



Pharming Group N.V.

Corporate Presentation

January 2024

NASDAQ: **PHAR** | EURONEXT Amsterdam: **PHARM**

This presentation may contain forward-looking statements. Forward-looking statements are statements of future expectations that are based on management's current expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results, performance, or events to differ materially from those expressed or implied in these statements. These forward-looking statements are identified by their use of terms and phrases such as "aim", "ambition", "anticipate", "believe", "could", "estimate", "expect", "goals", "intend", "may", "milestones", "objectives", "outlook", "plan", "probably", "project", "risks", "schedule", "seek", "should", "target", "will" and similar terms and phrases. Examples of forward-looking statements may include statements with respect to timing and progress of Pharming's preclinical studies and clinical trials of its product candidates, Pharming's clinical and commercial prospects, and Pharming's expectations regarding its projected working capital requirements and cash resources, which statements are subject to a number of risks, uncertainties and assumptions, including, but not limited to the scope, progress and expansion of Pharming's clinical trials and ramifications for the cost thereof; and clinical, scientific, regulatory and technical developments. In light of these risks and uncertainties, and other risks and uncertainties that are described in Pharming's 2022 Annual Report and the Annual Report on Form 20-F for the year ended December 31, 2022, filed with the U.S. Securities and Exchange Commission, the events and circumstances discussed in such forward-looking statements may not occur, and Pharming's actual results could differ materially and adversely from those anticipated or implied thereby. All forward-looking statements contained in this presentation are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. Readers should not place undue reliance on forward-looking statements. Any forward-looking statements speak only as of the date of this presentation and are based on information available to Pharming as of the date of this presentation. Pharming does not undertake any obligation to publicly update or revise any forward-looking statement as a result of new information, future events or other information.



Market RUCONEST[®] for acute HAE attacks in key markets – U.S. focus



Positive cash flow from RUCONEST[®] revenue funds Joenja[®] (leniolisib) launches & pipeline development

- ◆ Updated FY23 revenue guidance ~US\$227M* (+10% vs. FY22)
- ◆ Significantly exceeding previous guidance of low single digit revenue growth



Global approvals and commercialization of Joenja[®] (leniolisib) for APDS



Successful commercialization of Joenja[®] (leniolisib) for APDS

- ◆ Joenja[®] - First and only FDA approved treatment for APDS
FY23 revenue guidance ~US\$18M*
- ◆ Regulatory reviews ongoing in EUR, CAN, AUS, ISR
- ◆ Pediatric and Japan clinical trials ongoing



Ongoing pipeline development and management of rare disease assets

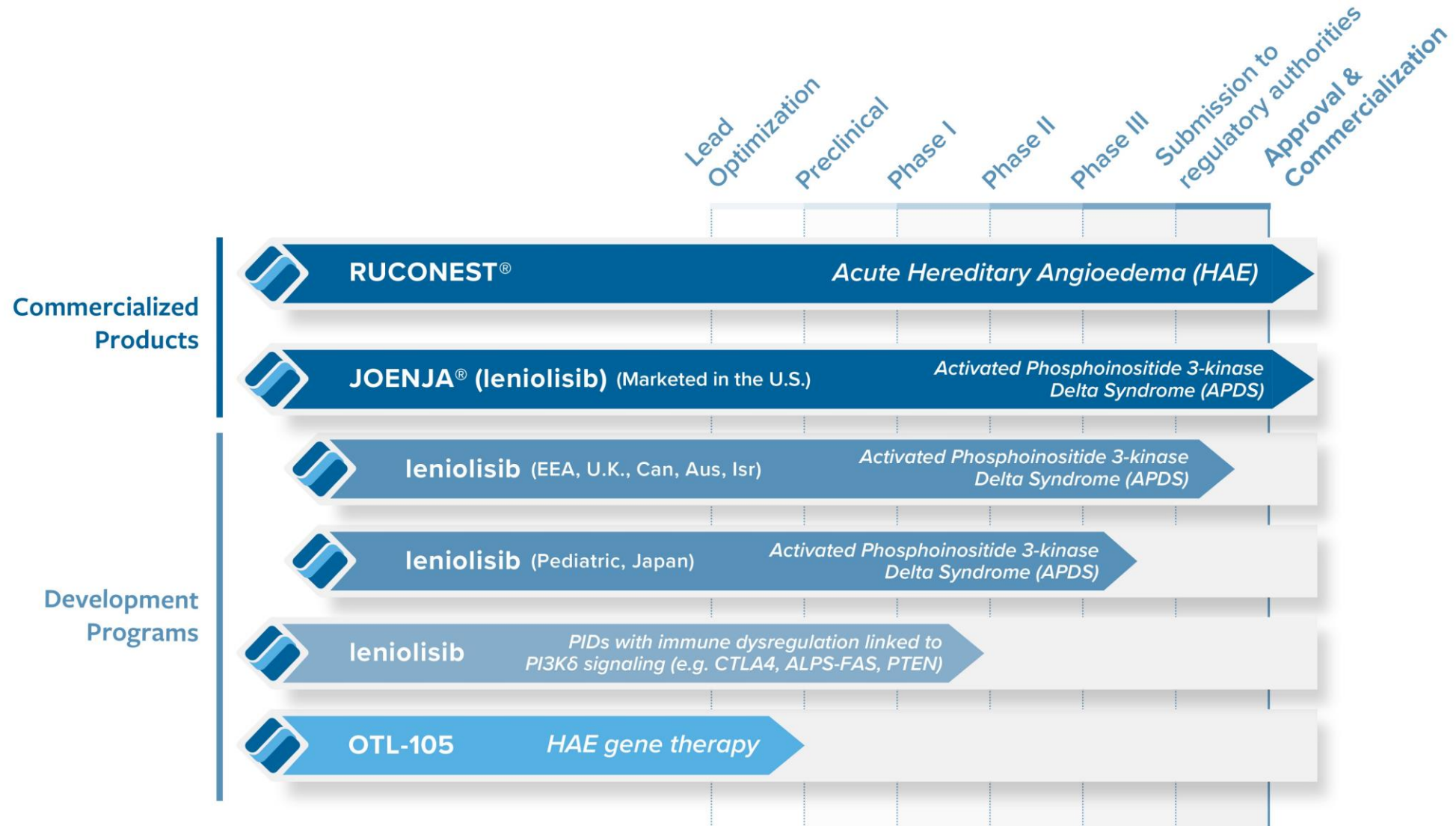


Advance internal projects and rare disease in-licensing and acquisition strategy

- ◆ Developing leniolisib for Primary Immunodeficiencies with immune dysregulation beyond APDS
- ◆ Partnership focus on early to late-stage clinical programs in immunology, hematology, respiratory and gastroenterology

*2023 financial guidance based on preliminary selected financial results that are unaudited and subject to adjustment. Pharming expects to issue full financial results for the fourth quarter and full year 2023 in March 2024. The Company has not completed its financial closing procedures for the quarter or year ended December 31, 2023 and actual results could differ from these preliminary financial results.

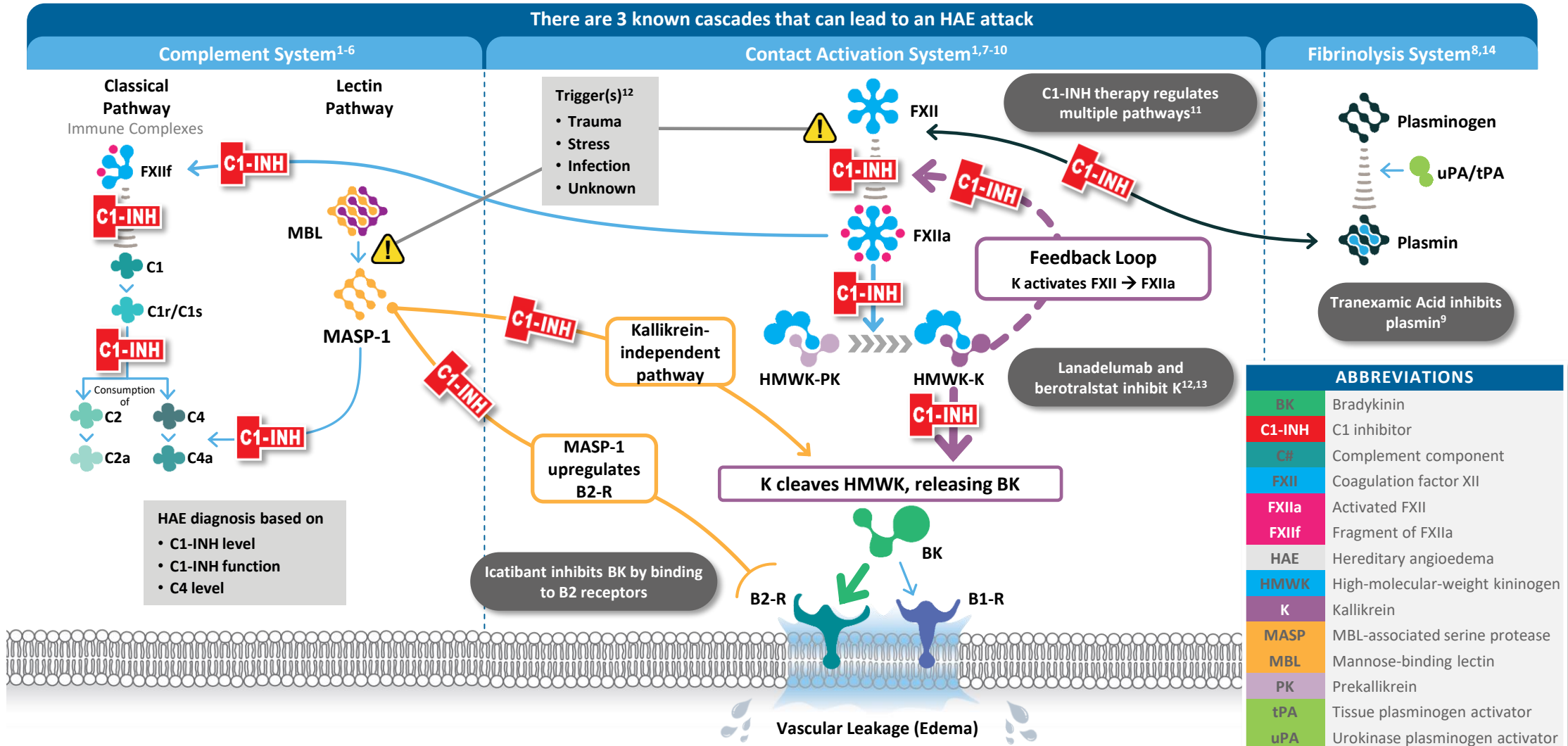
Pipeline – multiple commercial stage rare disease products



 Pharming® | **35** years

RUCONEST®

C1-INH targets the root cause of HAE



ABBREVIATIONS	
BK	Bradykinin
C1-INH	C1 inhibitor
C#	Complement component
FXII	Coagulation factor XII
FXIIa	Activated FXII
FXIIIF	Fragment of FXIIa
HAE	Hereditary angioedema
HMWK	High-molecular-weight kininogen
K	Kallikrein
MASP	MBL-associated serine protease
MBL	Mannose-binding lectin
PK	Prekallikrein
tPA	Tissue plasminogen activator
uPA	Urokinase plasminogen activator

Adapted from a clinical cascade developed in partnership with Dr. Allen Kaplan. This is a current scientific understanding of the cascades. Clinical implications are unknown.



The only recombinant treatment that targets the root cause of HAE by replacing missing or dysfunctional C1-INH



Second most prescribed product detailed for acute attacks



Well-tolerated and effective treatment option for acute hereditary angioedema (HAE) - including breakthrough attacks



97%: needed just 1 dose of RUCONEST®¹
93%: acute attacks stopped with RUCONEST® for at least 3 days²



Revenue:
FY22 \$205.6M
FY23 guidance ~US\$227M (+10%)



Strong U.S. in-market demand –
New patient enrollments up 25%
in FY23 vs. FY22



Significantly increased previous guidance of low single digit revenue growth



Performing well in leading revenue indicators in the U.S.:
active patients, vials shipped, #
physicians prescribing

Strong commitment to HAE community



Strong patient organization support since 2000

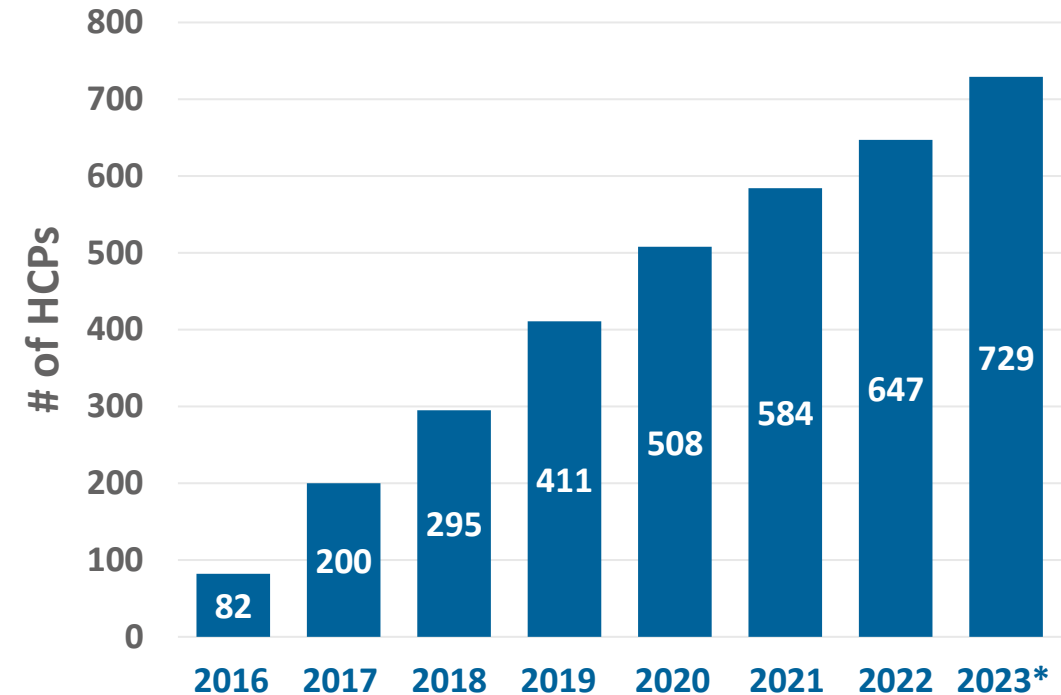


More than 720 U.S. physicians (and growing) prescribing RUCONEST®



>2,000 patients with HAE have been prescribed RUCONEST®

of unique U.S. physicians prescribing



*Data thru December 31, 2023





APDS Overview

APDS is a rare, primary immunodeficiency (PID) first characterized in 2013



Activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS)

Global prevalence estimated at 1.5 patients per million population*

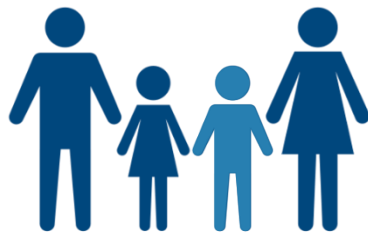
To date, Pharming has identified >840 diagnosed APDS patients in global markets targeted for commercialization*

(as of December 31, 2023)



Until now, treatments for APDS have addressed the symptoms of the disease which manifest early in childhood, but not the root cause of APDS

Without an indicated treatment specifically for APDS, physicians could only manage symptoms



The signs and symptoms of APDS vary widely, even among family members with the same genetic variant, resulting in potential delays in diagnosis and care



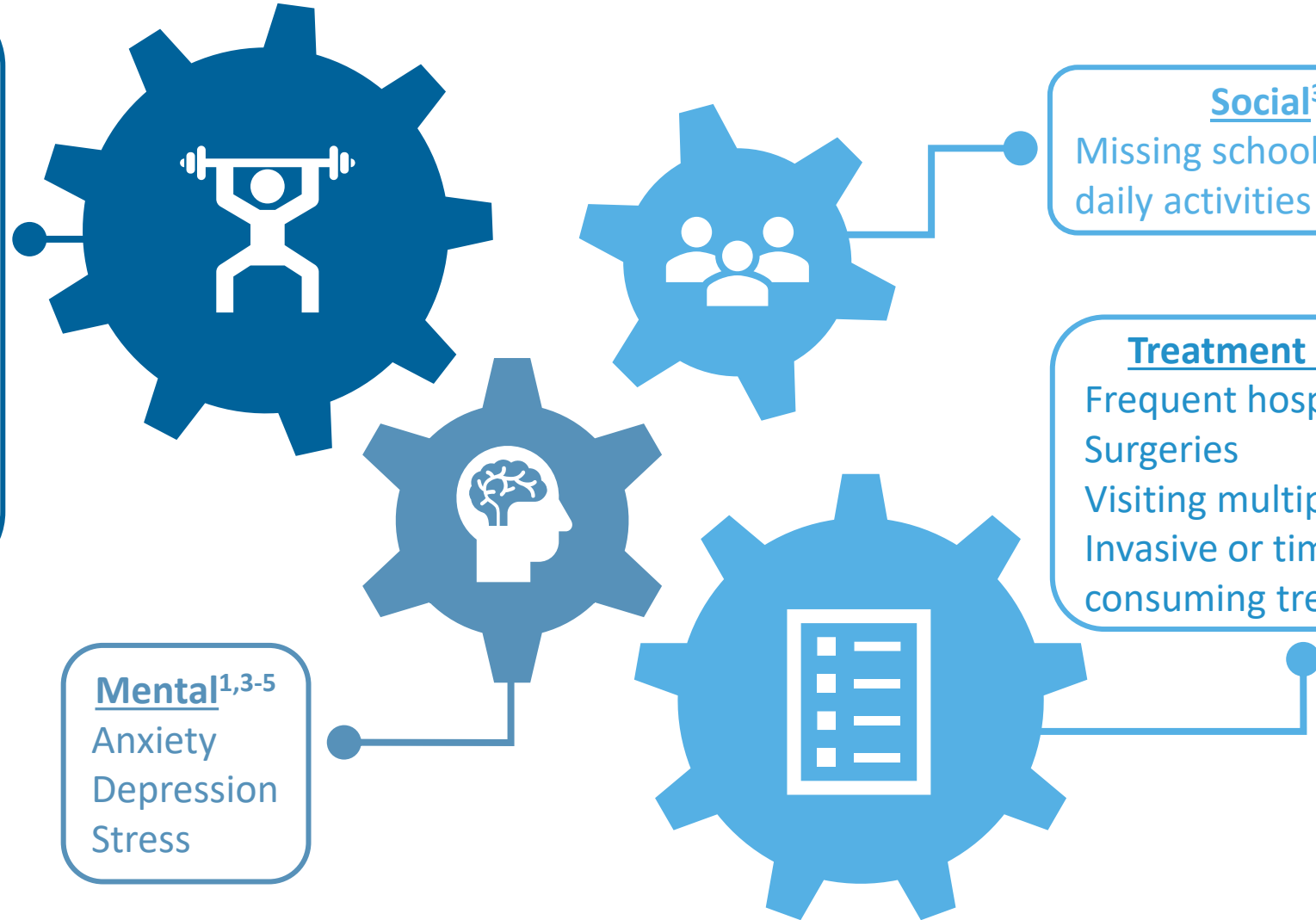
A genetic test can provide a definitive diagnosis of APDS

*Size based on estimate of 1.5 APDS patients per million (based on available literature)
>840 patients identified in global markets targeted by Pharming for commercialization
>730 of these patients are in key global launch markets in the U.S., Europe, U.K., Japan, MENA, Turkey, Asia, Canada, Australia, and Israel with total prevalence of ~2000 APDS patients

APDS can impact many facets of life

Physical^{1,2}

Frequent infections
Swollen glands
Shortness of breath
Coughing/wheezing
Chest or joint pain
Fatigue
Inability to exercise
Hearing loss
Diarrhea
Skin problems



Social^{3,4}

Missing school, work, or daily activities

Treatment Burden¹⁻⁴

Frequent hospitalizations
Surgeries
Visiting multiple doctors
Invasive or time-consuming treatments

Mental^{1,3-5}

Anxiety
Depression
Stress

APDS, activated phosphoinositide 3-kinase δ syndrome.

1. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606. 2. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218. 3. Rider NL, et al. *J Clin Immunol.* 2017;37(5):461-475.

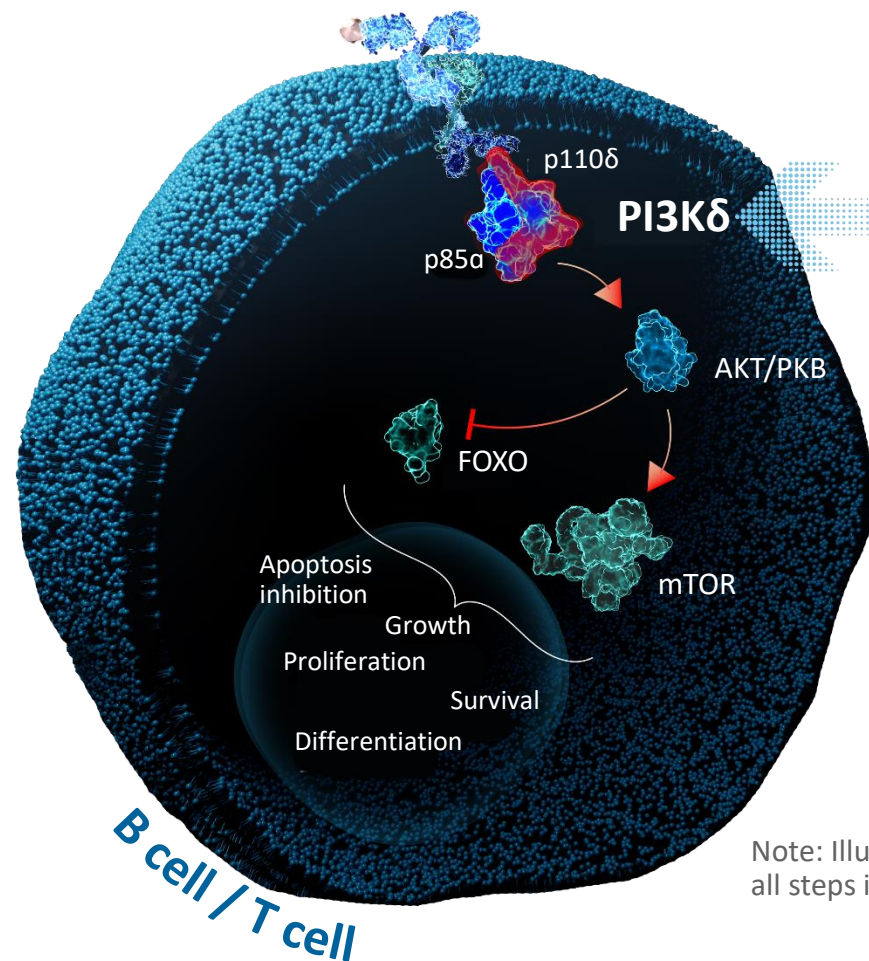
4. Jiang F, et al. *Allergy Asthma Clin Immunol.* 2015;11:27. 5. Kuburovic NB, et al. *Patient Prefer Adherence.* 2014;8:323-330.

Genetic defect leads to PI3K δ hyperactivity, disrupting immune cell balance

Hyperactive PI3K δ results in dysregulated B and T cell development¹⁻³

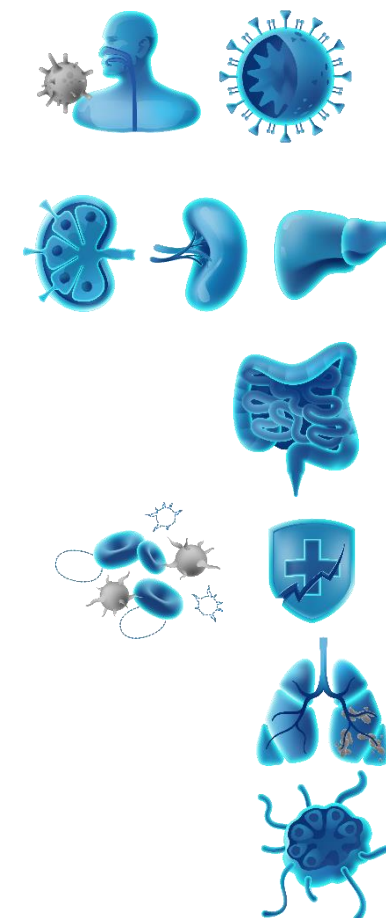


Immune imbalance leads to diverse signs and symptoms^{1,4-6}



The PI3K δ enzyme is at the beginning of a complex signaling pathway

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



Severe, recurrent, persistent infections

- Sinopulmonary
- Herpesvirus (especially EBV and CMV)

Lymphoproliferation

- Lymphadenopathy
- Splenomegaly/hepatomegaly
- Nodular lymphoid hyperplasia

Enteropathy

Autoimmunity

- Cytopenias
- Autoimmune disorders
- Autoinflammatory disorders

Bronchiectasis

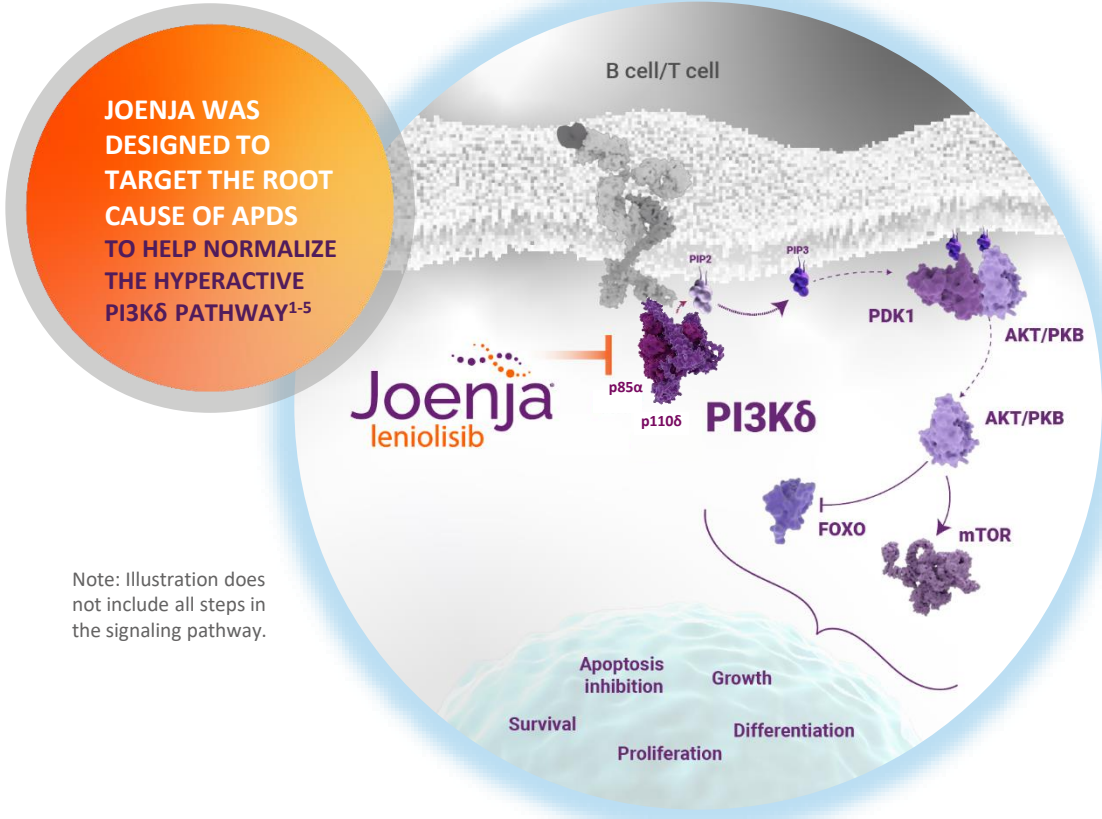
Lymphoma

FOXO, forkhead box O; mTOR, mammalian target of rapamycin; PI3K δ , phosphoinositide 3-kinase delta; PKB, protein kinase B.

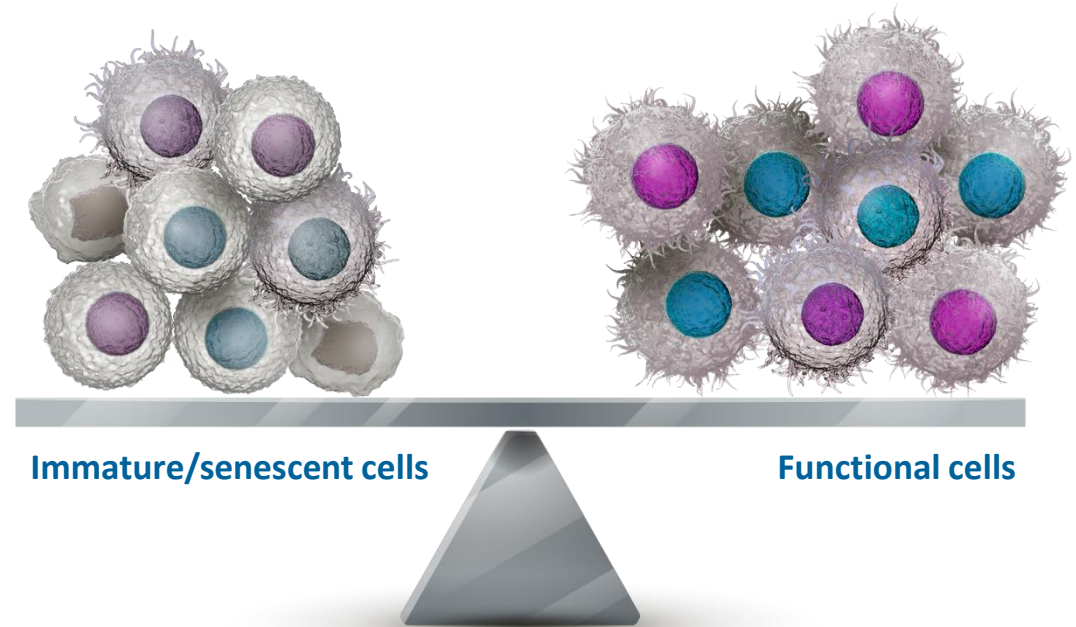
1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Fruman DA, et al. *Cell.* 2017;170(4):605-635. 3. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol.* 2003;3(4):317-330. 4. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606. 5. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218. 6. Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.



Joenja[®] (leniolisib)



Joenja[®] facilitates a balanced PI3Kδ pathway to support proper immune function⁶



This is a graphical representation of a complex biological process.

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.
 1. Fruman DA, et al. *Cell*. 2017;170(4):605-635. 2. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol*. 2003;3(4):317-330. 3. Hoegenauer K, et al. *ACS Med Chem Lett*. 2017;8(9):975-980. 4. Rao VK, et al. *Blood*. 2017;130(21):2307-2316. 5. Rao VK, et al. *Blood*. 2023;141(9):971-983. 6. Nunes-Santos CJ, et al. *J Allergy Clin Immunol*. 2019;143(5):1676-1687.

U.S. launch of Joenja®: a much-needed treatment for patients with APDS and another win for Pharming

Joenja® (leniolisib) is a prescription medicine that is used to treat activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adults and pediatric patients 12 years of age and older

In a randomized placebo-controlled trial of patients with APDS

- Joenja® met both primary end points with significant efficacy results
- Demonstrated significant improvement in other secondary and exploratory parameters



There were no drug-related serious adverse events or study withdrawals in Joenja® trials

Joenja® reported additional findings from an ongoing long-term open-label extension study interim analysis: reductions/discontinuations in IRT and reduction in infection rates

Extension study interim analysis demonstrated safety consistent with the randomized, controlled trial. We continue to collect observational long-term data on lymphadenopathy, naive B cells and IgM

- ◆ Strong commercial execution 9 months into U.S. launch
- ◆ Continue to enroll patients and add patients on paid therapy in 4Q23
92 enrollments, of which 81 patients on paid therapy at end 4Q23
- ◆ APDS Assist program ensures eligible patients have access to therapy
- ◆ FY23 revenue guidance ~US\$18M
- ◆ Significant focus on genetic family testing
- ◆ Validation studies to confirm which variants of uncertain significance (VUS)
should be classified as APDS to complete in 4Q24, focused on >1100 patients
identified in the U.S. with VUSs





Europe – CHMP opinion on MAA expected 1Q24 (approval ~ 2 months later)*



Japan clinical study – 1st patient enrolled Aug 2023



Pediatric study for 4 to 11 years: enrollment majority complete



Named patient program ongoing



UK – MHRA filing expected 1Q24**



AUS, CAN, ISR submissions under regulatory review

CAN & AUS approval 2Q24***
ISR approval 1H24***



Pediatric study for 1 to 6 years ongoing (first patient dosed)



Leniolisib development for PIDs with immune dysregulation (start 1st Phase 2 trial 2Q24)

* Received CHMP Day 180 second list of outstanding issues in November 2023. CHMP rescheduled the Ad-hoc Expert Group (AEG) meeting to the end of November 2023. Approval is subject to positive outcomes of the EMA CHMP review.

** Pharming intends to file an MAA through the International Recognition Procedure (IRP). MHRA would have 110 days from the date the IRP submission is validated to review and issue its decision.

*** Subject to positive AUS, CAN, ISR decisions



Medical education to raise awareness of APDS and share leniolisib data

- ◆ Conferences and congresses
- ◆ Abstracts
- ◆ Publications



Genetic testing

- ◆ Sponsored, no-cost testing program



- ◆ Genetic counselors to assist with testing and reviewing results
- ◆ Partnering with genetic testing companies to identify previously and newly diagnosed APDS patients



Family testing

- ◆ Inherited disease* but most APDS patients do not have diagnosed family members
- ◆ Patients may not be aware of genetics or have access to specialty physicians
- ◆ Cooperating with clinicians to encourage family testing
- ◆ Patients can request a genetic test through partner Genome Medical (if suspect APDS for themselves or family members)
- ◆ Reduces barrier for easier testing of those suspected with APDS

*APDS genes are autosomal dominant meaning there is a 50% chance that a blood relative of an APDS patient may also carry that gene and in turn have APDS.

Helping diagnose APDS patients: Variant of Uncertain Significance (VUS) resolution

Genetic testing frequently leads to inconclusive results - previously unseen genetic variants:



Patients have clinical symptoms compatible with APDS, but genetic variant test is inconclusive



Frustrating for patients and clinicians

Need to determine if Variant of Uncertain Significance (VUS) causes APDS

Pharming initiatives/partnerships to resolve VUSs



Variant Curation

- ◆ ClinGen expert panels develop gene/disease specific thresholds and criteria for classifying variants
- ◆ Partnership with Genomenon to develop Genomic Landscape (comprehensive, systematic review of all published variant data)



Functional testing

- ◆ Improve access to directly measure PI3K pathway activity in patient blood samples
- ◆ Sharing of results via public databases (ClinVar)



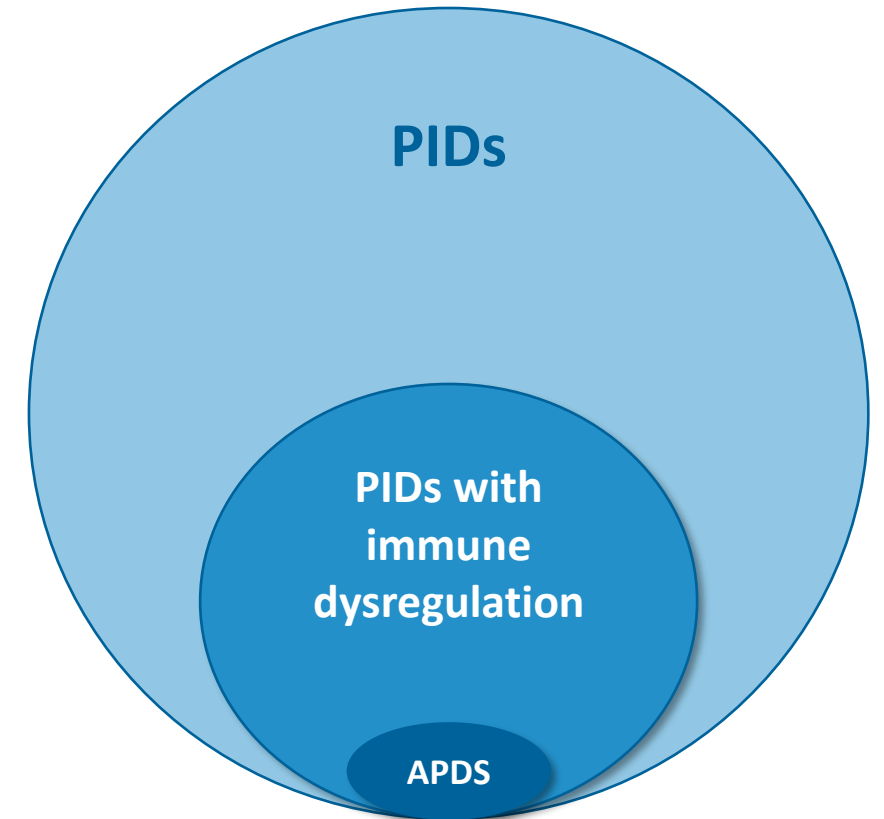
Multiplexed assays of variant effect (MAVE)

- ◆ Test nearly all possible variants in a single experiment
- ◆ Generate variant effect map, including variants already found and those not yet found (proactive)

PIDs are a broad group of disorders¹ with key features:

- ❖ Genetic basis, i.e., not secondarily caused by another disease
'Inborn Errors of Immunity' (IEI) is used interchangeably with PID
- ❖ An increased risk of infection may be the predominant manifestation, due to poor immune system function
- ❖ PID patients may have a predominance of immune dysregulation, for example: lymphoproliferation and autoimmunity²

APDS is an example of a PID with immune dysregulation

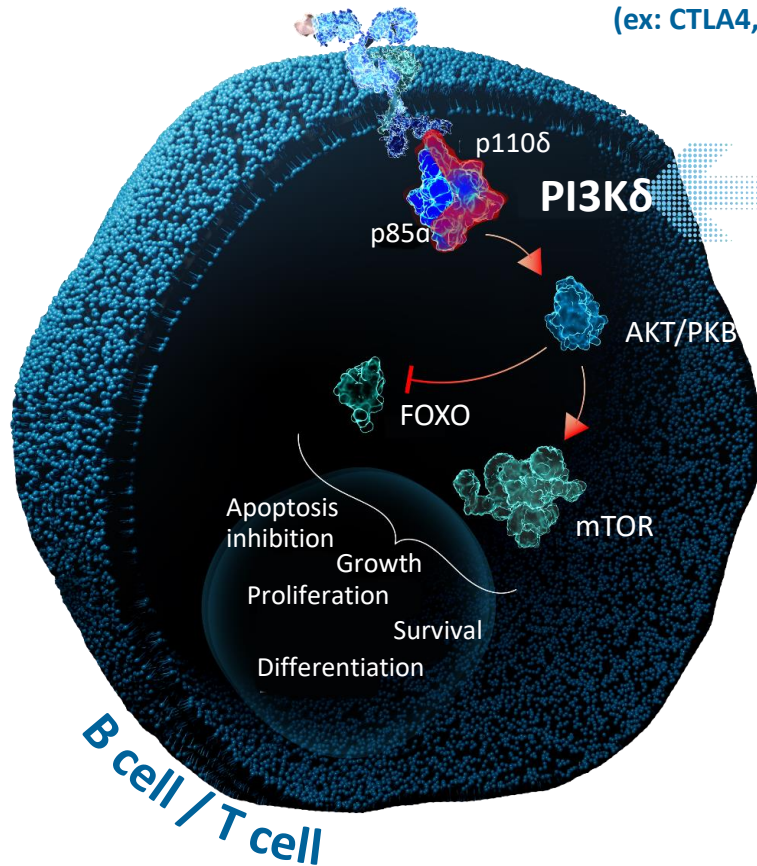


Not to scale with population sizes

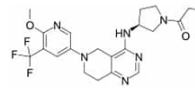
1. Bousfiha et al 2022 IUIS categorization
2. Chan and Torgerson 2020 Curr Opin Allergy Clin Immunol 20(6): 582-590

Given importance of PI3K δ in B & T cells, immune dysregulation in PIDs can occur via alterations in PI3K δ signaling

Altered PI3K δ signaling can occur in multiple PID genetic disorders beyond APDS (ex: CTLA4, PTEN, FAS)



leniolisib



High unmet medical need
- no approved therapies other than Joenja® (leniolisib) for APDS: SOC immunosuppressives (e.g. rapamycin) have limited efficacy and significant tolerability concerns

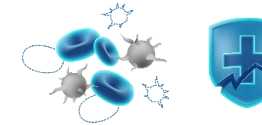
Note: Illustration does not include all steps in the signaling pathway.

Clinical manifestations, disease onset and severity similar to APDS



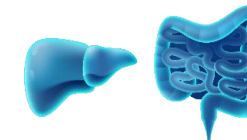
Lymphoproliferation

- Lymphadenopathy
- Splenomegaly/hepatomegaly
- Nodular lymphoid hyperplasia



Autoimmunity

- Cytopenias
- Autoimmune disorders
- Autoinflammation



GI Disease

- Autoimmune enteropathy
- Nodular regenerative hyperplasia



Pulmonary Disease

- GLILD
- Bronchiectasis



Infections

- Sinopulmonary
- Herpesvirus



Lymphoma

FOXO, forkhead box O; mTOR, mammalian target of rapamycin; PI3K δ , phosphoinositide 3-kinase delta; PKB, protein kinase B.

1. Lucas CL, et al. *Nat Immunol.* 2014;15(1):88-97. 2. Fruman DA, et al. *Cell.* 2017;170(4):605-635. 3. Okkenhaug K, Vanhaesebroeck B. *Nat Rev Immunol.* 2003;3(4):317-330. 4. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606. 5. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218. 6. Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.

- ◆ Based on APDS experience, leniolisib has potential to be an effective & tolerable chronic treatment approach for PIDs with immune dysregulation
- ◆ Leniolisib, by reducing PI3K δ activity, should help rebalance immune dysregulation in PIDs, positively impacting clinical manifestations including lymphoproliferation and autoimmunity
- ◆ Initial development in PID genetic disorders with immune dysregulation linked to PI3K δ signaling in lymphocytes with similar clinical phenotypes to APDS, e.g. PTEN¹, ALPS-FAS², CTLA4³
 - Epidemiology suggests prevalence of ~5/million
 - FDA review / feedback received on clinical trial plans
- ◆ Phase 2 proof of concept clinical trial to commence 2Q 2024

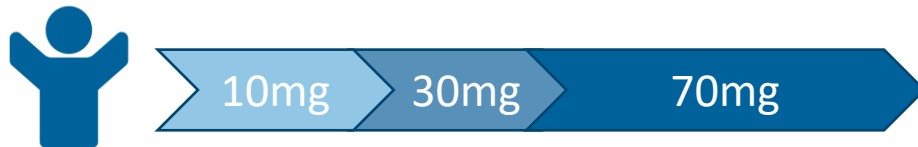
1. Eissing M, Ripken L, Schreibelt G, Westdorp H, Ligtenberg M, Netea-Maier R, Netea MG, de Vries IJM, Hoogerbrugge N. PTEN Hamartoma Tumor Syndrome and Immune Dysregulation. *Transl Oncol.* 2019;12(2):361-367

2. Rao VK and Oliveria JB. How I treat autoimmune lymphoproliferative syndrome. *Blood* 2011; 118(22):5741-51

3. Westerman-Clark et al 2021; Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. *J Allergy Clin Immunol.* 2018;142(6):1932-1946

Phase 2 proof of concept clinical trial – single arm, open-label, dose range-finding study

Ph2 (N=12)



- Primary: Safety & Tolerability
- Secondary/Exploratory: PK/PD, efficacy measures
- 10/30/70 mg: 4/4/12 wks treatment, respectively
- Pick Best Dose regimen for Ph3



National Institute of
Allergy and
Infectious Diseases

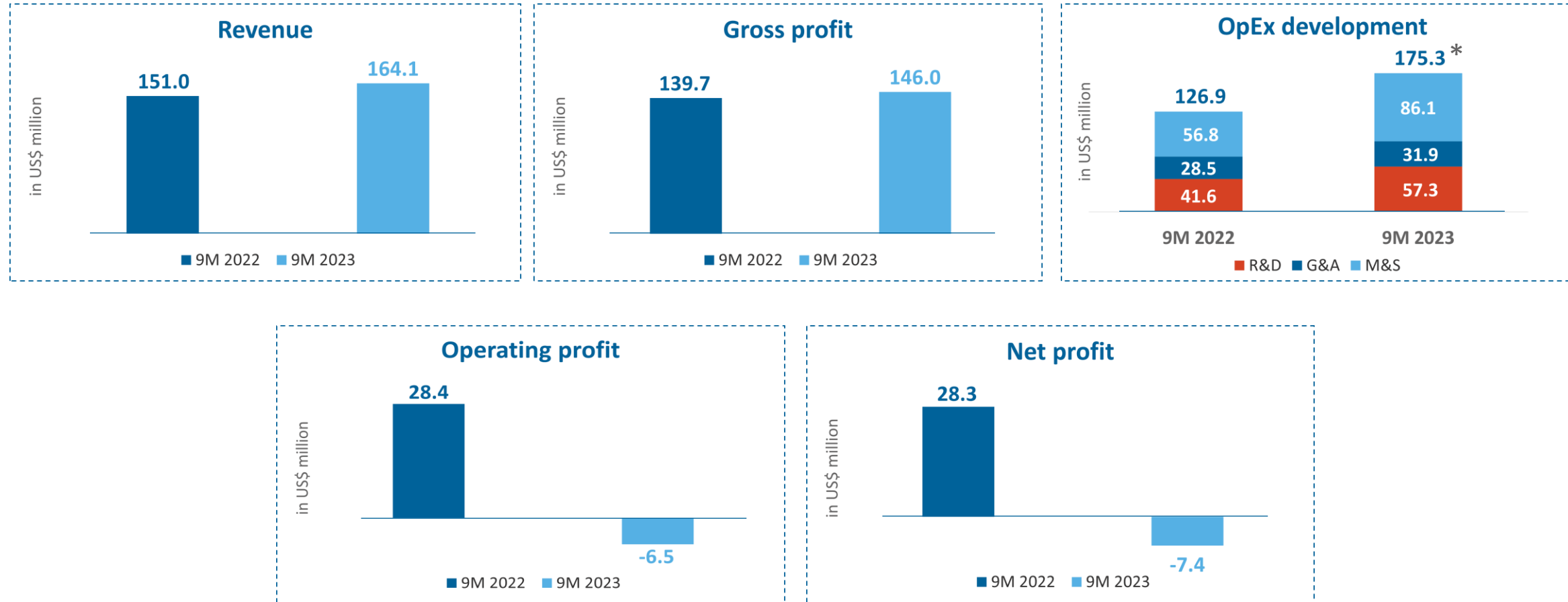
Lead Investigator: Gulbu Uzel, M.D., Senior
Research Physician

Co-Investigator: V. Koneti Rao, M.D., FRCPA,
Senior Research Physician
Primary Immune Deficiency Clinic (ALPS
Clinic)



Financials and Outlook

Financial highlights: 9M 2023 vs 9M 2022



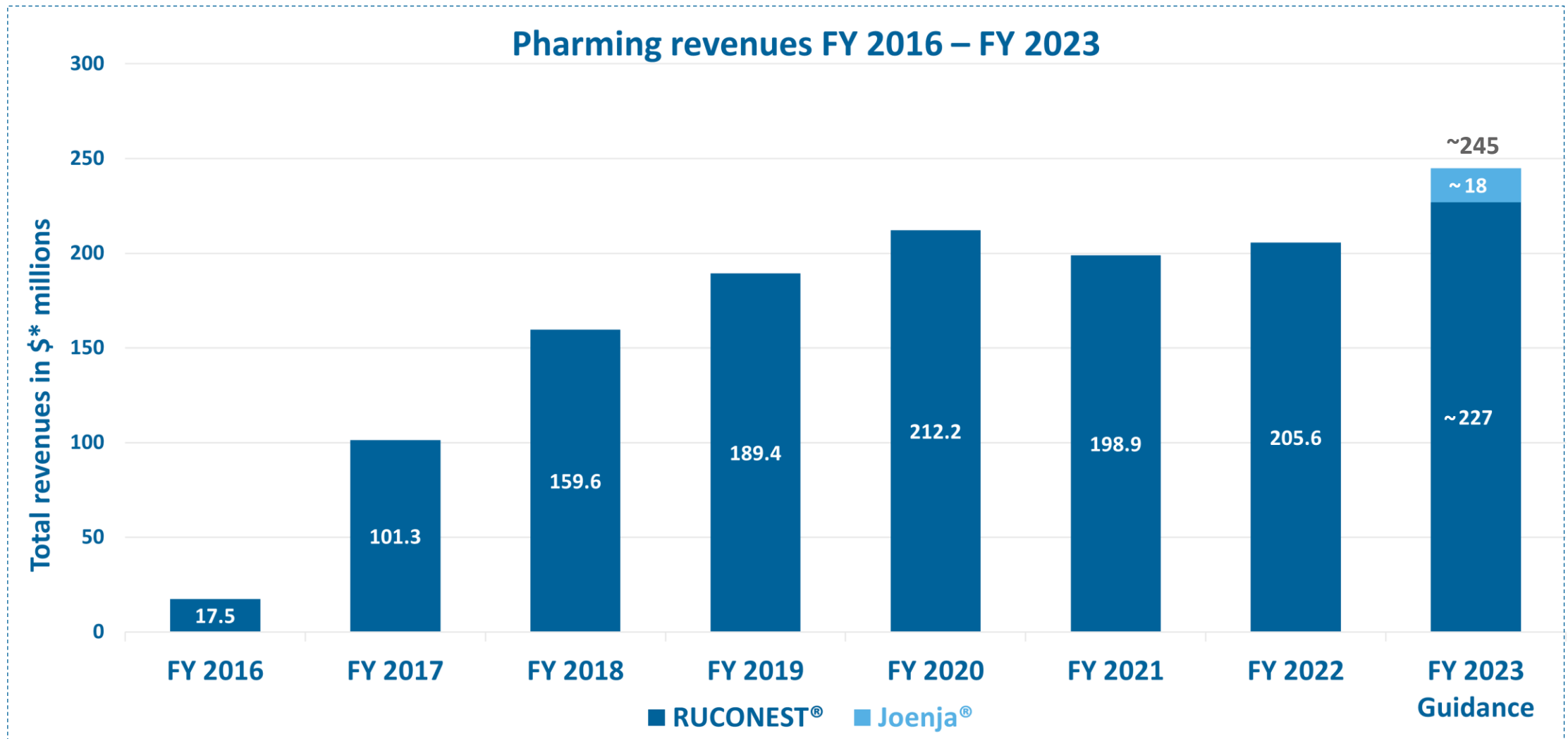
*2Q23 marketing and sales expenses includes US\$10M milestone payments paid

	FY 2023 Revenue Guidance (preliminary and unaudited)*	% Growth vs. FY 2022
RUCONEST®	~ US\$227 million	10%
Joenja®	~ US\$18 million	N/A
Total	~ US\$245 million	19%

- ◆ RUCONEST® guidance increased from previous low single digit revenue growth
- ◆ Cash and cash equivalents, together with restricted cash and marketable securities, are expected to increase to US\$215.0 million at the end of 2023, compared to US\$199.2 million at the end of 3Q 2023 and US\$208.7 million at the end of 2022

*2023 financial guidance based on preliminary selected financial results that are unaudited and subject to adjustment. Pharming expects to issue full financial results for the fourth quarter and full year 2023 in March 2024. The Company has not completed its financial closing procedures for the quarter or year ended December 31, 2023 and actual results could differ from these preliminary financial results.

RUCONEST® and Joenja® driving revenue growth



- From FY 2016 – FY 2020 Pharming Group reported earnings in EUR. Revenues during this time frame have been converted to USD. In 2021, Pharming Group began reporting earnings in USD.
- 4Q 2020 and 1Q 2021 quarterly fluctuations and volatility from COVID-19
- During the first quarter 2020, Pharming restructured and expanded its U.S. salesforce. 2023 was the first full year post-pandemic following this restructuring and expansion.
- 2023 financial guidance based on preliminary selected financial results that are unaudited and subject to adjustment. Pharming expects to issue full financial results for the fourth quarter and full year 2023 in March 2024. The Company has not completed its financial closing procedures for the quarter or year ended December 31, 2023 and actual results could differ from these preliminary financial results.



Significantly increased RUCONEST® 2023 revenue guidance to ~US\$227M (10% growth)



Joenja® launched early April 2023 – 81 patients on paid therapy & expect ~US\$18M revenues in 2023



Leniolisib CHMP opinion expected in 1Q24, marketing authorization in Europe ~2 months later*



Additional potential leniolisib regulatory approvals in 2024 – UK, CAN, AUS, ISR**



Continued operating cost investments to accelerate future growth



Developing leniolisib for additional PIDs genetic disorders with higher prevalence
Phase 2 clinical trial in PIDs with immune dysregulation linked to PI3Kδ to start 2Q 24



Investment and continued focus on in-licensing or acquisitions of early to late-stage rare disease clinical programs in immunology, hematology, respiratory and gastroenterology

* Approval is subject to positive outcomes of the EMA CHMP review.

** Pharming intends to file an MAA in the UK through the International Recognition Procedure (IRP). Subject to positive AUS, CAN, ISR decisions.



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Appendix

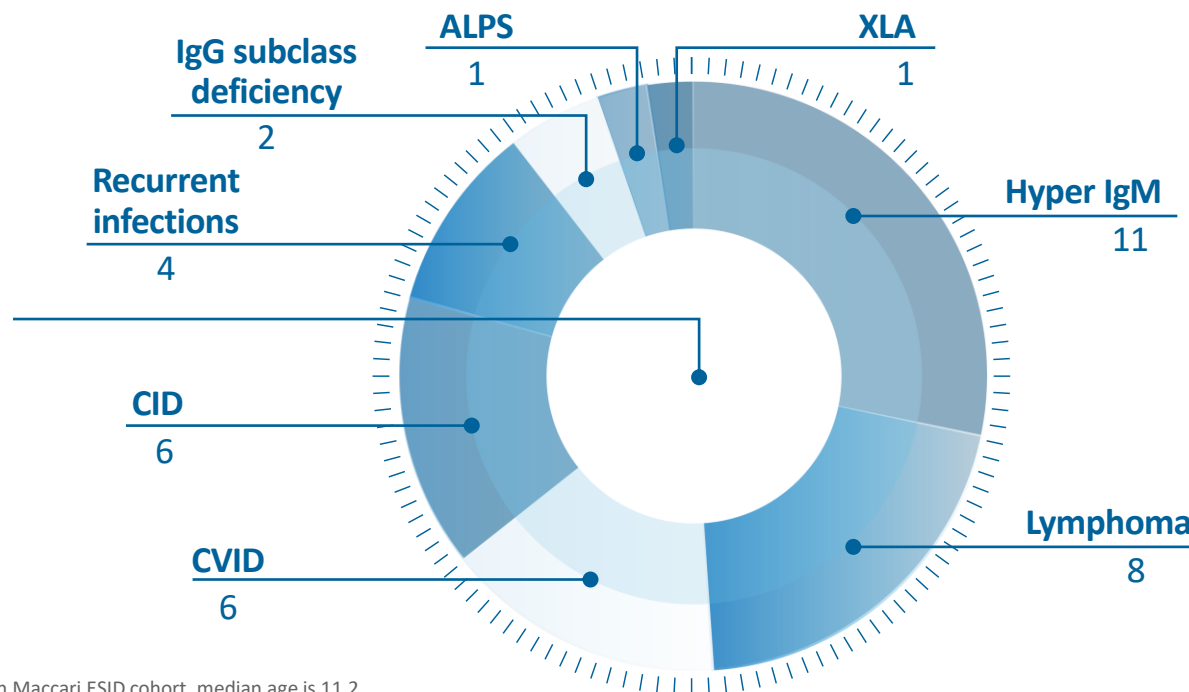
Heterogeneous, evolving symptomology can often lead to missed diagnoses

Timeline of the most common pathologies* seen in APDS¹⁻⁴

Median age at diagnosis:
12 years (7-year median diagnosis delay)



APDS has often been diagnosed as another PI or condition, causing delays in diagnosis¹



Improved identification of symptoms, increased genetic testing, and earlier diagnosis are needed

*Pathologies can occur at any time.

[†]In Elkaim APDS2 cohort, median age of bronchiectasis is 13; in Maccari ESID cohort, median age is 11.2.

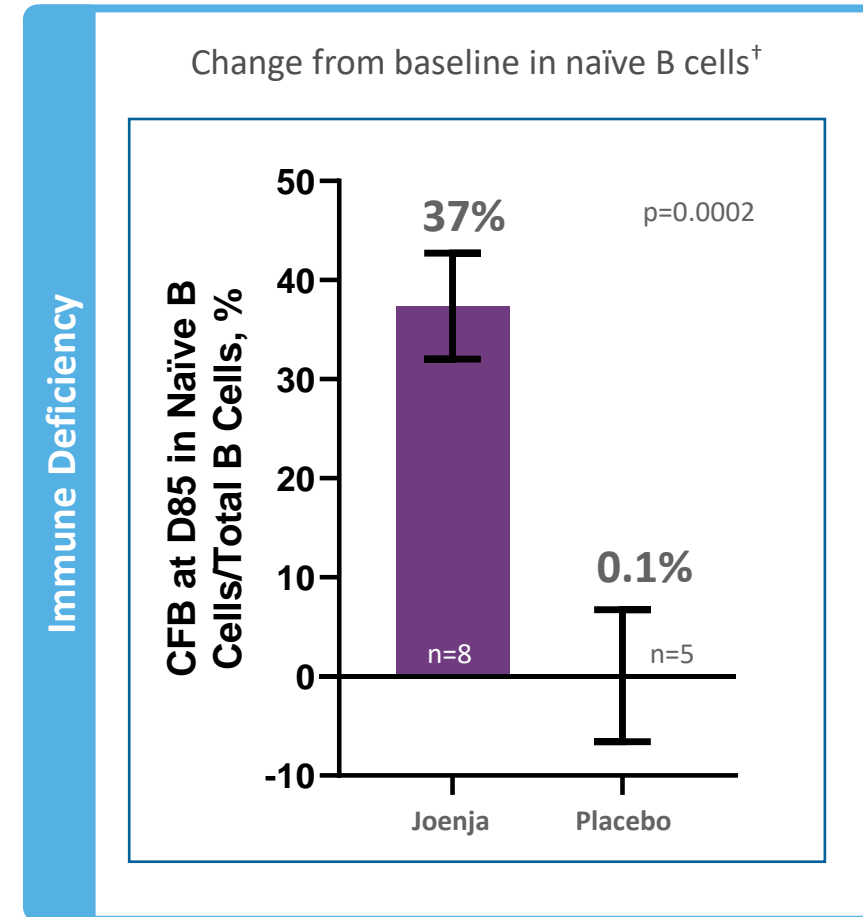
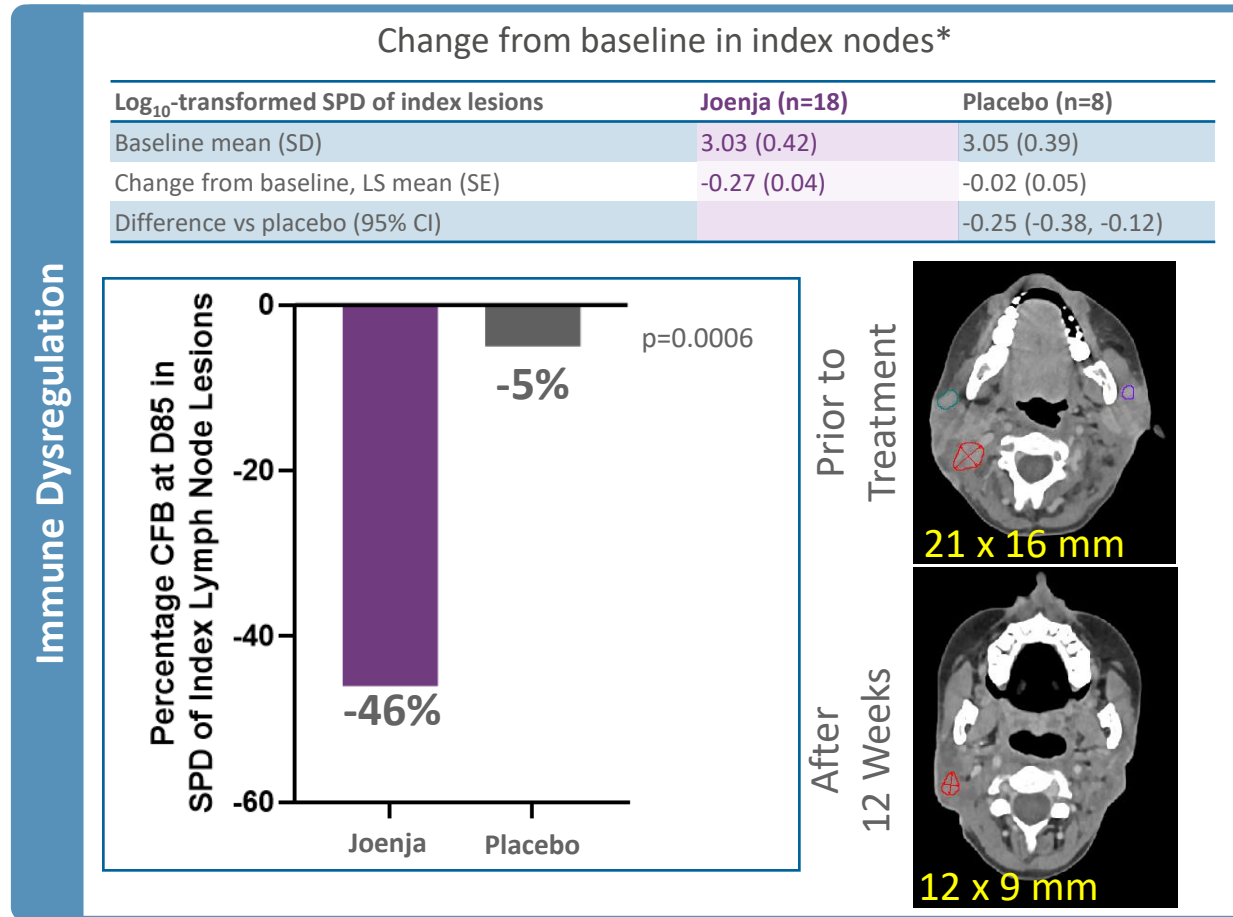
[‡]No median ages are available for these manifestations.

ALPS, autoimmune lymphoproliferative syndrome; CID, combined immunodeficiency; CVID, common variable immune deficiency; ESID, European Society for Immunodeficiencies; HIGM, hyper immunoglobulin M syndrome; IgG, immunoglobulin G; PI3Kδ, phosphoinositide 3-kinase delta; XLA, X-linked agammaglobulinemia.

1. Jamee M, et al. *Clin Rev Allergy Immunol.* 2020;59(3):323-333. 2. Maccari ME, et al. *Front Immunol.* 2018;9:543. 3. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218.e9. 4. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606.

Joenja® addresses the underlying cause of APDS to help restore immune balance – Phase 3 co-primary endpoints

At 12 weeks Joenja® decreased lymphadenopathy and increased naïve B cells



Data were analyzed using an ANCOVA model with treatment as a fixed effect and baseline as a covariate. Use of glucocorticoids and IRT at baseline were both included as categorical (Yes/No) covariates. Baseline is defined as the arithmetic mean of the baseline and D1 values when both are available, and if either baseline or the D1 value is missing, the existing value is used. P-value is 2-sided. Least square means are graphed. Error bars are standard error of the mean.

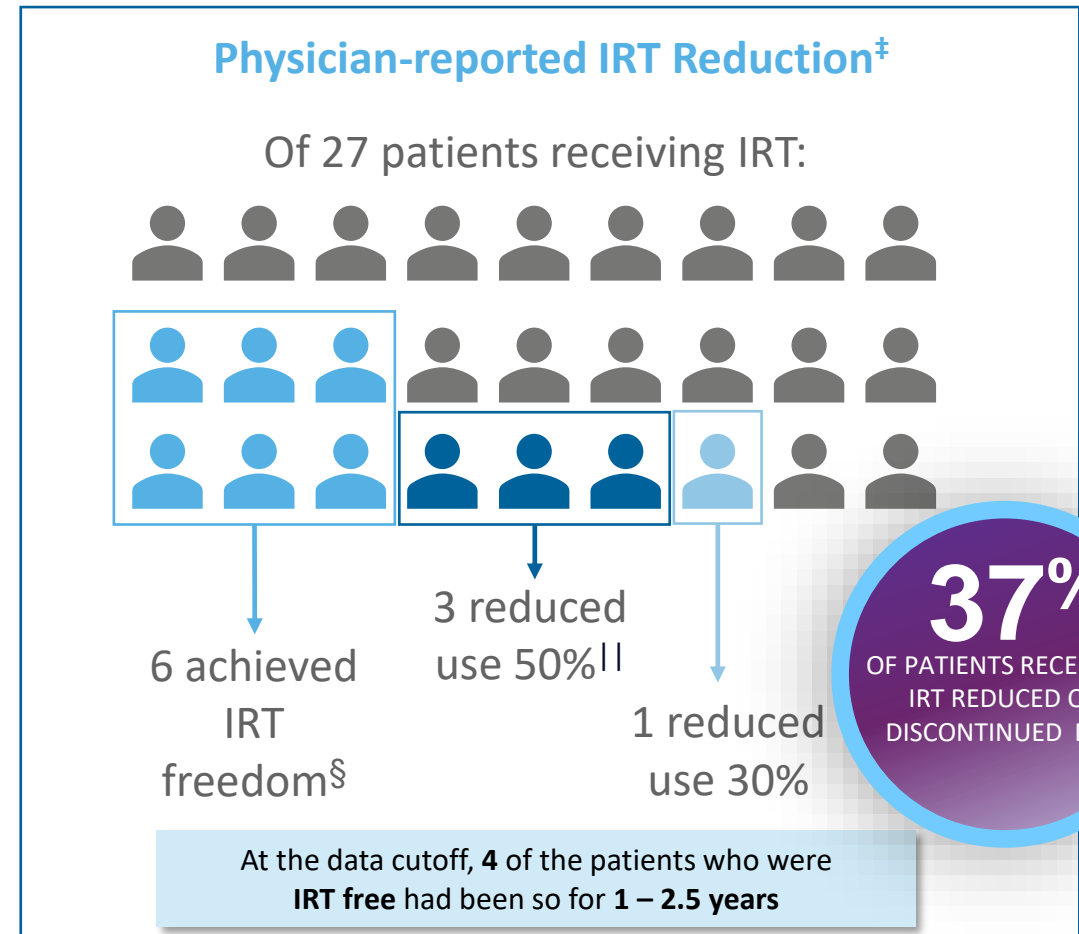
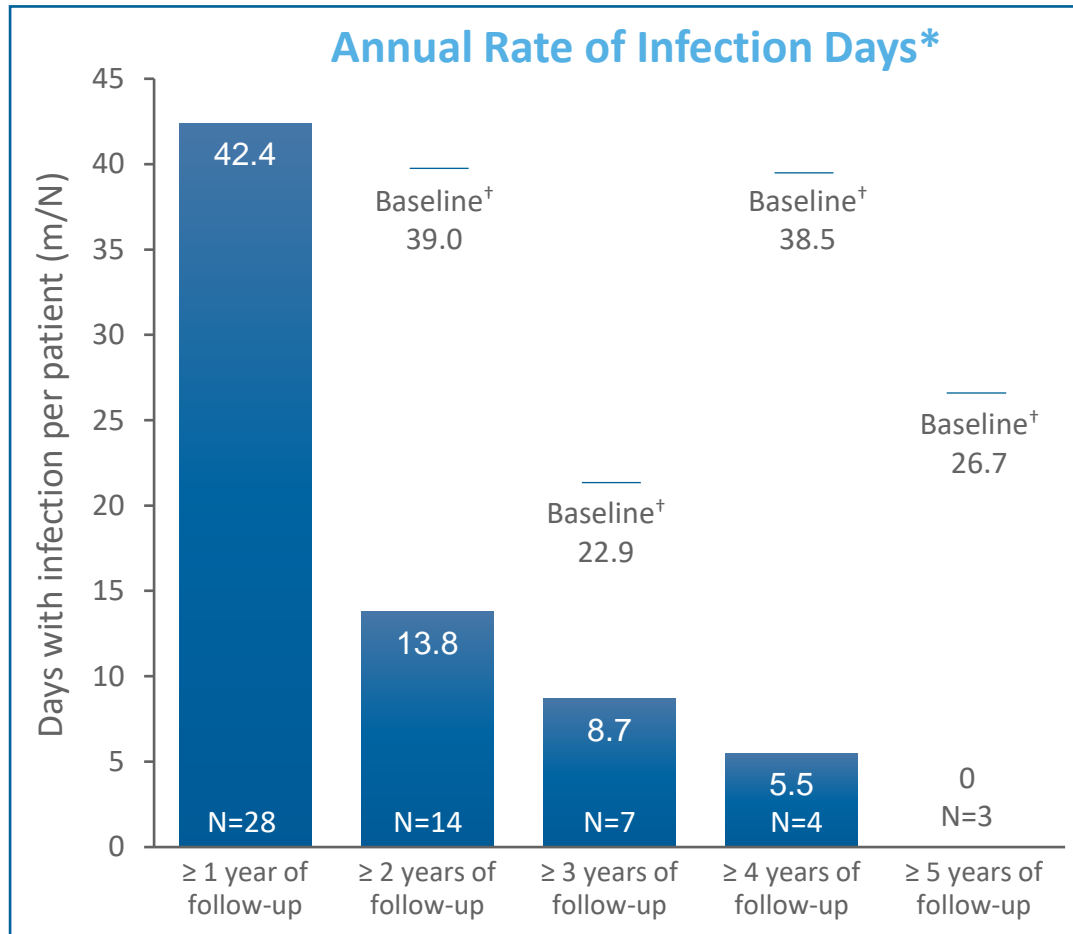
*The analysis excluded 2 patients from each treatment group due to protocol deviations and 1 Joenja patient having complete resolution of the index lesion identified at baseline.

†Out of 27 patients in the PD analysis set, 13 patients met the analysis requirements, including having a percentage of <48% of naïve B cells at baseline, to form the B-PD analysis set.

Joenja [package insert]. Leiden, The Netherlands: Pharming Technologies B.V.; 2023.

Please see Important Safety Information and full Prescribing Information available at joenja.com

Open-label extension interim analysis of days spent with infections and IRT reduction

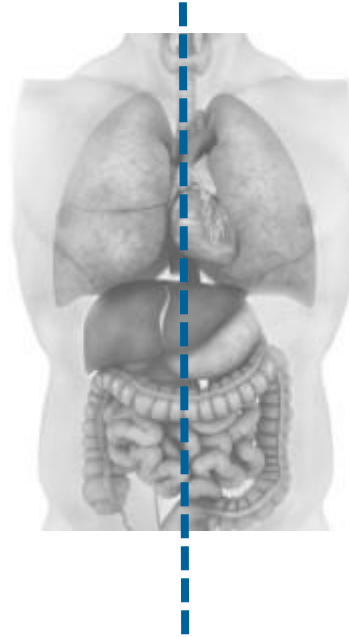


Although safety was the primary objective of the open-label study, this post hoc analysis from the open-label study was not powered to provide any statistical significance of efficacy and therefore no conclusions should be drawn.

*Infections that developed during the study were reported as adverse events. Investigators were requested to inquire about signs and symptoms of infections at each visit, with a particular focus on bacterial enterocolitis. Patients were not provided an infection diary to document infections occurring between visits. One patient was excluded from the analysis due to an incorrect year that was recorded for an infection.
 †Baseline infections are each group's year 1 annual rate of infections. N values changed because patients were in the OLE for different lengths of time. ‡Data on concomitant medication usage was reported at each patient visit. §One patient had a subsequent one-time dose. ||One patient achieved IRT freedom for 3 months but subsequently restarted IRT.
 Rao VK, et al. Poster presented at: 64th Annual American Society of Hematology Annual Meeting; December 10-13, 2022; New Orleans, LA.
 Please see Important Safety Information and full Prescribing Information available at joenja.com

Immune Deficiency

- Antimicrobial prophylaxis
- Immunoglobulin replacement therapy



Immune Dysregulation

- Corticosteroids
- Other immunosuppressants
- mTOR inhibitors

None of these therapies are FDA-approved for APDS treatment

Hematopoietic stem cell transplant

APDS, activated phosphatidylinositol 3-kinase δ syndrome; IRT, immunoglobulin replacement therapy; mTOR, mammalian target of rapamycin; PI, primary immunodeficiency; PIRD, primary immune regulatory disorder.

1. Coulter TI, et al. *J Allergy Clin Immunol.* 2017;139(2):597-606. 2. Elkaim E, et al. *J Allergy Clin Immunol.* 2016;138(1):210-218. 3. Chan AY, et al. *Front Immunol.* 2020;11:239. 4. Chinn IK, et al. *J Allergy Clin Immunol.* 2020;145(1):46-69.

Pivotal Trial - Part 1: Dose-finding^{1,2}



Nonrandomized, open-label, dose-escalating



6 patients with APDS



12 weeks



10 mg, 30 mg, 70 mg bid (4 weeks each dose)



70 mg bid selected for Part 2

Pivotal Trial - Part 2: Efficacy & Safety Evaluation³



Randomized, triple-blinded, placebo-controlled



31 patients with APDS (21 Joenja[®], 10 placebo)



12 weeks



70 mg bid



Co-primary efficacy end points

- Change from baseline in log¹⁰-transformed SPD of index lesions
 - Also assessed as % change
- Change from baseline in percentage of naïve B cells out of total B cells

Secondary and exploratory end points
Safety

Open-label extension study^{4,5}



Nonrandomized, open-label, long-term study



- 35 patients with APDS from Parts 1 and 2
- 2 patients with APDS previously treated with investigational PI3Kδ inhibitors



Ongoing



70 mg bid



Long-term safety, tolerability, efficacy, and pharmacokinetics

bid, twice a day; PI3Kδ, phosphoinositide 3-kinase delta; SPD, sum of product diameters

1. Rao VK, et al. *Blood*. 2017;130(21):2307-2316. 2. NCT02435173. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02435173>. Updated May 6, 2015. Accessed March 13, 2023. 3. Rao VK, et al. *Blood*. 2023;141(9):971-983.

4. NCT02859727. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02859727>. Updated October 31, 2022. Accessed March 3, 2023. 5. Data on file. Pharming Healthcare Inc; 2022.

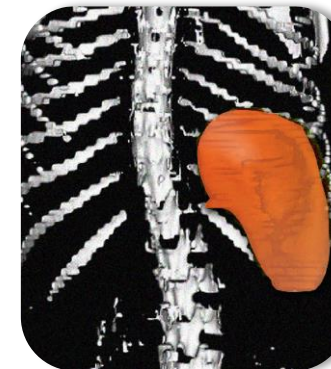
Secondary endpoint: Significant reductions in spleen size by 2D and 3D analysis compared to placebo

- 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. As individual results vary, images may not be representative of all patients.

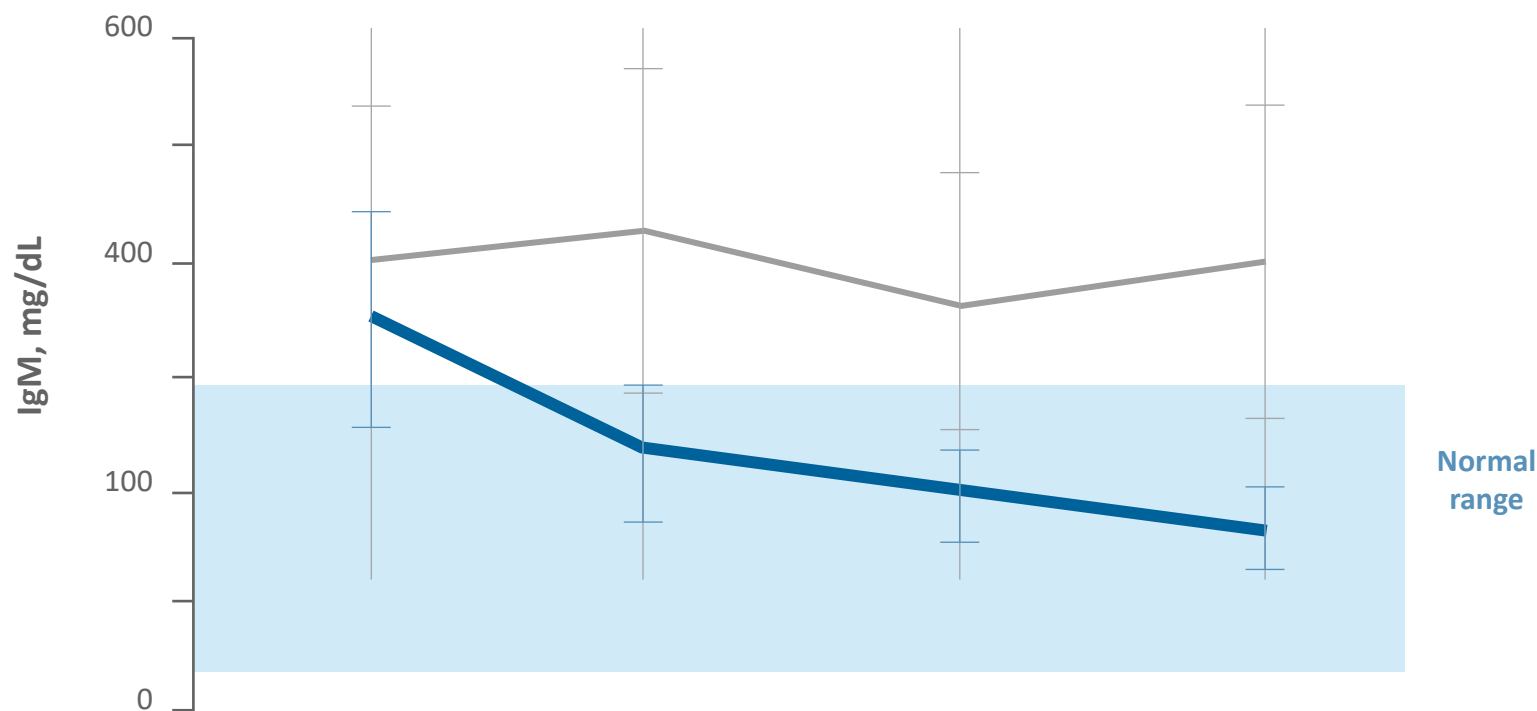
Rao VK, et al. Blood. 2023;141(9):971-983.

*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 IV 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.

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

Mean serum IgM rapidly reduced to within normal limits



- 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 week 12 levels remained stable or elevated, with 0% returning to within normal limits

		Baseline	Week 4	Week 8	Week 12
Joenja [®]	n	21	20	21	21
Placebo	n	10	10	10	10

Error bars are standard error of the mean. Safety analysis set (N=31) shown. Blue box indicates IgM normal range.

Soluble biomarkers, including IgM, were prespecified exploratory endpoints 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.

Rao VK, et al. Blood. 2023;141(9):971-983

Phase 3 Trial^{1,2}

Adverse reactions reported by ≥2 patients treated with Joenja 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)
Pyrexia	2 (10)	0
Back pain	2 (10)	0
Neck pain	2 (10)	0
Alopecia	2 (10)	0

- Study drug-related AEs occurred in 8 patients; the incidence was lower in the Joenja arm (23.8%) than in the placebo arm (30.0%)
- No AEs led to discontinuation of study treatment

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.

*Includes dermatitis atopic and eczema. [†]Includes tachycardia and sinus tachycardia.

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event.

1. Rao VK, et al. Blood. 2023;141(9):971-983. 2. Joenja [package insert]. Leiden, The Netherlands: Pharming Technologies B.V.; 2023. 3. Data on file. Pharming Healthcare Inc; 2022.

Please see Important Safety Information and full Prescribing Information available at joenja.com

Open-label Extension Study³

Data cutoff for interim analysis: December 13, 2021

- 32/37 patients reported ≥1 AE
- 78.4% of AEs were grade 1, 48.6% grade 2, 27.0% grade 3, 0% grade 4
- No SAEs related to Joenja

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

One patient with significant baseline cardiovascular comorbidities suffered cardiac arrest resulting in death at extension Day 879; determined by investigator not to be related to study drug

- Across all trials²**
- 38 patients had a **median exposure of ~2 years**
 - 4 patients had **>5 years of exposure**



◆ AMCP Nexus (October 2023)

- *A Real-world Comparison of Health Care Resource Utilization and Health Care Costs Among Patients With Activated PI3K-Delta Syndrome Versus a Control Cohort of Patients Without Activated PI3K-Delta Syndrome in the United States*



◆ ACAAI (November 2023)

- *Mortality in Patients With Activated Phosphoinositide 3-Kinase Delta Syndrome, a Systematic Literature Review*



IPIC2023

INTERNATIONAL
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CONGRESS

◆ IPIC (November 2023)

- *Results of a second interim analysis of an ongoing single-arm open-label extension study of leniolisib in activated PI3K delta syndrome: long-term efficacy and safety through to March 2023.*
- *Complicated course of activated PI3K delta syndrome-1 ameliorated by leniolisib: a case study.*
- *Gastrointestinal manifestations in patients with activated PI3K delta syndrome (APDS) treated with leniolisib.*
- *Assessing long-term treatment with leniolisib and its effects on bronchiectasis in patients with activated PI3K delta syndrome (APDS).*