Joenja
leniolisib

AT THE CENTER OF CHANGE

TARGETING THE MECHANICS
OF APDS

TO HELP RESTORE
IMMUNE BALANCE

Joenja

The first and only therapy that is designed to correct the underlying immune defect in APDS[1-4]

APDS, activated PI3Kδ syndrome.

Indications and Usage

JOENJA® (leniolisib) is a kinase inhibitor indicated for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older.

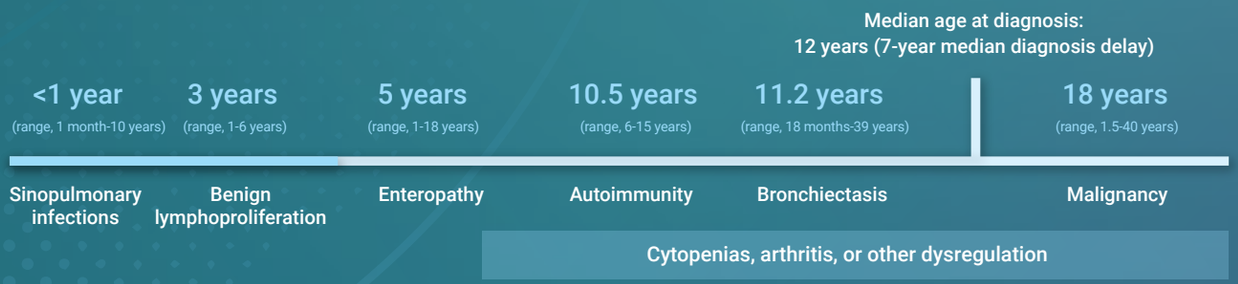
Select Safety Information

Verify pregnancy status in females of reproductive potential prior to initiating treatment with JOENJA.

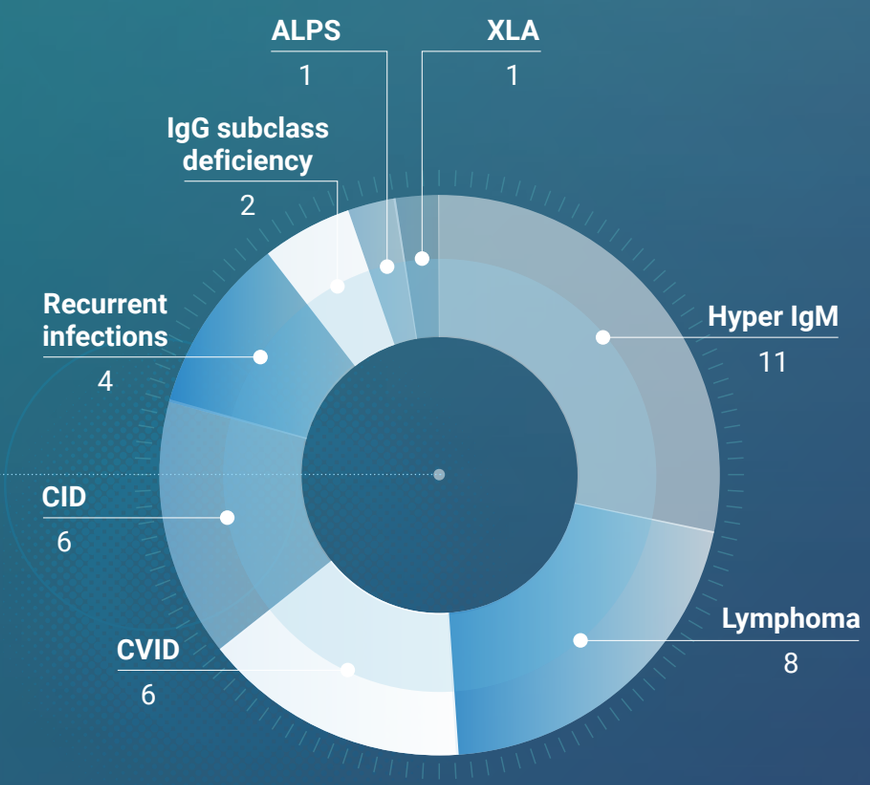
Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

APDS is a rare, primary immunodeficiency[5,6,*]

Timeline of the most common pathologies seen in APDS[6-8]



APDS has often been diagnosed as another PI or condition, causing delays in diagnosis[7,†]



Adapted from Jamee M, Moniri S, Zaki Dizaji M, et al. Clinical, immunological, and genetic features in patients with activated PI3Kδ syndrome (APDS): a systematic review. *Clin Rev Allergy Immunol*. 2020;59(3):323-333.

Improved identification of symptoms and increased genetic testing are needed for earlier diagnosis[4,6,9,10]

- APDS, characterized in 2013, is caused by variants of the genes encoding PI3Kδ
  - Genetic testing for APDS became available in 2017
- Pathogenic PI3Kδ variants have autosomal dominant inheritance patterns

A **genetic test** can provide a definitive diagnosis of APDS.
Visit **navigateAPDS.com** to learn more

*PI is also known as IEI.[11]

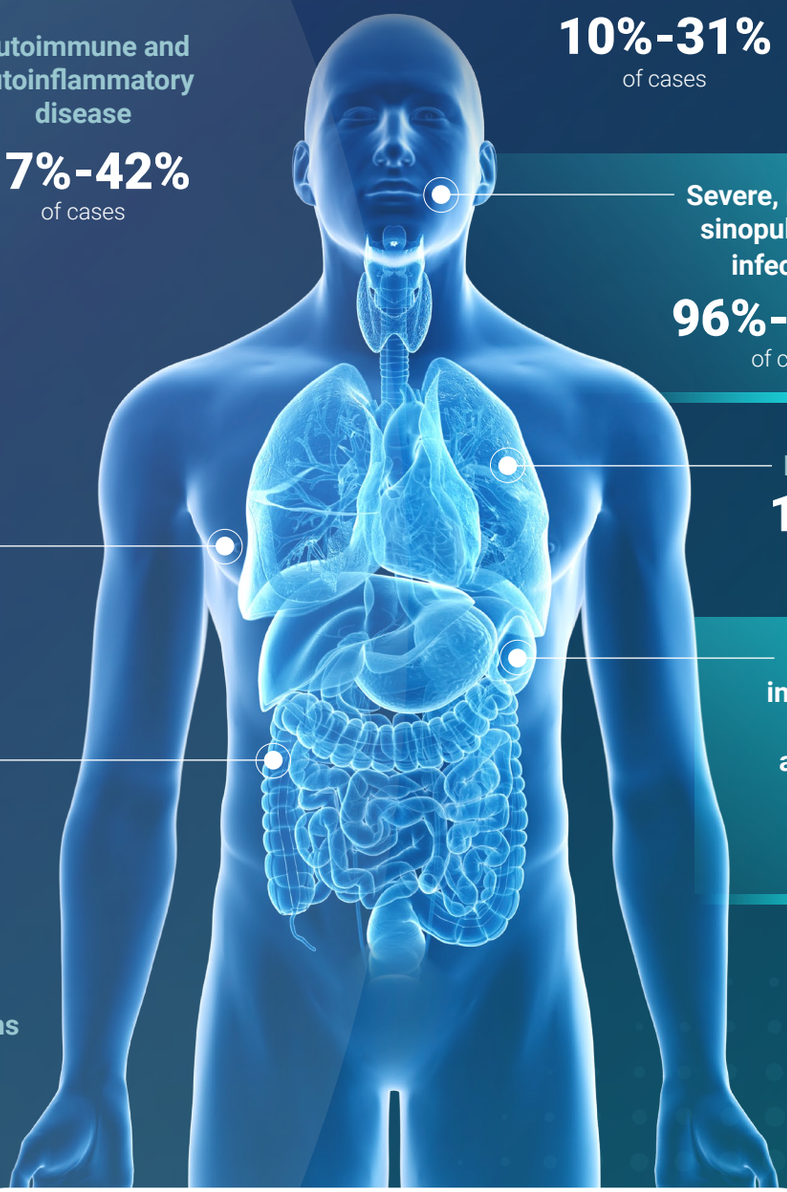
†This analysis of 39 patients with APDS revealed initial diagnoses of a range of other conditions.[7]

ALPS, autoimmune lymphoproliferative syndrome; CID, combined immunodeficiency; CVID, common variable immunodeficiency; IEI, inborn error of immunity; IgG, immunoglobulin G; IgM, immunoglobulin M; PI, primary immunodeficiency; XLA, X-linked agammaglobulinemia.

Signs and symptoms of APDS vary widely[4,7,10,12]

APDS signs and symptoms are heterogeneous, even among family members with the same genetic variant[4,13,14]

People with APDS usually experience 1 or more of the following symptoms[2,7,8,15,16]:



Neurodevelopmental delay
10%-31%
of cases

Autoimmune and autoinflammatory disease
17%-42%
of cases

Severe, recurrent sinopulmonary infections
96%-100%
of cases

Autoimmune cytopenias
19%-30%
of cases

Bronchiectasis
18%-60%
of cases

Lymphoma
12%-25%
of cases

Lymphoproliferation, including splenomegaly, hepatomegaly, and lymphadenopathy
71%-89%
of cases

Enteropathy
25%-51%
of cases

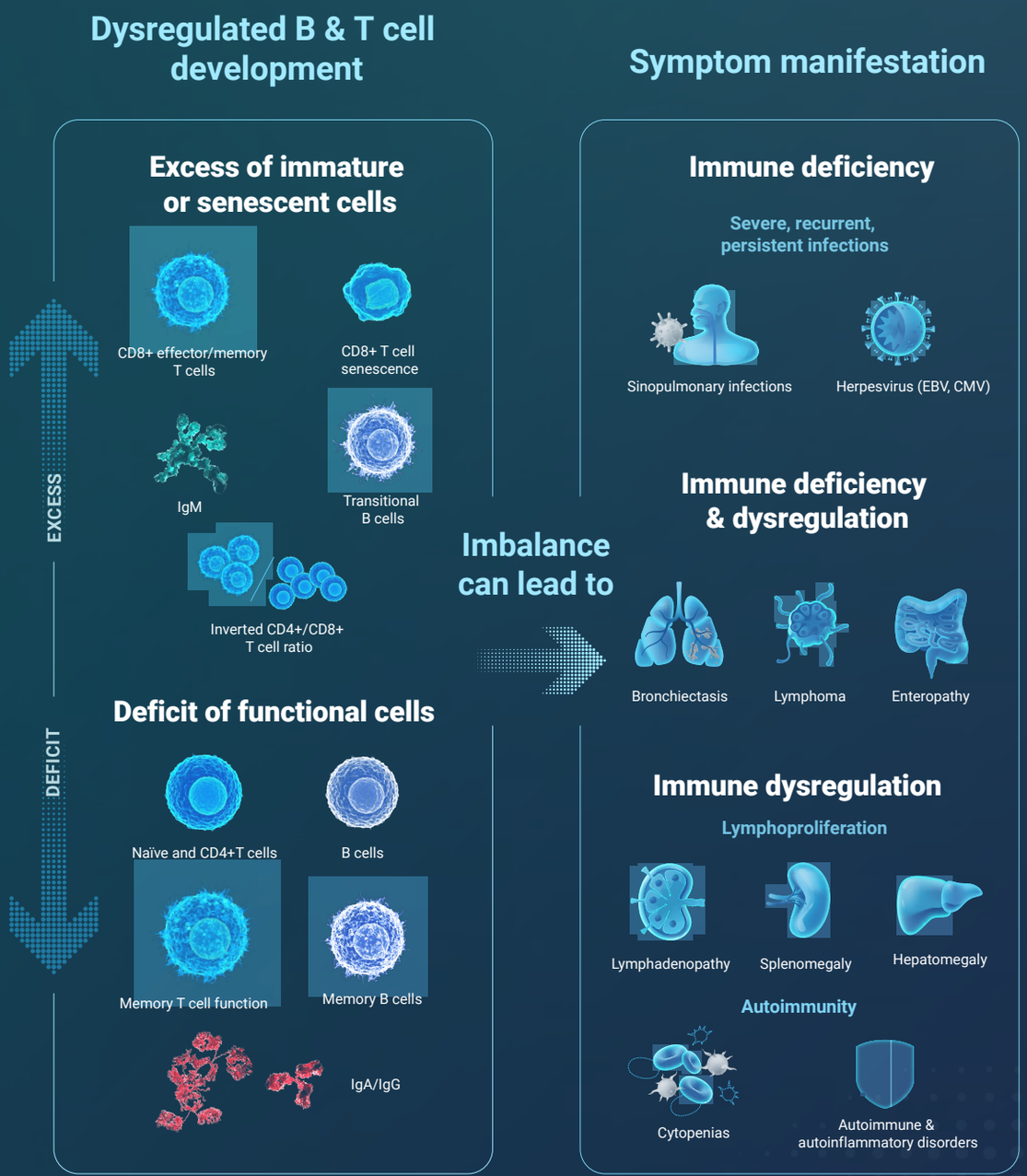
Persistent, severe, or recurrent herpes virus infections
36%-49%
of cases

Failure to thrive
45%-62%
of cases

Hyperactive PI3Kδ can lead to highly diverse manifestations of APDS[4,7,10,12]

Immune imbalance is primarily responsible for APDS disease progression[4,14]

In APDS, hyperactivity along the PI3Kδ signaling pathway disrupts immune cell balance[5]



In patients with APDS who experience disease progression[5]:

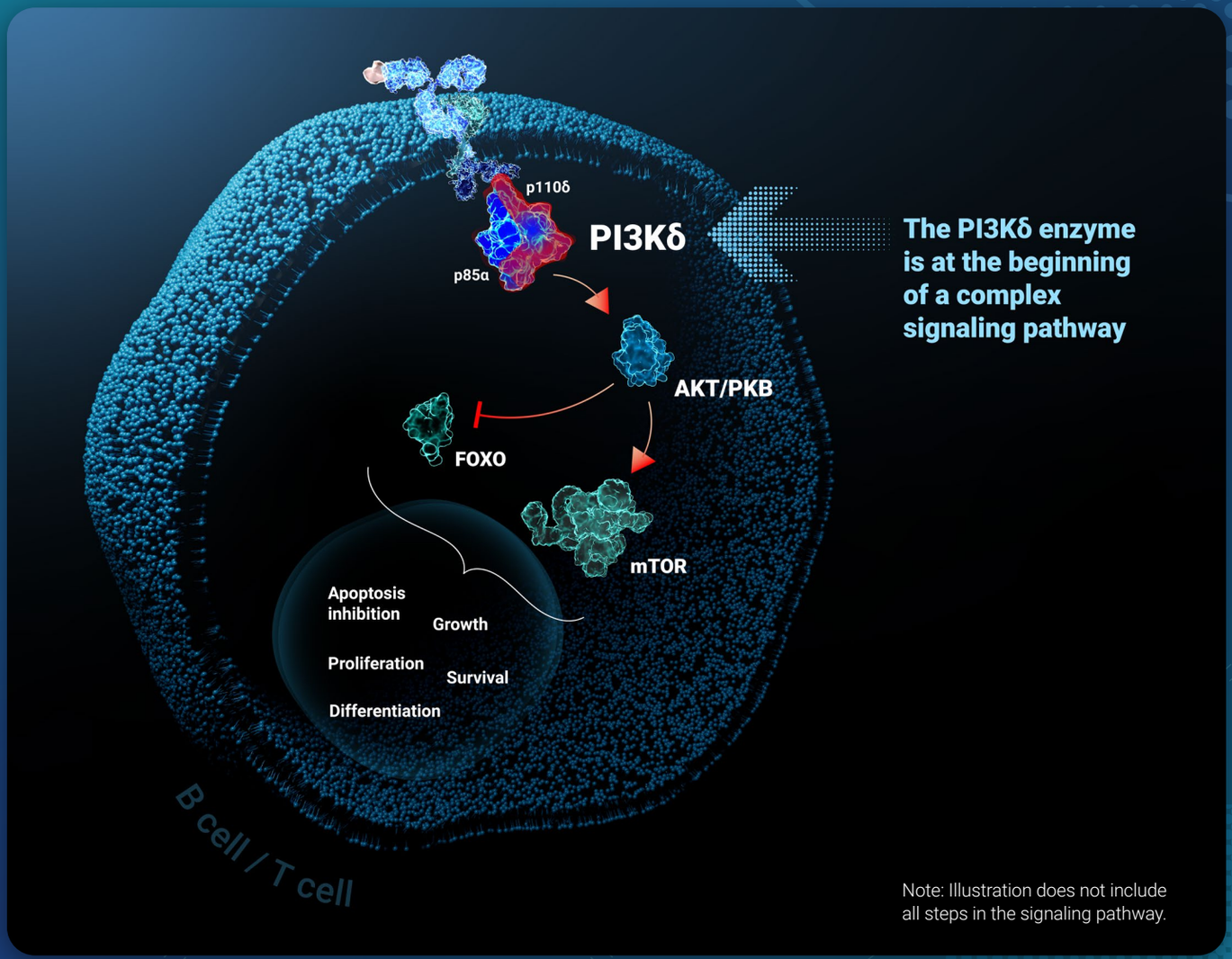
- Inadequate control of immune deficiency can lead to infections, end-organ lung damage such as bronchiectasis, or lymphoma
- Uncontrolled immune dysregulation may lead to lymphoproliferation including lymphadenopathy, splenomegaly, and potentially lymphoma
- End-organ damage has frequently preceded a confirmed diagnosis of APDS[15,17]

CD, cluster of differentiation; CMV, cytomegalovirus; EBV, Epstein-Barr virus; IgA, immunoglobulin A.

Recent studies have shown PI3Kδ to be a key factor in APDS progression[2-4]

APDS is caused by hyperactivity of the PI3Kδ enzyme early in the complex PI3Kδ pathway[5,18-20]

- The diverse manifestations of APDS are caused by the multiple downstream effects of a hyperactive PI3Kδ enzyme
- Balanced activity of the PI3Kδ signaling pathway is critical to normal immune cell development



Note: Illustration does not include all steps in the signaling pathway.

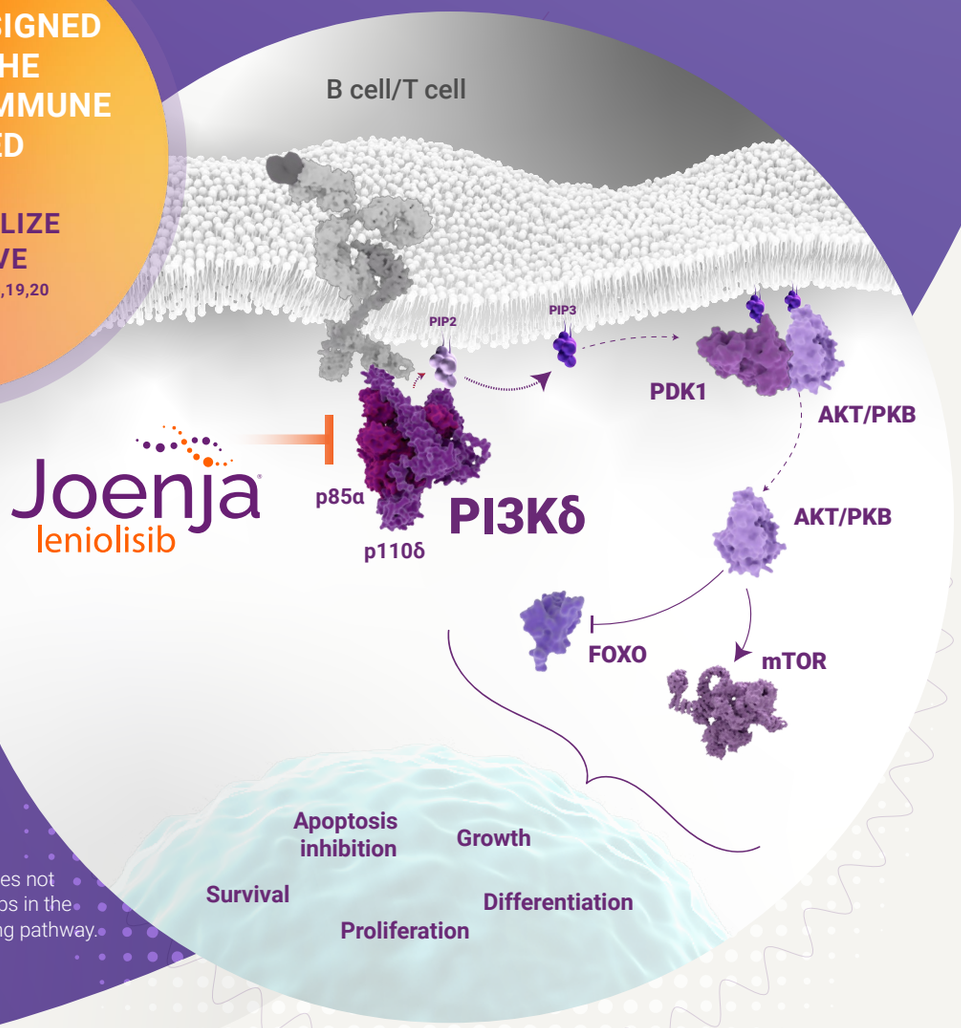
Adapted from Rao VK, Webster S, Šedivá A, et al. *Blood.* 2023;141(9):971-983. doi:10.1182/blood.2022018546

APDS is a complex syndrome caused by pathogenic variants of a single enzyme, PI3Kδ[2-4]

AKT/PKB, protein kinase B; FOXO, forkhead box O; mTOR, mammalian target of rapamycin; p85α, the regulatory subunit of the PI3Kδ enzyme; p110δ, the catalytic subunit of the PI3Kδ enzyme.

Joenja is the first and only selective PI3Kδ inhibitor indicated for the treatment of APDS[1-4]

JOENJA IS DESIGNED TO CORRECT THE UNDERLYING IMMUNE DEFECT CAUSED BY APDS
TO HELP NORMALIZE THE HYPERACTIVE PI3Kδ PATHWAY[4,19,20]



Note: Illustration does not include all steps in the signaling pathway.

PDK1, phosphoinositide-dependent kinase 1; PIP2, phosphatidylinositol (4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate.

Select Safety Information

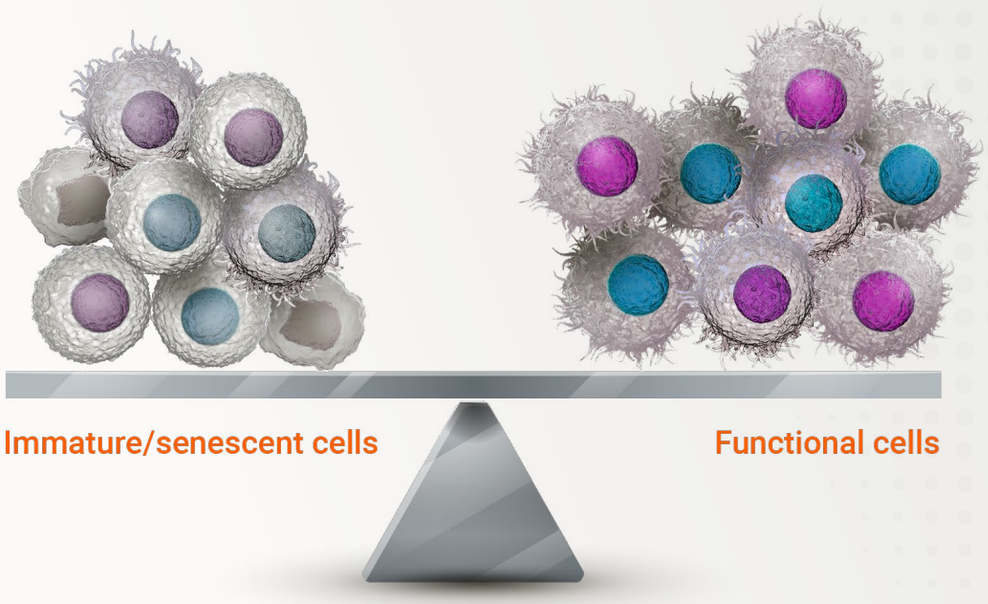
JOENJA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus and to use highly effective methods of contraception during treatment with JOENJA and for 1 week after the last dose of JOENJA.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja helps address both immune deficiency AND immune dysregulation[5]

Joenja leniolisib

Joenja facilitates a balanced PI3Kδ pathway to support proper immune function[1,14]



This is a graphical representation of a complex biological process.

Joenja is an oral, selective PI3Kδ inhibitor that is designed to help regulate the hyperactive signaling pathway[1,3]

Select Safety Information

Live, attenuated vaccinations may be less effective if administered during JOENJA treatment.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja pivotal clinical trials[1,3,4,21]

PART 1
Dose-finding

12 weeks
N=6

- Nonrandomized, open-label, dose-finding study in 6 patients with APDS; dose range was 10 mg, 30 mg, and 70 mg BID for 4 weeks at each dose
- Oral dose 70 mg BID selected for part 2

PART 2
Efficacy and Safety Evaluation

Randomized period
12 weeks
N=31

- Randomized, triple-blinded (patient, caregiver, investigator), placebo-controlled, fixed-dose study of 70 mg BID
- Co-primary efficacy end points (improvement in lymphoproliferation and normalization of immunophenotype)
  - Change from baseline in the $\log_{10}$-transformed SPD of index lesions
  - Change from baseline in percentage of naïve B cells out of total B cells
- Secondary and exploratory end point assessments
- Safety assessment

Open-label extension (OLE) study

N=37

- An open-label, non-randomized extension study to evaluate the long-term safety, tolerability, efficacy, and pharmacokinetics of Joenja in patients with APDS
  - Thirty-five patients from parts 1 and 2
  - Two patients previously treated with an investigational PI3Kδ inhibitor
- Primary outcome measure: long-term safety and tolerability

BID, twice a day; SPD, sum of product diameters.

Select Safety Information

Use of JOENJA in patients with moderate to severe hepatic impairment is not recommended. There is no recommended dosage for patients weighing less than 45 kg.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja was studied in patients with confirmed PI3Kδ variants[1,5]

Joenja® leniolisib

Baseline demographic and disease characteristics in patients with APDS

Demographics	Joenja (n=21)	Placebo (n=10)
Age, y (mean SD)	**22.2** (10)	**26.7** (13.43)
Age categories		
<18 y, n (%)	**8** (38)	**4** (40)
(min, max)	(12, 17)	(15, 17)
≥18 y, n (%)	**13** (62)	**6** (60)
(min, max)	(18, 54)	(18, 48)
Sex, n (%)		
Male	**11** (52)	**4** (40)
Female	**10** (48)	**6** (60)
Disease characteristics		
Baseline concomitant glucocorticoids, n (%)	**12** (57)	**6** (60)
Baseline concomitant IgG, n (%)	**14** (67)	**7** (70)
Previous sirolimus use, n (%)	**4** (19)	**3** (30.0)
Lymphoproliferation, n (%)	**15** (71.4)	**7** (70.0)
Chronic infections, n (%)	**18** (85.7)	**7** (70.0)
Asthma, n (%)	**7** (33.3)	**4** (40.0)
Bronchiectasis, n (%)	**8** (38.1)	**8** (80.0)
Cytopenias, n (%)	**13** (61.9)	**5** (50.0)
Gastrointestinal disease, n (%)	**10** (47.6)	**7** (70.0)

- More than half of patients in each treatment arm were receiving glucocorticoids, IRT, or both[1]

IRT, immunoglobulin replacement therapy.

Patients had nodal and/or extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI and clinical findings and manifestations compatible with APDS (eg, history of repeated oto-sino-pulmonary infections, organ dysfunction). Immunosuppressive medications or PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline (day -1 and the visit prior to first study drug administration) and throughout the study. In addition, patients who had previous or concurrent B cell depleters (eg, rituximab) within 6 months of baseline were excluded from the study unless absolute B lymphocytes in the blood were normal. B cell depleters were prohibited throughout the study.[1]

Select Safety Information

Seven (33%) patients receiving JOENJA developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL. No patients developed an ANC <500 cells/microL and there were no reports of infection associated with neutropenia.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Significant reductions in lymphadenopathy[1,5]

Log_{10}-transformed SPD of index lesions (excluding patients with 0 lesions at baseline) at week 12[1,*]

	Joenja (n/N=18/21)[†]	Placebo (n/N=8/10)[†]
Baseline mean (SD)	**3.03** (0.42)	**3.05** (0.39)
Change from baseline, LS mean (SE)	**-0.27** (0.04)	**-0.02** (0.05)
Difference vs placebo (95% CI)		**-0.25** (-0.38, -0.12)

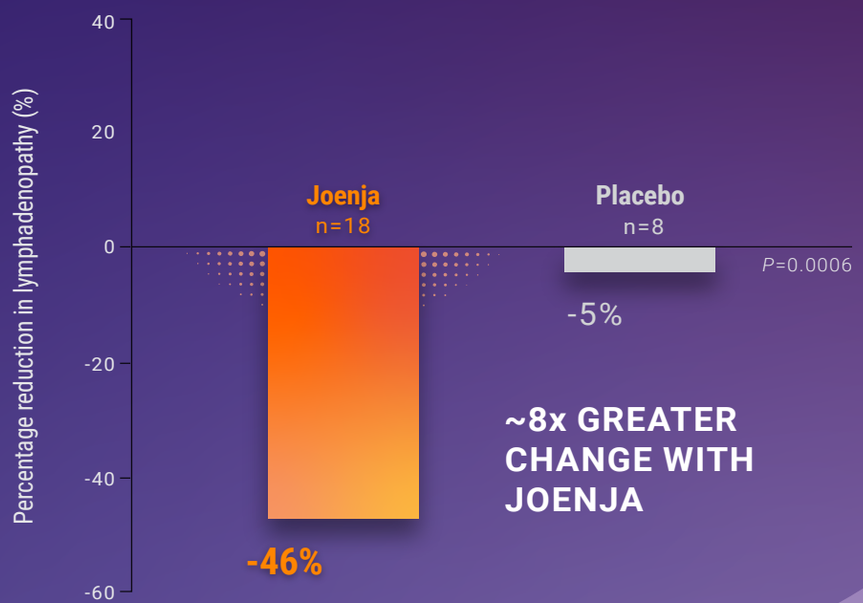
***P*=0.0006**

*The LS mean change from baseline, difference in LS mean change from baseline between Joenja and placebo and its *P* value, were obtained from an ANCOVA model with treatment, glucocorticoid use, and IRT at baseline, and baseline measurement as covariates.[1]

[†]The analysis excluded 2 patients from each treatment group due to protocol deviations and 1 Joenja patient having complete resolution of the index lesion identified at baseline.[1]

- Improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the log_{10}-transformed SPD of index lymph nodes[1]

At week 12, patients saw a significant reduction in lymphadenopathy[‡] with Joenja vs placebo[1]



46%
REDUCTION WITH JOENJA VS 5% WITH PLACEBO[4]

Reduction computed based on estimates for the adjusted mean changes.[4]

[‡]Change in index lesion size was measured using the log_{10}-transformed SPD of the largest lymph nodes (maximum of 6) identified as per the Cheson criteria on CT/MRI.

ANCOVA, analysis of covariance; LS, least squares; SD, standard deviation; SE, standard error.

Select Safety Information

The most common adverse reactions (incidence >10%) seen in clinical trials were headache, sinusitis, and atopic dermatitis.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

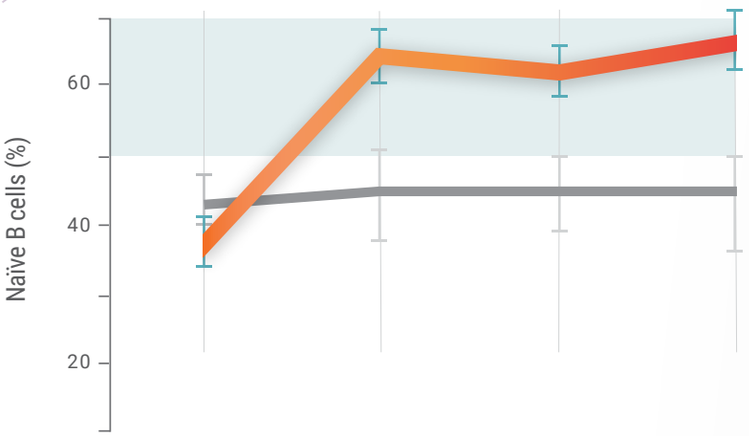
Significant increase in naïve B cells[1,4,5]

Joenja leniolisib

Significantly improved immunophenotype vs placebo at week 12

- In patients with <48% of naïve B cells at baseline,* the adjusted mean difference between Joenja (n=8) and placebo (n=5) in the percentage of naïve B cells out of total B cells was 37.30 (95% CI: 24.06, 50.54), *P*=0.0002†
- The adjusted mean change from baseline (SE) for Joenja was 37.39 (5.34) and 0.09 (6.66) for placebo

Absolute percentage of naïve B cells over time



		Baseline	Week 4	Week 8	Week 12
Joenja	n	20	19	19	16
Placebo	n	10	9	9	10

NORMAL RANGE FOR PERCENTAGE OF NAÏVE B CELLS INDICATED BY SHADED BAR IN GRAPH

MEAN NAÏVE B CELL LEVELS WITHIN NORMAL RANGE BY WEEK 4 AND MAINTAINED THROUGH WEEK 12 WITH JOENJA

*Cell surface markers used to distinguish naïve B cells on flow cytometry were CD19+, CD27-, and CD10-. Baseline is defined as the arithmetic mean of the baseline and day 1 values when both were available, and if either value was missing, the existing value was used.

†The analysis excluded 2 patients from each treatment group due to protocol deviations, 5 Joenja patients and 3 placebo patients with ≥48% naïve B cells at baseline, 5 Joenja patients with no day 85 measurement, and 1 Joenja patient with no baseline measurement.

Joenja effectively helped normalize immune balance in patients with APDS

Select Safety Information

Seven (33%) patients receiving JOENJA developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL. No patients developed an ANC <500 cells/microL and there were no reports of infection associated with neutropenia.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja significantly reduced splenomegaly[5]

Significant reductions in spleen by 2D and 3D analysis compared to placebo

- The adjusted mean difference in bidimensional spleen size between Joenja (n=19) and placebo (n=9) was -13.5 cm^2 (95% CI: -24.1, -2.91), *P*=0.0148
- The adjusted mean difference in 3D spleen volume between Joenja (n=19) and placebo (n=9) was -186 cm^3 (95% CI: -297, -76.2), *P*=0.0020

AT WEEK 12

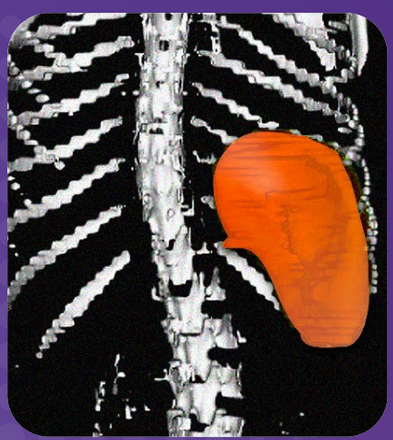
27%

REDUCTION IN 3D SPLEEN VOLUME*

Secondary measure: Spleen volume scan results of actual patient illustrate average improvement documented for patients taking Joenja

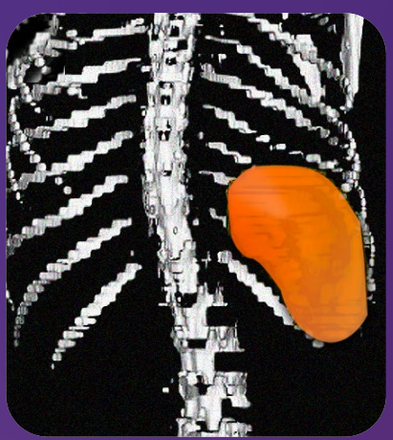
Prior to treatment:

491 mL



At week 12:

314 mL



Actual patient images of a 17-year-old male's median response. As individual results vary, images may not be representative of all patients.

*In the PD analysis set, the mean (SD) percentage change from baseline to week 12 in 3D spleen volume (mm^3) was -26.68% (12.137) with Joenja (n=19) and -1.37% (24.238) with placebo (n=9). The ANCOVA model was used with treatment as a fixed effect and log_{10}-transformed baseline as a covariate for index and non-index lesions. The use of both glucocorticoids and intravenous Ig at baseline was included as categorical (yes/no) covariates.

This analysis excluded 2 patients in each treatment group. In the Joenja group, 1 patient with a complete index lesion response was excluded, and 3 patients were excluded for no non-index lesion at baseline.

PD, pharmacodynamics.

Other secondary end points included patient-reported benefits with Joenja that were assessed using the SF-36 (Short Form 36) Survey and WPAI-CIQ (Work Productivity Activity Impairment plus Classroom Impairment Questionnaire), visual analogue scales for Physician's Global Assessment (PGA), and Patient's Global Assessment (PtGA), and patient narratives by investigator. Clinical relevance from these assessments was not established.

Select Safety Information

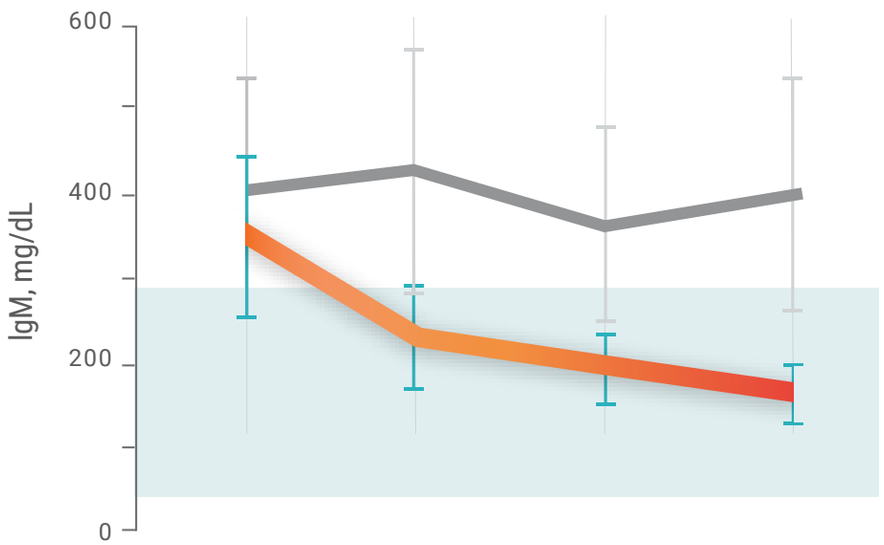
Use of JOENJA in patients with moderate to severe hepatic impairment is not recommended. There is no recommended dosage for patients weighing less than 45 kg.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

An exploratory end point showed Joenja reduced IgM levels[5]

- In the Joenja arm, IgM was elevated above normal limits in 6 patients at baseline, and by week 12 was reduced in all, with 50% returning to within normal limits
- In contrast, IgM was elevated above normal limits at baseline in 4 patients in the placebo arm, and by day 85 levels remained stable or elevated, with 0% returning to within normal limits

Mean serum IgM reduced to within normal limits



NORMAL RANGE FOR IgM INDICATED BY SHADED BAR IN GRAPH

		Baseline	Week 4	Week 8	Week 12
Joenja	n	21	20	21	21
Placebo	n	10	10	10	10

Soluble biomarkers, including IgM, were prespecified exploratory end points in the protocol. Although an observational decrease in IgM was noted in some patients, no statistical significance can be made from this analysis, and no conclusions should be drawn.

Select Safety Information

Live, attenuated vaccinations may be less effective if administered during JOENJA treatment.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja safety profile[1,5]

- The safety of Joenja is based on data from both the placebo-controlled pivotal trial and the interim results from the OLE study

Adverse reactions reported by ≥2 Joenja-treated patients and more frequently than placebo

	Joenja (n=21) n (%)	**Placebo** (n=10) n (%)
Headache	**5** (24)	**2** (20)
Sinusitis	**4** (19)	**0**
Dermatitis atopic*	**3** (14)	**0**
Tachycardia†	**2** (10)	**0**
Diarrhea	**2** (10)	**0**
Fatigue	**2** (10)	**1** (10.0)
Pyrexia	**2** (10)	**0**
Back pain	**2** (10)	**0**
Neck pain	**2** (10)	**0**
Alopecia	**2** (10)	**0**

*Dermatitis atopic: including dermatitis atopic and eczema.
†Tachycardia: including tachycardia and sinus tachycardia.

- No serious adverse drug reactions were reported
- No patients withdrew due to an adverse drug reaction
- The most common adverse reactions (>10%) were headache, sinusitis, and dermatitis atopic

Select Safety Information

Seven (33%) patients receiving JOENJA developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL. No patients developed an ANC <500 cells/microL and there were no reports of infection associated with neutropenia.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Additional safety results from an interim analysis[1,22]

Joenja® leniolisib

At the data cutoff

- Thirty-seven of 38 patients received Joenja 70 mg orally twice daily for at least 25 weeks; 66% were exposed for 96 weeks or longer
- Median duration of Joenja treatment was approximately 2 years
- Four patients had more than 5 years of Joenja exposure

Most common AEs	n
Upper respiratory tract infection	8
Headache	6
Pyrexia	6
Otitis externa	5
Weight increase	5
COVID-19 positive	5
COVID-19 negative	14

Distribution and grades* of AEs

- Thirty-two of 37 patients had ≥1 AE (333 AEs reported)
- 78.4% were grade 1, 48.6% were grade 2, and 27% were grade 3
- No grade 4 AEs reported
- One grade 5 patient with significant baseline comorbidities suffered cardiac arrest resulting in death on day 879; investigator determined that the death was not related to study drug
- No serious AEs were related to Joenja treatment

AEs associated with Joenja

- The AEs reported as related to study drug were weight increase (3 patients), arthralgia (1 patient), hyperglycemia (1 patient), and decreased neutrophil count (1 patient)

*CTCAE were used to determine AE grade. If CTCAE grading did not exist for an AE, the following definitions were used: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, death.

AE, adverse event; CTCAE, common terminology criteria for adverse events.

Select Safety Information

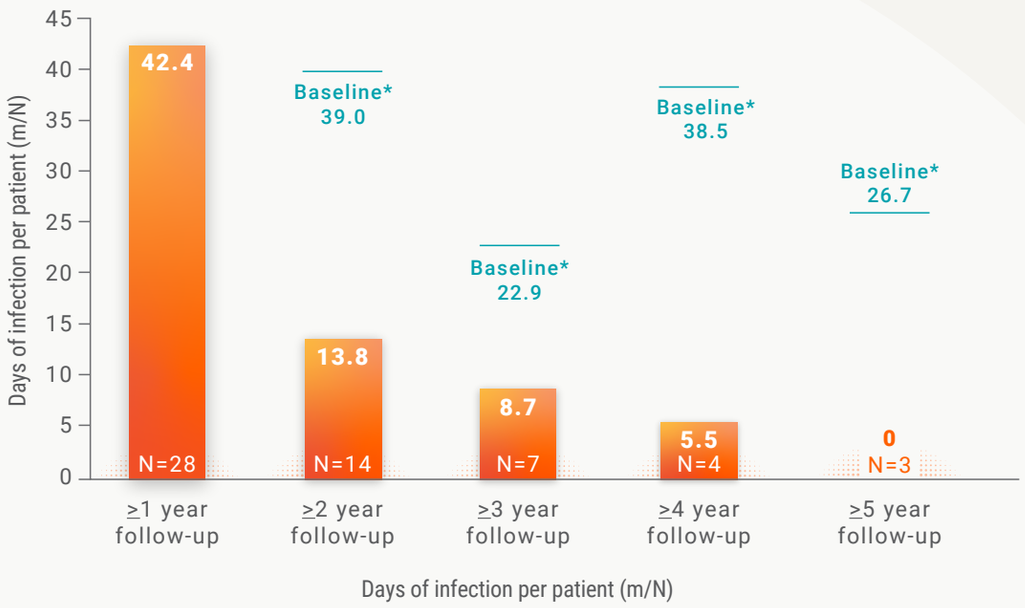
JOENJA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus and to use highly effective methods of contraception during treatment with JOENJA and for 1 week after the last dose of JOENJA.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Annual infection rates[22]

Infection rates reported per each additional year of treatment with Joenja

Infections that developed during the study were reported as AEs. Investigators were requested to inquire about signs and symptoms of infections at each visit, in particular bacterial enterocolitis. Patients were not provided an infection diary to document infections occurring between visits.



- No change in antibiotic use despite the reduction in IRT utilization

m/N, number of infection days/number of patients in follow-up category.

*Baseline infections are each group's year 1 annualized rate of infections. N values changed because patients were in the study for different lengths of time.

Data analyzed using a log-linear negative binomial model including an offset for time spent in study, an effect for time of the start of infection (in years), and presence of baseline infection as a covariate. One patient was excluded from the analysis due to a wrong year recorded for an infection.

Although safety was the primary objective of the open-label study, this post hoc analysis from the OLE study was not powered to provide any statistical significance of efficacy and therefore no conclusions should be drawn.

Select Safety Information

Seven (33%) patients receiving JOENJA developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL. No patients developed an ANC <500 cells/microL and there were no reports of infection associated with neutropenia.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Physician-reported IRT reductions and discontinuations[22]

- Data on concomitant medication usage was recorded at each patient visit

Twenty-seven Joenja patients were receiving IRT at the start of the OLE study

AT THE DATA CUTOFF

17 PATIENTS REMAINED ON IRT

4 PATIENTS REDUCED THEIR IRT UTILIZATION

6 PATIENTS DISCONTINUED IRT USE*

- Four patients had been IRT free for 1 to 2.5 years
- The median time to IRT reduction was 12.1 months and the median time to IRT discontinuation was 11.9 months

IRT use was captured by the investigator as concomitant medication at each study visit per protocol in this open-label study. IRT was not prespecified as an end point or analysis. This is an observation from a post hoc analysis and no determination of statistical significance can be made and no conclusions should be drawn.

*One of these patients had a subsequent one-time dose IRT.

The OLE study is ongoing and has 4 patients who have had more than 5 years of Joenja exposure[1]

Select Safety Information

Live, attenuated vaccinations may be less effective if administered during JOENJA treatment.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Twice-daily oral administration[1]

Recommended administration of Joenja

- 70 mg, orally
- Twice daily, ~12 hours apart
- In adult and pediatric patients ≥12 years of age and weighing ≥45 kg*

Joenja can be taken **with or without food**

Advise patients that if a dose is missed by more than 6 hours, **wait and take the next dose at the usual time**

Advise patients that if vomiting occurs

- **Within 1 hour** after taking Joenja, take Joenja as soon as possible
- **More than 1 hour** after taking Joenja, wait and take the next dose at the usual time

Joenja oral tablets can be taken anytime, anywhere

- Joenja should be taken twice a day, approximately 12 hours apart

*There is no recommended dosage for pediatric patients 12 years of age and older who weigh less than 45 kg.

Select Safety Information

Use of JOENJA in patients with moderate to severe hepatic impairment is not recommended. There is no recommended dosage for patients weighing less than 45 kg.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

APDS Assist—opening doors to help your patients with APDS move forward

Joenja leniolisib

APDS Assist

APDS Assist can help you:

- Enroll your patients with APDS in our comprehensive program
- Gain information about patient-specific insurance requirements for Joenja
- Learn more about our support services, including our APDS Clinical Educators (ACEs)

Visit Joenja.com to enroll your patients today.

APDS Assist provides comprehensive support for you and your patients every step of the way

APDS Care Coordinators

Here to help you navigate coverage, access, and other support options when you prescribe Joenja

ACEs

Provide one-on-one support and educational resources for you and your patients

APDS Assist Specialty Pharmacists

Available to answer questions you and your patients may have about their Joenja medication

Ways APDS Assist can help your patients with APDS

Our commitment is to **get your patients started on Joenja as quickly as possible** while we work with your office to provide insurance support.

ACEs* can help your patients connect with local and nationwide support groups and educational resources along their Joenja journey.

Access to Joenja is our priority. **Depending on the patient's insurance and other eligibility criteria, a Care Coordinator can help identify support resources as needed.**

*Please note that ACEs do not offer medical or treatment advice or replace discussions with a physician.

Select Safety Information

Verify pregnancy status in females of reproductive potential prior to initiating treatment with JOENJA.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Indications and Usage

JOENJA® (leniolisib) is a kinase inhibitor indicated for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older.

Important Safety Information

Verify pregnancy status in females of reproductive potential prior to initiating treatment with JOENJA.

JOENJA may cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus and to use highly effective methods of contraception during treatment with JOENJA and for 1 week after the last dose of JOENJA.

Live, attenuated vaccinations may be less effective if administered during JOENJA treatment.

Use of JOENJA in patients with moderate to severe hepatic impairment is not recommended. There is no recommended dosage for patients weighing less than 45 kg.

The most common adverse reactions (incidence >10%) seen in clinical trials were headache, sinusitis, and atopic dermatitis.

Seven (33%) patients receiving JOENJA developed an absolute neutrophil count (ANC) between 500 and 1500 cells/microL. No patients developed an ANC <500 cells/microL and there were no reports of infection associated with neutropenia.

Before prescribing JOENJA, please read the full Prescribing Information.

References: 1. Joenja (leniolisib). Prescribing information. Pharming Healthcare, Inc; 2023. **2.** Maccari ME, Abolhassani H, Aghamohammadi A, et al. Disease evolution and response to rapamycin in activated phosphoinositide 3-kinase δ syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry. *Front Immunol*. 2018;9:543. doi:10.3389/fimmu.2018.00543 **3.** Rao VK, Webster S, Dalm VASH, et al. Effective "activated PI3Kδ syndrome"—targeted therapy with the PI3Kδ inhibitor leniolisib. *Blood*. 2017;130(21):2307-2316. doi:10.1182/blood-2017-08-801191 **4.** Data on file. Pharming Healthcare, Inc. **5.** Rao VK, Webster S, Šedivá A, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. *Blood*. 2023;141(9):971-983. doi:10.1182/blood.2022018546 **6.** Angulo I, Vadas O, Garçon F, et al. Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage. *Science*. 2013;342(6160):866-871. doi:10.1126/science.1243292 **7.** Jamee M, Moniri S, Zaki-Dizaji M, et al. Clinical, immunological, and genetic features in patients with activated PI3Kδ syndrome (APDS): a systematic review. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. doi:10.1007/s12016-019-08738-9 **8.** Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: a cohort study. *J Allergy Clin Immunol*. 2016;138(1):210-218.e9. doi:10.1016/j.jaci.2016.03.022 **9.** Anderson JT, Cowan J, Condino-Neto A, Levy D, Prusty S. Health-related quality of life in primary immunodeficiencies: impact of delayed diagnosis and treatment burden. *Clin Immunol*. 2022;236:108931. doi: 10.1016/j.clim.2022.108931 **10.** Deau M-C, Heurtier L, Frange P, et al. A human immunodeficiency caused by mutations in the *PIK3R1* gene. *J Clin Invest*. 2014;124(9):3923-3928. **11.** Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2020;40(1):24-64. doi:10.1007/s10875-019-00737-x **12.** Lucas CL, Chandra A, Nejentsev S, Condliffe AM, Okkenhaug K. PI3Kδ and primary immunodeficiencies. *Nat Rev Immunol*. 2016;16(11):702-714. doi:10.1038/nri.2016.93 **13.** Genetic Alliance; The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services. *Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals*. Washington, DC: Genetic Alliance; July 8, 2009. **14.** Nunes-Santos CJ, Uzel G, Rosenzweig SD. PI3K pathway defects leading to immunodeficiency and immune dysregulation. *J Allergy Clin Immunol*. 2019;143(5):1676-1687. **15.** Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study. *J Allergy Clin Immunol*. 2017;139(2):597-606.e4. doi:10.1016/j.jaci.2016.06.021 **16.** Carpier J-M, Lucas CL. Epstein-Barr virus susceptibility in activated PI3Kδ syndrome (APDS) immunodeficiency. *Front Immunol*. 2018;8:2005. doi:10.3389/fimmu.2017.02005 **17.** Bloomfield M, Klocperk A, Zachova R, Milota T, Kanderova V, Sediva A. Natural course of activated phosphoinositide 3-kinase delta syndrome in childhood and adolescence. *Front Pediatr*. 2021;9:697-706. **18.** Okkenhaug K. Signalling by the phosphoinositide 3-kinase family in immune cells. *Annu Rev Immunol*. 2013;31:675-704. **19.** Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. *Cell*. 2017;170(4):605-635. doi:10.1016/j.cell.2017.07.029 **20.** Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. *Nat Rev Immunol*. 2003;3(4):317-330. doi:10.1038/nri1056 **21.** US National Library of Medicine. ClinicalTrials.gov/NCT02859727. **22.** Rao VK. Interim safety and efficacy analysis of an ongoing long-term open-label extension study of leniolisib for patients with activated PI3K delta syndrome (APDS). Presented at the European Society for Immunodeficiencies; October 12-15, 2022; Gothenburg, Sweden.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Joenja
leniolisib
AT THE CENTER OF CHANGE

Joenja—targeting the mechanics of APDS to help restore immune balance[1-5]

Significant reductions in lymphadenopathy

- Joenja delivered significant improvements in immune dysregulation (eg, lymph node and splenomegaly reductions)
  - Improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the $\log_{10}$-transformed SPD of index lymph nodes
  - At week 12 of the pivotal trial, patients taking Joenja saw a 46% reduction in lymphadenopathy vs a 5% reduction in patients taking placebo

Significant improvements in immunophenotype

- Joenja showed a significant increase in naïve B cells vs placebo in patients with <48% of naïve B cells at baseline

Joenja safety profile

- No serious adverse drug reactions were reported in the clinical trials
- No patients withdrew from the clinical trial due to an adverse drug reaction
- The most common adverse reactions (incidence >10%) seen in clinical trials were headache, sinusitis, and atopic dermatitis

The OLE study is ongoing

- 97% of patients in the OLE study received Joenja for at least 25 weeks
  - 66% were exposed for 96 weeks or longer
- Four patients had more than 5 years of Joenja exposure
  - Median duration of Joenja exposure was ~2 years

Target APDS with Joenja,
the first and only selective PI3Kδ inhibitor indicated for the treatment of APDS

Select Safety Information

Verify pregnancy status in females of reproductive potential prior to initiating treatment with JOENJA.

Please see Important Safety Information on page 20. Before prescribing JOENJA, please read the full Prescribing Information.

Pharming

JOE-US-2023-0077v4 09/23