≥ 0.5 log10 decrease from baseline at Week 25/EOS was found statistically significantly different from Control period (Day 0 to Day 6) at Week 25/EOS (62.5% with 95% CI (45.8%,77.3%) and are considered clinically relevant, refer to Table 17. For the PC population these results were 96.2% with 95% CI (80.4%,99.9%) at Week 25/EOS.

Proportion of Patients with HIV-1 RNA Levels <50 copies/ml and <400 copies/ml at Week 25 (EOS)

The proportion of patients achieving HIV-1 RNA levels <50 copies/ml and <400 copies/ml at Week 25 (EOS) is summarized in Table 17.

Table 17 Proportion of Patients Achieving Specific HIV-1 RNA Levels at Week 25 (EOS; ITT-MEF Population, Study TMB-301)

	All Patients N=40
Proportion of patients with <50 copies/mL at Week 25 (EOS)	
n	17 (42.5%)
95% CI	(0.2704, 0.5911)
Proportion of patients with <400 copies/mL at Week 25 (EOS)	
n	21 (52.5%)
95% CI	(0.3613, 0.6849)

Source: Appendix 14.2, Table 14.2.7.

CI=confidence interval; EOS=end of study (Week 25); HIV=human immunodeficiency virus; ITT=intent-to-treat; MEF=missing equals failure.

Note: For the analysis of viral load only, if a viral load measurement was missing for a given visit, the value was imputed by replacing it with the Baseline value such that change from Baseline=0 and the visit was treated as a failure.

There is a trend towards increasing virologic responses with increasing OSS values (Table 18) which is not unexpected in HIV treatment.

Table 18 Comparison of Mean ± SD Viral Load Change from Baseline by OSS in TMB-301 (Week 25 Analysis)

Overall Susceptibility Score (OSS)[1]	Ibalizumab + OBR $\log_{10}$ (n, %)
0	-0.5 ± 0.8 (5, 16%)
1	-1.5 ± 1.7 (11, 35%)
2	-2.1 ± 1.4 (14, 45%)
≥ 3	-2.2 ± 1.4 (15, 48%)

Mean Change from Baseline (Day 7) in CD4+ Cell Counts at Week 25 (EOS)

Mean CD4+ cell counts at Baseline (Day 7) were <200 cells/mm3 for both the ITT and PC populations. Mean CD4+ cell counts showed increases from Baseline at each scheduled time point during the study peaking at Week 21 for both the ITT and PC populations. Mean CD4+ cell count at Week 21 was 248.3 cells/mm3 for the ITT population (n=29) and 267.4 cells/mm3 for the PC population (n=23).

The observed increase in mean CD4+ T cell counts from 150 to 240 cells/mm3 is considered clinically relevant. Of note, Week 25 data was only available for 27 patients.

Ancillary analyses

Subgroup analysis have been performed by geographic location (United States vs. Taiwan), sex (male/female), age (<50 vs. ≥50), race (Caucasian, Asian, and Other), and concomitant fostemsavir use (yes/no). None of these factors had a relevant impact on the proportion of patients with ≥0.5 log10 decrease from Baseline (Day 7) in viral load at Day 14.

The virologic response (log10 reduction, proportion of patients that achieved RNA levels <50 copies/mL and <200 copies/mL in HIV-1 RNA) at Week 25 by CD4+ cell counts, viral load, OSS, and resistance to integrase inhibitors at Baseline in the ITT population is presented in Table 19.

Table 19 Virologic Response at Week 25 by Baseline CD4+ Cell count, Viral Load, OBR, OSS, and Integrase Inhibitors (ITT Population)

Variable at Baseline	Viral Load at Week 25 (EOS)		
	Log_{10} Reduction Mean (SD)	<50 copies/mL n (%)	<200 copies/mL n (%)
$CD4^+$ cell counts			
<50 (n=17)	-0.9 (1.4)	3 (18)	4 (24)
50-200 (n=10)	-2.4 (1.4)	6 (60)	7 (70)
>200 (n=13)	-2.0 (1.6)	8 (62)	9 (69)
Viral load			
≤100,000 (n=33)	-1.7 (1.5)	16 (48)	19 (58)
>100,000 (n=7)	-1.5 (1.7)	1 (14)	1 (14)
OBR			
With fostemsavir (n=17)[a]	-1.4 (1.5)	6 (35)	8 (47)
Without fostemsavir (n=23)[a]	-1.8 (1.5)	11 (48)	12 (52)
Resistance			
With INI resistance (n=27)	1.4 (1.5)	11 (40.7)	12 (44.4)
Without INI resistance (n=13)	2.1 (1.4)	6 (46.2)	8 (61.5)
OSS (historical test results)			
0 (n=5)	-0.5 (0.8)	1 (20)	1 (20)
1 (n=11)	-1.5 (1.7)	4 (36)	5 (45)
≥2 (n=15)	-2.2 (1.4)	10 (67)	11 (73)

Source: Appendix 16.2.5, Listing 16.2.5.5 and Appendix 16.2.6, Listings 16.2.6.2, 16.2.6.5, and 16.2.6.10.
CD4=cluster of differentiation 4 positive (glycoprotein expressed on the surface of T-helper cells; EOS=end of study; INI=integrase inhibitor; ITT=intent-to-treat; OBR=optimized background regimen; OSS=overall susceptibility score; SD=standard deviation.

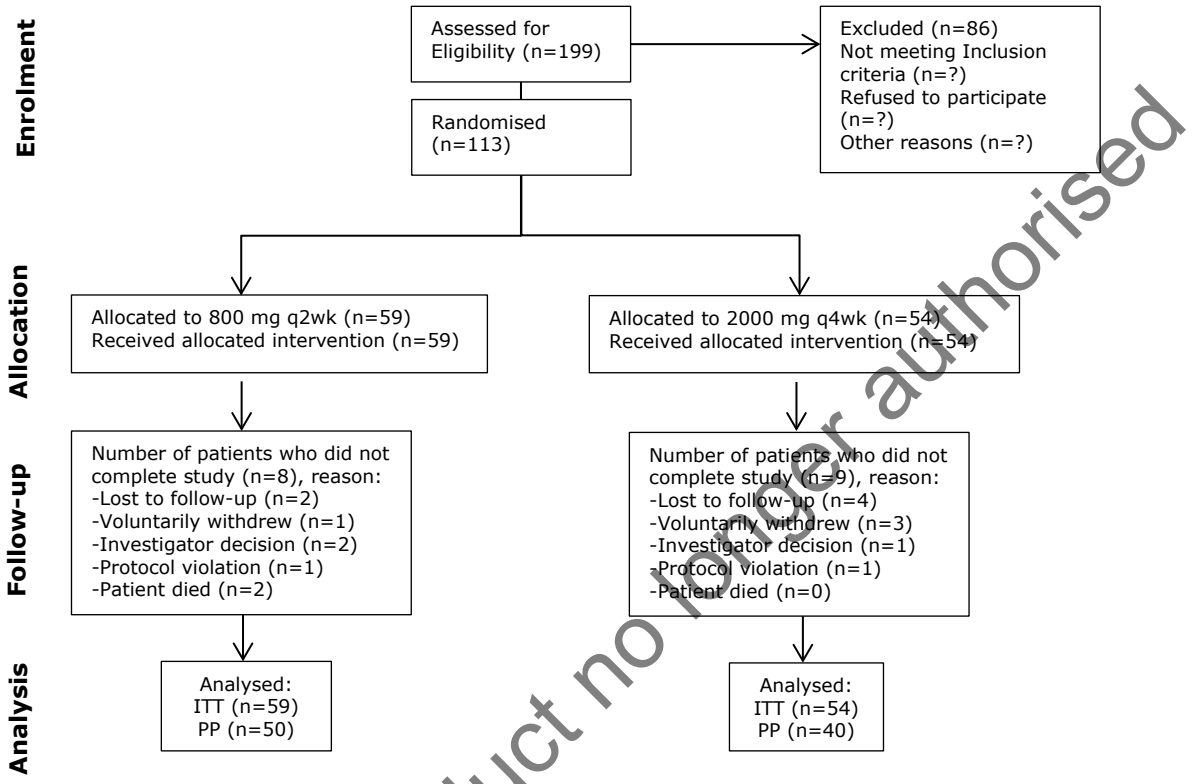
[a] One patient (01-001) was not included in Listing 16.2.5.5 as having received fostemsavir as part of the OBR because of an error in reporting by the site. After database lock, it was discovered that the patient had received fostemsavir as part of the OBR, but the source documentation in the study file did not include this information. Since the error was discovered after database lock and given that the addition of this patient and subsequent re-analysis would not substantially impact the results, none of the analyses were updated. So, although 18 patients actually received concomitant fostemsavir and 22 patients did not receive concomitant fostemsavir, the analysis was performed using the data as reported prior to database lock (n=17 and 23, respectively.

There is a clear trend that those patients that are most severely affected by their HIV-1 infection (i.e. those with low CD4 counts, high viral load, with INI resistance and with low OSS score), responded less

well in this study. Again, the impact of the individual patients' OBR cannot be determined from these data, but this may have very well influenced the outcome.

Results Study TMB-202

Figure 8 Participant flow



Study Initiation Date: 14 October 2008

Study Completion Date: 26 January 2011

Again, a substantial part of the screened patients were not enrolled (86/199 (43%), with main reasons being similar as reported for study TMB-301.

Baseline data

The mean age of all subjects was 48.1 years. More males (89.4%) than females (10.6%) were enrolled in the study and the majority of all subjects were white (61.9%).

There were no clinically meaningful differences in demographics between the two treatment groups. Baseline characteristics are depicted in Table 20.

Table 20 Baseline Characteristics Study TMB-202 (ITT Population)

	Ibalizumab + OBR		
Statistic	800 mg q2wk (N=59)	2000 mg q4wk (N=54)	Overall (N=113)
Hepatitis B surface antigen			
Negative	54 (91.5)	47 (87.0)	101 (89.4)
Positive	4 (6.8)	5 (9.3)	9 (8.0)
Missing	1 (1.7)	2 (3.7)	3 (2.7)
Hepatitis C surface antibody			
Negative	57 (96.6)	51 (94.4)	108 (95.6)
Positive	1 (1.7)	1 (1.9)	2 (1.8)
Missing	1 (1.7)	2 (3.7)	3 (2.7)
Duration of HIV infection (years)			
n	23	29	52
Mean (SD)	17.0 (4.4)	16.9 (6.2)	17.0 (5.4)
Minimum, maximum	8.1, 24.8	0.3, 26.3	0.3, 26.3
Median	16.3	17.1	17.0
Q1, Q3	14.1, 20.7	13.2, 20.6	13.6, 20.7
Baseline HIV-1 RNA viral load (copies/mL)			
n	59	54	113
Mean (SD)	114,675.3 (202,894.6)	136,197.2 (251,282.3)	124,859.8 (226,290.1)
Minimum, maximum	58.0, 1,087,333.3	1893.3, 1,573,333.3	58.0 to 1,573,333.3
Median	43,850.0	48, 766.7	46,633.3
Q1, Q3	13,175.0, 111,766.7	15,933.3, 161,333.3	13,661.7 , 132,720.8
Baseline HIV-1 RNA viral load (copies/mL) distribution			
≤100,000 to <150,000	43 (72.9)	35 (64.8)	78 (69.0)
>100,000	16 (27.1)	19 (35.2)	35 (31.0)
Baseline HIV-1 RNA viral load (log_{10} copies/mL)			
n	59	54	113
Mean (SD)	4.6 (0.8)	4.7 (0.7)	4.6 (0.7)
Minimum, maximum	1.8, 6.0	3.3, 6.2	1.8, 6.2
Median	4.6	4.7	4.6
Baseline HIV-1 RNA viral load (log_{10} copies/mL) distribution			
< 4.0	12 (20.3)	7 (13.0)	19 (16.8)
4.0 to <4.4	9 (15.3)	12 (22.2)	21 (18.6)
4.4 to <4.7	12 (20.3)	8 (14.8)	20 (17.7)
4.7 to <5.0	10 (16.9)	8 (14.8)	18 (15.9)
5.0 to <5.2	5 (8.5)	5 (9.3)	10 (8.8)
≥ 5.2	11 (18.6)	5 (9.3)	25 (22.1)
Baseline $CD4^+$ count (cells/mL)			
n	59	54	113
Mean (SD)	106.4 (91.3)	112.4 (118.5)	109.3 (104.7)
Minimum, maximum	19.0, 375.0	10.0, 476.5	10.0, 476.5
Median	80.5	54.0	69.5
Q1, Q3	21.0, 150.0	19.0, 160.0	19.0, 154.0
Baseline $CD4^+$ count (cells/mL) distribution			
< 20	12 (20.3)	17 (31.5)	29 (25.7)
20 to <100	21 (35.6)	14 (25.9)	35 (31.0)
100 to <200	16 (27.1)	11 (20.4)	27 (23.9)
200 to <350	9 (15.3)	8 (14.8)	17 (15.0)
≥ 350	1 (1.7)	4 (7.4)	5 (4.4)

Source: Table 14.1.4.3, Listing 16.2.4, Listing 16.2.7, Listing 16.2.9.1.4

HIV=human immunodeficiency virus; OBR=optimized background regimen; Q1=first quartile; q2wk=every 2 weeks; Q3=third quartile; q4wk=every 4 weeks; SD=standard deviation

Even though there are notable differences between the patients enrolled in Study TMb-202 and the envisioned target population, this study is considered to provide relevant information .The median OSS based on net assessment at baseline for all patients was 2.0 (range, 0.0 to 3.0), indicating that most patients had sensitivity to 2 drugs in the OBR (Table 21).

Table 21 Baseline Sensitivity/Susceptibility to Optimal Background Regimen Agents (ITT Population, Study TMB-202)

	Ibalizumab + OBR		
Statistic	**800 mg q2wk (N=59)**	**2000 mg q4wk (N=54)**	**Total (N=113)**
OSS			
n	59	54	113
Mean (SD)	1.6 (1.0)	1.4 (0.9)	1.5 (1.0)
Median	2.0	1.0	2.0
Min, Max	0, 4	0, 4	0, 4
Distribution of OSS			
0	9 (15)	9 (17)	18 (16)
1	17 (29)	20 (37)	37 (33)
2	24 (41)	20 (37)	44 (39)
≥3	9 (15)	5 (9)	14 (12)
NRS			
n	59	54	113
Mean (SD)	1.1 (0.8)	0.8 (0.8)	1.0 (0.8)
Median	1.0	1.0	1.0
Min, Max	0, 3	0, 3	0, 3
Distribution of NRS			
0	18 (31)	22 (41)	40 (35)
1	21 (36)	21 (39)	42 (37)
2	19 (32)	9 (17)	28 (25)
≥3	1 (2)	2 (4)	3 (3)

The ibalizumab mean MPI for all patients was 92.1%.

Numbers analysed

The intent-to-treat (ITT) population included all randomized patients. Patients were counted in the treatment group to which they were randomized regardless of whether they received any dose of study medication.

The per protocol (PP) population was a subset of the ITT population and included all randomized patients through the last observed visit without major protocol violation who were considered to be sufficiently compliant with the protocol (i.e. receiving at least 80% of the required dosage regimen and OBR per protocol, no violations of study entry eligibility criteria, no excluded concomitant treatment, treatment remained blinded and patient completed the 24 weeks treatment).

As can be seen in Table 22, 23 subjects (20%) were not included in the per protocol population, with a numerical difference between the two treatments arms (9/59 (15%) vs 14/54 (26%)).

Table 22 ITT and PP populations - number of subjects per dosing regimen

	800 mg q2wk	2000 mg q4wk	Total
ITT	59	54	113
PP	50	40	90

Outcomes and estimation

Primary Efficacy Variable – Viral Load <50 copies/mL at Week 24

In the ITT-MEF analysis, the proportion of patients having a viral load of <50 copies/ml at Week 24 overall was 36.3%, with the proportion of patients in the 800 mg q2wk treatment group (44.1%) being greater compared with the 2000 mg q4wk treatment group (27.8%). The difference between treatment groups was not statistically significant (p=0.160) (Table 23).

Table 23 Proportion of Patients with Viral Load <50 copies/mL at Week 24 (ITT-MEF Analysis, Study TMB-202)

	Ibalizumab + OBR		
Description	800 mg q2wk (N=59)	2000 mg q4wk (N=54)	Total (N=113)
Proportion of patients (<50 copies/mL), n/N (%)	26/59 (44.1)	15/54 (27.8)	41/113 (36.3)
95% exact CI	(31.2, 57.6)	(16.5, 41.6)	(27.4, 45.9)
Observed difference between treatment groups, %	—	-16.3	—
95% exact CI	—	(-33.7, 1.1)	—
Hazard ratio	—	0.63	—
95% CI	—	(0.3, 1.2)	—
p-value	—	0.160[a]	—

Source: Table 14.2.1.1 and Listing 16.2.7

[a] P-value calculated using Wald chi-square test

CI=confidence interval; OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks

Secondary Efficacy Variables

Mean Change from Baseline in HIV-1 RNA Levels at Week 24/End of Study

In the ITT-MEF analysis, mean values for HIV-1 RNA levels showed similar decreases from baseline to Week 24 for the 800 mg Q2W treatment group (-1.6 log10 copies/ml) and the 2000 mg Q4W treatment group (-1.5 log10 copies/ml) (Table 24).

Table 24 Mean Change from Baseline in HIV-1 RNA Levels at Week 24/End of Study (ITT-MEF Analysis, Study TMB-202)

Time point Statistic	Ibalizumab + OBR 800 mg q2wk (N=59)	Ibalizumab + OBR 2000 mg q4wk (N=54)	Ibalizumab + OBR Total (N=113)
HIV-1 RNA level (log_{10} copies/mL)			
Baseline			
n	59	53	113
Mean (SD)	4.6 (0.8)	4.7 (0.7)	4.6 (0.7)
Median	4.6	4.7	4.7
Minimum to maximum	1.8 to 6.0	3.3 to 6.2	1.8 to 6.2
Week 24			
n	59	54	113
Mean (SD)	2.9 (1.5)	3.2 (1.4)	3.0 (1.5)
Median	1.9	2.8	2.4
Minimum to maximum	1.4 to 5.9	1.4 to 5.9	1.4 to 5.9
Change from baseline to Week 24			
n	59	54	113
Mean (SD)	-1.6 (1.3)	-1.5 (1.4)	-1.6 (-1.4)
Median	-1.8	-1.5	-1.7
Minimum to maximum	-3.8 to 0.0	-4.1 to 0.1	-4.1 to 0.1

Source: Table 14.2.3.1.2.1, Table 14.2.3.1.5.1, and Listing 16.2.7
OBR=optimized background regimen; q2wk=every 2 weeks; q4wk=every 4 weeks; SD=standard deviation

Mean Change from Baseline in CD4+ T-Cell Counts at Week 24/End of Study

In the ITT-MEF analysis, mean values for CD4+ T-cell counts showed increases from baseline to Week 24 for both the 800 mg Q2W treatment group (36.5 cells/µl) and the 2000 mg Q4W treatment group (39.8 cells/µl).

Ancillary analyses

Subgroup analyses were overall in line with what was expected. Differences in response rate (with response defined as achieving a viral load<50 copies/ml) at Week 24 were observed for the overall population in the following subgroups:

- males, n=101 and females, n=12 (38.6% and 16.7%, respectively; p=0.0306)
- white patients, n=70 and other patients, n=43 (44.3% and 23.3%, respectively; p=0.0058)
- patients with different baseline CD4+ T-cell counts: <20 cells/µl, n=29; 20 to <100 cells/µl, n=35; 100 to <200 cells/µl, n=27; 200 to <350 cells/µl, n=17; and ≥350 cells/µl, n=5 (13.8%, 34.3%, 59.3%, 52.9%, and 0, respectively; p=0.0000)
- patients with a baseline viral load <100,000 copies/ml, n=78 and patients with a baseline viral load ≥100,000 copies/ml, n=35 (41.0% [51.2% for the 800 mg q2wk treatment group and 30.6% for the 2000 mg q4wk treatment group] and 23.5% [25.0% for the 800 mg q2wk treatment group and 25.7% for the 2000 mg q4wk treatment group], respectively; p=0.0181);
- patients with good adherence (≥80% compliance) to OBR, n=108 and patients with poor adherence (i.e., <80% compliance) to OBR, n=5 (38.0% and 0, respectively; p=0.0064)

- patients with different values for MPI of ibalizumab: 0 to <50%, n=1; 50 to <80%, n=15; and ≥80%, n=89 (0, 13.3%, and 39.3%, respectively; p=0.0094)

Age, weight, and type of agents included in the OBR did not appear to have an effect on response rate (with response defined as achieving a viral load<50 copies/ml) at Week 24.

As also seen in TMB-301, there is a clear trend that those patients that are most severely affected by their HIV-1 infection (i.e. those with low CD4 counts and/or high viral load) responded less well in this study. Patients with good adherence to OBR, an intermediate to high CD4 RO rate and/or an OSS score ≥2, in contrast, responded clearly better. The observed differences in outcome between male and female patients, as well as between white and other patients, are less straightforward and more likely to be due to change or interference with one or more of the above described factors that seem to influence treatment outcome.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).(Table 25 and Table 26)

Table 25 Summary of efficacy for trial TMB-301

Title: A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab Plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected With Multi-Drug Resistant HIV-1		
Study identifier	TMB-301	
Design	Single-arm, multicenter study	
	Duration of control phase: Duration of monotherapy phase: Duration of maintenance phase:	Day 0 – day 6 Day 7- day 13 Day 14 – Week 25
Hypothesis	No formal statistical hypotheses were tested	
Treatments	Ibalizumab + OBR	2000 mg loading dose at Day 7, followed by 800 mg every other week (Q2W) from Day 21 until Week 23, each patient received a personalised OBR starting at Day 14 N=40 patients enrolled
Endpoints and definitions	Co-primary endpoint	Proportion of patients achieving a ≥ 0.5 log10 decrease from baseline (Day 7) in viral load at Day 14
	Co-primary endpoint	Proportion of patients achieving a ≥ 0.5 log10 decrease from baseline (Day 7) in viral load at Week 25/end of study (EOS)
	Secondary endpoint	Mean change from baseline (Day 7) in viral load at Day 14 and Week 25 (EOS)
	Secondary endpoint	Proportion of patients with HIV-1 RNA levels <50 copies/mL at Week 25 (EOS)

	Secondary endpoint	Mean change from baseline (Day 7) in CD4+ cell counts at Day 14 and Week 25 (EOS)
	Additional endpoint	Changes in HIV-1 sensitivity/susceptibility associated with ibalizumab administration in combination with OBR
Database lock	10-Mar-2017	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat- missing equals failure (ITT-MEF) time point: Day 14 or Week 25 (EOS)			
Descriptive statistics and estimate variability	Treatment group, N	Ibalizumab 2000 mg loading dose followed by 800 mg Q2W + OBR, N=40		
		Timepoint	n/N (%)	95% CI
Co-primary endpoints	≥0.5 log10 decrease	Day 0-6	1/40 (2.5%)	(0.1, 13.2)%
		Day 7-13	33/40 (82.5%)	(67.2, 92.7)%
		Day 7-Week 25	25/40 (62.5%)	(45.8, 77.3)%
Secondary endpoints	<50 copies/mL	Week 25	17/40 (42.5%)	(27.0, 59.1)%
	Mean change in viral load (copies/mL)	Day 7-13	-76,211.0	SD (126,900)
		Day 7-Week 25	-67,351.5	SD (143,300)
	Mean change in CD4 counts (cells/uL)	Day 0-Week 25	+62.4	SD (105.8)
	Virologic failure or viral rebound	Day 7-Week 25	10/40 (25%)	

Table 26 Summary of efficacy for trial TMB-202

Title: A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab Plus an Optimized Background Regimen in Treatment-Experienced Patients Infected With HIV-1 (Amended to 24-Week Study)				
Study identifier	TMB-202			
Design	Randomized, double-blinded, multicentre, dose-response study			
	Duration of screening period: Duration of treatment phase:	6 weeks 24 weeks		
Hypothesis	No formal statistical hypotheses were tested			
Treatments	800 mg Q2W	800 mg ibalizumab every 2 weeks+ OBR (n=59 randomised)		
	2000 mg Q4W	2000 mg Q4W + OBR (n=54 randomised)		
Endpoints and definitions	Primary endpoint	Proportion of patients with HIV-1 RNA levels <50 copies/mL at Week 25 (EOS)		
	Secondary endpoint	Mean change from baseline in viral load at Week 25 (EOS)		
		Secondary endpoint	Mean change from baseline in CD4+ cell counts at Week 25 (EOS)	
	Additional endpoint	Changes in HIV-1 sensitivity/susceptibility associated with ibalizumab administration in combination with OBR		
Database lock	11-May-2011			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat- missing equals failure (ITT-MEF) time point: Week 25 (EOS)			
Descriptive statistics and estimate variability	Treatment group, N	800 mg Q2W + OBR N=59	2000 mg Q4W + OBR N=54	
		n/N (%) 95%CI	n/N (%) 95%CI	
Primary endpoints	<50 copies/mL	26/59 (44.1%) (31.2, 57.6)%	15/54 (27.8%) (16.5, 41.6)%	

Secondary endpoints	Mean (SD) change in viral load (log10copies/mL)	-1.6 (1.3)	-1.5 (1.4)
	Mean (SD) change in CD4 counts (cells/uL)	36.5 (63.0)	39.8 (80.1)
	Virologic failure or viral rebound	12/59 (20.3%)	13/54 (24.1%)

Analysis performed across trials (pooled analyses and meta-analysis)

The provided comparison of results across studies TMB-301 and TMB-202 suggested that the percentage of patients with a viral load <50 copies/ml at End of Study was similar for the 800 mg Q2W maintenance dose in Study TMB-301 (42.5%) and the 800 mg Q2W group in Study TMB-202 (44.1%). The percentage for the 2000 mg Q4W group, in Study TMB-202, was numerically lower (27.8%) (Table 27). A similar pattern was observed for the proportion of patients with a viral load <400 copies/ml at End of Study.

Table 27 Proportion of Patients with HIV-1 RNA Levels <50 Copies/mL and <400 Copies/mL at End of Study (Study TMB-301 and Study TMB-202, Intent-to-Treat Population)

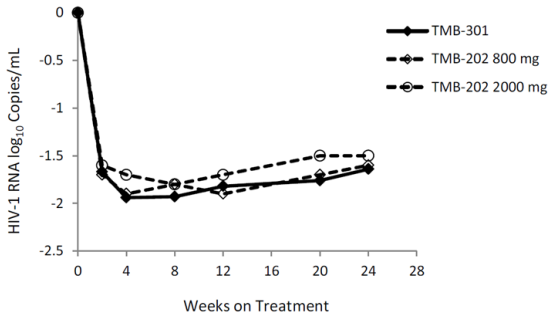
Response	Study TMB-301	Study TMB-202	
	2000 mg on Day 7 800 mg Q2W Starting at Day 21 (N = 40)	800 mg Q2W (N = 59)	2000 mg Q4W (N = 54)
HIV-1 RNA <50 copies/mL, n (%) 95% confidence interval	17 (42.5) 27.04, 59.11	26 (44.1) 31.2, 57.6	15 (27.8) 16.5, 41.6
HIV-1 RNA <400 copies/mL, n (%) 95% confidence interval	21 (52.5) 36.13, 68.49	34 (57.6) 44.1, 70.4	25 (46.3) 32.6, 60.4

Source: Module 5.3.5.1 TMB-301 CSR Statistical Table 14.2.7, TMB-202 CSR Statistical Tables 14.2.1.1 and 14.2.2.1.3.1
CSR = clinical study report; HIV = human immunodeficiency virus; Q2W = every 2 weeks; Q4W = every 4 weeks; RNA = ribonucleic acid
Note: Missing values were imputed as failures.

The proportion of patients with a ≥0.5 log10 decrease in viral load from baseline to End of Study was similar for the 800 Q2W maintenance dose in Study TMB-301 (62.5%) and the 800 mg Q2W group in Study TMB-202 (67.8%). The percentage for the 2000 mg Q4W group in Study TMB-202 was 59.3%. The mean change in viral load from baseline to End of Study was -1.5 to -1.64 log10 copies/mL across the three treatment groups in Study TMB-301 and Study TMB-202.

Mean HIV-1 RNA viral loads decreased rapidly after the initial infusion of ibalizumab and reached a nadir after approximately 4 weeks on treatment (Figure 9). Mean viral loads increased slightly during Weeks 8 through 24, but remained at least 1.5 log10 copies/ml below the baseline mean.

Figure 9 Mean Change From Baseline in HIV-1 RNA Viral Load (Studies TMB-301 and TMB-202, Intent-to-Treat Population)



Source: Study TMB-301 CSR Statistical Table 14.2.5.1 and Study TMB-202 CSR Statistical Table 14.2.3.1.5.1
CSR = clinical study report; HIV = human immunodeficiency virus; RNA = ribonucleic acid
Notes: Missing values imputed as zero change. Statistical tables for Study TMB-301 identify weeks from start of the 7-day Control Period; for example, Week 5 in the statistical tables corresponds to Week 4 on treatment.

The baseline mean CD4+ cell count and the mean increase from baseline in CD4+ cell counts to End of Study was larger in Study TMB-301 than in Study TMB-202 (Table 28).

Table 28 Change in CD4+ Cell Count from Baseline to End of Study (Study TMB-301 and Study TMB-202, Intent-to-Treat Population)

Time Point Statistic	Study TMB-301 2000 mg on Day 7 800 mg Q2W Starting at Day 21 (N = 40)	Study TMB-202 800 mg Q2W (N = 59)	Study TMB-202 2000 mg Q4W (N = 54)
Baseline, cells/μL			
N	40	59	54
Mean (standard deviation)	150.2 (181.85)	106.4 (91.3)	112.4 (118.5)
Median	73.0	80.5	54.0
Minimum, maximum	0, 676	19.0, 375.0	10.0, 476.5
Change to End of Study, cells/μL			
N	27	59	54
Mean (standard deviation)	62.4 (105.75)	36.5 (63.0)	39.8 (80.1)
Median	42.0	7.0	0.0
Minimum, maximum	-119, 341	-56.0, 285.5	-126.5, 367.5

Source: Module 5.3.5.1 TMB-301 CSR Statistical Table 14.2.9 and TMB-202 CSR Statistical Tables 14.2.3.1.3.1 and 14.2.3.1.6.1
CSR = clinical study report; Q2W = every 2 weeks; Q4W = every 4 weeks

Clinical studies in special populations

No dedicated studies in special populations have been performed.

Supportive studies

Starting in October 2009, patients who completed ibalizumab treatment in Study TMB-202 (Amendment 2) and who had a significant viral load response were permitted to continue to receive ibalizumab via an Investigator-sponsored protocol. The purpose of the protocol was to extend the successful treatment for patients beyond the endpoints provided by Study TMB-202.

Additional patients who had never participated in Study TMB-202, but who qualified to receive ibalizumab, were also enrolled and treated (also under Investigator-Sponsored INDs).

The objectives of this Investigator-sponsored study were to:

- Continue to provide ibalizumab to patients currently receiving ibalizumab treatment
- Demonstrate the longer term safety and tolerability of ibalizumab in treatment-experienced HIV-positive patients
- Provide access to ibalizumab for heavily treatment-experienced HIV-positive patients with limited treatment options

Efficacy was not the primary purpose of this Investigator-sponsored IND protocol and was not formally assessed. However, as part of an evaluation of continued eligibility under the protocol, viral load measurements (HIV-1 RNA) were assessed. As per the protocol, patients who experienced VF were to be discontinued. VF was defined per the protocol as two consecutive HIV-1 RNA level measurements, at least 14 days apart, that were above the limit of detection at or beyond Week 24 or two consecutive HIV-1 RNA level measurements, at least 14 days apart, that were <1 log10 decline from Baseline at or beyond Week 16, or completion of Study TMB 202. Thus, the proportion of patients achieving / maintaining a ≥0.7 log10 decrease from baseline in viral load was used to determine effectiveness.

A summary of the disposition of patients previously enrolled in Study TMB-202 who were treated with ibalizumab (at doses of either 800 mg Q2W or 2000 mg Q4W) under Investigator-sponsored INDs between 2009 and 2015 is provided in Table 29

Disposition of the 7 patients not previously enrolled in Study TMB-202 treated under Investigator-sponsored INDs is depicted in Table 30.

Table 29 Patient Disposition by Treatment Group for Patients Previously Enrolled in Study TMB-202 Treated with Ibalizumab Under Investigator-Sponsored INDs Between 2009 and 2015

	800 mg Q2W n (%)	2000 mg Q4W n (%)	Total N (%)
Enrolled	31	26	57
Discontinued	31 (100)	26 (100)	57 (100)
Death	0 (0.0)	5 (19.2)	5 (8.7)
Noncompliance	2 (6.5)	0 (0.0)	2 (3.5)
Other[a]	2 (6.5)	0 (0.0)	2 (3.5)
Patient decision/withdrew consent	3 (9.7)	2 (7.7)	5 (8.8)
PI decision	3 (9.7)	0 (0.0)	3 (5.3)
Protocol violation/not eligible	0 (0.0)	2 (7.7)	2 (3.5)
Switched to alternative regimen	2 (6.5)	3 (11.5)	5 (8.8)
Unknown	7 (22.6)	2 (7.7)	9 (15.8)
Virologic failure	7 (22.6)	5 (19.2)	12 (21.0)
Enrolled in Study TMB-311	5 (16.1)	7 (26.9)	12 (21.0)

IND=Investigational New Drug Application; PI=Principal Investigator; Q2W=every 2 weeks; Q4W=every 4 weeks.

Denominator for percentage of patients discontinued is the total number of patients who discontinued.

[a] Other reasons were patient relocation, liver cancer (chemo required).

Table 30 Patient Disposition for Patients Not Previously Enrolled in Study TMB-202 Treated with Ibalizumab Under Investigator-Sponsored INDs Between 2009 and 2015

	800 mg Q2W n (%)	2000 mg Q4W n (%)	Total N (%)
Enrolled	6	1	7
Discontinued	6 (100.0)	1 (100.0)	7 (100.0)
Death	1 (16.7)	0 (0.0)	1 (14.3)
Adverse event	1 (16.7)	0 (0.0)	1 (14.3)
Virologic failure	3 (50.0)	0 (0.0)	3 (42.9)
Enrolled in Study TMB-311	1 (16.7)	1 (100.0)	2 (28.6)

IND=Investigational New Drug Application; Q2W=every 2 weeks; Q4W=every 4 weeks.

The study ran between 2009 and 2015. Although no formal efficacy analysis has been done, it can be concluded that a significant number of patients experienced virologic failure (12/57 (21%)) or switched to an alternative regimen (5/57 (8.8%)) which is most likely also related to virologic failure. From the patients, not previously enrolled in TMB-202, almost half (3/7 (42.9%)) experienced virologic failure.

Time from start of treatment (either in TMB-202 or in the IND) to discontinuation by discontinuation reason as listed in Table 30 were provided as well as time to discontinuation analyses.

TMB-311 is an ongoing multicentre expanded access study of ibalizumab plus an OBR in treatment-experienced patients infected with MDR HIV-1. The study consists of 2 cohorts and includes patients already receiving ibalizumab treatment in other studies (rolling over from Studies TMB-301 and TMB-202), as well as compassionate use [Cohort 1], and new patients who are naïve to ibalizumab treatment [Cohort 2]. Cohort 1 patients continued on their current dosage of ibalizumab (800 mg q2wk or 2000 mg q4wk). Cohort 2 patients receive a 2000 mg loading dose at Baseline/Day 0 followed by 800 mg maintenance doses every 2 weeks. In addition to ibalizumab, all patients receive an OBR, which is a standard-of-care regimen selected by the investigator based on treatment history and the results of viral resistance testing.

Enrolment in Cohort 1 closed on 24 July 2017 and enrolment for Cohort 2 closed on 5 April 2018. A high level summary of initial results is provided below.

When looking at the 27 patients who rolled over from TMB-301 to Study TMB-311 [Cohort 1], 18/27 (66.6%) achieved a ≥0.5 log10 decrease from baseline in VL at Week 48. Six (6) patients discontinued the efficacy portion of the study because of virologic failure, but continued for the safety part. The remaining patients either had a <0.5 log10 decrease in VL (n=2) or discontinued for other reasons with a ≥0.5 log10 decrease from baseline in VL (n=1).

The proportion of patients achieving HIV-1 RNA levels <50 copies/ml and <400 copies/ml at Day 7, Week 12, Week 24, and Week 48 is summarized for Cohort 2 patients in Table 31.

Table 31 Proportion of Patients in Cohort 2 Achieving Specific HIV-1 RNA Levels at Weeks 24 and 48 (ITT Population)

	800 mg Q2W N=38
Proportion of patients with <50 copies/mL	
Week 24, n/NT (%)	11/24 (45.8%)
95% CI	(0.2555, 0.6718)
Week 48, n/NT (%)	8/17 (47.1%)
95% CI	(0.2298, 0.7219)
Proportion of patients with <400 copies/mL	
Week 24, n/NT (%)	17/24 (70.8%)
95% CI	(0.4891, 0.8738)
Week 48, n/NT (%)	10/17 (58.8%)
95% CI	(0.3292, 0.8156)

It is appreciated that a relevant proportion of patients was able to achieve a reduced viral load upon receiving ibalizumab infusions, which in some cases was sustained until at least 48 weeks of treatment.

2.5.3. Discussion on clinical efficacy

The clinical development plan of ibalizumab relies mainly on two studies, the Phase III study TMB-301 and the Phase II study TMB-202. Of the latter study, especially the 800 mg given every other week (Q2W) arm is of interest, as this resembles the maintenance dose as currently suggested in the SmPC. The posology as recommended in the SmPC, starting with a 2000 mg loading dose which is followed by a 800 mg Q2W maintenance dose, was however only studied in the 40 patients enrolled in Study TMB-301.

Dose selection

Initial studies with ibalizumab were based on a mg/kg dosage strategy. After a first dose-escalation study, it was found that a single dose of at least 10 mg/kg resulted in complete coating of CD4 cells (see also pharmacodynamics discussion) and was able to temporarily reduce HIV-1 viral load. The next two studies investigated ibalizumab given either weekly (Q1W) or biweekly (Q2W) in several concentrations and either as functional monotherapy (TMB-355.02) or together with an active OBR (TMB-355.03). From these studies, it was evident that monotherapy induced selection of viral variants with reduced ibalizumab susceptibility, resulting in rapid viral rebound. It also was found that ibalizumab, together with OBR, significantly reduced HIV-1 viral load, with no notable differences in virologic response between the 15 mg/kg Q2W arm (arm A) and the 10 mg/kg Q1W for 9 weeks, followed by 10 mg/kg Q2W arm (arm B). By Week 16, i.e. prior to the possible switching of patients in the Placebo arm to the 15 mg/kg dose of ibalizumab every 2 weeks and/or to change in OBR for all patients, mean viral load decrease was 1.07 log10 copies/mL in Arm A, 1.33 log10 copies/mL in Arm B and only 0.26 log10 copies/ml in the Placebo arm. The applicant concluded that a serum ibalizumab concentration of >5 µg/ml was associated with high CD4 receptor coating of T cells and generally correlated with significant viral RNA suppression, and hence aimed to next study a fixed-dose regimen that was predicted to achieve the desired trough level of >5 µg/ml. The weight-based dosages used in the dose-finding studies were subsequently replaced with a fixed-dose regimen because, as the applicant states, body weight is not known to correlate well with the number of CD4+ T-cells, CD4 receptors, or the rate of CD4+ T-cell turnover.

In study TMB-202, two regimens were tested, patients were randomized to receive either 800 mg Q2W (corresponding to ~10 mg/kg in an 80 kg patient) or 2000 mg Q4W (corresponding to ~25 mg/kg in an 80 kg patient). All patients received a personalised OBR next to the ibalizumab infusions. Based on all available information, the applicant finally concluded that patients with serum concentrations below a certain threshold, i.e. 0.15 µg/ml, during the course of ibalizumab treatment had a lower virologic response – specifically the viral load reduction from Baseline. In patients whose serum concentrations are always maintained above 0.15 µg/ml, no relationship was observed between serum concentrations and virologic outcomes. In TMB-202, the Ctrough serum concentrations in the 2000 mg dose every 4 weeks arm dipped to levels very close to the limit of 0.15 µg/ml, yet still above that value. The median Ctrough levels in the 800 mg dose at Week 2 were also very close to the 0.15 µg/ml threshold. The observation that the 2000 mg every 4 weeks arm provided better efficacy at Week 2, likely due to higher exposure achieved by the higher dose at Week 2, while the 800 mg every 2 weeks demonstrated better efficacy at Week 24, likely due to the higher Ctrough maintained throughout the trial period as a result of the shorter dosing interval, resulted in the final recommendation of a 2000 mg loading dose followed by 800 mg Q2W which was tested in the Phase III study TMB-301.

Design and conduct of clinical studies

Study TMB-301 was a Phase III, single-arm, multicentre, open-label study, consisting of a control period (days 0-6) in which patients were monitored on current failing therapy (or no therapy), a functional ibalizumab monotherapy period (days 7-13) and a maintenance period during which patients received OBR next to ibalizumab infusions (day 14-week 25). The design of the study has not been discussed with EU regulators. The applicant has had discussions with FDA regarding the development program and clinical trial designs. The design of this pivotal study is considered fit for the purpose of showing an early effect of ibalizumab monotherapy on viral load, but it is not designed to determine the (longer-term) additional effect of ibalizumab over OBR alone. For this, a comparator arm receiving active OBR without ibalizumab would have been needed. However, given the patient population and difficulties in selecting an OBR with enough active drugs, and given the results from prior studies showing that ibalizumab has antiviral activity, the chosen design is accepted.

Study TMB-202 was a Phase IIb, randomized, double-blind, multicentre, 24-week, dose-response study. As both arms received ibalizumab (albeit in different regimens) in this study, no real comparison can be made with other treatments to put the observed virologic outcome data into perspective.

For study TMB-301, the primary endpoint, the proportion of patients achieving a ≥0.5 log 10 decrease in viral load during 7 days of treatment, is considered relevant. The chosen strategy circumvents the interference of other ARVs while enabling a direct comparison with no or failed treatment for each patient individually. As ibalizumab monotherapy was shown to result in viral rebound and decreased viral susceptibility rapidly (see study TNX 355.02), a longer than 7 days functional monotherapy period would not have been appropriate. A ≥0.5 log 10 decrease in 7 days can be considered proof of antiviral activity and hence the strategy of the applicant to compare the proportion of patients who achieve this goal during the control period (day 0-6) and ibalizumab monotherapy (day 7-14) is relevant. Of note, given that the primary objective was to demonstrate antiviral activity at Day 14 and at Week 25, also the week 25 results are considered important for study success.

The primary endpoint for study TMB-202 was the proportion of patients with HIV-1 RNA levels <50 copies/mL at week 24, which is a widely used and accepted endpoint in studies investigating HIV antiretroviral therapy.

Secondary objectives and endpoints (such as Mean change from baseline in viral load, CD4 count and ibalizumab susceptibility at Week 25/EOS) in both studies are also considered of relevance and appropriate.

Patient population

Given the limitations of available data on efficacy and safety (see further below for more details), ibalizumab should only be used in patients who are unlikely to achieve virological suppression with presently available agents. The applicant reworded the proposed indication accordingly.

There are several uncertainties that may impact the level of benefit that has been shown (most importantly the small number of patients treated, the very different OBRs that have been given concomitantly, and the rather short follow-up period). The patients treated in study TMB-202 are not considered to be directly comparable to the population that may be treated after marketing authorisation. The study ran between 2008 and 2011, which is quite long ago, and the current treatment options are substantially different from what was available in 2008. The entry inhibitors enfuvirtide and maraviroc were already in clinical use and the first-in-class integrase inhibitor raltegravir had been recently approved at that time, but elvitegravir, dolutegravir and bictegravir (with improved tolerability and higher barriers to resistance) were not yet available, nor were boosted PIs (given that cobicistat and ritonavir were not yet approved) part of the treatment options. No information on prior ARV use could be located in the CSR of Study TMB-202.

Of importance is also that while in TMB-202 patients eligible for enrolment needed to be infected with virus with documented decreased susceptibility to at least one agent in each of the NRTI, NNRTI and PI class, in the currently proposed indication (correctly reflected in the inclusion criteria of study TMB-301) patients need to be infected with virus with documented resistance to at least one ARV medication from each of three classes of ARV medications. It can be questioned where decreased susceptibility ends and resistance begins, and to what extent these populations can both be considered supportive for the claimed indication (in which resistance to at least 1 agent in 3 different classes is required) or are essentially different. Even though there are notable differences between the trial population of Study TMB-202 and the envisioned target population, it is agreed with the applicant that the population enrolled in TMB-202 provides relevant information.

Efficacy data and additional analyses

In both studies, a significant proportion of screened patients were not enrolled in the study (36.5% in study TMB-301 and 43% in study TMB-202, respectively). Main reasons for screen failures were 1) viral load <1000 copies/mL, 2) no resistance to at least 1 drug from 3 different ARV classes, or 3) not having at least one fully active agent.

Study TMB-301

From earlier studies, it was shown that ibalizumab has antiviral efficacy. This was further confirmed in study TMB-301, where the 2000 mg loading dose, given without any other active antiretroviral therapy, resulted in significant viral load decrease (≥0.5 log10) between days 7 to 14 in 33 out of 40 patients (82.5%), compared to 1 out of 40 (2.5%) patients who achieved this goal during the initial 7 days. The seven patients without a ≥0.5 log10 decrease in viral load do not seem to differ from the 33 patients with a ≥0.5 log10 decrease in viral load in baseline characteristics such as viral load or CD4+ T cell counts. The applicant stated that there was no relation with susceptibility to ibalizumab or receptor occupancy/density levels that may explain this outcome. All patients had high serum concentrations and CD4 receptor occupancy at Day 14, so drug exposure was also not a factor in nonresponse. As also the co-primary endpoint (≥0.5 log10 decrease in viral load at Week 25) was found statistically significantly different from zero, the study can be considered successful.

After day 14, patients received an OBR together with ibalizumab. Mean HIV-1 RNA levels further decreased with a nadir at day 21, after which these levels slightly increased again. At end of study (week 25), mean HIV-1 RNA levels were approximately one third of baseline levels. While the effect of ibalizumab in reducing viral load during the 7 day monotherapy period is clear and appreciated, it is

unknown what part of the effect between day 14 and end of study can be attributed to ibalizumab and what part to the OBR.

There was a clear trend toward increasing virologic responses with increasing OSS values, which is typical for HIV treatment studies, as stated by the applicant. To gain further insight in the contribution of OBR, a thorough investigation around the number and type of active ARVs in the OBR for each individual patient in relation to virologic outcome considered needed in order to reveal if there is evidence of an added value of ibalizumab over OBR alone. Per individual patient, the likely activity of the OBR was analysed based on the mutations in the patient's viral sequences and the Stanford HIV drug resistance database (https://hivdb.stanford.edu/hivdb/by-mutations/). The patient's virologic response during the study was then carefully reviewed. Given that there were some patients for whom it was very unlikely that the outcome would have been reached solely based on the predicted activity of the OBR, and given the significant viral load decrease observed upon ibalizumab monotherapy between days 7 to 14 in the far majority of patients, it was considered that there is a clear suggestion of an added effect of ibalizumab on top of the OBR. Of note, all patients for whom this was applicable, had an OSS score of 0 or 1. Hence, it is considered justified to support approval of ibalizumab, in a restricted population of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. The applicant has committed to set-up a prospective product registry and perform a post-authorization study to provide more evidence that ibalizumab has additional efficacy on top of OBR in patients suffering from multi-drug resistant HIV-1 infection.

Table 32 Overview of individual patient's OBR and virologic outcome

	OBR																
Screen ID	OBR1	OBR2	OBR3	OBR4	OBR5	OBR6	NRTI OSS	NNRTI OSS	PI OSS	INI OSS	MVC OSS	ENF OSS	FOST OSS	TOTAL OSS	HIV-1 RNA load Day 7	Day 14	EOS	Outcome
01-001	DTG	DRV	FTC	TFV			2	0	1	0	0	0	0	4	27700	3460		disc due to VF
01-002	FSV	DRV	DTG	FTC	TFV		0	0	0	0	0	0	1	1	217000	16400		disc due to AE/death
01-005	FTC	TFV	DRV	DTG	FSV		0	0	0	1	0	0	1	2	73700	2700	TND	Virologic succes
01-006	ATV	FTC	TFV	DTG	FSV		0	0	0	1	0	0	1	2	6530	882	TND	Virologic succes
02-001	FTC	TFV	DTG	FSV			0	0	0	1	0	0	1	2	70300	20900	34	Virologic succes
02-002	DTG	FSV	DRV	FTC	TFV		0	0	0	0	0	0	1	1	75100	2170		disc due to AE/death
04-001	DRV	FTC	TFV	DTG	FSV	ENF	0	0	0	0	0	1	1	2	5660	11400	535	VF
04-002	DTG	DRV	FTC	TFV	FSV		0	0	0	0	0	0	1	1	88600	15200	63	Virologic succes
05-001	ABC	DTG	3TC				1	0	0	1	0	0	0	2	2860	2680	TD	Virologic succes
05-003	DTG	DRV					0	0	1	1	0	0	0	2	21700	15300	TD	Virologic succes
05-004	ABC	DTG	3TC	DRV			1	0	1	1	0	0	0	3	62500	1640		disc due to AE/death
05-005	DRV	DTG	MVC				0	0	1	1	1	0	0	3	205000	19800	TND	Virologic succes
08-001	TPV	FTC	TFV	FSV			0	0	0	0	0	0	0	0	57300	27300	66100	<0,5 log 10 drop, VF
09-002	DTG	FTC	TFV				0	0	0	1	0	0	0	1	61500	5160		disc due to other reasons and <0,5 log10 drop
13-001	DTG	DRV	FTC	TFV	LPV		0	0	0	1	0	0	0	1	7980	133	TND	Virologic succes
13-002	DTG	DRV	FTC	TFV	MVC		0	0	0	1	0	0	0	1	15100	228	TD	Virologic succes
17-001	FSV	DTG	DRV	FTC	TFV		0	0	0	0	0	0	1	1	36000	1680		disc due to other reasons and <0,5 log10 drop
17-002	DRV	DTG	ETR	FSV	TFV	FTC	0	0	0	0	0	0	0	0	648	<50	TND	Virologic succes
17-003	DRV	DTG	FSV	FTC	TFV		1	0	0	0	0	0	1	2	743000	519000	271000	Suboptimal response at EOS
18-002	ABC	FSV	DRV	FTC	TFV	TFV	1	0	0	0	0	0	1	2	14600	3620		disc due to VF
19-001	ETR	TFV	MVC	ABC	3TC		0	1	0	0	1	0	0	2	6630	162	TND	Virologic succes
19-002	ETR	DTG					0	1	0	1	0	0	0	2	19000	240	TND	Virologic succes
21-001	DRV	MVC	FTC	TFV			0	0	0	0	0	0	0	0	577000	23300	66500	Virologic rebound
21-002	DTG	DRV	FTC	TFV			1	0	0	0	0	0	0	1	301000	146000		disc due to other reasons and <0,5 log10 drop
22-001	FTC	TFV	DRV				2	0	1	0	0	0	0	3	24100	2440	18800	<0,5 log 10 drop, VF
22-002	DTG	DRV	ETR				0	0	1	1	0	0	0	2	450000	54800	224	Virologic succes
22-003	fAPV	FTC	TFV				1	0	1	0	0	0	0	2	38000	5420		disc due to other reasons and <0,5 log10 drop
23-002	DTG	FTC	TFV				0	0	0	1	0	0	0	1	43300	820	TND	Virologic succes
25-001	TFV	DRV					1	0	1	0	0	0	0	2	480000	26100	10200	Suboptimal response at EOS
25-002	RPV	DRV					0	1	1	0	0	0	0	2	34700	363	TD	Virologic succes
26-001	FTC	TFV	DRV	FSV			0	0	0	0	0	0	1	1	72500	1010	TND	Virologic succes
27-001	DTG	FSV	FTC	TFV			0	0	0	1	0	0	1	2	6290	7690	TD	Virologic succes
27-002	DRV	DTG	FTC	TFV	FSV		0	0	0	0	0	0	1	1	7420	97	8820	<0,5 log 10 drop, VF
29-001	FTC	TFV	LPV	RAL			2	0	1	1	0	0	0	4	14300	1580	TND	Virologic succes
29-002	DRV	3TC	RAL	TFV			1	0	0	1	0	0	0	2	48800	3130	12800	Virologic rebound
30-001	ATV	RPV	FTC	TFV			0	1	0	0	0	0	0	1	67600	18800	TD	Virologic succes
30-004	LPV	3TC	AZT				1	0	1	0	0	0	0	2	304	80	57	Virologic succes
32-001	FTC	TFV	FSV				0	0	0	0	0	0	0	0	18500	1160	11300	<0,5 log 10 drop, VF
32-002	TFV	DRV	DTG	FSV			0	0	0	1	0	0	1	2	8390	73	61	Virologic succes
32-003	ETR	DTG	FTC	TFV	DRV		0	0	0	0	0	0	0	0	873	107	1080	<0,5 log 10 drop

Mean CD4+ T cell counts increased during the study from 150 cells/mm3 at baseline to 208 cells/mm3 at week 25, which is considered clinically relevant. There is however a quite extensive proportion of missing data at week 25 (15%), which may have an impact on this outcome.

Efficacy results stratified by CD4 cells show a low response rate in patients with a CD4 count below 50/mm3. Given the ibalizumab CD4-dependent mechanism of action and the intended advanced target population, this aspect is required to be highlighted in the SmPC.

There does not seem to be a difference in outcome by sex (male/female), age (<50 vs. ≥50), race (Caucasian, Asian, and Other), and geographic location (United States vs. Taiwan), although the single-arm design and small patient numbers do not allow any confirmatory conclusions.

Subjects treated with fostemsavir seemed to perform worse compared to those who did not receive the investigational agent. This could have been due to more advanced HIV disease and lower average OSS in these patients. Use of the investigational agent fostemsavir as a component of the OBR in TMB-301 was assigned a score of '1' for OSS calculations, assuming it was fully active, unless susceptibility results were provided by sites that indicated reduced susceptibility to fostemsavir.

Study TMB-202

The primary endpoint of Study TMB-202, the proportion of patients having a viral load of <50 copies/ml at Week 24, was 26/59 (44.1%) in the 800 mg Q2W arm and 15/54 (27.8%) in the 2000 mg Q4W arm. Although the difference between the two treatment regimens was not statistically significant, there was a numerical difference in favour of the 800mg q2wk regimen. Although cross-study comparisons need to be interpreted with much caution, the observed proportion of patients having a viral load of <50 copies/ml at Week 24 (44%) was very much comparable to what is observed in study TMB-301 (42%). Secondary endpoint analyses were in line with the primary analysis, and the provided subgroup analyses did not reveal new insights.

Expanded access study TMB-311

Patients who received ibalizumab under the TMB-301 or TMB-202 protocol were eligible to roll-over to the expanded access study TMB-311 (cohort 1). Also, a cohort of ibalizumab naïve patients was enrolled under the TMB-311 protocol (cohort 2). A post-hoc analysis was provided for the patients enrolled in Study TMB-301 at US sites (n=36), with a data cut-off date of 20 April 2017. A draft summary report on the 39 patients in Cohort 2 was provided, with a cut-off date of 31 March 2018.

The submitted Cohort 1 data provide reassurance regarding the longer-term effect of ibalizumab, with 18 of the 27 patients who actually rolled over from the parent study to Study TMB-311 (66.6%) having achieved a ≥0.5 log10 decrease from baseline in VL at Week 48, and 16 of the 27 patients (59.3%) having achieved virologic suppression (i.e. suppress to <50 copies at any time after primary endpoint while not having a ≥1 log10 increase from nadir on any two consecutive scheduled efficacy assessments after achieving the ≥0.5 log10 decline from Baseline).

It should be noted that assessment of Cohort 2 data is currently not possible given the limited information provided. Especially in depth assessment of patient characteristics was not possible, which hampers interpretation of any efficacy outcome. However, it is appreciated that a relevant proportion of patients was able to achieve a reduced viral load upon receiving ibalizumab infusions, some of which was sustained until at least 48 weeks of treatment.

The chosen fixed-dose regimen raises concerns of possible under-dosing of ibalizumab in patients with high body weight. In study TMB-202 and TMB-301, patients with higher body weight showed lower drug trough concentration when compared to those with less high body weight. Further, in the TMB-202 ibalizumab 800 mg Q2W arm, average trough concentrations in patients with high body weight were far below 300 ng/ml, which is considered the threshold necessary to obtain intermediate or high CD4+ receptor occupancy. PopPK analysis indicated that body weight was the only statistically significant covariate and ibalizumab concentrations decreased as body weight increased. Response rate data at the 800 mg q2wk dose however indicate no clear effect on the % observed for a body weight of <70 kg, 70 - 85 kg and >85 kg. However, the lower drug trough concentrations are unlikely to impact virologic outcome and does not warrant a dose adjustment.

Additional expert consultation

During the CHMP meeting on **28 February 2019,** the CHMP concluded that a SAG shall be convened. This SAG meeting was held on 11 April 2019.

The following questions were discussed regarding efficacy:

1. What is the prevalence of multidrug resistant (MDR) HIV-1 in the EU, such that the availability of an agent like ibalizumab might be relevant to achieve durable viral suppression?

It is acknowledged that, currently, the percentages of patients with MDR HIV in the European countries are below 3-5%. It is however further pointed out that the target population for this product would be mainly the MDR HIV patients who have detectable viral load and therefore those who experience virological failure. In this last scenario, the estimated prevalence at the moment is definitely below 1%, however, it is considered an unmet need as these patients have limited therapeutic options with higher risk of disease progression, and are in need of new therapies such as ibalizumab. The role of adherence and the availability of other medicines to build an effective treatment were also discussed:

- Adherence is always a key point to obtain undetectable viral load and in this case it seems even more important as the patients have to be willing to attend the Clinic frequently because the administration is intravenous.
- The availability of other therapeutics for the OBR in addition to Ibalizumab to achieve the virological suppression and therefore to improve their immunovirological situation must be also considered since those who have an overall susceptibility score (OSS) of $\leqslant 1$ could have more risk of virological failure.

*OSS: Overall susceptibility score is defined as the number of fully active antiretroviral in the OBR established at baseline based on Monogram's genotypic and phenotypic test results and historical results.
In conclusion, although the target population for this drug is small, still it is considered an unmet need for patients with MDR HIV-1 infection who had advanced disease and limited treatment options.

2. The experts are asked if the additional efficacy to the overall treatment effect of ibalizumab as add-on to OBR is sufficiently demonstrated in patients with MDR HIV in whom it is otherwise not possible to construct an antiretroviral treatment regimen?

Experts agreed that besides short-term antiviral effect (14 days), data on long-term efficacy are missing precluding the possibility of having an accurate estimation of the effect of the medicine in addition to the OBR in controlling viral replication. However, they were also in agreement regarding the suitability of this product in the case of patients with limited treatment options taking also into account that at the moment there are no major safety concerns and that its use would not have an impact on future regimens as emergence of cross resistances to other antiretrovirals is not expected. In conclusion, although the applicant must provide more data regarding the efficacy of the product and therefore different post authorization measures have to be considered to address these issues, still the use in this population is considered justified.

3. The experts are asked to reflect upon the need for generating further long-term clinical data to further characterize the efficacy, safety and barrier to resistance of this drug, and if so, what kind of collection methods (trial, registry) are relevant and feasible to conduct?

As it was discussed during the meeting, post authorization measures are considered absolutely needed to better address the efficacy of the product, the safety profile and to further explore risk factors/predictors of virological response and/or failure. It was agreed that despite ideally being the best option for gathering robust evidence, a new randomised clinical trial of Ibalizumab +OBR versus OBR+placebo would not be feasible also in light of the small of number of patients that could be enrolled in such a study. Based on this, it is considered that setting up a product registry that should include patients that receive the products, would be an adequate approach. It is also suggested to include also those patients who receive the product outside of the final accepted indication (i.e, patients with infection due to HIV-2,

patients admitted to the intensive care who could need the medicine even temporarily (IV drug), in selected circumstances in which drug-drugs interactions with other agents is particularly problematic). It was also proposed to liaise with the ongoing and well established HIV registries to be able to perform a control case study to compare patients on Ibalizumab with patients with the same characteristics but exposed to other drugs.
The experts also considered that other research topics such as penetration in viral sanctuaries, e.g. CSF and urogenital tract, could be further explored. The role in treatment of HIV-2 would be also of great interest considering the current unmet medical need.

2.5.4. Conclusions on the clinical efficacy

Taken together, although the interpretation of ibalizumab efficacy data is hampered by the complexity of the patient population, the single arm design of the Phase III study, a primary objective focused on 7-days antiviral activity of ibalizumab with the consequences of unresolved uncertainties regarding the impact of OBR in relation to the effect induced by ibalizumab and the small patient number included. Overall, it seems proven that ibalizumab has antiviral activity and can be of added value for the treatment of patients suffering from multi-drug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

However, due to the limitations of current knowledge, it is considered necessary to address concerns with respect to the maintenance of a positive benefit-risk balance due to potential lack of efficacy in the long term. Therefore, the CHMP considers the following measures necessary to address issues related to efficacy: The applicant has to set-up a prospective product registry and perform a post-authorization study to provide more evidence on the efficacy of ibalizumab in combination with other anti-retroviral medicinal products in adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

2.6. Clinical safety

Patient exposure

A total of 323 patients with HIV infection have been exposed to ibalizumab IV infusion, with 309 patients participating in sponsor-initiated studies, 12 patients that were originally in study TMB-202 and then on investigator-sponsored INDs, 2 patients that were on investigator-sponsored INDs (compassionate use). Extent and duration of exposure ranged from single doses of 0.3 mg/kg to 800 mg Q2W/2000 mg Q4W for more than 9 years. An additional 58 patients with HIV-1 infection and subjects at risk for HIV-1 infection have been exposed to ibalizumab administered subcutaneously or intramuscularly.

For the primary analysis of safety, the combined safety database of Study TMB-301 (N=40 patients treated with the proposed 2000 mg loading dose followed by 800 mg every two weeks)) and Study TMB-202 (N=59 in the 800 mg every two weeks arm and N= 54 in the 2000 mg every 4 weeks arm) will be used.

Adverse events

In the combined safety database of study TMB-202 and TMB-301 most patients (127 out of 153; 83.0%) experienced at least one TEAE. Of them 25 (16.3%) reported a severe AE. In 9 patients (5.9%) the AE led to study discontinuation. Six (n=6; 3.9%) patients died during treatment.

The most frequent TEAEs (reported in ≥10.0% of patients) were diarrhoea (8; 20%), nausea, fatigue, pyrexia, and dizziness (5; 12.5% each), and nasopharyngitis, vomiting, and lymphadenopathy (4; 10.0%

each). Rashes in general were reported for 5 (12.5%) patients and included rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash, each of which was reported in 1 patient.

Treatment-emergent AEs considered definitely related to study drug were vomiting and immune reconstitution inflammatory syndrome (1; 2.5% each). Treatment-emergent AEs probably or possibly related to study drug were diarrhoea, all rashes (2; 5.0% each) (which included erythematous rash and generalized rash in 1 patient each), nausea and pruritus (1; 2.5%) and dizziness (3; 7.5%).

Serious adverse events and deaths

Serious adverse events

For Studies TMB-301 and TMB-202, SAEs were reported for 16 (16.2%) patients in the combined 800 mg Q2W group and 19 (12.4%) patients in the all patients combined group. The only SAEs reported for more than 1 patient included pyrexia in 2 patients in the combined 800 mg Q2W group (2.0%) and the all patients combined group (1.3%) and cytomegalovirus viremia (n=1; 1.0% in the 800 mg Q2W group and n=3 (2.0%) in the all patients combined group).

One SAE (immune reconstitution inflammatory syndrome) was considered treatment-related.

In the other studies renal failure, depression, grand mal convulsion, bradycardia, hepatic failure, staphylococcal cellulitis, hepatic encephalopathy, hypotension, coronary artery disease, vertigo, lower abdominal pain, diarrhoea, hypersensitivity, intentional overdose, presyncope, generalized rash, and maculo-papular rash were reported as SAEs.

Death

A total of 9 deaths were reported. Six (6) for Studies TMB-301 and TMB-202 and 3 for study TNX-355.03 (Phase 2). None was considered treatment-related. An additional 6 deaths were reported in the Ibalizumab Safety Summary of Investigator-Sponsored IND Patients (expanded-access study).

Laboratory findings

No clinically meaningful changes from baseline to end of treatment in haematology parameters were observed. ≥Grade 3 haematology abnormalities were reported for 11 (8.2%) patients. ≥Grade 3 abnormalities were reported for decreased haemoglobin (n=7; 5.2%), decreased neutrophils (n=3; 2.2%), decreased leukocytes (n=2; 1.5%) and decreased platelets (n=1; 2.5%).

No clinically meaningful changes from baseline to end of treatment in chemistry parameters were observed during Study TMB-301 and TMB-202. Grade 3 or 4 chemistry abnormalities were reported for 49 (36.6%) patients. These abnormalities were reported for decreased phosphate (n=28; 20.9%), increased bilirubin (n=5; 3.7%), increased lipase (n=5; 3.7%), and increased urate (n=5; 3.7%).

No clinically meaningful changes from baseline to end of treatment in vital signs were observed during Study TMB-301 and TMB-202.

None of the ECG changes observed during Study TMB-301 and TMB-202 were considered clinically relevant.

Skin rashes were the only clinical relevant shift from normal. These are reported as AE (see discussion under adverse events of special interest). No other clinically meaningful changes from baseline to end of treatment in physical examination were observed during Study TMB-301 and TMB-202.

Safety in special populations

Age

For the combined 800 mg Q2W group in Studies TMB-301 and TMB-202 46 patients below the age of 50 years and 53 patients ≥ 50 years were included. For the all patients combined group 84 patients below the age of 50 years and 69 patients ≥ 50 years were included. The youngest patient was 23 years old, the oldest patient was 75 years old. No children were included in the clinical program.

In the combined 800 mg Q2W group from Studies TMB-301 and TMB-202, the overall incidence of TEAEs was higher for the <50 years subgroup compared with the ≥50 years subgroup (91.3% vs 77.4%). SAEs were reported for 6 (13.0%) patients in the <50 years subgroup and 10 (18.9%) patients in the ≥50 years subgroup. TEAEs leading to discontinuation of study drug were reported for 2 (4.3%) patients in the <50 years subgroup and 6 (11.3%) patients in the ≥50 years subgroup.

The subgroup analysis of haematology and chemistry did not reveal any trend in age related adverse events.

The SAE and adverse events leading to discontinuation appeared higher in the ≥50 group.

The PDCO has waived the obligation to submit the results of studies with ibalizumab in pre-term and/or term neonates (0-27 days), infants and toddlers (1 month to 23 months), and children (2 to 5 years) for the treatment of HIV-1 infection. The European Medicines Agency has deferred the obligation to submit the results of studies with ibalizumab in children and adolescents (aged 6 to less than 18 years) for the treatment of HIV-1 infection.

Gender

For the combined 800 mg Q2W group in Studies TMB-301 and TMB-202 85 male and 14 female patients were included. For the all patients combined group 135 male patients and 18 female patients were included.

The subgroup analysis did not show striking differences between male and female patients for TEAEs, SAEs, TEAEs leading to discontinuation, haematology and chemistry.

Race

For the combined 800 mg Q2W group in Studies TMB-301 and TMB-202 64 Caucasian patients, 5 Asian patients and 30 patients of other races were included. For the all patients combined group 91 Caucasian patients, 8 Asian patients and 54 patients of other races were included.

In the combined 800 mg Q2W group from Studies TMB-301 and TMB-202, the overall incidence of TEAEs, SAE and changes in haematology and chemistry was similar for white patients compared with patients of other races (82.8% vs 83.3%). For the combined 800 mg Q2W group in Studies TMB-301 and TMB-202, TEAEs leading to discontinuation of study drug were reported for 4 (6.3%) white patients and 4 (13.3%) patients of other races.

Geographic Region

For the combined 800 mg Q2W group in Studies TMB-301 and TMB-202 94 US patients and 5 patients from Taiwan were included. For the all patients combined group 145 US patients and 8 patients from Taiwan were included.

No firm conclusions about the influence of geographic region on the safety profile can be drawn due to the skewness of the patient distribution (145 from US and 8 from Taiwan). The subgroup analysis, however, did not show striking differences between patients from US vs Taiwan for TEAEs, SAEs, TEAEs leading to discontinuation, haematology and chemistry.

Immunological events

At baseline none of the patients evaluated showed a positive antibody response.

Only incidental patients with an antibody response were reported (2 patients in study TNX-355.03 and one patient in TMB-202). Contrary to the other studies, in phase 1b study TNX-355.02 7 out of 22 patients (31.8%) had a positive antibody response at some time during the study. In some patients the presence of antibodies was demonstrable until the end of the study.

The only patient with antibody repeated activity in study TMB-202 did not show any negative effect on efficacy or safety of ibalizumab.

The applicant did not discuss nor reported the development of neutralising antibodies.

Safety related to drug-drug interactions and other interactions

No drug-interaction studies have been conducted with ibalizumab.

Discontinuation due to AES

Twenty-four (24.2%) patients in the 800 mg Q2W group and 40 (26.1%) patients in the all patients combined group did not complete study treatment. The most frequently reported reasons for discontinuation for the combined 800 mg Q2W group were virologic failure (7 patients) and AE (6 patients; 5 of whom died due to AE). The most frequently reported reasons for discontinuation for the all patients combined group was virologic failure (13 patients).

The overall incidence of discontinuations due to TEAE is 9 out of 134 patients (6.7%; Study TMB-301 n=5, 12.5%; Study TMB-202 800 mg Q2W n=3, 5.1%; 2000 mg Q4W n=1, 1.9%)

Post marketing experience

Post marketing experience with ibalizumab is very limited, as expected. According to the applicant, a review of the available safety data from the Periodic Adverse Drug Experience Reports submitted to the EMA, did not identify new safety signals that change the safety profile of ibalizumab.

2.6.1. Discussion on clinical safety

The number of patients included in the safety database is limited. A total of 323 patients with HIV infection have been exposed to ibalizumab IV infusion. Extent and duration of exposure ranged from single doses of 0.3 mg/kg to 800 mg Q2W/2000 mg Q4W for more than 9 years.

For the to be marketed treatment regimen, 2000 mg loading dose followed by 800 mg Q2W, safety data from only 40 patients from a single-arm study and 38 patients from the expanded access study is available.

For the primary analysis of safety, the combined safety database of Study TMB-301 (N=40 treated with the proposed 2000 mg loading dose followed by 800 mg every two weeks) and Study TMB-202 (N=59 in the 800 mg every two weeks arm and N=54 in the 2000 mg every 4 weeks arm) is used.

In Studies TMB-301 and TMB-202, the most frequently reported TEAEs (in >10% of patients in either combined group) were all rashes and diarrhoea (14.1% each), nasopharyngitis (11.1%), and cough (10.1%) for the combined 800 mg Q2W group and all rashes (17.6%), diarrhoea (15.0%), and rash (11.8%) for the all patients combined group.

The incidence of TEAEs was generally similar between the 800 mg Q2W group in Study TMB-202 and Study TMB-301.

The majority of TEAEs were considered unrelated to treatment with ibalizumab. Treatment-emergent AEs considered definitely related to study drug were vomiting and immune reconstitution inflammatory syndrome (n=1; 2.5% and n=2; 5%, respectively). Treatment-emergent AEs probably related to study drug were diarrhoea, all rashes (n=2; 5.0% each). The only TEAE considered possibly related to study drug and reported in more than 1 patient was dizziness (n=3; 7.5%) A tabulated presentation of all treatment related TEAEs with corresponding frequencies (without splitting in definitely, probably, or possibly related TEAEs) by SOC and by PT has been presented.

The incidence of severe TEAEs was similar between Study TMB-301 (17.5%) and the 2000 mg Q4W groups from Study TMB-202 (16.7%), but higher than the 800 mg Q2W group (6.8%) from Study TMB-202. None of the events was judged by the investigator's to be study drug-related and in 3 cases SAEs were typical AIDS-associated disorders.

Rash, which was a commonly observed event in both studies, is recognized as a predictable and often manageable side effect of treatment with monoclonal antibodies. In general, rashes have an early onset (i.e., within 1 to 3 weeks of the first dose of ibalizumab), are mild to moderate in intensity, and resolve without treatment or dose adjustment. Among TMB-202 and TMB-301 studies, 18 rashes out of 25 (72%) were judged by the investigator as possibly or probably related to ibalizumab. No rash-specific analyses were performed. Hematology results obtained from overall patients participating in the two studies do not add significant information regarding rash etiology and confounding factors do not allow to identify risk factors for rash.

Other TEAEs of interest that were examined for a potential association with ibalizumab treatment included malignancy and events relating to hepatotoxicity. Seven (7) malignancy events were reported (4 patients in Study TMB-301, 1 patient in the 800 mg Q2W group of Study TMB-202, and 2 patients in the 2000 mg Q4W group of Study TMB-202), 6 events were considered unrelated by the investigator. One (monoclonal gammopathy of uncertain significance, 2000 mg Q4W group of Study TMB-202) of these events was considered treatment-related. Two (2) events relating to hepatotoxicity were reported (1 patient in Study TMB-301 and 1 patient in the 800 mg Q2W group of Study TMB-202) and none was considered treatment-related.

In all studies combined the following SAEs were reported; pyrexia, cytomegalovirus viremia, renal failure, depression, grand mal convulsion, bradycardia, hepatic failure, staphylococcal cellulitis, hepatic encephalopathy, hypotension, coronary artery disease, vertigo, lower abdominal pain, diarrhoea, hypersensitivity, intentional overdose, pre-syncope, generalized rash, and maculo-papular rash. Depression, pyrexia and cytomegalovirus viremia were reported more than once. One SAE (immune reconstitution inflammatory syndrome) was considered treatment-related. The applicant provided a re-evaluation of the relationship of ibalizumab and TEAEs reported, and concluded that some of the AEs were related to advanced AIDS related diseases and not to ibalizumab.

A total of 9 deaths were reported. Six (6) for Studies TMB-301 and TMB-202 and 3 for study TNX-355.03 (Phase 2). None was considered treatment-related by the investigator. An additional 6 deaths were reported in the Ibalizumab Safety Summary of Investigator-Sponsored IND patients (expanded-access study). The 10% rate of death is in line with what was observed in other studies.

The most common abnormality across all groups was decreased phosphate. The Applicant specified that

the approx. 20% hypophosphatemia noted in TMB-202 was an artefact and that in the Study TMB-202 the real reported cases with grade 3 or grade 4 abnormality in phosphate were 2. Moreover, the lack of data on renal functionality, such as creatinine elevations and/or urine protein, was noted. Firm conclusions on a causal relationship between ibalizumab administration and renal abnormalities cannot be drawn. Nevertheless, the SmPC includes a statement to alert physicians that Grade 3 creatinine elevations occurred frequently in subjects with underlying renal disease, risk factors for renal disease, and/or in subjects taking concomitant medications known to be nephrotoxic.

No drug-drug-interaction studies have been conducted with ibalizumab. As no interactions are expected, this is considered acceptable.

Antibodies against ibalizumab were measured in all patients. At some time during treatment antibodies against ibalizumab could be demonstrated in 10 patients. In the pivotal studies only one patient reported a continuing antibody titer. The low antibody titer (Ab titer was 16) did not interfere with efficacy (HIV-1 RNA remained undetectable while $CD4^+$ cells increased) nor safety (no AEs were reported by the patient). Therefore, it might be concluded that there is a low risk of immunogenicity for ibalizumab. This is in line with the findings reported in literature where IgG4 antibodies are considered to be less immunogenic compared to other therapeutic antibodies.

Surprisingly, in phase 1b study TNX-355.02 7 out of 22 patients (31.8%) had a positive antibody response at some time during the study. The applicant provided more information on the observed antibodies in Study TNX-355.02. It remains however unknown why there were relatively many patients in this study in whom antibodies were observed. Neutralizing antibodies were not measured, but given the low incidence of ADA development with ibalizumab, the risk of developing neutralizing antibodies is also low.

Overall, the safety profile of ibalizumab from the extension **Study TMB-311** does not seem to show new or unexpected adverse events. 68 of 75 patients (90.7%) have reported treatment-emergent adverse events (TEAEs). However, it was noted that vascular disorders occurred in 12 (16%) patients of whom 5 (6.7%) were deep vein thrombosis (DVT). All 5 observed Deep vein thrombosis events were considered by investigators to be unrelated to ibalizumab treatment. Furthermore, occurrence with regards to start of ibalizumab was temporally heterogeneous, making causal relationship between these SAEs and the study drug unlikely.

The subgroup analyses for age, gender, race, and geographic region were performed using the combined 800 mg Q2W group in Studies TMB-301 and TMB-202. A total of 99 patients were included. Based on these limited data it can be concluded that no striking difference for any safety issue related to the subgroups studied was observed.

No pregnancies occurred and no women were breast-feeding in the clinical development program.

No children were included in the clinical program. The PDCO has waived the obligation to submit the results of studies with ibalizumab in pre-term and/or term neonates (0-27 days), infants and toddlers (1 month to 23 months), and children (2 to 5 years) for the treatment of HIV-1 infection. The PDCO has deferred the obligation to submit the results of studies with ibalizumab in children and adolescents (aged 6 to less than 18 years) for the treatment of HIV-1 infection.

The number of patients discontinuing due to AE appears high (40 (26.1%) in the pivotal studies). However, the relation between treatment and the observed AEs remains to be established. Therefore, no conclusions can be drawn from this high number of patients discontinuing due to AE. Post marketing

experience with ibalizumab is very limited. As the safety database of the product is limited, the Applicant has discussed whether additional pharmacovigilance activities could be introduced to enhance characterizing the safety profile of the product; the applicant has contacted the organisers of registries and is currently investigating whether data from these registries can be used.

2.6.2. Conclusions on the clinical safety

Given the limited number of patients included in the database, the open label design and lack of a control arm in the main studies, the individualised optimized background regimen (OBR), the progression of the disease (most patients had $CD4^+$ cell count <50 cells/µl), interpretation of the safety data of ibalizumab is hampered.

Despite the limitations and uncertainties of the safety profile, no serious safety risks emerged. Routine pharmacovigilance will be utilized to further characterize the safety profile of ibalizumab post-authorisation.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Immune Reconstitution Inflammatory Syndrome (IRIS)
Missing information	Use in Pregnant Women and Breast-feeding Women Use in Elderly Patients (>65 years of Age) Long-term safety

Pharmacovigilance plan

Routine pharmacovigilance activities were considered sufficient to monitor the safety profile of ibalizumab.

There are no planned additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risk		
None	N/A	N/A
Important Potential Risk		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immune Reconstitution Inflammatory Syndrome (IRIS)	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PIL Section 2, Warning and precautions	Routine pharmacovigilance activities
Missing Information		
Use in Pregnant Women and Breast feeding Women	Routine risk minimisation measures: SmPC section 4.6 and 4.8 PIL section 2 Pregnancy and Breast feeding	Routine pharmacovigilance activities
Use in Elderly Patients	Routine risk minimisation measures: SmPC section 5.2	Routine pharmacovigilance activities
Long-term Safety	Routine risk minimisation measures: SmPC section 4.8	Routine pharmacovigilance activities

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06 March 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that ibalizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers ibalizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Trogarzo (Ibalizumab) is included in the additional monitoring list as it is a new substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The following indication is claimed for ibalizumab:

Ibalizumab is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 resistant to at least 1 agent in 3 different classes.

During the procedure this indication was updated as follows:

Trogarzo, in combination with other antiretroviral(s), is indicated for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (see section 5.1).

The eventually proposed posology is:

The recommended dose of ibalizumab is a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks.

If the treating physician determines there is no additional clinical benefit for the patient in terms of viral load reduction, discontinuation of ibalizumab treatment should be considered.

The sought indication is in patients infected with multidrug resistant (MDR) HIV-1. MDR HIV-1 is defined as those patients with HIV-1 who have phenotypic or genotypic resistance to at least three of the standard antiretroviral therapy drug classes. MDR HIV-1 is usually established by at least one major resistance mutation within each drug class present in genotypic resistance testing, but in these patients often many resistance mutations are seen simultaneously. Upon virologic failure to their current antiretroviral regimen, these patients often have limited (or no) treatment options remaining.

3.1.2. Available therapies and unmet medical need

Standard treatment for HIV-1 infection consists of a combination of 3 antiretroviral agents (ARV), from at least 2 different classes, and typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI class. This treatment works well to suppress HIV-1 viral load to undetectable levels in the far majority of patients. However, viral resistance to any regimen can develop, due to e.g. poor adherence, too low exposure due to drug interactions, or low potency of the drug.

Patients with multidrug resistant (MDR) HIV-1 have very few treatment options left due to high viral resistance. When viral replication is not suppressed to an undetectable level, patients are at increased risk for disease progression, AIDS, and ultimately death. Also, there is a risk of transmission of HIV-1 to uninfected partners when the infected partner is not virologically suppressed. Treatment regimens in MDR HIV-1 patients typically include drugs at higher than standard dosages and drugs from less frequently used classes such as Fusion inhibitors and CCR5 antagonists. It is recommended in HIV-1 treatment guidelines that, in case of MDR HIV-1, to use at least 2 and preferably 3 active drugs in the new regimen and to also consider investigational agents for patients for whom it is not possible to construct a sustainable suppressive regimen using approved treatment options.

The main goal in any HIV-1 infected patient is full virologic suppression, i.e. having HIV-1 RNA load below the limit of detection of most commonly used assays (often <50 copies/mL blood). If virologic suppression cannot be achieved, the next best becomes preserving immunologic function, preventing clinical progression, and minimizing the increasing resistance to drug classes that could potentially include newly developed drugs.

The applicant determined the prevalence of MDR-HIV-1 infection in the EU as of 6 October 2017 to be about 52,000 people out of 840,000 people living with HIV in the EU (6.2%). Out of the 52,000 people living with MDR HIV-1, the applicant estimates that approximatively 5 to 10% of these patients have limited treatment options and have immediate need for a new treatment. The target population for this product would be mainly the MDR HIV patients who experience virological failure. While the estimated prevalence at the moment is definitely below 1%, it is considered an unmet need as these patients have limited therapeutic options with higher risk of disease progression, and are in need of new therapies such as ibalizumab.

3.1.3. Main clinical studies

Three studies are considered most important for this application, Phase III study TMB-301 and Phase II studies TMB-202 and TNX-355.03.

Study TMB-301 was a single-arm, multicentre, open-label study in treatment-experienced patients infected with multi-drug resistant HIV-1 (n=40). The study consisted of a control period during which patients remained on their failing regimen, or received no treatment (days 0-6), a functional ibalizumab monotherapy period (days 7-13, 2000 mg ibalizumab) and a maintenance period during which patients received an OBR (day 14-week 25) with ibalizumab infusions (800 mg ibalizumab every other week starting at day 21).

Study TMB-202 was a randomized, double-blind, multicentre, 24-week, dose-response study in treatment-experienced patients infected with HIV-1 (n=113). Patients received one of the following two dose regimens: 800 mg of ibalizumab every 2 weeks (Q2W) plus OBR, or 2000 mg of ibalizumab every 4 weeks (Q4W) and placebo on the intervening 2-week period visit, plus OBR.

Study TNX-355.03 was a multicenter, randomized, double-blinded, placebo-controlled, multi-dose, 3-arm safety and efficacy study in subjects with HIV-1 and who were failing or had failed highly active antiretroviral therapy (n=82). Subjects all received OBT plus 1 of the following regimens: alternating intravenous (IV) infusions of 15 mg/kg ibalizumab and placebo, weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 15 mg/kg ibalizumab every 2 weeks (Arm A); 10 mg/kg ibalizumab IV infusions weekly for the first 9 doses (through the Week 8 visit), then IV infusions of 10 mg/kg ibalizumab every 2 weeks (Arm B); or weekly placebo IV infusions for the first 9 doses (through the Week 8 visit), then IV infusions of placebo every 2 weeks (Placebo arm).

3.2. Favourable effects

In study TMB-301, the estimated proportion of patients in the ITT population achieving a ≥0.5 log10 decrease from day 0 at day 7/baseline (control period) was 1/40 (2.5% [95% CI (0.6%, 13.2%)]). The estimated proportion of patients in the ITT population achieving a ≥0.5 log10 decrease from day 7/baseline at day 14 (monotherapy period) was 33/40 (82.5% [95% CI (67.2%, 92.7%)]). At week 25/EOS, the estimated proportion of patients in the ITT population achieving a ≥0.5 log10 decrease from

baseline was 25/40 (62.5% [95% CI (45.8%, 77.3%)]). In the ITT-MEF (missing evaluated as failure) analysis, 17 of 40 patients (42.5%) achieved HIV-1 RNA levels <50 copies/mL at week 25/EOS with a 95% CI of (27.0%, 59.1%) and 21 of 40 patients (52.5%) achieved HIV-1 RNA levels <400 copies/ml at week 25/EOS with a 95% CI of (36.1%, 68.4%).

In study TMB-202, the ITT-MEF analysis resulted in an estimated proportion of patients having a viral load of <50 copies/ml at Week 24 of 44.1% (95% CI (31.2%, 57.6%)) in the 800 mg Q2W treatment group, and 27.8% (95% CI (16.5%, 41.6%)) in the 2000 mg Q4W treatment group.

In study TNX-355.03, by Week 16, i.e. prior to the possible switching of patients in the Placebo arm to the 15 mg/kg dose of ibalizumab every 2 weeks and/or to change in OBR for all patients, mean viral load decrease was 1.07 log10 copies/ml in Arm A, 1.33 log10 copies/mL in Arm B and 0.26 log10 copies/ml in the Placebo arm (p=0.002 vs Arm A, p <0.001 vs Arm B).

In Study TMB-301 the estimated increase in mean values for CD4+ T-cell counts from baseline to Week 25 was 62.4 cells/ul (SD=105.8 cells/ul). In Study TMB-202, the estimated increase in mean CD4+ T cell counts from baseline to Week 24 was 36.5 cells/ul (SD=63.0 cells/ul) in the 800 mg Q2W treatment group, and was 39.8 cells/ul (SD=80.1 cells/ul) in the 2000 mg Q4W treatment group.

3.3. Uncertainties and limitations about favourable effects

There are several uncertainties in the submitted material, due to the chosen single arm design of the Phase III study with a primary objective focusing on 14-days antiviral activity of ibalizumab, that do have an impact on the level of benefit and uncertainty that has been shown. Most importantly: the lack of a control arm, the very different OBRs that have been given concomitantly, the small number of patients treated, the rather short follow-up period, and the external validity of the study results.

Patient population. The comparability of the trial populations in Study TMB-301 and TMB-202, as well as their comparability to the envisioned target population, is suboptimal (especially for study TMB-202), although relevant information can still be obtained. Efficacy results stratified by CD4 cells shows a low response rate in patients with a CD4 count below 50/mmc.

Lack of a control arm. Both Study TMB-301 and TMB-202 lack a control arm. This hampers the interpretation of the study outcome.

OBR. While the effect of ibalizumab in reducing viral load during the 7 day monotherapy period is clear and appreciated, it is unknown what part of the antiviral effect between day 14 and end of study can be attributed to ibalizumab and what part to the OBR. There was a clear trend toward increasing virologic responses with increasing OSS values (Overall sensitivity score; sum of active drugs in OBR based on a net assessment of information from genotypic and phenotypic testing results). A thorough investigation around the number and type of active ARVs in the OBR for each individual patient in relation to virologic outcome revealed that there were some patients for whom it was very unlikely that the outcome would have been reached solely based on the predicted activity of the OBR.

Dose selection. The choice of dose has been made on the basis of PK/PD assumptions. It is unknown whether the chosen dose is optimal for durable efficacy.

Sample size. The total number of patients treated (n=326 overall, n=40 with the recommended posology) leaves uncertainties on the clinical benefits (and risks) of ibalizumab, especially for subgroups. No data is available in special populations. The applicant has committed to set-up a prospective product registry and perform a post-authorization study to gain more data.

Long-term benefit. The added value of ibalizumab on long-term health, including life-expectancy, is unknown. The planned product registry and post-authorization study may provide further information.

3.4. Unfavourable effects

In Studies TMB-301, TMB-202 and TMB-311, the most frequently reported AEs were all rashes (9.2%) diarrhoea (3.9%), dizziness (3.9%), headache (3.9%), nausea (3.9%), fatigue (2.0%) and vomiting (2.0%).

AEs considered definitely-related to study drug were vomiting, immune reconstitution inflammatory syndrome and hypersensitivity (n=1; 0.7% each). AEs probably-related to study drug according to the physician were diarrhoea (n=3; 2%), all rashes and vomiting (n=2; 1.3% each), dermatitis, fatigue, headache, nausea and pruritus (n=1, 0.7% each). Dizziness and dry skin were considered possibly-related to study drug and reported in more than 1 patient (n=6; 3.9%; n=2 1.3%, respectively).

A total of 9 deaths were reported. Six for Studies TMB-301 and TMB-202 (n=4 and n=2, respectively), and 3 earlier during clinical development (in Phase II study TNX-355.03). None was considered treatment-related by the physician. An additional 6 deaths were reported in the Ibalizumab Safety Summary of Investigator-Sponsored IND patients.

Virologic failure or rebound occurred in 10/40 (25%) patients in TMB-301 and 30/113 (26.5%) patients in TMB-202. Phenotypic and genotypic analyses showed a reduced susceptibility to ibalizumab in the virologic failure vs. baseline samples.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties and limitations about the unfavourable effects are related to the small sample size of the treated population, the advanced disease of many patients enrolled in the studies, the single-arm design of the main study TMB-301, and the lack of a comparator arm in both main studies.

3.6. Effects Table

Table 33 Effects Table for ibalizumab

Effect	Short Description (unit)	Time	Outcome	Uncertainties/ Strength of evidence
Favourable Effects				
Viral load TMB-301	≥0.5 log10 decrease n/N (%)	Day 0-6	1/40 (2.5%)	95% CI (0.1, 13.2)%
		Day 7-13	33/40 (82.5%)	95% CI (67.2, 92.7)%
		Day 7-Week 25	25/40 (62.5%)	95% CI (45.8, 77.3)% Unknown additional effect of OBR
	<50 copies/mL n/N (%)	Week 25	17/40 (42.5%)	95% CI (27.0, 59.1)% Unknown additional effect of OBR
Viral load TMB-202	<50 copies/mL n/N (%)	Week 25, arm 800 mg Q2W	26/59 (44.1%)	95% CI (31.2, 57.6)% Unknown additional effect of OBR
		Week 25, arm 2000 mg Q4W	15/54 (27.8%)	95% CI (16.5, 41.6)% Unknown additional effect of OBR
Viral load TNX-355.03	Decrease in viral load by week 16 in log_{10} copies/mL	Arm A: 15 mg/kg Q2W	1.07	Active arms were statistically significant when compared to Placebo (p=0.002 vs Arm A, p<0.001 vs Arm B) at week 16. After week 16, changes in OBR were allowed and patients on the Placebo arm were eligible to switch over to the 15 mg/kg dose.
		Arm B: 10 mg/kg Q1W/Q2W	1.33	
		Placebo	0.26	
CD4 counts	Mean increase in CD4 counts Day 0 – EOS Cells/uL (SD)	TMB-301	62.4 cells/uL	SD (105.8)
		TMB-202, arm 800 mg Q2W	36.5 cells/uL	SD (63.0)
		TMB-202, arm 2000 mg Q4W	39.8 cells/uL	SD (80.1)
Unfavourable Effects				
TEAEs reported in >10% of patients	All rashes	Combined 800 mg Q2W group (TMB-301& TMB-202)	14.1%	Unknown relation with ibalizumab and/or OBR Based on limited sample size and treatment duration
	Diarrhoea		14.1%	
	Nasopharyngitis		11.1%	
	Cough		10.1%	

Effect	Short Description (unit)	Time	Outcome	Uncertainties/ Strength of evidence
TEAEs definitely related	Vomiting	TMB-301	1/40 (2.5%)	Based on limited sample size and treatment duration
	IRIS		1/40 (2.5%)	
TEAEs probably related	Diarrhoea	TMB-301	2/40 (5%)	
	Rash		2/40 (5%)	
TEAEs possibly related	Dizziness	TMB-301	3/40 (7.5%)	
Deaths		All studies	9/326 (2.8%)	None was considered treatment-related
VF	Virologic failure or viral rebound	TMB-301	10/40 (25%)	Unknown contribution of lack of response to OBR to overall VF rates
		TMB-202	30/113 (26.5%)	

Abbreviations: CI: confidence interval; OBR: optimized background regimen; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; TEAEs: treatment-emergent adverse events; VF: virologic failure.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patients with multidrug resistant HIV-1, it is not always possible to construct an antiretroviral regimen that will be fully suppressive. Hence, in these patients, treatment is often aimed to at least preserve CD4 cell counts, and delay clinical progression. Additionally, an aim of treatment may be to lower viral load to such a level that the risk of further spread of the infection to the patient's partner(s) is reduced. There is an unmet medical need for novel treatment options for these patients who cannot be adequately treated with the existing therapeutic arsenal due to extensive viral resistance.

Ibalizumab may be able to address some of this unmet medical need. It has a novel mechanism of action compared to currently available ARVs and has activity against both CCR5 and CXCR4 tropic viruses. Existing resistance towards other ARVs does not hamper the activity of ibalizumab.

Antiviral activity of ibalizumab has most convincingly been shown in the short monotherapy period in Phase III study TMB-301. The estimated proportion of patients who achieved a ≥0.5 log10 decrease with 7 days functional monotherapy was 82.5% (95% CI [67.2%, 92.8%]), which is considered to be of clinical relevance. After this period, each patient received an OBR, with a variable number of active ARVs, next to the ibalizumab infusions every two weeks. Due to this setup, and the lack of a control arm without ibalizumab, the contribution of OBR to the overall treatment effect cannot be determined. Evidence that

ibalizumab as add-on to OBR contributes to durability of virologic response can be inferred from estimating the likely activity of each patient's individual OBR based on the mutations in the patient's viral sequences and the Stanford HIV drug resistance database (https://hivdb.stanford.edu/hivdb/by-mutations/), and comparing this to the observed virologic response during treatment with OBR + ibalizumab. Given that there were some patients for whom it was very unlikely that the outcome would have been reached solely based on the predicted activity of the OBR, and given the significant viral load decrease observed upon ibalizumab monotherapy between days 7 to 14 in the far majority of patients, it was considered that there is a clear suggestion of an added effect of ibalizumab on top of the OBR. All patients for whom this was applicable, had an OSS score of 0 or 1 and hence a restricted indication in adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, is justified.

The safety data is difficult to interpret, due to the limited number of patients included in the database, the open label design of the Phase III study, the lack of a control arm in the two main studies, the individually optimized background regimen (OBR), and the advanced disease status of most patients (many had CD4+ cell count <50 cells/µl). However, no major safety concerns have emerged.

3.7.2. Balance of benefits and risks

Although the interpretation of ibalizumab efficacy data is hampered by the small patient numbers, the complexity of the patient population, the single-arm design of the pivotal study, short follow-up time, and uncertainties regarding the impact of OBR in relation to the effect induced by ibalizumab, overall it seems proven that ibalizumab has antiviral activity and can be of added value for the treatment of a restricted population of patients suffering from multi-drug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. The applicant committed to set-up a product registry, in which patients treated with ibalizumab will be actively followed for efficacy, and to perform a post-authorisation efficacy study, in which clinical progression of participants enrolled in the registry will be compared with patients who did not receive ibalizumab, by matching on at least OBR and main baseline patient and disease characteristics.

Overall, the safety profile seems to be acceptable, taking the patient population and their need for novel treatment options into account. However, no major safety concerns have emerged. Routine pharmacovigilance will be utilized to further characterize the safety profile of ibalizumab post-authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Due to the limitations of current knowledge, it is considered necessary to address concerns with respect to the maintenance of a positive benefit-risk balance due to potential lack of efficacy in the long term. Therefore, the CHMP considers the following measures necessary to address issues related to efficacy: In order to further characterise the efficacy of ibalizumab in combination with other anti-retroviral medicinal products, for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, the MAH should conduct and submit the results of a study based on data from a product registry. This study should be conducted according to an agreed protocol.

3.8. Conclusions

The overall B/R of Trogarzo is positive for the indication for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Trogarzo in the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of ibalizumab in combination with other anti-retroviral medicinal products, for the treatment of adults infected with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, the MAH should conduct and submit the results of a study based on data from a product registry. This study should be conducted according to an agreed protocol.	Final report submission: 31-Oct-2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers ibalizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.