26 March 2026
EMA/88598/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Joenja

International non-proprietary name: leniolisib

Procedure No. EMEA/H/C/005927/0000

Note

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

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List of abbreviations

AE	Adverse event
AHEG	Ad Hoc Expert Group
AIHA	Autoimmune Hemolytic Anemia
Akt	Protein kinase B
ANCOVA	Analysis of covariance
APDS	Activated Phosphoinositide 3-kinase-Delta Syndrome
bid	Twice a day
BMI	Body Mass Index
CMV	Cytomegalovirus
COVID-19	Coronavirus disease-19
CRF	Case Report/Record Form (paper or electronic)
CRP	C- reactive protein
CT	Computed tomography
CV	Coefficient of variation
CVIDs	common variable immunodeficiencies
CYP	Cytochrome P450
DDI	Drug-drug interaction
EBV	Epstein-Barr virus
EOS	End of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HMA	Heads of Medicine Agencies
hs-CRP	High sensitivity C-reactive protein
HSCT	Allogenic haematopoietic stem cell transplantation
ITP	Idiopathic Thrombocytopenic Purpura
IRB	Institutional Review Board
IRT	immunoglobulin replacement therapy
iv	intravenous
Kd	Kilo dalton
LDH	Lactate dehydrogenese
LLOQ	Lower Limit of Quantification

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	The Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
NIH	National Institute of Health
pAkt	Phosphorylated Akt
PASLI	p110 δ -activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDK1	Phosphoinositide-dependent protein kinase
PGA	Physician Global Assessment
PID	Primary Immunodeficiencies
PIK3CD	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1
PI3K	Phosphoinositide 3-kinases
PI3K δ	Phosphoinositide 3-kinase delta
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	Pharmacokinetics
PRO	Patient reported outcome
pSS	Primary Sjögren's Syndrome
PtGA	Patient's Global Assessment
QTcF	QT corrected by Fridericia's formula
SAE	Serious adverse event
SF-36	Short Form 36
SPD	Sum of product of diameters
SOC	System organ class
ULOQ	Upper Limit of Quantification
VAS	Visual analogue scale
WPAI-CIQ	Work Productivity and Activity Impairment and Classroom Impairment Questionnaire

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pharming Technologies B.V. submitted on 4 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Joenja, through the centralised procedure falling within the Article 3(1) and point 4 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2021.

Joenja was designated as an orphan medicinal product EU/3/20/2339 on 19 October 2020 in the following condition: treatment of activated phosphoinositide 3-kinase delta syndrome (APDS). Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Joenja as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: Joenja | European Medicines Agency (EMA)

The applicant applied for the following indication: treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0259/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0259/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Applicant's requests for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.5.2. Accelerated assessment

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

1.5.3. New active Substance status

The applicant requested the active substance leniolisib 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.

1.6. Protocol assistance

The applicant did not seek Protocol assistance from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau

Co-Rapporteur: Paolo Gasparini

The application was received by the EMA on	4 October 2022
Accelerated Assessment procedure was agreed-upon by CHMP	21 July 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	03 January 2023
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	05 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 January 2023
The procedure reverted to a standard timetable on	05 April 2023

The applicant submitted the responses to the CHMP consolidated List of Questions on	16 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 July 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 July 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 October 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 November 2023
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	09 November 2023
An Expert group was convened to address questions raised by the CHMP on The CHMP considered the views of the Expert group as presented in the minutes of this meeting.	27 November 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	19 January 2024
The CHMP agreed on a third list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 January 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	16 May 2024

to all CHMP and PRAC members on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 May 2024
The CHMP agreed on a fourth list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 February 2026
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 February 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 March 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 March 2026
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 Joenja on	26 March 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 March 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant applied for a Marketing Authorisation (MA) in the following indication: treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older.

2.1.2. Epidemiology and risk factors

APDS is a rare heterozygous autosomal dominant heritable disease of the immune system caused by a mutation in either the PIK3CD or PIK3R1 genes coding for the catalytic and regulatory domains of the PI3K dimer, respectively. The APDS incidence rate around the world is estimated to be 1 to 2 per million people.

At the time of orphan designation for leniolisib in the treatment of APDS (EU/3/20/2339), APDS affected approximately 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of around 500 people.

In a study of 886 index cases of primary immune deficiency, only 4 patients were found with APDS mutations (Thaventhiran, 2020). The largest systematic review of APDS to date identified a total of 243 APDS cases in the published literature (Jamee, 2020).

There are no known risk factors for the development of APDS outside of a relevant family history for autosomal dominant transmission of the mutation. The gender make-up of the APDS population in a review of the largest published APDS population of 243 patients is 123/243 (50.6%) male, 87/243 (35.8%) female, and 33/243 (13.6%) unknown (Jamee, 2020).

2.1.3. Biologic features

APDS is a disease that was recently identified in 2006 (Jou, 2006) and fully described in 2013 (Angulo, 2013). These activating mutations increase activity of PI3Kδ, a promoter of activity in the immune system. Activated PI3Kδ syndrome has also been referred to as p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI).

Gain of function mutation in PIK3CD codes for the p110δ catalytic subunit and leads to the development of APDS1. Loss-of-function mutation in PIK3R1 codes for the p85α regulatory subunit and leads to the development of APDS2. Both the catalytic and regulatory subunits together create the PI3Kδ lipid kinase dimer and are vital to the development and function of immune cells in the body through intercellular signal transduction (Nunes-Santos et al., 2019).

Although PI3 kinases are ubiquitous in almost all cell types in the body, PI3Kδ signaling is predominantly enriched in leukocytes, although expression has been measured in neurons and microglia, spleen, platelets, and endothelial cells (Fruman et al., 2017).

Mutations in the PIK3CD and PIK3R1 ultimately lead to hyperactive PI3Kδ signaling. The PI3Kδ enzyme, formed by the p85α regulatory subunit and p110δ catalytic subunit, is engaged with multiple receptors in cells of the immune system, including the B-cell and the T-cell receptors, as well as

cytokine and costimulatory receptors (Lucas et al., 2014a; Lucas 2016). Its principal function is the generation of PIP3. PIP3 serves as an important cellular second messenger activating Akt (*via* phosphoinositide-dependent kinase-1 [PDK1]) and regulates the downstream mTOR/FOXO pathways, controlling key cellular activities (Kandel et al., 1999; Fruman et al., 2017).

Overall, hyperactive PIK3δ signalling significantly impacts the development, differentiation, and effector function of all populations of human lymphocytes. Hyperactive PI3Kδ signaling alters the differentiation of both B cells and T cells, leading to inappropriate and inadequate cell populations. In B cells, elevated levels of immature transitional B cells develop in patients with APDS. These cells are sequestered in the lymph nodes or spleen, leading to an increase in the size of these organs. Also, naïve B cells fail to develop. These cells interact with an antigen and undergo class switch recombination to produce more selective IgG and IgA immunoglobulins.

Transitional B cells only produce IgM, which leads to the hyper IgM signal that is often seen in patients diagnosed with APDS. T-cell homeostasis is also altered in patients with APDS, resulting in a switched CD4/CD8 ratio and increase in population of PD-1+P and CD57+ expressing terminally differentiated CD8+ effector T-cells. The C8+ T cell increase demonstrates increased immunosenescence and exhaustion. It is hypothesized that this could drive the poor response to Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) infections and autoimmune complications (Preite et al., 2018, Singh et al., 2019). These defects operate intrinsically, as well as combinatorically, to manifest as the predominant clinical features in patients with APDS: impaired immunophenotype, lymphoproliferation, autoimmune disease, infection susceptibility, and malignancy (Lucas 2016; Okkenhaug 2013; Tangye et al., 2019).

2.1.4. Clinical presentation, diagnosis

APDS is a progressive and potentially life-threatening condition with recurrent upper and lower respiratory tract infections routinely progressing to irreversible bronchiectasis, lymphadenopathy, splenomegaly, autoimmune complications, and an increased risk of developing lymphomas. APDS is characterised as a heterozygous autosomal dominant heritable immune deficiency with defects of the humoral and cell mediated immune system.

The diagnosis of APDS is made by sequencing the genes PIK3CD or PIK3R1 in patients with a compatible phenotype, i.e., immunodeficiency and lymphoproliferation of unknown origin, or a relevant family history.

For those who do present with symptoms, the clinical presentation of APDS is highly variable (Coulter, 2017; Jia, 2020; Singh, 2020). Presentations include recurrent respiratory tract infections, persistent infection with herpesviruses, chronic non-neoplastic lymphoproliferation, hepatosplenomegaly, autoimmunity, and an increased risk for lymphoma (Coulter, 2017; Jia,2020; Singh, 2020). In a systematic review of 243 patients identified in the literature, the most common manifestations were respiratory tract infections (pneumonia 43.6%, otitis media 28.8%, and sinusitis 25.9%), lymphoproliferation (70.4%), autoimmunity (28%), enteropathy (26.7%), failure to thrive (20.6%), and malignancy (12.8%) (Jamee, 2020). Recurrent respiratory infections are often associated with airway scarring (bronchiectasis) as well as ear and sinus damage with associated B-cell deficiency (Lucas, 2016). The challenge with non-specific clinical manifestations is distinguishing APDS from other monogenic common variable immunodeficiencies (CVIDs) such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and LPS-responsive beige-like anchor protein (LRBA) deficiency (Coulter, 2017).

2.1.5. Management

Existing treatment options for the management of APDS are predominantly supportive such as immunoglobulin replacement therapy, antibiotics, antiviral agents, immunosuppressive agents (e.g., steroids, azathioprine, mycophenolate), splenectomy, rituximab, and sirolimus (rapamycin). The only exception is haematopoietic stem cell transplantation (HSCT) which is potentially curative.

In cohort studies in patients with APDS1 (Coulter 2018) and APDS2 (Elkaim 2016, approximately 60% of patients received antibiotic prophylaxis, although this alone was insufficient for most patients as they required supplemental immunoglobulin replacement therapy (IRT) especially with respiratory tract infections (Coulter, 2018). Despite an association with persistent, severe or recurrent herpesvirus infections, few patients were on long-term antiviral therapy (6%) (Coulter, 2018).

As these patients can have defect in antibody production and functions, most studies have shown response to immunoglobulin replacement therapy (IRT) (Coulter 2018, Elkaim 2016) It can be given either by intravenous (IVIG) or subcutaneous (SCIG) route. It is beneficial in decreasing recurrent respiratory infections, however it may not be of much aid in preventing herpes infections, autoimmunity and lymphoproliferation.

HSCT has been described in 33 patients with significant pre-HSCT morbidity. Data suggests HSCT can be curative with a similar level of survival reported with HSCT in other Primary Immunodeficiencies (PIDs) (around 80%) (Coulter, 2018; Okano, 2019; Nademi, 2017). However, data on long term follow-up of these patients who have been transplanted is still lacking (Notarangelo, 2019).

Immuno-modulatory therapy is useful in presence of clinical features of autoimmunity eg. cytopenias, renal disease, arthritis, inflammatory colitis, sclerosing cholangitis etc. Autoimmune cytopenias have been managed with steroids, rituximab and splenectomy although rituximab treatment can be complicated by sustained B-cell lymphopenia (Singh 2020, Coulter, 2018).

Due to its role downstream of PI3K, the mTOR inhibitor sirolimus has been used in trials in patients with APDS and was shown to have a benefit in the treatment of non-neoplastic lymphoproliferative disease in around 65% of patients. However, adverse events and limited effect on gastrointestinal disease and cytopenias remain an unmet need with this treatment approach (Coulter, 2018; Tangye, 2019).

However, there are significant treatment-limiting serious adverse effects that impede their clinical development such as toxicities (primarily hepatotoxicities), pneumocystis pneumonia and other forms of pneumonitis, as well as colitis with severe diarrhoea (Smolewski, 2020). Clinical development programs for other PI3Kδ inhibitors have shown significant off target toxicity in the APDS population (Diaz, 2020 and Helmer, 2016). Leniolisib was specifically developed to offer selectivity for the PI3Kδ isoform over other PI3K isoforms thought to be related to off target toxicity (Hoegenauer, 2017).

2.2. About the product

Leniolisib (previously referred to as CDZ173) is a small molecule oral inhibitor of phosphoinositide 3-kinase delta (PI3Kδ) catalytic subunit p110δ that selectively inhibits the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). Leniolisib targets the p110δ catalytic subunit of phosphoinositide 3-kinase (PI3K) signal transducer dimer, specifically targeting the causative factor in immune cells resulting in the pathogenesis of activated PI3Kδ syndrome (APDS).

The initially claimed indication of leniolisib was the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older.

The proposed dose in adult and adolescent patients who weigh more than 45 kg is 70 mg leniolisib twice daily approximately 12 hours apart.

2.3. Type of Application and aspects on development

Accelerated assessment

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 unmet medical need for patient with APDS and on the preliminary results of the randomized phase I/II study 2201.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as several major objections were raised regarding methodological issues and the starting material, demonstration of bioequivalence between tablets used in the pivotal clinical study and the proposed commercial tablets and potential impurities formed (including nitrosamines).

Marketing authorisation under exceptional circumstances

The applicant submitted an application for a full marketing authorisation. However, upon suggestion from the CHMP, the applicant requested during the procedure a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 since the totality of data were not considered comprehensive, especially with regard to long-term safety and efficacy, and the condition (activated phosphoinositide 3-kinase delta syndrome) is so rare, that the collection of comprehensive evidence within a reasonable timeframe is not possible.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets (FCT) containing leniolisib phosphate equivalent to 70 mg leniolisib as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose (E460), hypromellose (E464), sodium starch glycolate (Type A), magnesium stearate (E572), and colloidal anhydrous silica (E551).

Tablet film-coating: hypromellose (E464), titanium dioxide (E171), iron oxide monohydrate yellow (E172), iron oxide red (E172), talc (E553b), and polyethylene glycol (E1521).

The product is available in high density polyethylene bottles with aluminium induction seals and child resistant polypropylene screw caps as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of leniolisib phosphate is 1-[(3*S*)-3-{[6-(6-methoxy-5-trifluoromethylpyridin-3-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl]amino}pyrrolidin-1-yl]propan-1-one phosphoric acid (1:1) corresponding to the molecular formula $C_{21}H_{25}F_3N_6O_2.PO_4H_3$. The free base has a relative molecular weight of 450.47 and leniolisib phosphate has the following structure:

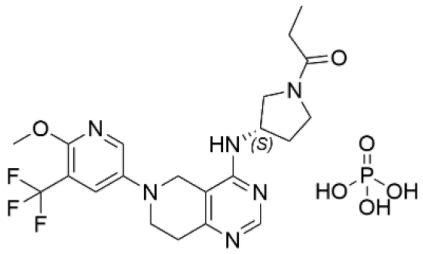


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, infrared spectroscopy (IR), ultraviolet absorption spectroscopy (UV), proton, carbon, fluorine and phosphorous nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS).The solid-state properties of the active substance were characterised by XRPD, X-ray diffraction, thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) curves.

The active substance is a non-hygroscopic white to yellowish to yellowish greenish powder, which exhibits pH-dependent solubility, being practically insoluble at neutral pH with a slight increase in solubility in strongly acidic media.

Leniolisib exhibits stereoisomerism due to the presence of one chiral centre, the absolute configuration is *S*. Enantiomeric purity is controlled routinely by chiral HPLC in the active substance specifications.

Polymorphism has been observed for leniolisib. Form A is the most thermodynamically stable, the proposed commercial polymorphic form and is controlled in the active substance specifications by XRPD.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Evidence of GMP compliance has been provided in the QP declaration.

The active substance is manufactured in a convergent ten-step synthetic process, including 6 isolated intermediates, followed by milling.

The CHMP considered that the initial proposed starting materials were not justified in line with ICH Q11. Furthermore, the carryover of potentially mutagenic impurities had not been adequately investigated, relying primarily in theoretical purge calculations. Therefore, the CHMP raised a Major Objection (MO) requesting redefinition of the initially proposed starting materials further upstream, to ensure critical manufacturing steps are included in the dossier and conducted under GMP. The applicant provided impurity fate and purge data and amended the specification to include a test and acceptance criteria for a potentially mutagenic impurity. The applicant redefined an intermediate and defined 2 upstream compounds as regulatory starting materials, these compounds are isolated substances of defined chemical properties and structure, representing significant structural fragments of the final active substance. The dossier was updated to include process descriptions for these additional steps. Along with redefinition, a new manufacturing chain including new sites for the final active substance and the critical intermediate was proposed and the QP declaration updated. The whole module 3.2.S was revised with the required information on new sites, starting materials, intermediates and IPCs, validation, impurities, etc. The process used at the new manufacturing site is the same in terms of steps, process parameters and in process controls. The already accepted specification for the active substance is not impacted by carry over of impurities from the starting

materials which is ensured by the applied control strategy. It was demonstrated that active substance produced by the new manufacturers is equivalent to that produced by the initially proposed manufacturer. The responses from the applicant were considered satisfactory and the issue was resolved.

Information on potential and actual impurities including synthesis and degradation products, elemental impurities, residual solvents, mutagenic impurities and nitrosamines throughout the synthetic process were provided. Relevant impurities are well discussed with regards to their origin and characterised. Organic impurities of the process, they are either shown to be purged or adequately controlled. The control strategy for mutagenic impurities is in line with ICH M7, solvents are controlled according to ICH Q3C.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

The active substance is packaged in double low-density polyethylene (LDPE) bags closed with tie wraps and then placed into plastic drums and sealed tightly. The primary packaging material complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, chiral HPLC), assay of salt-forming agent (titration), assay (UHPLC), specified, unspecified and total impurities (UHPLC), specified mutagenic impurities (XRF, LC-MS, GC-MS, and GC-HS)), *R*-enantiomer (chiral HPLC), residual solvents (GC-HS), elemental impurities (ICP-MS), polymorphic form (XRPD), particle size (LDS), bulk density (Ph. Eur.), water content (KF), and microbial limits (Ph. Eur.).

There is not specified impurities higher than the qualification threshold.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data from 5 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the initially proposed manufacturing site stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability data from 3 commercial scale batches of active substance from the new proposed commercial manufacturer of the active substance stored in the intended commercial package for up to 3 months under long term conditions (25 ºC / 60% RH) and for up to 3 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, specified impurities, *R*-enantiomer unspecified impurities, total unspecified impurities, total impurities, water content, and microbial limits.

Stability data from batches show that the active substance is stable at long term and accelerated conditions. Chemical and physical stability data remained well within specifications at all time points. No significant changes in the tested quality characteristics were observed as compared to the initial values.

The available stability data from the current manufacturing site batches demonstrate a stability profile that is comparable to active substance from the previous manufacturing site at the corresponding timepoints. Therefore, the retest period established from the previous manufacturing site is considered applicable to batches from the new manufacturing site.

A photostability study was performed according to ICH Q1B on one batch which concluded that the active substance requires protection from light, which is ensured by the secondary packaging material.

Forced degradation was investigated on one batch exposed to heat, humidity, oxidant, acid and base. Significant degradation occurs with base, acid or an oxidant demonstrating the stability indicating nature of relevant analytical methods. The solid state properties are not impacted by thermal or oxidative stress.

A freeze and thaw cycle testing has been performed on two development batches for 28 days. The active substance was found to be stable towards freeze and thaw cycles.

The submitted stability data demonstrate that a retest period of 48 months with the storage precaution ‘do not exceed 25 °C, protect from light/ keep inside the drum’ is acceptable. Therefore, despite the fact that only 3-month stability data have been obtained for batches manufactured at the new site and considering the route of synthesis has not been modified at the new site, a retest period of 48 months with the above precaution storage are deemed acceptable.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as yellow, oval-shaped, biconvex, bevelled edge film-coated tablets debossed with “70” on one side and “LNB” on the other side, approximately 16 mm in length, 6.3 mm in width, and 6.0 mm in thickness.

The qualitative and quantitative compositions of the finished product have been provided,

The active substance is a BCS class 2 compound with low solubility and good permeability. Critical quality attributes of the active substance which can influence its solubility rate are particle size distribution (PSD), polymorphic form and bulk density. These properties are controlled in the active substance.

Compatibility of the active substance with excipients was assessed by analysing binary mixtures including under stressed conditions. Most of the excipients studied are compatible with leniolisib phosphate. A moderate increase in degradation products was observed for Opadry white but only at high temperature. Therefore, this excipient is still suitable for use. There was an increase in degradation products with most of the excipients used on exposure to light, but it is already known from active substance stability studies that leniolisib phosphate is photosensitive. The active substance was found to be compatible with the selected excipients through long-term stability studies and will continue to be monitored during stability studies throughout the product's shelf life.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except Opadry which complies with in-house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

An *in vivo* bioequivalence study comparing the hard gelatine capsules and film-coated tablets was carried out, and it was demonstrated that hard capsules and film-coated tablets are bioequivalent. The film-coated tablet process was transferred to new manufacturing site for commercial supply.

An *in vitro* dissolution method was developed. During evaluation, the CHMP considered that the dissolution profiles of the biobatch showed significant differences compared to tablets manufactured at the new site and that bioequivalence was not demonstrated, resulting in a major objection. In response, the applicant provided the results of an *in vivo* study demonstrating bioequivalence of the tablets manufactured at the new site with those from the previous site. The *in vitro* profiles are not considered equivalent; however, the PK data provides reassurance of bioequivalence and therefore takes precedence, and the issue was considered resolved.

Due to the lack of *in vitro* equivalence, the suitability of the dissolution method for QC purposes was questioned. The choice of apparatus and dissolution conditions was not fully justified and discriminatory power with respect to meaningful changes in composition or manufacturing process parameters had not been demonstrated. To address this, the applicant tightened the specification limit which was considered acceptable. The applicant also developed a new dissolution method and investigated different media pH and rotation speeds. The new dissolution method was able to discriminate batches manufactured with less disintegrant, increased lubricant, and with higher hardness following compression and gives a similar release profile to the other dissolution method but with less variability, especially at early timepoints and is thus considered more robust. The CHMP recommends that the applicant re-evaluate the dissolution method post-approval and introduce the new dissolution methodto the dossier *via* variation within 3 months after approval.

The development of the manufacturing process was explained. The applicant used prior knowledge and risk assessment to inform which parameters to investigate experimentally with a focus on unit operations and process parameters in the wet granulation step.

Based on the experimental results, the process was optimised and proposed the control strategy is considered acceptable.

The primary packaging is high density polyethylene bottles with aluminium induction seals and child resistant polypropylene screw caps. The materials comply with Ph. Eur. and EC requirements. The

choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process along with CPPs and IPCs consists of 6 main steps: pre-blending, wet granulation, blending, compression, coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive batches of finished product, and it is considered suitably robust. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Nonetheless, a recommendation is made with respect to the proposed hardness IPC at the new manufacturing site.

The applicant was asked to re-assess the IPC specification limit of hardness with increased manufacturing experience as well as the potential impact of higher hardness values on the dissolution CQA. The IPC hardness limit for core tablets was re-assessed considering additional batches and the correlation with dissolution was evaluated. However, the CHMP recommends re-assessing the specification limit for hardness as appropriate within 3 months after approval.

The evaluation of PSD and density *via* IPC demonstrates that the granulation and blending steps lead to consistent output and quality. All monitored parameters remain well within the statistical control limits and exhibit only random variability.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (UPLC, UV), assay (UPLC), degradation products (UHPLC), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (Ph. Eur.), water content (KF), and microbial limits (Ph. Eur.).

Based on a maximum daily dose, and in line with the identification and qualification thresholds stated in ICH Q3B, limits for each unspecified degradation product and for total degradation products are considered appropriate.

A risk assessment on the potential presence of elemental impurities in the finished product was provided and complies with ICH Q3D. The results of the risk assessment indicate that none of the evaluated elemental impurities are likely to exceed 30% of the established PDEs.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished active substance was performed, however it was considered deficient by the CHMP as risk factors associated with the finished product were not included. Therefore, the CHMP raised a MO requesting an updated nitrosamine risk assessment taking into account guidance available. The applicant provided an updated risk assessment considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A potential nitrosamine impurity was identified due to the presence of a secondary amine in the active substance structure. The applicant attempted to synthesize the impurity under a range of conditions, including forcing conditions, but was unable to detect the potential nitrosamine. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary, and the MO was considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 5 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability studies initiated with batches from the manufacturing development site under long term and accelerated conditions are considered complete at 42 months and 6 months.

Samples were tested for appearance, assay, degradation products, dissolution, water content, and microbial limits. The analytical procedures used are stability indicating.

Stability data from batches show that the tablets are stable under long term, intermediate and accelerated conditions. No significant changes were observed. Chemical and physical stability data remained well within specification at all time points.

Photostability was performed on one batch with and without packaging according to ICH Q1B conditions. Results shows that the finished product is photostable when stored in the proposed container closure system.

A freeze and thaw cycle test was performed on one batch packaged in a HDPE bottle. The stability samples were subjected to four complete freeze and thaw cycles (-20°C/ambient RH for 6 days, followed by 1 day at 25 °C/60% RH). Samples were taken after 28 days and the chemical and physical characteristics were analysed. No particularities were observed in the freeze and thaw test.

An open dish study has been conducted at 5 ºC/ambient RH and at 30 ºC/75% RH. The finished product meets the acceptance criteria.

Based on available stability data, the proposed shelf-life of 30 months and without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents *Via* Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Three major objections were raised during the procedure concerning (1) the proposed starting materials of the active substance, (2) the demonstration of bioequivalence between tablets used in the pivotal clinical study and the proposed commercial tablets, and (3) the nitrosamines risk assessment. In response to MO1, the applicant re-defined one of the initially proposed starting materials upstream to 2 new starting materials and improved the control strategy of the other. Results from a bioequivalence study were provided to address the MO2, showing that tablets from the new manufacturing site are bioequivalent to the bio batch, which overrides the *in vitro* dissolution results. In response to MO3, the nitrosamines issue was resolved by justifying that the potential nitrosamine in the finished product could not be synthesized. All three MOs are thus considered resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to reassess the QC dissolution apparatus, and reassessing the IPC specification limits for hardness, these are summarized as recommendations for future quality development.

2.4.5. 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. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The MAH should re-evaluate the dissolution method post-approval within 3 months after approval.
- The MAH should re-assess the IPC specification limit for hardness as appropriate within 3 months after approval.

2.5. Non-clinical aspects

2.5.1. Introduction

The applicant submitted primary and secondary pharmacodynamic studies performed *in vitro* and *in vivo* on leniolisib, as well as pharmacokinetic profile studies, toxicology studies, and genotoxicity i*n vitro* and *in vivo* studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In the activated PI3K-delta syndrome, the version PI3K containing the p110δ subunit, called PI3K-delta (PI3Kδ), is specifically found in white blood cells, including B cells and T cells. PI3K-delta signalling is involved in the growth and division (proliferation) of white blood cells, and it helps direct B cells and T cells to mature (differentiate) into different types, each of which has a distinct function in the immune system. The hallmark of immune phenotype is increased proportions of transitional B cells and plasmablasts (PB), progressive B-cell loss, and elevated levels of serum IgM.

The effects on B-cell and T-cell functions and on other immune cell functions (neutrophils, granulocytes, plasmacytoid dendritic cells (pDCs) and mast cells) were investigated in lymphocytes and blood derived from various species (mouse, rat, cynomolgus monkey and human).

Studies were conducted to characterize the *in vitro* properties of leniolisib, a potent, and selective inhibitor of PI3Kδ. Its activity against and selectivity for Class I PI3K isoforms were first assessed with biochemical enzyme assays and then further evaluated with the PI3K isoform specific signalling assays in cells. The cellular activity against PI3Kδ function was extensively investigated with assays measuring biological consequences of PI3Kδ inhibition in primary leukocytes from different species and in haematological tumour cell lines.

In biochemical assay, leniolisib was shown to be a potent and selective inhibitor for the p110δ isoform of Class IA PI3K with a half maximal effective concentration (EC50) of 11 nM measured in enzymatic assays. The inhibition of the α, β and γ isoforms is at least 28-fold less potent. The PI3Kδ is a class IA lipid kinase heterodimer composed of a p110δ polypeptide (PI3Kδ specific catalytic subunit) and a p85α (nonspecific regulatory subunit). The p110δ catalytic subunit is mainly expressed in cells of the hematopoietic system, primarily lymphocytes and myeloid cells. The APDS2 mutations in p85α lead to the disease that phenocopy APDS1, despite that p85α is ubiquitously expressed and interacts not only

with p110δ but also with p110α and p110β. The p85α mutation leads to a strong basal activation of PI3Kδ, while it only weakly increases PI3Kα activity. This differential effect explains why the impact of this mutation is largely restricted to the immune system.

Moreover, another p110δ inhibitor idelalisib shows potent inhibition of all APDS mutations (Dornan et al., 2017).

The potency and selectivity translated well to cellular systems. In Rat-1 fibroblast cells transfected with human myr-p110 PI3K isoforms, p110δ expressing cells were inhibited by a mean half maximal inhibition concentration (IC50) of 56 nM with a 29-fold selectivity over PI3Kα, 42-fold selectivity over PI3Kβ and a window greater than 132-fold over PI3Kγ.

In vitro, selectivity over the p110α-isoform of PI3K is predicted to avoid PI3Kα mediated side effects such as hyperglycaemia. Moreover, the selectivity window to target-unrelated protein kinases, proteases, receptors and ion channels was tested. More precisely, DNA-PK was inhibited with an IC50 of 0.88 µM. However, this inhibition did not translate to an inhibition of p53 further down in the pathway of DNA-repair. Leniolisib have no significant inhibitory effect on other members of the wider PI3K family and showed an IC50 value of greater than 10 µM for all kinases and proteases tested except for RPS6KA5 (76% inhibition). Leniolisib have no significant inhibitory effect on Nav1.5 and Cav1.5.

However, at 10 µM concentration, leniolisib showed significant inhibition of the G-protein coupled receptor GPR8 (72% inhibition), hPDE4D (IC50=4.7 µM) and 5HT2B (IC50=7.7 µM). At the considered clinical dose of 70 mg twice daily, the measured maximal unbound therapeutic steady-state plasma concentration in human plasma of 0.449 µM is at least 10 times lower when compared to the IC50 values of GPR8, hPDE4D, and 5HT2B. Considering this margin of safety and the selectivity of leniolisib for its target, the clinical risk is not considered consequential.

The effect of on the activation and function of a variety of cells of the innate and adaptive immune system was tested *in vitro*. Leniolisib demonstrates suitable pharmacokinetic in animals resulting in time-dependent reduction of *ex-vivo* stimulated B cell activation. This correlates with inhibition of antibody formation in immunized rats and efficacy in rat collagen-induced arthritis. In specific animal tumour models, leniolisib reduces tumour growth of injected tumour cell lines.

In vitro, leniolisib inhibited multiple B-cell functions such as anti-IgM-stimulated mouse splenocyte proliferation, interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα) secretion of mouse B-cell induced by protein antigens or Toll-like receptor (TLR) agonists, intracellular Akt phosphorylation and CD86 (B-cell activation marker) upregulation in rat, monkey and human induced by B-cell receptor engagement. In addition, human T-cell proliferation is inhibited with a potency that varies depending on the stimulus and readout. The effects on T-cell proliferation were investigated in the allogeneic mixed lymphocyte reaction (MLR) in mice and humans and in the anti-CD3-stimulated proliferation of T-cells from human peripheral blood mononuclear cells (PBMC's). Furthermore, leniolisib prevented the differentiation of mouse and human T-cells into Th1, Th2 and Th17 helper cells. Lastly, in addition to its inhibition of B- and T-cell functions, leniolisib inhibited the oxidative burst in human neutrophils and monocytes as well as anti-IgE-induced basophil activation and interferon alpha (IFNα) secretion of primary pDCs. The stem cell factor (SCF)-dependent stimulation of mouse bone marrow derived mast cells was potently reduced.

The *in vitro* cellular profile of leniolisib shows a strong inhibition of B cell activation, proliferation, antigen presentation and antibody production, a potent inhibition of TLR9 ligand-induced IFNα production by pDCs, an inhibition of human basophil activation and degranulation, an inhibition of oxidative burst of human neutrophils and monocytes and an inhibition of mouse mast cell activation but a variable inhibition of T cells (dependent on stimulus and readout).

Leniolisib was evaluated in two mechanistic and one relevant disease model of PI3Kδ activation.

In vivo, leniolisib has been shown to be efficacious in a sheep red blood cell model of the T-cell dependent antibody response (TDAR) in rats, with 54% inhibition of antibody production at a dose of 3 mg/kg bid (bis in die; i.e., twice a day).

As monotherapy, leniolisib reduced clinical symptoms in a prophylactic (3 mg/kg bid) as well as a therapeutic (10 mg/kg bid) setting of rat collagen-induced arthritis. However, in a study report provided by the applicant, for the same dosage (10 mg/kg and 30 mg/kg), the results showed a significant variability (for the dosage 10 mg/kg: -66% group A and -73% group B; for the dosage 30 mg/kg: -75% group A and -96% group B), due inter variability between the individuals.

The Pik3cdE1020K/+ mice model of patients with APDS was used as a surrogate for an APDS animal disease model based on the mode of action.

Moreover, the effect on innate immune cells was shown in a mouse model of ozone-induced lung inflammation where leniolisib prevented the infiltration of neutrophils at a dose of 10 mg/kg bid.

2.5.2.2. Secondary pharmacodynamic studies

Leniolisib potently inhibits PI3Kδ with good selectivity over other P13K isoforms, target-unrelated protein kinases, proteases, receptors and ion channels. The *in vitro* off-target assay of leniolisib shows no significant inhibitory effect on other members of the wider PI3K family, nor interference with a broad panel of tested kinases, proteases, receptors and ion channels.

Leniolisib was tested *in vitro* and demonstrated no interference with general growth-factor-mediated proliferation and no significant inhibition of tumour suppression protein p53.

In vivo, single or repeated administration of leniolisib at 30 or 100 mg/kg/day for consecutive 15 days was clinically well tolerated and resulted in no test item related clinical signs, effects on food intake and only minor body weight losses in individual males at 100 mg/kg/day.

Effects on glucose metabolism are specifically mediated by the p110α isoform of the PI3K/Akt pathway. Leniolisib was shown to have a 29-fold selectivity of PI3Kδ over PI3Kα. Leniolisib weakly inhibited glucose uptake with an IC50 of 1.50 µM and the insulin receptor-pathway with an IC50 of 1.72 µM. Based on these *in vitro* data, sufficient safety margins are expected to prevent an impact on insulin and blood sugar levels in humans. Moreover, in a predictive oral glucose and intraperitoneal insulin tolerance test in mouse, insulin resistance was only found after a dose of 100 mg/kg/day with no clinical signs or relevant macroscopic or microscopic findings in the pancreas and liver.

2.5.2.3. Safety pharmacology programme

Leniolisib was evaluated in safety pharmacology core battery studies at doses up to 300 mg/kg. These studies were conducted in accordance with ICH S7A guideline.

Cardiovascular safety was evaluated *in vitro* in patch clamped mammalian cells expressing the human ether-a-go-go related gene (hERG) channel. Leniolisib inhibited the hERG current with an IC50 of 11.9 µM (5.4 µg/mL). The hERG IC50 is 27-fold higher than the Cmax at steady state in humans dosed with 140 mg of leniolisib (70 mg BID).

Cardiovascular safety was further evaluated in conscious and unrestrained telemetered male cynomolgus monkeys using single oral doses of leniolisib of 50, 100, and 150 mg/kg. Leniolisib at 150

mg/kg was shown to transiently prolong the QTc interval with a mean of 32 ms (13%). Plasma levels of leniolisib were not determined in this study.

The effects of leniolisib on the central nervous system and respiratory system were evaluated using functional observational battery (FOB) evaluations and respiratory function assessments after administration of leniolisib at 300 mg/kg to male Wistar Han rats. No effects of leniolisib on the CNS and respiratory systems were noted.

2.5.2.4. Pharmacodynamic drug interactions

Not applicable

2.5.3. Pharmacokinetics

The applicant has submitted the reports of the analytical assays that were used to characterize *in vitro* studies, the non-clinical pharmacokinetic and toxicokinetic studies, including assay accuracy, precision, and limits of quantification. Acceptance criteria and validation parameters were determined according to the EMA Guideline on Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2, July 2011. Statements on GLP compliance indicated that these validation studies were conducted in a manner consistent with the GLP principles and no significant deviations from the GLP Regulations affecting the quality, integrity, or interpretation of the study were known to occur.

Following single oral administration, leniolisib was rapidly absorbed with Tmax values of 0.25h (rat) to 2.6h (monkey). The bioavailability of leniolisib was medium in rats (59.4%). Although inconsistent (>100%), in cynomolgus, the bioavailability was of 141%.,

Following repeated oral administration, TK analysis showed that leniolisib was rapidly absorbed in mice, rats and monkeys. In mice and rats the mean Cmax and AUC values in females were higher than in males while in monkeys, mean Cmax and AUC in male were higher than in female.

In general, the mean Cmax and AUC values increased with dose, but not always in a dose proportional manner. After multiple dosing, there is no significant accumulation in mice under these conditions. TK parameters will be assessed with toxicological studies.

The plasma protein binding was moderate to high and not affected by varying concentrations of leniolisib. The average fraction unbound (fu) was 12.4 % (mouse), 8.18% (rat), 3.83 % (dog) 9.85% (monkey) and 5.54% (human). Blood partitioning data indicates minor to no preferential partitioning of leniolisib into blood cells except in rat. The average plasma fraction was 85.3% in mouse, 52.2-71.8% in rat (at 10 ng/mL and at 10000 ng/mL, respectively), 47.3% in dog, 81.7% in monkey and 87.1% in human, which corresponds to blood to plasma concentration ratios (Cb/Cp) of 0.778, 0.752-1.03, 1.21, 0.673 and 0.643, respectively.

In rat, after single oral gavage administration of 10mg/kg, leniolisib was moderately distributed to the majority of investigated tissues with the highest radioactivity exposures in the bile, hair follicle, liver, intestinal wall, and kidney. Maximum tissue concentrations were generally observed at 3h post-dose.

Concentrations in all groups was declined with time and radioactivity and generally not detectable by 168 h after administration except in liver and blood contained traces of radioactivity (between LOD and LLOQ).

In pigmented rats (Long Evans), the highest exposures based on AUC-last were found in melanin-containing structures (eg. eye, hair follicle, skin) and in non-melanin-containing structures such as

gastrointestinal tractus (caecum, colon and small intestine walls), liver and kidney, harderian gland and adrenal (cortex). No brain penetration was detected.

For most tissues, the calculated T1/2 values were between 3.79 and 10.4 hours. Longer retention was observed in liver (up to 45.8 h) and various melanin containing structures such as pigmented hair follicle and up to 1550 h in eye ciliary body.

No major plasma metabolites superior to 10% were identified in human hepatocytes in an *in vitro* study. Leniolisib was the major component present *in vitro* from all species (> 40%) except in dog (leniolisib was of 14.8%). The metabolites of leniolisib were formed by hydroxylations, hydrations, demethylation, dealkylations and oxidations. The most abundant metabolite detected in human plasma was M7 (hydroxylation) at 6.8%. Metabolites M4 (hydration), M5 (di-hydroxylation), M6 (hydroxylation), M13 (di-dehydrogenation), M14 (demethylation and hydroxylation), M16 (demethylation and hydroxylation), M18 (hydroxylation), M21 (hydroxylation) were the other metabolites present in human plasma detected at levels from 1.8% to 6.6% % of total radioactivity in plasma.

In rat and monkeys, leniolisib was also the major drug-related material found in plasma but in dog, metabolite M3 (di-hydroxylation) was the most abundant compound and leniolisib was present in 14.8%. M5 and M7 were the most abundant in rat male (9.5 and 9.8%) and M5 was the most abundant metabolite with 2.4% in rat female and 21.2 % in monkeys. *In vitro*, M18 (resulting from demethylation and hydration of the pyrrolidine ring of the parent compound) was only found in plasma human at 1.8% but in animals, this metabolite resulting from combination of pathways and was identified in the excreta of rat in *in vivo* study. *In vivo* metabolism was evaluated in rats male and monkeys. As *in vitro*, unchanged leniolisib was the major component in both species and the major metabolites found in plasma were M6 and M7 (hydroxylation for both). CYP3A4 was the most predominant enzyme involved in the metabolism (94.5%) with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6).

The main route of excretion was *via* faeces in rats around 90% of the radioactivity dose (IV or oral), renal excretion was quick and low, 7.05 % and 6.08% of the dose were excreted *via* urine during 0-24h after IV and oral administration respectively. In rat and monkey, the elimination of drug-derived radioactivity after oral and IV dosing was complete.

In rats, 9.48% and 0.31% of the leniolisib dose was found in faeces and urine. The main metabolites M1 and M28 were observed in rats faeces. In monkey, less than 1% of leniolisib dose was observed in excreta.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity study was performed in rats. Single dose toxicity was evaluated in an exploratory two phases (single and repeat dose) study in cynomolgus monkeys.

2.5.4.2. Repeat dose toxicity

Ten studies were performed in rats or monkeys to determine the toxic profile in these two species. Leniolisib has been administrated in rats up to 120mg/kg/day and up to 26weeks.

All female rats in the 26-week study at 120mg/kg/day (high dose group) and one female rat at 40mg/kg/day (mild dose) were euthanized due to skin sores (inflammation and ulceration) correlated with subacute inflammation in the dermis/epidermis especially in the dorsal skin. The presence of bacterial colonies (*Staphylococcus aureus*) was observed. In non-pivotal 2-week study in rats, mortality was observed at 300mg/kg due to severe diarrhoea and inflammation in gastrointestinal tract. No mortality occurred in the 4-week and 13-week studies in rats up to 90 and 120mg/kg/day and leniolisib was well tolerated up to 40 mg/kg/day for 26 weeks.

Salivation and lymphoid depletion were observed in all studies. Indeed, lymphoid depletion was revealed by lymphoid cell depletion of the marginal zone (B-cell area), decreased haematopoiesis and/or decreased cellularity in multiple lymphoid organs, including lymph nodes, spleen, thymus, and GALT(B-cell regions). The dose-related findings in the lymphoid system were coherent with the pharmacodynamics properties of leniolisib driven. Indeed, all plasma exposure were largely above EC50 for inhibition of PI3Kδ (EC50 = 11 nM).

Lymphoid depletion was observed in spleen and in lymph nodes from 30mg/kg/day in females and males in a 4-week study characterized by a lymphoid cell depletion of the marginal zone (B-cell area) and a light lymphoid cell hyperplasia in periarteriolar lymphoid sheaths (PALS, T-cell areas) as well as a decreased haematopoiesis in males. These effects were correlated with a decrease of spleen weight and were reversible. The exposure was about two to three times higher in female animals when compared to male rats irrespective of day and dose. In this study, the NOAEL was 30mg/kg/day.

The results of 7-day oral study and a 4-week oral study in CByB6F1-Tg(HRAS)2Jic wt/wt mice have been provided. Leniolisib was administrated up to 240mg/kg/day in mice by oral gavage during 7 days. In this study, no morality and no clinical signs were observed. Slight reduction of weight liver and spleen was observed at 120mg/kg and with significant effect at 240mg/kg/day in males suggesting a dose-related effect.

Leniolisib was administrated to CByB6F1-Tg(HRAS)2Jic wt/wt mice up to 500mg/kg/day during 4 weeks. Mortality was observed at 240mg/kg/day in 2/10 females (found dead or euthanized) but the cause of death was not determined. The highest dose was toxic, and an important mortality was observed, 5 males (principal / satellite group) were found dead or euthanized on day 4 and 5, and from day 4 and 7, all remaining animals were euthanized due to their poor clinical conditions. The effects observed in animal at 500mg/kg/day were hematologic (low haematocrit and mean cell volume) as well as low lymphocyte and reticulocyte counts. Squamous hyperplasia, ulceration and/or mixed cell inflammation of the non-glandular stomach and vacuolation (kidney, liver and/or pancreas) were observed and considered as the cause of mortality or morbidity. At 100 and 240mg/kg/day, effects observed were similar to dose-repeated studies and were related to the pharmacological activity of leniolisib. Based on these results, the NOAEL was 100mg/kg/day.

Rats were treated with leniolisib at 0, 10, 30 and 90 then 120 mg/kg/day by oral gavage during the 13-week study. Same effects on spleen and lymph nodes were observed than in 4-week study. Indeed, from 30mg/kg/day, a decrease of haematopoiesis and at the highest dose, a decrease of cellularity in marginal zone were observed in spleen with a partially recovery concerning the haematopoiesis as the highest dose. Moreover, in mesenteric and/or mandibular lymph node an increased incidence of absence of germinal centres and/or a decreased germinal centre development were observed. Microscopic findings were observed in thymus and sternum with a decrease of cellularity of the medulla and a minimal to slight atrophy (thymus) and an increase of adipocytes in marrow fat (sternum). At all doses, inflammatory cell foci were also observed in liver. Immune response by T-cell dependant antibody was evaluated and has shown a negligible or absence of immune response. A dose-dependent decrease of B cell and slightly reduced numbers of T-cells and natural killer (NK)-cells at 90/120mg/kg/d were observed. All these findings were reversible. Based on these results, the NOAEL

was 30mg/kg/day. The exposure was approximately 1.5 times higher in female than male up to NOAEL. In the last group, the dose was increased to 120mg/kg/day on week 6 and no significative difference was observed between male and female.

Lymphoid depletion and impact on lymphoid organ were also observed during the 26-week study. Rats were treated with leniolisib at 0, 15, 40 and 120mg/kg/day by oral gavage. In addition to similar effects on lymphoid and hematopoietic systems to 13-week study, findings on dorsal skin and male reproductive organs were observed. Indeed, 90% of females at the highest dose were removed from study from week 7 and week 24 due to skin sores consistent with inflammation and ulceration. The presence of bacterial colonial of *Staphylococcus aureus* was observed. At this dose, the exposure was 3-times higher in female than male with an accumulation ratio in female of 1.30 at day 181 (week 26). From 40mg/kg/day in 3 males/20 and 120mg/kg/day in 10males/19, a decreased secretion in prostate has been observed as well as a decreased germinal epithelium in testes. The quantitative evaluation showed that leniolisib induced a reduction of differentiation form spermatogonia type 1 to type B at 120mg/kg/day. This effect was reverse and suggested a recovery of the spermatogenesis. However, based on these results, leniolisib induced findings on hematopoietic and lymphoid systems, skin, and male reproductive organs which were reversed or trended to reduced severity after recovery period. The NOAEL was the smallest dose 15mg/kg/day. There was a higher exposure in females compared with males.

Leniolisib has been administrated in monkeys by oral gavage for 2 weeks, 13 weeks and 39 weeks with 4-week recovery period. Daily administration of leniolisib for 2 weeks (30, 100, 300 mg/kg) was tolerated up to a dosage of 100 mg/kg/day. At 300 mg/kg/day, severe diarrhoea, emesis, pronounced weight loss, accompanying changes in haematology and clinical chemistry parameters, as well as histopathological findings in lymphoid organs and intestine were observed. The NOAEL was set to 100 mg/kg/day, corresponding to Cmax values of 15,300 and 13,700 ng/mL (approximately 4.2 and 4-fold the human steady state exposure at the therapeutic dose) and AUC0-24h values of 132,000 and 78,200 ng·h/mL (approximately 3.5 and 2-fold the human steady state exposure at the therapeutic dose) in males and females, respectively.

During the 13-week study, the dose was reduced due to severe skin and gastrointestinal toxicities: dose levels of 0 (vehicle control on Days 1 to 91), 40/20 mg/kg/day (i.e., 40 mg/kg/day on Days 1 to 30 and 20 mg/kg/day on Days 31 to 91), 80/40 mg/kg/day (i.e., 80 mg/kg/day on Days 1 to 23, followed by washout phase of 7 days, 40 mg/kg/day on Days 31 to 98), 160/120/60 mg/kg/day (i.e., 160 mg/kg/day on Days 1 to 13, followed by washout phase of 5 days, 120 mg/kg on Days 19 to 23, another washout phase of 7 days, 60 mg/kg/day on Days 31 to 105).

Mortality was observed in both studies in monkey, in 13-week at day 90 in one male at 160/120/60mg/kg due to regurgitation and subsequent aspiration of leniolisib. In a 39-week study, during week 10 and 17, 4 animals (3 at 20mg/kg/d and one at 40mg/kg/day) has a rapid and marked body weight loss and dehydration leading up to death or euthanized. Concerning these animals, findings were systemic inflammation, gastrointestinal protein loss and electrolyte imbalance as well as an infection with bacterial pathogens (*C. Jejuni* and *E. Coli*). Then, all animals remained were treated with antibiotic treatment to prevent overall infectious burden and further deaths.

From 13-week study, emesis and soft/fluid faeces were observed in monkeys from 80/40mg/kg/day with a severity dose dependant. Moreover, an increase of salivation was observed before and/or after dosing in both studies. In the 39-week study, leniolisib was administrated by oral gavage in monkeys at 0, 20, 40 and 60mg/kg/day. The main effect was gastrointestinal infection leading to liquid/soft faeces, electrolytes loss and systemic inflammation in all group and resulted in the death of four animals.

Cutaneous findings were observed with spots on the abdomen, arms and legs in two males at 160mg/kg/day, this effect disappeared after dose reduction to 60mg/kg/d in 13-week study.

Abnormal green, soft contents in the large intestine were observed and correlated with histopathology findings in caecum, colon, and rectum, which consisted of subacute to chronic inflammation and micro abscesses in 13- and 39-week studies. This effect was reversed after 4 weeks of recovery except in 39-week study, crypt micro abscess formation still present in at least one segment of large intestine. This lesion is caused by *C. Jejuni* and is not considered related to leniolisib directly.

Some clinical pathology findings were observed induced by gastrointestinal electrolyte loss (Sodium/chloride decreased) or inflammatory response (increased globulin concentration, albumin decreased) but in 13-week study only the increase of creatine kinase activity was still present in male at the highest dose. In 39-week study, reversible increase in eosinophil counts were present from day 23 and correlated with the inflammation in the intestinal tract (reversible).

From 13-week study, depletion in CD20+ B cells and CD16+ NK cells and an increase of CD3+ T helper Cells from 40mg/kg/d were observed on day 14. Due to reduction of dose, this effect was not present on day 90.

In a 39-week study, depletion in cell B in lymphoid organ in males from 20mg/kg and in females from 60mg/kg/d was observed and was partially reversible. Indeed, in spleen or GALT/peyer's patch the depletion was no present but in the mandibular lymph node in one female and in thymus in males at 60mg/kg/d the depletion was still present.

A cardiac effect was observed only in 39-week study and showed an increase in QT and QTc intervals from 40mg/kg/day. In addition to the QT effects seen after a single dose of leniolisib in cynomolgus monkeys at 150 mg/kg (exposure in male monkeys was approximately 9-fold and 6-fold the human steady state exposure at the therapeutic dose on a Cmax and AUC0-24h,ss,u basis, respectively), a cardiac effect was also observed in monkeys at 300 mg/kg/day during the 2-week repeat dose-study (approximately 11.5- and 7.7-fold (male) and 14- and 5.7-fold (female) the human steady state exposure at the therapeutic dose on a Cmax and AUC0-24h,ss,u basis, respectively) in which one animal exhibited premature bigeminal ventricular complexes alternating with sinus complexes and a slight increase in QTcI values was observed in some animals. Moreover, a cardiac effect was observed in the 39-week study and showed an increase in QT and QTc intervals from 40mg/kg/day. At this dose level, the combined-sex plasma exposure (AUC0-24h, u) was 2.3-fold the human steady state exposure at the therapeutic dose. A more prolonged QT and QTc were observed in 20mg/kg/day group but there is a variability between individuals' animals. No effects on heart rate, PR, RR or QRS intervals or body temperature were observed.

After repeat dose in monkey during 13-week of treatment, a pronounced accumulation (1.5-fold to 5.2-fold) was observed for all dose levels when comparing the exposure of Day 31 with Day 85, Day 96 and Day 99. Based on these results, the NOAEL for this study in monkey was 20mg/kg/day. The exposure was different between the sexes according to the doses. At 40/20mg/kg/day the exposure was higher in females than males (6-fold at the NOAEL) whereas from 40/80, the exposure was higher in males than females (around 1.9-fold). Whereas, in the 39-week study, no accumulation was observed in male or female and no gender difference was observed. Based on these results in the 39-week study, the NOAEL was 20mg/kg/day.

The safety margins in toxicity studies were 0.8 (15mg/kg/day) and 1.0 (20 mg/kg/day) at the NOAEL in rat and monkeys.

2.5.4.3. Genotoxicity

A standard test battery was performed with leniolisib according to ICH guideline S2(R1). Leniolisib was not mutagenic in the performed Ames assay. Negative results were observed in non-GLP micronucleus test using TK6 cells. Negative results were also observed in an *in vitro* chromosome aberration assay in absence of metabolic activation but with cytotoxicity. In presence of S9 mix, 2,5% of chromosome aberration in cells at 325 µg/mL with 50% of cytotoxicity in experiment 1 was observed and in experiment 2, at 350µg/mL, 4% of chromosome aberration in cells with 46% of cytotoxicity was observed. This value of 4% is close to the higher historical range of 3%, but a slight dose-dependent effect seems observed with cytotoxicity.

From the *in vivo* study, the maximal tolerated dose was 700mg/kg/day in Han Wistar rats male and 400mg/kg/day in female. According to toxicokinetic data from the dose-repeated studies, the dose and the use of male rats were acceptable and corresponding to around 30-fold the clinical exposure. The result of this study was negative. Moreover, the systemic and bone marrow exposures were not determinate, especially by the absence of any significative reduction of the percentage of PCE. However, according to distribution study in Han Wistar rats, the bone marrow is exposed with same magnitude to blood.

2.5.4.4. Carcinogenicity

No definitive carcinogenicity studies have been completed yet. The applicant is currently performing a 2-year rat carcinogenicity study for which the results will be submitted by June 2026 as a post-authorisation measure (REC). The report should describe the type of tumours, as the results are very important for the reassurance of safety in clinical use. In particular, a focus on GI carcinogenicity is desired. Preliminary results from the 6-month transgenic (rasH2) mouse carcinogenicity study were provided by the applicant during the procedure. The study was conducted in transgenic CB6F1-Tg rasH2 hemizygous mice up to 80mg/kg/day for a minimum of 26 weeks. Non-neoplastic effects in spleen were observed with an increase of extramedullary haematopoiesis from 10mg/kg/day and a decrease of cellularity at 80mg/kg/day. Those effects were observed in chronic non-clinical studies. The NOAEL was 80mg/kg/day.

2.5.4.5. Reproductive and developmental toxicity

The assessment of male and female fertility and early embryonic development was included in the toxicity study conducted on juvenile rats. No treatment-related effect was noted on female fertility. In males, findings on reproductive organs at ≥30 mg/kg were in line with those observed in the 26-week rat toxicity study at ≥40 mg/kg: decreased testes and epididymis weights, decreased round spermatids and/or decreased spermatocytes in testes related to decreased differentiation from type A to type B spermatogonia, and increased incidence of inflammatory cell foci in epididymis. This was associated with decreased sperm count. Following a 7-week recovery period in the toxicity subset, lower organ weights and histopathological findings in epididymis were still observed. The male fertility index at the high dose level was decreased compared to controls to a value in the low range of a large historical control database.

Embryo foetal development studies were performed in rats and rabbits. At high dose levels corresponding to 6.6- (120 mg/kg/day, rat) and 2.3-fold (100 mg/kg/day, rabbit) the clinical exposure (AUC) at the maximal recommended human dose, ocular malformations were reported in both species with additional foetal weight decrease in rabbits. A pharmacological rationale is viewed as likely for

ocular malformations since similar findings were already reported with other compounds of the same class.

The pre- and postnatal development study was performed in rats dosed orally by gavage at doses ranging from 10 to 90 mg/kg/day from implantation to weaning of F1 generation offspring. No drug-related adverse effect was observed in maternal animals. In F1 pups, there was a statistically significant reduction in the lactation index (percentage of pups born that survived 21 days postpartum) at 90 mg/kg/day that was determined to be adverse. In addition, there were reduced pup weights at 90 mg/kg/day and the effects on growth continued into the postweaning period in the F1 generation males and females; however, the reductions during the postweaning period were variable and were not considered adverse. There were no leniolisib related effects detected during necropsy examinations nor on sexual maturation, neurobehavioral or reproductive function in the F1 generation rats at any dose level. Based on effects on pup viability and pup body weight, the preweaning developmental NOAEL for leniolisib was established at 30 mg/kg/day and the postweaning NOAEL for leniolisib was established at 90 mg/kg/day. Leniolisib was detected in all the milk samples from the F0 maternal rats, in a dose - dependent manner.

Juvenile animal studies (JAS) were conducted to support the development for treatment of APDS in children from 1 year of age. The pivotal study was initiated in 7 days old rats treated for 10 weeks, with evaluation of reversibility after a 7-week recovery period. Additional groups of animals were included to evaluate any effect on immune function and fertility (see above). In general, the targets organs for toxicity observed in juvenile rats were the same as those identified in adult rats, i.e. lymphoid tissue with subsequent effects on immune function in line with the pharmacological activity of leniolisib, and male reproductive organs. However, the submitted data point to an increased sensitivity of juvenile animals considering the mortality observed mainly in preweaning animals at the top dose level due partly to metabolic immaturity (CYP3A) inducing higher systemic exposure to leniolisib, with a suggested contribution of increased brain exposure in relation to P-gp immaturity at the BBB level.

2.5.4.6. Toxicokinetic data

Not applicable

2.5.4.7. Other toxicity studies

Phototoxicity

Absorption studies with leniolisib showed absorption between 290 – 330 nm with a molar extinction coefficient above the guideline limit of 1000 L/mol/cm (i.e. 2,261 and 2,042 L/mol/cm). Two *in vitro* 3T3 Neutral Red Uptake (NRU) phototoxicity tests have been performed and showed different results. In the first assay (non-GLP), at >500 µM (pH 6.8), precipitation of leniolisib was observed and the Photo Irritation Factor (PIF) was 5.3, indicating that leniolisib was weakly positive. However, the second assay GLP, the PIF was 1.8, indicating that leniolisib was negative under this condition.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1: Summary of main study results

Substance (INN/Invented Name): leniolisib			
CAS-number (if available): 1354690-24-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5: Log10 Pow = 2.2 pH 7: Log10 Pow = 3.2 pH 9 : Log10 Pow = 3.2	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	7×10^{-5}	µg/L	> 0.01 threshold N

The ERA of leniolisib was performed in accordance to the current guidelines, a phase I ERA was provided with a refined Fpen based on the orphan designation of leniolisib. The prevalence mentioned in orphan designation could be used FPEN as reported in Q&A of ERA guideline (EMA/CHMP/SWP/44609/2010 Rev. 1). The updated $PEC_{surfacewater}$ for leniolisib is below the action limit of 0.01. Consequently, a Phase II risk assessment is not required. There is no PBT potential and toxicity data in animals and human raised no endocrine concern. However, according to the EMA Guideline on Environmental Risk Assessment of Medicinal Products for Human use, the submission of log K_{ow} data is part of a Phase I ERA to allow for a PBT screening.

2.5.6. Discussion on non-clinical aspects

Overall, the non-clinical studies were considered GLP compliant.

Primary and secondary pharmacodynamic studies performed *in vitro* and *in vivo* on leniolisib show efficacy, specificity and selectivity in regard to the p110δ subunit.

In biochemical assay, leniolisib was shown to be a potent and selective inhibitor of PI3Kδ with a half maximal effective concentration (EC50) of 11 nM measured in enzymatic assays. The inhibition of the α, β and γ isoforms is at least 28-fold less potent. The PI3Kδ is a class IA lipid kinase heterodimer composed of a p110δ polypeptide (PI3Kδ specific catalytic subunit) and a p85α (nonspecific regulatory subunit). The p110δ catalytic subunit is mainly expressed in cells of the hematopoietic system, primarily lymphocytes and myeloid cells. The APDS2 mutations in p85α lead to the disease that

phenocopy APDS1, despite that p85α is ubiquitously expressed and interacts not only with p110δ but also with p110α and p110β. The p85α mutation leads to a strong basal activation of PI3Kδ, while it only weakly increases PI3Kα activity. This differential effect explains why the impact of this mutation is largely restricted to the immune system. Taken together, the data explains why leniolisib remains PI3Kδ specific in both APDS1 and APDS2.

From *in vitro* study, at 10 µM concentration, leniolisib showed significant inhibition of the G-protein coupled receptor GPR8 (72% inhibition), hPDE4D (IC50=4.7 µM) and 5HT2B (IC50=7.7 µM). At the considered clinical dose of 70 mg twice daily, the measured maximal unbound therapeutic steady-state plasma concentration in human plasma of 0.449 µM is at least 10 times lower when compared to the IC50 values of GPR8, hPDE4D, and 5HT2B. Considering this margin of safety and the selectivity of leniolisib for its target, there is no significant clinical risk.

On the effects of leniolisib on glucose metabolism (mediated by the p110α isoform of the PI3K/Akt pathway), the findings in the mouse model are not considered relevant at clinical doses (70mg/ twice daily approximately 12 hours apart): sufficient safety margins are expected to prevent an impact on insulin and blood sugar levels in humans.

In vivo, leniolisib has been shown to be efficacious in a sheep red blood cell model of the T-cell dependent antibody response (TDAR) in rats, with 54% inhibition of antibody production at a dose of 3 mg/kg bid (bis in die; i.e., twice a day).

Leniolisib potently inhibits PI3Kδ with good selectivity over other P13K isoforms, target-unrelated protein kinases, proteases, receptors and ion channels. The *in vitro* off-target assay of leniolisib shows no significant inhibitory effect on other members of the wider PI3K family, nor interference with a broad panel of tested kinases, proteases, receptors and ion channels.

Leniolisib was also evaluated in standard safety pharmacology core battery studies, according to the relevant recommendations (ICH guideline S7). The nonclinical safety pharmacology data suggest that leniolisib may be associated with an increased risk of cardiac arrhythmias. Nevertheless, in the completed clinical studies with leniolisib, no clinically meaningful changes were observed in ECG parameters. No effects of leniolisib on the CNS and respiratory systems were noted.

The pharmacokinetic profile of leniolisib was extensively studied *in vitro* as well as in non-clinical species using Han Wistar rats and cynomolgus monkeys. Following single oral administration, leniolisib was rapidly absorbed with Tmax values of 0.25h (rat) to 2.6h (monkey). The bioavailability of leniolisib was medium in rats (59.4%). The PK bioavailability data in clinical and non-clinical were sufficient to determine a security profile for the patients. In mice and rats, the mean Cmax and AUC values in females were higher than in males while in monkeys at the highest dose, mean Cmax and AUC in male were higher than in female. Gender differences were observed but inconsistent between species and doses. Male rats appeared to be the species closest to human in terms of metabolism according to *in vitro* studies. CYP3A4 was the most predominant enzyme involved in the metabolism (94.5%) with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6). The main route of excretion was *via* faeces in rats and renal excretion was quick and low. In rat and monkey, the elimination of drug-derived radioactivity after oral and IV dosing was complete.

Leniolisib was evaluated in toxicology studies that meet requirements as defined in ICH M3 in ten studies in rats or monkeys up to 26-week and 39-week, respectively. Mortality was observed in rats and monkeys and was attributed to skin and gastrointestinal infections. These deaths led to dose reductions or to the introduction of antibiotic therapy. The repeated toxicity studies as well as the long-term clinical data do not indicate a significant risk of variability in efficacy or safety.

Salivation and lymphoid depletion were observed in all studies in rats and monkeys. Indeed, lymphoid depletion was revealed by lymphoid cell depletion of the marginal zone (B-cell area), decreased haematopoiesis and and/or decreased cellularity in multiple lymphoid organs, including lymph nodes, spleen, thymus, and GALT (B-cell regions). The dose-related findings in the lymphoid system were coherent with the pharmacodynamics properties of leniolisib driven and were reversible.

The immunomodulatory pharmacological effect caused a reduction of immune response by T-cell dependant antibody (TDAR) at the highest dose in 13-week study in rats. Due to the immune response reduced, opportunistic infections in gastrointestinal tract and skin were observed and leading to mortality or moribund conditions in rats and monkeys.

The nonclinical safety pharmacology data suggest that leniolisib may be associated with an increased risk of cardiac arrhythmias. Nevertheless, in the completed clinical studies with leniolisib, no clinically meaningful changes were observed in electrocardiogram (ECG) parameters. A cardiac effect was observed in monkeys and showed an increase in QT and QTc intervals from 40mg/kg/day. A more prolonged QT and QTc were observed in 20mg/kg/day group but there is a variability between individual's animals. No effects on heart rate, PR, RR or QRS intervals or body temperature were observed. However, the cardiac effect on QT interval was considered adverse and altogether; Nevertheless, in the completed clinical studies with leniolisib, no clinically meaningful changes were observed in ECG parameters.

The animal exposure at the NOAEL is similar to the exposure in human at the therapeutic dose.

The potential genotoxicity of leniolisib was evaluated in a bacterial reverse mutation assay, *in vitro* chromosomal aberrations assay in human peripheral blood lymphocytes, and *in vivo* micronucleus study in rats. Leniolisib was not considered as genotoxic.

No definitive carcinogenicity studies have been completed yet. The applicant has committed to submit for regulatory assessment the results of the ongoing 2-year rat carcinogenicity study by June 2026 as a post-authorization measure (REC). In preliminary results in transgenic rasH2 mice model, leniolisib was not found carcinogenic. The SmPC section 5.3 adequately reflects the lack of carcinogenic potential observed in chronic nonclinical studies and that long-term animal studies to evaluate the carcinogenic potential of leniolisib have not been conducted and is considered acceptable.

Regarding reproductive and developmental toxicity studies, taking into account the low sensitivity of mating trials to fertility effects in rodents and the effects noted at low exposure multiples on the male reproductive organs (weight, histology, semiology) in toxicity studies, as well as the overall nonclinical data, an effect on human male fertility cannot be ruled out. In the 26-week rat study, lower prostate weights correlated with a decreased secretion seen microscopically. In this study and the 10-week juvenile rat study, lower testes and epididymis weights and lower sperm counts were linked to decreases in the germinal epithelium and round spermatids and loss of spermatocytes. These histological findings occurred at 90 and ≥40 mg/kg/day, respectively (corresponding to 2.4- and 1.5-fold the maximum human recommended dose based on AUC). No effects on male or female fertility or reproductive performance was noted in rats up to 90 mg/kg/day (corresponding to 2.4- to 3.8-fold the maximum human recommended dose based on AUC). SmPC sections 4.6 and 5.3 appropriately reflect this information.

Based on the embryo foetal development studies, it can be concluded that leniolisib is teratogenic in rats and rabbits and it could represent a clinical potential risk. The findings observed in the animal studies are reflected in the SmPC Section 5.3. Further precautionary measures are implemented in the product information so that Joenja is not recommended during pregnancy and in women of childbearing potential not using highly effective methods of contraception; women of childbearing potential should use highly effective methods of contraception during treatment with Joenja and for

1 week after the last dose. The pregnancy status in females of reproductive potential should also be verified prior to initiating treatment with Joenja. Embryo-foetal toxicity is listed as an important potential risk in the RMP.

Leniolisib was shown to induce microphthalmia (ocular malformations) in both rats and rabbits without safety margins, and anophthalmia (rats only) at the highest dose levels (120 and 100 mg/kg/day, respectively). In the pivotal embryo-foetal development study conducted in rabbits, aglossia (congenital absence of the tongue) and split palatine were reported in two foetuses at 30 and 100 mg/kg/day. It cannot be excluded that split palatine occurred as a background finding in foetuses affected by other oromandibular malformations. As regards aglossia, the probability that it occurred as a chance finding in 2 foetuses from the mid dose group was considered as low since this appeared to be a rare malformation in rabbits (not found in various database). Overall, the biological relevance of aglossia seen from the mid-dose level cannot be ruled out. The NOAELs for embryo-foetal development were 30 mg/kg/day in rats and 10 mg/kg/day in rabbits corresponding to approximately 1.7- and 0.1-fold, respectively, the maximum recommended human dose based on AUC. SmPC section 5.3 appropriately reflects this information.

In the pre- and postnatal developmental rat toxicity study, adverse reactions on the progeny during the preweaning period, manifested as reduced pup survival and persistently lower pup weight during postweaning, were seen at maternal doses of 90 mg/kg/day. Leniolisib was detected in all lactation study samples, with leniolisib concentrations increasing in a dose-dependent manner resulting in a concentration that was approximately 2- to 3-fold higher than the maternal plasma concentration at 10 to 30 mg/kg/day. As such, a risk to breastfed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Joenja. This is considered appropriately reflected in the SmPC section 4.6 and section 5.3.

Phototoxicity was investigated in an *in vitro* neutral red uptake study in BALB/c 3T3 mouse fibroblasts: leniolisib is not considered as phototoxic.

Leniolisib $PEC_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore, leniolisib is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

The pre- and postnatal development study showed adverse effects on the progeny during the preweaning period at the high dose level of 90 mg/kg/day, manifested as reduced pup survival and persistently lower pup weight persisting postweaning.

The target organs of toxicity highlighted in juvenile rats dosed from 7 days of age were similar to those of adult rats with an increase in sensitivity of preweaning animals based on treatment-related mortality during the preweaning period. The applicant explained that the increased mortality reported in high dosed animals during the pre-weaning period is likely related to very high systemic exposure levels which may be caused by low CYP3A and P-gp expression, and increased brain penetration of leniolisib resulting from immature P-gp function in the developing BBB. The cause of death was not elucidated, and there is no further data supporting increased brain penetration of leniolisib alongside the weaning period (e.g. no measure of brain levels). In addition, it has to be taken into account that this effect is consistent with the increased mortality of rat pups in the PPND study. Although it is acknowledged that relevance for patients from 12 years of age is not likely, increased mortality in preweaning rats is reported in SmPC section 5.3 as human relevance cannot be dismissed.

2.5.7. Conclusion on the non-clinical aspects

The toxicological package available for leniolisib was found adequate for the treatment of APDS and in line with the relevant guidelines.

Leniolisib carries a risk of immunosuppression, leading to opportunistic infections and gastrointestinal toxicity (severe diarrhoea and emesis) in animals.

A reduction in the weight of reproductive organs and sperm count, as well as teratogenic effects (microphthalmia, anophthalmia), have been observed. Developmental studies have shown decreased offspring survival, reduced weight, and high milk concentration. The SmPC section 5.3 appropriately reflects these findings. Precautionary measures for use during pregnancy, in women of childbearing potential and breast-feeding women, as well as information about a possible risk affecting male fertility are included in the product information. Furthermore, embryo-foetal toxicity is an important potential risk in the RMP and will be further characterised in pharmacovigilance studies as described in the agreed RMP.

No carcinogenic potential has been shown in available studies, but long-term studies have not been conducted; this is adequately addressed in SmPC Section 5.3. The CHMP considers the following measures necessary to address the lack of long-term carcinogenic data: the applicant should submit the results of the ongoing long-term 2-years carcinogenicity study as a post-authorisation measure by June 2026.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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.

- **Tabular overview of clinical studies**

Table 2: Clinical studies relevant for pharmacodynamics and pharmacokinetics-pharmacodynamics

Study Number	Study Type	Study Objective(s)	Study Design	Sample Size Gender Age (Years)	Treatment	Study Status
APDS						
CCDZ173X2201 Part 1	Safety and tolerability	Primary Dose-PD and PK/PD relationship for dose selection in Part 2. Secondary PK, clinical outcome assessments, biomarkers.	OL, non- randomized, dose finding; multicenter	Leniolisib 6 Male/Female 12-75	10 mg, 30 mg, and 70 mg bid, sequentially each dose for 4 weeks/PO	Complete
CCDZ173X2201 Part 2	Efficacy	Primary Lymphadenopathy and immune-phenotype normalization. Secondary Effect on non-index lesions and spleen, clinical outcome and systemic inflammatory measures, PK, safety, tolerability.	Blinded, randomized, multicenter, PBO-controlled	Leniolisib 21 Placebo: 10 Male/Female 12-75	70 mg bid/PO	Complete
CCDZ173X2201E1 (Long-Term Extension)[a]	Long term Safety and Efficacy	Primary Long-term safety and tolerability. Secondary Long-term efficacy on clinical outcome and systemic inflammatory measures, PK, relative BA.	OL, non-randomized, multicenter	Leniolisib 37[a] Male/Female 12-75	70 mg bid/PO	Ongoing

Study Number	Study Type	Study Objective(s)	Study Design	Sample Size Gender Age (Years)	Treatment	Study Status
Healthy Volunteer						
CCDZ173X2101	SAD/MAD	Safety and tolerability (Parts 1, 2, 3) and maximum tolerated dose (Parts 1, 3). PK (Parts 1, 2, 3). PK of fed and fasted conditions (Part 2). PD on Akt phosphorylation in B cells (PD read-out) after *ex vivo* stimulation of peripheral blood (Part 1, 3).	Single-center, randomized Part 1 DB, PBO-controlled, single ascending dose Part 2 OL, 2-way XO, food effect Part 3 DB, PBO-controlled, MAD	Leniolisib Part 1: 64 Part 2: 12 Part 3: 42 Total: 118 Placebo Part 1: 44 Part 2: 0 Part 3: 26 Total: 70 Male/Female 18-45	Part 1: fasted state; ascending 10, 20, 40, 80, 110, 140, 200, 300, and 400 mg/PO Part 2: 70 mg/PO, fasted and fed Part 3: ascending 20, 40, 70, and 140 mg bid/PO	Complete
CCDZ173X2102	DDI	Effect of itraconazole, cytochrome P450, P-glycoprotein inhibitor on PK.	Single-center, OL, single-sequence, 3-period XO	Leniolisib 20 Male 12-75	10 mg/PO	Complete
CCDZ173X2104	PK	PK on single-dose oral contraceptive.	Single-center, OL, 2-period single tablet of EE 30 µg and LVG150 µg on Day 1 and Day 15	Leniolisib 30 Female 18-65	70 mg bid/PO	Complete
LE1101	BE	Bioequivalence of leniolisib HGC (Novartis) to FCT (Pharming).	Single-center, OL, randomized, 2-way XO	Leniolisib 20 Male/female 18-60	70 mg/PO	Complete
LE2101	ADME	Total recovery and relative excretion of radioactivity in urine and feces.	Single-center, OL	Leniolisib 6 Male 18-45	Single oral dose of 70 mg ^{14}C-leniolisib (40 µCi)/oral solution in the fasted state	Complete

ADME=absorption, distribution, metabolism, and elimination; BA=bioavailability; BE=bioequivalence; bid=twice daily; DB=double blind; DDI=drug-drug interaction; FCT=film coated tablet; HGC=hard gelatin capsule; MAD=multiple ascending dose; mg=milligrams; OL=open label; PBO=placebo; PD=pharmacodynamic; PK=pharmacokinetic; PO=per os (oral); SAD=single ascending dose; XO=crossover.

a: An interim analysis of this study was conducted with a data cutoff date of 13 December 2021. At the time of the data cutoff, 37 patients were enrolled and 36 patients were continuing to receive leniolisib 70 mg twice daily.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Leniolisib (also referred as CDZ173), is a potent, selective, orally small molecule inhibitor of phosphoinositide 3-kinase delta (PI3Kδ) catalytic subunit p110δ that selectively inhibits the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). This specifically targets the causative factor in immune cells resulting in the pathogenesis of activated phosphoinositide 3-kinase delta syndrome (APDS).

Additionally to *in vitro* investigations (*in vitro* metabolite profiling, CYP inhibition and induction, cell permeability, and protein binding …), the clinical pharmacologic program for leniolisib includes 8 clinical studies presented in Table 3. The PK and PD properties of leniolisib following single-(10 to 400 mg) and multiple-dose administration (20 to 140 mg twice daily) have been characterized in 5 completed Phase 1 studies in healthy participants (hereafter referred to as studies LE1101, LE2101, 2101, 2102, and 2104), 1 completed study in patients with primary Sjögren's syndrome (Study 2203), and the completed and ongoing extension studies 2201 and 2201E1 in patients with APDS (10 to 70 mg twice daily).

In addition to formal PK analyses, a modelling and simulation approach was also used to support PKPD of leniolisib.

A plasma leniolisib PopPK model was established from the healthy participant data in Study 2101 and used to generate individual post hoc PK parameter estimates for exposure corrected QT interval (QTc) analysis. In addition, PK data from patients with APDS in Study 2201 were fitted to a 1-compartment model, and the estimated PK parameters were used for PK/PD analysis of pAkt inhibition in B cells. PBPK analyses were also performed using data from Studies 2101 and 2102 to support evaluation of the DDI potential with leniolisib.

Table 3: Clinical Pharmacology studies

Study Number; Summary; Phase	Key Clinical Pharmacology Objectives	Study Design (Number of Participants[a])	Treatments[b]
Studies in Healthy Participants			
CCDZ173X2101 (CSR Study 2101); Section 2.2.1; Phase 1	• Assess PK of ascending single and multiple oral doses of leniolisib • Investigate PK of leniolisib under fed and fasted conditions • Investigate PD effect of leniolisib on pAkt in B cells after *ex vivo* stimulation of peripheral blood • Explore the PK/PD relationship of different single and multiple oral doses of leniolisib • Explorative ADME and metabolite profiling and identification (using ^{19}F-NMR)	Multicenter, randomized, double-blind, placebo-controlled, ascending single- and multiple-dose study in healthy participants Part 1: Randomized, double-blind, placebo-controlled, single ascending dose study (N=64) Part 2: Randomized, open-label, 2-way crossover, food effect study (N=12) Part 3: Randomized, double-blind, placebo-controlled, multiple ascending dose study (N=42)	Part 1: Single oral dose of placebo or leniolisib in the fasted state at ascending dose levels of 10, 20, 40, 80, 110, 140, 200, 300, and 400 mg Part 2: Single oral dose of leniolisib 70 mg (1 × 70 mg capsule) given in the fasted and fed state Part 3: Oral placebo or leniolisib bid in the fasted state at ascending dose levels of 20, 40, 70, and 140 mg for 15 days Parts 1 and 3 used 10, 70 (Part 1, Cohort 20 only), and 100 mg capsules to make the required dose. The 10 and 100 mg capsules were CSF1 formulation, while the 70 mg capsules were CSF2 formulation.
LE1101 (CSR Study LE1101); Section 2.2.2; Phase 1	• Determine if (Novartis)70 mg leniolisib hard gelatin capsules are bioequivalent to (Pharming) 70 mg leniolisib film-coated tablets	Single-center, randomized, open-label, 2-way crossover study in healthy participants (N=18)	Single oral dose of leniolisib 70 mg in the fasted state as Novartis capsule (1 × 70 mg capsule) and as Pharming tablet (1 × 70 mg tablet) formulations
LE2101 (CSR Study LE2101); Section 2.2.3; Phase 1	• Determine total recovery and relative excretion of radioactivity in urine and feces after a single dose of 70 mg ^{14}C-leniolisib, containing 40 µCi of ^{14}C-radioactivity • Determine plasma PK parameters of total ^{14}C-radioactivity and of leniolisib	Single-center, open-label, ADME study in healthy male participants (N=6)	Single oral dose of 70 mg ^{14}C-leniolisib (40 µCi) as oral solution in the fasted state
CCDZ173X2102 (CSR Study 2102); Section 2.2.4; Phase 1	• Evaluate effect of itraconazole, a strong dual CYP3A/P-gp inhibitor, on single-dose PK of oral leniolisib • Evaluate effect of quinidine, a strong P-gp inhibitor, on single-dose PK of oral leniolisib	Single-center, open-label, single-sequence, 3-period crossover DDI study in healthy male participants (N=20)	Single oral dose of leniolisib 10 mg (1 × 10 mg capsule) on Day 1 of Period 1, on Day 5 of Period 2 (approximately 3 h after the itraconazole dose), and on Day 1 of Period 3 (approximately 1 h after the initial quinidine dose); Single oral dose of itraconazole 200 mg (2 × 100 mg capsule) on Days 1 through 9 of Period 2; Two oral doses of quinidine 300 mg (1 × 300 mg tablet) 4 h apart on Day 1 of Period 3 All morning doses were administered after an overnight fast, a standard light breakfast, and another fasting period. Leniolisib was administered at least 3.5 h after the start of the breakfast.
CCDZ173X2104 (CSR Study 2104); Section 2.2.5; Phase 1	• Assess effect of multiple oral doses of leniolisib on the PK of a single dose of a monophasic oral contraceptive containing ethinylestradiol and levonorgestrel in healthy female participants • Evaluate PK of oral leniolisib	Single-center, open-label, fixed-sequence, 2-period DDI study in healthy female participants (N=30)	Single dose of oral contraceptive tablet containing 30 µg ethinylestradiol and 150 µg levonorgestrel on Day 1 of Period 1 and on Day 15 of Period 2 (coadministered with leniolisib dose); Oral leniolisib 70 mg (1 × 70 mg capsule) bid on Days 1 through 17 of Period 2 All morning doses were administered after an overnight fast. Evening doses of leniolisib were given at least 1 h after dinner was consumed.
Studies in Patients with Sjögren's Syndrome			
CCDZ173X2203 (CSR Study 2203); Section 2.3.1; Phase 2	• Explore relationship between leniolisib PK, clinical efficacy outcomes, PD markers, and potential protein soluble serum and salivary biomarkers • Assess PK of leniolisib in patients with primary Sjögren's syndrome	Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-design study in patients with primary Sjögren's syndrome (N=20)	Oral placebo or leniolisib 70 mg (1 × 70 mg capsule) bid for 12 weeks Morning doses on Days 1, 8, 15, 29, 57, and 85 were given following an overnight fast; all other doses were given irrespective of food.

Studies in Patients with APDS			
CCDZ173X2201 (CSR Study 2201 Part 1 and CSR Study 2201 Part 2); Section 2.4.1; Phase 2/3	• Assess dose-PD and PK/PD relationship of leniolisib in patients with APDS for dose selection in Part 2 • Assess PK of leniolisib in patients with APDS	Part 1: Multicenter, multinational, open-label, nonrandomized, dose-finding study in patients with APDS (N=6) Part 2: Multicenter, multinational, participant-, investigator-, and sponsor-blinded, randomized, placebo-controlled, fixed-dose study in patients with APDS (N=19)	Part 1: Oral leniolisib bid at sequentially increasing dose levels every 4 weeks from 10 mg (1 × 10 mg capsule), to 30 mg (3 × 10 mg capsule), to 70 mg (1 × 70 mg capsule). Evening doses of 10 and 30 mg on Days 28 and 56, respectively, were not taken to allow for pAkt washout Part 2: Oral placebo or leniolisib 70 mg (1 × 70 mg capsule) bid for 12 weeks
CCDZ173X2201E1[c] (Interim CSR Study 2201E1); Section 2.4.2; Phase 2/3	• Characterize PK of leniolisib in patients with APDS • Evaluate PK and relative bioavailability of (Novartis) leniolisib film-coated tablets compared to (Novartis) leniolisib hard gelatin capsules[d]	Multicenter, multinational, open-label, nonrandomized, active-treatment extension study in patients with APDS (N=35)	Oral leniolisib 70 mg bid initially as Novartis capsule (1 × 70 mg capsule) then as Novartis tablet (1 × 70 mg tablet) formulation[e] through the end of treatment period, up to a maximum of 6 years Treatment was given in fasted state or 0.5 h after a light breakfast for morning doses when serial PK sampling was performed and irrespective of food for all other doses.

Methods

Bioanalysis

Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, accuracy, dilution factor linearity, matrix effect. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR for each clinical study were provided with satisfactory results.

Pharmacokinetic analyses

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters.

Additionally, population PK (PPK) and PK/PD, E-R analyses were conducted based on the non-linear mixed effects modeling.

Absorption

BCS classification

The drug substance has pH-dependent solubility and high permeability across Caco-2 cells (85 × 10−5 cm/min), similar to the high permeability positive control propranolol. Therefore, a BCS II classification (low solubility and high permeability) is proposed for leniolisib.

Healthy volunteers

In healthy participants, absorption of oral leniolisib in the fasted state was rapid, with median Tmax ranging from 0.75 to 2 hours postdose following a single dose from 10 to 400 mg (Study 2101 Part 1) or a BID dosing from 20 to 140 mg (Study 2101 Part 3).

After a single dose of 70 mg in healthy volunteers, the geometric mean Cmax and AUCinf ranged from 3020 ng/mL and 13900 ng.h/mL at Day 1 (CV% = 22.5% and 28% respectively) to 3650 ng/mL and 19000 at D15 (CV% = 29.7% and 43.5%, respectively).

Patients with APDS

Following a single dose of 10 to 70 mg leniolisib as a capsule in patients with APDS Study **2201**, the median Tmax ranged from approximately 2 to 3 hours postdose indicating that absorption is rapid.

Following the first dose of 70 mg BID leniolisib as a capsule, geometric mean Cmax and AUC0-8 ranged from 2060 to 2180 and 10300 ng*h/mL to 10600 ng*h/mL, respectively, with median Tmax of 2.87 hours postdose.

Following multiple doses of 70 mg BID leniolisib as a capsule, in patients with APDS (Study 2201E1) median Tmax was approximately 2 hours, geometric mean Cmaxss and AUCtauss were 3288 ng/mL and 22013 ng.h/mL.

After switching from multiple doses of 70 mg BID leniolisib as a capsule, to the FCT tablet (manufactured by Novartis) in patients with APDS (Study 2201E1), median Tmax was 1 hour, geometric mean Cmaxss and AUCtauss were 3928 ng/mL and 22758 ng.h/mL.

Absolute bioavailability

The absolute bioavailability of leniolisib has not been investigated.

Relative bioavailability/ Bioequivalence

The leniolisib drug product claimed to be marketed is a film coated tablet (FCT) and proposed at one strength 70 mg.

In study 2201E1, a relative bioavailability study investigating the performance of the reference hard gelatine capsule (HGC) 70 mg formulation used during the clinical development with a FCT was performed in patients using a single sequence cross-over design. Results of this study indicated the 90% CIs of the ratio of the GMRs leniolisib exposure for AUC0-12 only (estimate: 103.39 [85.83-124.53]) was well contained within the standard bioequivalence range (80-125%). A 20% increased Cmax is observed with the FCT formulation (estimate 119.42 [97.63-146.08]).

A formal bioequivalence study LE1101 was performed in healthy volunteers to demonstrate the relative bioavailability similarity between the to-be marketed drug product and the reference hard gelatine capsule (HGC) 70 mg formulation used during the clinical development in initial PK studies (Studies 2101, 2104) and also in the pivotal Phase 2/3 study in patients with APDS (Study 2201).

Based on the provided PK results in study LE1101, the 90% CIs of the ratio of the GMRs leniolisib exposure with test/reference formulations for Cmax (estimate 1.0799 [0.9737 - 1.1977]), AUC0-t (estimate 1.0375 [0.9756 - 1.1032], and AUC0-inf (estimate 1.0374 [0.9756 - 1.1032]) were well contained within the standard bioequivalence range (0.80 - 1.25). Therefore, the reference hard gelatine capsule used during the clinical development and the leniolisib a film coated tablet 70 mg formulation could be bioequivalent.

Influence of food

The effect of a standardized high fat meal on leniolisib PK was investigated in 12 healthy volunteers who were administered a single oral dose of 70 mg leniolisib (as capsules) in the fasted and the fed states (Part 2 of Study 2101).

PK results indicated that administration of a high fat meal delayed the Tmax (3.51 versus 0.64 hours) and decreased the geometric mean of Cmax on average by 41% (1890 versus 3190 ng/mL) in comparison to the reference fasted state, but unaffected the extent of absorption (AUCinf and AUCt). Indeed, the fed/fasted GMR [90% CI] for Cmax and AUCinf, AUCt were 0.59 [0.53, 0.66] and 0.996 [0.92, 1.07] and 0.99400 [0.92, 1.07], respectively, consistent with the similar CL/F and t1/2 observed regardless of food status. Based on these data, leniolisib could be taken with or without food.

Influence of gastric modifier

Leniolisib exhibits pH-dependent solubility, with lower solubility at higher pH values. Consequently, gastric acid-reducing agents may impair the absorption of leniolisib. No dedicated clinical study evaluating the effects of acid-reducing agents on leniolisib PK has been conducted. However, based on a retrospective analysis of the interim data from Phase 2/3 Study 2201E1, leniolisib systemic exposures (C_{max} and $AUC_{0\text{-}8h}$) in target APDS patients with reported concomitant use of proton pump inhibitor (PPI) appear to be comparable between to those without PPI for both Novartis HGC and FCT formulations. As per the provided results, using the HGC formulation, the geometric mean of Cmax and AUC was 3260 ng/mL and 16478 ng.h/mL for patients with reported use of PPI versus 3190 ng/mL and 16945 ng.h/mL, respectively for patients without PPI. Based on these data, the applicant concluded that concomitant use of PPIs did not have a marked effect on leniolisib exposure requiring dose adjustment.

Distribution

Based on *in vitro* investigations (Study R1100674), leniolisib was found to be moderately bound (mean of 94.5%) to human plasma proteins, and is primarily associated with plasma. The mean blood-to-plasma ratio was 0.643 less than 1, suggesting limit penetration of leniolisib into red blood cells.

In healthy volunteers, the geometric mean apparent volume of distribution (Vz/F) ranged overall from 33 to 57.2 L. Pop-PK data in target patients with APDS (1-compartement model) indicate a geometric mean Vc/F of 28.5 L (CV=20%). Overall, leniolisib showed a low-to-moderate Vd.

Elimination

Healthy volunteers

- Across clinical studies in healthy subjects following single ascending dose of 10 to 400 mg leniolisib (as a capsule), the geometric mean terminal half-life (T1/2) of leniolisib was in the range of 5.3 to 10.9. After repeated administration of ascending 20 to 140 BID doses, steady state mean T1/2 ranged from 9.38 to 10.9 h and CLss/F was low ranging from 3.33 to 3.69 L/h.

In the Bioequivalence study LE1101, after single dose of 70 mg leniolisib as a tablet, geometric mean T1/2 and CL/F were 6.67 h and 4.04 L/h.

Patients

Following oral leniolisib repeated BID at sequentially increasing dose levels from 10 mg to 30 mg to 70 mg in patients with APDS (Study 2201), based on PopPK modelling, the geometric mean steady state apparent clearance CLss/F from a 1-compartment model was low, estimated at approximately 3.72 L/h (CV% = 27.7%).

- Mass balance

As a part of Phase 1 study 2101 (Part 1), a first PK mass balance study R1500425 investigated the excretion and biotransformation of a leniolisib in the 400 mg single oral dose cohort through ^{19}F-NMR/ LCMS. PK samples were collected up to 96 (blood) and 120 (urine and feces) hours postdose. However, only 65.5% of the administered dose was recovered.

Following a single 400 mg oral dose of leniolisib in 5 healthy subjects, the overall mean recovery after 120 h was incomplete about 65.5% (± 7.41%) with 23.0% (± 2.49%) and 42.4% (± 7.04%) of the total administered dose in urine and faeces, respectively. Given that excretion in urine appears to be complete after the first 24 hours (cumulative urinary recovery remained constant from 24 to 120h),

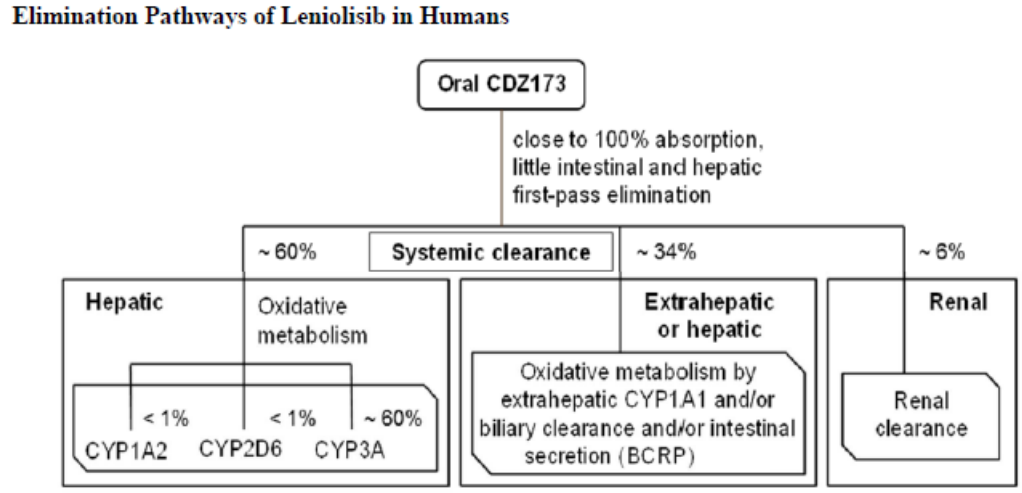
this suggests that most of the unrecovered ~35% of drug related material is likely to be eliminated / excreted in faeces after 120 h (incomplete faeces excretion at 120 h).

Thus, a subsequent dedicated ADME study LE2101 using ^{14}C-leniolisib with longer urinary and feces collection period was conducted to elucidate the mass balance of leniolisib. After a single oral dose of 70 mg ^{14}C-leniolisib, the mean recovery of total radioactivity was 92.5% at 168 hours postdose. Excretion of leniolisib and its metabolites was predominantly through the faeces (67.0%) followed by the urine (25.5%). However, details on drug-related materials recovered in feces and urine are unknown as monitoring the parent compound and metabolites in the excreta's of this study was not performed or could not be found.

It is important to note that urinary excretion appeared complete at 48 hours postdose and that both studies found a comparable renal excretion of about 25% regardless of duration of collection (120 h versus 168h), which confirms that urinary excretion was complete at 120h and that the incomplete mass balance in the explorative ^{19}F-NMR study was likely due to inadequate length of fecal sampling.

The proposed fractional contributions of different pathways to the total elimination of leniolisib in humans is presented in the following table.

Table 4: Elimination pathways of leniolisib in humans



The geometric mean of renal clearance (CLR) at steady state in healthy volunteers ranged from 0.0861 to 0.251 L/h, approximating to <5% of the oral dose. CL/R is less than the typical glomerular filtration rate (~ 7.5 L/h), indicating no active secretion of leniolisib by renal route.

- Metabolism

Leniolisib was found to be extensively metabolized; 85.4 (56% of 65.5% mass balance) was recovered as metabolites in excreta and only <10% as unchanged leniolisib.

Metabolite profiling was performed and up to 26 metabolites were identified (16 in urine and 17 in feces). The primary metabolic processes for leniolisib were hydroxylation to M6 and M7 and their potential secondary metabolites obtained by oxidation (M3 and M5), reduction (M4 and M21), dihydroxylation and reduction (M52, M53, M54, M55 and M56) and *O*-demethylated metabolites representing 29% to 44% of dose and 2) O-demethylation to M1 and potential secondary metabolites M14, M16, M18, M20, M34 and M57 representing 6% to 18% of dose.

In plasma, unchanged leniolisib was the predominant component (93.0% to 96.6% of AUC0-24) and metabolites M6 and M7 (C-hydroxylation) were only present at low levels (3.41% of AUC0-24).

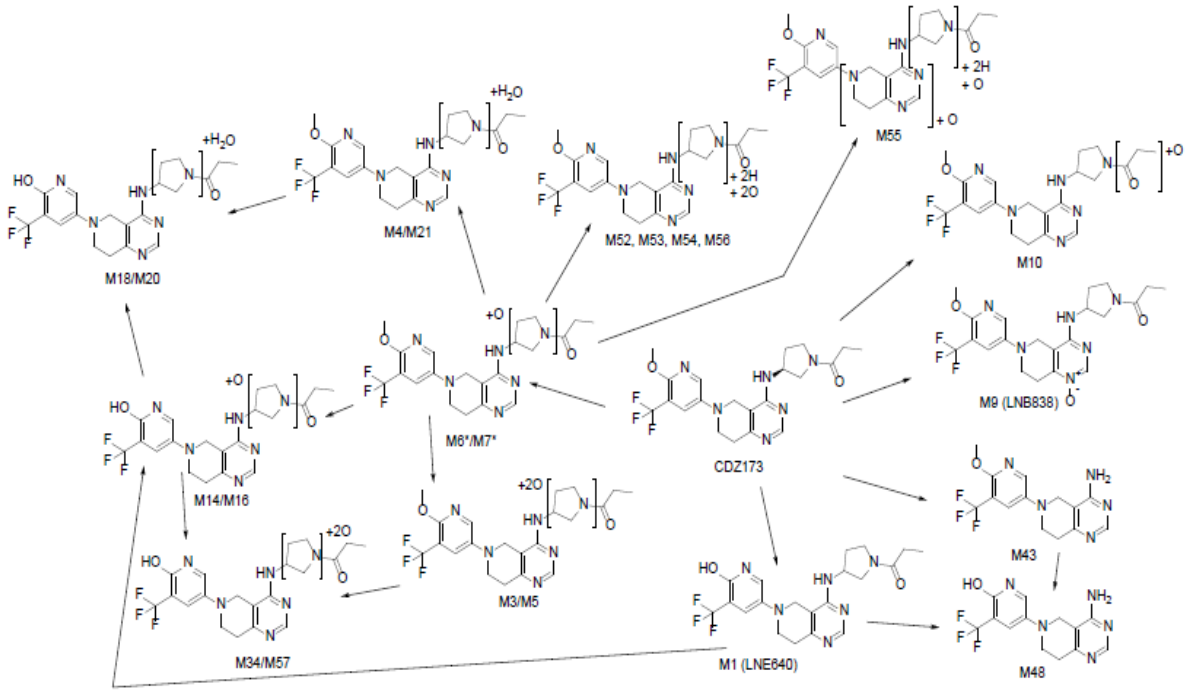
In urine, unchanged leniolisib was the major component (6.32% of dose), and the main metabolites were M3, M6, and M7 (total 4.35% of dose), and M4 and M43 (total 2.81% of dose).

Other metabolites were detected in small amounts (<2% of dose).

In faeces, M3 and M5 (dihydroxylation) were the major components (6.69% and 10.6% of dose, respectively), followed by M18 and M20 (5.40% of dose), M1 (4.73% of dose), M4 (3.72% of dose), and unchanged leniolisib (2.94% of dose).

Other metabolites were detected in small amounts (<2% of dose).

In vitro investigations suggested that leniolisib is primary metabolised by CYP3A4 (95.4%) with minimal contribution from other enzymes (3.5%, 0.7%, and 0.4% from CYP3A5, CYP1A2, and CYP2D6, respectively). The major metabolic pathway of leniolisib occurred largely by Phase 1 oxidative metabolism, mainly hydroxylation and dealkylation (Figure 2). No phase 2 metabolism was identified.



*Detected in plasma; all other metabolites were only detected in excreta

Figure 2: Proposed pathways for the in vivo biotransformation of ^{14}C-leniolisib

- Interconversion

Leniolisib is chiral. A dedicated bioanalytical method to quantify leniolisib stereoisomers was used in Study **2201E1**. No interconversion from (S)- to (R)-enantiomer of leniolisib was observed in the plasma of patients with APDS who received oral leniolisib. All samples analyzed for (R)-leniolisib had concentrations below the lower limit of quantitation (<3 ng/mL). All mention of leniolisib in this document refer to the (S)-enantiomer.

- Pharmacokinetic of metabolites

No major metabolites were detected in plasma.

- Consequences of possible genetic polymorphism

No formal investigations of CYP1A2 or CYP2D6 genetic polymorphism on the PKs of leniolisib were performed.

Dose proportionality and time dependency

Leniolisib dose proportionality is demonstrated between 10 to 400 mg following single dose and from 20 to 140 mg BID following multiple doses in healthy volunteers (Study 2101). In patients with APDS (Study 2201, Part 1), leniolisib exposure (AUC and Cmax) appeared to increase dose proportionally over the dose range investigated (10, 30, and 70 mg BID).

Leniolisib show low to moderate accumulation with Racc ranging from 1.32 to 1.57 for both AUCtau and Cmax. Steady-state appears to be reached within Day 3 after onset of therapy.

Intra-and inter-individual variability

Across studies in patients and using NCA approach, the between-patient variability in leniolisib was moderate ranging from 21.7% to 38.6% for Cmax and 18.4% to 35.3% for AUC0-t (variability shown as CV%).

In the BE study LE1101 after administration of leniolisib as a capsule and the to-be tablet formulations in a crossover design, the intra-subject variability on C_{max} and AUCs was 17.9% and 10.6% respectively.

Data from PPK1 in healthy volunteers show moderate to high between-patient variability for CL/F, Vc/F, Vp/F, Q/F, ALAG and ka (CV of 30.5%, 14.9%, 44.8%, 53.2%, 24.7% and 101%).

Pharmacokinetic in target population

PK in target population was investigated in Study 2201, a Phase 2/3, multicenter, multinational study assessing the PK, dose-PD, and PK/PD relationships of leniolisib in patients with APDS. The study was conducted in 2 parts: an open-label, nonrandomised, dose-finding study (Part 1) and a participant-, investigator-, and sponsor-blinded, randomised, placebo-controlled, fixed-dose study (Part 2).

In Part 1, 6 patients received oral leniolisib twice daily at sequentially increasing dose levels every 4 weeks from 10 mg to 30 mg to 70 mg. Evening doses of 10 and 30 mg on Part 1, Days 28 and 56, respectively, were not taken to allow for pAkt washout.

In Part 2, a total of 31 patients were randomized in a ratio of 2:1 to receive oral leniolisib 70 mg (N=21) or placebo (N=10) twice daily for 12 weeks.

PK parameters estimates of patients receiving leniolisib in Part 1 and Part 2 are presented in **Table 5** and **Table 6** respectively.

Table 5: PK parameters summary (Study 2201-Part 1)

Leniolisib Dose Regimen Visit	n	Geometric Mean (Geometric CV%)[a]				
		C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-8} (ng*h/mL)	C_{trough} (ng/mL)
10 mg bid						
Day 1	6	372 (38.6)	2.01 [0.92, 4.78]	1710 (29.4)	1730 (28.9)	–
Day 8	5	–	–	–	–	109 (61.1)
Day 15	6	–	–	–	–	116 (39.1)
30 mg bid						
Day 29	6	1040 (21.7)	3.05 [0.25, 4.87]	4700 (18.4)	4770 (18.1)	–
Day 36	5	–	–	–	–	340 (53.6)
Day 43	6	–	–	–	–	333 (60.1)
70 mg bid						
Day 57	6	2440 (31.0)	1.93 [0.97, 4.95]	10300 (35.3)	11800 (21.6)	–
Day 64	6	–	–	–	–	872 (42.7)
Day 71	6	–	–	–	–	916 (50.1)
Day 84	5	–	–	–	–	870 (51.3)

Table 6: PK parameters summary (Study 2201-Part 2)

Compound: CDZ173, Analyte: CDZ173, Matrix: PLASMA						
Age group	Visit	Statistic	AUClast (h*ng/mL)	AUC0-8h (h*ng/mL)	Cmax (ng/mL)	Tmax (h)
<18 years	DAY1	n	7	7	7	7
		Mean (SD)	10300 (3020)	10500 (2890)	2130 (584)	
		CV% mean	29.4	27.4	27.4	
		Geo-mean	9890	10200	2070	
		CV% geo-mean	31.1	28.4	25.4	
		Median	9730	9980	1840	3.00
		[Min; Max]	[6190; 14800]	[6790; 14800]	[1680; 3270]	[1.00; 5.05]
≥18 years	DAY1	n	12	11	12	12
		Mean (SD)	10500 (2790)	10900 (2790)	2160 (597)	
		CV% mean	26.6	25.6	27.6	
		Geo-mean	10100	10600	2090	
		CV% geo-mean	26.9	26.3	26.6	
		Median	9420	9850	1940	1.16
		[Min; Max]	[6840; 15500]	[6840; 15800]	[1420; 3220]	[0.92; 7.78]
Overall	DAY1	n	19	18	19	19
		Mean (SD)	10400 (2800)	10800 (2750)	2150 (576)	
		CV% mean	26.9	25.5	26.8	
		Geo-mean	10100	10400	2080	
		CV% geo-mean	27.6	26.3	25.4	
		Median	9450	9910	1870	2.87
		[Min; Max]	[6190; 15500]	[6790; 15800]	[1420; 3270]	[0.92; 7.78]

CV% = coefficient of variation(%) = (sd/mean)*100; CV% geo-mean = sqrt (exp(variance for log transformed data)-1) * 100

Population PK modelling and simulation

Additional to formal PK investigations in healthy volunteers and in patients with APDS, the applicant has performed a population PK analysis (PPK) in order to describe the PK and identify sources of variability of Leniolisib in healthy volunteers [PPK1]. Then a new PPK was performed with PK data from patients with APDS [PPK2].

PPK1 (healthy volunteers)

PPK1 included PK data from study 2101 with 118 participants and 2803 observations (≈24 observations/subject).

Final PPK1 model consisted of a two-compartment model with first order absorption with a lag time and first order elimination from the central compartment parameterized with CL/F, Vc/F, Q/F, Vp/F, ka and ALAG and IIV terms on all PK parameters. The ITS followed by the IMP method with a full covariance matrix was used for parameter estimation to obtain a successful covariance step procedure. Final PK parameter estimates are provided in Table 7, GOF and pcVPC in Figure 3 and Figure 4 respectively.

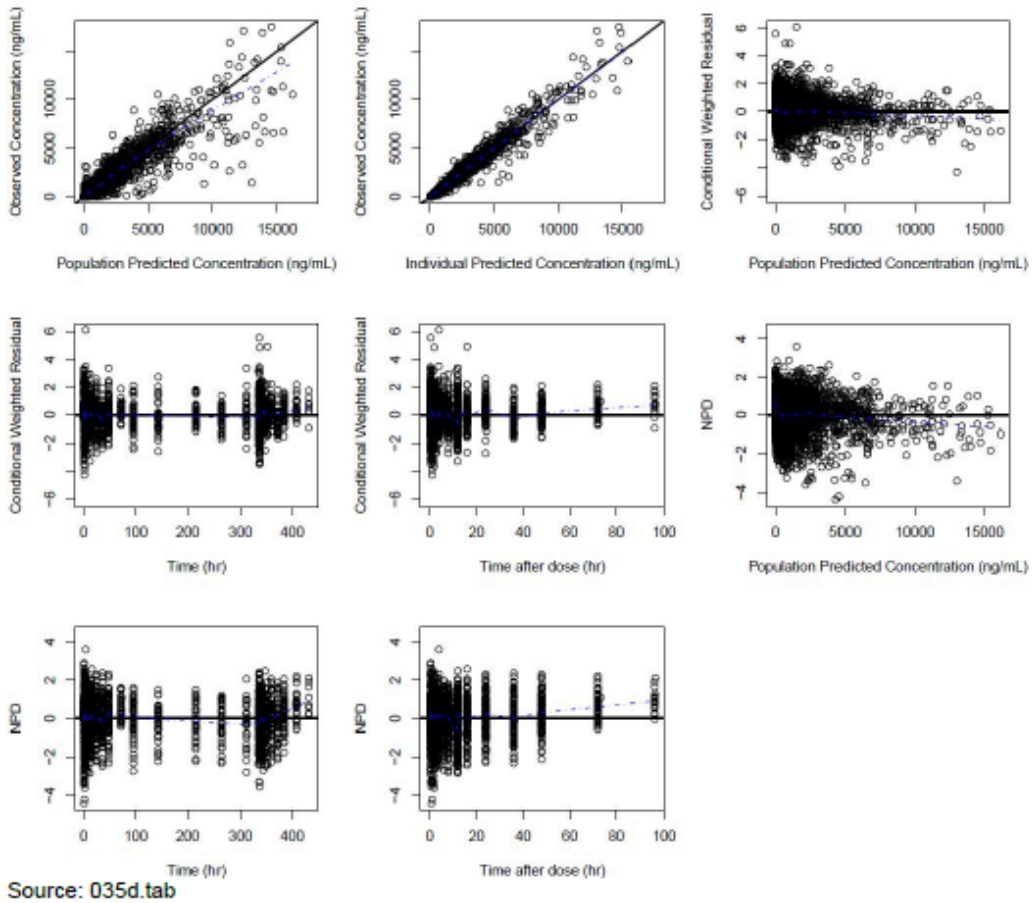
Overall PK parameters were estimated with a good precision for fixed effects (<30%) and random effects (RSE < 50%). For a typical subject, the estimated typical ka, CL/F, Vc/F, Vp/F and ALAG were 3.97 h^{-1}, 4.01 L/h, 21.8 L, 5.1 L and 0.242 h, with associated high IIV of 101%, 30.5%, 14.9%, 44.8% and 24.7%. CL/F and Vc/F were highly correlated 0.793. RUV was estimated at 17.3% for the proportional component and 3.96 ng/mL for the additive term. The shrinkages of individual random effects were estimated as 3% for CL/F, 17% for Vc/F, 56% for Q/F, 39% for Vp/F, 11% for Ka fasted, 55% for Ka fed, 24% for lag-time fasted and 66% for lag-time fasted. The eps-shrinkage was estimated at 16%.

Weight was found to have an effect on both Vc/F and Vp/F, Vc/F (as $(WT/70)^{0.662}$ for Vc/F and Vp/F). For the range of weights in the present analysis population (50-105 kg), Vc/F ranged from 17.4-28.5 L and Vp/F ranged from 4.08-6.67 L which was 20% lower to 31% higher compared to the typical value for a 70-kg subject. Leniolisib CL/F was 37% higher (95% CI: 10% to 65% higher) for Japanese subjects compared to non-Japanese subjects in the analysis population. Finally fed status was found to have a significant effect on both ka and ALAG.

Table 7: Final PPK1 model Parameter estimates of Leniolisib

Parameter* [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
CL/F [L/hr]	4.01	3.06	3.77-4.26	
V_c/F [L]	21.8	2.14	20.8-22.7	
Q/F [L/hr]	0.510	11.0	0.400-0.620	
V_p/F [L]	5.10	5.30	4.57-5.63	
Ka fasted [hr^{-1}]	3.97	9.44	3.24-4.71	
ALAG fasted [hr]	0.242	2.21	0.231-0.252	
Ka fed [hr^{-1}]	0.393	15.6	0.273-0.513	
ALAG fed [hr]	0.729	28.4	0.323-1.13	
Ka~Dosetime (Evening dose Part 3)	0.0643	19.1	0.0402-0.0884	
V_c/F&V_p/F~WT	0.662	12.5	0.500-0.824	
CL/F~Japanese	1.37	10.2	1.10-1.65	
Inter-individual variability				**CV%* or R**
ω^2_{CL}	0.0930	13.1	0.0691-0.117	30.5%
Covar $\eta_{CL, \eta Vc}$	0.0361	17.7	0.0236-0.0486	R=0.793
ω^2_{Vc}	0.0223	17.9	0.0145-0.0301	14.9%
Covar $\eta_{CL, \eta Q}$	-0.00516	781	-0.0841-0.0738	R=-0.0339
Covar $\eta_{Vc, \eta Q}$	-0.0126	142	-0.0477-0.0225	R=-0.169
ω^2_{Q}	0.249	51.8	-0.00384-0.502	53.2%
Covar $\eta_{CL, \eta Vp}$	0.0268	107	-0.0295-0.0831	R=0.205
Covar $\eta_{Vc, \eta Vp}$	0.0126	119	-0.0168-0.0420	R=0.197
Covar $\eta_{Q, \eta Vp}$	0.156	37.6	0.0411-0.271	R=0.731
ω^2_{Vp}	0.183	29.5	0.0774-0.289	44.8%
Covar $\eta_{CL, \eta Ka\ fasted}$	0.00423	797	-0.0618-0.0703	R=0.0166
Covar $\eta_{Vc, \eta Ka\ fasted}$	-0.0133	181	-0.0605-0.0339	R=-0.107
Covar $\eta_{Q, \eta Ka\ fasted}$	0.0196	474	-0.162-0.202	R=0.0470
Covar $\eta_{Vp, \eta Ka\ fasted}$	-0.0336	200	-0.165-0.0981	R=-0.0939
$\omega^2_{Ka\ fasted}$	0.699	18.2	0.450-0.948	101%
Covar $\eta_{CL, \eta ALAG\ fasted}$	0.00395	222	-0.0132-0.0211	R=0.0525
Covar $\eta_{Vc, \eta ALAG\ fasted}$	0.00866	66.1	-0.00255-0.0199	R=0.235
Covar $\eta_{Q, \eta ALAG\ fasted}$	-0.0142	312	-0.101-0.0726	R=-0.115
Covar $\eta_{Vp, \eta ALAG\ fasted}$	0.00459	542	-0.0442-0.0534	R=0.0435
Covar $\eta_{Ka\ fasted, \eta ALAG\ fasted}$	-0.0726	44.1	-0.135--0.00988	R=-0.352
$\omega^2_{ALAG\ fasted}$	0.0609	44.8	0.00739-0.114	24.7%
Covar $\eta_{CL, \eta Ka\ fed}$	0.0597	138	-0.102-0.222	R=0.469
Covar $\eta_{Vc, \eta Ka\ fed}$	0.0233	412	-0.165-0.212	R=0.374
Covar $\eta_{Q, \eta Ka\ fed}$	0.0860	116	-0.110-0.282	R=0.413
Covar $\eta_{Vp, \eta Ka\ fed}$	0.0309	293	-0.147-0.208	R=0.173
Covar $\eta_{Ka\ fasted, \eta Ka\ fed}$	0.0313	569	-0.318-0.380	R=0.0897
Covar $\eta_{ALAG\ fasted, \eta Ka\ fed}$	-0.0309	340	-0.237-0.175	R=-0.300
$\omega^2_{Ka\ fed}$	0.174	114	-0.216-0.564	43.6%
Covar $\eta_{CL, \eta ALAG\ fed}$	0.0607	138	-0.104-0.225	R=0.250
Covar $\eta_{Vc, \eta ALAG\ fed}$	0.0445	179	-0.112-0.201	R=0.374
Covar $\eta_{Q, \eta ALAG\ fed}$	0.0628	530	-0.590-0.715	R=0.158
Covar $\eta_{Vp, \eta ALAG\ fed}$	0.172	108	-0.191-0.535	R=0.504
Covar $\eta_{Ka\ fasted, \eta ALAG\ fed}$	-0.00728	4660	-0.672-0.657	R=-0.0109
Covar $\eta_{ALAG\ fasted, \eta ALAG\ fed}$	-0.00659	2350	-0.310-0.297	R=-0.0335
Covar $\eta_{Ka\ fed, \eta ALAG\ fed}$	-0.0736	276	-0.471-0.324	R=-0.221
$\omega^2_{ALAG\ fed}$	0.636	61.9	-0.136-1.41	94.3%
Residual variability				**CV% or SD**
σ^2_{prop}	0.0299	7.32	0.0256-0.0342	17.3%
σ^2_{add}	15.7	28.8	6.84-24.6	SD=3.96

Abbreviations: %RSE=percent relative standard error of the estimate (SE/parameter estimate*100); 95% CI=95%



Source: 035d.tab
Blue dashed line: Local regression (Loess) smoothing line

Figure 3: Goodness-of-fit of the final population PK model for Leniolisib

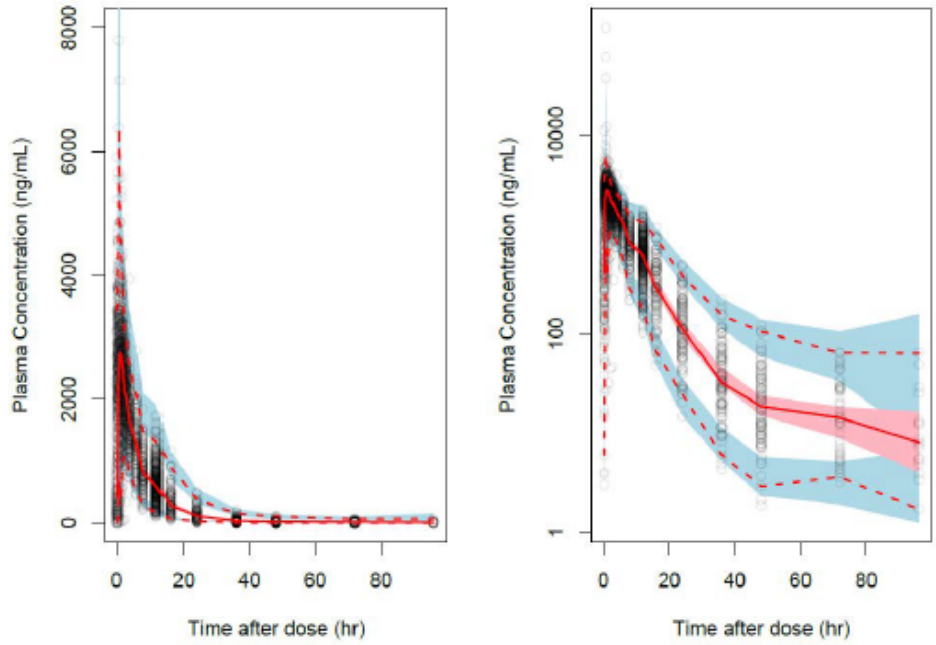


Figure 4: pcVPCs of the final population PK model for Leniolisib

PPK2 (APDS patients)

PK data from patients from Study 2201 Part 1 (N=6) were fitted using a one compartment model and median PK parameter estimates for CL/F, Vc/F and ka were 4.18 L/h, 28.3 L and 3.47 h^{-1}, suggesting that PK is similar between healthy volunteers and patients. However, model performance was not reported, so it is not clear if model assumptions adequately predict PK steady state parameters.

Specials Populations

- Renal impairment

No formal dedicated PK study was performed in subjects with impaired renal function compared to matched-control healthy subjects to investigate the effect of different degree of renal impairment (RI) on the PK of leniolisib.

- Hepatic impairment

No formal dedicated PK study was performed in subjects with impaired hepatic function compared to matched-control healthy subjects to investigate the effect of different degree of hepatic impairment (HI) on the PK of leniolisib.

- Race/ethnicity

No formal PK study investigating the effect of race/ethnicity on leniolisib PK was performed. Based on PPK1, Japanese subjects which account for 5% of the entire PK dataset have a 37% increase in CL/F compared to non-Japanese subjects.

- Gender/Age

Based on PPK1, gender or age were not found to have a significant effect on leniolisib PK.

- Weight

No formal investigations with regard to weight have been performed. Based on PPK1, weight was found to have an effect on both Vc/F and Vp/F. For the range of weights in the present analysis population (50-105 kg), Vc/F and Vp/F ranged from 20% lower to 31% higher compared to a 70-kg individual. Information on patients weighting less than 45 kg and also on how to manage patients reaching a weight below 45 kg during treatment (but above 45 kg at the beginning) has been provided during the review. The simulations indicate that adolescents or children <45 kg receiving 70 mg BID would be expected to have higher exposure compared to the reference group ≥45 kg and would likely require lower doses to achieve comparable exposures. Since no appropriate lower-strength formulation is yet available to allow dose adaptation in this subgroup is missing, dosing for patients weighting less than 45 kg will be addressed in a separate procedure during the product life cycle.

- Elderly

There are no data on patients aged 65 years and older.

- Children

PopPK analysis of data from healthy participants in Study 2101 did not determine age to be a significant predictor of leniolisib PK and did not include it as a covariate effect in the final model. The PopPK analysis dataset included 118 participants with median [range] age of 31 [20, 45] years.

Leniolisib PK is similar between adolescent (12 years and up) and adult patients with geometric mean Cmax and AUC0-8h of 2070 vs 2090 ng/mL and 10200 vs 10600 ng.h/mL, respectively, following a 70 mg dose (Study 2201 – Part 2 Day 1).

Pharmacokinetic interaction studies

In vitro

- **Leniolisib (CDZ173) as a CYP450 inhibitor**

The ability of leniolisib to inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 was assessed in pooled human liver microsomes. No reversible inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2E1, and CYP3A4/5 was observed at concentration of leniolisib lower than 100µ. However, leniolisib showed a reversible inhibition for CYP2C9, CYP2C19, CYP2D6 and CYP2C8 enzymes. The determined unbound Ki values were 29 µM, 29 µM, 36 µM and 23 µM for CYP2C9, CYP2C19, CYP2D6 and CYP2C8, respectively.

A time-dependent (irreversible) inhibition was observed on CYP1A2 (KI,u= 28µM), and not on CYP2C8, CYP2B6, CYP2C9, CYP2D6, and CYP3A4/5.

According to the *In Vitro-In Vivo* Extrapolation (IVIVE process), a clinically relevant drug-drug interactions driven by the inhibition of CYP2D6 by leniolisib at therapeutic level is unlikely since its Ki values is above the worst concentration estimated at systemic level, i.e. $50 \times C_{max,u}$= 22.45µM. Likewise, leniolisib acts as a reversible inhibitor on CYP2C9 and CYP2C19 with ki= 29µM and as a time-dependant inhibitor on CYP1A2 with a KI= 28 µM. Theoretically, since these values of ki and KI are above the systemic cut-off value, no clinically relevant DDI are expected. However, the Applicant has calculated R2 value (from FDA Guideline) for CYP1A2 and R2> 1.25 translating a risk of meaningful DDI in the clinical setting.

- **Leniolisib (CDZ173) as a CYP450 inducer**

In vitro activation of pregnane X-receptor (PXR) and aryl hydrocarbon receptor (AhR) by leniolisib was evaluated using human hepatoma cell lines DPX-2 and CYP1A2-DRE, respectively. Significant activation of PXR was observed in the presence of ≥ 25µM leniolisib, indicating possible PXR-mediated induction of CYP3A4 *in vivo* at sufficiently high concentrations, such as at intestinal level where the worst estimated concentration is 62.15µM. No significant activation of AhR at leniolisib concentrations ≤100 µM was observed. Hence, AhR-mediated induction of CYP1A2 is not anticipated.

The potential of leniolisib to induce CYP enzymes (activity and mRNA) was assessed in human hepatocytes of four individual donors after 48h of treatment. The cell viability, with respect to the vehicle control was acceptable (≥ 75%) for all treatments with CDZ173 and the positive controls (RIF, PB, BNF) in Livers 1, 2 and 4. (Study 1300388). In Liver 3, the viability was below the threshold value with the highest CDZ173 concentration of 75 µM and it was not considered. Leniolisib was incubated with primary human hepatocyte cultures at concentrations up to 75 µM and induction of mRNA was evaluated relative to vehicle and positive control while enzyme activity was evaluated from metabolism of CYP-selective probe substrates. Concentration-dependent induction of CYP2B6, CYP2C9, and CYP3A4 mRNA and activity was observed, but there was no significant induction (<20% of maximal positive control induction) for CYP1A2 mRNA or activity.

However, a 48-hour incubation was tested instead of 72 hours to avoid potential inhibition of cytochrome CYP1A2 activity and subsequent masking of induction, as leniolisib has been shown to be a time-dependent inhibitor of CYP1A2.

- **Leniolisib as an *in vitro* inhibitor of UGT and (SULT)-mediated metabolism of ethinylestradiol**

The effect of leniolisib on the uridine diphosphate glucuronosyltransferase (UGT) and sulfotransferase (SULT)-mediated metabolism of ethinylestradiol was tested *in vitro* using pooled human liver microsomes (HLM) and human liver cytosol (for both, a pool from 150 individual donors was used), respectively. Leniolisib showed a concentration-dependent inhibition of UGT1A1-mediated

ethinylestradiol glucuronidation (IC50 = 8.49 µM, corresponding to an unbound IC50 of 7.24 µM) in pooled human liver microsomes (HLM), while no inhibition effects of leniolisib were observed on sulfation of ethinylestradiol mainly by SULT1E1 in human liver cytosol. Therefore, since IC50= 7,24µM of leniolisib for UGT1A1 is lower than the cut-off value of $50\times C_{max,u}$= 22.45µM. The applicant has used the basic model for inhibition by parent drug to investigate the potential clinical DDI of leniolisib. The results ([I] / Ki = 0.062) confirmed that a clinical DDI cannot be ruled out.

Interaction with transporters

Leniolisib is a substrate of P-gp and BCRP based on the *in vitro* study, therefore co-administration of P-gp and BCRP inhibitors or inducers may change its disposition. The clinical impact on leniolisib exposure resulting from P-gp strong inhibitor co-administration has been assessed in a clinical DDI study with repeated itraconazole and quinidine on the single-dose PK of oral leniolisib in healthy volunteers and it is concluded that leniolisib is not a sensible substrate of P-gp transporter.

In vitro study using in cryopreserved hepatocyte suspensions to investigate the involvement of several candidate transporter families (OCT, OAT, OATP) has indicate that uptake of CDZ173 into human hepatocytes occurs, most likely, by a passive permeation process modulated by one or several solute-carrier systems and is not a substrate for OCT, OAT or OATP.

The potential of CDZ173 to inhibit efflux transporters was assessed using recombinant MDCKII or LLC-PK1 cells overexpressing BCRP and P-gp, respectively. Although leniolisib was found to not inhibit P-gp up to the highest concentration investigated 200 µM, leniolisib inhibits BCRP with an IC50 = 18.9 µM, which is lower than the worst estimated concentrations at intestinal level (i.e. 62.15µM). It is therefore concluded that leniolisib may lead to clinically relevant interactions with drugs substrates of BCRP such as rosuvastatin, pitavastatin, and letermovir.

The ability for leniolisib to inhibit uptake transporters was also assessed *in vitro* using recombinant HEK293 cells overexpressing OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K and recombinant Sf9 (inside-out) vesicles overexpressing the human bile salt export pump (BSEP, ABCB11) protein. Leniolisib was found to inhibit *in vitro* OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, and BSEP.

The applicant considered that clinically relevant interactions at the therapeutic dose of leniolisib (70 mg twice daily) could not be excluded for inhibition of BCRP, OATP1B1 and OATP1B3. This is supported by the CHMP. However, clinically relevant interactions at the therapeutic dose of leniolisib (70 mg twice daily) related to the inhibition of OAT3 (IC50 15.2 ± 2.0µM; Ki 10 µM), MATE1 (IC50 =6.70 µM; Ki =6.70), MATE2K (IC50 = 0.85 µM; ki= 0.85 µM) and OCT2 (IC50 =3.5 µM, Ki=3.4 µM) could not be excluded, since IC50 is lower than the relevant concentration estimated i.e.50×Cmax,ss,unbound which represent 22.45µM

In Silico

Study 1500108:

A modelling software was used to predict the DDI effect of oral CDZ173 (CYP3A4 inducer; 70 and 140 mg BID for 20 days) on the PK of the prototypical CYP3A4 substrate midazolam (single 2 mg oral dose on day 15 of the CDZ173 dosing; steady-state of CDZ173 PK).

Data from this Model show that the expected induction effect of CDZ173 at 70 mg BID on midazolam was small when CYP3A4 induction parameters derived from enzyme activity data were used: Cmax and AUC of midazolam decreased from 100% in the absence of CDZ173 to 92% and 91%, respectively, in its presence and this effect is contained, despite being stronger, when using induction parameters

derived from data CYP3A4 mRNA (decrease of Cmax and AUC from 100% to 77% and 76%, respectively).

Study 1600092:

A PBPK model was used to predict the effect of moderate CYP3A inhibitors and strong/moderate CYP3A4 inducers on leniolisib PK. The PBPK model was established using a mixed approach combining physicochemical and *in vitro* data together with PK parameters derived from noncompartmental and PopPK analysis of data from clinical studies and itraconazole DDI study. The final PBPK model was optimized for the fraction metabolized by CYP3A4 (fmCYP3A4, 60%) based on clinical observations in the itraconazole DDI study. Next, the model was verified by comparing model-predicted single- and multiple-dose PK of leniolisib against observed clinical data. Finally, once the model was verified, the model was used to predict the effects of moderate CYP3A inhibitors and strong/moderate CYP3A4 inducers on leniolisib PK.

Simulations with the PBPK model were performed to predict how leniolisib PK will be affected by coadministration with erythromycin (a moderate CYP3A4 inhibitor), rifampicin (a strong CYP3A4 inducer), and efavirenz (a moderate CYP3A4 inducer).

The model predicted increased leniolisib AUC0-12 and Cmax in the presence of erythromycin (approximately 60% and 30% increase, respectively) and decreased leniolisib AUC0-12 and Cmax in the presence of rifampicin (approximately 80% and 50% decrease, respectively) and efavirenz (approximately 60% and 30% decrease, respectively).

In vivo

Study 2102:

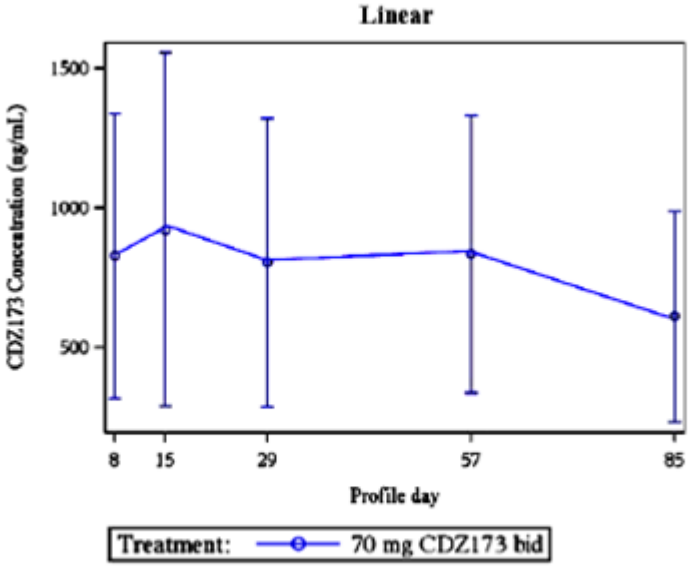
The results showed that coadministration with itraconazole (a strong dual inhibitor of CYP3A4 and P-gp) increased leniolisib AUC0-∞ by approximately 2-fold and C_{max} by 25%, while coadministration with quinidine (a strong dual inhibitor of CYP2D6 and P-gp) did not affect leniolisib exposure.

Study 2104:

Coadministration with leniolisib at steady state increased ethinylestradiol exposure (AUC and Cmax) by approximately 30% relative to when oral contraceptive (ethinylestradiol/levonorgestrel) was given alone, but had no effect on levonorgestrel exposure.

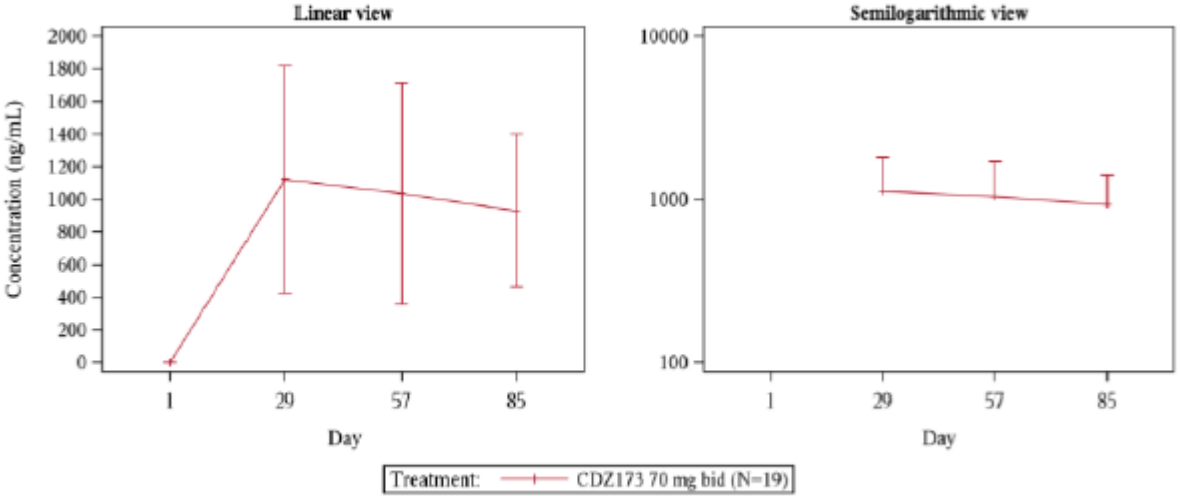
CYP3A4 autoinduction

In vivo, no substantial CYP3A4 autoinduction was observed in healthy participants receiving leniolisib at doses up to 140 mg twice daily for 14 days (Study 2101; Figure 5).



Source: 5.3.5.4 CSR Study 2203, Figure 11-10.
bid=twice daily; SD=standard deviation.

Figure 5: Mean (SD) Leniolisib Plasma Trough Concentration-Time Profile With Twice Daily Dosing of Leniolisib 70 mg in Patients with Primary Sjögren's Syndrome (Study 2203)



Source: 5.3.5.1 CSR Study 2201 Part 2, Figure 14.2-1.3.1b.
APDS=activated PI3Kδ syndrome; bid=twice daily; SD=standard deviation.

Figure 6: Mean (SD) Leniolisib Plasma Trough Concentration-Time Profile Following Twice Daily Dosing of 70 mg Leniolisib Capsule in Patients With APDS (Study 2201, Part 2)

Exposure relevant for safety evaluation

A C-QTc analysis was performed to characterize the relationship between ΔQTc with leniolisib plasma concentration and predicted concentration-related QTc interval prolongation with a 90% CI in healthy subjects.

The total dataset consisted of 4617 QT interval measurements with time matched leniolisib concentrations from 188 participants of study **2101**.

A linear mixed-effects model adequately quantified the relationship between plasma concentrations of leniolisib and ΔQTc (Figure 7). The model included baseline QTc, placebo subject, and time point

effects on its intercept term, and estimated a negative intercept (-0.700 msec) and drug effect slope (-0.263 msec/µg/mL), indicating no treatment-related QTc prolongation. Predicted mean (90%CI) ΔΔQTc at various concentrations are presented in **Table 8**.

The model-predicted 90% CI upper bound placebo-corrected ΔQTc was <3 msec at all concentration levels (from 0 to 16000 ng/mL), well below a 10 msec threshold for clinical relevance.

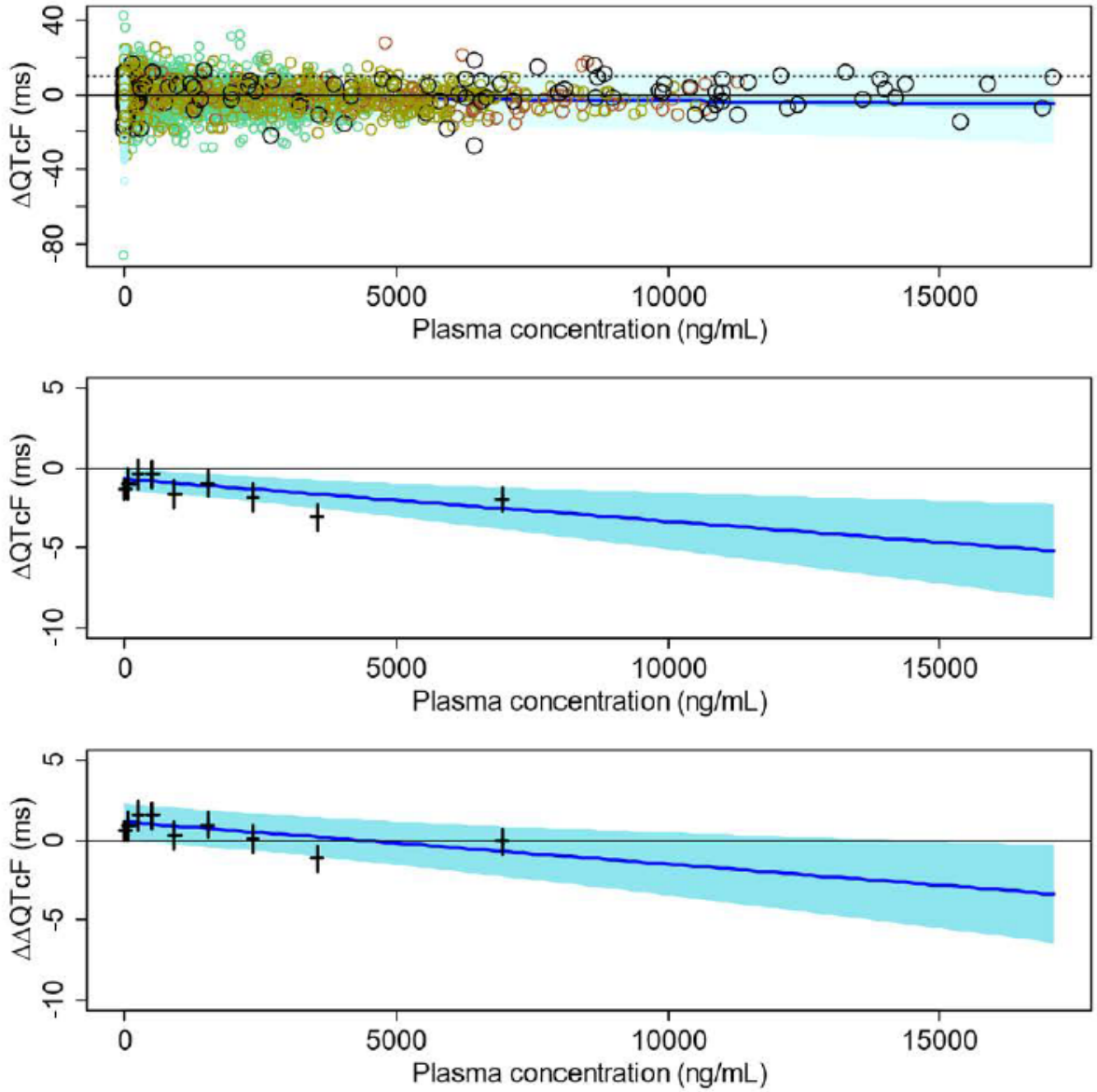


Figure 7: Model predicted and observed ΔQTcF and ΔΔQTcF vs leniolisib plasma concentration

Table 8: Predicted mean (90% CI) ΔΔQTc at various concentrations

Concentration	Predicted ΔΔQTcF (ms)		Predicted ΔΔQTcP (ms)	
(ng/mL)	Mean	90% CI	Mean	90% CI
0	1.136	(-0.017, 2.289)	0.998	(-0.219, 2.215)
2000	0.611	(-0.555, 1.776)	0.170	(-1.065, 1.405)
4000	0.085	(-1.191, 1.361)	-0.657	(-2.009, 0.695)
6000	-0.440	(-1.903, 1.022)	-1.485	(-3.030, 0.060)
8000	-0.966	(-2.666, 0.735)	-2.312	(-4.102, -0.522)
10000	-1.491	(-3.462, 0.480)	-3.140	(-5.208, -1.072)
12000	-2.016	(-4.279, 0.247)	-3.967	(-6.335, -1.599)
14000	-2.542	(-5.110, 0.027)	-4.795	(-7.477, -2.112)
16000	-3.067	(-5.951, -0.184)	-5.622	(-8.629, -2.615)

Relationship between plasma concentration and response

Based on the Emax model developed following the dose finding study 2201 Part 1, treatment with leniolisib 10, 30 and 70 mg BID is expected to result in time-averaged pAkt inhibition in B cells of approximately 38%, 63%, and 78%, respectively, and time-averaged pAkt inhibition at 50% (ED50), 70% (ED70), and 90% (ED90) of Emax are expected with leniolisib doses of 15, 35, and 136 mg twice daily. Therefore the selected dose of 70 mg BID increased the time-averaged %pAkt inhibition by 25% compared to the 30 mg BID dose.

2.6.2.2. Pharmacodynamics

Mechanism of action

Leniolisib is a PI3Kδ inhibitor targeting the catalytic p110δ subunit of PI3Kδ, thereby inhibiting hyperactivated PI3K pathway. APDS can be observed either due gain of function mutation in the gene coding for the catalytic p110 δ subunit (APDS1) or due to a loss of function mutation in the gene coding for the regulatory subunit p85α (APDS2).

Primary and Secondary pharmacology

Primary pharmacology

The effect of leniolisib was assessed through pAkt inhibition which is usual for measuring PI3K inhibitors effect. In healthy participant (study 2101), doses ranged from 10 to 400 mg as single administration in part 1 and from 20 mg to 140 mg BID as multiple administration in part 3. In this Part 3, inhibition peaked approximately 1 hour post dose and was the highest at 70 mg and 140 mg BID. Although the dose of 40 mg BID could also achieve a high pAkt inhibition, this effect seems to lower after 6 hours while the inhibition was sustained for 70 and 140 mg BID.

In patients with APDS, dose ranged from 10 mg to 70 mg, including thus the intended dose. Although data suggest a similar inhibition of 30 mg and 70 mg BID dose regarding the delay and the maximum effect, the effect appears more sustained with the dose of 70 mg BID. To evaluate further PI3K inhibition, phosphorylation of S6 which is a downstream target of mTOR was assessed in *ex vivo*

stimulated and unstimulated B cells, endogenous phosphorylation levels of Akt and S6 in B and T cells was assessed in whole blood. Results for pS6 in *ex vivo* stimulated and unstimulated B cells are consistent with pAkt results.

Overall, these results support the choice of 70 mg BID for part 2 of study 2201.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of leniolisib have been studied in both healthy subjects and APDS patients (adults and adolescents).

Methods

PK methods were appropriately developed and validated and comply with acceptance criteria of the bioanalytical method validation EMA Guideline.

Absorption

After a single 400 mg oral administration of leniolisib to healthy subjects and based on ^{19}F-NMR / LC-MS analysis (mass balance Study R1500425 as part of study 2101 Part 1), the oral absorption fraction of leniolisib could be approximated around 62% (total urinary excretion 23% plus excretion of metabolites in faeces 39%) out of the total recovery of 65.5% after 120h post dose.

Due to the apparent complete renal excretion after the first 24 hours, it could be assumed that the unrecovered drug related material (around 35%) is likely to be excreted in faeces after 120h, suggesting that oral absorption could be estimated to ≥85%. Such finding of incomplete faeces excretion at 120 h appears to be confirmed by results from the second mass balance 14C-study where a complete recovery (92.5%) at 168h postdose was observed with 67.0 and 25.5% of the dose excreted in faeces and urine, respectively. It is important to note that the renal fraction was comparable to the 23% fraction observed in the ^{19}F-NMR analysis after 120h. Unfortunately, monitoring the parent compound and metabolites in the excreta of this study was not performed but this is partially covered by results from the first study.

Overall, even if provided data do not formally support a high degree (≥85%) of absorption in humans (while plausible), the conclusion that leniolisib is readily absorbed is agreed.

Based on *in vitro* investigations, using a Caco-2 cell assay leniolisib exhibits a high permeability for concentrations greater or equal to 40 µM, even in the presence of efflux transporter activity.

Finally, the drug substance has pH-dependent solubility with highest solubility observed in water at pH 3. In addition, the drug amount (and comparison to the highest 70 mg single dose) completely dissolved in 250 ml of buffers is unknown or could not be found. Therefore, given the lack of *in vivo* data demonstrating formally a fraction absorbed ≥ 85%, the applicant's proposal that leniolisib can be classified as a BCS class II compound was not fully agreed since evidence from *in vitro* high permeability is not sufficient. However, since no claim regarding BCS classification was made in the SmPC, the issue was not further pursued.

Regarding bioavailability/bioequivalence, the 70 mg capsule used during the clinical development is considered bioequivalent to the 70 mg capsule of leniolisib drug product.

Influence of food

In a placebo controlled, ascending single and multiple dose study in healthy participants, leniolisib was rapidly absorbed in the fasted state, with median time to maximum plasma concentration (tmax) at about 1 hour post dose. Tmax appeared independent of dose and was not altered after multiple oral doses.

Co-administration of a single 70 mg dose of leniolisib with a high fat meal delayed the rate of absorption (T_{max}) by 3 hours (0.64 h [fasting] to 3.51 h [fed]) and decreased C_{max} on average by 41% but not the extent of absorption (area under the curve [AUC]) Therefore, the clinical impact of food is expected to be minor and consequently the proposed recommendation to administer leniolisib irrespective of food conditions (with or without food) is supported. This is considered adequately presented in SmPC section 4.2 and 5.2.

Influence of gastric modifier

No dedicated clinical study evaluating the effects of acid-reducing agents on leniolisib PK has been conducted. However, a retrospective analysis of the interim data from Phase 2/3 Study 2201E1 showed that concomitant use of PPIs did not have a marked effect on leniolisib exposure requiring dose adjustment. For patients using antacids chronically, the antacid should be taken either 2 hours before or 2 hours after leniolisib administration (see SmPC sections 4.2, 4.4 and 4.5 - Gastric acid reducing agents).

Distribution

In vitro investigation have shown that leniolisib has a low-to-moderate volume of distribution. In humans, the *in vitro* blood/plasma ratio is 0.643. This is considered adequately presented in SmPC section 5.2.

Metabolism

Metabolite profiling is considered appropriate.

Elimination

The biliary route could be considered as the predominant route of elimination: leniolisib and its metabolites are predominantly excreted through the faeces (67.0%) followed by the urine (25.5%). Renal excretion of parent drug is a minor elimination route for leniolisib. This is acknowledged. No dosing modifications are recommended for patients with renal impairment, which is appropriately reflected in the SmPC section 4.2.

Consequence of possible genetic polymorphism

No formal investigations of CYP1A2 or CYP2D6 genetic polymorphism on the PKs of leniolisib were performed. However, clinical DDI study with quinidine (a strong CYP2D6 and P-gp inhibitor) indicate that leniolisib exposure was unchanged with quinidine co-administration. Thus, leniolisib does not appear to be a substrate of CYP2D6. Hence, leniolisib may be coadministered with CYP2D6 and P-gp inhibitors without dose adjustment.

Besides, given that leniolisib metabolism is mediated predominantly by the CYP3A4 enzyme and to a lesser extent by CYP1A2, the issue was not pursued.

Population PK modelling

The applicant performed a PPK modelling to describe the PK data of leniolisib in healthy volunteers from study 2101 (PPK1). Another PPK model was developed for APDS patients from study 2201 Part 1 (PPK2), and its extension phase 2201E1. However, model performance of PPK2 was not reported.

Results from these models (PPK1 and PPK2) are only descriptive. The initial MA indication only includes patients weighting 45 kg and up, as represented in the model – see Special Populations section below.

The initial MA indication will not include adolescents below 45 kg, since an appropriate formulation for this population is not yet available. This has been received during the review and is acceptable.

Special Populations

Renal impairment

Based on PPK1, any information related to individual CLcr (creatine clearance) was not reported and then no tested as a covariate of interest.

Based on the mass balance study (^{19}F-NMR - Study 2101, Report 1500425), unchanged leniolisib recovered in urine was 6.32% of the dose. Renal clearance is a minor pathway in leniolisib elimination. Furthermore, renal impairment is rarely reported in patients with APDS. In the SmPC section, it is stated that leniolisib has not been studied in patient with renal impairment and that no dosing modifications are recommended, this is acceptable.

Hepatic impairment

Based on PPK1, any information related to individual hepatic function biomarker (as ALAT, ASAT, albumin…) was not reported and then no tested as a covariate of interest.

Leniolisib is approximately 90% eliminated through metabolism (unchanged leniolisib recovered less than 10%, 19F-NMR), therefore it is agreed that in patients with APDS with moderate to severe hepatic impairment leniolisib plasma concentration would exceed those observed on dosing with 140 mg twice daily. As such, use of leniolisib in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C) is not recommended (See SmPC section 4.2).

Children

Comparison of exposure in adults vs. adolescents

The indication has been restricted to patients aged ≥12 years and weighing ≥45 kg, due to the lack of clinical and pharmacokinetic (PK) data below these cut-offs, as well as the potential impact of body weight on the PK of leniolisib, which may consequently affect the dosing requirements in patients weighing <45 kg.

Using the proposed dose of 70 mg, the observed PK parameter exposures (although AUC_{0}–8h at Day 1 is only partially informative) are similar between adolescents and adults. Therefore, the same dose (70 mg BID), shown to be efficacious in adults, was considered appropriate in adolescents ≥45 kg.

It is considered that the effect on exposure in adolescents aged 12–18 years is primarily driven by body weight rather than age, as supported by the Pop-PK analysis showing an increase of Vc/F and Vp/F with body weight.

The indication reads as follows: Joenja is indicated for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more. Indeed, the indication has been restricted to patients aged ≥12 years and weighing ≥45 kg, due to the lack of clinical and PK data below these cut-offs, the absence of posology recommendations for patients weighing <45 kg, and the unavailability of a lower-strength formulation to allow dose adjustment.

Consequently, patients aged ≥12 years weighing less than 45 kg are not covered by the current indication. In the absence of data to support an appropriate posology in this subgroup and given that no lower-strength formulation is available, no dosing recommendation can be provided at this stage. In

order to further inform dosing recommendations in adolescents ≥12 years but weighing <45 kg, the applicant provided an updated Pop-PK model in this subgroup during the MAA, including supportive data from Study LE 3301 in paediatric subjects aged 4–11 years (n=21). Simulations for <45 kg, comparing exposures to patients ≥45 kg at 70 mg BID, were provided.

The simulations indicate that adolescents or children <45 kg receiving 70 mg BID would be expected to have higher exposure compared to the reference group ≥45 kg and would likely require lower doses to achieve comparable exposures. However, no appropriate lower-strength formulation is available to allow dose adaptation in this subgroup, and these patients are not covered by the current indication. Therefore, no SmPC modification is warranted at this time. This is considered acceptable.

Pharmacodynamics

The effect of leniolisib was assessed *Ex vivo* through pAkt inhibition, both in healthy subjects and in patients with APDS. A similar inhibitory effect was seen in healthy patients and in patients with APDS. Within the explored dose range, higher leniolisib plasma concentrations were generally associated with higher reduction of pAkt-positive B cells and higher doses were associated with a slightly higher peak reduction as well as more sustained reduction. Treatment with leniolisib 70 mg twice a day at steady state is estimated to produce time-averaged reduction of pAkt-positive B cells by approximately 80%. This is considered adequately presented in SmPC section 5.2. Although data suggest a similar inhibition of 30 mg and 70 mg BID dose regarding the delay and the maximum effect, the effect appears more sustained with the dose of 70 mg BID.

Overall, these results support the choice of 70 mg BID dose, i.e., the proposed dose for Joenja.

PK interactions

As a victim:

Leniolisib is cleared primarily through oxidative metabolism (primarily hydroxylation and dealkylation) by CYP isoenzymes (predominantly CYP3A4, 95.4%). In a study of healthy adults, coadministration of leniolisib and itraconazole, a strong CYP3A4 inhibitor, resulted in a 2-fold increase in leniolisib exposure. No interaction studies have been conducted with leniolisib and strong and moderate CYP3A4 inducers. Concomitant use may result in reduced leniolisib exposure and thus, reduced leniolisib efficacy. Therefore, concomitant use of leniolisib with strong CYP3A4 inhibitors or strong and moderate CYP3A4 inducers should be avoided – as reflected in SmPC section 4.4 and 4.5.

Leniolisib is also a substrate of P-gp and BCRP based on the *in vitro* study. The clinical impact on leniolisib exposure resulting from P-gp strong inhibitor co-administration has been assessed in a clinical DDI study with repeated itraconazole and quinidine on the single-dose PK of oral leniolisib in healthy volunteers and it is concluded that leniolisib is not a sensible substrate of P-gp transporter. However, no clinical DDI has been performed to assess the clinical impact on leniolisib exposure when co-administrated with a strong BCRP inhibitor. An instruction to avoid concomitant use of leniolisib with BCRP inhibitors was included in the SmPC section 4.4 and 4.5.

Leniolisib exhibits pH-dependent solubility, with lower solubility at higher pH-values. Therefore, gastric acid reducing agents (locally acting antacids) should be taken 2 hours before or 2 hours after leniolisib administration. This is considered appropriately reflected in SmPC 4.4 and 4.5.

As a precipitant:

In vitro studies identified leniolisib as a time-dependent inhibitor of CYP1A2, an inducer of CYP3A4, and an inhibitor of BCRP, OATP1B1/1B3, OAT3, MATE1/2-K, and OCT2. To assess this effect *in vivo*, a clinical DDI study was conducted. This open-label study evaluated the effect of leniolisib (70 mg twice

daily for 15 days) on probe substrates, caffeine (CYP1A2), midazolam (CYP3A4), rosuvastatin (BCRP/OATP1B1/1B3), furosemide (OAT3), and metformin (MATE/OCT2), in 20 healthy subjects.

Results demonstrated clinically significant exposure increases for rosuvastatin (2-fold AUC_{0-a44} increase; 90% CI: 186.25–215.91%), indicating a strong interaction with BCRP/OATP1B1/1B3, and a moderate increase for furosemide (1.4-fold; 90% CI: 133.01–157.30%), suggesting relevant OAT3 inhibition; caffeine and metformin showed modest increases (1.2-fold and 1.1-fold, respectively), while midazolam exposure remained unchanged (90% CI: 92.00–105.90%), though its metabolite (1-hydroxy midazolam) increased slightly (1.1-fold; 90% CI: 106.58–121.53%). Leniolisib was well tolerated both alone and in combination.

Based on these data, which show no clinically relevant effects on CYP1A2, CYP3A4, or MATE1/2-K/OCT2, but significant interactions with BCRP and OATP1B1/1B3 substrates and a non-negligible effect on OAT3, the SmPC has been updated to recommend avoiding concomitant use with drugs dependent on BCRP or OATP1B1/1B3 due to the risk of increased exposure and DDIs.

In addition, the SmPC section 4.3 and 4.5 includes a warning that co-administration of leniolisib with OAT3 substrates, particularly those with a narrow therapeutic index, should be avoided, as the increase in exposure is not negligible. This is acceptable.

Based on *in vitro* studies, Leniolisib showed a concentration-dependent inhibition of UGT1A1-mediated ethinylestradiol glucuronidation (IC50 = 8.49 µM, corresponding to an unbound IC50 of 7.24 µM). Therefore, since IC50= 7,24µM of leniolisib for UGT1A1 is lower than the cut-off value of $50 \times C_{max,u}$= 22.45µM, a clinically relevant DDI with an UT1A1 substrate, such as irinotecan, cannot be ruled out. As such, the *in vitro* inhibitory effect on UGT-1A1, and that concomitant administration of leniolisib with a UGT1A1 substrate should be avoided was added in the SmPC sections 4.4 and 4.5 accordingly.

The effect of leniolisib on hormonal contraceptive was assessed during a clinical study. The results showed that administration of leniolisib with a single dose oral contraceptive containing ethinylestradiol and levonorgestrel increased ethinylestradiol exposure by approximately 30% with no effect on levonorgestrel exposure. The increase in ethinylestradiol exposure is unlikely to reduce the effectiveness of a combined oral contraceptive composed of ethinylestradiol and levonorgestrel.

The information is considered adequately reflected in the SmPC sections 4.4 and 4.5.

PBPK models to support expected interaction magnitude of moderate and strong CYP3A4 perpetrator drugs (inhibitor and inducer) on leniolisib PK.

A model was applied to simulate DDI potential of leniolisib (as victim) with CYP3A4 (moderate) inhibitors and (strong and moderate) inducers. The applicant has provided adequate description of model development, sensitivity analysis and verification of the predictive performance of the model. However, this model was not sufficiently qualified and not fully compliant with what reported in the relevant Guidelines. However, although for moderate inhibitors data from PBPK cannot be considered reliable at present, the following recommendation is reported in SmPC section 4.4: Concomitant therapy with a strong cytochrome P450 (CYP)3A4 inhibitor increased leniolisib exposure. Concomitant use of leniolisib with strong CYP3A4 inhibitors should be avoided (see section 4.5). If use of strong CYP3A4 inhibitors is required, it is recommended that Joenja be discontinued 2 days before administration of CYP3A4 inhibitor. Joenja may be restarted 7 days after CYP3A4 inhibitor discontinuation. This is the most restrictive as it suggests for moderate inhibitors the same approach that for strong inhibitors. The SmPC adequately reflects this information.

Pharmacodynamics

Leniolisib selectively inhibits PI3Kδ by blocking the active binding site of PI3Kδ.

The effect of leniolisib was assessed through pAkt inhibition, both in healthy subjects and in patients with APDS. A similar inhibitory effect was seen in healthy patients and in patients with APDS. Although data suggest a similar inhibition of 30 mg and 70 mg BID dose regarding the delay and the maximum effect, the effect appears more sustained with the dose of 70 mg BID. Overall, these results support the choice of 70 mg BID dose.

2.6.4. Conclusions on clinical pharmacology

The PK of leniolisib was thoroughly investigated using the non-compartmental and nonlinear-mixed effects modelling approaches. Data from 5 Phase 1 studies in healthy volunteers and 2 Phase 2/3 studies in the claimed patients with APDS were used for analyses. Overall, the PK properties of leniolisib to be administered by oral route are considered sufficiently characterized.

The proposed posology (70 mg leniolisib twice daily approximately 12 hours apart for adolescents 12 years and older and weighting 45 Kg or more) is acceptable.

2.6.5. Clinical efficacy

Table 9: Leniolisib clinical development programme in patients with APDS

Study No.	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	Number of Subjects by Arm Entered/ Completed	Duration	Sex M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
CCDZ173X2201 Part 1	3 Czech Republic, Netherlands, and US	24 Aug 2015 Completed 17 Oct 2016 6/6	OL, non-randomized, within-patient, dose-finding, multicenter	Leniolisib (10, 30, and 70 mg PO bid sequentially each dose for 4 weeks)	Dose-PD and PK/PD relationship for dose selection in Part 2 Safety and tolerability	6/6	12 weeks	M=4 F=2 22 years (16-31)	APDS Nodal and/or extranodal lympho-proliferation and clinical findings of APDS	PD=% pAkt-positive B cells PK=E_{max} to measure concentration-response
CCDZ173X2201 Part 2	10 Belarus, Czech Republic, Germany, Ireland, Italy, Netherlands, Russia, UK, and US	05 Dec 2017 Completed 06 Aug 2021 31/30	Randomized, blinded, multicenter, PBO-controlled	Leniolisib (70 mg PO bid) or PBO	Clinical efficacy (lymphadenopathy and immunophenotype normalization)	Leniolisib 21/21 PBO 10/10	12 weeks	M=15 F=16 20 years (11-54)	APDS Nodal and/or extranodal lympho-proliferation and clinical findings of APDS	Lympho-proliferation (log10-transformed SPD in the index lesions) and immunopheno-type normalization (% of naïve B cells out of total B cells)
CCDZ173X2201E1 Extension	8 Belarus, Czech Republic, Germany, Italy, Netherlands, Russia, and US	08 Sept 2016 Completed 37/42	OL, non-randomized, multicenter	Leniolisib (70 mg PO bid)	Long-term safety and tolerability	Leniolisib 37/0	Up to 6 years	M=21 F=16 20 years (12-55)	APDS Must have enrolled in CCDZ173X2201 or was treated previously with P13Kδ inhibitors other than leniolisib	Safety and tolerability

Efficacy data were derived from a phase 2/3 study (CCDZ173X2201, study 2201) of which part 1 was an open label non-randomised, within-patient, dose finding part and part 2 was a randomized, blinded, controlled versus placebo part. Part 2 was followed by an extension study (CCDZ173X2201E1, 2201E1) in which all patients from part 1/2 could be included along with additional patients who previously received another PI3K inhibitor.

2.6.5.1. Dose-response study

Study 2201 part 1 was an open label, non-randomized, dose finding study performed in 6 patients with APDS.

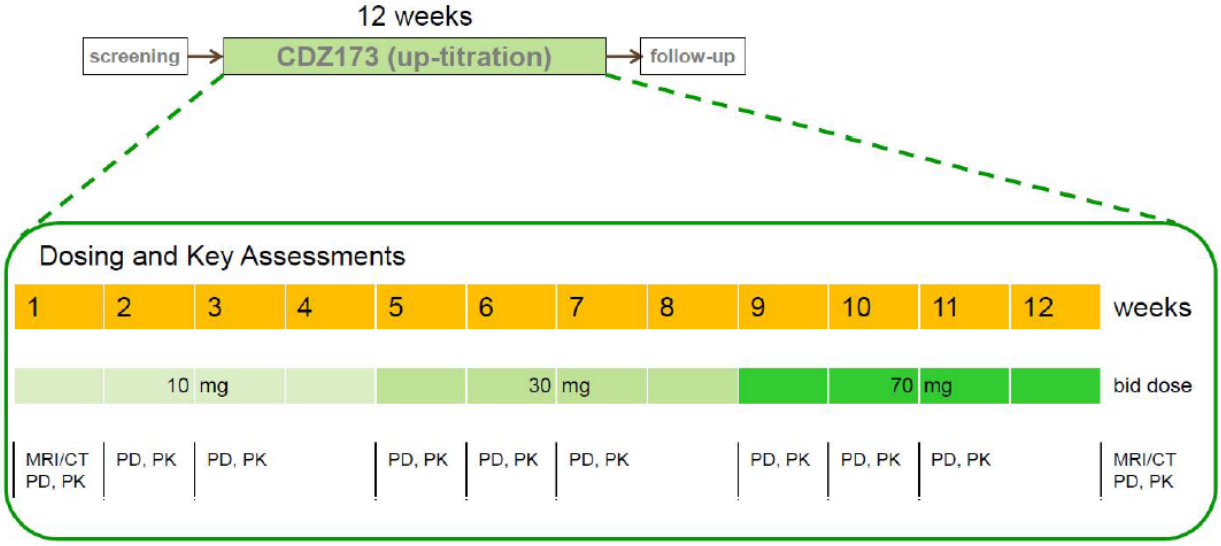


Figure 8: Study Design (Part 1)

The primary objective was the dose-PD and PK/PD relationship of leniolisib in patients with APDS. Efficacy was the secondary endpoint. Safety, tolerability, PK, and *in vivo* PD were assessed at 10, 30, and 70 mg of leniolisib twice daily.

6 patients (4 males and 2 females) of which 2 were < 18 years of age (16 and 17 years of age) were included and received increasing doses of leniolisib. 10 mg, 30 mg then 70mg BID were each administered for 4 weeks. Pharmacodynamic results are described in section 2.5.2. of this report and resulted in the choice of the 70 mg BID dose for part 2 of the study, which is currently the intended dose for patients with APDS.

The sample size of Study 2201-Part I (6 patients) is mainly based on feasibility, while still providing adequate precision to identify an appropriate dose for part II. In healthy volunteers, at steady state, average pAkt inhibition in stimulated B-cells over the dosing interval was expected to be below 50% at 10 mg b.i.d. of CDZ173, around 70% at 30 mg b.i.d. and around 90% at 70 mg b.i.d. The standard deviation of the pAkt inhibition was expected to be around 16% in healthy volunteers. Assuming similar variability in APDS patients, the width of an 80% confidence interval of the average pAkt inhibition in unstimulated B-cells at a given dose level was expected to be around 8.5% on each side of the estimated mean pAkt inhibition when studying 6 patients.

Secondary endpoints included health related quality of life assessments, but were considered inconclusive.

- Both the short form 36 survey (SF-36) and the work productivity and activity impairment plus classroom impairment questionnaire (WPAI-CIQ) did not provide conclusive results which is probably due to the small sample size, the relatively short evaluation period and the heterogeneity of the patient group including adolescent patients according to the applicant.
- Regarding Patient's Global assessment, although the applicant states an increase in wellbeing, both the lack of control arm and the large variability precludes from any conclusion. At the individual level, only half of the patients had a clear VAS score at D84 higher than at baseline score.

- Results for Physician's Global assessment are more homogeneous than patient Global assessment questionnaire. All patients had a VAS score at D84 lower than baseline score (i.e. decrease in disease activity). Nevertheless, the limited data (6 patients) and the absence of controlled group do not allow to draw any conclusion.

Exploratory endpoints of the dose response part of study 2201 could help to support data suggesting a benefit of leniolisib treatment with regards to the limited data.

Imaging for lymphoproliferation showed a reduction of spleen volume and index lesion for all 6 patients, but no change was observed on liver volume.

The percentage of transitional B cells was decreased at the end of the 70 mg bid treatment period, accompanied by a decrease in IgM by while naïve B-cells were increased, suggesting a shift into a more favourable immunological context. In addition, assessment of T cell subsets showed that senescent CD57+CD8+ and PD-1+CD4+ T cells were reduced at the end of the 70 mg bid treatment period.

2.6.5.2. Main study

CCDZ173X2201, study 2201 part 2

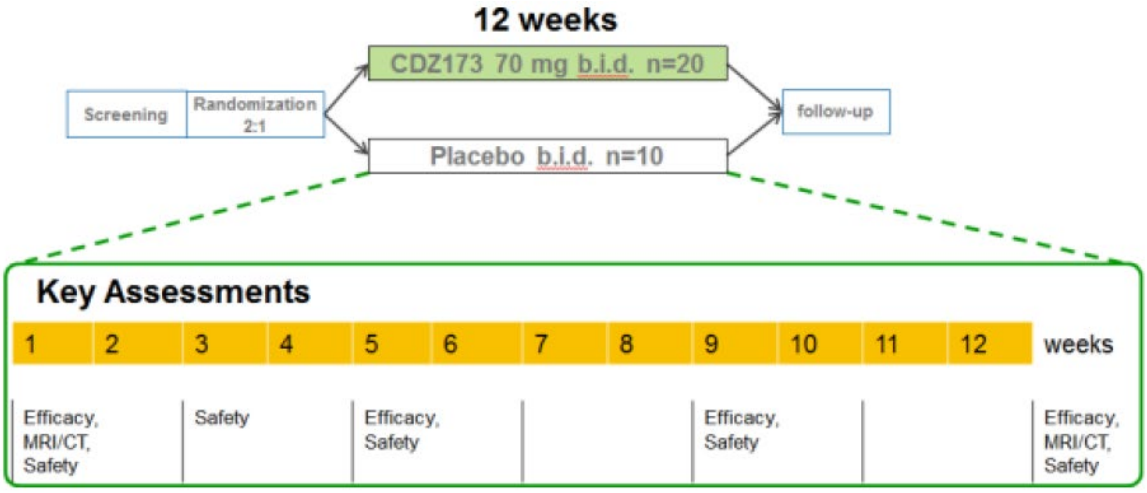


Figure 9: Design of study 2201 Part 2

Study 2201 part 2 was a randomized, placebo-controlled, blinded part of study 2201. The main objective of this part was to assess the efficacy of leniolisib at the selected dose of 70 mg BID. Patients received leniolisib or placebo (2:1) for 12 weeks. At the end of part 2, patients could receive leniolisib in the extension part 3 of study 2201 (study 2201E1).

Methods

- **Study Participants**

Main inclusion criteria were male and female patients aged 12 to 75 years (inclusive) who had a documented APDS/PASLI-associated genetic PI3K delta mutation. Patients with mutations in either PIK3CD or PIK3R1 could be included.

Main exclusion criteria were previous or concurrent use of immunosuppressive medication, current use of medication known to be strong inhibitors, or moderate or strong inducers of isoenzyme CYP3A,

current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index, uncontrolled chronic or recurrent infectious disease (with the exception of those that are considered to be characteristic of APDS/PASLI).

- **Treatments**

In Study 2201 part 2, patients received leniolisib or matching placebo at 70mg BID.

Leniolisib or matching placebo was used on top of standard of care treatment and pre-established symptomatic and supportive treatments.

Immunosuppressive concomitant medications (mTOR, B-cell depleting medications) were an exclusion criteria based on their potential to increase susceptibility to infections.

- **Objectives**

The primary objective was to assess the efficacy of leniolisib at the selected dose of 70 mg BID.

The secondary objective was to assess the safety, PK, clinical outcome assessments and biomarkers.

- **Outcomes/endpoints**

The two co-primary endpoints were "change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging" and "change from baseline in percentage of naïve B-cells out of total B-cells". Secondary objectives included the effect on non-index lesion and spleen, health related quality of life questionnaires, Physician's and Patient's Global assessment, assessment of biomarkers of systemic inflammatory components of the disease, and benefit to individual patients. In addition, exploratory objectives included effect on physical activity level, impact of lymphadenopathy (liver), effect of B and T-cells, frequency of infections and alternative biomarkers.

Frequency of infections, which is an important feature of APDS because recurrent upper and lower respiratory tract infections routinely progress to irreversible bronchiectasis was only assessed as an exploratory endpoint. Both the duration of this part 2 (12 weeks) and the low number of patients would make infection rate difficult to assess.

- **Sample size**

The sample size of Study CCDZ173X2201-Part II (20 patients in CDZ173 and 10 patients in placebo group for a total of 30 patients) was mostly driven by the analysis of one of the two co-primary efficacy variables, the change from baseline in the log10-transformed SPD of index lesions.

The assumptions for the sample size and power calculations were calculated assuming comparable variability of the change from baseline in log10-transformed SPD of index lesions between a patient population with participants with Mantle Cell Lymphoma (standard deviation of 0.2 on the log10 scale) and patients with APDS/PASLI-associated genetic PI3K delta mutation. Based on this, 30 patients would grant 80% power in the 2201 part 2 study to detect a statistically significant p-value comparing the difference in the change from baseline in the log10-transformed SPD between active and placebo groups using a 5% type I error in a two-sided two-sample t-test assuming a true difference of -0.225. On the original scale, this corresponded to a decrease of around 40%.

The observed standard deviation in the six patients tested in the Part I of this study was actually slightly lower (0.14). Assuming a standard deviation of 0.14, with 30 patients, the 2201 part 2 study would have a 97% power to detect a statistically significant p-value.

Assuming that 10% of patients were excluded from the analysis of the other co-primary variable, the change from baseline in the percentage of naïve B cells out of total B cells, due to no reduced

percentage of naïve B cells at baseline, it was anticipated that 27 patients would provide data for the analysis. Assuming an increase of 25% points and comparable variability as in Part I for the change from baseline to 12 weeks in the percentage of naïve B cells (standard deviation of 14), with 27 patients this part of the study would have 98% power to detect a statistically significant p-value at the 5% level. With the above assumptions, the power to achieve a statistical significance in both endpoints was at least 78%.

No interim analysis was planned for Study CCDZ173X2201-Part 2.

- **Randomisation and blinding (masking)**

A randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the randomization assignment of treatment arms to randomization numbers in the specified ratio (2:1 for CDZ173:placebo).

The patients, investigator staff, and sponsor persons performing the assessments, and data analysts remained blinded to the identity of study treatments. An independent data monitoring committee (DMC) evaluated the unblinded data for safety purposes. The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance and odour. Randomization data were kept strictly confidential until the time of unblinding and was not accessible to anyone else involved in the study with the following exceptions: DMC members, unblinded pharmacist or authorised designee at site, unblinded monitor (where used) and the PK bioanalyst.

- **Statistical methods**

Analysis populations

For all analysis sets, patients were analysed according to the study treatment(s) received.

The safety analysis set included all patients that received any study drug.

The PK analysis set included all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data. PK endpoints were reported by age group (≥18 years old and < 18 years old) and by APDS diagnosis (APDS1 and APDS2).

The PD analysis set included all patients who received any study drug and with no protocol deviations with relevant impact on PD data. In Part II, the key safety and efficacy endpoints was reported by age group (≥18 years old and < 18 years old) and by APDS diagnosis (APDS1 and APDS2).

Primary endpoints

Estimands for the two co-primary endpoints are defined below.

Table 10: Estimands for lymphadenopathy and immune function co-primary

	Lymphadenopathy		Immune function		
Analysis	Primary analysis	Supportive analysis	Primary analysis	Sensitivity analysis	Supportive analysis
Population	Patients in PD analysis set and without 0 lesions at baseline	All patients in PD analysis set	Patients in PD analysis set and with a percentage of less than 48% of naïve B cells at baseline	Patients in PD analysis set and with a percentage of less than 48% of naïve B cells at baseline	Patients in PD analysis set
Variable	Change of log10 transformed SPD from baseline	Change of the sum of the square root of the products of diameters	Change from baseline in the naïve B cells	Change from baseline in the naïve B cells	Change from baseline in the naïve B cells
Intercurrent event	NA	NA	NA	NA	NA
Population-level Summary	Difference in variable means between treatment and control	Difference in variable means between treatment and control	Difference in variable means between treatment and control	Difference in variable means between treatment and control	Difference in variable means between treatment and control
Analytic method	Analysis of covariance at D85	Analysis of covariance at D85	Analysis of covariance at D85	Longitudinal mixed model at time points D29, D57 and D85	Analysis of covariance at D85

NA = not applicable

The co-primary variables were to assess the change from baseline in the log10-transformed SPD of the index lesions and the change from baseline in the percentage of naïve B cells out of total B cells.

Index lesions were selected from measurable nodal and extranodal lesions as per the Cheson methodology (Cheson et al 1999). A maximum of six of the largest dominant lesions were selected and documented at baseline and assessed again at the end of treatment (i.e. the Day 85 assessment for patients who completed the 12-week treatment period or the treatment discontinuation visit for patients who discontinued treatment prematurely prior to Day 85 visit).

The percentage of naïve B cells was assessed at baseline, Day 1, Day 29, Day 57 and Day 85, and at the discontinuation visit for patients who discontinued treatment prematurely prior to Day 85 visit.

An analysis of covariance was performed to compare the change of the log10 transformed SPD from baseline between the treatment groups with a treatment as a fixed effects and log10 transformed baseline SPD as a covariate. The baseline intake of glucocorticoids as well as the information about being treated with intravenous immunoglobulin G (IgG) were both included as categorical (Yes/No) covariates. The comparison of the two treatment groups was two-sided, with a 5% type I error. Patients with zero lesions at baseline were excluded from the analysis.

A supportive analysis was performed using an analysis of covariance model with treatment as a fixed effect and the baseline of the sum of the square root of the PD as covariate to compare the sum of the square root of the products of diameters between treatment groups. The use of glucocorticoids and

intravenous IgG at baseline were included as categorical (Yes/No) fixed effects. In this supportive analysis all patients were included, irrespective of the number of lesions at baseline.

An analysis of covariance was performed to compare the change from baseline in the naïve B cells at the end of treatment (i.e. Day 85 assessment for patients who completed the 12-week treatment period or the treatment discontinuation visit for patients who discontinued treatment prematurely prior to Day 85 visit) between the two treatment groups, adjusted for baseline naïve B cells frequencies. The use of glucocorticoids and intravenous IgG at baseline were included as categorical (Yes/No) fixed effects. Comparison of the two treatment groups was two-sided, with a 5% type I error. Only patients with a reduced percentage of naïve B cells at baseline (defined as below 48 % van Gent et al 2009) were included in the analysis. Baseline was defined as the arithmetic mean of the baseline and Day 1 values when both are available, and if either baseline or the Day 1 value was missing, the existing value was used.

A supportive analysis of covariance was performed to compare the change from baseline in the naïve B cells at the end of treatment (i.e. Day 85 assessment for patients who completed the 12-week treatment period or the treatment discontinuation visit for patients who discontinued treatment prematurely prior to Day 85 visit) between the two treatment groups, adjusted for baseline naïve B cells frequencies. The use of glucocorticoids and intravenous IgG at baseline was included as categorical (Yes/No) fixed effects. Comparison of the two treatment groups was two-sided, with a 5% type I error. All patients in the PD analysis set were included in this analysis. Model estimated mean (SE) profiles were provided by treatment.

Handling of missing data

The inferential analyses of the lymphadenopathy included only patients with baseline and end of treatment lymphadenopathy measurements. Also, patients with zero lesions at baseline were excluded from the primary and sensitivity analysis for lymphadenopathy.

The primary analysis of the naïve B cells included only patients who had baseline and end of treatment naïve B cells measurements and who also had a reduced percentage of naïve B cells at baseline (defined as below 48 % van Gent et al 2009).

A supplementary analysis of naïve B cells was performed using the full safety analysis set.

Moreover, post-hoc analyses of both primary endpoints were provided when performing multiple imputations (MI) of missing data. These MIs followed missing at random assumptions as well as missing not at random assumptions, i.e. using a control-based missing data imputation. These supplementary analyses were provided on the PD analysis set as well as based on the full safety analysis set. For the percentage of naïve B cells, the analysis was also repeated on the subset of patients with less than 48% of naïve B cells at baseline (for both PD analysis set and safety analysis set).

Sensitivity for the primary endpoint / estimand

As a sensitivity analysis, the change from baseline in naïve B cells was analysed using a longitudinal mixed model, with treatment, time, treatment by time interaction, baseline and baseline by time interaction as fixed effects. The use of glucocorticoids and intravenous IgG at baseline were both be included as categorical (Yes/No) fixed effects. An unstructured covariance matrix was fitted to adjust for correlations among the measurements made on the same patient. The difference between the treatment groups in the change from baseline after 12 weeks of treatment were assessed at two-sided 5% significance level. Only patients with a reduced percentage of naïve B cells at baseline were included to the analysis. Baseline was defined as the arithmetic mean of the baseline and Day 1 values when both were available, and if either baseline or the Day 1 value was missing, the existing value was

used. For patients who completed the treatment period, these repeated measures analysis included all measurements in the treatment period (Baseline, Day 29, Day 57 and Day 85).

Changes in planned analyses

Changes in the database

Study initiation of Part II of CCDZ173X2201 was on 5-Dec-2017 (first patient first visit), and the study completion was on 16-Aug-2021 (last patient last visit).

The clinical database was locked on 07-Sep-2021 and following a planned unlock, the clinical database was re-locked on 19-Oct-2021. The planned unlock was performed to include a MRI image, final biomarker and PK re-conciliation and Actibelt data.

Subsequently, an unplanned unlock of the clinical database was performed to include two additional protocol deviations; one patient had taken prohibited medication (prednisone) within 14 days of first dose (exclusion criterion 3) and one patient did not have nodal lesion at baseline (inclusion criterion 3). One patient was excluded from PD analysis and one patient was excluded from PD and PK analysis. The clinical database was relocked on 23-Dec-2021.

Changes introduced in the protocol

The protocol, which covers both Part I and II of the study, was amended ten times. The design, endpoints and analysis plan were adjusted as part of Protocol Version 7 (July 2017) based on the results obtained from study Part I.

With version 8 (February 2019), the study Part II eligibility criteria were changed, notably to allow the inclusion of APDS patients with more severe phenotypes. Exclusion criterion related to IG replacement treatment has been deleted, and the criterion on systemic glucocorticoids has been changed. The analysis models were also updated to include an additional adjustment for the intake of glucocorticoids and intravenous immunoglobulin G treatment at baseline.

Changes introduced in the Statistical Analysis Plan (SAP)

SAP amendment was issued prior to database lock on 05-Sep-2021. The purpose of the amendment was to include:

- Objectives for gender split analysis
- Variables and descriptive analysis for gender split analysis
- Descriptive analysis for vital signs, ECG evaluations, clinical laboratory evaluations and AEs

SAP addendum was issued post database lock on 05-Jan-2022. The addendum included:

- Updates to patients' exclusion from analysis sets: subjects who reported protocol deviation being inclusion criteria 3 (Subject did not have measurable nodal lesion on a CT or MRI scan at Baseline) and exclusion criteria 3 (subjects who had taken prednisone 40 mg medication within 14 days to first dosing of study medication) were excluded from PK and PD analysis set.
- Post-hoc analysis for comparing the efficacy between CDZ173 70 mg bid group and placebo group in APDS1 and APDS2 patients.

Post-hoc analyses introduced in the clinical overview

A number of post-hoc analyses were provided in the supplemental summary tables produced to support the clinical overview, including:

- An analysis of change from baseline at day 85 in the log10 transformed SPD in the safety analysis set with and without imputation of missing data.
- An analysis of change from baseline at day 85 in naive B cells in the safety analysis set with less than 48% of naive B cells at baseline with and without imputation of missing data.

When data imputation is performed, missing changes from baseline are imputed to 0.

Results

- **Participant flow**

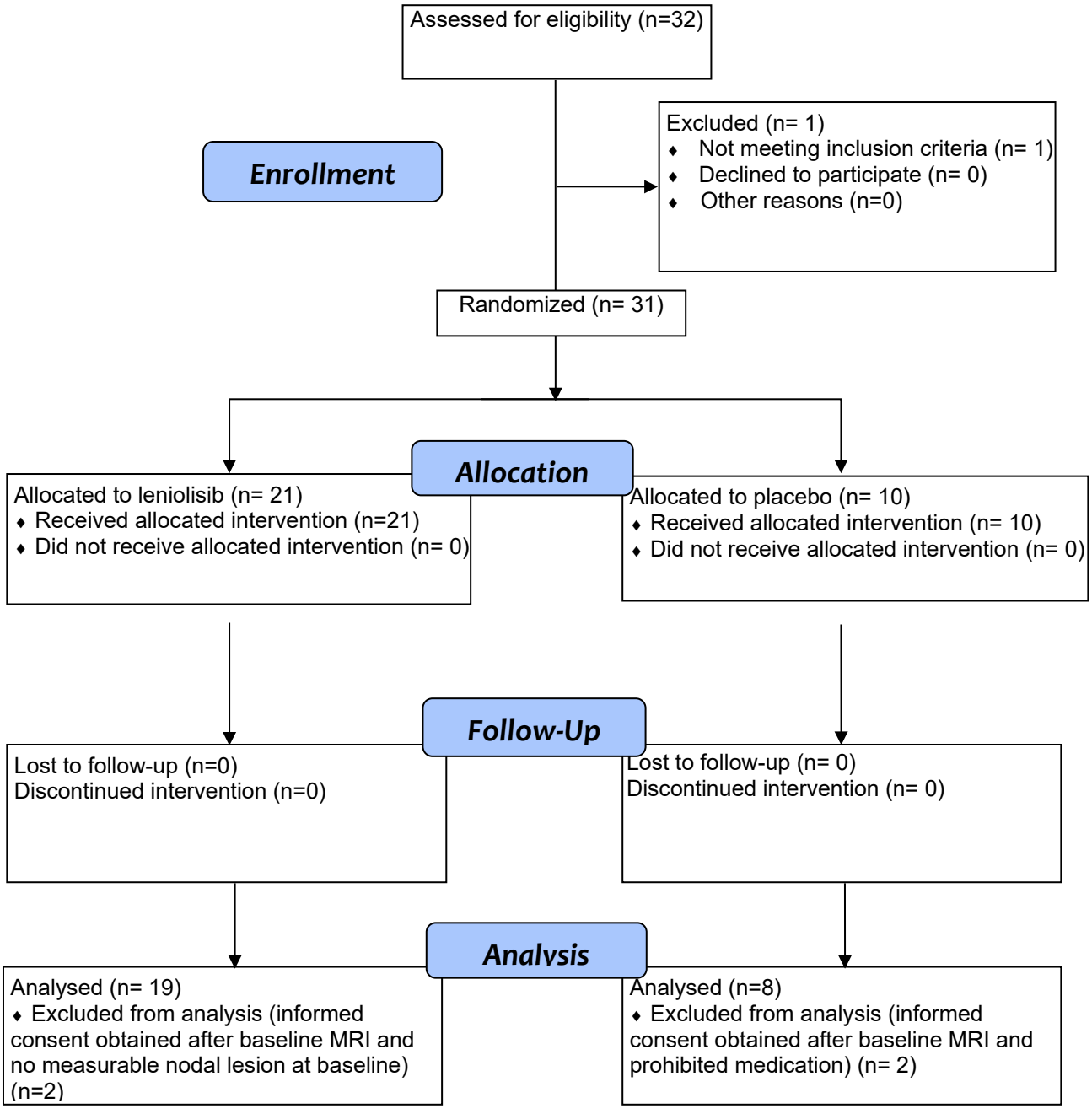


Figure 10: Participant flow

- **Recruitment**

First patient first visit: 05 December 2017

Last patient last visit: 16 August 2021

Patients were permitted to directly roll over from Part II to treatment in the extension study (2201E1) at the Part 2 End of treatment visit. The patients who did not directly roll over from Part 2 into the extension study were followed up for safety four weeks after the last day of dosing in the core study. On Day 112 these patients underwent the end of study visit.

- **Conduct of the study**

From amendment 8, exclusion criterion related to IG replacement treatment has been deleted allowing patients with more severe disease to be included. In addition, higher doses of systemic glucocorticoids (10mg to 25mg) were allowed for patients in need of this rescue medication.

Otherwise, protocol amendments were mainly related to safety improvement/adjustment based of completed non-clinical studies (DDI, contraception) or related to COVID-19 pandemic.

5 patients had protocol deviations due to COVID-19 pandemia. In addition, 9 patients in leniolisib arm and 3 patients in placebo arm had a failure to perform key procedure in accordance with the protocol. Furthermore, 3 patients in leniolisib arm (none in placebo arm) had a GCP related deviation. Of these, 1 patient had a deviation that impacted assessment of immunophenotyping (sample out of quality condition at baseline), however, a sampling was also planned at J1, one hour pre-dose and one patient completed VAS after the visit, thus potentially impacting secondary endpoint of patient global assessment.

Furthermore, 2 patients in leniolisib arm and 1 patients in placebo arm had a use of prohibited medication during the study (1 patient in each treatment group had topic ketoconazole and 1 patient in leniolisib group received prednisone 40 mg before screening MRI) and 3 patients in leniolisib arm and 2 patients in placebo arm had a deviation from selection criteria which were ‘mainly, pulse rate, diastolic BP slightly above normal range and baseline MRI done before informed consent.

- **Baseline data**

Table 11: Patient demographics-Part II (safety analysis set)

Age group: Overall

		CDZ173 70 mg bid N=21	Placebo N=10	Total N=31
Age (years)	Mean (SD)	22.2 (10.00)	26.7 (13.43)	23.7 (11.19)
	Median	20.0	19.5	20.0
	Range	11, 54	15, 48	11, 54
Age group - n (%)	<18 years	8 (38.1)	4 (40.0)	12 (38.7)
	≥18 years	13 (61.9)	6 (60.0)	19 (61.3)
Sex - n (%)	Male	11 (52.4)	4 (40.0)	15 (48.4)
	Female	10 (47.6)	6 (60.0)	16 (51.6)
Predominant Race - n (%)	Asian	1 (4.8)	1 (10.0)	2 (6.5)
	Black	1 (4.8)	1 (10.0)	2 (6.5)
	Caucasian	18 (85.7)	7 (70.0)	25 (80.6)
	Other	1 (4.8)	1 (10.0)	2 (6.5)
Ethnicity - n (%)	Hispanic or Latino	0	1 (10.0)	1 (3.2)
	Not Hispanic or Latino	14 (66.7)	7 (70.0)	21 (67.7)
	Not Reported	7 (33.3)	2 (20.0)	9 (29.0)
Weight (kg)	Mean (SD)	66.14 (15.550)	68.55 (11.661)	66.92 (14.259)
	Median	67.10	68.90	67.10
	Range	46.9, 100.6	50.0, 88.0	46.9, 100.6
Height (cm)	Mean (SD)	163.15 (8.248)	166.19 (8.153)	164.13 (8.208)
	Median	164.90	170.15	166.70
	Range	149.8, 177.0	151.5, 174.9	149.8, 177.0

		CDZ173 70 mg bid N=21	Placebo N=10	Total N=31
Body Mass Index (kg/m^2)	Mean (SD)	24.76 (5.121)	24.89 (4.345)	24.80 (4.811)
	Median	25.31	25.55	25.38
	Range	17.3, 36.1	18.9, 31.6	17.3, 36.1
PIK3CD mutation - n (%)	E1021K	8 (38.1)	5 (50.0)	13 (41.9)
	E525K	3 (14.3)	1 (10.0)	4 (12.9)
	N334K	1 (4.8)	0	1 (3.2)
	OTHER, E522K	0	1 (10.0)	1 (3.2)
	OTHER, R108L	1 (4.8)	0	1 (3.2)
	OTHER, Y524D	1 (4.8)	0	1 (3.2)
	OTHER, c.3071G>A (p.ARG1024His)	0	1 (10.0)	1 (3.2)
	OTHER, c.371G>A	0	1 (10.0)	1 (3.2)
	OTHER, exon24	1 (4.8)	0	1 (3.2)
	OTHER, p.Glu525_ His625delinsAspPro	1 (4.8)	0	1 (3.2)
PIK3R1 mutation - n (%)	OTHER, 9bp deletion (c.1418_1425+1	0	1 (10.0)	1 (3.2)
	OTHER, 9bp deletion (c.1418_1425+1d	1 (4.8)	0	1 (3.2)
	OTHER, c.1425+1 G>T	1 (4.8)	0	1 (3.2)
	OTHER, c.1425+1G>T	1 (4.8)	0	1 (3.2)
	OTHER, c.1425G>A	1 (4.8)	0	1 (3.2)
	OTHER, c1425+1G toA	1 (4.8)	0	1 (3.2)
Baseline Glucocorticoids - n (%)	No	9 (42.9)	4 (40.0)	13 (41.9)
	Yes	12 (57.1)	6 (60)	18 (58.1)
Baseline Intravenous IgG - n (%)	No	16 (76.2)	9 (90.0)	25 (80.6)
	Yes	5 (23.8)	1 (10.0)	6 (19.4)

- **Numbers analysed**

The first co-primary endpoint "change from baseline in the log10 transformed SPD in the index lesions selected as per the Cheson methodology from MRI/CT imaging" was analysed on the "PD analysis set" restricted population. The "PD analysis set" excluded 2 treated patients in each treatment group (2 patients for not obtaining informed consent before MRI, 1 patient had no measurable lesion at baseline and 1 patient took a prohibited medication within 14 days prior to dosing), resulting in n=20 patients analyses in the leniolisib group and n=8 patients analysed in the placebo group

Regarding the second primary endpoint, "change from baseline in percentage of naïve B cells out of total B cells", a significant number of patients were excluded from the analysis, further reducing the number of patients analysed. Indeed, only 8 patients in leniolisib group and 5 patients in placebo group were analysed. The main reason for exclusion from this analysis was a percentage of more than 48% of naïve B cells at baseline which was determined as the cut-off for reduced percentage of naïve B cells in the protocol.

- **Outcomes and estimation**

Primary outcomes

The change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging are presented below.

Table 12: Primary analysis of change from baseline at Day 85 in log10 transformed SPD - PD analysis set excluding patients with 0 lesion at baseline

Overall age group						
Test vs Ref. (comparison)	Adjusted mean change (SE)		Comparison of adjusted means			Test vs Ref.
	CDZ173 70 mg bid	Placebo	Diff.	(SE)	(95%CI)	P*-value
CDZ173 70 mg bid (N=18) vs placebo (N=8)	-0.30 (0.04)	-0.06 (0.06)	-0.24	0.06	(-0.37, -0.11)	0.0012

*p-value is 2-sided

Data were analyzed using ANCOVA model with treatment as a fixed effect and log10 transformed baseline SPD as a covariate. The use of glucocorticoids and intravenous IgG at baseline were both included as categorical (Yes/No) covariates.

LS Mean=Least square mean, N= number of patients. Data were analyzed using an ANCOVA model with treatment as fixed effect and log10 transformed baseline SPD as a covariate. The use of glucocorticoids and intravenous IgG at baseline were both included as categorical (Yes/No) covariates

Figure 11: LS Mean (SE) of the change from baseline at Day 85 in the log10 transformed sum of product of diameters (SPD) in the index lesions (primary analysis) – (PD analysis set excluding patients with 0 lesion at baseline)

Although data of 19 patients in leniolisib group were analysed for the primary endpoint "change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions", results for 18 patients are presented as 1 patient had an index lung lesion identified at baseline that had fully resolved (0 mm) by Day 85. Therefore, the log10 could not be derived. Thus, this one patient with a complete resolution had not been analysed although it could have positively impacted the results.

The change from baseline in the log10 transformed SPD (SE) was -0.30 (0.04) in the leniolisib group vs 0.06 (0.06) in placebo group. Thus, the difference in adjusted mean change (95% CI) of leniolisib 70 mg bid (N=18) vs placebo (N=8) was -0.24 (-0.37, -0.11). The results were statistically significant with 2-sided p-value observed as p=0.0012.

The applicant presented subgroup results for patients < 18 years old and > 18 years old suggesting an absence of significance for patients < 18 years.

A subgroup analysis was also presented for patients with APDS1 or APDS2, while results in APDS1 patients remained consistent with the primary analysis, no comparison could be presented for patients with APDS2 as there was only 4 patients in leniolisib group and no patient in placebo group. Of note, results of patients with APDS2 in leniolisib group were consistent with the primary analysis.

A higher reduction in the size of lymph nodes (as well as a slightly higher increase in the mean change from baseline in naïve B cells) was observed in male patients compared to female patients following treatment with leniolisib.

In addition, a sensitivity analysis with the use of glucocorticoids and concomitant Ig replacement therapy as a categorical covariate was consistent with the primary analysis.

Finally, the supportive analysis of change from baseline at Day 85 in the sum of the square root of the products of diameters of index lesions, including the patient with complete resolution of lung lesion was also consistent with the primary analysis.

The change from baseline in percentage of naïve B-cells out of total B-cells is presented below.

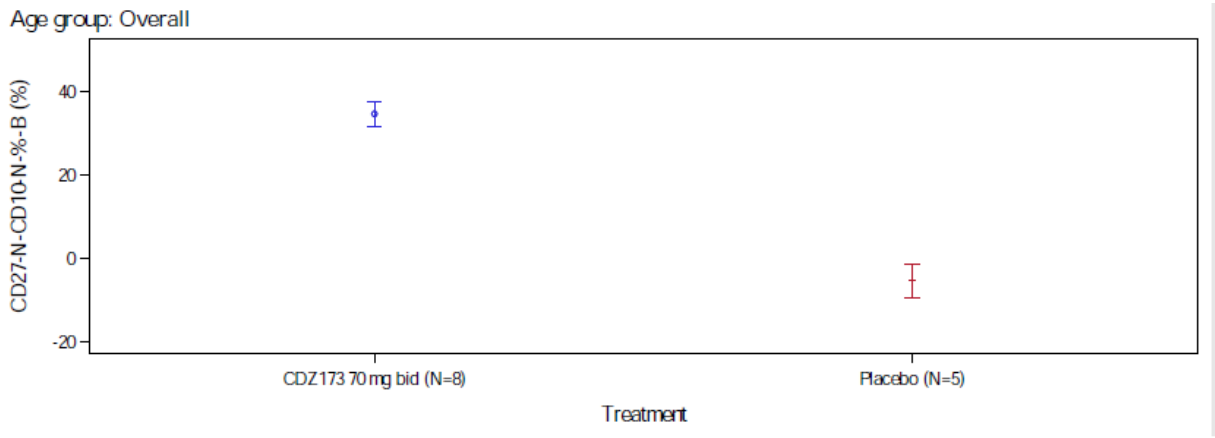
Table 13: Primary analysis of change from baseline at day 85 in naïve B cells - PD analysis set and with a percentage of less than 48% of naive B cells at baseline

Overall age group						
Test vs Ref. (comparison)	Adjusted mean change (SE)		Comparison of adjusted means			Test vs Ref.
	CDZ173 70 mg bid	Placebo	Diff.	(SE)	(95%CI)	P*-value
CDZ173 70 mg bid (N=8) vs placebo (N=5)	34.76 (3.08)	-5.37 (3.95)	40.13	5.04	(28.51, 51.75)	<0.0001

*p-value is 2-sided

Data were analysed using an ANCOVA model with treatment as a fixed effect and baseline as a covariate. The use of glucocorticoids and intravenous IgG at baseline were both included as categorical (Yes/No) covariates.

Baseline is defined as the arithmetic mean of the baseline and Day 1 values when both are available, and if either baseline or the Day 1 value is missing, the existing value is used.



LS Mean = least squares mean, N = number of patients

The figure illustrates data for patients in the PD analysis set with a percentage less than 48% of naïve B cells at baseline.

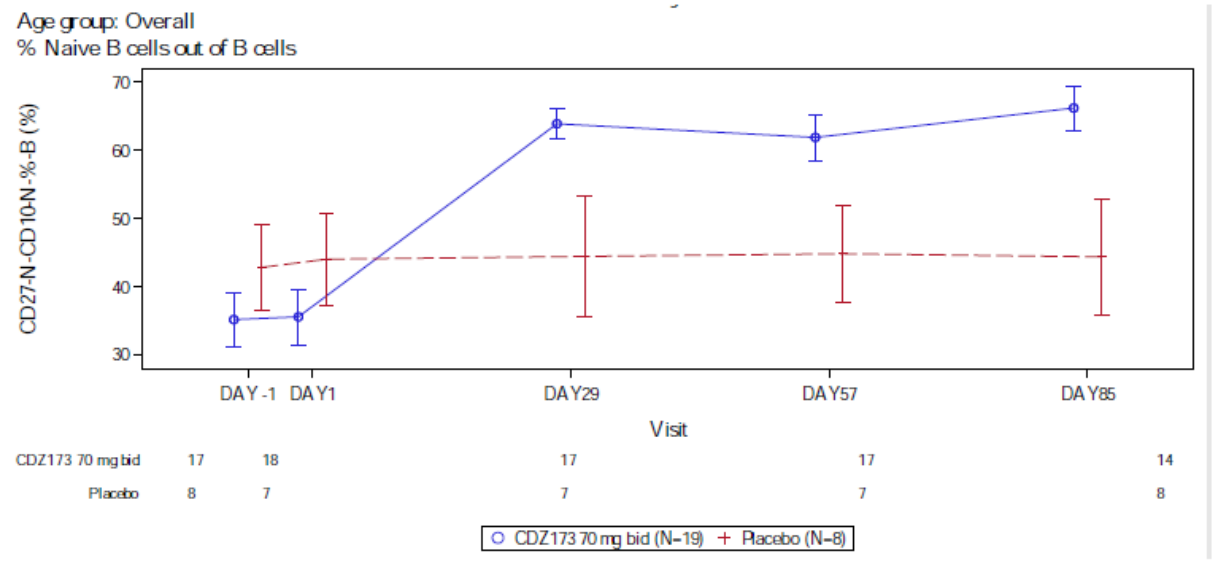
Data were analyzed using an ANCOVA model with treatment as a fixed effect and baseline as a covariate. The use of glucocorticoids and intravenous IgG at baseline were both included as categorical (Yes/No) covariates.

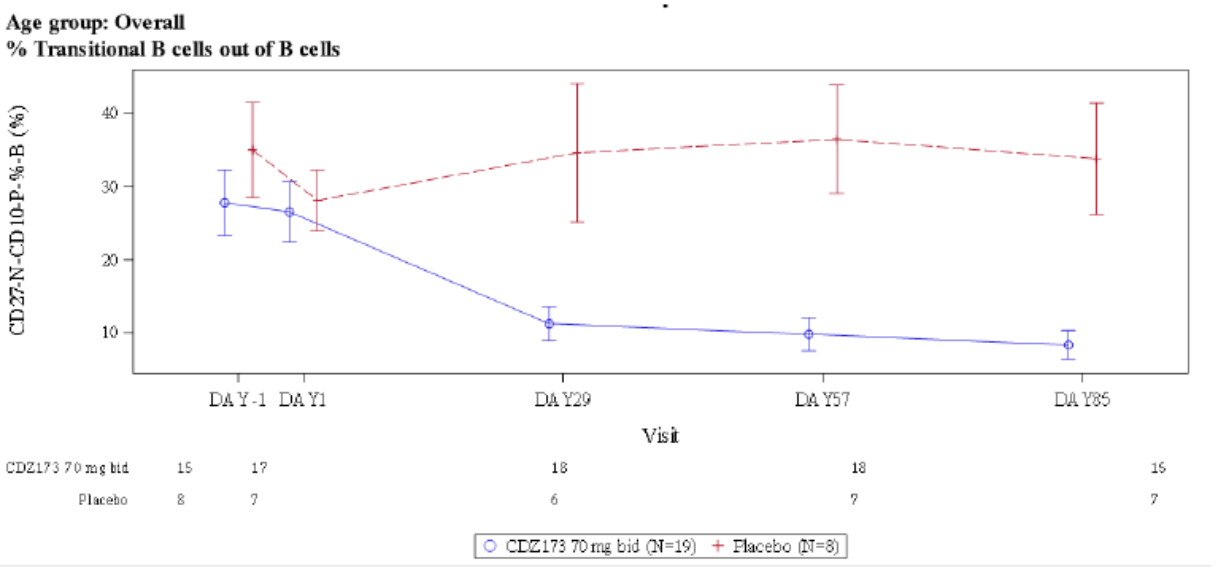
Figure 12: LS Mean(SE) of the change from baseline at Day 85 in percentage of naïve B cells out of total B cells (primary analysis) – Part II

The primary analysis of change from baseline in naïve B cells in patients with a percentage of less than 48% of naïve B-cells at baseline (adjusted mean change, SE) shows a statistically significant increase in leniolisib arm (34.76, 3.08) compared to placebo arm (-5.37, 3.95).

The sensitivity analysis, including patients with a baseline percentage of naïve B-cells at baseline > 48%, is also impaired by the lack of assessment at different time points (notably at D85). Those results seem however consistent with the primary analysis. Individual data of patients shows an increase from baseline in naïve B cells for all the patients in leniolisib group (and no or modest increase from baseline for patients in placebo group as observed from the listings). The modified sensitivity analysis with the use of glucocorticoids and any concomitant Ig therapy (not just IV Ig) as a categorical covariate was consistent with the primary analysis.

A supportive analysis was conducted on PD analysis set, increasing thus the number of patients analysed. Results show a significant increase in naïve B-cell compared to placebo from D29 up to D85, consistently with primary analysis. In addition, immature transitional B-cell that are elevated and sequestered in the lymph nodes or spleen of patients with APDS, significantly decreased to reach 8.7% at D85 in leniolisib group compared to 33.8% in placebo group (Figure 13 below).





N= number of patients

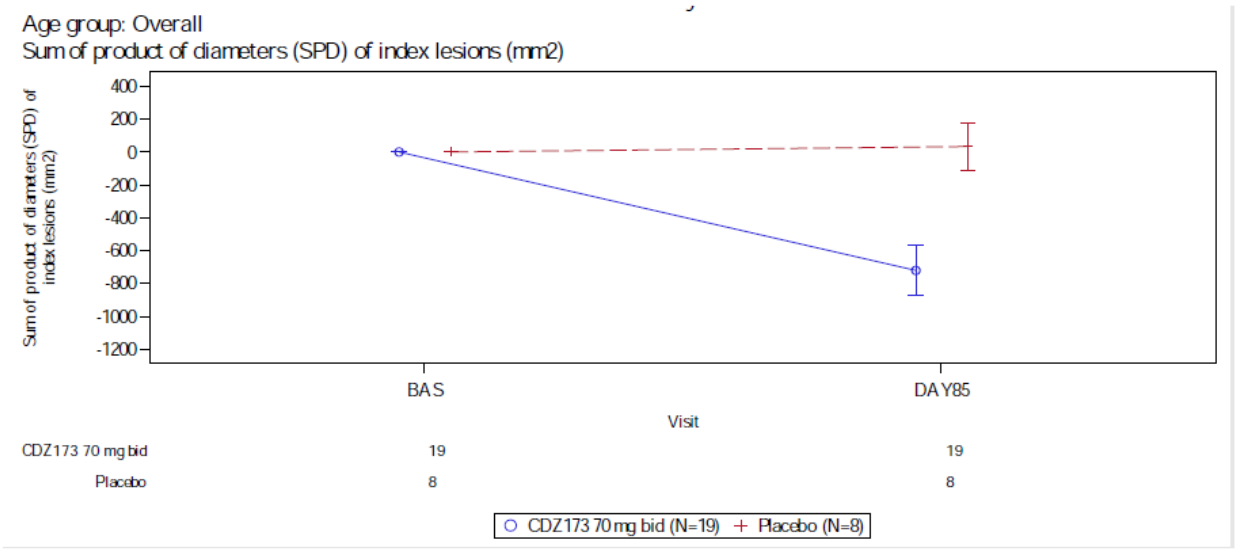
Figure 13: Mean (SE) of immuno-phenotyping: B cell panel – Part II (PD analysis set) Overall, patients treated with leniolisib had an increase in the percentage of naïve B-cells compared to placebo group, with a mean in change of 40% allowing the majority of the patients to reach the pre-determined cut-off of 48% of nave B-cell.

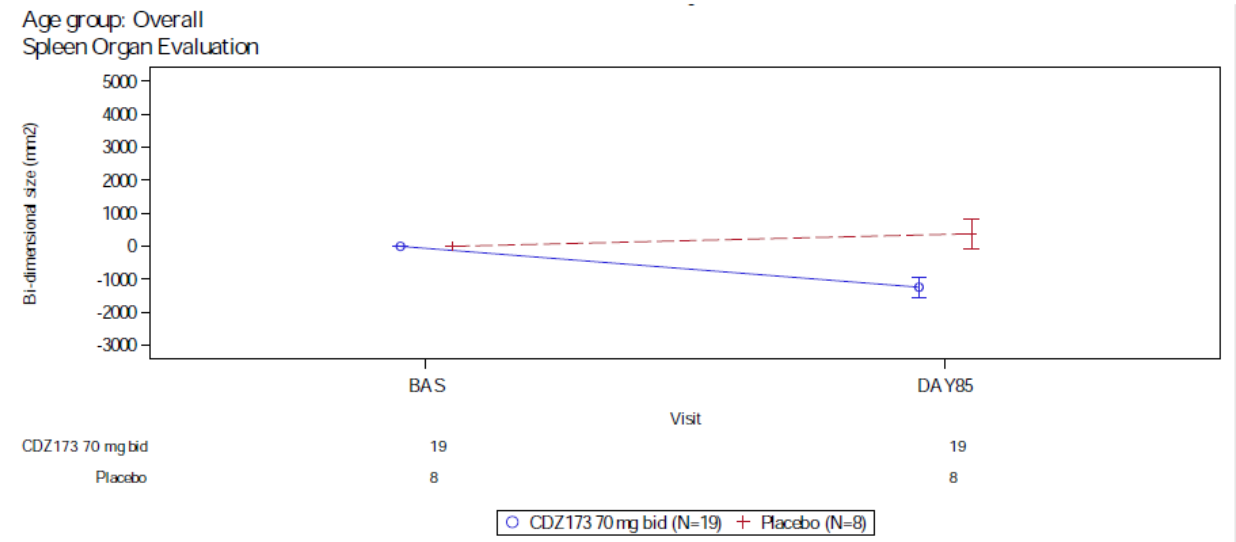
Secondary efficacy outcomes

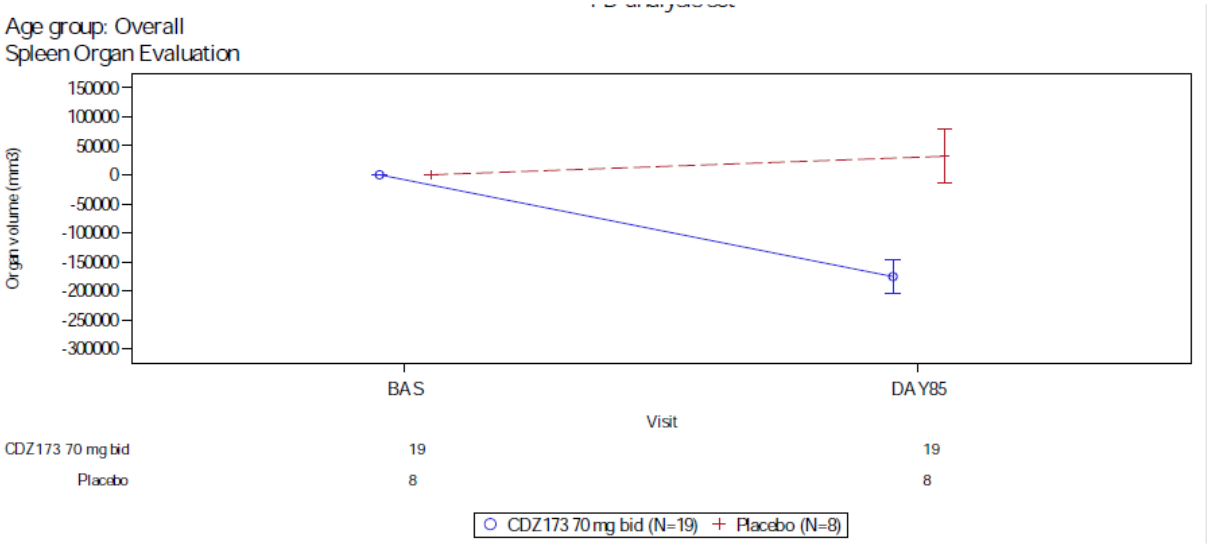
- *MRI/CT imaging*

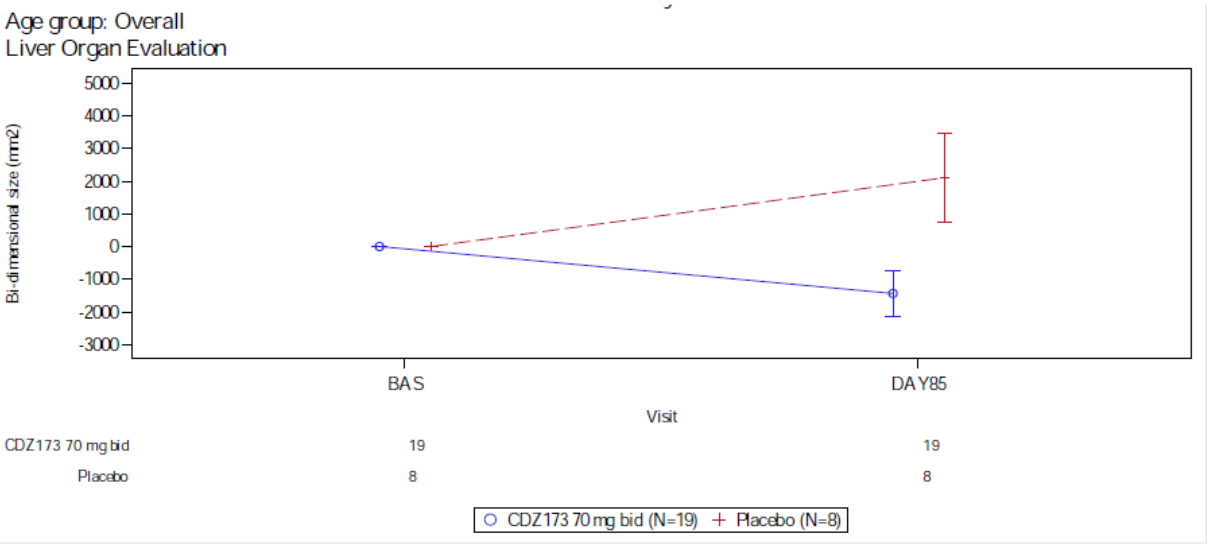
Imaging secondary endpoints included 3D volume assessment of index and measurable non-index lesions selected as per the Cheson methodology, and 3D volume and bi-dimensional size of the spleen while liver assessment was an exploratory endpoint. These assessments were conducted on PD analysis set (27 patients).

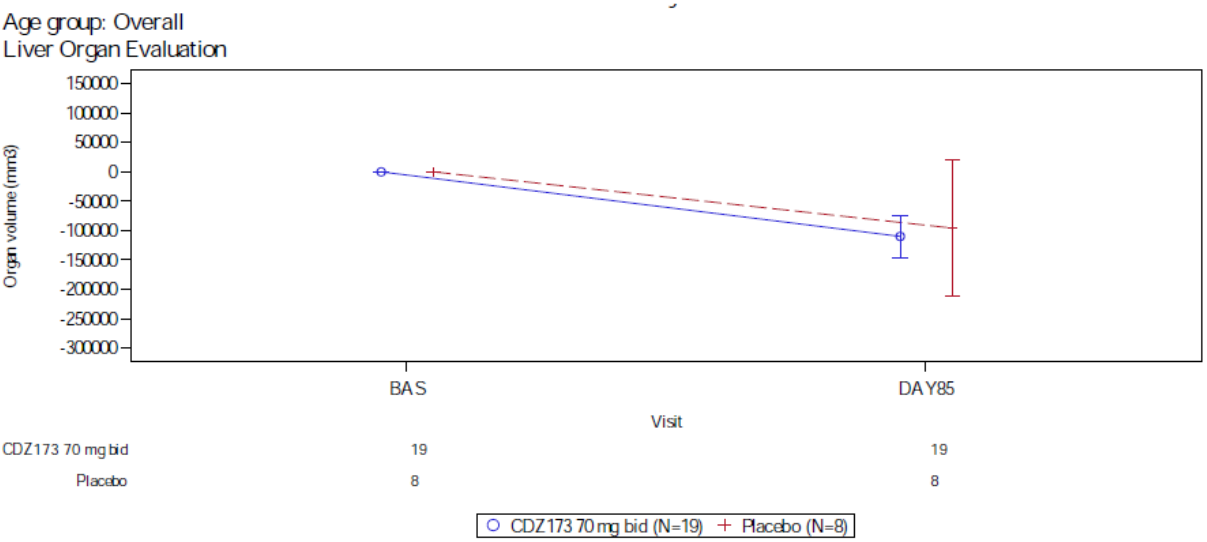
Overall, mean SPD volume of index lesion, mean bi-dimensional size and volume of spleen decreased at End of treatment compared to baseline in leniolisib group while there was no or minimal change in placebo group.


Age group: Overall
Sum of product of diameters (SPD) of index lesions (mm2)
Sum of product of diameters (SPD) of index lesions (mm2)
400
200
0
-200
-400
-600
-800
-1000
-1200
BAS
DAY85
Visit
CDZ173 70 mg bid 19 19
Placebo 8 8
CDZ173 70 mg bid (N=19) Placebo (N=8)


Age group: Overall
Spleen Organ Evaluation
Bi-dimensional size (mm2)
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
BAS
DAY85
Visit
CDZ173 70 mg bid 19 19
Placebo 8 8
CDZ173 70 mg bid (N=19) Placebo (N=8)







Baseline is defined as day -1, N= number of patients

Figure 14: Mean (SE) change from baseline in each quantitative MRI/CT evaluation parameter over time - Part II (PD analysis set)

The supportive analysis of these secondary endpoints showed that the decrease in the sum of the log10 transformed 3D volume of non-index lesion in leniolisib group was different from placebo group. But for index lesion, although SPD were decreased at D85 compared to baseline in leniolisib group, the decrease in sum of the log10 transformed 3D volume (N=26) was not different for leniolisib group as compared to placebo.

Bi-dimensional size and volume of spleen also decreased from baseline to D85 in leniolisib group compared to placebo group.

Regarding the exploratory endpoint of liver imaging, although mean bi-dimensional size of liver decreased from baseline to D85 in leniolisib group compared to placebo group, the decrease in liver volume was not different from placebo group although it is noted that variability was high in placebo group.

- *Narratives and Patient Global assessment (PtGA) and Physician Global assessment (PGA)*

For the health-related quality of life assessment (SF-36 survey and WPAI-CIQ), the Physician's Global Assessment (PGA) and the Patient's Global Assessment (PtGA) with VAS, results did not suggest any improvement in leniolisib group compared to placebo group.

- Parameters reflecting systemic inflammatory components of APDS/PASLI

Regarding assessment of inflammatory component of APDS, a reduction was observed for hsCRP, beta-2 microglobulin and ESR by Day 85 in the leniolisib group, while no relevant reduction was observed for fibrinogen, ferritin and LDH.

However, from the provided figures and data for hsCRP, beta-2 microglobulin and ESR, it is difficult to conclude on a reduction of inflammatory markers with leniolisib treatment compared to placebo.

- **Exploratory efficacy outcomes**

Overall, 17 patients (9 patients in CDZ173 70 mg bid group and 8 patients in placebo group) received at least one antibiotic medication prior to and/or after the start of study treatment. Azithromycin was the most frequently used medication, 10 patients (7 in CDZ173 70 mg bid group and 3 in placebo group) received at least once during the study. Two patients in CDZ173 70 mg bid group required antibiotic medication post treatment start compared to 6 patients in placebo group; while 7 patients in CDZ173 70 mg bid group and 3 in placebo group received antibiotics prior to treatment start and continued beyond the duration of treatment. Almost 2/3 of patients received antibiotic medication which was started in many cases prior to treatment start with study medication. Azithromycin was the most frequently used antibiotic. Evaluating the use of antibiotic medication does not allow an unequivocal differentiation between leniolisib and placebo-treated patients as a longer treatment duration might be required.

In the CDZ173 70 mg bid group, the proportion of %CD57+ out of CD8+ T cells were in average reduced from 14.4% at baseline (N=17) to 7.34% at Day 85 (N=15). The reduction was not observed with placebo, the proportion of %CD57+ out of CD8+ T cells were in average increased from 15.4% at baseline (N=8) to 17.71% at Day 85 (N=7) in the placebo group.

The mean change from baseline was -6.93% in CDZ173 70 mg bid group and 1.8% in placebo group for overall patient population

Although a reduction in senescent CD57+ cells out of CD8+ cells in leniolisib treated patients compared to placebo treated patient can be acknowledged, results are less obvious for PD-1+ out of CD4+ cells for which the mean change from baseline values fluctuated particularly in placebo group.

In the CDZ173 70 mg bid group, the proportion of %PD-1+ out of CD4+ T cells were in average reduced from 26.52% at baseline (N=17) to 12.4% at Day 85 (N=15). The reduction was not observed with placebo, the proportion of %PD-1+ out of CD4+ T cells were in average increased from 25.8% at baseline (N=8) to 29.53% at Day 85 (N=7) in the placebo group.

The mean change from baseline was -12.83% in CDZ173 70 mg bid group and 2.4% in placebo group for overall patient population

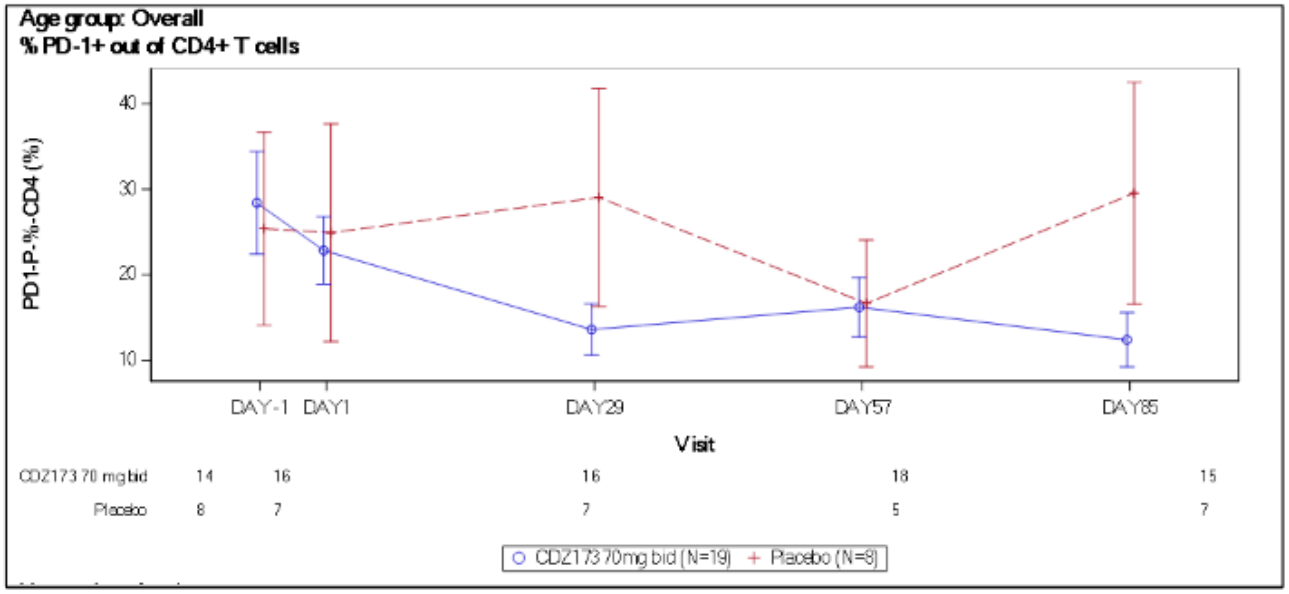


Figure 15: Mean (SE) of %PD-1+ out of CD4+ T cells – Part II (PD analysis set)

Encouraging results were obtained with the decrease of inflammatory biomarkers such as CXCL13 (In the CDZ173 70 mg bid group, the concentrations (mean) of CXCL13 were decreased from 401 pg/mL at baseline (N=19) to 114.3 pg/mL at Day 85 (N=19). In the placebo group, the concentrations of CXCL13 were increased from 473.8 pg/mL at baseline (N=8) to 594.4 pg/mL at Day 85 (N=7). The mean change from baseline was -61.68% in CDZ173 70 mg bid group and 9.35% in placebo group for overall patient population), IP-10 (In the CDZ173 70 mg bid group, the concentrations (mean) of IP-10 were decreased from 748.97 pg/mL at baseline (N=19) to 611.91 pg/mL at Day 85 (N=19). In the placebo group, the concentrations of IP-10 were increased from 392.4 pg/mL at baseline (N=8) to 501.9 pg/mL at

Day 85 (N=8). The mean change from baseline was -0.60% in CDZ173 70 mg bid group and 26.65% in placebo group for overall patient population.) and TNF-α (In the CDZ173 70 mg bid group, the concentrations (mean) of TNF-alpha were decreased from 18.2 pg/mL at baseline (N=19) to 12.7 pg/mL at Day 85 (N=19). In the placebo group, the concentrations of TNF-alpha were 18.1 pg/mL at baseline (N=8) and 18.8 pg/mL at the end of the treatment period (Day 85) (N=8). The mean change from baseline was -27.3% in CDZ173 70 mg bid group and -0.47% in placebo group for overall patient population) as well as a reduction of IgM compared to placebo group. However, no difference could be observed for activity parameters.

The immune reconstitution that occurs after initiation of leniolisib with respect to correction of immunoglobulin profile normalization is most apparent in IgM reduction in the 12-week treatment period. This change in IgM aligns with the early correction of % naïve B cells. In the CDZ173 70 mg bid group, the concentrations (mean) of IgM were decreased from 3.70 g/L at baseline (N=19) to 1.65 g/L at Day 85 (N=19). In the placebo group, the concentrations of Ig M were 4.54 g/L at baseline (N=8) and 4.54 g/L at the end of the treatment period (Day 85) (N=8). The mean change from baseline was -33.52%

in CDZ173 70 mg bid group and 2.99% in placebo group for overall patient population. IgG value interpretations are extremely difficult, as most patients were on supplemental Ig during the 12-week treatment period and baseline IgG prior to IRT was not known. Therefore, the applicant's conclusion that this data might be considered as an indication of appropriate class switching and normalization of antibody function with continued leniolisib exposure can be supported.

- **Ancillary analyses**

Subgroup analyses are described in the above section Outcomes and estimation.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later section 3. Benefit-Risk Balance).

Table 14: Summary of Efficacy for trial 2201

<table>
<tr><td colspan="3"><u>Title</u>: An open-label, non-randomized, within-patient dose-finding study followed by a randomized subject, investigator and sponsor-blinded, placebo-controlled study to assess the efficacy and safety of CDZ173 (leniolisib) in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)</td></tr>
<tr><td>Study identifier</td><td colspan="2">Study code: CCDZ173X2201 (part II)
EudraCT number: 2014-003876-22</td></tr>
<tr><td>Design</td><td colspan="2">Double-blind, randomised, assessor-blind, placebo-controlled, multicenter (Europe and North America) trial to evaluate the efficacy and safety of leniolisib compared to placebo in patients (children from 12 years old and adults) with documented activated phosphoinositide 3-kinase delta syndrome (APDS).
Patients were randomly allocated to one of the two treatment groups in a 2:1 ratio to receive either 70 mg CDZ173 bid or matching placebo for a 12-week period in a patient, investigator and sponsor blinded fashion.
Efficacy, safety and PK assessments were performed at scheduled times.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:

Duration of Extension phase:</td><td>12 weeks of treatment.
Study initiation date: 05-Dec-2017 (FPFV)
Study completion date: 16-Aug-2021 (LPLV)

not applicable

not applicable.
Patients were permitted to roll over to the extension study (CCDZ173X2201E1) at the End of treatment visit.</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Leniolisib is superior to placebo in the improvement of lymphadenopathy and immunophenotype normalization over a 12-week treatment period as measured by respectively:
- Change of the log10 transformed SPD of index lesions from baseline
- Increased percentage of naïve B cells out of total B cells</td></tr>
</table>

Treatments groups	CDZ173		Leniolisib 70 mg bid 21 patients randomized 12 weeks of treatment
	placebo		Placebo bid 10 patients randomized 12 weeks of treatment
Endpoints and definitions	Co-Primary endpoint	Lymphadenopathy	Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions
	Co-Primary endpoint	Immunophenotype normalization	Change from baseline in percentage of naïve B cells out of total B cells
	Secondary endpoint	Log-Transformed Non-Index Lesions	MRI/CT imaging: Log10-transformed 3D volume of measurable non-index lesions
	Secondary endpoint	Log-Transformed Index Lesions	MRI/CT imaging: log10-transformed 3D volume of index lesions
	Secondary endpoint	Spleen Organ Volume	MRI/CT imaging: 3D volume of the spleen
	Secondary endpoint	Spleen Bi-Dimensional Size	MRI/CT imaging: bi-dimensional size of the spleen
	Secondary endpoint	SF-36	SF-36 (Short Form 36) Survey - Physical and Mental Functioning
	Secondary endpoint	WPAI-CIQ	WPAI-CIQ (Work Productivity Activity Impairment plus Classroom Impairment Questionnaire)
	Secondary endpoint	PAG	Visual analogue scales for PGA
	Secondary endpoint	PtGA	Visual analogue scales for PtGA
	Secondary endpoint	PK	Single dose CDZ173 PK parameters (including but not limited to Cmax and AUC) and trough evaluations after multiple dose
	Secondary endpoint	Biomarkers	C-reactive protein (CRP), Lactate dehydrogenase (LDH) Beta2 microglobulin, ferritin, fibrinogen and erythrocyte sedimentation rate (ESR)
	Secondary endpoint	Safety	All safety parameters, including adverse events (AEs), physical exam, vital signs, electrocardiogram (ECG), safety laboratory (hematology, blood chemistry, urinalysis)
	Secondary endpoint	Narratives	Narratives to assess the treatment benefit to individual patients

Database lock	19-Oct-2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The safety analysis set will include all patients that received any study drug. The PK analysis set will include all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data. The PD analysis set will include all patients who received any study drug and with no protocol deviations with relevant impact on PD data. Primary analysis of PD population: change from baseline at Day 85.		
Descriptive statistics and estimate variability	Treatment group	CDZ173	placebo
	Number of subjects	18	8
	Lymphadenopathy Adjusted Mean Change (SE)	-0.30 (0.04)	-0.06 (0.06)
	Number of subjects	8	5
	Immunophenotype normalization Adjusted Mean Change (SE)	34.76 (3.08)	-5.37 (3.95)
Effect estimate per comparison	Co-Primary endpoint Change from baseline in the log10 transformed sum of product diameters (SPD) of index lesions	Comparison groups	CDZ173 (N=18) and placebo (N=8)
		difference in adjusted mean change (SE)	-0.24 (0.06)
		95% CI	-0.37, -0.11
		P-value ANCOVA	0.0012
	Co-Primary endpoint Change from baseline in percentage of naïve B cells out of total B cells	Comparison groups	CDZ173 (N=8) and placebo (N=5)
		difference in adjusted mean change (SE)	40.13 (5.04)
		95% CI	28.51, 51.75
		P-value ANCOVA	p<0.0001
	Secondary endpoint Log-Transformed Non-Index Lesions	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		Adjusted mean difference (95%CI)	-1.84 (-2.85, -0.84)
		P-value	p=0.0011
	Secondary endpoint	Comparison groups	CDZ173 (N=19)

	Log-Transformed Index Lesions		and placebo (N=8)
		Adjusted mean difference (95%CI)	-0.90 (-2.67, 0.88)
		P-value	P > 0.05
	Secondary endpoint Spleen Organ Volume	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		Adjusted mean difference (95% CI)	-194665.95 (-300125.06, -89206.83)
		P-value	p=0.0009
	Secondary endpoint Spleen Bi-Dimensional Size	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		Adjusted mean difference (95% CI)	-1472.70 (-2517.15, -428.26)
		P-value	p=0.0079
	Secondary endpoint SF-36	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		The analysis of covariance of change from baseline at Day 85 in SF-36 did not show statistically significant results, neither on mental component summary (2-sided p=0.6336) nor on physical component summary (2-sided p=0.8041) for CDZ173 70 mg bid group vs placebo group.	
	Secondary endpoint WPAI-CIQ	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		The analysis of covariance of change from baseline at Day 85 in WPAI-CIQ for all patients did not show statistically significant results on percent activity impairment due to health (2-sided p=0.7975) for CDZ173 70 mg bid group vs placebo group.	
	Secondary endpoint PAG	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		Adjusted mean difference (95% CI)	-4.74 (-19.94, 10.46)
		P-value	p=0.5248
	Secondary endpoint PtGA	Comparison groups	CDZ173 (N=19) and placebo (N=8)
		Adjusted mean difference (95% CI)	9.64 (-5.56, 24.84)
		P-value	p=0.2021
Notes	The primary analysis of naïve B cells included only patients who had Baseline and end of treatment naïve B-cell measurements and who also had a reduced percentage of naïve B-cell counts (defined as below 48%) at Baseline.		

2.6.5.3. Clinical studies in special populations

Although the applicant plans to conduct paediatric studies in patients aged from 1 to 12 years (a waiver has been granted from birth to less than 1 year of aged), no data on children below 12 or below the weight of 45 kg are currently available, as reflected in SmPC section 4.2.

In addition, no data are available for patients >65 years old. This is reflected in section 4.2 of the SmPC. No study was conducted in patients with hepatic or renal impairment either, as reflected in SmPC section 4.2.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Patients were genetically tested to confirm documented activated phosphoinositide 3-kinase delta syndrome (APDS).

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

Not applicable

2.6.5.6. Supportive study

Study 2201E1 part 3 was the open label long term extension part of study 2201. 37 patients were enrolled; 35 patients were previously treated with leniolisib or placebo in Study 2201 (Part 1 and Part 2); and 2 patients were previously treated with seletalisib, an investigational PI3Kδ inhibitor other than leniolisib.

The two patients previously treated with seletalisib were not included in the Study 2201 Part 2 Randomised Controlled Trial (RCT) and as such do not contribute to the 12-week controlled dataset. These two patients met the inclusion/exclusion criteria for the open label extension (OLE) Study 2201E1, and in particular the previous or concurrent use of immunosuppressive medication such as use of a PI3Kδ inhibitor within 6 weeks prior to first dosing. These patients, initially included in the placebo group in the first OLE interim analysis dated 13 December 2021 (placebo n=11), were excluded from the placebo group in the second OLE interim analysis with a data extraction date of 13 March 2023 (placebo n=9).

In extension part 3 of study 2201, all patients received leniolisib. The primary objective of this study part was to evaluate the long term safety and tolerability of leniolisib in patients with APDS. Secondary objectives included the long-term efficacy of leniolisib to modify health-related quality of life and the long-term efficacy of leniolisib by means of biomarkers reflecting the efficacy of leniolisib to reduce systemic inflammatory components of the disease in patients with APDS.

None of the patients discontinued from the study due to lack of efficacy.

At the data lock point of study 2201E1 (23 September 2025), the mean [SD] duration of exposure was 214.5 weeks [84.78], range 62.3 to 362.7 weeks. Overall, in the extension study, all participants had at least 60 weeks of leniolisib treatment, 31/37 participants (83.8%) had ≥108 weeks of leniolisib exposure, and 10 participants (27.0%) had ≥260 weeks of leniolisib exposure.

Results for health-related endpoints were overall consistent with results from part 2 of study. Mean changes from baseline were minimally improved, although the absence of comparison impairs the assessment.

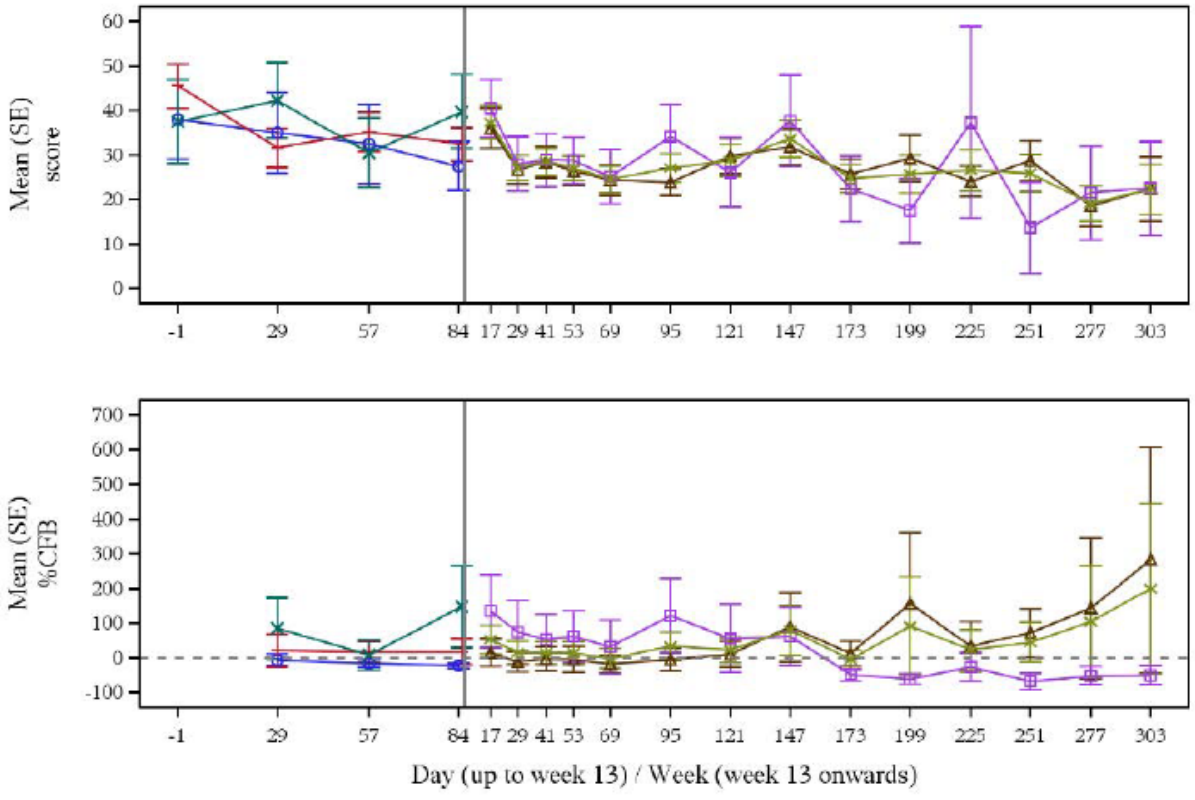
Patients and physician global assessment both suggested decreases from D84 to D2002. Both questionnaires suggested a diminished disease activity (physician's questionnaire) and a better well-being (patient's questionnaire). However, these results should be interpreted cautiously as this extension part is not controlled. Indeed, in controlled part 2 of the study, Physician's global assessment tended to decrease in placebo group similarly to leniolisib.

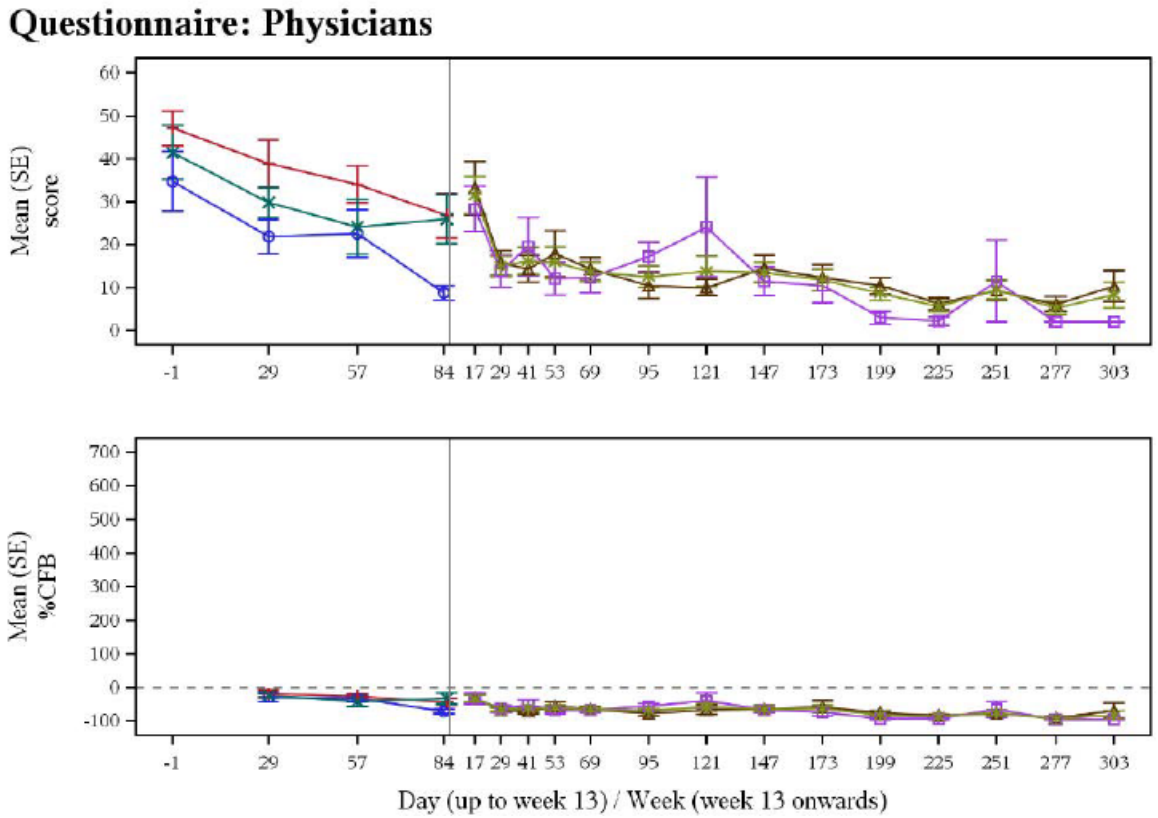
Table 15: Mean (SE) Global Physician and Patient Global Assessment Questionnaire Profiles in Study 2201E1 through Week 303 - PD Analysis Set

Study	N	Day 84 (Week 12) Mean CFB (SD)	N	Day 364 (Week 52) Mean CFB (SD)	N	Day 2002 (Week 286) Mean CFB (SD)
Physician Global Assessment						
2201E1	31	-31.4131 (17.81740)	30	-31.8086 (18.92644)	4	-34.6628 (13.56075)
Patient Global Assessment						
2201E1	37	-14.6591 (21.41781)	33	-16.0616 (20.44174)	8	-14.4234 (32.12125)

CFB=change from baseline, SD=standard deviation.
For Parts 1 and 2 baseline was the respective baseline from Part 1 or Part 2. For the extension study the baseline was taken as the Part 1 or 2 baseline if there was no gap longer than 6 weeks between the end of the respective Part 1 or 2 to the beginning of the extension study. If there was a gap longer than 6 weeks, the baseline was the start of the extension. For subjects that did not participate in either Part 1 or Part 2 then the start of the extension study was their baseline.

Questionnaire: Patients



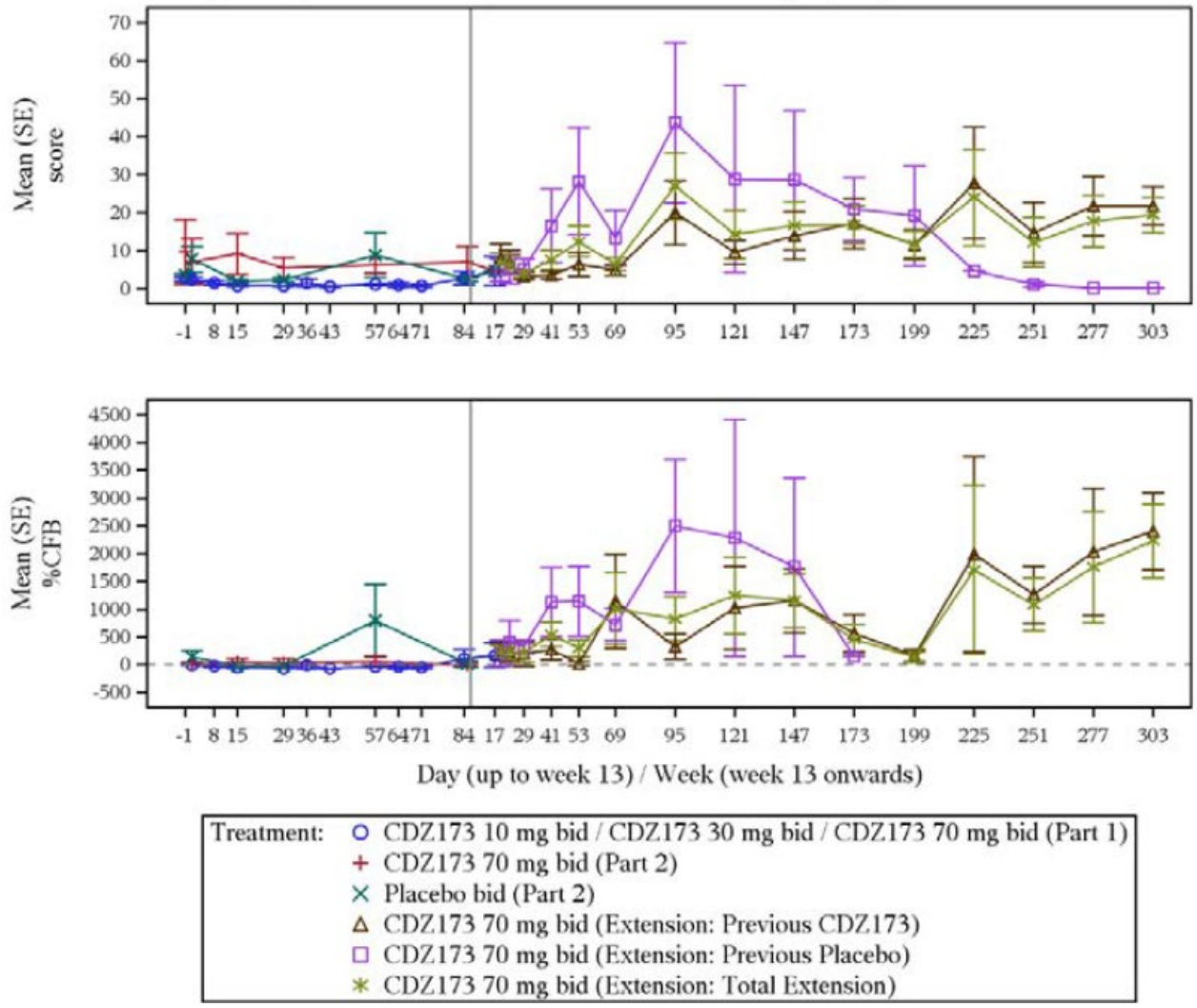


Vertical reference line indicates the change in units on the x-axis from Day to Week. Week is relative to the start of Study CCDZ173X2201. Data have been scaled to increase the area up to week 13. Physician questionnaire: Considering all the ways APDS/PASLI affects your patient, how well his or her condition A rating of 0 indicates no disease activity, and 100 indicates maximal disease activity.
Patient questionnaire: Considering all the ways APDS/PASLI affects you, please indicate how well you are doing. Original rating of 0 indicates very poor, and 100 indicates very good.
For the purposes of this output these scores of patient questionnaire have been transformed so that 0 indicates very good and 100 indicates very poor to be comparable to the Physician questionnaire.

Figure 16: Mean Patient Global Assessment Questionnaire and Physician Global Assessment Questionnaire Profiles through Week 303 (PD Analysis Set)

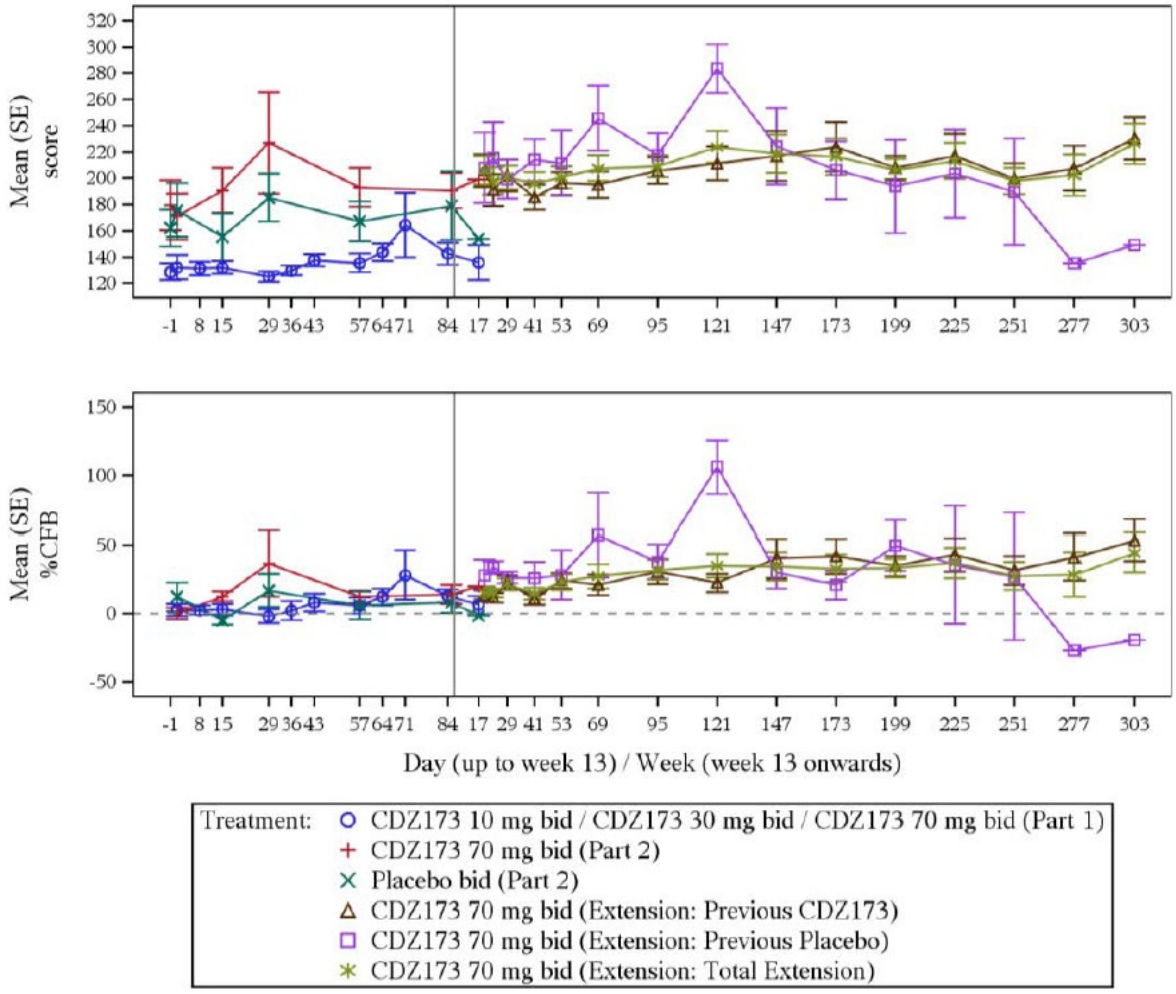
In general, results for the patients with/without prior exposure to leniolisib were comparable to all extension study patients combined.

HsCRP and LDH were assessed as secondary endpoints to evaluate the long-term effect of leniolisib on systemic inflammatory biomarkers, but results did not evidence a decrease from D84.



Vertical reference line indicates the change in units on the x-axis from Day to Week. Week is relative to the start of Study CCDZ173X2201. Data has been scaled to increase the area up to Week 13

Figure 17: Mean hsCRP (mg/L) Profiles (PD Analysis Set)



Vertical reference line indicates the change in units on the x-axis from Day to Week. Week is relative to the start of Study CCDZ173X2201. Data has been scaled to increase the area up to Week 13.

Figure 18: Mean LDH Profiles (PD Analysis Set)

Exploratory outcomes

Exploratory objectives were the exploration of biomarkers that may provide additional measures of efficacy (soluble biomarkers, EBV and CMV viremia, EBV and CMV lytic and latent in blood, EBV DNA in saliva, IgM, IgG, IgA, T and B cell immunophenotyping) and the assessment of the impact on lymphadenopathy (non-index lesions and spleen) on patients who participated in study 2201.

Shift in EBV DNA from negative at baseline to positive post-baseline were reported for 1 participant (4.5%) at Extension Day 1, 5 participants (20.0%) at Day 84, 4 participants (16.7%) at Day 168, and for 5 participants (20.8%) at Day 252 and shifts in CMV DNA from negative at baseline to positive post-baseline were reported for 1 participant (4.8%) at Extension Day 1, 1 participant (4.3%) at Day 169, and 1 participant (4.5%) at Day 252.

Overall, for inflammatory biomarkers, on top of the fact that part 3 was not controlled, the majority of results for CFB are impaired by a large variability. Nevertheless, most of the biomarkers showed decrease from baseline.

Updated analyses of cell biomarkers suggest that the percentage of naïve B cells increased while transitional B cells decreased with continued leniolisib 70 mg twice daily treatment.

Overall, for all class of Ig, after an initial increase, the mean return to baseline. For all the class also, the mean Ig stays approximately at the baseline value for all patients. The initial spikes (IgA/IgE) and persistent low IgG/IgM are not further commented.

For imaging results (up to week 13), decrease from baseline in liver bi-dimensional size was very modest (less than 2.5%, with a large variability) and was similar for 3D volume (except that change from baseline was closer to 5%). However, results for spleen bi-dimensional size and 3D volume and sum of product diameters of index lesions were supportive of efficacy findings in part 2.

Infection rate was assessed as a secondary endpoint during the extension part of study 2201.

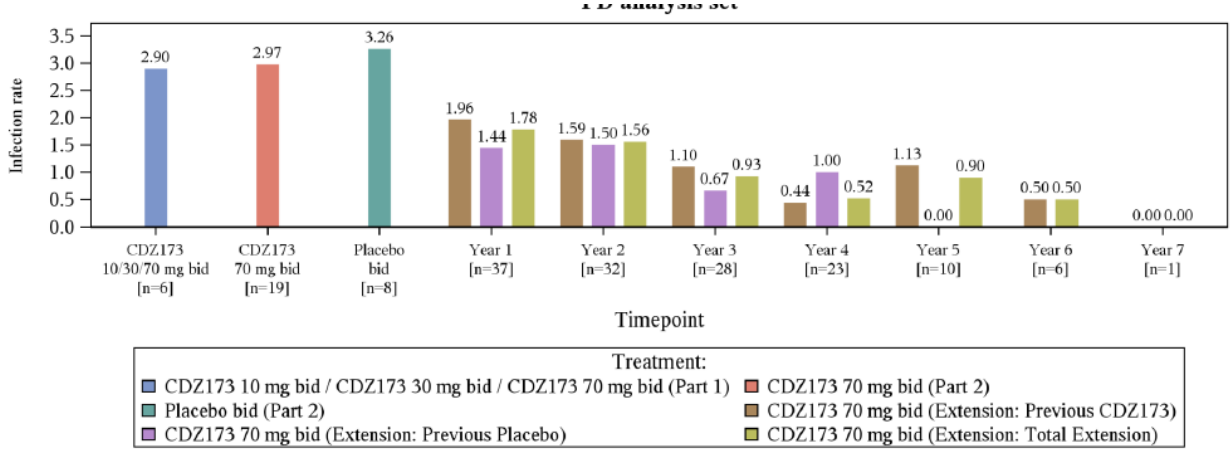


Figure 19: Barchart of Infection Rates in Study 2201E1 – PD Analysis Set

In addition, the frequency of antibiotic intake did not decrease along the years as a result of the claimed reduction of infections.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The initial Marketing Authorisation Application for leniolisib included the results from the pivotal Phase 2/3 study (2201 part 1 and part 2) in APDS patients, as well as the analyses from the long-term extension study (2201E1).

Study 2201 part 1 was an open label, non-randomized, dose finding study performed in 6 patients with APDS. The primary objective was the dose-PD and PK/PD relationship of leniolisib in patients with APDS. Efficacy was the secondary endpoint. Safety, tolerability, PK, and *in vivo* PD were assessed at 10, 30, and 70 mg of leniolisib twice daily.

Study 2201 part 2 was the randomised, triple-blind, placebo-controlled study in which 31 APDS patients received 70 mg bid leniolisib or placebo bid for 12 weeks.

The extension Study 2201E1 was an open-label, non-randomised study and included patients who rolled over from Study 2201 (part 1 or part 2) or patients who "were treated with another PI3Kδ inhibitor" (n= 37 patients total in Extension Study [n= 6 from Study 2201-part 1; n= 29 from Study

2201-part 2; n=2 new patients not involved in previous trials]). A total of 38 patients with APDS were treated with leniolisib in the clinical program.

The primary support for the efficacy of leniolisib are the efficacy data from Study 2201 part 2: the randomized, placebo-controlled, blinded part of study 2201. The main objective was to assess the efficacy of leniolisib at the selected dose of 70 mg BID. Patients received leniolisib or placebo (2:1) for 12 weeks. At the end of part 2, patients could continue to receive leniolisib in the extension part 3 of study 2201. Main inclusion criteria were male and female patients aged 12 to 75 years who had a documented APDS/PASLI-associated genetic PI3K delta mutation. Patients with mutations in either PIK3CD or PIK3R1 could be included. Of note, denomination APDS and PASLI refer to the same pathology. Thus, the intended indication is in line with the studied population. Leniolisib is expected to be active in patient with a PIK3R1 mutation based on the mechanism of action and the fact that there is currently no evidence that PIK3CD and PIK3R1 mutation led to different phenotypes and no evidence that APDS1 and APDS2 should be treated differently. In Study 2201, patients needed to have documented APDS/PASLI, as confirmed genetic testing. No genetic testing is required in the SmPC since the diagnosis of APDS includes genetic testing and treatment must be initiated by a physician experienced in the management of primary immune deficiencies.

Main exclusion criteria were previous or concurrent use of immunosuppressive medication, current use of medication known to be strong inhibitors, or moderate or strong inducers of isoenzyme CYP3A, current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index and uncontrolled chronic or recurrent infectious disease (except those that are considered to be characteristic of APDS/PASLI). This is acceptable.

The applicant justified the use of a placebo *in absence of disease-modifying approved treatment*. This was acceptable to the CHMP as leniolisib is used on top of standard of care treatment and pre-established symptomatic and supportive treatments. Patients treated with immunosuppressive medications such as mTOR or PI3Kδ inhibitors within 6 weeks of baseline as well as with previous or concurrent B-cell depleting medications (e.g., rituximab) within 6 months of baseline were excluded. The applicant justified that immunosuppressive concomitant medications (mTOR, B-cell depleting medications), were an exclusion criteria based on their potential to increase susceptibility to infection. Immunosuppressive therapies were not allowed during the treatment period. Thus, at least 7 patients had sirolimus treatment interrupted before they entered the study, some of which received sirolimus for several years.

Main exclusion criteria were previous or concurrent use of immunosuppressive medication, current use of medication known to be strong inhibitors, or moderate or strong inducers of isoenzyme CYP3A, current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index and uncontrolled chronic or recurrent infectious disease (except those that are considered to be characteristic of APDS/PASLI). This is acceptable.

The two co-primary endpoints were "change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging" and "change from baseline in percentage of naïve B-cells out of total B-cells". Given the recent identification of the disease, there are not yet established clinical endpoints for APDS. The applicant did not seek for scientific advice from the CHMP. The co-primary endpoints were met. However, the CHMP requested input from an ad hoc expert group to discuss the clinical relevance of the co-primary study endpoints and of the observed effects (see below). Secondary objectives did include some clinical criteria: the effect on index lesion, non-index lesion and spleen by MRI/CT imaging, health related quality of life, Physician's and Patient's Global assessment, assessment of biomarkers of systemic inflammatory components of the disease, and benefit to individual patients through narrative. In addition, exploratory objectives included patient and physician global assessment, effect on physical

activity level, impact of liver, effect of B and T-cells, frequency of infections and alternative biomarkers.

Frequency of infections, which is an important feature of APDS because recurrent upper and lower respiratory tract infections routinely progressing to irreversible bronchiectasis, was only assessed as an exploratory endpoint.

Whereas the CHMP noted that infections should have been considered as an important endpoint, it was acknowledged that, differences in infection rates would have been difficult to assess considering the short duration of this part of the study (12 weeks) and the low number of patients.

Study 2201 Part 2 was a double-blind randomised study. It was noted, however, that the randomisation was not stratified for any patient characteristics at baseline. In the absence of stratification, the balance of demographics, baseline characteristics and any variable known to be associated with efficacy outcomes required careful assessment. Following a clarification from the applicant, the randomisation assignment scheme and validated system are considered adequately described by the applicant.

There were a few methodological issues raising concerns over the reliability of efficacy analyses. Indeed, the analysis population for each primary endpoint excluded a substantial number of patients, especially considering the already small total sample size. In particular, the rationale for excluding subjects with a percentage of more than 48% of naïve B cells at baseline from the co-primary endpoint analysis was not understood. In addition, the definition of the primary analysis sets was modified post-hoc, i.e., after database lock, with an updated list of protocol deviations leading to exclusion from the analysis populations. The handling of missing data in efficacy analyses raised further concerns: the analyses of both primary endpoints simply excluded patients with either missing baseline or end of treatment measurements. Unless data are missing completely at random (not a realistic assumption), the CHMP raised concerns as the exclusion of patients with missing data would likely result in biased treatment effect estimates. The applicant's responses confirmed the lack of pre-specification of the deviations leading to exclusion of the PD analysis, as well as the arbitrariness of the 48% threshold for defining the subset for the analysis of naive B cells. This highlighted the need for an assessment of consistency with results based on a wider analysis set. Upon the CHMP's request, the applicant provided analyses on the full safety analysis set, as well as statistical analyses exploring alternative handling of missing data. These analyses showed consistent results supporting the reliability of the primary study results.

Overall, 20 out of 31 patients reported at least one protocol deviation, under the deviation categories "other" (16 patients, 51.6%), prohibited concomitant medication (3 patients, 9.7%), selection criteria not met (5 patients, 16.1%) and study treatment deviation (1 patient, 3.2%). Five patients reported protocol deviations due to COVID-19 pandemic restrictions. These protocol deviations were reported under categories of drug supply method changed due to COVID-19 pandemic restrictions (one patient in the leniolisib 70 mg bid group and none in the placebo group), assessment or procedure changed due to COVID-19 pandemic restrictions (2 patients in the leniolisib 70 mg bid and 3 patients in the placebo group), missed visit due to COVID-19 pandemic restrictions (one patient in the leniolisib 70 mg bid and none in the placebo group) and visit done outside of study site due to COVID-19 pandemic restrictions (one patient each in the leniolisib 70 mg bid and in the placebo group).

Of note, 9/21 patients in the leniolisib arm (42.9%) and 3/10 (30%) subjects in the placebo arm showed failure to perform key procedures in accordance with protocol requirements (in total 12/31 patients [38.7%]. It should be also noted that only 13 patients were included in the naïve B cell analysis. The rate of protocol deviation was high (reported in 20 out of 31 patients). Nevertheless,

supplementary analyses provided reassurance on the consistency of study conclusions when considering wider analysis sets, i.e. regardless of the inclusion of patients with protocol deviations.

There was no multiplicity adjustment necessary for the testing of the two (co)primary endpoints given that both required statistical significance at two-sided 5% level for a successful trial. Nevertheless, it is noted that there was no planned control of the type I error for secondary endpoints.

The applicant considered two different data transformations for the analysis of change from baseline in the index lesions: log10 transformation of the SPD (primary) and sum of the square root of the products of diameters (supportive). The applicant provided a non-parametric test for the comparison between leniolisib and placebo treatment groups. The results were consistent with the parametric analyses making use of log10 and square-root transformations, thereby confirming that the treatment effect does not appear to depend on the scale used for analysis. This is accepted.

Efficacy data and additional analyses

Dose finding study (Study 2201 part 1)

Pharmacodynamic results from this study are described in section 2.6.2.2. and resulted in the choice of the 70 mg BID dose for part 2 of the study, which is currently the intended dose for patients with APDS.

Results from secondary endpoints related to quality of life did not provide conclusive evidence which is probably due to the small sample size, the relatively short evaluation period and the heterogeneity of the patient group including adolescent patients.

Exploratory endpoints of the dose response part of study 2201 provided supportive evidence of the benefit of leniolisib treatment with regard to the limited data.

Main study (Study 2201 part 2):

On the 32 patients who were assessed for eligibility in the efficacy part 2 of study 2201, 31 patients were included, of which 21 were randomized in leniolisib arm and 10 in placebo arm. Of these, 19/21 patients in leniolisib arm and 8/10 in placebo arm were included in the PD analysis set.

Although the randomization was not stratified (considering the limited number of patients), demographic characteristics were balanced between treatments groups with a median age (range) of 20.0 years (12, 54) and 19.5 years (15, 48) in leniolisib and placebo group respectively and with around 60% of patients > 18 years in both groups. To be noted, the older patient was 54 years at the start of the treatment. Male and female were balanced within both treatments groups and patients were predominantly Caucasian.

In the leniolisib arm of study 2201 part 2, 61.9% of patients (n=13/21) were ≥18 years of age and 38.1% of patients (n=8/21) were <18 years of age. Additionally, approximately 1 year after the start of part 2, the minimum age was lowered from 16 to 12 years. The CHMP noted the low number of patients aged <18 years, in particular of patients aged 16 to 12 years. However, regarding efficacy, there were no differences in treatment effect seen in adolescents (12 to <18 years of age) compared with adults (≥18 years). Regarding safety, no significant differences in safety profiles were apparent in the adolescent population compared to the adult population. Therefore, taking into account the comparable data in efficacy and safety in adult and adolescent, the claim for an indication covering adolescents 12 years and older is agreed.

<u>Different pattern mutations</u>

While PIK3CD mutation represented the majority of mutations in both treatment groups, only 5 patients in leniolisib group and 1 patient in placebo group presented a PIK3R1 mutation.

It should be noted that sites recruited patients with PIK3R1 mutation (APDS2 patients) at a later stage than patients with PIK3CD mutation (APDS1 patients). This could explain the lower number of patients diagnosed with APDS2 (n=6) versus APDS1 (n=25) in study 2201. Also, in extension Study 2201E1, 78.4% of patients had documented APDS with a variant PIK3CD (n=29/37), whereas 21.6% of them (n=8/37) had PIK3R1 variant.

The applicant provided justification that leniolisib is expected to be active in patients with a PIK3R1 mutation based on the mechanism of action. Indeed, gain of function mutation in PIK3CD codes for the p110d catalytic subunit and leads to the development of APDS1. Loss of function in PIK3R1 codes for the p85a regulatory subunit and leads to the development of APDS2. Given the recognised phenotypic heterogeneity of APDS and the shared downstream activation of the PI3Kδ pathway associated with mutations in both catalytic and regulatory subunits, no clear evidence is currently available to support clinically meaningful differences at baseline or the need for differentiated treatment strategies between APDS1 and APDS2.

The comparison of concomitant medication between both treatment groups was impaired by the limited number of patients. It can however be noticed that the use of corticosteroids and anilides, the two most represented class of concomitant medications were similar between both groups but that antibiotics appeared twice more frequently used in placebo group than in leniolisib group.

Outcomes

The first co-primary endpoint "change from baseline in the log10 transformed sum of product diameter (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging" was analysed on the PD analysis set.

Although data of 19 patients in leniolisib group were analysed for this first co-primary endpoint, results for 18 patients were included as 1 patient had an index lung lesion identified at baseline that had fully resolved (0 mm) by Day 85. Therefore, the log10 could not be derived. Thus, this one patient with a complete resolution had not been analysed although it could have positively impacted the results.

In the analysed population, the change from baseline in the log10 transformed SPD (SE) was -0.30 (0.04) in the leniolisib group vs 0.06 (0.06) in placebo group. The difference in adjusted mean change (95% CI) of leniolisib 70 mg bid (N=18) vs placebo (N=8) was -0.24 (-0.37, -0.11). The results were statistically significant with 2-sided p-value observed as p=0.0012 and the difference was higher than the difference of -0.225 used to calculate the sample size.

A subgroup analysis was presented for patients with APDS1 or APDS2, while results in APDS1 patients remained consistent with primary analysis, no comparison could be presented for patients with APDS2 as there was only 4 patients in leniolisib group and no patient in placebo group. Of note, results of patients with APDS2 in leniolisib group were consistent with primary analysis.

A higher reduction in the size of lymph nodes (as well as a slightly higher increase in the mean change from baseline in naïve B cells) was observed in male patients compared to female patients following treatment with leniolisib. Gender differences in the magnitude and timing of improvement in lymphoproliferation and immunophenotype correction cannot be ruled out.

Finally, the supportive analysis of change from baseline at Day 85 in the sum of the square root of the products of diameters of index lesions, including the patient with complete resolution of lung lesion was consistent with the main analysis, providing additional evidence of beneficial effect of leniolisib on lymphadenopathy which is one of the main hallmarks of APDS.

Thus, the analysis of lymphadenopathy supported a beneficial effect of leniolisib in patients with APDS.

Regarding the second co-primary endpoint, "change from baseline in percentage of naïve B cells out of total B cells", a significant number of patients were excluded from the analysis, further reducing the number of patients analysed. Indeed, only 8 patients in leniolisib group and 5 patients in placebo group were analysed. The main reason for exclusion from this analysis was a percentage of more than 48% of naïve B cells at baseline, which was determined as the cut-off for considering reduced percentage of naïve B cells in the protocol. This probably reflected the heterogeneity in the presentation of the population. Overall, while the population is already limited for one co-primary endpoint, the data become scarce for the second primary endpoint. Although acknowledging the limitations, the results were still considered relevant.

Patient demographics for patients included in naïve B-cell analysis showed that only one patient harboured PIK3R1 mutation (leading to APDS2) in leniolisib group and none in placebo group.

The results for the primary analysis of change from baseline in naïve B cells in patients with a percentage of less than 48% of naïve B-cells at baseline (adjusted mean change, SE) showed a statistically significant increase in leniolisib arm (34.76, 3.08) compared to placebo arm (-5.37, 3.95).

A sensitivity analysis which included patients with a baseline percentage of naïve B-cells at baseline > 48%, was also impaired by the lack of assessment at different time points (notably at D85). Nevertheless, those results suggested a consistency with the primary analysis.

A supportive analysis was conducted on the PD analysis set (n=19 in leniolisib group and n=8 in placebo group), thus increasing the number of patients analysed. Results showed a significant increase in naïve B-cell compared to placebo from D29 up to D85, consistently with primary analysis. In addition, immature transitional B-cell that are elevated and sequestered in the lymph nodes or spleen of patients with APDS, significantly decreased to reach 8.7% at D85 in leniolisib group compared to 33.8% in placebo group further supporting primary analysis.

Secondary endpoints

Secondary endpoints were considered particularly important in this procedure in which both co-primary endpoints do not reflect clinical outcome *per se*. Secondary endpoints included imaging, health-related questionnaires, Patient's and Physician's global assessment and inflammatory biomarkers.

Imaging secondary endpoints included 3D volume assessment of index and measurable non-index lesions, and 3D volume and bi-dimensional size of the spleen (liver assessment was an exploratory endpoint). These assessments were conducted on PD analysis set (27 patients).

Overall, in the leniolisib group, the mean SPD volume of index lesion, and the mean bi-dimensional size and volume of spleen both decreased at the end of treatment compared to baseline, while there was no or minimal change in the placebo group. This also supports a beneficial effect of leniolisib.

Results of health quality of life questionnaire, Patient's and Physician's global assessment and inflammatory biomarkers failed to highlight any difference between treatment groups. Narratives have been read and overall it is difficult to highlight global improvement not already captured by other endpoints. Indeed narratives report mostly patients feeling or daily activities/sport, fatigue or lymphadenopathy.

No studies examined the measurement characteristics of the APDS-specific PGA/PtGA among APDS patients. Therefore, despite an improvement in activity and energy levels reported in leniolisib group, PtGA and PGA should only be considered supportive, but not clinically meaningful.

Infections were captured as an exploratory endpoint, but the use of antibiotic medication did not allow to highlight a difference between treatment groups. As expected, almost 2/3 of patients received antibiotic medication which was started in many cases prior to treatment start with study medication. Azithromycin was the most frequently used antibiotic. Evaluating the use of antibiotic medication did not allow an unequivocal differentiation between leniolisib and placebo-treated patients; as, the study duration was too short (12 weeks) to assess any assess clinically meaningful measure. However, considering that infections are an important hallmark of APDS, it should be further investigated. Thus, in order to explore any effect of leniolisib on infection rate, the applicant provided an externally controlled cohort comparison with a cohort from the ESID (European Society for Immunodeficiencies registry) registry. Overall, while the results of these data would have supported a clinical benefit of leniolisib in patients with APDS, the important differences in both study groups prevent from any conclusion. In the context of a marketing under exceptional circumstances, the applicant has committed to perform Specific Obligations that will provide further data on long term efficacy of leniolisib in patients with APDS as further discussed in Section 3.7.3.

Although a reduction in senescent CD57+ cells out of CD8+ cells in leniolisib treated patients compared to placebo treated patient was acknowledged, results were less obvious for PD-1+ out of CD4+ cells. Encouraging results were obtained with the decrease of inflammatory biomarkers such as CXCL13, IP-10 and TNF-α as well as a reduction of IgM compared to placebo group. However, no difference could be observed for activity parameters.

The immune reconstitution that occurred after initiation of leniolisib with respect to correction of immunoglobulin profile normalization was most apparent in IgM reduction in the 12-week treatment period. This change in IgM aligned with the early correction of % naïve B cells. IgA and IgE concentrations increased during treatment with leniolisib while IgG and its sub-classes IgG1, IgG2 and IgG3 showed small decreases. IgG value interpretations were extremely difficult, as most patients were on supplemental Ig during the 12-week treatment period and baseline IgG prior to IRT was not known. Therefore, the CHMP considered that these data were indicative of appropriate class switching and normalisation of antibody function with continued leniolisib exposure.

The efficacy of leniolisib in the pivotal Study 2201 was based only on the PD co-primary endpoints. Considering the input from the experts during the Ad Hoc Expert Group (AHEG) consultation (see below), the CHMP agreed that these PD endpoints are expected to correlate into clinically relevant effects. The applicant also conducted a Delphi study to identify the most important outcomes when evaluating the effectiveness of APDS treatments in clinical practice and the amount of change in these outcomes that would indicate a meaningful benefit for a patient. Results were in favour of a clinically relevant effect associated with the co-primary endpoints analyses, supporting thus the expert's consensus. The CHMP agreed to include only the results of the co-primary endpoints in SmPC Section 5.1.

Supportive data

Supportive Open Label Extension study: 2201E1 OLE (study 2201 Part 3)

As of the data cut-off (25 Sept 2025), 37 patients received leniolisib 70 mg twice daily in the extension study, including all patients from Study 2201 part 1 and all but 2 patients from Study 2201 part 2. This also includes 2 patients who were not treated in Study 2201 but who were previously treated with an investigational PI3Kd inhibitor other than leniolisib. These two patients, previously treated with seletalisib, were not included in the Study 2201 Part 2 Randomised Controlled Trial (RCT) and as such did not contribute to the 12-week controlled dataset. These patients, initially included in the placebo group in the first OLE interim analysis dated 13 December 2021 (placebo n=11), were excluded from the placebo group in the second OLE interim analysis with a data extraction date of 13 March 2023

(placebo n=9). Comparative results on primary endpoints, including and excluding respectively these two patients, did not shown any significant difference and impact on clinical outcomes and effectiveness of the OLE study. The mean [SD] duration of exposure was 214.5 weeks [84.78], range 62.3 to 362.7 weeks. Overall, in the extension study, all participants had at least 60 weeks of leniolisib treatment, 31/37 participants (83.8%) had ≥108 weeks of leniolisib exposure, and 10 participants (27.0%) had ≥260 weeks of leniolisib exposure. None of the patients discontinued from the study due to lack of efficacy.

This study included efficacy secondary endpoints (inflammatory biomarkers, health related quality of life questionnaires and Patient's and Physician's global assessments).

The majority of results for change from baseline of inflammatory biomarkers were impaired by a large variability. Nevertheless, most of the biomarkers showed a decrease from baseline. Analyses of cell biomarkers suggested that the percentage of naïve B-cells increased while transitional B-cells decreased with continued leniolisib 70 mg twice daily treatment.

Results on health-related endpoints were consistent overall consistent with the results from the study's part 2. Mean changes from baseline were minimally improved, although the absence of comparison impaired the assessment.

Patient's and Physician's global assessment both decreased from D84 to D2002 thus suggesting diminished disease activity (physician's questionnaire) and a better well-being (patient's questionnaire). However, these results should be interpreted very cautiously as this extension part was not controlled. Indeed, in the controlled part 2 of the study, Physician's global assessment tended to decrease in placebo group similarly to leniolisib group.

Regarding EBV and CMV infections, periodic EBV/CMV DNA negative to positive shifts were observed and discussed. It is clinically plausible that intermittent low-level EBV and CMV viremia, including shifts from undetectable to detectable viral DNA, is part of the underlying disease biology rather than necessarily a treatment effect (Cohen 2018, Coulter 2018, Carpier 2018). The increased susceptibility to virus infections in these patients is likely due to a reduced number of long-lived memory CD8 T cells and an increased number of terminally differentiated effector CD8 T cells as well as impaired NK-cell cytotoxic function. The data provided do not allow for a conclusion on the potential role of leniolisib in CMV or EBV reactivation. Nevertheless, additional data on viral infections will be collected in the 10-years, registry-based, post-authorisation study (SOB01).

Regarding imaging results (up to week 13), decrease from baseline in liver (bi-dimensional and 3D) size was very modest. However, results for spleen bi-dimensional size and 3D volume and sum of product diameters of index lesions were supportive of efficacy findings in part 2.

An analysis of the infection rate over time was conducted to determine if there was a discernible trend in infection rates over the long-term extension study compared to the rates observed in the 12-week treatment period of the randomized controlled trial (study 2201 Part 2). Data from study 2201E1 suggested a pattern of decreasing infection rate with the limitation of small sample size and absence of comparative data. While a decrease in Ig replacement therapy is claimed by the applicant, results are difficult are difficult to interpret, especially on frequency of IRT along the years, as the number of patients with an assessment decreased with time. Additional analyses were requested to support these observations and a comparison study with patient from the ESID registry was provided. However, important bias pertaining to the comparability of both population (study 2201 and ESID) prevented any conclusion and was therefore not considered supportive. The clinical impact on infection rate must hence be taken into consideration. SOB01 will collect additional long-term data on this topic.

Overall, supportive data from the extension part were suggestive of a sustained effect, although formal conclusions are impaired by the lack of control group.

Additional expert consultation

Considering the rarity of the disease and the need for the treatment of these patients, an Ad-Hoc Expert Group (AHEG) has been consulted on the clinical relevance of the study results. The meeting took place on 27 November 2023.

Questions raised and input provided by the experts at this AHEG were as follows:

1. The pharmacodynamic activity of leniolisib has been demonstrated through the co-primary study endpoints. However, it is unclear whether this would translate into clinically relevant effects. Is the demonstrated activity likely to translate into clinical benefit for APDS patients? If yes, please explain why you think so.

Summary: The experts were of the consensus view that the pharmacodynamic activity of leniolisib, demonstrated through the co-primary endpoints in the studied population in Study 2201, could translate into clinically relevant effects in patients with APDS. The experts highlighted however that the chosen outcome measures in Study 2201 were not entirely optimal.

They also agreed that it would aid reassurance if the benefits seen in Study 2201 were demonstrated to be sustained over time with longer term efficacy data. There remain uncertainties about the clinical benefit in lung and gastrointestinal disease, but again longer-term efficacy data may also clarify this. Based on the data presented, uncertainties also remain regarding potential clinical effect in patients who have more severe disease at commencement of treatment with leniolisib, taking also into account the risks related to concurrent use of immunosuppressive medication, for which no data are available for the moment.

In detail: The experts agreed that significantly reduced lymphoproliferation (lymph nodes in particular in the lungs, GIT, and decreased spleen size) as a marker of the decreased disease activity which occurred quickly (pivotal study 2201) and was maintained (extension study 2201E) is of benefit to the patients, as it reduces disease symptoms and can be anticipated to improve the quality of life. The restoration of the B cell subsets/function is also important to lower the risk of infections and need for IRT (Immunoglobulin Replacement Therapy). All of those effects will have positive impact on patients' everyday activities, social life etc.

The experts noted that the improvement in the annualised infection rate was not seen in all patients; however, this may be due to the heterogenous or reduced response in particular in patients with more severe disease (e.g., bronchiectasis and older patients). Some experts mentioned that infection type was not well defined and this is important to clarify Joenja benefit in means of decreasing infections.

The experts would have preferred to have also seen data showing clear effect on other immune system function parameters, e.g. lymphocytes T, vaccination (e.g. pneumococcal vaccine) response, incidence of viral vs non-viral infections as well as improvement in pulmonary function and BMI/GIT function. One expert mentioned that the metabolic function assessment of lymph nodes (PET scan) would have been of interest.

Some experts saw leniolisib as a potential bridging treatment before the haematopoietic stem cell transplantation (HSCT), but data is lacking in this scenario.

The experts were appreciative of having data from a RCT (given the rarity of the condition) showing positive outcome even though the choice of endpoints may have not been ideal. They were also reassured that the outcomes observed in the extension study were moving in the same direction.

The experts would like to see more long-term data and in more varied patient population – broader spectrum of disease.

The patient representatives mentioned that the current treatment includes multiple medications with many adverse reactions and affects their life in a negative way. They hope that the new treatment will help them to increase the quality of their lives.

2. The primary mechanism of action of leniolisib is similar to that of idelalisib. The latter drug is known to cause opportunistic infections as well as autoimmune phenomena due to PI3Kδ inhibition. The extent of the safety database for leniolisib is not sufficient to exclude such effects when treating APDS with leniolisib. The applicant argues that the known safety concerns for this drug class are not relevant when treating APDS, due to the presence of germline mutations in the target. The AHEG is invited to comment on the plausibility of this claim.

3. Do you consider that the uncertainties about the clinical safety of leniolisib are acceptable with respect to use in the APDS population?

Summary: The experts agreed with the applicant's claim that the known safety concerns for this drug class in Haematological diseases are likely not relevant when treating APDS patients and so there is no need to compare the safety profile of leniolisib and idelalisib. The experts were of the view that haematology-oncology patients have a different underlying mechanism for their immune disfunction, compared to patients with APDS. Patients with APDS who are successfully treated with leniolisib would be expected to partially restore immune competence during treatment and thus have a lower rate of opportunistic or serious infections. The experts noted that there was no significant increase in opportunistic and recurrent infections seen thus far in the data presented for leniolisib, but that longer term safety data are required. The lack of an optimal functional assay to measure impact on immune function in the long-term was also highlighted in relation to potential infection risk.

In detail: The experts agreed that a risk of serious infections present for idelalisib have not been reported in patients treated with leniolisib. In general, the short-term safety findings do not raise concerns. In particular, there were no reports of autoimmunity, opportunistic or recurrent infections, however, the experts acknowledged the limited number of patients exposed to leniolisib in the RCT.

The long-term potential safety concerns include occurrence of malignancies, in particular lymphomas, which would have to be monitored for. This will be challenging since the disease itself poses patients at a higher risk of cancer and therefore assigning it -if occurs- to the drug or the disease will be quite difficult (please see below).

The experts agreed that the safety profile of PI3Kδ inhibitors will be expected to be different in haematological malignancies and in APDS due to a different underlying pathophysiology and clinical picture of those conditions. In the latter case administration of PI3Kδ inhibitors is expected to lead to a restoration of normal PI3Kδ function and immunocompetence. Some experts were suggesting long-term monitoring of Treg lymphocytes function (other immune system function tests if feasible) and infection rates. However, the experts agreed that monitoring Treg lymphocytes function is not routinely available in all institutions caring for APDS patients.

Some experts mentioned that the treatment could offer the chance to reduce use/dose of currently used treatments and decrease the polytherapy-related AEs. However, this would require confirmation. Some experts were wondering whether the treatment could influence the need for HSCT for some patients.

The patients' representatives mentioned that other therapeutic approaches (they commented on liver transplant since it was their particular case) do have serious AE and leniolisib has, in their opinion, a better safety profile.

The experts concluded that uncertainties regarding the clinical safety profile of leniolisib in the proposed APDS population were considered acceptable at this time. Gaps in knowledge regarding concomitant use of leniolisib with immunosuppressant medicines, impact on transplant grafts, long-term malignancy risk as well as information relating to any potential reproductive toxicity were noted by the experts. It was acknowledged that the generation of further long-term safety data would be needed. The experts were also conscious of the fact that the gathering of information on secondary malignancies (e.g., lymphomas) might be hampered by the difficulties in differentiating between the course of the disease and a potential influence of treatment.

4. Post-authorisation efficacy and safety studies are considered necessary to collect further long-term efficacy and safety data from APDS patients treated with leniolisib in the EU. What data/endpoints might realistically be collected to better characterize leniolisib clinical benefit and safety profile in the target indication?

The experts considered that for a specific study design a more dedicated discussion would be needed but to address post-authorisation the main deficiencies of the current data package the following endpoints of interest were suggested: incidence of deaths; rate of hospitalisation; rates of lymphomas, data on autoimmunity; need for transplants and the outcome after HSCT; granular information on infections, with data on aetiology and treatment (including CMV, EBV); T / B lymphocyte counts and function (there were disagreements on the feasibility of monitoring Treg count/function); vaccine challenge to test T-cell independent response; assessing Ig subclasses; pulmonary function tests; BMI/weight monitoring; antibiotic use monitoring; use of concomitant medicines (IgRT, immunosuppressive medications such as mTOR or B-cell depleters [e.g., rituximab] immunomodulators, HSCT); impact on different genotypes (APD1 vs APD2); impact on fertility pregnancy outcomes; QoL and PRO.

The experts recommend the use of the IDDA (Immune Deficiency and Dysregulation Activity) score which includes most of the endpoints mentioned and is a validated tool for studies in immunodeficiencies.

The experts also emphasised that long-term follow up will be needed in particular for malignancies, autoimmunity and potential effects on fertility and pregnancy outcomes. It was considered that younger patients should be followed for at least 10 years; 5 years might be only acceptable for older patients. The general agreement was that the longer the follow-up the better.

All experts agreed that this was a preliminary list but some work needs to be done to define the issues to monitor.

Patient representatives suggested collecting QoL data.

Additional efficacy data needed in the context of a MA under exceptional circumstances

Considering the data available, the CHMP agreed that the efficacy of leniolisib in the treatment of APDS has been shown based on pharmacodynamic endpoints, as adequately addressed in the SmPC Section 5.1. These PD endpoints are expected to translate into clinically relevant effects in patients with APDS. The CHMP considered that efficacy on the long-term use, especially on the reduction of signs and symptoms is insufficiently characterised. These concerns are not expected to be addressed within a reasonable timeframe. As a specific obligation, the applicant committed to conduct a registry-based safety study collecting data on the long-term efficacy of leniolisib, and a long-term, yearly updates on any new information concerning the safety and efficacy of leniolisib. The yearly updates will be given in the annual re-assessment.

2.6.7. Conclusions on the clinical efficacy

A marketing authorisation under exceptional circumstances has been assessed for leniolisib in the treatment APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more. The proposed indication is supported by the phase 2/3 pivotal study 2201 part 2.

Although APDS is a rare disease, the efforts of the applicant are acknowledged in conducting a blinded, randomized, placebo-controlled study which included 21 patients in the leniolisib arm and 10 patients in the placebo arm.

Both primary endpoints on lymphadenopathy and on immunophenotype normalization showed a statistically significant difference between leniolisib and control arm and were supported by sensitivity and additional analyses. While the majority of the patients were included in lymphadenopathy analysis supporting clinical relevance for this endpoint, less than half of the patients were analysed for immunophenotype normalization. Following further analysis, and an Ad-Hoc Expert Group meeting, these PD endpoints are expected to translate into clinically relevant effects in patients with APDS. Furthermore, the applicant conducted a Delphi study to identify the most important outcomes when evaluating the effectiveness of APDS treatments in clinical practice and the amount of change in these outcomes that would indicate a meaningful benefit for a patient. Results were in favour of a clinically relevant effect associated with the co-primary endpoints analyses, supporting thus the expert's consensus. As such, results of both co-primary endpoints were considered positive and clinically relevant.

Outcomes were evaluated over a 12-week period. However, no conclusion could be drawn on efficacy on the long-term use especially on the infection frequency, hospitalization, antimicrobial use, and continued need for IRT.

The CHMP considers the following measures necessary to address the missing efficacy data on the long-term use of leniolisib in the context of a MA under exceptional circumstances:

- Non-interventional post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of leniolisib in the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.
- In order to ensure adequate monitoring of safety and efficacy of leniolisib in the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of leniolisib.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

To date, 38 APDS adolescents and adults patients have been exposed to leniolisib as part of the clinical development programme.

Support for the safety of leniolisib relative to placebo in patients with APDS is derived from Study 2201 Part 2. Long-term safety in patients with APDS is derived from the interim analysis of Study 2201E1. The final CSR has been provided during the review (stop date 30 January 2025).

Supportive safety data comes from the following studies:

- Dose-finding portion (Part 1) of Study 2201 in APDS patients
- Phase 2 Study 2203 in patients with primary Sjogren's syndrome (pSS)
- Phase 1 Studies 2101, 2102, 2104, LE1101, and LE2101 in healthy participants

Table 16: Overall Extent of Exposure – Study 2201 (Part 1 and Part 2) and Study 2201E1

	Part 1				Part 2		Extension CDZ173 70 mg bid		
	CDZ173 10 mg bid N=6	CDZ173 30 mg bid N=6	CDZ173 70 mg bid N=6	Total N=6	Placebo bid N=10	CDZ173 70 mg bid N=21	Previous CDZ173 N=26	Previous Placebo N=9	Total Extension N=37
Total exposure (mg)									
n	6	6	6	6	10	21	26	9	37
mean	550.0	1690.0	3920.0	6160.0	0.0	11770.0	217638.1	171352.2	208564.1
SD	10.95	24.49	88.54	77.97	0.00	251.69	88892.83	65554.14	84035.19
minimum	540	1680	3780	6060	0	10920	61040	90370	61040
median	550.0	1680.0	3920.0	6150.0	0.0	11760.0	230860.0	165480.0	220640.0
maximum	560	1740	4060	6300	0	12180	355460	287140	355460
Duration of exposure (weeks)									
n	6	6	6	6	10	21	26	9	37
mean	3.93	4.02	4.00	11.95	12.01	12.09	223.27	178.35	214.51
SD	0.078	0.058	0.090	0.117	0.196	0.146	90.150	65.319	84.782
minimum	3.9	4.0	3.9	11.9	11.7	11.7	62.3	92.3	62.3
median	3.93	4.00	4.00	11.93	12.00	12.14	235.57	175.71	225.57
maximum	4.0	4.1	4.1	12.1	12.3	12.4	362.7	294.3	362.7
Maximum duration of exposure (weeks) - n (%)									
1-2 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2-4 weeks	3 (50.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4-10 weeks	3 (50.0)	6 (100.0)	5 (83.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
10-11 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11-12 weeks	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	4 (40.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
12-24 weeks	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	6 (60.0)	19 (90.5)	0 (0.0)	0 (0.0)	0 (0.0)
24-36 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
36-48 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
48-60 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
60-72 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.1)
72-84 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
84-96 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.7)
96-108 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.4)
108-156 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	1 (11.1)	4 (10.8)
156-208 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	4 (44.4)	5 (13.5)
208-260 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (38.5)	1 (11.1)	12 (32.4)

2.6.8.2. Adverse events

Overall incidences of the AEs

Table 17: Overall Incidence of Adverse Events - Number of Events and Number of Patients (Safety Analysis Set)

	Part 1				Part 2			Extension CDZ173 70 mg bid				
	CDZ173 10 mg bid N=6 nE, nS (%)	CDZ173 30 mg bid N=6 nE, nS (%)	CDZ173 70 mg bid N=6 nE, nS (%)	Total N=6 nE, nS (%)	CDZ173 70 mg bid N=21 nE, nS (%)	Placebo bid N=10 nE, nS (%)	Total N=31 nE, nS (%)	Previous CDZ173 N=26 nE, nS (%)	Previous Placebo N=9 nE, nS (%)	Total Extension (Previous Parts 1/2) N=35 nE, nS (%)	Total Extension N=37 nE, nS (%)	Total CDZ173 N=38 nE, nS (%)
AEs, Patients with AEs	4, 2 (33.3)	3, 2 (33.3)	11, 4 (66.7)	18, 4 (66.7)	92, 18 (85.7)	46, 9 (90.0)	138, 27 (87.1)	356, 24 (92.3)	134, 8 (88.9)	490, 32 (91.4)	511, 34 (91.9)	621, 36 (94.7)
Rates per patient-year*: AEs	8.855	6.484	22.076	3.906	18.008	17.912	17.976	3.180	4.168	3.401	3.314	3.789
Grade 1 AEs	1, 1 (16.7)	2, 1 (16.7)	9, 4 (66.7)	12, 4 (66.7)	65, 15 (71.4)	27, 8 (80.0)	92, 23 (74.2)	242, 24 (92.3)	41, 6 (66.7)	283, 30 (85.7)	303, 32 (86.5)	380, 33 (86.8)
Rates per patient-year*: Grade 1 AEs	2.214	4.322	18.062	2.604	12.723	10.514	11.984	2.162	1.275	1.964	1.965	2.319
Grade 2 AEs	2, 1 (16.7)	1, 1 (16.7)	2, 1 (16.7)	5, 3 (50.0)	19, 9 (42.9)	13, 5 (50.0)	32, 14 (45.2)	73, 17 (65.4)	45, 7 (77.8)	118, 24 (68.6)	119, 25 (67.6)	143, 29 (76.3)
Grade 3 AEs	1, 1 (16.7)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (16.7)	3, 2 (9.5)	4, 3 (30.0)	7, 5 (16.1)	17, 7 (26.9)	32, 4 (44.4)	49, 11 (31.4)	49, 11 (29.7)	53, 12 (31.6)
Grade 4 AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	3, 2 (9.5)	1, 1 (10.0)	4, 3 (9.7)	1, 1 (3.8)	0, 0 (0.0)	1, 1 (2.9)	1, 1 (2.7)	4, 3 (7.9)
Grade 5 AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (10.0)	1, 1 (3.2)	1, 1 (3.8)	0, 0 (0.0)	1, 1 (2.9)	1, 1 (2.7)	1, 1 (2.6)
Study drug-related AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	6, 5 (23.8)	8, 3 (30.0)	14, 8 (25.8)	4, 3 (11.5)	2, 1 (11.1)	6, 4 (11.4)	7, 5 (13.5)	13, 9 (23.7)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	5, 3 (14.3)	6, 2 (20.0)	11, 5 (16.1)	16, 7 (26.9)	28, 3 (33.3)	44, 10 (28.6)	44, 10 (27.0)	49, 11 (28.9)
Deaths	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (3.8)	0, 0 (0.0)	1, 1 (2.9)	1, 1 (2.7)	1, 1 (2.6)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (3.8)	1, 1 (11.1)	2, 2 (5.7)	2, 2 (5.4)	2, 2 (5.3)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to study withdrawal	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (3.8)	1, 1 (11.1)	2, 2 (5.7)	2, 2 (5.4)	2, 2 (5.3)
Study-drug related AEs leading to study withdrawal	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

Abbreviations: AE = adverse event; BID = twice daily; N = number of patients studied; nE = number of AE events in the category; nS = number of patients with at least one AE in the category
% is based on the number of patients
*AE rate patient year = Total_AEs / Total_pt_follow-up_yrs (AE rate in units of events per patient-year)
Total_AEs is the total number of AEs for a given study or treatment arm (some patients have multiple AEs that contribute to the total)
Total_pt_follow-up is the total amount of patient follow-up in years for a study or treatment arm
Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal
The cut-off for the extension study data was 13DEC2021
Source: Listing 16.2.7-1.1

Most common AEs

Table 18: Adverse Events With at Least 5% Incidence in Total Leniolisib by Preferred Term – Study 2201 Part 1 and Part 2 and Study 2201E1 (Safety Analysis Set)

	Part 1				Part 2			Extension Leniolisib 70 mg BID				
	Leniolisib 10 mg BID N=6 n (%)	Leniolisib 30 mg BID N=6 n (%)	Leniolisib 70 mg BID N=6 n (%)	Total N=6 n (%)	Leniolisib 70 mg BID N=21 n (%)	Placebo BID N=10 n (%)	Total N=31 n (%)	Previous Leniolisib N=26 n (%)	Previous Placebo N=9 n (%)	Total Extension (Previous Parts 1/2) N=35 n (%)	Total Extension N=37 n (%)	Total Leniolisib N=38 n (%)
Patients with at least one AE	2 (33.3)	2 (33.3)	4 (66.7)	4 (66.7)	18 (85.7)	9 (90.0)	27 (87.1)	24 (92.3)	8 (88.9)	32 (91.4)	34 (91.9)	36 (94.7)
Preferred term												
SARS-CoV-2 test negative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (42.3)	4 (44.4)	15 (42.9)	15 (40.5)	15 (39.5)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (30.8)	3 (33.3)	11 (31.4)	12 (32.4)	12 (31.6)
Headache	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	5 (23.8)	2 (20.0)	7 (22.6)	5 (19.2)	1 (11.1)	6 (17.1)	8 (21.6)	12 (31.6)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	2 (20.0)	4 (12.9)	7 (26.9)	2 (22.2)	9 (25.7)	10 (27.0)	11 (28.9)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	5 (19.2)	4 (44.4)	9 (25.7)	9 (24.3)	10 (26.3)
Sinusitis	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	4 (19.0)	0 (0.0)	4 (12.9)	3 (11.5)	3 (33.3)	6 (17.1)	6 (16.2)	10 (26.3)
Otitis externa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	6 (23.1)	1 (11.1)	7 (20.0)	7 (18.9)	8 (21.1)
Diarrhoea	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	2 (9.5)	0 (0.0)	2 (6.5)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	6 (15.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	1 (10.0)	1 (3.2)	4 (15.4)	1 (11.1)	5 (14.3)	6 (16.2)	6 (15.8)
Rhinitis	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)	4 (11.4)	5 (13.5)	6 (15.8)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (10.0)	2 (6.5)	2 (7.7)	3 (33.3)	5 (14.3)	5 (13.5)	6 (15.8)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	3 (11.5)	2 (22.2)	5 (14.3)	5 (13.5)	5 (13.2)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)	4 (11.4)	5 (13.5)	5 (13.2)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	5 (13.2)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (4.8)	0 (0.0)	1 (3.2)	4 (15.4)	0 (0.0)	4 (11.4)	4 (10.8)	5 (13.2)
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	5 (13.2)
Oropharyngeal pain	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	5 (13.2)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	5 (13.2)
Respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	4 (15.4)	1 (11.1)	5 (14.3)	5 (13.5)	5 (13.2)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (10.0)	2 (6.5)	4 (15.4)	1 (11.1)	5 (14.3)	5 (13.5)	5 (13.2)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	4 (10.5)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	4 (10.5)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	4 (10.5)
Cough	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (10.0)	1 (3.2)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	4 (10.5)
Dental caries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	4 (15.4)	0 (0.0)	4 (11.4)	4 (10.8)	4 (10.5)
Oral herpes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	4 (10.5)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)	4 (11.4)	4 (10.8)	4 (10.5)
Seborrhoeic dermatitis	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	4 (10.5)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (10.0)	2 (6.5)	3 (11.5)	1 (11.1)	4 (11.4)	4 (10.8)	4 (10.5)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	1 (3.8)	0 (0.0)	1 (2.9)	2 (5.4)	3 (7.9)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	2 (22.2)	3 (8.6)	3 (8.1)	3 (7.9)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	3 (7.9)
Haematochezia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	3 (7.9)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	3 (7.9)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	3 (7.9)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	3 (30.0)	4 (12.9)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	3 (7.9)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	3 (7.9)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	3 (7.9)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	3 (7.9)
Seasonal allergy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	1 (11.1)	3 (8.6)	3 (8.1)	3 (7.9)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Anal fissure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)

Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Illusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Joint injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Keratosis pilaris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	2 (5.4)	2 (5.3)
Limb injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Lyme disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Obesity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Otitis media acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Paronychia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	2 (5.4)	2 (5.3)
Productive cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)
Skin papilloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	2 (5.3)

A patient with multiple AEs within a dose/study part is counted only once in the 'at least one AE' row
A patient with multiple AEs within a dose/study part with the same preferred term is counted only once for that preferred term Arranged in descending order of frequency (in Total leniolisib group) and alphabetically by preferred term AEs were coded using MedDRA version 27.0

Related Adverse Events

Table 19: Incidence of Adverse Events Related to Treatment by Preferred Term - n (%) of Patients (Safety Analysis Set)

	Part 1				Part 2			Extension Leniolisib 70 mg BID				
	Leniolisib 10 mg BID N=6 n (%)	Leniolisib 30 mg BID N=6 n (%)	Leniolisib 70 mg BID N=6 n (%)	Total N=6 n (%)	Leniolisib 70 mg BID N=21 n (%)	Placebo BID N=10 n (%)	Total N=31 n (%)	Previous Leniolisib N=26 n (%)	Previous Placebo N=9 n (%)	Total Extension (Previous Parts 1/2) N=35 n (%)	Total Extension N=37 n (%)	Total Leniolisib N=38 n (%)
Patients with at least one AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (23.8)	3 (30.0)	8 (25.8)	3 (11.5)	1 (11.1)	4 (11.4)	5 (13.5)	9 (23.7)
Preferred term												
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	2 (7.7)	1 (11.1)	3 (8.6)	3 (8.1)	4 (10.5)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.3)
Aphthous ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.6)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Taste disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vasculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Analysis of Adverse Events by Organ System or Syndrome

Table 20: Incidence of Adverse Events by Primary System Organ Class - n (%) of Patients (Safety Analysis Set)

	Part 1				Part 2			Extension CDZ173 70 mg bid				
	CDZ173 10 mg bid N=6 n (%)	CDZ173 30 mg bid N=6 n (%)	CDZ173 70 mg bid N=6 n (%)	Total N=6 n (%)	CDZ173 70 mg bid N=21 n (%)	Placebo bid N=10 n (%)	Total N=31 n (%)	Previous CDZ173 N=26 n (%)	Previous Placebo N=9 n (%)	Total Extension (Previous Parts 1/2) N=35 n (%)	Total Extension N=37 n (%)	Total CDZ173 N=38 n (%)
Patients with at least one AE	2 (33.3)	2 (33.3)	4 (66.7)	4 (66.7)	18 (85.7)	9 (90.0)	27 (87.1)	24 (92.3)	8 (88.9)	32 (91.4)	34 (91.9)	36 (94.7)
System organ class												
Infections and infestations	0 (0.0)	2 (33.3)	3 (50.0)	4 (66.7)	11 (52.4)	4 (40.0)	15 (48.4)	22 (84.6)	7 (77.8)	29 (82.9)	31 (83.8)	33 (86.8)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	7 (33.3)	4 (40.0)	11 (35.5)	17 (65.4)	7 (77.8)	24 (68.6)	25 (67.6)	26 (68.4)
Investigations	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	5 (23.8)	2 (20.0)	7 (22.6)	14 (53.8)	4 (44.4)	18 (51.4)	18 (48.6)	20 (52.6)
Nervous system disorders	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	6 (28.6)	3 (30.0)	9 (29.0)	9 (34.6)	3 (33.3)	12 (34.3)	14 (37.8)	18 (47.4)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	0 (0.0)	1 (16.7)	2 (33.3)	2 (9.5)	2 (20.0)	4 (12.9)	11 (42.3)	5 (55.6)	16 (45.7)	16 (43.2)	17 (44.7)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (23.8)	2 (20.0)	7 (22.6)	11 (42.3)	4 (44.4)	15 (42.9)	15 (40.5)	16 (42.1)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	7 (33.3)	1 (10.0)	8 (25.8)	11 (42.3)	2 (22.2)	13 (37.1)	13 (35.1)	16 (42.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (23.8)	2 (20.0)	7 (22.6)	9 (34.6)	1 (11.1)	10 (28.6)	11 (29.7)	15 (39.5)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	3 (14.3)	1 (10.0)	4 (12.9)	8 (30.8)	1 (11.1)	9 (25.7)	10 (27.0)	14 (36.8)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	7 (26.9)	2 (22.2)	9 (25.7)	9 (24.3)	10 (26.3)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	6 (23.1)	1 (11.1)	7 (20.0)	7 (18.9)	8 (21.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	4 (15.4)	2 (22.2)	6 (17.1)	6 (16.2)	6 (15.8)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (10.0)	2 (6.5)	2 (7.7)	2 (22.2)	4 (11.4)	4 (10.8)	5 (13.2)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	3 (33.3)	5 (14.3)	5 (13.5)	5 (13.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	3 (33.3)	5 (14.3)	5 (13.5)	5 (13.2)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (10.0)	2 (6.5)	1 (3.8)	3 (33.3)	4 (11.4)	4 (10.8)	4 (10.5)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	3 (7.9)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (4.8)	2 (20.0)	3 (9.7)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	3 (7.9)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.5)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	3 (7.9)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	2 (6.5)	1 (3.8)	2 (22.2)	3 (8.6)	3 (8.1)	3 (7.9)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

A patient with multiple AEs within a dose/study part is counted only once in the 'at least one AE' row
A patient with multiple AEs within a dose/study part with the same primary system organ class is counted only once for that primary system organ class Arranged in descending order of frequency (in Total CDZ173 group) and alphabetically by preferred term AEs were coded using MedDRA version 27.0

Table 21: Infection Adverse Events Occurring in at Least 2 Patients in Total Leniolisib by Preferred Term – Study 2201 Part 1 and Part 2 and Study 2201E1 (Safety Analysis Set DCO 13 Dec 2021)

	Study 2201 Part 1	Study 2201 Part 2		Study 2201E1	
SOC	Leniolisib 10/30/70 mg bid (N=6)	Leniolisib 70 mg bid (N=21)	Placebo (N=10)	Leniolisib 70 mg bid (N=37)	Total Leniolisib (N=38)
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Infections and Infestations	4 (66.7)	11 (52.4)	4 (40.0)	26 (70.3)	29 (76.3)
Sinusitis	1 (16.7)	4 (19.0)	0	4 (10.8)	8 (21.1)
Upper respiratory tract infection	0	2 (9.5)	2 (20.0)	7 (18.9)	8 (21.1)
Otitis externa	0	1 (4.8)	0	5 (13.5)	6 (15.8)
COVID-19	0	0	0	5 (13.5)	5 (13.2)
Pharyngitis	0	0	0	4 (10.8)	4 (10.5)
Respiratory tract infection	0	0	1 (10.0)	4 (10.8)	4 (10.5)
Rhinitis	1 (16.7)	0	0	3 (8.1)	4 (10.5)
Gastroenteritis	1 (16.7)	1 (4.8)	0	2 (5.4)	3 (7.9)
Otitis media	0	0	0	3 (8.1)	3 (7.9)
Pneumonia	0	1 (4.8)	0	2 (5.4)	3 (7.9)
Acute sinusitis	1 (16.7)	0	0	1 (2.7)	2 (5.3)
Folliculitis	0	0	0	2 (5.4)	2 (5.3)
Herpes zoster	0	0	0	2 (5.4)	2 (5.3)
Lyme disease	0	0	0	2 (5.4)	2 (5.3)
Nasopharyngitis	1 (16.7)	0	1 (10.0)	2 (5.4)	2 (5.3)
Oral herpes	0	1 (4.8)	0	2 (5.4)	2 (5.3)
Otitis media acute	0	0	0	2 (5.4)	2 (5.3)
Urinary tract infection	0	1 (4.8)	1 (10.0)0	2 (5.4)	2 (5.3)

Source: 5.3.5.2 Interim CSR Study 2201E1 Table 14.3.1-1.1.
AE=adverse event; bid=twice daily; COVID-19=coronavirus disease 2019; CSR=clinical study report; SOC=system organ class.
Note: Under one treatment, a patient with multiple occurrences of an AE is counted only once in the AE category.

Table 22: skin and Study 2201E1 subcutaneous tissue disorders (Safety Analysis Set)

		Extension CDZ173 70 mg bid				
Primary system organ class	Preferred term	Previous CDZ173 N=26 n (%)	Previous Placebo N=9 n (%)	Total Extension (Previous Parts 1/2) N=35 n (%)	Total Extension N=37 n (%)	Total CDZ173 N=38 n (%)
Patients with at least one AE		11 (42.3)	2 (22.2)	13 (37.1)	13 (35.1)	16 (42.1)
Skin and subcutaneous tissue disorders	-TOTAL	11 (42.3)	2 (22.2)	13 (37.1)	13 (35.1)	16 (42.1)
	Alopecia	1 (3.8)	1 (11.1)	2 (5.7)	2 (5.4)	4 (10.5)
	Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Dermatitis atopic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
	Dry skin	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.3)
	Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
	Keratosis pilaris	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Skin and subcutaneous tissue disorders	Perioral dermatitis	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Petechiae	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Photosensitivity reaction	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
	Pigmentation disorder	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Pruritus	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	3 (7.9)
	Rash	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	3 (7.9)
	Rash erythematous	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Rash macular	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Rash maculo-papular	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	2 (5.3)
Skin and subcutaneous tissue disorders	Rash pruritic	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Seborrhoeic dermatitis	3 (11.5)	0 (0.0)	3 (8.6)	3 (8.1)	4 (10.5)
	Urticaria	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
	Vitiligo	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)

2.6.8.3. Serious adverse event/deaths/other significant events

Death

One death was reported in the leniolisib clinical development programme while patients were enrolled in clinical studies. This patient experienced an AE of cardiac arrest that was considered not related to study treatment by the investigator. This male patient was 22 years old at the time of enrolment in the study at the US National Institutes of Health. The patient received leniolisib in Study 2201 Part 2 and continued treatment in Study 2201E1, with treatment ending on Day 877 after significant elevation of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]).

Death from cardiac arrest occurred on Day 879, 2 days after discontinuation of treatment. The patient had a long and protracted medical history of failure to thrive, metabolic and nutritional disorders, chronic mastoiditis, parotitis, chronic otitis media, recurrent/chronic pneumonia, aspiration pneumonia, chronic bronchitis, bronchiectasis, chronic necrotizing histiocytic lymphadenitis, lymphadenopathy, splenomegaly, chronic cytopenia, chronic fever, chronic norovirus enterocolitis with protein wasting enteropathy, chronic disseminated mycoplasma orale, hypotension, chronic tachycardia, and chronic elevation of liver function tests. The patient's death from cardiac arrest was attributed to the multiple medical issues the patient was experiencing, including a worsening of the chronic disseminated mycoplasma orale infection and underlying cardiomyopathy. The patient had no clinically significant ECG findings while on leniolisib either during the Study 2201 Part 2 nor during Study 2201E1.

Other Serious Adverse Events

Table 23: Incidence of Serious Adverse Events by Preferred Term - n (%) of Patients (Safety Analysis Set)

	Part 1				Part 2			Extension CDZ173 70 mg bid				
	CDZ173 10 mg bid N=6 n (%)	CDZ173 30 mg bid N=6 n (%)	CDZ173 70 mg bid N=6 n (%)	Total N=6 n (%)	CDZ173 70 mg bid N=21 n (%)	Placebo bid N=10 n (%)	Total N=31 n (%)	Previous CDZ173 N=26 n (%)	Previous Placebo N=9 n (%)	Total Extension (Previous Parts 1/2) N=35 n (%)	Total Extension N=37 n (%)	Total CDZ173 N=38 n (%)
Patients with at least one AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)	2 (20.0)	5 (16.1)	7 (26.9)	3 (33.3)	10 (28.6)	10 (27.0)	11 (28.9)
Preferred term												
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (5.7)	2 (5.4)	2 (5.3)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (5.7)	2 (5.4)	2 (5.3)
Abscess soft tissue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Acute sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Alcohol poisoning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Anal fissure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Anaphylactic reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Arthritis reactive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Coma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Facial pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Failure to thrive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Hodgkin's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Hypocalcaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Mastoiditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Parotitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Periorbital cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Respiratory disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Staphylococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Transitional cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.9)	1 (2.7)	1 (2.6)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.9)	1 (2.7)	1 (2.6)
Dependence on oxygen therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infective exacerbation of bronchiectasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

patient with multiple SAEs within a dose/study part is counted only once in the 'at least one SAE' row
A patient with multiple SAEs within a dose/study part with the same preferred term is counted only once for that preferred term Arranged in descending order of frequency (in total CDZ173 group) and alphabetically by preferred term AEs were coded using MedDRA version 27.0

2.6.8.4. Laboratory findings

Haematology

Study 2201 Part 1 (Dose-finding)

Haematologic parameters were largely within normal ranges. There were few instances where haematologic parameters were outside of the normal ranges for patients during Study 2201 Part 1; none were considered to be clinically significant by the investigator.

No notable trends were observed in haematology parameters; however, a small reduction was seen in mean neutrophil counts (normal range: 2.1 to 7.8×109/L) at Day 36 (1.78×109/L), Day 64 (1.88×109/L), and Day 71 (1.90×109/L) compared with the mean baseline value (2.26×109/L).

Similar observations were noted in mean lymphocyte counts (normal range: 0.8 to 3.3×109/L) during treatment with 10 and 30 mg twice daily, showing reduction at Day 15 (0.63×109/L), Day 29 (0.48×109/L), and Day 57 (0.42×109/L) compared with the mean baseline value (0.78×109/L). However, during treatment with 70 mg twice daily, individual lymphocyte counts of all patients increased, in 3 of them to clearly higher numbers than those observed at baseline. It is considered that no meaningful reduction was seen in WBC counts during the study compared with the mean baseline values.

An evaluation of cytopenias by grade showed some Grade 3 occurrences of low lymphocyte and neutrophil counts during treatment. One patient with a history of lymphopenia and with a low lymphocyte count at Screening continued to have a Grade 3 low lymphocyte count through Part 1. Another patient with a history of neutropenia and with a low lymphocyte count at Screening and Baseline continued to have a Grade 3 low lymphocyte count through Part 1.

There were no haematology-related AEs of cytopenias reported in Study 2201 Part 1.

Study 2201 Part 2 (Placebo-controlled)

Few haematologic parameters were outside the normal ranges during Study 2201 Part 2; none of them were considered clinically significant by the investigator.

As in Part 1, a reduction was observed in neutrophil count in leniolisib-treated patients, with nadir on Day 15. Neutrophil counts increased again until Day 85 and the End-of-Study Visit.

Four patients treated with leniolisib had neutrophil counts below 1000/µL, with values ranging from 700 to 900/µL (0.70 to 0.90×109/L) as follows:

- Patient: 800/µL (0.80×109/L) on Day 15
- Patient: 700/µL (0.70×109/L) on Day 29
- Patient: 900/µL (0.90×109/L) on Day 85
- Patient: 790/µL (0.79×109/L) on Day 29

None of these patients had symptoms, no interventions were required, and neutrophil counts were >1000/µL at the following.

An evaluation of cytopenias by grade also showed some occurrences of Grade 3 low lymphocyte counts during treatment. One patient with a history of lymphopaenia and a low lymphocyte count at Screening and Baseline, continued to have Grade 3 low lymphocyte counts through Part 2. This patient also had a low haemoglobin level at Baseline and Day 1. Another patient with a low lymphocyte count at Screening and Baseline also had a low lymphocyte count on Day 1. Another patient with an ongoing AE of WBCs in the urine had a low lymphocyte count on Day 85.

There were no haematology-related AEs reported in the leniolisib group in Study 2201 Part 2.

Study 2201E1 (Part 3: Open-label Extension)

Low neutrophils were transiently noted in patients in Study 2201E1. One patient had a clinically significant decreased neutrophil count reported as a Grade 3 AE and an additional patient experienced an AE of neutropenia, which was considered unrelated to study treatment by the investigator.

Neutropoenias were found to be transient and not requiring intervention. None of the events of neutropoenia decreased below an absolute neutrophil count (ANC) of 500 cells/µL (Grade 4). The one neutropenia value below an ANC of 1000 cells/µL (Grade 3), which was considered related to study treatment by the investigator, resolved without intervention.

An evaluation of cytopenias by grade also showed some occurrences of Grade 3 or 4 low lymphocyte count during Study 2201E1 in 2 patients with a history of lymphopenia that also had Grade 3 low lymphocyte count at the extension Screening, as well as throughout Study 2201 Part 1 or 2. An additional patient with a history of lymphopenia had Grade 3 low lymphocyte count on Day 728.

Additional individual out-of-range values were reported periodically throughout the extension study. Clinically significant out-of-range values for individual patients had not been determined by the investigator at the time of the interim analysis. Note that for two patients, there were a few haematologic values that were imputed incorrectly; these values represent data errors.

Clinical Chemistry

Study 2201 Part 1 (Dose-finding)

Clinical chemistry parameters that were outside the normal range in Study 2201 Part 1 occurred either pretreatment or both pre- and post-treatment. The majority of the abnormalities were not considered clinically significant by the investigator. One patient had clinically significant elevations of amylase, blood creatine phosphokinase, and lipase that were reported as AEs but were not considered related to study treatment. All 3 AEs resolved after 7 days with no action taken on dose and no concomitant treatment.

Study 2201 Part 2 (Placebo-controlled)

No notable trends were observed in clinical chemistry parameters in Study 2201 Part 2. There were few instances where clinical chemistry parameters were outside of the normal ranges for patients during Study 2201 Part 2; however, the majority of them were not considered clinically significant by the investigator. In the leniolisib group, 1 patient had clinically significant elevations of amylase and lipase, and another patient had clinically significant elevations of pancreatic enzymes that were reported as AEs. The elevation of lipase was a Grade 4 event that was considered serious. However, none of these events were considered related to study treatment by the investigator.

Study 2201E1 (Open-label Extension)

No notable trends were observed in clinical chemistry parameters in Study. Clinical chemistry parameters that were outside of the normal ranges were reported periodically throughout the extension study. Hyperinsulinemia was very common across the entire population both at screening and on study treatment, but without any associated hypoglycaemia.

Liver Enzymes

Study 2201 Part 1 (Dose-finding)

There were no notable trends in liver enzymes, no newly occurring liver enzyme abnormalities, and no liver-related AEs in Study 2201 Part 1.

Study 2201 Part 2 (Placebo-controlled)

There were no notable trends in liver enzymes in Study 2201 Part 2 or newly occurring liver enzyme abnormalities. One patient in the leniolisib group had an AE of aspartate aminotransferase increased that was considered unrelated to study treatment by the investigator.

Study 2201E1 (Part 3: Open-label Extension)

Newly occurring liver enzyme abnormalities were ALT increase > 3x ULN in 1 participant at Day 14 and Day 564, total bilirubin (TBL) in 1 to 3 participants per visit between Day 14 and end of treatment with a maximum of >3x ULN for 1 participant at Day 14, and alkaline phosphatase (ALP) in 1 participant at Days 168 and 252, at Day 546 (with a maximum of >3x ULN), Day 1456, and at end of treatment.

Laboratory values or changes that were considered relevant by the investigator were reported as AEs

Electrocardiograms

Study CCDZ173X2101

An analysis was conducted to characterize the relationship between QTc and leniolisib exposure utilizing the data from the first-in-human (FIH) healthy volunteer Study CCDZ173X2101: a randomized, double-blind, placebo-controlled, ascending single and multiple dose study to explore the safety, tolerability, pharmacokinetics including food effect, and pharmacodynamics of orally administered CDZ173 in healthy subjects. The study consisted of three parts: a single ascending dose (SAD) escalation (Part 1); a food effect (Part 2) and a 15 –day (b.i.d. regimen) multiple ascending dose (MAD) escalation (Part 3); to assess the safety and tolerability of the compound.

Table 24: Number and percentage of subjects reaching QTcF clinically notable values (Parts 1, 2 and 3)

Part 1: Single ascending dose (SAD)

		CDZ173 10mg N=8		CDZ173 20mg N=8		CDZ173 40mg N=6		CDZ173 80mg N=6		CDZ173 110mg N=6	
ECG test	Criteria	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)
QTcF	> 450 ms	8	0 (0.0)	8	0 (0.0)	6	0 (0.0)	6	0 (0.0)	6	0 (0.0)
	> 480 ms	8	0 (0.0)	8	0 (0.0)	6	0 (0.0)	6	0 (0.0)	6	0 (0.0)
	> 500 ms	8	0 (0.0)	8	0 (0.0)	6	0 (0.0)	6	0 (0.0)	6	0 (0.0)
Change from baseline in QTcF	>= 30 ms	8	0 (0.0)	8	1 (12.5)	6	0 (0.0)	6	0 (0.0)	6	0 (0.0)
	>= 60 ms	8	0 (0.0)	8	0 (0.0)	6	0 (0.0)	6	0 (0.0)	6	0 (0.0)

Part 1: Single ascending dose (SAD)

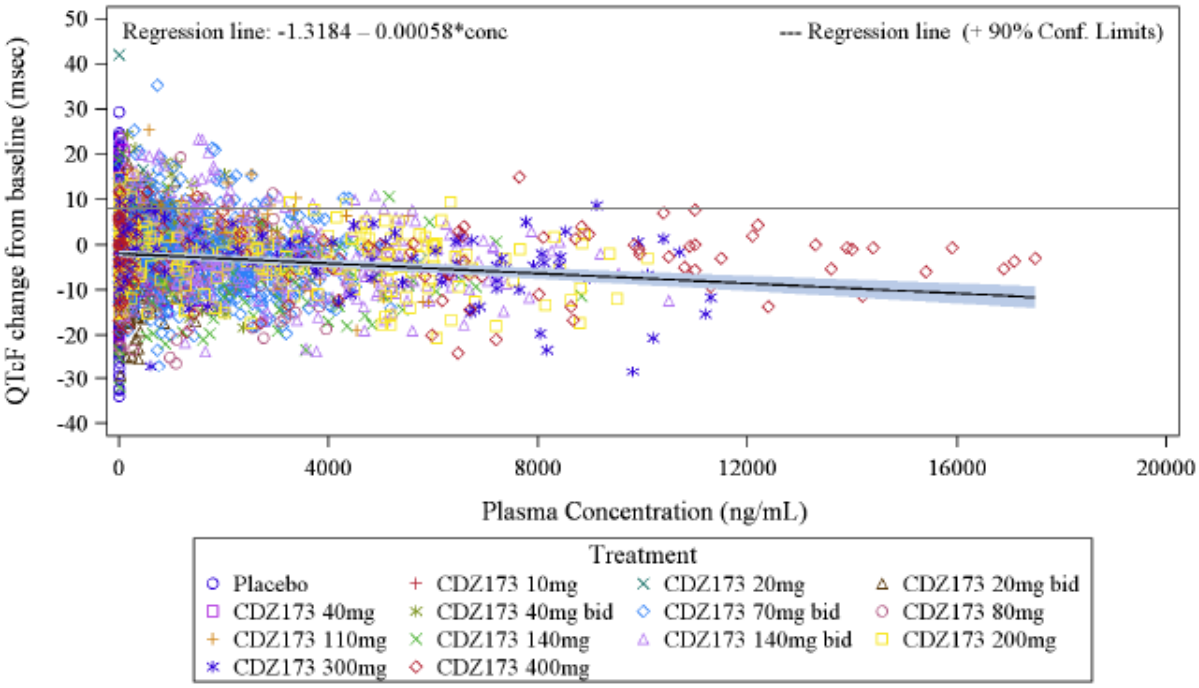
		CDZ173 140mg N=6		CDZ173 200mg N=12		CDZ173 300mg N=6		CDZ173 400mg N=6		Placebo N=44	
ECG test	Criteria	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)
QTcF	> 450 ms	6	0 (0.0)	12	0 (0.0)	6	0 (0.0)	6	0 (0.0)	44	0 (0.0)
	> 480 ms	6	0 (0.0)	12	0 (0.0)	6	0 (0.0)	6	0 (0.0)	44	0 (0.0)
	> 500 ms	6	0 (0.0)	12	0 (0.0)	6	0 (0.0)	6	0 (0.0)	44	0 (0.0)
Change from baseline in QTcF	>= 30 ms	6	0 (0.0)	12	0 (0.0)	6	0 (0.0)	6	0 (0.0)	44	0 (0.0)
	>= 60 ms	6	0 (0.0)	12	0 (0.0)	6	0 (0.0)	6	0 (0.0)	44	0 (0.0)

Part 2: Food effect evaluation

		CDZ173 70mg fasted/fed N=6		CDZ173 70mg fed/fasted N=6	
ECG test	Criteria	N*	n (%)	N*	n (%)
QTcF	> 450 ms	6	0 (0.0)	6	0 (0.0)
	> 480 ms	6	0 (0.0)	6	0 (0.0)
	> 500 ms	6	0 (0.0)	6	0 (0.0)
Change from baseline in QTcF	>= 30 ms	6	0 (0.0)	6	0 (0.0)
	>= 60 ms	6	0 (0.0)	6	0 (0.0)

Part 3: Multiple dose escalation (MAD)

		CDZ173 20mg bid N=6		CDZ173 40mg bid N=6		CDZ173 70mg bid N=22		CDZ173 140mg bid N=8		Placebo N=26	
ECG test	Criteria	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)	N*	n (%)
QTcF	> 450 ms	6	0 (0.0)	6	0 (0.0)	22	0 (0.0)	8	0 (0.0)	26	0 (0.0)
	> 480 ms	6	0 (0.0)	6	0 (0.0)	22	0 (0.0)	8	0 (0.0)	26	0 (0.0)
	> 500 ms	6	0 (0.0)	6	0 (0.0)	22	0 (0.0)	8	0 (0.0)	26	0 (0.0)
Change from baseline in QTcF	>= 30 ms	6	0 (0.0)	6	0 (0.0)	22	1 (4.5)	8	1 (12.5)	26	0 (0.0)
	>= 60 ms	6	0 (0.0)	6	0 (0.0)	22	0 (0.0)	8	0 (0.0)	26	0 (0.0)



The horizontal reference line represents the upper threshold of concern. The line is drawn at the estimated intercept (i.e. the mean placebo QTcF value) + 10 ms.

Figure 20: Scatterplot and regression line of QTcF change from baseline vs CDZ173 plasma concentration (Safety analysis set)

Study 2201E1 (Part 3: Open-label Extension)

No apparent clinically meaningful mean changes from baseline were observed in the 12-lead ECG parameters. One extension study participant that entered from the leniolisib group in Part 2 had single clinically significant ECG abnormalities at end of study Day 470. Another extension study participant with no previous exposure to leniolisib had clinically significant ECG abnormalities at screening, and extension Days 14, 43, 85, 168, 260, and 736, but also during Part 2 of Study CCDZ173X2201. No QTc prolongation was observed.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Intrinsic Factors

Safety analyses were evaluated for the following subgroups for Study 2201 Part 2: age (<18 or ≥18 years of age), sex (male or female), and genetics (PIK3CD or PIK3R1).

Safety Analyses by Age

Of the 31 patients, 12 (38.7%) were <18 years of age and 19 (61.3%) were ≥18 years of age. The proportion of patients with at least 1 AE was 83.3% in patients <18 and 89.5% in patients ≥18 years of age. The incidence of treatment-related AEs in the leniolisib group was 25.0% in patients <18 and in patients 23.1%≥18 years of age. The incidence overall of SAEs in the ≥18 years of age group was 21.1% while it was 8.3% in the <18 years of age group; however, none of the SAEs were considered treatment related. In the leniolisib group, Grade 3 AEs were reported in 1 patient in each age category.

There were no Grade 4 or 5 AEs reported in patients <18 years of age compared with 3 patients with Grade 4 events and 1 patient with a Grade 5 event in the ≥18 years of age category; none of these events were considered related to study treatment.

No relevant differences were observed in haematologic or clinical chemistry parameters in patients aged <18 years versus ≥18 years of age. No notable trends were observed in the vital signs or ECGs.

Safety Analyses by Sex

Of the 31 patients, 15 (48.4%) were male and 16 (51.6%) were female. The overall incidence of AEs was 93.8% in female patients and 80.0% in male patients. In the leniolisib group, there were 3 male patients (27.3%) who experienced Grade 3 or 4 AEs compared with 1 female patient (10.0%); however, none of them were considered related to study treatment.

No relevant differences were observed in hematologic or clinical chemistry parameters in male versus female patients. No notable trends were observed in the vital signs or ECGs.

Safety Analyses by Gene Mutation

Of the 31 patients, the majority had the PIK3CD mutation (80.6%).

Overall incidence of AEs was 88.0% in patients with the PIK3CD and 83.3% in patients with the PIK3R1 gene mutation. All 8 patients who reported study-drug related AEs had the PIK3CD gene mutation. Overall, 80% of patients with the PIK3CD mutation and 50% of patients with the PIK3R1 mutation had Grade 1 AEs. The incidence of SAEs in patients with the PIK3R1 mutation was 33.3%, while in patients with the PIK3CD mutation the incidence was 12.0%; however, the applicant indicates that none of the SAEs were considered treatment related.

Extrinsic Factors

Extrinsic factors were not analysed in the safety analysis set.

Pregnant and breastfeeding women

There is no available data on leniolisib use in pregnant women. Studies in animals have shown reproductive toxicity. Based on this, a teratogenic effect is expected clinically, and measures must be put in place to avoid that a foetus is exposed *in utero* to leniolisib.

No subjects have breastfed while receiving leniolisib. No animal data available on excretion of leniolisib in milk. Because leniolisib is 94.5% bound to plasma proteins, the amount in milk is likely to be low.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Drugs that may affect exposure to leniolisib and drugs that have their exposure altered by leniolisib:

Please refer to section 2.6.2.1.

Use of leniolisib with live viral vaccines

The applicant indicates that the safety of immunisation with live viral vaccines, including live attenuated vaccinations, following leniolisib therapy has not been studied, and it is not known if live or attenuated vaccines would be less effective when undergoing treatment with leniolisib.

Study 2102

Study 2102 was a Phase 1, single-center, open-label, single-sequence, 3-period crossover, drug-drug interaction study that evaluated the effect of itraconazole and quinidine coadministration on the PK of oral leniolisib in healthy male participants. 6 patients received a single oral dose of 10 mg leniolisib administered alone and in combination with itraconazole or quinidine. There were no deaths in this study and one 47-year-old participant experienced an SAE of chest discomfort. No aetiology for the chest pain was determined, and the investigator assessed the event as unrelated to study treatment. A total of 6 of 20 participants (30.0%) experienced AEs during the study, 3 participants (15.0%) during Period 2 (i.e., leniolisib in combination with itraconazole), and 3 participants (15.8%) during Period 3 (i.e., leniolisib in combination with quinidine). Most events were mild (5 of 6 participants). There were no severe events. There were no reports of AEs during Period 1 (i.e., leniolisib alone). Two participants (10.0%) reported AEs considered by the investigator to be related to study treatment: 1 participant (5.0%) reported headache during Period 2 and 1 participant (5.3%) reported diarrhoea during Period 3.

Study 2104

Study 2104 was a Phase 1, single-center, open-label, fixed-sequence, 2-period drug-drug interaction study that evaluated the effects of multiple oral doses of leniolisib on the PK of a single dose of a monophasic oral contraceptive in healthy female participants. A total of 30 participants were enrolled in this study, and in Period 2, leniolisib 70 mg was administered twice daily for 17 days, with a single dose of oral contraceptive (30 µg ethinylestradiol/150 µg levonorgestrel) on Day 15. There were no deaths, SAEs, or severe AEs reported during the study. There were no deaths, SAEs, or severe AEs reported during the study. A total of 16 of 30 participants (53.3%) experienced at least 1 AE. Most events were mild (15 of 16 participants). The AEs related to leniolisib were reported in 8 of 30 participants (26.7%) and included neutropenia (3 participants), maculo-papular rash (2 participants), abdominal pain (2 participants), pruritus, diarrhoea, frequent bowel movements, nausea, and vomiting (1 participant each). Clinically relevant changes in haematology included decreases in absolute neutrophils and neutrophil/leukocyte percentage over time. A decrease in absolute neutrophils was observed in all participants; 16 participants had absolute neutrophils below the normal range and 3 participants had absolute neutrophils below the clinical significance threshold of 1.0×109/L. Seven participants had leukocyte values below the normal range. The decrease in leukocytes was accompanied by a decrease in absolute neutrophils at most timepoints assessed. None of the participants with low neutrophil/leukocyte counts showed any clinical symptoms. In the 3 participants who prematurely discontinued treatment with leniolisib due to neutropenia, the absolute neutrophils returned to values within the normal range within approximately 1 day. There were no clinically relevant changes in clinical chemistry and urinalysis evaluations. There were no clinically relevant changes in vital sign measurements, 12-lead ECG results, and physical examination findings.

2.6.8.9. Discontinuation due to adverse events

In Study 2201E1, treatment discontinuation occurred in 1 patient who died of cardiac arrest.

2.6.8.10. Post marketing experience

Post-marketing data were available, with total reporting periods of 24-Mar-2024 to the data lock point on 23-Sep-2025. The cumulative data show that 2702 bottles of Joenja were shipped worldwide corresponding to a patient-year exposure of 225. The number of unique US patients cumulatively having been provided at least 1 dose of Joenja is 138.

An additional 138 patients with APDS receive leniolisib through an Early or Expanded Access Program (EAP) of which 95 patients were aged 12 years or older at the start of their treatment (PSUR #05). One 24-year-old female developed Hodgkin's lymphoma 3 years after starting EAP. The patient deceased 3 months later. The causality assessment by both reporter and MAH was considered not related to leniolisib treatment and most likely related to the progression of underlying disease (APDS).

Based on these post-marketing data, there were no new major findings regarding the overall benefit-risk profile of leniolisib. Available post-marketing data and data from EAP did not change the conclusions in terms of clinical safety.

2.6.8.11. Safety data from patients with other non-APDS disease

Study 2203

Thirty patients with primary Sjogren's syndrome (pSS) were enrolled in Study 2203, a randomized, double-blind, placebo-controlled, parallel-group study: 20 to receive leniolisib 70 mg and 10 to receive placebo twice daily for 12 weeks.

Table 25: Overall Summary of AEs – Study 2203 (Safety Analysis Set)

	Leniolisib 70 mg bid (N=20) n (%)	Placebo (N=10) n (%)
Number of patients with any AE	20 (100.0)	8 (80.0)
Severity		
Grade 1	14 (70.0)	5 (50.0)
Grade 2	16 (80.0)	8 (80.0)
Grade 3	6 (30.0)	1 (10.0)
Grade 4	0	0
Grade 5	0	0
Related AEs	19 (95.0)	8 (80.0)
Serious AEs	1 (5.0)	0
AEs leading to discontinuation of study treatment	8 (40.0)	1 (10.0)
Related AEs leading to discontinuation of study treatment	8 (40.0)	1 (10.0)
AEs leading to study withdrawal	3	0
Number of deaths	0	0

Source: 5.3.5.4 CSR Study 2203 Table 12-3 and Listing 16.2.7-1.1.
AE=adverse event; bid=twice daily; CSR=clinical study report.
Toxicity grades: 1: Mild; 2: Moderate; 3: Severe; 4:Life-threatening; 5: Death.

Table 26: Incidence of AEs By Primary System Organ Class – Study 2203 (Safety Analysis Set)

System Organ Class	Leniolisib 70 mg bid (N=20) n (%)	Placebo (N=10) n (%)
Number of patients with at least 1 AE	20 (100.0)	8 (80.0)
Gastrointestinal Disorders	11 (55.0)	4 (40.0)
Infections and Infestations	9 (45.0)	6 (60.0)
Skin and Subcutaneous Tissue Disorders	12 (60.0)	3 (30.0)
Musculoskeletal and Connective Tissue Disorders	9 (45.0)	1 (10.0)
Nervous System Disorders	8 (40.0)	2 (20.0)
General Disorders and Administration Site Conditions	6 (30.0)	2 (20.0)
Respiratory, Thoracic and Mediastinal Disorders	6 (30.0)	2 (20.0)
Eye Disorders	3 (15.0)	1 (10.0)
Reproductive System and Breast Disorders	2 (10.0)	1 (10.0)
Investigations	2 (10.0)	0
Metabolism and Nutrition Disorders	2 (10.0)	0
Psychiatric Disorders	0	1 (10.0)
Vascular Disorders	0	1 (10.0)

Source: 5.3.5.4 CSR Study 2203 Table 12-1.
AE=adverse event; bid=twice daily; CSR=clinical study report.

Table 27: Incidence of AEs by Preferred Term With at Least >5% Incidence in the Total Group – Study 2203 (Safety Analysis Set)

Preferred Term	Leniolisib 70 mg bid (N=20) n (%)	Placebo (N=10) n (%)	Total (N=30) n (%)
Number of patients with at least 1 AE	20 (100.0)	8 (80.0)	28 (93.3)
Rash	11 (55.0)	1 (10.0)	12 (40.0)
Viral upper respiratory tract	7 (35.0)	4 (40.0)	11 (36.7)
Headache	7 (35.0)	1 (10.0)	8 (26.7)
Diarrhea	5 (25.0)	1 (10.0)	6 (20.0)
Flatulence	1 (5.0)	3 (30.0)	4 (13.3)
Dyspnea	3 (15.0)	0	3 (10.0)
Fatigue	2 (10.0)	1 (10.0)	3 (10.0)
Oropharyngeal pain	3 (15.0)	0	3 (10.0)
Pyrexia	2 (10.0)	1 (10.0)	3 (10.0)
Upper respiratory tract infection	3 (15.0)	0	3 (10.0)
Abdominal pain	2 (10.0)	0	2 (6.7)
Abdominal pain upper	1 (5.0)	1 (10.0)	2 (6.7)
Back pain	2 (10.0)	0	2 (6.7)
Chest discomfort	1 (5.0)	1 (10.0)	2 (6.7)
Decreased appetite	2 (10.0)	0	2 (6.7)
Dizziness	2 (10.0)	0	2 (6.7)
Dry eye	1 (5.0)	1 (10.0)	2 (6.7)
Dry skin	2 (10.0)	0	2 (6.7)
Dysmenorrhea	1 (5.0)	1 (10.0)	2 (6.7)
Eczema	1 (5.0)	1 (10.0)	2 (6.7)
Feeling cold	2 (10.0)	0	2 (6.7)
Hyperhidrosis	1 (5.0)	1 (10.0)	2 (6.7)
Nausea	2 (10.0)	0	2 (6.7)
Paresthesia	1 (5.0)	1 (10.0)	2 (6.7)
Sjogren's syndrome	2 (10.0)	0	2 (6.7)
Toothache	2 (10.0)	0	2 (6.7)

Source: 5.3.5.4 CSR Study 2203 Table 12-2.
AE=adverse event; bid=twice daily; CSR=clinical study report.

Study LE1101

Study LE1101 was a Phase 1, single-center, open-label, randomized, 2-way crossover bioequivalence study. A total of 20 participants were randomized to treatment sequence. 19 participants received a single oral dose of leniolisib 70 mg as capsule (1×70 mg capsule) and as tablet (1×70 mg tablet) formulation. A total of 10 (50.0%) participants experienced 34 AEs. All AEs were mild. There were no deaths, SAEs, discontinuation of study treatment or study withdrawals due to AEs, or other significant AEs. AEs reported by 2 or more participants were headache (25.0%), diarrhea (20.0%), dizziness (10.0%), and nausea (10.0%). Seven (35.0%) subjects had 20 AEs that were considered related to the study treatment by the investigator. The related AEs included events of headache (20.0%), diarrhea (15.0%), dizziness (10.0%), nausea (10.0%), abdominal distension (5.0%), flatulence (5.0%), frequent bowl movements (5.0%), asthenia (5.0%), and peripheral coldness (5.0%).

Study LE2101

Study LE2101 was a Phase 1, single-centre, open-label absorption, distribution, metabolism, and excretion study. A total of 6 participants were enrolled and received a single dose of 70 mg. A total of 5 (83.3%) participants experienced 8 AEs. All AEs were mild and considered unrelated to study

treatment by the investigator. There were no deaths, SAEs, discontinuation of study treatment or study withdrawals due to AEs, or other significant AEs.

2.6.9. Discussion on clinical safety

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Patient disposition and exposure

The safety database includes patients with APDS from a dose finding Phase 2 study (Study 2201 Part 1), a pivotal Phase 3 study versus placebo (Study 2201 Part 2), and an extension study (Study 2201E1 Part 3). This extension trial allowed to include all patients (active and the placebo groups) of Studies 2201 Part 1 and 2, but also patients not enrolled in studies 2201 and who were previously treated with another PI3Kδ inhibitor. Only 1 patient from the leniolisib arm of Study 2201 Part 2 did not continue in the extension study because she became pregnant.

Supportive data from the Phase 1 studies in healthy volunteers and from a Phase 2 study conducted in patients with primary Sjogren's syndrome are also provided separately. The clinical safety is in line with the APDS patients.

The safety database includes 38 adolescent and adult APDS patients. Although it is acceptable considering that APDS is a rare disease (i.e. prevalence <1 / 1 000 000), this is very limited and cannot allow to sufficiently characterise the safety profile of leniolisib. The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the safety of Joenja under normal conditions of use, because APDS is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Thus, during the review, a marketing authorisation under exceptional circumstances has been applied as discussed under Section 3.7.3. .

Considering that APDS is a genetic life-long condition, long-term data are particularly of importance. However, controlled data are limited to a 12-week period (Study 2201 Part 2). All patients have been treated for at least 60 weeks, of which 10 have been treated ≥ 260 weeks.

Regarding demographics and baseline characteristics, patients from 12 years and up were enrolled in consistency with the proposed indication. Elderly being older than 75 were excluded; however, no patient over 54 could be enrolled. Patients with mutations in either PIK3CD or PIK3R1 could be included; only 8 patients with PIK3R1 mutation have been enrolled in the whole clinical programme, and a clear imbalance can be observed in the Study 2201 Part 2: 23.8% (=5) in the leniolisib arm vs. 10.0% (n=1) in the placebo arm. This is still considered acceptable as it is a rare disease, and the safety of leniolisib is not expected to differ between the two mutations. It is also noted that no patients with moderate/severe renal and/or hepatic impairment were enrolled in the clinical programme, as reflected in section 4.2 of the SmPC. This is acceptable. Additionally, the clinical programme for leniolisib was conducted in the United States and Europe, which did not raise concern on the generalisation of results to the European population.

Adverse events

The results on adverse events were considered difficult to interpret given the low number of patients and events.

In the total leniolisib group, 94.7% of the subjects experienced at least 1 AE. However, looking at the comparative data from the Study 2201 Part 2, 85.7% of the subjects in the leniolisib arm had at least 1 AE vs 90.0 % in the placebo arm.

In Study 2201 Part 2, the incidence of the grade 3 AEs were higher in the placebo group (30.0% vs 9.5% in the leniolisib group), and the incidence of the grade 4 AEs was similar across the two arms (9.5 % in the leniolisib group vs 10% in the placebo group). 1 grade 5 AE (10%) occurred in the placebo arm, none in the leniolisib group. Overall, the safety comparative data, in term of incidence or severity, suggested an acceptable profile of tolerability. However, the evolution of the tolerability of leniolisib (e.g. stable, improving, worsening…) over the time is insufficiently characterised, in particular considering the expected long-term treatment. The conduct of two specific obligations SOB01 and SOB02 will help further characterise the long-term safety data on this topic. Indeed, registry-based study SOB01 will obtain real-world evidence concerning the long-term safety of leniolisib in patients with APDS and characterise or invalidate the important potential risks of: serious colitis/diarrhoea, serious hepatotoxicity, serious and opportunistic infections, pneumonitis, severe cutaneous adverse events (SCARs) and embryo-foetal toxicity, as well as help address other remaining safety concerns.

Subgroup safety analysis were made by age, sex and gene mutation. However, the interpretability of the results is difficult given the low number of patients and events.

There was a fatal case due to cardiac arrest which was considered not related to the study treatment by the Investigator. No further concern was raised.

The most common AEs in the total leniolisib group were reported for the Infection and infestation SOC with an incidence of 86.8%, followed by the Gastrointestinal disorders SOC (68.4%), Investigations (52.6%), the Nervous system disorders SOC (47.7%), the Skin and subcutaneous disorders SOC (42.1%), the , the Respiratory, thoracic and mediastinal disorders SOC (44.7%), the General disorders and administration site conditions SOC (42.1%) and the Musculoskeletal and connective tissue disorders (39.5%). Additionally, the most common AE were headache (31.6%), Upper respiratory tract infection (28.9%), Pyrexia (26.3 %), Sinusitis (26.3%), Otitis externa (21.1%), and Diarrhoea (15.8%).

The incidence of infection and infestation AEs in the total leniolisib group was 76.3%, and 5 SAE were reported (Mastoiditis, Colitis, Parotitis, Periorbital cellulitis, and sinusitis). Patients with APDS are known to be more sensitive to infections, in particular on respiratory tract. However, the higher incidence of AEs for the Infection and infestation SOC for the leniolisib group vs placebo (52.4% vs 40.0%) in the Study 2201 Part 2 together with the fact that infections are a known risk observed with other PI3K inhibitors were considered of concern. Moreover, an increased risk of infection was observed in nonclinical studies, in particular skin and gastrointestinal infections. Serious and opportunistic infections is an important potential risk in the RMP and will be further characterised in the SOB01, a registry-based Post Authorisation Safety Study will help characterise the long-term safety of leniolisib with real world evidence, including on serious and opportunistic infections, and pneumonitis (see section 3.7.3. Additional considerations on the benefit-risk balance).

Regarding skin disorders, in the comparative Study 2201 Part 2, a higher incidence of AEs for the Skin and subcutaneous tissue disorders (33.3% vs 10%) was observed. Additionally, an incidence of 21.0% of rash was reported in overall patient treated with leniolisib (8 cases, but none considered as drug related by the investigator). The PI3Kδ class of drugs have been associated with skin rash, and a high incidence of this was also observed in the Phase 2 Study in patients with primary Sjogren's syndrome (55% vs 10% for placebo). Following further discussion, skin rash has been added as ADR in section 4.8 of the SmPC as Atopic dermatitis and Rash. The applicant will also follow the risk of seborrheic dermatitis (i.e. observed in 10.5 % of the subjects) in the PSURs.

Regarding the cardiac risk profile, the applicant conducted an analysis to characterise the relationship between QTc and leniolisib exposure utilizing the data from the first-in-human (FIH) healthy volunteer. Results from the C-QTc analysis indicate that no QTc prolongation is expected at the recommended dose of 70 mg BID.

On haematology, 6 cases (15.8%) of neutrophil counts decrease were reported. Among them, there was a grade 3 AE and considered related to study treatment by the investigator. Together with the fact that PI3Kδ class of drugs have been associated with decreased neutrophil count, and that neutrophil counts decrease was also seen in numbers of healthy volunteers of the Phase 1 Study 2104 (16/30 participants had absolute neutrophils below the normal range and 3 participants had absolute neutrophils below the clinical significance threshold of 1.0×109/L), "neutrophil counts decreased" was added as ADR in section 4.8 of the SmPC under frequency very common.

At data cut-off 13 Dec 2021, liver-related AEs (21% of the total leniolisib group) were reported in patients under leniolisib treatment, including 3 case (7.9%) of Grade 3. Although presented as infrequent, newly occurring liver enzyme abnormalities were reported under treatment. Additionally, no other possible aetiology for these cases was presented. Together with that, no cases were observed in the placebo group and other PI3Kδ inhibitors have been associated with elevation of liver enzymes, the applicant will follow Liver enzymes elevation in the PSURs.

Additionally, the risk of elevation of lipase will also be followed in the PSURs.

Safety of DDI

Since, leniolisib is cleared primarily through oxidative metabolism predominantly by CYP3A4, 95.4%. In a clinical DDI study in healthy adults, showed that co administration of leniolisib and itraconazole, a strong CYP3A4 inhibitor, resulted in a 2-fold increase in leniolisib exposure. Therefore, the concomitant use of leniolisib with strong and moderate CYP3A4 inhibitors and inducers should be avoided.

In addition, according to the *in vitro* data, leniolisib is a BCRP substrate. Since, no clinical DDI has been performed to assess the clinical impact on leniolisib exposure when co-administered with a strong BCRP inhibitor, the concomitant use of leniolisib with BCRP inhibitors should be avoided.

Leniolisib can increase rosuvastatin exposure 2-fold, and its use with OATP1B1, OATP1B3, and BCRP substrates like rosuvastatin and pitavastatin should be avoided. Additionally, leniolisib is an inhibitor of UGT1A1 and should not be administered with UGT1A1 substrates like irinotecan. However, when given with hormonal contraceptives containing ethinylestradiol and levonorgestrel, leniolisib increases ethinylestradiol exposure by approximately 30%, but this is unlikely to affect the contraceptive's effectiveness.

Safety in special populations

There is no available data on leniolisib use in pregnant women, but studies in animals have shown reproductive toxicity, thus a teratogenic effect is expected. Precautionary measures are implemented in the SmPC to make sure no pregnant woman would receive leniolisib. As such, the SmPC adequately reflects this information in section 4.4 and 4.6: Women of childbearing potential should use highly effective contraception while taking Joenja and for 1 week after the last dose, and that testing should be done prior to treatment with Joenja to check pregnancy status in females of childbearing potential. Furthermore, Embryo-foetal toxicity is listed as an important potential risk in the RMP.

Renal impairment: leniolisib has not been studied in patient with renal impairment, no dosing modifications are recommended. The SmPC is considered acceptable (See SmPC section 4.2).

Hepatic impairment: use of leniolisib in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C) is not recommended. The SmPC adequality reflects this information in section 4.2,

and the safety in patients with hepatic impairment is considered a missing information in the RMP. The applicant will provide further data in a category 3 study (LE 6101), as listed in the RMP, which will evaluate the safety profile of a single 70 mg oral dose of leniolisib in hepatic impairment patients in the post-authorisation phase.

Safety concerns

Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other PI3Kδ inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in APDS patients. However, in view of the seriousness of those safety concerns, a warning has been implemented in the product information.

Pneumonitis, severe cutaneous adverse reactions (SCAR) were considered important potential risks in the RMP, since they all are class effect of PI3K inhibitors, and since a higher incidence of events of diarrhoea, elevated liver enzymes, infections, and rash have been observed in the randomized part of the study in the leniolisib arm compared to placebo arm, and considering also the limited exposure (in terms of number of subjects and length of exposure) precluding the identification of ADRs. These events will be assessed in the SOB01.

Missing information includes "Safety in patients with hepatic impairment", which will be reviewed following the results of the ongoing category 3 study (LE6101) as listed in the RMP, which will evaluate the safety profile of a single 70 mg oral dose of leniolisib in hepatic impairment patients in the post-authorisation phase, and "Long-term safety" which will be assessed in the registry-based specific obligation SOB01.

Additional expert consultation

An Ad-Hoc Expert Group has been consulted on the 27 November 2023. Questions included clinical safety (see section 2.6.6)

Assessment of paediatric data on clinical safety

The phase II/III study (Study 2201) assessed patients with APDS, including paediatric patient 12 years and above. The number of patients aged <18 years, in particular of patients aged 16 to 12 years is low, follow-up for these patients is lower. Regarding safety, no significant differences in safety profiles were apparent in the adolescent population compared to the adult population.

Although the applicant plans to conduct paediatric studies in patients aged from 1 to 12 years (a waiver has been grated from birth to less than 1 year of aged), no data are currently available in children aged less than 12 years.

Additional safety data needed in the context of a MA under exceptional circumstances

Regarding the safety, only 38 patients with APDS have been treated with leniolisib for at least 60 weeks, of which 10 have been treated ≥ 260 weeks. Acknowledging that the APDS is a very rare disease, the relevant safety database although limited in size, provided a reasonable amount of data to evaluate very common safety aspects. However, the length of the follow-up for a reasonable number of participants in view of the intended use of the product as a lifelong treatment for APDS was considered limited. As a result, the CHMP considered that the long-term safety is insufficiently characterised. This concern is not expected to be adequately addressed within a reasonable timeframe. The applicant thus committed, to further characterise the long-term safety profile of leniolisib, to conduct a registry-based safety study to collect data on the long-term safety of leniolisib (SOB01) and to submit yearly updates on long term safety to be assessed within the annual reassessments for an unlimited time (SOB02). For more details, please refer to the section 3.7.3.

2.6.10. Conclusions on the clinical safety

The results of the clinical programme conducted in patients with APDS suggest that leniolisib has an acceptable tolerability. The observed AEs were overall consistent with the safety profile of the PI3Kδ class. The most commonly reported adverse reactions during leniolisib treatment were headache, vomiting, weight increase, and alopecia. Based on laboratory data from the clinical studies, a third of patients experienced a decrease in neutrophil counts.

The CHMP considers the following measures necessary to address the missing safety data on the long-term use of leniolisib in the context of a MA under exceptional circumstances:

- Non-interventional post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of leniolisib in the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.
- In order to ensure adequate monitoring of safety and efficacy of leniolisib in the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of leniolisib.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 28: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious diarrhoea/colitis Serious hepatotoxicity Serious and opportunistic infections Pneumonitis Severe cutaneous adverse reactions (SCAR) Embryo-foetal toxicity
Missing information	Safety in patients with hepatic impairment
	Long-term safety

2.7.2. Pharmacovigilance plan

Table 29: Table Part III.3: On-going and planned additional pharmacovigilance activities

Study *Status*	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
SOB01 (LE 4401) *Planned*	Efficacy objectives are: • To obtain real-world evidence concerning the long-term efficacy of leniolisib in patients with APDS • To provide further evidence of the long-term efficacy of leniolisib in APDS as measured by a reduction of signs and symptoms of APDS Safety objectives are: • To obtain real-world evidence concerning the long-term safety of leniolisib in patients with APDS • To characterise or invalidate the important potential risks of.: o Serious colitis/diarrhoea o Serious hepatotoxicity o Serious and opportunistic infections o Pneumonitis o SCARs o Embryo-foetal toxicity • To evaluate the risks safety of leniolisib used in a patient population for which safety information is limited or missing (e.g., paediatric and geriatric age groups, patients with hepatic impairment and co-medication with mTOR inhibitors) • To assess patterns of drug	Long-term safety and important potential risks: • Serious colitis/diarrhoea • Serious hepatotoxicity • Serious and opportunistic infections • Pneumonitis • SCARs • Embryo-foetal toxicity	Protocol submission Progress reports Final report	V0.1 on 10-Oct-2023 (D180 response) V0.2 on 19-Dec-2023 (2nd D180 response) V0.3 on 12-Apr-2024 (3rd D180 response) Final protocol to be submitted within 3 months after EC Decision Yearly updates and progress status within Annual Assessment 1 year after study completion (10 years follow-up).

Study *Status*	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	utilisation that add knowledge regarding the safety of the medicinal product (e.g., collection of information on indication, off-label use, dosage, co-medication, or medication errors in clinical practice that may influence safety, as well as an estimate of the public health impact of any safety concern) • To assess the incidence and causes of death • To assess the impact on fertility, if applicable • To assess pregnancy outcomes if applicable			
SOB02	To update annually the regulators on any new information concerning the safety and efficacy. To characterise or invalidate the important potential risks of: ▪ Serious colitis/diarrhoea ▪ Serious hepatotoxicity ▪ Serious and opportunistic infections ▪ Pneumonitis ▪ SCARs ▪ Embryo-foetal toxicity Use of haematopoietic stem cell transplantation (HSCT) will be systematically collected in the context of post-authorisation safety and effectiveness data generation. Specifically, information on HSCT will include, where available: ▪ Whether HSCT was performed (yes/no) ▪ Timing of HSCT in relation to leniolisib treatment (during or after treatment discontinuation) ▪ Reason for HSCT (e.g., disease progression, lack of	• Serious colitis/diarrhoea • Serious hepatotoxicity • Serious and opportunistic infections • Pneumonitis • SCARs • Embryo-foetal toxicity	Yearly reports	Yearly updates after approval of the marketing authorisation application (within Annual Assessment)

Study ***Status***	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	efficacy, other clinical considerations) ▪ Relevant outcomes, including graft status and major complications			
Category 3 – Required additional pharmacovigilance activities (by the competent authority)				
Hepatic impairment study (LE 6101) *Ongoing*	Primary: To investigate the effect of hepatic impairment on the plasma PK of leniolisib after oral administration, compared to subjects with normal hepatic function. Secondary: To evaluate the safety profile of a single 70 mg oral dose of leniolisib in hepatic impairment patients.	Safety and PK in patients with moderate to severe hepatic impairment	Protocol submission Progress report Final report	V1.0 dated 17 Oct 2023 submitted on 19-Dec-2023 (2nd D180 response) V2.0 dated 11 Dec 2023 submitted on 16-Apr-2024 (briefing document clarification meeting 7 May 2025) V2.1 dated 31 Mar 2025 (4th D180 LoOIs response) Update in every PSUR June 2026

2.7.3. Risk minimisation measures

Table 30: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Serious diarrhoea/colitis	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Serious hepatotoxicity	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Serious and opportunistic infections	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Pneumonitis	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
SCAR	Routine risk minimization measures: *Information on these safety concerns is included in SmPC Section 4.4 and PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date:1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*
Embryo-foetal toxicity	Routine risk minimisation measure: *Instruction for women of childbearing potential/contraception in females is included in SmPC Sections 4.2, 4.4, and 4.6, PL Section 2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up)* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Safety in patients with hepatic impairment	Routine risk minimisation measures: *Recommendation for patients with moderate to severe hepatic impairment is included in SmPC Section 4.2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Hepatic impairment study (LE 6101)* *Final study report due date: 2026.*
Long-term safety	Routine risk minimization measures: *None* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting, signal detection: *None* Additional pharmacovigilance activities: *SOB01 (LE 4401)* *Final study report due date: 1 year after study completion (10 years follow-up).* *SOB02 (new information concerning the safety and efficacy including the important potential risks and HSCT)* *Annual updates*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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 24 March 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

- An English only bottle label and outer carton with the appropriate blue box has been found acceptable. The request has been accepted since it is an orphan disease and the prevalence across the EU is very low, and although the patients ultimately take Joenja themselves, the prescription of the product is limited to hospitals and/or specialists. Packet leaflets should still be in local language inside the outer carton.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the languages as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Joenja (leniolisib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore, the summary of product characteristics and the package leaflet include 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

APDS is a rare (0.01 in 10,000 people in the EU) heterozygous autosomal dominant heritable disease of the immune system caused by a mutation in either the PIK3CD or PIK3R1 genes coding for the catalytic and regulatory domains of the PI3K dimer, respectively.

Hyperactive PI3Kδ signalling alters the differentiation of both B cells and T cells, leading to inappropriate and inadequate cell populations. In B cells, elevated levels of immature transitional B cells develop in patients with APDS. These cells are sequestered in the lymph nodes or spleen, leading to an increase in the size of these organs. Also, naïve B cells fail to develop. These cells interact with an antigen and undergo class switch recombination to produce more selective IgG and IgA immunoglobulins.

APDS is a progressive and potentially life-threatening condition with recurrent upper and lower respiratory tract infections routinely progressing to irreversible bronchiectasis, lymphadenopathy, splenomegaly, autoimmune complications, and an increased risk of developing lymphomas.

The initially applied indication for Joenja was the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older.

During the course of the evaluation the CHMP agreed to the following indication: treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more.

3.1.2. Available therapies and unmet medical need

There is currently no authorised treatment for APDS. Existing treatment options for the management of APDS are predominantly supportive such as immunoglobulin replacement therapy, antibiotics, antiviral agents, immunosuppressive agents (e.g. steroids, azathioprine, mycophenolate), splenectomy, rituximab, and sirolimus (rapamycin). The only exception is haematopoietic stem cell transplantation (HSCT) which is potentially curative.

Available symptomatic treatments address only part of the manifestations of the disease, provide only temporal relief, and are associated with undesired side effects or are associated with significant risks. Given the severity of the disease, there is a high unmet medical need for the treatment of the condition.

3.1.3. Main clinical studies

The primary efficacy supported for the proposed indication is based on the part 2 of a Phase 2/3 study (study 2201): a randomised, blinded, placebo-controlled study. Patients received leniolisib 70 mg (n=21) or placebo (n=10) BID during 12 weeks. Supportive data were provided by the part 1 (phase 2, dose-finding part) and part 3 (open label extension including patients who rolled over from Study 2201 (Part 1 or Part 2) and patients who were treated with another PI3Kδ inhibitor) of the same study. In this extension part, all patients received leniolisib 70 mg BID.

The included population were male and female patients aged 12 to 54 years who had a documented APDS/PASLI-associated genetic PI3K delta mutation (PIK3CD mutation leading to APDS1 or PIK3R1 mutation leading to APDS2).

3.2. Favourable effects

In the efficacy part of study 2201 (part 2), both co-primary endpoints ("change from baseline in the log10 transformed sum of product diameter (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging" and "change from baseline in percentage of naïve B cells out of total B cells") were met, and showed an improvement associated with leniolisib treatment. Indeed, the change from baseline in the log10 transformed SPD (SE) was -0.30 (0.04) in the leniolisib group vs 0.06 (0.06) in placebo group, leading to a difference in adjusted mean change (95% CI) of leniolisib 70 mg bid (N=18) vs placebo (N=8) of -0.24 (-0.37, -0.11). The results were statistically significant with 2-sided p-value observed as p=0.0012.

Results for the second co-primary endpoint which was change from baseline in naïve B cells out of total B-cells in patients with a percentage of less than 48% of naïve B-cells at baseline (adjusted mean change, SE) showed a statistically significant increase in leniolisib arm (34.76, 3.08) compared to placebo arm (-5.37, 3.95).

As per the AHEG meeting held on 27 November 2023, these PD endpoints are expected to translate into clinically relevant effects in patients with APDS. The applicant conducted a Delphi study to identify the most important outcomes when evaluating the effectiveness of APDS treatments in clinical practice and the amount of change in these outcomes that would indicate a meaningful benefit for a patient. Results were in favour of a clinically relevant effect associated with the co-primary endpoints analyses, supporting thus the expert's consensus.

A supportive analysis conducted, increasing thus the number of patients analysed, showed that immature transitional B-cells that are elevated and sequestered in the lymph nodes or spleen of patients with APDS, significantly decreased to reach 8.7% at D85 in leniolisib group compared to 33.8% in placebo group.

Several secondary endpoints further supported those co-primary endpoints: mean SPD volume of index lesion and mean bi-dimensional size and volume of spleen both decreased at the end of treatment compared to baseline in leniolisib group, while there was no or minimal change in placebo group. This was expected to reflect clinically relevant effects.

3.3. Uncertainties and limitations about favourable effects

As APDS is a rare disease, the number of patients in the single pivotal study is very limited as only 26 patients (n=18 in leniolisib group and n=8 in placebo group) were analysed for the co-primary endpoint "change from baseline in the log10 transformed SPD". Data become very scarce for the second co-primary endpoint change from baseline in naïve B cells with only 15 patients analysed (n=10 in leniolisib group and n=5 in placebo group). Due to the limited number of patients, there is inherent uncertainty in the study results, and conclusions about the treatment's effects are interpreted with caution.

Infections, which are an important hallmark of APDS, could not be adequately assessed in the efficacy part 2 of the pivotal study. Indeed, the duration of this controlled part was 12 weeks which is considered too short to assess effect on infection rate.

Part 3 (open label) provided further long-term data. Results of this open label extension suggest a decrease of infections over time. However, given the limited sample size and the absence of a control arm, the interpretation of the treatment effect on clinical outcomes is associated with uncertainty. Nevertheless, during the AHEG held on 27 November 2023, experts reached the consensus that the co-primary endpoints are expected to translate into clinically relevant effects.

In the context of marketing authorisation under exceptional circumstances, the registry-based safety study (SOB01) will help to collect real-world evidence including on the long-term efficacy of leniolisib in patients with APDS. Furthermore, the applicant agreed to a second specific obligation (SOB02) to provide yearly updates on any new information, including on the efficacy of leniolisib within each annual reassessment, for an unlimited period.

3.4. Unfavourable effects

The most common AEs in the total leniolisib group were reported for the Infection and infestation SOC with an incidence of 86.6%, followed by the Gastrointestinal disorders SOC (68.4%), Investigations (52.6%), the Nervous system disorders SOC (47.7%), the Skin and subcutaneous disorders SOC (42.1%), the Respiratory, thoracic and mediastinal disorders SOC (44.7%), the General disorders and administration site conditions SOC (42.1%) and the Musculoskeletal and connective tissue disorders (39.5%).

Regarding comparative data (i.e., Study 2201 Part 2), it can be observed higher incidence of AEs for the Infection and infestation SOC for the leniolisib group vs placebo (52.4% vs 40.0%), as well as for the Skin and subcutaneous tissue disorders (33.3% vs 10%).

The most common AEs in the total leniolisib group were headache (31.6%, n=10), Upper respiratory tract infection (28.9%), Pyrexia (26.3 %), Sinusitis (21.1%, n=8) Otitis externa (21.1%), and Diarrhoea (15.8%).

Within the infection and infestation SOC, the most commonly reported events were COVID-19 (31.6%), Upper respiratory tract infection (28.9%), Sinusitis (26.3%), , Otitis externa (21.1%, n=8), , nasopharyngitis (15.8%, n=6), Rhinitis (15.8%, n=6), pneumonia (13.2%, n=5), gastroenteritis (13.2%, n=5), and Respiratory tract infection (13.2%, n=5).

Within the Skin and subcutaneous tissue disorders SOC, it is emphasized 18.4% (n=7) of rash, alopecia (10.5% n=4) and seborrhoeic dermatitis (10.5%, n=4) ;1 case of phototoxicity was reported.

Within the Gastrointestinal disorders SOC, the most commonly reported AEs were diarrhoea (15.8%, n=6) and abdominal pain (13.2%, n=4).

Regarding the laboratory findings at cut-off 13 December 2021, 15.8% (n=6) of neutrophil counts decrease were reported, of which 1 event of grade 3. It is also reported 15.8% (n=6) of lymphopenia (for 5 cases, patients had a history of lymphopenia), of which 3 events of grade 3. Additionally, it is noted 2 cases (5.2 %) of elevation of lipase, of which 1 event of grade 4, and 8 cases (21%) of elevated liver enzymes.

Since leniolisib is metabolised by CYP3A4, potential drug-drug interactions were expected to be a concern and were investigated. Recommendations for concomitant use of medicinal products interacting with leniolisib are implemented in SmPC Sections 4.4 and 4.5 and in the corresponding sections of the package leaflet

Serious, sometimes fatal, immune-related adverse events such as severe infections, SCARs, pneumonitis, severe diarrhoea/colitis, and hepatotoxicity have occurred in patients receiving other

PI3Kδ inhibitors for the treatment of haematological or solid cancers. These serious events have not been associated with the use of Joenja in APDS patients. However, in view of the seriousness of those safety concerns, a warning has been implemented in the product information.

3.5. Uncertainties and limitations about unfavourable effects

Thirty-eight (n=38) adolescent and adult APDS patients have been exposed to leniolisib at any dose in clinical studies. Although it is acknowledged that the condition is a rare disease (i.e., prevalence <1/1 000 000), the safety data base remains limited and cannot allow a thorough characterization of the safety profile. However, results of the clinical programme conducted in patients with APDS suggest that leniolisib has an acceptable tolerability and the observed adverse events were overall consistent with the safety profile of the PI3Kδ class.

The pivotal study was placebo-controlled, with both groups receiving standard of care. However, the controlled period was limited to 12 weeks, whereas APDS is a lifelong genetic condition requiring long-term treatment. Long-term safety data are available only from the single-arm extension study 2201E1, which introduced limitations, as the absence of a control group makes it difficult to attribute observed outcomes to the treatment and to robustly assess long-term safety. The length of the follow-up for a reasonable number of participants in view of the intended use of the product as a lifelong treatment for APDS was considered limited rendering the safety dataset limited overall. However in the in the context of marketing authorisation under exceptional circumstances, the CHMP agreed that it is acceptable that additional data will be collected in post marketing setting in SOB01 (a registry-based study) and in SOB02 (yearly updates on long term safety to be assessed within the annual reassessments for an unlimited time), to help characterise the long-term safety profile of leniolisib.

The important potential risks of serious diarrhoea/colitis, serious hepatotoxicity, serious and opportunistic infections, pneumonitis, severe cutaneous adverse reactions (SCAR), embryo-foetal toxicity are expected to be further characterised in the registry-based study SOB01. Due to the important potential risk of embryo-foetal toxicity, the use of leniolisib is not recommended during pregnancy and precautionary measures regarding the use of contraception methods are implemented as reflected in section 4.6 of the SmPC.

No safety data in patients with liver impairments are available. The applicant will provide further data in a category 3 study (LE 6101), as listed in the RMP, which will evaluate the safety profile of a single 70 mg oral dose of leniolisib in hepatic impairment patients in the post-authorisation phase.

Regarding subgroups analysis, only 8 patients with PIK3R1 mutations, with a clear imbalance in the comparative study (23.8% (n=5) in the leniolisib arm vs. 10.0% (n=1) in the placebo arm) were enrolled making challenging to characterise the safety profile in this subset.

3.6. Effects Table

Table 31: Effects Table for Joenja in the treatment of APDS (Efficacy and safety for the randomized study part: study 2201 completion date: 16 August 2021; data cut-off for final CSR: January 2025).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Lymphadenopathy	Lymphadenopathy Adjusted Mean Change (SE)		-0.30 (0.04)	-0.06 (0.06)	Very small sample size	Study 2201 Part 2
Naïve B-cell	Immunophenotype normalization Adjusted Mean Change (SE)		34.76 (3.08)	-5.37 (3.95)		
Volume of spleen	Mean (SD) values change from baseline at D85	mm^3	-26.68 (12.14)	-1.37 (24.24)		
Bi-Dimensional Size of Spleen	Mean (SD) values change from baseline at D85	mm^2	-12.05 (12.75)	6.22 (21.98)		
3D volume of index lesions	Mean (SD) values change from baseline at D85	mm^3	-58.05 (22.43)	-7.93 (28.82)		
SPD of index lesion	Mean (SD) values change from baseline at D85	mm^2	-47.83 (20.35)	-4.53 (27.7)		
Unfavourable Effects						
Headache	Incidence	%	31.6	NA	limited size of the safety database. Limited safety data on the long-term use	Total leniolisib group*
Sinusitis	Incidence	%	26.3	NA		Total leniolisib group*
Upper respiratory tract infection	Incidence	%	28.9	NA		Total leniolisib group*
Pyrexia	Incidence	%	26.3	NA		Total leniolisib group*
Diarrhoea	Incidence	%	15.8	NA		Total leniolisib group*
Otitis externa	Incidence	%	21.1	NA		Total leniolisib group*
Infection and infestation	Incidence of all of the AEs SOC	%	52.4	40.0		Study 2201 Part 2
Gastrointestinal disorders	Incidence of all of the AEs SOC	%	33.3	40.0		Study 2201 Part 2
Nervous system disorders	Incidence of all of the AEs SOC	%	28.6	30.0		Study 2201 Part 2
Skin and subcutaneous tissue disorders	Incidence of all of the AEs SOC	%	33.3	10.0		Study 2201 Part 2

* final CSR final data cut-off: January 2025
NA: Not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although APDS being a very rare disease, the applicant conducted a randomized controlled versus placebo study on top of standard of care, in an acknowledged effort to provide an acceptable level of evidence.

The most important effects observed are on the two co-primary endpoints, "change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions" and "change from baseline in naïve B cells in patients with a percentage of less than 48% of naïve B-cells at baseline". Indeed, a reduction of lymphadenopathy and an increase in naïve B-cell were observed in leniolisib group compared to placebo group. This later result was accompanied by a decrease in transitional B-cell.

While the results of the first co-primary endpoint (i.e. lymphadenopathy) are agreed, those for the second co-primary endpoint were less compelling, as fewer than half of the patients were analysed mainly due to a percentage of B-cells > 48% and missing data. However, additional requested sensitivity analyses including patients with a baseline percentage of naïve B-cells at baseline > 48%, supported the primary analysis.

Both co-primary endpoints reflect two important features of APDS i.e. lymphoproliferation and immunodeficiency. During the AHEG meeting, the experts reached the consensus that these results of the co-primary endpoints are expected to translate into clinically relevant effects. This is also in line with the outcome of the Delphi study. Imaging secondary endpoints were supportive of the co-primary endpoint assessing lymphadenopathy. Some encouraging results were obtained with the decrease of inflammatory biomarkers such as CXCL13, IP-10 and TNF-α as well as a reduction of IgM compared to placebo group. However, no difference could be observed for activity parameters. Other secondary endpoints, such as health-related quality of life questionnaires, patient's and physician's global assessment did not show a benefit from leniolisib treatment compared to placebo treatment. In addition, although infections could not be fully characterized within the 12-week duration of the pivotal Phase II/III study, the available data suggest a decrease over time, supporting a potential beneficial effect with longer treatment.

Overall, the safety profile of leniolisib from the available clinical programme suggested an acceptable tolerability with respect of the APDS condition. Uncertainties remained on the long-term safety especially on the risk of increased infections, including respiratory tract infections. As Leniolisib has been shown to have embryo-foetal toxicity, adequate precautionary measures have been implemented in the product information. Furthermore, embryo-foetal toxicity is listed as important potential risk in the RMP and will be further characterised in long-term studies.

In the context of marketing authorisation under exceptional circumstances, the CHMP agreed that additional data on the long-term safety will be collected in the registry-based study (SOB01) and in yearly updates on long term safety to be assessed within the annual reassessments for an unlimited time (SOB02), to further characterise the long-term safety profile of leniolisib.

3.7.2. Balance of benefits and risks

Overall, the totality of the data indicates consistent improvement across key hallmarks of the disease (e.g. lymphadenopathy, splenomegaly, and naïve B-cell proportion) in a controlled trial setting, with effects that continued to improve in the extension study. The reduction in lymphadenopathy is

considered relevant, and the findings for the second co-primary endpoint (increase in naïve B cells) are supportive of a treatment effect. In addition, the AHEG reached a consensus that the pharmacodynamic activity of leniolisib, as demonstrated through the co-primary endpoints in Study 2201, is likely to translate into clinically meaningful benefits for patients with APDS. While some methodological limitations and the limited evidence on important clinical outcomes, such as infections and quality of life, introduce a degree of uncertainty, the overall results provide sufficient evidence of benefit for APDS patients. The safety profile of leniolisib from the available clinical programme suggested an acceptable tolerability and no important identified risk was identified.

Notwithstanding the rarity of the disease the applicant's effort for conducting a randomized placebo-controlled study are acknowledged by the CHMP. The CHMP agreed that additional data to further characterise the long-term efficacy and safety of leniolisib will be generated in post marketing setting through two specific obligations: a registry-based study (SOB01) and annual updates on all newly emerging data concerning safety and efficacy (SOB02). The applicant will submit annual results for both obligations within the annual reassessment procedures.

Overall, the safety profile of leniolisib and the observed benefits in patients with ADPS, together with the specific obligations, support a positive benefit–risk balance of leniolisib for the following indication: "treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more".

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied APDS indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Indeed, APDS is a very rare heterozygous autosomal dominant heritable disease of the immune system caused by a mutation in either the PIK3CD or PIK3R1 genes coding for the catalytic and regulatory domains of the PI3K dimer, respectively. The APDS incidence rate around the world is estimated to be 1 to 2 per million people and affects approximately 0.01 in 10,000 people in the EU. This was equivalent to a total of around 500 people.

Although APDS being a very rare disease, the applicant conducted a randomized controlled versus placebo study in an effort to provide an acceptable level of evidence, and 38 adolescents (over 12 years) and adult APDS patients have been exposed to leniolisib at any dose in clinical studies. The inclusion criteria were overall consistent with the indicated population. Statistically significant results were shown for both PD co-primary endpoints of "change from baseline in the log10 transformed sum of product diameter (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging" and "change from baseline in percentage of naïve B cells out of total B cells". Since APDS was relatively recently identified, there are no established clinical endpoints for APDS. The PD endpoints chosen in the pivotal study are expected to translate into clinically relevant endpoints; this is in line with the outcome of the expert consultation (AHEG). Considering the data available, the CHMP agreed that efficacy has been shown based on the PD endpoints as adequately reflected in the SmPC Section 5.1.

The available safety data indicate a generally manageable and tolerable safety profile of leniolisib in patients with APDS. The safety database includes only 38 adolescent and adult APDS patients, which is

acceptable in this ultra-rare disease setting.

There is a positive benefit-risk balance for leniolisib for the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more. The CHMP considered that efficacy on the long-term use of leniolisib, especially on the reduction of signs and symptoms is insufficiently characterised. Similarly, the CHMP did not consider the safety dataset with regards to long term exposure with leniolisib as comprehensive, in particular with regards to long-term safety. Neither of these concerns are expected to be addressed within a reasonable timeframe, which is why CHMP requested SOB01, a registry study that will collect real-world evidence concerning the long-term safety and efficacy of leniolisib, and SOB02, to collect long-term safety data of leniolisib.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate. As a first specific obligation (SOB01), the applicant committed to conduct a registry-based study to further characterise the long-term safety and efficacy of leniolisib and provide annual update within the annual reassessment. Furthermore, the applicant agreed to a second specific obligation (SOB02) to provide yearly updates on any new information concerning the safety and efficacy of leniolisib within each annual reassessment, for an unlimited period.

3.8. Conclusions

The overall benefit/risk balance of Joenja is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit-risk balance of Joenja is favourable in the following indication(s):

Joenja is indicated for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances 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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
Non-interventional post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of leniolisib in the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.	Annually (with annual reassessment) Final CSR after 10-year follow up
In order to ensure adequate monitoring of safety and efficacy of leniolisib in the treatment of APDS in adults and adolescents 12 years of age and older and weighing 45 kg or more, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of leniolisib.	Annually (with annual reassessment)

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 that leniolisib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0259/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.