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Long-Term Treatment With Selective PI3Kδ Inhibitor Leniolisib in Adults With Activated PI3Kδ Syndrome

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Abstract:
Activated phosphoinositide 3-kinase delta syndrome (APDS) is an inborn error of immunity that manifests as immune deficiency and dysregulation; symptoms include frequent infections and lymphoproliferation. In our dose-finding and phase 3 placebo-controlled trials, treatment with the selective PI3Kδ inhibitor leniolisib reduced lymphoproliferation and normalized lymphocyte subsets. Here, we present 6 years of follow-up from the 6 adult patients in the original dose-finding trial receiving leniolisib. We used data from the ongoing open-label extension study, which was supplemented at later time points by investigators, including health-related quality of life assessed through a clinician-reported questionnaire. We observed improvements in health-related quality of life: 5/6 patients experienced an increase in physical capabilities and socialization and a decrease in prescribed medications. Immune subsets improved in all patients: mean transitional B-cell levels decreased from 38.17% to 2.47% and the CD4:CD8 T-cell ratio normalized to 1.11. Manifestations seen before and within the first year of leniolisib exposure, such as infections and gastrointestinal conditions, attenuated following year 2 with few new conditions emerging out to year 6. Thrombocytopenia or lymphopenia remained present in half of patients at year 6. Of 83 adverse events through year 5, 90.36% were grade 1; none were grade 4-5 nor deemed leniolisib-related. Collectively, we saw an enhancement in health-related quality of life as well as durable changes in lymphocyte subsets and clinical manifestations, further supporting the use of leniolisib as a long-term therapeutic option for the treatment of APDS. (Funded by Novartis Pharmaceuticals Corporation and Pharming Group NV; ClinicalTrials.gov identifier: NCT02859727.)

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): ClinicalTrials.gov identifier: NCT02859727

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Data Sharing Statement

Pharming is committed to responsibly share data generated by interventional clinical trials with researchers. Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices), may be shared. Data will be made available beginning 12 months and ending 36 months following publication of this article. Researchers who have a

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Main Text

Abstract (word count: 249/250)

Activated phosphoinositide 3-kinase delta syndrome (APDS) is an inborn error of immunity that manifests as immune deficiency and dysregulation; symptoms include frequent infections and lymphoproliferation. In our dose-finding and phase 3 placebo-controlled trials, treatment with the selective PI3Kδ inhibitor leniolisib reduced lymphoproliferation and normalized lymphocyte subsets. Here, we present 6 years of follow-up from the 6 adult patients in the original dose-finding trial receiving leniolisib. We used data from the ongoing open-label extension study, which was supplemented at later time points by investigators, including health-related quality of life assessed through a clinician-reported questionnaire. We observed improvements in health-related quality of life: 5/6 patients experienced an increase in physical capabilities and socialization and a decrease in prescribed medications. Immune subsets improved in all patients: mean transitional B-cell levels decreased from 38.17% to 2.47% and the CD4:CD8 T-cell ratio normalized to 1.11. Manifestations seen before and within the first year of leniolisib exposure, such as infections and gastrointestinal conditions, attenuated following year 2 with few new conditions emerging out to year 6. Thrombocytopenia or lymphopenia remained present in half of patients at year 6. Of 83 adverse events through year 5, 90.36% were grade 1; none were grade 4-5 nor deemed leniolisib-related. Collectively, we saw an enhancement in health-related quality of life as well as durable changes in lymphocyte subsets and clinical manifestations, further supporting the use of leniolisib as a long-term therapeutic option for the treatment of APDS. (Funded by Novartis Pharmaceuticals Corporation and Pharming Group NV; ClinicalTrials.gov identifier: NCT02859727.)

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Key Points *(limit 140 characters per bullet, including spaces)*

- HRQoL improved in all 6 patients with APDS receiving selective PI3Kδ inhibitor leniolisib for up to 6 years, with minimal toxicities
- Patients with APDS receiving leniolisib saw beneficial changes in the mean percentage of lymphocyte subsets and clinical manifestations

Main Text (4232/4000 words)

Introduction

Activated phosphoinositide 3-kinase delta syndrome (APDS) is an inborn error of immunity (IEI) driven by hyperactive PI3Kδ signaling resulting from pathogenic heterozygous variants in *PIK3CD* or *PIK3R1* that encode the PI3Kδ heterodimer.[1-3] PI3Kδ hyperactivation alters lymphocyte development and function, causing immune deficiency and dysregulation.[4-6]

B- and T-cell alterations cause recurrent sinopulmonary infections, herpesvirus viremia, chronic lymphoproliferation including nodular lymphoid hyperplasia of the gastrointestinal and respiratory tracts, and autoimmunity.[5,7-9] Patients have a high risk of developing lymphoma, which may occur in part due to uncontrolled antigen- or Epstein Barr virus (EBV)-driven PI3Kδ hyperactivity in B cells and impaired T-cell–mediated tumor surveillance.[4,5,8-11]

Chronic conditions such as recurrent infections and bronchiectasis seen in APDS may negatively impact perceived health.[8,12] Children with chronic illness were reported to have more illness-related school absenteeism than healthy peers, affecting academic performance and social well-being.[13-15] Similarly,

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chronic illness in adults was a barrier to employment, increased the number of missed workdays, and was associated with lower health-related quality of life (HRQoL) scores.[16,17]

HRQoL can also be impacted by treatment burden, a lifelong possibility for patients with IEIs.[18,19] Current treatment strategies for APDS are empirical and include prophylactic antimicrobials, immunoglobulin replacement therapy (IRT), immunomodulatory therapies, surgeries, and hematopoietic stem cell transplantation. Most do not target the root cause of disease: hyperactive PI3Kδ signaling.[4,5,8] Selective PI3Kδ inhibition addresses disease pathogenesis.[3] We previously reported reduced PI3Kδ/AKT pathway hyperactivity and ameliorated immune dysregulation and deficiency in two studies of patients with APDS treated with PI3Kδ inhibitor leniolisib.[20,21] In our recent long-term open-label extension (OLE) study, leniolisib was well tolerated with safety and efficacy outcomes remaining durable up to years 5 and 1, respectively.[22]

Here, we expand upon efficacy outcomes not addressed in the OLE and present case vignettes of 6 adult patients with APDS who received leniolisib for 6 years. Given the paucity of validated HRQoL instruments for IEIs, we developed a standardized clinician-reported questionnaire to elucidate APDS-specific aspects of HRQoL, including clinical signs, physical abilities, socialization, schooling/employment, healthcare resource utilization, and general health status before and after receiving leniolisib.[23,24] To our knowledge, this work represents one of the longest targeted treatment studies in the IEI field.

Methods

Patients and Treatment

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Patients were enrolled in a dose-finding trial (DFT) and are participating in an ongoing extension study (NCT02859727) examining the long-term use of leniolisib in patients with APDS.[20,22] Full eligibility criteria were described previously.[20,22] The 6 patients, who are from the United States (n=3), Canada (n=1), Czech Republic (n=1), and the Netherlands (n=1), receive 70-mg leniolisib orally every 12 hours in the OLE (Figure S1).

Clinical and Laboratory Outcomes

The OLE's primary endpoint is safety, including adverse events, laboratory parameters, and physical examinations.[22] Safety measurements from the clinical study report (CSR) were collected out to the latest time point with available data (generally year 6; data cutoff in December 2022); efficacy measurements to approximately year 1. Adverse events (AEs), viral load of EBV and cytomegalovirus measured by polymerase chain reaction, and lymphoproliferation data for spleen, liver, and lymph nodes are reported from the CSR; details regarding lymphoproliferation measurement were reported previously.[21,22]

Cytopenias were assessed via safety data reported in the CSR, with some data at year 6 being provided by trial investigators (medical doctors and registered nurses) via a standardized file (Supplementary Appendix S1). Immunoglobulin levels and lymphocyte subsets were reported out to year 1 by the CSR; afterwards by investigators. IgG levels at DFT baseline were also provided by investigators. Infections, organ function (eg, gastrointestinal, neurological, dermatologic, respiratory) and IRT use were collected via the CSR; year 6 via investigators. No statistical analyses were performed.

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Due to COVID-19 restrictions, complete lymphocyte phenotype data at year 5 were only available for patient 3. The only data past year 1 for patient 5 were total $CD4^+$ and $CD8^+$ T cells. Markers for immune subsets differed between patients (Table S1).

HRQoL & Case Vignettes

HRQoL was assessed out to year 5 of treatment via patient answers to the Short-Form Health Survey 36, Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire, and patient and physician global assessments. To expand on these results, trial investigators completed a standardized questionnaire in December 2022 and responded to queries to clarify responses (Supplementary Appendix S2). The questionnaire included open-ended and yes/no objective and subjective questions that addressed patient symptoms, response to COVID-19 infections and vaccine challenges, physical abilities, socialization, healthcare resource utilization, and general health before and during treatment with leniolisib. We used responses to assess HRQoL and construct case vignettes. No statistical analyses were performed.

Trial Oversight

We used data from the DFT and an interim analysis of an ongoing OLE study. Novartis, in collaboration with investigators, designed both studies. Novartis oversaw trial conduct and analyzed data, with Pharming Group, NV acquiring rights to leniolisib in 2019 and full trial management in December 2022. Both studies were conducted and reported in accordance with the protocols (including the statistical analysis plan). Data were gathered locally, and protocol-defined laboratory samples and imaging were processed centrally. The trials were conducted in accordance with the Declaration of Helsinki and the

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International Council for Harmonisation Good Clinical Practice guidelines. Independent ethics committees or institutional review boards at each center approved the protocols. Patients and/or their guardians provided written informed consent/ascent. An independent data and safety monitoring committee monitored safety and protocol compliance.

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Results

Patients

This study included 4 male and 2 female patients currently aged 23 to 39 years with a gain-of-function variant in *PIK3CD* along with clinical symptoms compatible with APDS (Table 1A). Aggregate data are described in text, while individual patient data are reported in Case Vignettes and tables.

Health-Related Quality of Life

Patient- and Physician-Reported Outcomes

Short-Form Health Survey 36 mean physical component score increased by 4.0 points and social functioning by 7.9 at year 5, both of which are considered clinically meaningful improvements (Figure 1).[25] Mean overall activity impairment due to health, as assessed via the Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire, reduced by 70.0%. Patient and physician general assessments showed reductions in mean disease activity of 63.2% and 86.3%, respectively.

Infections and Treatment Burden

Prior to receiving leniolisib, all patients had difficulty fighting infections (Table 1C). While receiving leniolisib, the number or severity of infections decreased for all, from a mean of 3 in year 1 to 0.2 in year 6 (Figure 2).

Clinician visits per year and number of specialists seen reduced for all. During the course of the study, patients received an average of 13.3 (range, 5-22) prescription medications excluding leniolisib; at year 6, 3.83 (range, 2-7). Largely, prophylactic or therapeutic antibiotic use decreased. Two of 5 patients discontinued IRT. Changes in medication were not protocolized and occurred at investigator discretion (Table S2).

Physical Capabilities

All patients had been sedentary or physically limited due to shortness of breath or fatigue. Physical activity improved in 5/6 within 6 months of receiving leniolisib. Four patients were able to walk several miles, run, or partake in physically demanding activities.

Fatigue

Fatigue affected the ability to attend school, work, or complete daily chores in 4/6 patients. During treatment, patients experienced reduced fatigue severity, increased energy, and ability to pursue activities.

Mental Well-being

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Two of 6 patients experienced anxiety before receiving leniolisib. One case resolved during year 1 of treatment. Questionnaires reported increased socialization and the development of a more positive outlook on life, and mood improved in 4/6.

Socialization

Social life improved in 5/6 patients within 1 year of treatment. Two of 5 returned to school and created friendships. Activities included traveling overseas to visit friends and increasing socialization. Half used online resources such as video games for socializing during the COVID-19 pandemic.

School and Work

At enrollment, half of patients missed school or required homeschooling. The same 3 patients finished high school, college, or secondary education during the trial. Five of 6 joined the workforce via remote or in-person jobs. One patient finished high school before the trial and did not seek higher education or employment.

Clinical and Laboratory Outcomes

Means correspond to all patients with data at reported time point.

Lymphoproliferation

Mean index lymph node sum of product of diameters decreased 56.7%, liver volume by 4.7%, and spleen volume by 43.1% around year 1 (Table 1B, Figure 3). Collectively, lymphadenopathy and

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splenomegaly decreased in all patients, with spleen size reaching normal range in 2/6 patients. Hepatomegaly was absent in 5/6 patients through year 6, and persistently mild in 1.

Immune Profiling

The mean percentage of senescent ($CD57^+$) $CD4^+$ T cells (2.0%) reached normal range by year 1 and generally remained within normal limits (WNL) through year 6; senescent $CD8^+$ T cells remained WNL (Figure 4A-B). The mean percentage of total $CD8^+$ T cells reduced to 41.77%, and total $CD4^+$ T cells increased to 46.39%, normalizing the CD4:CD8 T-cell ratio from 0.63 at the DFT baseline to 1.11 at year 6 (Figure 4C). Neither naïve $CD4^+$ nor $CD8^+$ T cells reached normal limits (Figure 4D). Mean percentage of effector memory T cells remained unchanged, while terminally differentiated effector memory $CD4^+$ and $CD8^+$ T cells (T_{EMRA}) remained WNL until year 6 (Figure S2A-B). $CD8^+$ central memory T cells (T_{CM}) remained WNL throughout the study; $CD4^+$ T_{CM} cells approached normal range by year 6 (48.40%; Figure S2C).

The mean percentage of naïve B cells reached 58.16% at extension screening and remained WNL through the latest time point, year 1 (82.56%; Figure 4E). Switched memory B cells fell WNL (12.06%) at year 1; non-switched memory B cells remained unchanged (Figure 4F-G). Elevated transitional B cells decreased to 2.47% and largely remained WNL through year 6 (Figure 4H).

Mean IgM levels fell WNL by year 1 (198.5 mg/dL); IgA (154.3 mg/dL), IgE (306.5 ug/L), and IgG (1469.0 mg/dL) by extension screening (Figure 5A-D). IgG subclass data beyond year 1 were only available for patients 5 and 6 (see Figure S3).

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IRT Use

Five patients received IRT at baseline; 2 patients discontinued and 2 reduced dose (Figure 5E-I). Following IRT discontinuation, immunoglobulin levels remained WNL through year 6 for both patients, excepting consistently high IgE in 1 patient. Following IRT reduction in 1 patient, IgA was low whereas IgG was high at year 6, while another patient had low IgG3 at year 5. All 4 patients experienced a total of ≤4 infections each after termination or decrease in dosage.

Clinical Manifestations

Before receiving leniolisib, all patients experienced recurrent upper respiratory tract infections. Two experienced recurrent cytomegalovirus and EBV infections. During the studies, the highest observed level of EBV was ~2000 copies/mL, which, while clinically significant, did not result in infection.[26,27] Four patients were vaccinated against COVID-19; all were positive for anti-S SARS-CoV-2 antibodies. Half tested positive for SARS-CoV-2 and experienced mild symptoms. Following year 2, the number or severity of infections declined in 4/6 patients (Figure 2).

Laboratory values were used to determine the presence of cytopenias (Figure 6). Histories included thrombocytopenia (n=6), lymphopenia (n=4), neutropenia (n=1), and anemia (n=1). By the end of the DFT, 3 lymphopenia and 3 thrombocytopenia cases resolved. During continued treatment, 4 patients presented with cytopenias that included thrombocytopenia (n=3), neutropenia (n=1), anemia (n=1), and lymphopenia (n=2). At the latest time with available data, the neutropenia and anemia case resolved,

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while thrombocytopenia improved in 2 patients and resolved in 1 around year 1. Both lymphopenia cases improved but persist.

Gastrointestinal manifestations were present in 4/6 patients. Most emerged before or within 1 year of treatment. Reflux esophagitis, a minor case of diarrhea, and a stomachache developed in 1 patient each in years 2-5.

All patients reported neurologic conditions such as anxiety and headaches in the first year; 2 patients experienced resolution.

Dermatologic symptoms were present in 4 patients before or within the first year of leniolisib exposure; no new dermatologic symptoms were reported in any patients through year 6.

Five of 6 patients had a history of respiratory disorders. Half had bronchiectasis before receiving leniolisib; none progressed and all are stable at year 6 (Figure 7). Pulmonary function tests in 5/6 patients revealed no new or worsening conditions through year 6.

Three patients had a history of B-cell lymphoma and achieved full remission prior to receiving leniolisib. No recurrence or new lymphoma occurred in these 3 patients, nor did lymphoma appear in the other half.

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Tolerability

Leniolisib was well tolerated during the DFT (Tables 3 and 4). At the 70-mg bid dose, 4 patients experienced 11 AEs; 9 were grade 1; common cold and fungal skin infection were grade 2. In the extension, 6 patients experienced 83 AEs, mostly grade 1 sinopulmonary infections in the first 2 years. Reactive arthritis in year 4 was the only serious AE. No AEs were deemed leniolisib-related by investigators.

Case Vignettes

Detailed medication and AE information is reported in Tables S2 and 4, respectively.

Patient 1

Patient 1 (P1) is a 24-year-old male. Before enrollment, he was frequently prescribed antibiotics and hospitalized approximately yearly for infections. He had thrombocytopenia (129 x 10^9/L; normal range, 140-370 x 10^9/L) and bronchiectasis (Figure S4). P1 had difficulties attending school due to infections, gastrointestinal issues, and migraines. He experienced fatigue from IRT infusions, anxiety, and difficulty coping with treatment burden.

Throughout leniolisib treatment, P1 had 5 infections within the first 1-2 years: none recurrent, unlike his prior infections. P1 discontinued IRT before year 2, after which IgG levels remained WNL and he developed 2 infections that cleared. Platelet counts increased by year 6 (144 x 10^9/L; normal range, 161-347 x 10^9/L). Bronchiectasis did not progress through year 6. Over the course of the trials, he received 14 prescription medications; at year 6, 2 He experienced no hospitalizations since receiving leniolisib, and regularly visits only his immunologist.

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P1's other AEs included gastroparesis and hypertriglyceridemia. All were grade 1-2, resolved, and occurred within 2 years of treatment.

P1 graduated from high school, an online university, and works a full-time job. While finishing his last year of high school, he attended in-person schooling, a school dance, and graduated. Physical capabilities improved; he can walk and drive without difficulty and manages his own medical care. His fatigue improved following IRT discontinuation.

Patient 2

Patient 2 (P2) is a 31-year-old female. Before the trial, she was fatigued and had difficulty fighting frequent sinopulmonary infections. P2 had thrombocytopenia (53 x 10^9/L; normal range, 140-370 x 10^9/L) and neutropenia (0.4 x 10^9/L; lower limit of normal, 1.5 x 10^9/L). She was homeschooled due to illness and mostly sedentary. She was diagnosed with stage IV diffuse large B-cell lymphoma at age 19 and achieved full remission prior to receiving leniolisib.

P2 had 2 infections during the first 2 years of treatment. Her IRT dose decreased from 65 to 30 g/mo by year 1 yet has had no infections requiring antibiotics since 2019. Thrombocytopenia improved by year 6 (148 x 10^9/L; normal range, 173-369 x 10^9/L). Neutrophil counts were WNL around year 2 and remained stable. Currently, P2 visits her local doctor regularly. Over the trials she received 8 prescription medications; at year 6, 3

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P2's other AEs included allergic rhinitis, dental caries, neutropenia, reactive arthritis, and elevated liver enzymes. All were grades 1-2, except grade 3 alanine aminotransferase increase and reactive arthritis; all resolved. The latter was a serious AE occurring in year 4.

Despite a learning impairment, P2 completed a post-secondary program and has a full-time job. She manages her own medical care without parental assistance, which was previously needed. She takes aerobics classes and walks for exercise. P2 experienced changes in her mood, becoming more talkative and upbeat. She traveled overseas to visit friends. P2 continues to report increases in energy with more time to pursue activities.

Patient 3

Patient 3 (P3) is a 23-year-old female. She experienced chronic sinopulmonary infections that required consistent antibiotics and affected her ability to attend school and socialize; she also suffered anxiety. She had lymphopenia (0.7 x 10^9/L; normal range, 0.8-3.3 x 10^9/L). Her recurrent EBV infections had persistently high viral levels (12,500 copies/mL).

In the trial, she experienced 12 infections through year 5 (<2/year discrete episodes) and efficiently cleared them. As a schoolteacher, she has chronic exposure to antigens. P3 contracted SARS-CoV-2 in year 5 but had mild symptoms (cough and rhinorrhea) that resolved. Her highest EBV levels during the extension (~2000 copies/mL) were clinically significant but no infection was observed.[26,27] Lymphopenia resolved by completion of the DFT. Her anxiety is ongoing, but she discontinued her medication and

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regularly visits her therapist. Over the trials, she received 17 prescription medications; at year 6, 7, with pulmonary medications prescribed as needed. P3 visits her immunologist and pulmonologist with decreased frequency.

Besides infections, P3's AEs included sunburn, rash, hair loss, seborrheic dermatitis, oral ulcer, myalgia, weight gain, and temporomandibular joint pain. All were grade 1-2 and resolved, except for weight gain and myalgia.

During the study, P3 worked a part-time job, graduated from college, and started working full-time as a schoolteacher. She became more assertive, remained active, and expanded her circle of friends.

Patient 4

Patient 4 (P4) is 27-year-old male. He experienced recurrent infections that occasionally required hospitalization, failure to thrive, low body mass index, anemia (111 g/L; normal range, 130-175 g/L), and lymphopenia (0.5 x 10^9/L; normal range, 0.8-3.3 x 10^9/L). He was unable to walk up a flight of stairs or engage in long conversations without dyspnea. P4 contracted infectious pneumonia and developed bronchiectasis (Figures S5). Before receiving leniolisib, he discontinued IRT and has not restarted.

Following trial entry, P4 experienced only 1 AE: Lyme disease (grade 1) in year 1, which resolved. His anemia resolved within 6 weeks of the extension and lymphopenia improved through year 6 (0.85 x 10^9/L; normal range, 1.32-3.57 x 10^9/L). He experienced neutropenia shortly after the OLE started (1.26 x

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10^9/L; lower limit of normal, 1.5 x 10^9/L) that resolved around year 2. His infectious pneumonia improved within a year, but infiltrates were present in his left lower lobe. His bronchiectasis did not progress and was stable at year 6. Although 5 medications were prescribed over the course of the study, P4 regularly took 3, which decreased to 2 by year 6. P4 gained weight and has had no hospitalizations.

P4 completed school prior to the trials and decided not to pursue higher education or work. Since receiving leniolisib, breathing improved and he can walk up to 15 miles without difficulty. P4's overall demeanor and outlook on life noticeably improved. Family members noted differences in his physical capacities and increased socialization following 6 months of treatment.

Patient 5

Patient 5 (P5) is a 32-year-old male. P5 experienced arthralgia with edema of the joints, repeated airway infections, shortness of breath, and dermatitis. He had lymphopenia (0.6 x 10^9/L; normal range, 0.8-3.3 x 10^9/L) that resolved by year 2. He was diagnosed with Hodgkin lymphoma at age 11 and achieved full remission prior to receiving leniolisib.

While on treatment, P5 had 8 relapses of respiratory infections. His IRT dose reduced from 15 to 10 g/mo in year 6. P5 clears acute infections quicker, from 14 days to around 3. During year 5, he contracted SARS-CoV-2 with a 1-day fever; symptoms resolved within the week. His dermatitis and joint pain resolved. Respiratory and gastrointestinal conditions improved. Over the trials he received 22 prescription medications; at year 6, 7 of which the investigator deemed 3 crucial. Bronchiectasis that developed prior to the trials remained stable out to year 6 (Figure S6). He is only monitored by his

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pneumologist, and visits have decreased. Frequency and severity of infections reduced; prophylactic antibiotics ceased.

Besides infections, P5's AEs included pruritis, sore throat, seborrheic dermatitis, diarrhea, productive cough, anxiety, non-cardiac chest pain, petechiae, bilateral paresthesia of the fingers, hypercholesterolemia, xerostomia, stomachache, and hepatopathy. All were grade 1 and resolved, except for COVID-19 associated mild dyspnea, hypercholesterolemia, and hepatopathy, with the latter 2 improving.

Positive changes in P5's mood were noted as symptoms improved. P5 did not report any changes in shortness of breath; however, he has bronchial stenosis from lymphoma chemotherapy in 2011. He works a full-time labor-intensive job.

Patient 6

Patient 6 (P6) is a 39-year-old male. P6 experienced recurrent respiratory tract infections and was on a constant regimen of antibiotics. Fatigue negatively impacted his exercise tolerance: he was unable to work or perform daily activities due to loss of energy. P6 had thrombocytopenia (123 x 10^9/L; normal range, 140-370 x 10^9/L). He was diagnosed with mucosa-associated lymphoid tissue lymphoma at age 20 and achieved full remission prior to receiving leniolisib.

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Throughout the trial, P6 experienced periodic infections through year 4. He had 2 confirmed cases of SARS-CoV-2, 1 in year 5 with mild rhinitis and another in year 6. After 2 years of titration, P6 discontinued IRT at year 4; total IgG levels remained WNL through year 6. Following IRT termination, P6 experienced 4 mild infections through year 6. The number and severity of infections and need for prophylactic antibiotics declined. Thrombocytopenia resolved around year 1 (173 x 10^9/L; normal range, 150-370 x 10^9/L). Over the trials he received 14 prescription medications; by year 6, 2 and no longer required recurrent antibiotics. P6 visits an immunology-pulmonology clinic yearly and remains under the care of his otolaryngologist where visits declined.

Besides infections, P6's AEs included hearing loss, epistaxis, diarrhea, headache, inflammation at bone-anchored hearing aid, jaw pain, sore throat, tickling cough, painful wrist, reflux esophagitis, and Fuchs heterochromic iridocyclitis. All were grade 1 or 2 and resolved.

Since receiving leniolisib, P6 displays a more relaxed demeanor. His fatigue resolved, allowing him to partake in activities with his children. Within 2 months of treatment, he returned to work and socialized after work hours.

Discussion

Patients with an IEI such as APDS report a lower perception of general health and overall well-being compared to healthy individuals.[19,28-30] We report improvements in several aspects of HRQoL assessed by standardized instruments. Our clinician-reported questionnaire bolsters HRQoL improvements by

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addressing aspects not assessed in standardized tools, such as decreased treatment burden and doctor's office visits.

Many of the positive changes reported in HRQoL can be supported by clinical improvements, such as an increased ability to fight infections and decreased need for antibiotics. Sustained changes in lymphocyte subsets, including decreased transitional B cells and increased CD4:CD8 T-cell ratio, suggest an improvement in immune deficiency and dysregulation. Most patients had stable immunoglobulin levels through year 6, including those who decreased dose or discontinued IRT. Changes in immune subsets may explain the reduction in both number and severity of infections reported in most patients receiving leniolisib, and patients who contracted SARS-CoV-2 experienced mild symptoms.

Regarding lung disease, bronchiectasis in all 3 affected patients showed no progression. More than half of the cytopenias that were present during treatment across the trials resolved by year 6. Patients whose cytopenias did not fall WNL improved; notably P2 had a marked increase of platelets from 53 to 148 x 10^9/L by year 6.

This study has several limitations. Initially, patients visited trial investigators every 2-3 months; time between visits increased to every 6-7 months following year 2, during which time patients may have experienced symptoms that were not reported at their next visit. Additionally, there was a treatment gap between the dose-finding and extension trials, with 3 patients not receiving leniolisib for 25-50 days and 2 for roughly 1 year, in which manifestations may have gone unreported. Small sample size and lack of a placebo-controlled arm also limit generalizability. Lastly, the subjective portion of the clinician-

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reported questionnaire is subject to recall and investigator bias. Furthermore, we acknowledge that data captured in our clinician-reported questionnaire is subjective by nature and limits the general applicability of data that was generated from it. For instance, infection susceptibility data had no standardized protocol for collection as it was not a primary outcome measure; it was collected and evaluated per site investigator discretion. Moreover, several years of data collection occurred during the COVID-19 pandemic, when most evaluations were completed remotely.

In addition to these limitations, gaps in knowledge remain. The rate of malignancy in patients treated with leniolisib compared to untreated warrants further investigation. Early onset of APDS can be a risk factor for developing severe disease, and accordingly, the safety and efficacy of leniolisib is being examined in 2 pediatric trials (NCT05693129 and NCT05438407). Questions remain around the use of leniolisib as a bridge to hematopoietic stem cell transplant. Risks such as graft failure should be considered during the decision-making process.[31,32]

Remarkably, within 10 years of the discovery of APDS, leniolisib was developed as a novel and selective treatment option.[1,33] The mechanism of action of leniolisib precisely matches the molecular underpinnings that cause manifestations of APDS.[1,6] Our previous work has shown long-lasting improvements in immune subsets and lymphadenopathy in patients with APDS who received leniolisib.[20-22]

Here, we had the unprecedented opportunity to examine HRQoL and clinical outcomes in adult patients with APDS exposed to leniolisib for 6 years. Overall, we observed positive and enduring changes in both

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with minimal toxicity, supporting the use of leniolisib as a long-term precision therapy for the treatment of APDS in appropriate patients.

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Contribution

V.K.R., E.K., S.W., A.S., V.A.D., and G.U. performed research and collected data. J.G., D.B., and H.C. are the local providers of patients involved in the study and provided feedback during manuscript development. J.B. was involved in oversight of the data reports.

Conflict of Interest

E.K. is an employee of Leidos Biomedical Research, Inc. S.W. is a consultant for Pharming Group, NV. A. Šedivá is a consultant for Octapharma, Takeda, and Pharming Group, NV. V.A.D. is a consultant for and/or receives honoraria from AstraZeneca, Kedrion, Takeda, CSL Bering, Pfizer, and Pharming Group, NV. V.A.D. also receives research funding from Takeda. J.B. is a current employee and stock option holder of Pharming Group, NV and holds individual stock in Neoclone.

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Tables

Table 1A. Patient Demographics

Patient	P1	P2	P3	P4	P5	P6
Sex	Male	Female	Female	Male	Male	Male
Variant	E525K	E1021K	E1021K	E1021K	E1021K	E1021K
Age of onset*/enrollment into extension/current, y	0.5/18/24	2/25/31	2/18/23	6/21/27	0.5/26/32	0.5/32/39
Leniolisib exposure, y	6	6	5	6	6	6

*Age of onset is the onset of symptoms due to hypogammaglobulinemia.

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Table 1B. Medical History Before Leniolisib & Latest Time Point of Treatment

Patient	P1		P2		P3		P4		P5		P6	
Time point	***DFT baseline***	***Latest time point***	***DFT baseline***	***Latest time point***	***DFT baseline***	***Latest time point***	***DFT baseline***	***Latest time point***	***DFT baseline***	***Latest time point***	***DFT baseline***	***Latest time point***
BMI, kg/m^2	22.5	26.9	24.6	24.3	27	36.5	18.9	27.6	18.0	22.0	21.4	25.2
IRT use	Yes	No	Yes	Yes, decreased dose	Yes	Yes	No	No	Yes	Yes, decreased dose	Yes	No
Spleen 3D volume[*]**,** cm^3 (Normal range, 159-314 cm^3)	978.78	782.80	792.04	392.96	385.83	128.20	782.21	467.21	419.84	212.89	721.83	336.20
Liver 3D volume, cm^3	1849.59	1669.64	1438.04	1375.58	1349.16	1475.39	1398.93	1143.93	1396.21	1274.87	1817.80	1878.45
Index lymph node SPD, cm^2	24.52	5.49	19.26	14.43	12.35	3.09	7.48	4.12	2.58	1.35	8.58	3.89
EBV/CMV, copies/mL	ND/<344[†]	ND/ND	ND/ND	ND/ND	740/<344	2000/ND	ND/ND	ND/ND	ND/ND	24.61/ND	ND[†]/380	ND/ND
Platelets, x 10^9/ L (Normal range, x 10^9/L)	*129* (140-370)[‡]	*144* (161-347)[§]	*53* (140-370)[‡]	*148* (173-369)[§]	*103* (140-370)[‡]	224 (173-369)[§]	*134* (140-370)[‡]	213 (161-347)[§]	*121* (140-370)[‡]	260 (150-400)[§]	*123* (140-370)[‡]	211 (150-370)[§]
Neutrophils, x 10^9/L (Lower limit of normal, 1.5 x 10^9/L)[‖]	2.9	2.1	*0.4*	1.68	2.9	4.04	1.9	2.4	2.1	3.63	3.1	4.18
Lymphocytes, x 10^9/L (Normal range, 10^9/L)	1.0 (0.8-3.3)[‡]	1.64 (1.32-3.57)[§]	*0.6* (0.8-3.3)[‡]	*0.95* (1.18-3.74)[§]	*0.7* (0.8-3.3)[‡]	2.03 (1.18-3.74)[§]	*0.5* (0.8-3.3)[‡]	*0.85* (1.32-3.57)[§]	*0.6* (0.8-3.3)[‡]	1.16 (0.8-4)[§]	0.8 (0.8-3.3)[‡]	0.94 (0.5-5)[§]
Hemoglobin, g/L (Normal range, g/L)	132 (130-175)[‡]	150 (139-175)[§]	114 (113-156)[‡]	124 (112-157)[§]	120 (113-156)[‡]	131 (112-157)[§]	*111* (130-175)[‡]	163 (139-175)[§]	143 (130-175)[‡]	152 (135-175)[§]	136 (130-175)[‡]	153.1 (138.6-169.2)[§]

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; DFT, dose-finding trial; EBV, Epstein-Barr virus; IRT, immunoglobulin replacement therapy; ND, not detected; SPD, sum of product of diameters.

[*]Spleen, liver, and lymph node data were collected from the clinical study report. To minimize radiation exposure, computerized tomography or magnetic resonance imaging were completed around year 1 of treatment (either extension day 168 or 252). The index lymph node sum of product of diameters was determined by multiplying the length and width of ≤6 nodes and calculating the sum.

[†]Experimental day 29 and 1 were used for patient 1 and 6, respectively.

[‡]Normal ranges are from the dose-finding trial.[20] Values outside the normal range are italicized.

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[§]Normal ranges are from the open-label extension and varied per patient. Values outside normal range are italicized.

[¶]ASH guidelines were used to determine neutropenia (lower limit of normal, 1.5 x 10^9/L). Values outside normal range are italicized.

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Table 1C. Clinical Manifestations Before and During Treatment With Leniolisib

Patient	P1		P2		P3		P4		P5		P6	
Time point	***Before**** *(current status)*	***During**†* (y of treatment, current status)	***Before*** *(current status)*	***During*** (y of treatment, current status)	***Before*** *(current status)*	***During*** (y of treatment, current status)	***Before*** *(current status)*	***During*** (y of treatment, current status)	***Before*** *(current status)*	***During*** (y of treatment, current status)	***Before*** *(current status)*	***During*** (y of treatment, current status)
Infections‡	*CMV* **(RES)** *EBV* **(RES)** *Sinusitis* **(CON)** *Herpes simplex* **(CON)** *Parotitis* **(CON)** *Pulmonary* **(CON)**	Otitis media acute (1; **RES**) Gastroenteritis (1; **RES**) Influenza A (1; **RES**) Cellulitis (1; **RES**) Cold sore (2; **RES**) HPV (5; **RES**)	*Sinus* **(CON)** *Pneumonia* **(CON)**	Upper respiratory viral x 2 (2; **RES**)	*CMV* **(RES)** *Parotitis* **(RES)** *EBV* **(CON)** *Otitis media* **(CON)** *Herpes oral* **(CON)** *Acute bronchitis* **(CON)** *Thrush oral* **(CON)** *Sinusitis* **(CON)** *Upper respiratory* **(CON)**	Upper respiratory x 3 (2, 5; **RES**) Stye on right eyelid (3; **RES**) Otitis externa (3; **RES**) Otitis media x 2 (3, 4; **RES**) SARS-CoV-2 (5; **RES**) Pharyngeal sore (5; **RES**) Sinus x 3 (4-5; **RES**)	*Periorbital abscess* **(RES)** *Otitis media* **(CON)** *Sinus* **(CON)** *Pneumonia* **(CON)**	Lyme disease (1; **RES**)	*Otitis media* **(RES)** *Upper and lower respiratory* **(CON)** Exudative pericarditis (coxsackie virus) **(RES)**	Rhinitis (1; **CON**) Multiple relapses of respiratory (1, 2, 4, 5; **CON**) SARS-CoV-2 (5: **RES**)	*Upper airway* **(CON)**	Fungal skin on chest, back and shoulders (1; **RES**) Multiple common colds (1, 4; **RES**) Folliculitis chin (3; **RES**) Otitis externa x 3 (1, 2; **RES**) Flu-like symptoms (1); **RES**) Otitis media (4; **RES**) SARS-CoV-2 x 2 (5, 6; **RES**)
GI involvement		Gastroparesis (1; **RES**)		Diarrhea (4; **RES**)					Protracted non-infectious diarrhea **(CON)** Chronic gastritis **(CON)** GI tract lymphoid hyperplasia **(CON)**	GI disorder§ **(RES)** Vomiting§ **(RES)** Worsening of diarrhea x 2 (1; **RES**) Stomachache (5; **RES**)		Gastroenteritis (1; **RES**) Diarrhea (1; **RES**) Reflux esophagitis x 2 (2; **CON**)
Neurological involvement	Anxiety **(CON)** Migraines **(CON)**		Recurrent headaches **(CON)**		Recurrent headache **(CON)**	Anxiety§ **(CON)**	White matter watershed zone		Facial nerve paresis **(RES)**	Anxiety (1; **RES)** Bilateral paresthesia		Headache (1; **RES**) Autism spectrum

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							defects **(CON)**			of fingers (3; **RES**)		disorder (6; **CON**)
Dermatological involvement	Keratosis pilaris on upper extremities **(CON)** Plantar warts **(CON)** Acne **(CON)**		Plantar warts **(CON)**			Non-pruritic rash on forearm and abdomen (1; **RES**) Seborrheic dermatitis (1; **RES**)			Seborrheic dermatitis **(CON)**			
Pulmonary conditions	Asthma **(CON)** Bronchiectasis **(CON)**				Asthma **(CON)**		Bronchiectasis **(CON)** Restrictive airway disease **(CON)**		Bronchiectasis **(CON)** Worsened productive cough **(CON)** Small airways disease with COPD features **(CON)** Lung lymphoid hyperplasia **(RES)**	COVID-19–associated mild dyspnea (5; **CON**)	Bronchial wall thickening **(CON)**	Tickling cough (2; **RES**)
Malignancy[II]			Stage IV DLBCL (2010)						Hodgkin lymphoma with nodular sclerosis (2001)		MALT lymphoma (2005)	
Other	Aseptic meningitis **(RES)**	Hypertriglyceridemia (1; **CON**)	Wolff-Parkinson-White syndrome **(CON)**	Reactive arthritis (4; **RES**)	Hypertriglyceridemia **(CON)** Obesity **(CON)** Scoliosis **(CON)**		Failure to thrive **(RES)**			Hepatopathy (5; **CON**)[¶]		

Abbreviations: CMV, cytomegalovirus; CON, continuing; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; GI, gastrointestinal; HPV, human papillomavirus; MALT, mucosa-assisted lymphoid tissue; RES, resolved; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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[*]Manifestations that were reported prior to treatment ("Before") were gathered from the open-label extension relevant medical history and current medical conditions.

[†]Manifestations that were reported during treatment were collected from the open label extension relevant medical history and current medical conditions, AE files, and by trial investigators. The relevant medical history and current medical conditions files contain manifestations that occurred during the dose-finding trial as well as the open-label extension.

[‡]Chronic or recurrent infections are italicized. Infections and determination of status (resolved or continuing) were reported by trial investigators at their discretion.

[§]Condition occurred following the DFT but prior to entry into the extension study.

[‖]All patients achieved full remission prior to entry into the trial, and there has been no recurrence of new lymphoma.

[¶]Hepatopathy was considered mild and stable at year 6.

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Table 2. Immune Profiling

		P1	P2	P3	P4	P5	P6
Naïve B cells, %* Normal range, 58-86.7%	DFT baseline	*30.70*	*26.80*	*38.50*	*11.00*	*30.30*	*53.60*
	Latest time point	↑, *90.20*	↑, 81.70	↑, *50.80*	↑, 75.00	↑, 84.50	↑, 81.40
Switched memory B cells, %* Normal range, 3.3-18.9%	DFT baseline	*45.60*	*46.60*	*45.10*	*31.60*	*60.50*	*32.00*
	Latest time point	↓, 4.20	↓, 3.80	↓, *34.90*	↓, 5.80	↓, 18.10	↓, *28.40*
Non-switched memory B cells, %* Normal range, 4.6-21.4%	DFT baseline	4.90	*38.60*	*1.10*	*58.70*	17.80	*0.40*
	Latest time point	↑, 7.30	↑ *47.80*	↑, *3.00*	↓, *44.80*	↑, 18.20	↑, *0.60*
Transitional B cells, % Normal range, 1.5-19.1%	DFT baseline	*60.50*	*19.20*	*46.60*	*27.00*	*44.10*	*31.60*
	Latest time point	↓, *0.98*	↓, 6.45	↓, 2.53	↓, *0.00*	↓, 3.30	↓, 11.25
Senescent CD4⁺ T cells, % Normal range, 0.18-5.99%	DFT baseline	*21.10*	*13.80*	*15.50*	*34.00*	*7.30*	0.90
	Latest time point	↓, 5.08	↓, 5.10	↓, *15.09*	↓, 5.39	↓, 0.60	↓, *0.10*
Senescent CD8⁺ T cells, % Normal range, 1.83-33.4%	DFT baseline	33.20	21.60	24.60	*43.00*	19.70	14.60
	Latest time point	↓, 24.44	↑, 24.10	↑, *35.77*	↓, 31.46	↓, 4.80	↓, 3.10
CD4⁺ T cells, % Normal range, 29.3-52.9%	DFT baseline	34.00	49.40	33.10	43.30	42.10	*28.60*
	Latest time point	↑, 39.90	↓, 47.38	↑, 47.85	↑, *59.27*	↓, 39.0	↑, 46.40
CD8⁺ T cells, % Normal range, 13.5-23.5%	DFT baseline	*65.30*	*49.50*	*66.40*	*55.60*	*56.30*	*70.80*
	Latest time point	↓, *51.56*	↑, *50.50*	↓, *48.54*	↓, *34.03*	↓, *31.00*	↓, *54.7*
Naïve CD4⁺ T cells, % Normal range, 49.3-72%	DFT Baseline	*11.70*	*19.20*	*6.90*	*6.40*	*4.90*	*12.90*
	Latest time point	↑, *28.49*	↑, *28.02*	↑, *22.64*	↑, *18.06*	↑, *8.60*	↑, *15.20*

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Naïve CD8⁺ T cells, % Normal range, 48.6-87.5%	DFT baseline	*18.90*	*37.10*	*15.40*	*23.60*	*23.00*	*17.00*
	Latest time point	↑, *29.90*	↓, *26.30*	↑, *32.90*	↑, *25.82*	↓, *21.40*	↑, *41.30*
CD4⁺ T_{EM} cells, % Normal range, 2.1-7.4%	DFT baseline	*24.50*	*21.50*	*31.30*	*27.40*	*27.00*	*25.40*
	Latest time point	↓, *18.69*	↑, *24.19*	↓, *28.16*	↓, *25.34*	↑, *28.60*	↓, *8.90*
CD8⁺ T_{EM} cells, % Normal range, 0.2-6.9%	DFT baseline	*41.30*	*22.40*	*27.50*	*36.60*	*25.90*	*29.40*
	Latest time point	↓, *29.49*	↑, *31.47*	↓, *25.32*	↑, *39.91*	↑, *33.30*	↓, *14.90*
CD4⁺ T_{EMRA} cells, % Normal range, 0.1-8.5%	DFT baseline	0.10	0.10	0.10	*0.00*	*27.00*	0.10
	Latest time point	↓, *0.00*	↑, 1.27	↑, 0.58	↑, 0.27	↓, 0.10	↓, *0.00*
CD8⁺ T_{EMRA} cells, % Normal rang, 0.8-14%	DFT Baseline	8.00	13.20	3.10	7.80	*25.90*	*22.90*
	Latest time point	↓, 5.06	↑, *33.47*	↑, 7.44	↑, 13.62	↓, 13.70	↓, 11.50
CD4⁺ T_{CM} cells, % Normal range, 24.3-44.4%	DFT baseline	*64.30*	*59.30*	*61.80*	*66.20*	*68.10*	*61.70*
	Latest time point	↓, *52.63*	↓, 36.52	↓, *48.77*	↓, *56.06*	↓, *62.80*	↑, *75.90*
CD8⁺ T_{CM} cells, % Normal range, 9.8-37.6%	DFT baseline	31.90	27.40	*54.10*	32.10	*39.80*	30.80
	Latest time point	↑, 35.53	↓, *8.56*	↓, 34.33	↓, 13.62	↓, 31.80	↑, *43.80*
IgM, mg/dL Normal range, 20-230 mg/dL	DFT baseline	220	*335*	*282*	*752*	*686*	190
	Latest time point	↓, *18*	↓, 66	↓,68	↓, *264*	↓, 166	↓, 91
IgA, mg/dL Normal range, 87-386 mg/dL	DFT baseline	125	*81*	137	*50*	253	149
	Latest time point	↑, 157	*81*	↑, 188	↑, 102	↑, 346	↑, 153
IgE, µg/L Normal range, 6-495 µg/L	DFT baseline	7	8	7	7	194	*6063*
	Latest time point	↑, 25	↑, 25	↑, 25	↓, *1*	↑, 221	↓, *630*

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IgG, mg/dL Normal range, 586-1613 mg/dL	DFT baseline	1444 (IRT)	*2036* (IRT)	*1644* (IRT)	711	773 (IRT)	*1670* (IRT)
	Latest time point	↓, 599	↓, *1631* (IRT)	↓, 1412 (IRT)	↓, 603	↑, 782 (IRT)	↓, 890
IgG1, mg/dL Normal range, 248-846 mg/dL	DFT baseline	*910*	*1150*	*1130*	510	620	*1250*
	Latest time point	↓, 770	↓, *1030*	↑, *1210*	↑, 540	↑, 631[§]	↓, 574[§]
IgG2, mg/dL Normal range, 130-555 mg/dL	DFT baseline	336	*710*	280	*60*	340	480
	Latest time point	↓, 300	↓, *640*	↓, 170	↓, *20*	↓, 293[§]	↓, *118*[§]
IgG3, mg/dL[†] Normal range, 15-109 mg/dL	DFT baseline	44	60	100	80	*10*	90
	Latest time point	↓, 20	↓, 30	↓, 60	↓, 60	*10*[§]	↓, 68[§]
IgG4, mg/dL[†] Normal range, 2-104 mg/dL	DFT baseline	67	50	10	10	10	30
	Latest time point	↓, 10	↓, 40	↓, *0*	↓, *0*	↑, 24[§]	↓, 13[§]

Abbreviations: DFT, dose-finding trial; IRT, patient receiving immunoglobulin replacement therapy; ↓, below normal limits; ↑, above normal limits.

[*]Denotes immune subsets that were only collected up to year 1 of the extension study.

[†]For values that were reported <[value], the actual value was entered.

[§]Data were collected past year 1.

Values for DFT baseline were collected from the DFT B and T cell immunophenotyping files. Values for latest time point were captured from both the OLE B and T cell immunophenotyping files and by trial investigators. Values outside the normal range are italicized. Normal laboratory values are from the literature.[34-43]

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Table 3. Adverse Events During Exposure to Leniolisib

	DFT	OLE				
	70-mg[§]	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Overall AE incidence[*,†,‡]						
All, nE, nS (%)	11, 4 (36)	36, 6 (100)	14, 5 (83)	10, 4 (36)[‖]	14, 5 (83)[‖]	9, 3 (50)[‖]
Grade 1, nE, nS (%)	9, 4 (67)	32, 6 (100)	13, 5 (83)	7, 4 (36)	6, 3 (50)	8, 2 (33)
Grade 2, nE, nS (%)	2, 1 (17)	4, 2 (33)	1, 1 (17)	2, 2 (33)	5, 2 (33)	0, 0 (0)
Grade 3, nE, nS (%)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	2, 1 (17)	0, 0 (0)
Grade 4, nE, nS (%)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)
Grade 5, nE, nS (%)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)
Study drug–related, nE, nS (%)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)
Serious, nE, nS (%)	0, 0, (0)	0, 0 (0)	0, 0 (0)	0, 0 (0)	1, 1 (17)	0, 0 (0)

Abbreviations: AE, adverse event; DFT, dose-finding trial; nE, number of events in the category; nS, number of patients with at least 1 AE in the category; OLE, open-label extension.

[*]% is based on the number of patients.

[†]Common Toxicity Criteria were used to determine AE grade.

[‡]AEs captured in the DFT and OLE were collected from AEs files that had a cutoff date of December 13, 2021.

[§]Only AEs from 70-mg treatment period are included.

[‖]Includes negative COVID-19 test result(s) that did not have a grade.

Adverse events (AEs) were reported through clinical assessments, nondirective interviewing of each patient or as volunteered by the patient. Detected AEs were followed until resolution.

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Table 4. Incidence of Adverse Events During the Dose-Finding and Open-Label Extensions Trials With Leniolisib

Adverse Event[*†]	nS (%)
Acute sinusitis	1 (17)
Allergic rhinitis	1 (17)
ALP increase	1 (17)
ALT increase	1 (17)
Anxiety	1 (17)
Cellulitis	1(17)
Chest pain	1 (17)
Common cold	1 (17)
Cold sore	1 (17)
Cough	2 (33)
COVID dyspnea	1 (17)
COVID negative	3 (50)
COVID positive	2 (33)
Dental caries	1 (17)
Diarrhea	2 (33)
Folliculitis	1 (17)
Fuchs heterochromic cyclitis	1 (17)
Fungal infection	1 (17)
Gastroenteritis	2 (33)
Gastroparesis	1 (17)
GGT increase	1 (17)
Gut infection	1 (17)
Hair loss	1 (17)
Hearing loss	1 (17)
Hepatopathy	1 (17)
Hypercholesterolemia	1 (17)
Hypertriglyceridemia	1 (17)
Influenza	1 (17)
Joint pain	1 (17)
Lyme disease	1 (17)
Myalgia	1 (17)
Neutropenia	1 (17)
Oral ulcer	1 (17)
Otitis externa	2 (33)
Otitis media	3 (50)
Paresthesia	1 (17)
Petechiae	1 (17)
Pruritus	1 (17)
Rash	1 (17)
Reactive arthritis	1 (17)
Reflex esophagitis	1 (17)
Seborrheic dermatitis	2 (33)

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Skin infection	1 (17)
Sore throat	2 (33)
Stomachache	1 (17)
Sunburn	1 (17)
Upper respiratory infection	3 (50)
Weight gain	1 (17)
Xerostomia	1 (17)

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine transaminase; COVID, coronavirus disease; GGT, gamma-glutamyl transferase; nS, number of patients with at least 1 AE in the category.

*A patient with multiple occurrences of an AE is counted only once in the AE category. Only AEs occurring at or after first drug intake are included.

†AEs were captured from OLE AEs files. Adverse events (AEs) were reported through clinical assessments, nondirective interviewing of each patient or as volunteered by the patient. Detected AEs were followed until resolution.

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Figure Legends

Figure 1. Changes in health-related quality of life over time. (A) Normed subscale and component scores from the SF-36 survey, with higher scores indicating greater health-related quality of life.[44] MIDs for patients with inborn errors of immunity are from the literature.[25] The latest time point for patients 1, 2, 3, 4, 5, and 6 are as follows: year 5, 5, 3, 5, 5, 4. Differences in scores between DFT baseline and latest time point that exceed MIDs are illustrated with a delta symbol (Δ) followed by the value of the difference. Dotted line indicates general US population average. (B) Individual and mean WPAI-CIQ overall activity impairment due to health scores over time, with lower scores indicating less impairment due to health. n values for DFT baseline, Ext Scr and years 1, 2, 3, 4, and 5 are as follows: 6, 6, 6, 6, 6, 5, 4. (C) Individual and mean patient general assessment scores are shown with lower scores indicating a reduction in disease activity. n values for DFT baseline, Ext Scr and years 1, 2, 3, 4, and 5 are as follows: 6, 6, 6, 6, 6, 5, 4. (D) Individual and mean physician general assessment scores are shown with lower scores indicating a reduction in disease activity. There were no values reported for Ext Scr. n values for DFT baseline and years 1, 2, 3, 4, and 5 are as follows: 6, 1, 6, 6, 5, 4. Error bars are standard error of the mean. BP, bodily pain; DFT, dose finding trial; Ext Scr, extension screening; GH, general health; MCS, mental component score; MH, mental health; MID, minimally important difference; PCS, physical component score; PF, physical functioning; PGA, physician general assessment; PtGA, patient general assessment; RE, role – emotional; RP, role – physical; SF-36, Short-Form Health Survey 36; SF, social functioning; VT, vitality; WPAI-CIQ, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questionnaire.

Figure 2. Number of infections over time. Mean number of infections before and throughout exposure to leniolisib. n values for before leniolisib and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 6, 6, 6, 6, 5. "Before leniolisib" comprises multiple years of recurrent/unresolved infection history. Post-leniolisib exposure includes only acute infections. Dotted line separates infections that occurred before and during treatment with leniolisib. Error bars are ± standard error of the mean.

Figure 3. Changes in lymphoproliferation parameters. (A) Individual and mean untransformed SPD of index lymph nodes. n values for all time points are 6. Reference range (≤1.5 x 1.5 cm) not shown as up to 6 lymph nodes may be counted per patient.[45] (B) Individual and mean liver volumes. n values for all time points are 6. (C) Individual and mean spleen volumes. n values for all time points are 6. Gray box indicates the reference range for adults.[46] Imaging used to determine lymphoproliferation for each patient at their first OLE readout was completed around year 1 (either ED168 or 252) of the OLE. (D-F) Representative radiographic renderings of spleen volume from patient 6 at (D) screen of dose-finding trial (SCR), (E) end of the dose-finding trial (D84), and (F) first extension study readout (ED168) where splenomegaly was absent. Patient 6 had a 2-month gap in treatment between the end of part 1 and entry into the extension. D, day; DFT, dose finding trial; ED, extension day; OLE, open-label extension.

Figure 4. Sustained changes in B- and T-cell subsets. (A) Individual and mean senescent ($CD57^+$) $CD4^+$ T-cell percentages over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and

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6 are as follows: 6, 6, 4, 1, 3, 2, 1, 3. (B) Individual and mean senescent $CD8^+$ T-cell percentages over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 4, 3, 3, 2, 1, 3. (C) Mean $CD4^+$ and $CD8^+$ T-cell percentages overtime. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 6, 5, 6, 5, 3, 4. (D) Mean naïve T-cell percentages ($CD4^+$ or $CD8^+$ $CD45RACD62L^+$) over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 4, 4, 5, 2, 1, 3. (E) Individual and mean naïve B-cell percentages ($CD19^+CD27^-CD10^-$) over time. n values for dose-finding trial baseline, extension screening, and year 1 are as follows: 6, 5, 5. (F) Individual and mean switched memory B-cell percentages ($CD19^+CD27^+IgD^-$) over time. n values for dose-finding trial baseline, extension screening, and year 1 are as follows: 6, 5, 5. (G) Individual and mean non-switched memory B-cell percentages ($CD19^+CD27^+IgD^+$) over time. n values for dose-finding trial baseline, extension screening, and year 1 are as follows: 6, 4, 5. (H) Individual and mean transitional B-cell ($CD19^+CD27^-CD10^+$ or $CD20^+CD10^+$) percentages over time. n for dose-finding trial baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 5, 4, 5, 3, 1, 3. Normal ranges are from personal communication (A and B; Manish Butte, University of California, Los Angeles, email, 29 March 2022) and literature (C-H).[42,43] In A, B, and E-H, gray boxes indicate normal ranges. In C and D, gray boxes indicate normal ranges for $CD4^+$ cells, and dotted lines indicate normal ranges for $CD8^+$ cells. Error bars are ± standard error of the mean. DFT, dose-finding trial; Ext, extension; Scr, screening.

Figure 5. Changes in serum immunoglobulin levels and IRT throughout treatment with leniolisib. (A) Individual and mean IgM values over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 6, 6, 6, 6, 3, 5. (B) Individual and mean IgA values over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 6, 6, 6, 6, 2, 5. (C) Individual and mean IgE values over time. The graph on the far left illustrates all individual and mean IgE values over time. The far-right portion depicts individual IgE values for patients 1-4 over time as indicated by the dotted lines. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 6, 6, 6, 5, 6, 6, 2, 5. (D) Individual and mean IgG values over time. n values for part 1 baseline, extension screening, and years 1, 2, 3, 4, 5, and 6 are as follows: 5, 6, 6, 6, 6, 6, 3, 5. For values that were <, the actual number was entered to graph data. IRT usage in (E) patient 1, (F) patient 2, (G) patient 3, (H) patient 5, and (I) patient 6 over time. Day 0 is the dose-finding trial baseline. Gray boxes in A-D indicate age-matched normal ranges from LabCorp.[34-37] Error bars are ± standard error of the mean. DFT, dose-finding trial; Ext, extension; Scr, screening.

Figure 6. Changes in hematologic parameters over time. (A) Platelet levels for individual patients over time. n values for DFT baseline, Ext Scr and years 1, 2, 3, 4, 5, 6 are as follows: 6, 6, 6, 6, 6, 4, 1, 2. There was no reported value at year 3 for patient 3; data from year 3.5 of treatment was used. (B) Lymphocyte levels for individual patients over time. n value for DFT baseline, Ext Scr and years 1, 2, 3, 4, 5, 6 are as follows: 6, 5, 6, 5, 6, 3, 1, 1. Patient 1 and 6 (dashed lines) were the only patients within range at the DFT. Asterisk denotes the latest time point for patient 6 which exceeded their individual lower limit of 0.5×10^9/L. C) Neutrophil levels for individual patients over time. n values for DFT baseline, Ext Scr and years 1, 2, 3, 4, 5 are as follows: 6, 5, 6, 5, 6, 3, 1. For lymphocytes and neutrophils, there was no reported value at year 3 or 1 for patients 3 and 1, respectively; data from year 3.5 and 0.5, respectively, were used. (D) Hemoglobin levels over time for individual female patients. n values for all time points are 2. There was no reported value at year 3 for patient 3; data from year 3.5 of treatment was used. (E)

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Hemoglobin levels over time for individual male patients. n values for DFT baseline, Ext Scr and years 1, 2, 3, 4, 5 are as follows: 4, 4, 4, 4, 4, 4, 1. Patient 1 and 6 (dashed lines) were the only patients within range at DFT baseline. Gray boxes indicate mean normal range that was determined by averaging lower and upper limit for all 6 patients (A-C), female patients only (D), or male patients only (E). DFT, dose-finding trial; Ext Scr, extension screening; HGB, hemoglobin.

Figure 7. Bronchiectasis throughout treatment with leniolisib. Lung computed tomography scans from (A) patient 1, (B) patient 4, and (C) patient 5 who developed bronchiectasis before entry into the trial (left) and year 6 of treatment with leniolisib (right). L, left; P1, patient 1; P4, patient 4; P5, patient 5; Pos, posterior; R, right. *Images for patients 1 and 4 were taken approximately 1 year prior to entry into the dose-finding trial, and the image for patient 5 was taken approximately 4 years prior to exposure to leniolisib.

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Figure 1

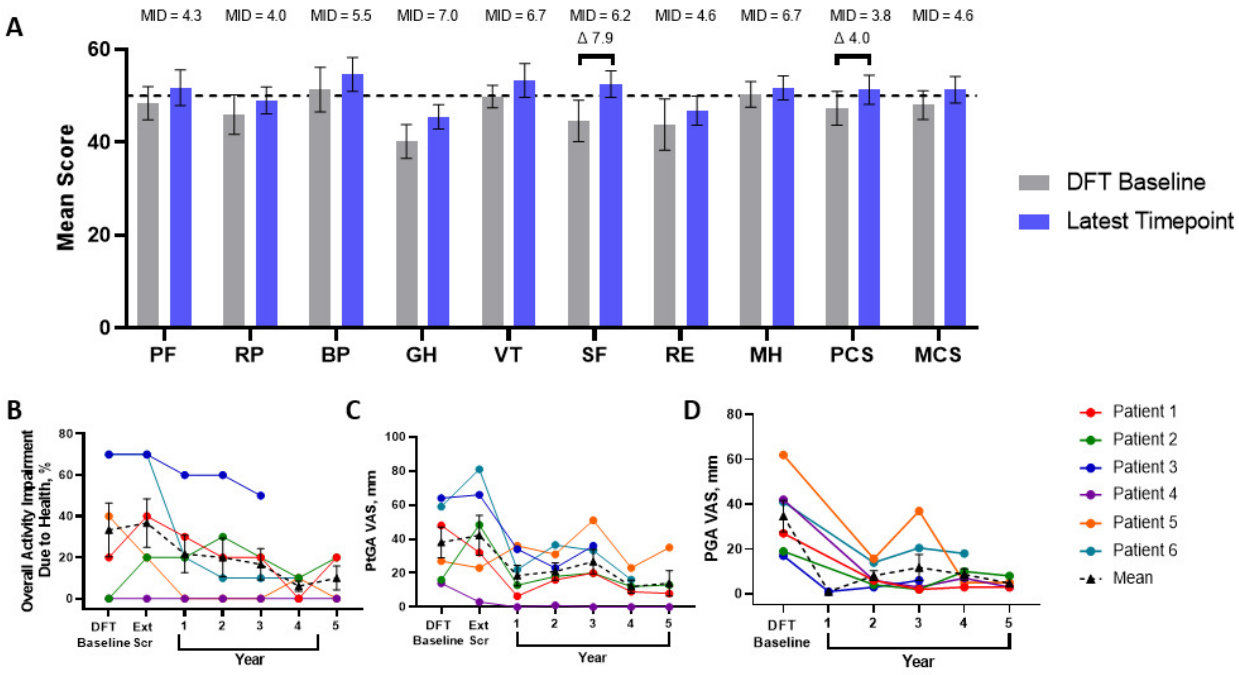

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Figure 2

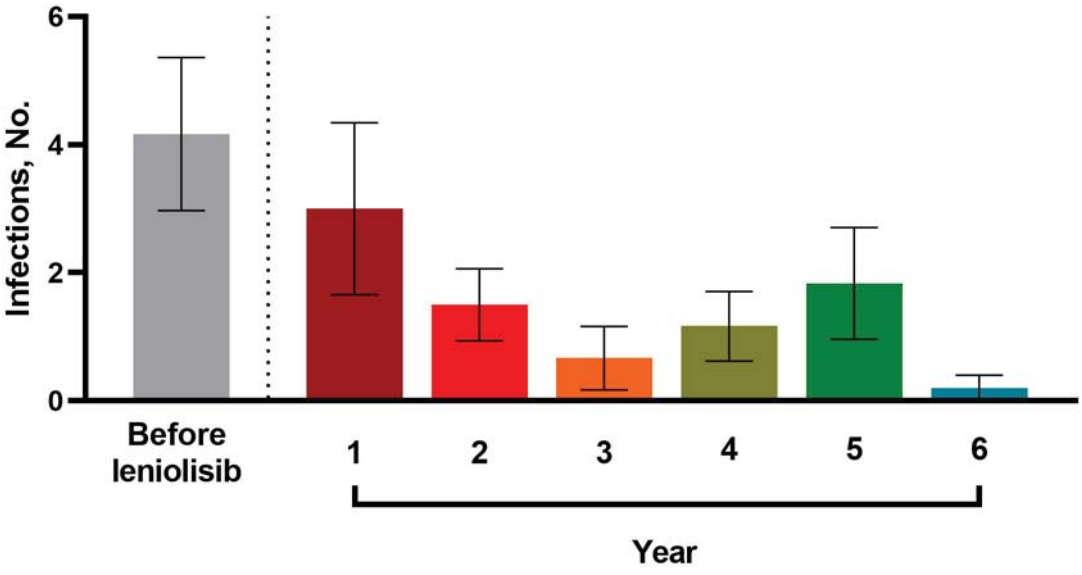

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Figure 3

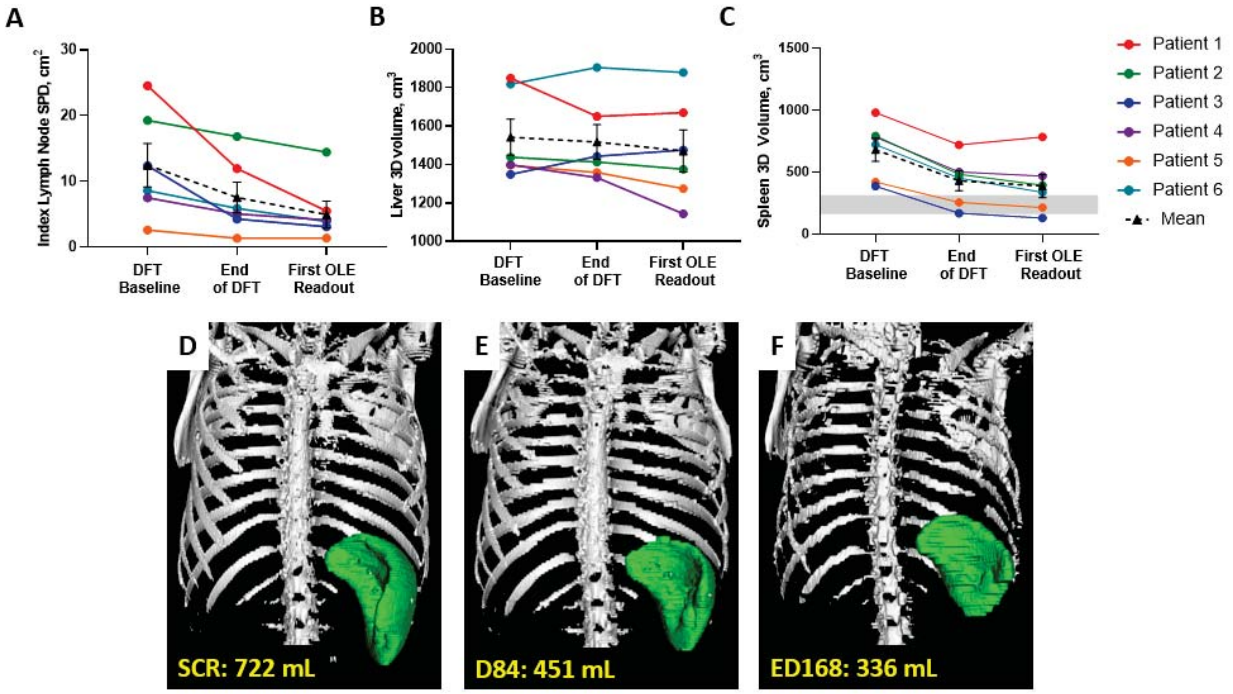

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Figure 4

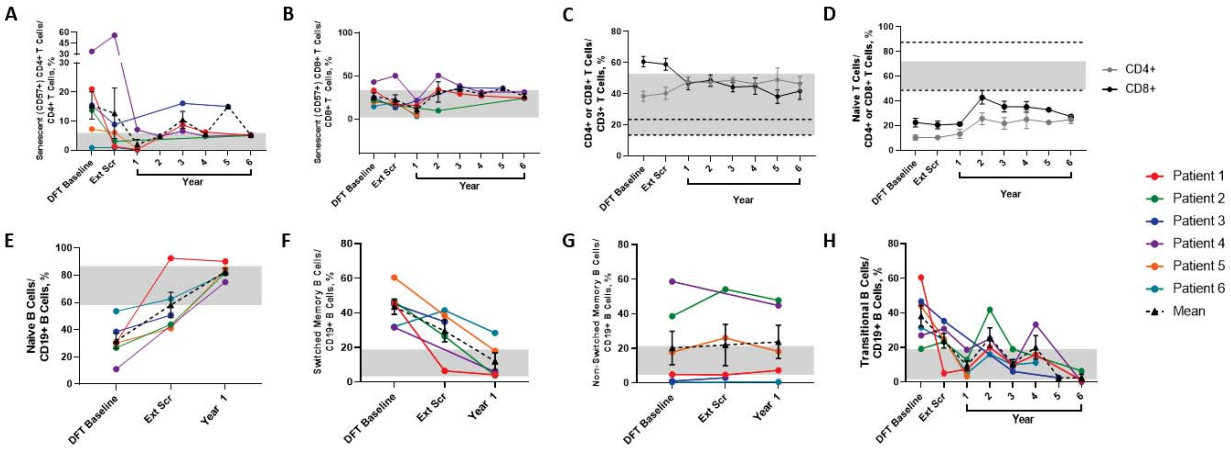

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Figure 5

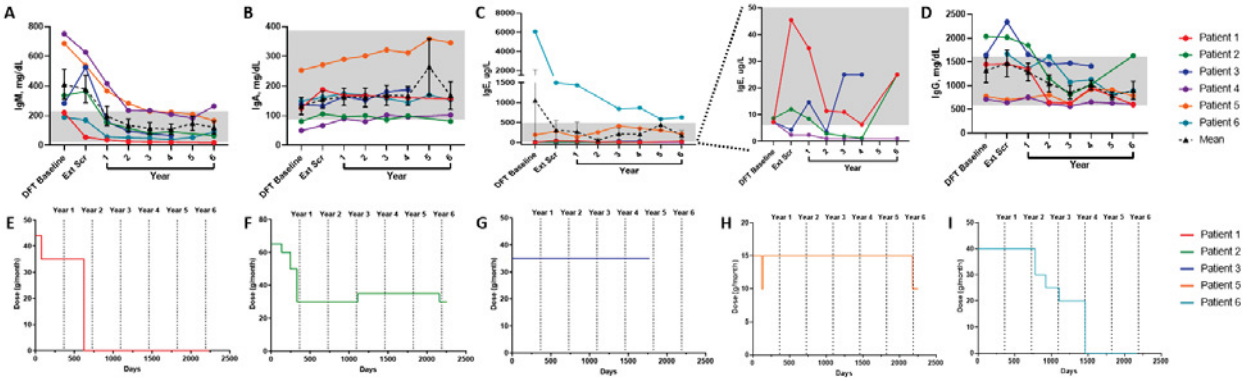

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Figure 6

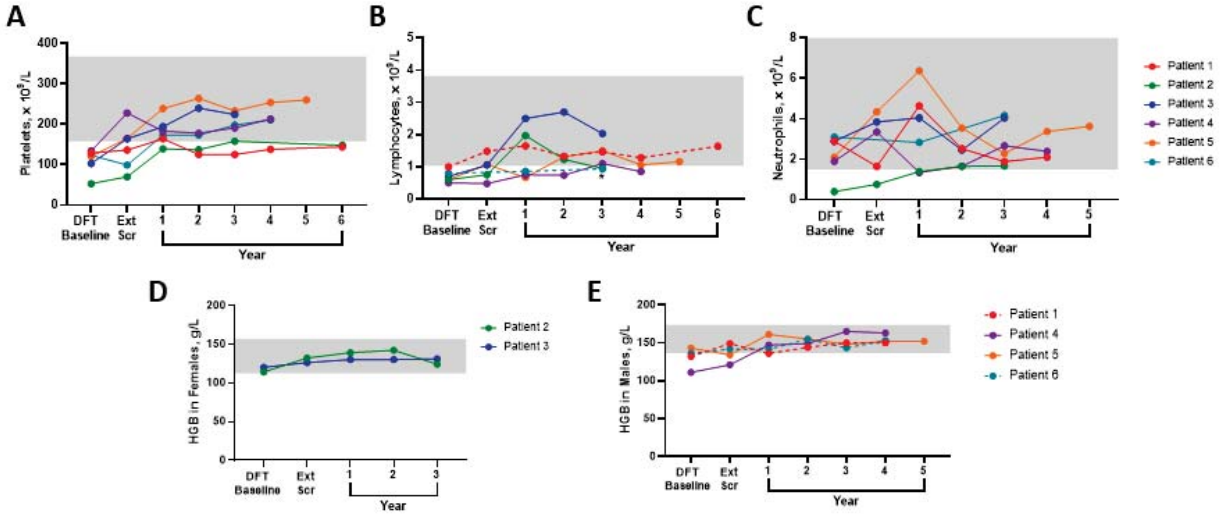

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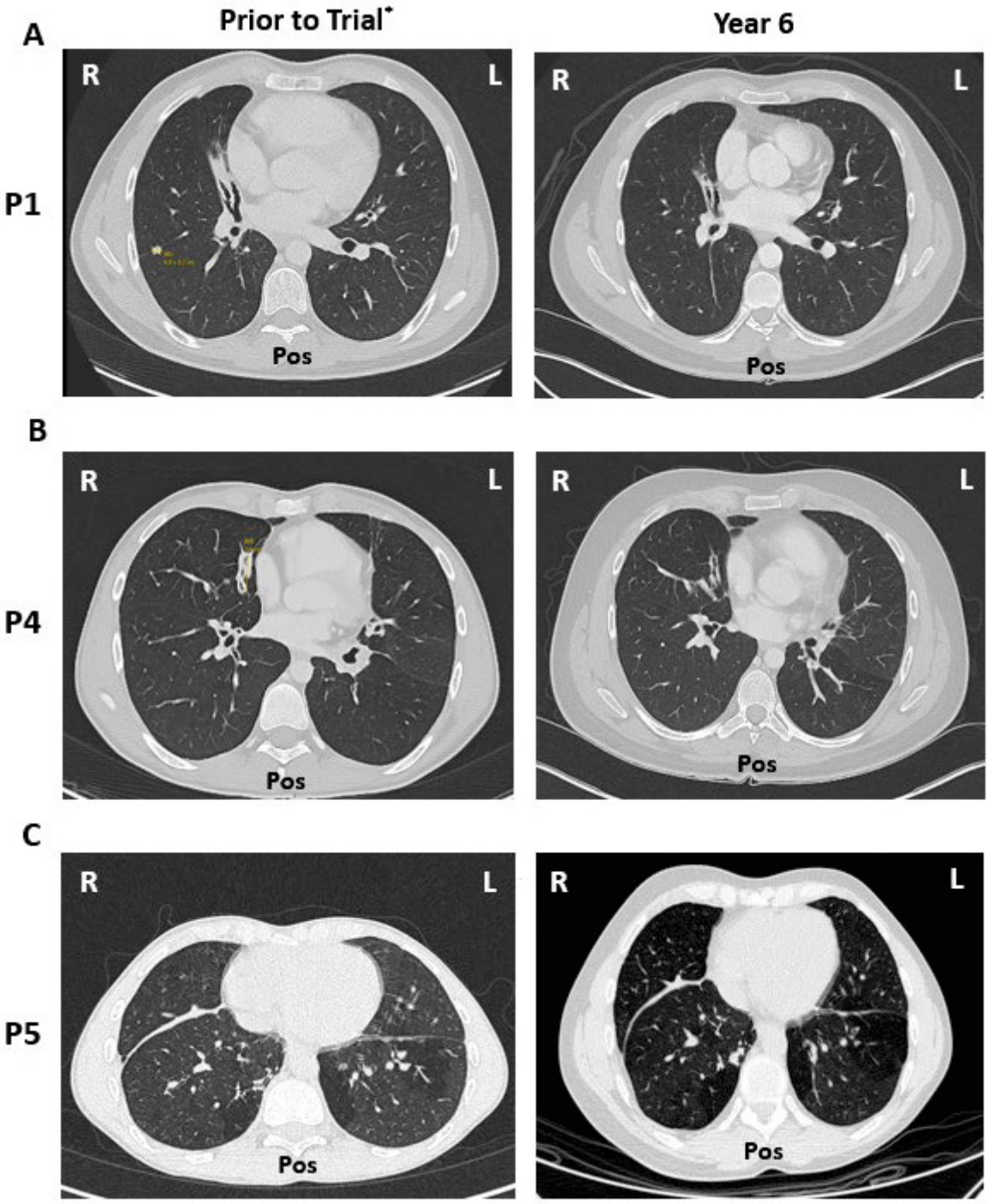
Figure 7



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