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Pharming Group N.V.

37th Annual Roth Conference

March 16 - 18, 2025

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Forward-looking statements

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Building a leading global rare disease biopharma company
Strong performance reinforces growth foundation

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Revenues: FY24: US$297 million (+21%)
4Q24: US$93 million (+14%)

Operating profit and positive operating cash flow in 3Q-4Q 2024

EURONEXT AMS: PHARM
Nasdaq: PHAR

Growing commercial portfolio

- RUCONEST® for acute HAE attacks
- Joenja® (leniolisib) for APDS – U.S. and EU/Rest of World

Reaching more APDS patients with Joenja®

- Additional patient finding
- Targeted geographic expansion
- Pediatrics label expansion

Pipeline addresses large opportunities

- Leniolisib new indications (PIDs with immune dysregulation) – 2 Phase IIs
- Abliva KL1333 (mtDNA mitochondrial disease) – pivotal study

Growing commercial portfolio

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RUCONEST®

- **Strong U.S. in-market demand**

  U.S. physician prescriber base +11% in FY24

  New enrollments up 24% in FY24

- **Revenue:**

  4Q24 US$79.6M (+9%)
  FY24 US$252.2M (+11%)

- **Well-positioned vs. new acute orals**

Joenja®

- **Increasing APDS patients on therapy**

  Found >240 in the U.S. and >880 globally

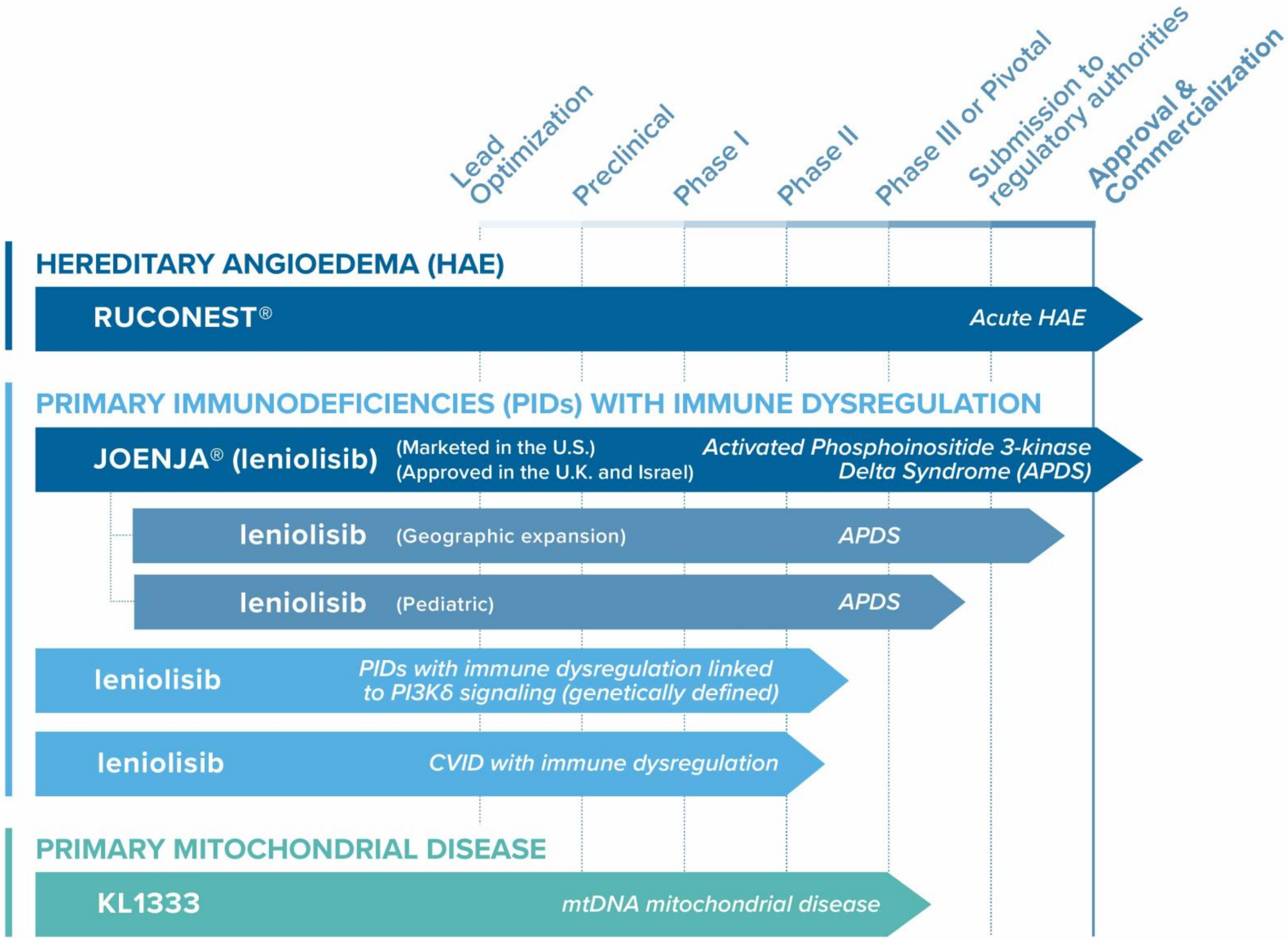
  Paid therapy: 96 patients + 5 pending (U.S.)

  Additional 188 patients on therapy globally (access programs and clinical studies)

- **Revenue:**

  4Q24 US$13.1M (+65%)
  FY24 US$45.0M (+147%)

Expanding rare disease pipeline



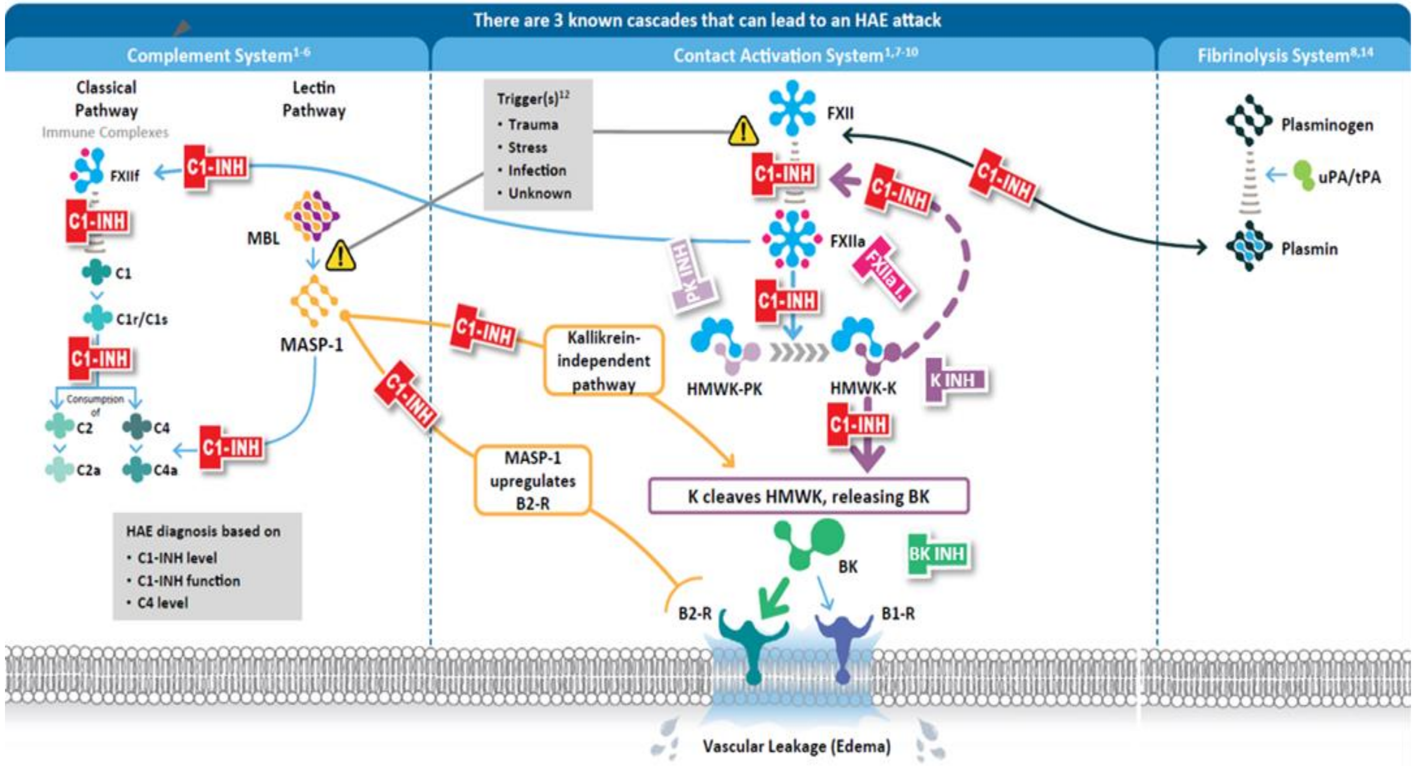
RUCONEST® for HAE

RUCONEST® (rhC1INH):
2nd most prescribed therapy for acute HAE attacks in the US

Only recombinant treatment that targets the root cause of HAE by replacing C1-INH

Only recombinant treatment that acts at multiple points in the cascades leading to HAE attacks

97% patients needed just 1 dose[1]
93% acute attacks stopped for at least 3 days[2]



References: 1. RUCONEST®. Prescribing information. Pharming Healthcare Inc; 2020. 2. Bernstein JA, et al. *Ann Allergy Asthma Immunol.* 2017;118(4):452-453. 3. Data on file. Pharming Healthcare Inc; 2019
The most common adverse reactions (incidence ≥2%) were headache, nausea and diarrhea. The most serious adverse reaction reported in clinical trials was anaphylaxis.

RUCONEST® addresses patient needs unmet by other therapies

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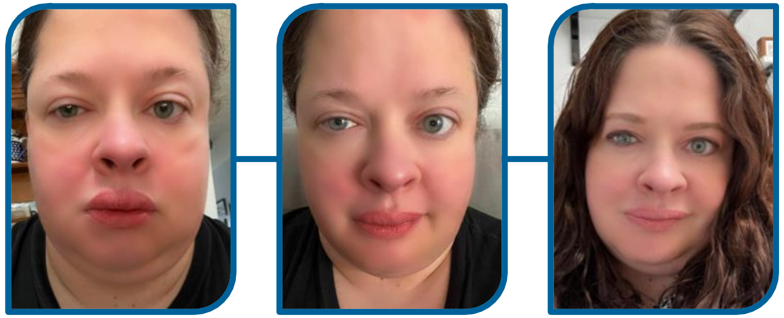
- **Type 1, Type 2, and Normal C1-INH HAE patients rely on RUCONEST**
- **RUCONEST patients experience moderate to severe attacks, and attack more frequently**
- **RUCONEST patients switching from other acute treatments**
  - Fail on icatibant and other acute therapies
  - Need to re-dose to resolve attacks



Time of taking RUCONEST | 4 hours after | 24 hours after

Joenja® (leniolisib) for PIDs

APDS is a rare primary immunodeficiency (PID)
Genetic defect leads to PI3Kδ hyperactivity

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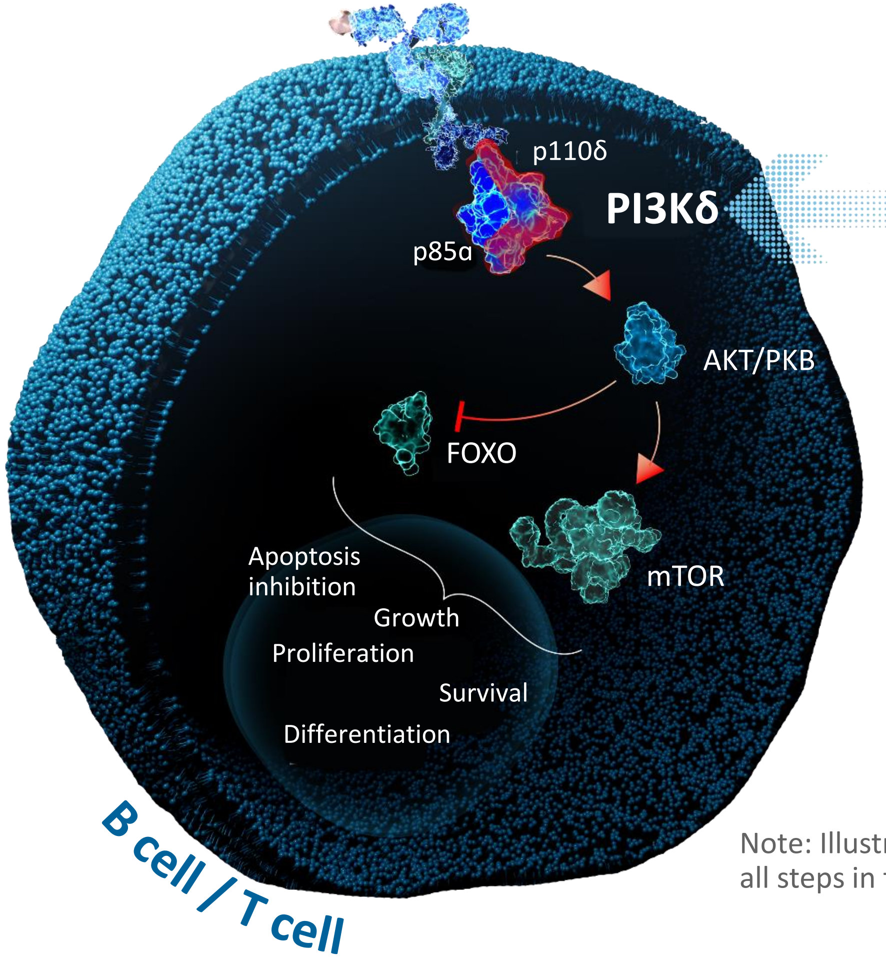
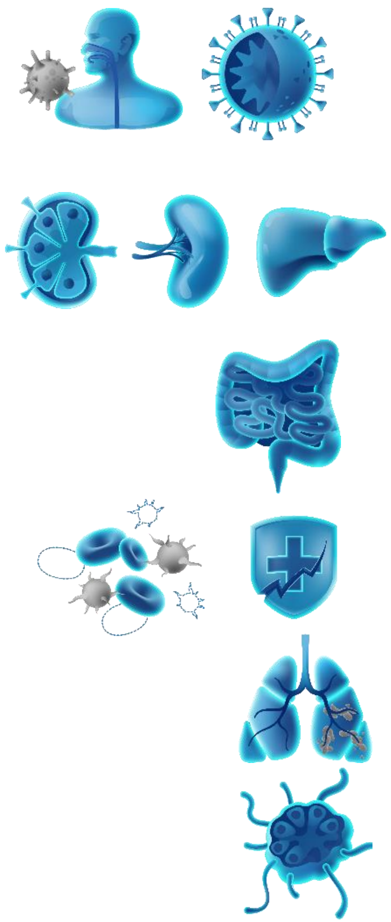
Hyperactive PI3Kδ results in dysregulated B and T cell development[1-3]



The PI3Kδ enzyme is at the beginning of a complex signaling pathway

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

Immune imbalance leads to diverse signs and symptoms[1,4-6]



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; PI3Kδ, 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®: first and only approved therapy for APDS, corrects the underlying immune defect

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

APDS is a complex syndrome caused by pathogenic variants of the PI3Kδ enzyme, with significant mortality

Joenja® is an oral, selective PI3Kδ inhibitor designed to help regulate the hyperactive signaling pathway

FDA approval (March 2023) based on randomized pivotal study and OLE study

U.S. launch (April 2023)

Joenja® is an oral immune modulator targeting the root cause of APDS

- Normalizes the hyperactive PI3Kδ pathway to correct the underlying immune defect in APDS patients
- Helps address both immune deficiency and immune dysregulation

No drug-related serious adverse events or study withdrawals in Joenja® trials

Clinical data and tolerability for long term treatment

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

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

Rao VK, et al. Poster presented at: 64th Annual American Society of Hematology Annual Meeting; December 10-13, 2022; New Orleans, LA.

Joenja® (leniolisib) – Reaching more APDS patients and expanding the addressable patient population

Potential total prevalence
~40 patients / million

Genetic PIDs prevalence
+7.5 patients / million

APDS prevalence
~1.5 patients / million

Joenja® marketed in the U.S.*

Europe/ROW access programs

VUS resolution

Pediatric label expansion

Targeted geographic expansion

Joenja for PIDs with immune dysregulation linked to PI3Kδ signaling
Phase II trial ongoing

Joenja for CVID with immune dysregulation
Phase II trial started

Joenja (leniolisib) for APDS	leniolisib new indications: PIDs with immune dysregulation

* 96 patients on paid therapy + 5 pending. U.S. Pricing: 30-day supply $49,500, Annual cost (WAC) $594,000

Finding more APDS patients - VUS focus

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Variants of Uncertain Significance

- VUSs: insufficient data to determine if variant is disease causing
- >1200 patients in the U.S.
- VUSs may be reclassified as APDS with additional evidence*

VUS study results

- High throughput screening (MAVE) study, completed in December, identified novel variants leading to PI3Kδ hyperactivity
- Genetics testing labs to review study data, reclassify variants and update test reports
- Additional APDS patients to be identified over the course of 2025

* As results become available, patients with validated variants could be diagnosed with APDS and be eligible for Joenja® treatment.

Pediatric APDS clinical trial results support regulatory filings

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Pediatric

Phase III trial for children 4-11 years old with APDS

Positive topline data announced December 2024

- 21 patients enrolled in U.S., Europe, and Japan
- Both co-primary endpoints show improvement consistent with the RCT in adolescents and adults
- Benefits seen across the four tested dose levels
- No deaths/discontinuations due to AEs. No new safety findings
- Data to be presented at CIS conference in May
- Regulatory filings beginning with the U.S. in second half 2025

Leniolisib for PIDs with immune dysregulation beyond APDS

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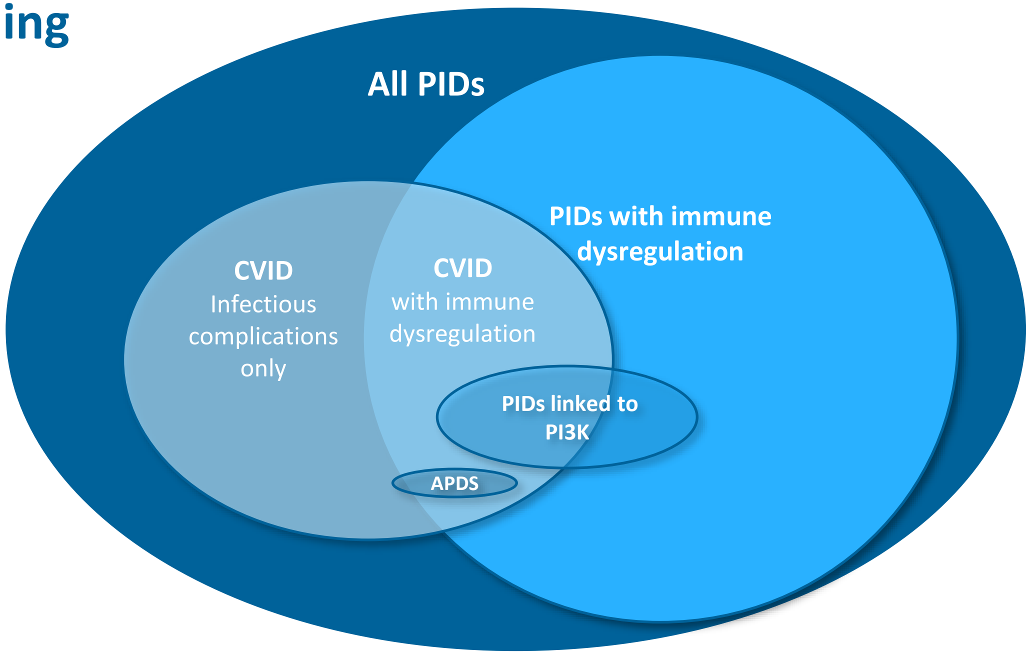
PI3Kδ activity drives immune dysregulation in PIDs, providing strong rationale for development of leniolisib

PIDs with immune dysregulation linked to PI3Kδ signaling

- Multiple genetically identifiable PIDs[1]
- Clinical manifestations, disease onset, and severity similar to APDS
- No approved therapies
- Phase II study started October 2024[2]
- FDA Fast Track designation

Common variable immunodeficiency (CVID) with immune dysregulation

- Similar clinical phenotype to APDS
- Identified independently of genetics
- Positive regulatory feedback on large unmet medical need and rationale
- Phase II study started; first patient expected to be dosed late-March



Not to scale with population sizes

Prevalence estimates	
APDS	1.5/million
PIDs linked to PI3K	7.5/million
CVID with immune dysregulation	39/million[3]

1. PIDs include ALPS-FAS, CTLA4 haploinsufficiency, NFKB1 haploinsufficiency and PTEN deficiency, amongst others
2. Single arm, open-label, dose range-finding study
3. CVID prevalence excludes APDS but includes most of the PIDs linked to PI3K indication patient population

Joenja® (leniolisib) development status
Expanding the addressable patient population

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Geographic expansion (APDS)

Europe – review extended to Jan. 2026
Single outstanding CMC request
Positive clinical benefit and safety concluded

U.K. – Marketing authorization 2024
Reimbursement: NICE positive final draft guidance

CAN, AUS regulatory reviews
Canada decision in 2026*
Australia approval in 2025*

Japan clinical study: Patient enrollment complete, positive interim analysis
PMDA filing mid-2025

Other country regulatory approvals/filings
Access Programs

Pediatric expansion (APDS)

4 to 11 years – Positive topline data
Filing to begin 2H 2025

1 to 6 years – Enrollment continuing

Indication expansion (additional PIDs)

PIDs with immune dysregulation linked to PI3Kδ signaling
Phase II trial ongoing

CVID with immune dysregulation
Started Phase II trial

* Anticipate regulatory action in 2025 for Australia and in 2026 for Canada

KL1333 for mtDNA Mitochondrial Disease

KL1333 for mtDNA mitochondrial disease (Abliva acquisition)

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Primary mitochondrial diseases – rare disorders impairing mitochondrial energy production
- Severe fatigue, myopathy (muscle weakness), and reduced life expectancy
- Poor quality of life (e.g., loss of job, social isolation, depression)

KL1333 positioned to become first standard of care in mitochondrial DNA (mtDNA) disease
- Novel mechanism of action addresses the underlying disorder
- >30,000 diagnosed patients*

Pivotal study ongoing with positive interim analysis confirming FDA-agreed primary endpoints
- Patient recruitment for second wave of pivotal FALCON clinical trial to start as soon as possible
- Read-out anticipated in 2027 with potential FDA approval by end of 2028

Significant unmet medical need and no approved therapies
- Builds on Pharming's existing rare disease expertise and infrastructure
- Concentrated centers of excellence and strong advocacy groups

* in US, EU4 and UK

FALCON study – positive interim analysis

Pivotal FALCON Study

WAVE 1 – Fully enrolled

- 40 patients recruited across six countries (U.S., UK, France, Spain, Belgium, Denmark)
- 18 sites activated
- Interim analysis at 24 weeks conducted in Q3 2024

WAVE 2 – Expansion

- 180 total patients treated for 48 weeks
  - Wave 1 sites ready to start enrolling
  - Wave 2 sites undergoing activation
- Readout anticipated 2027

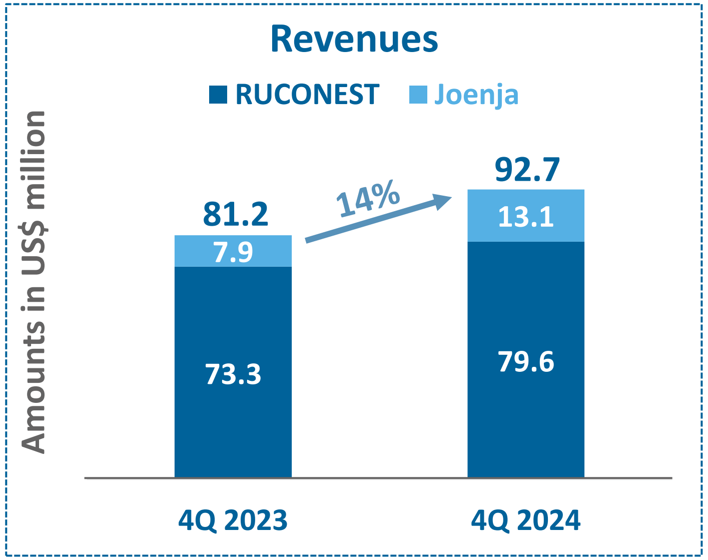
Interim Futility Analysis:

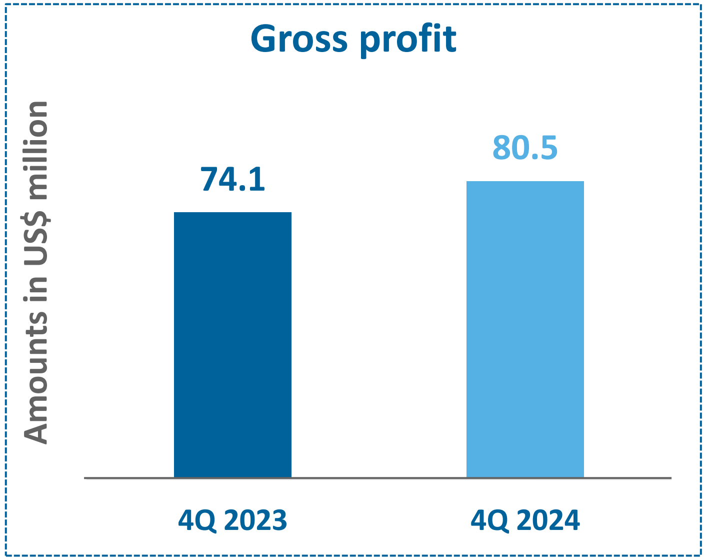
Positive outcome achieved, with both primary endpoints having passed futility

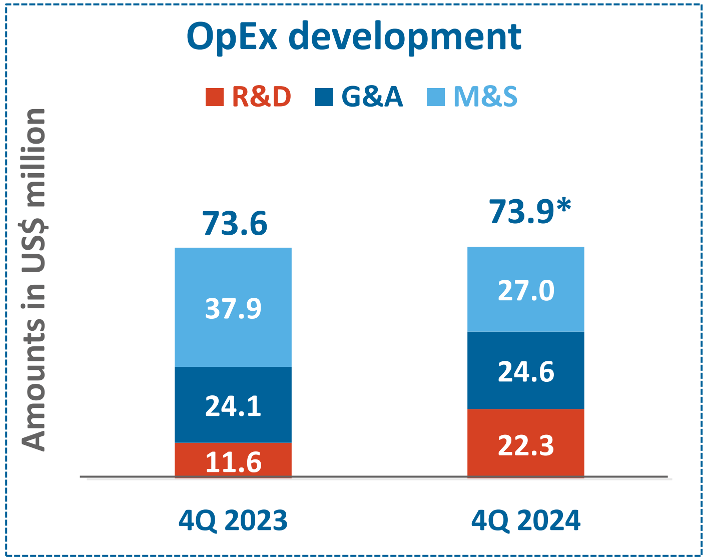
- Promising differences favoring the active arm vs. placebo for both primary efficacy endpoints; if trends continue consistently, we expect a successful result at the completion of this trial
- Data monitoring committee (DMC) recommended continuing with Wave 2:
  - Safety and tolerability profile acceptable
  - No changes to study design
  - 180 total patients confirmed in the study

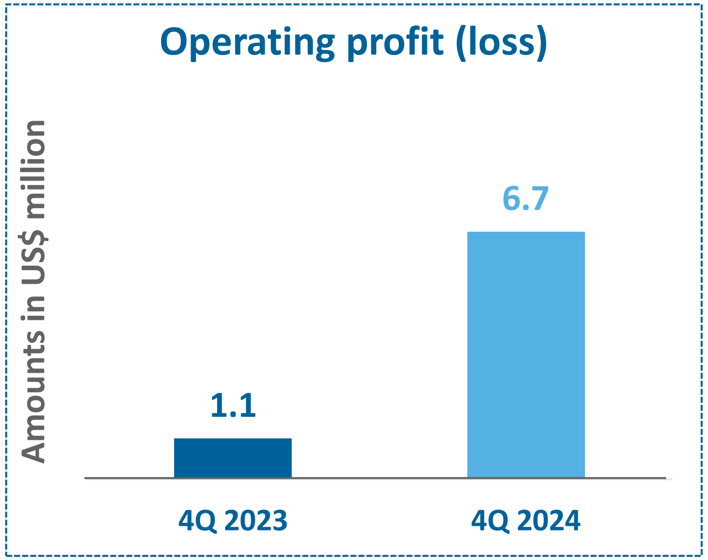
Financials and Outlook

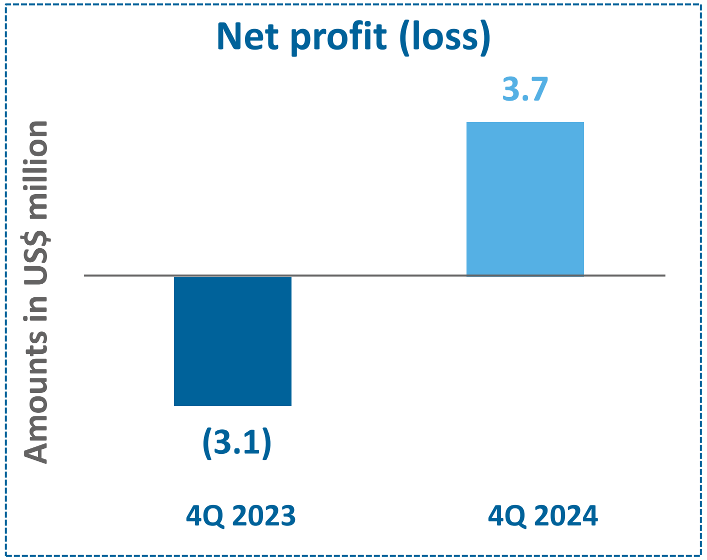
Financial highlights: 4Q 2024 vs 4Q 2023

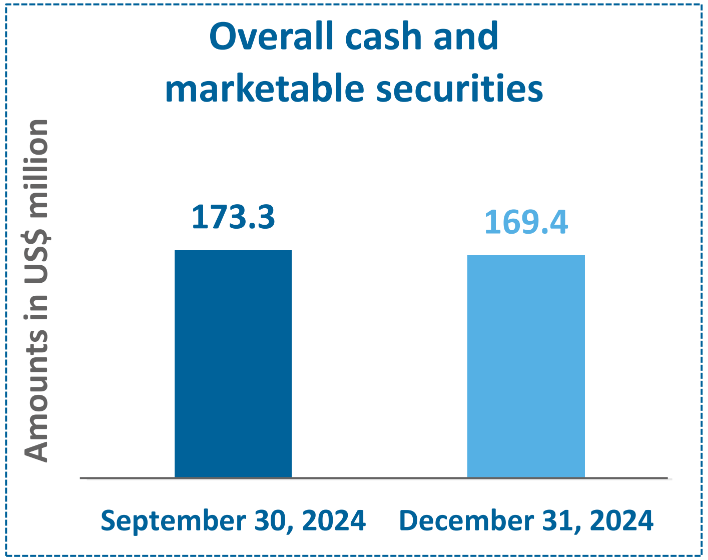












* G&A expenses for 4Q 2024 include one-off items - impairment of the DSP facility (2024: US$5.1 million, 2023: US$4.7 million) and Abliva AB acquisition legal and advisory fees (US$1.1 million).

Financial highlights: FY 2024 vs FY 2023

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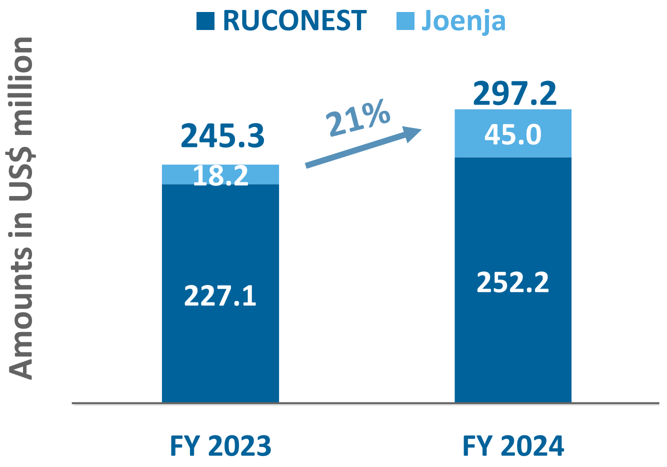
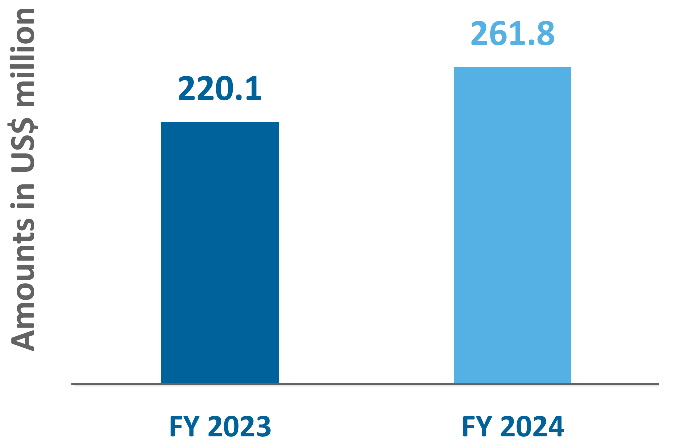
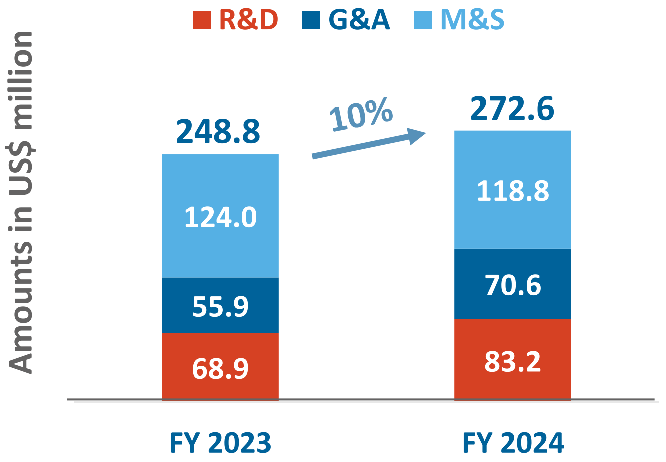
Revenues



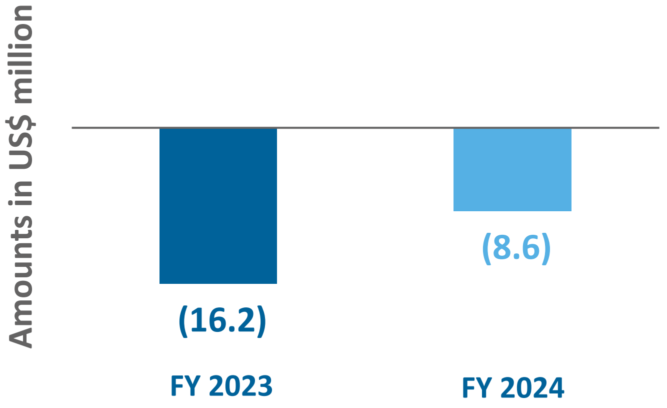
Gross profit



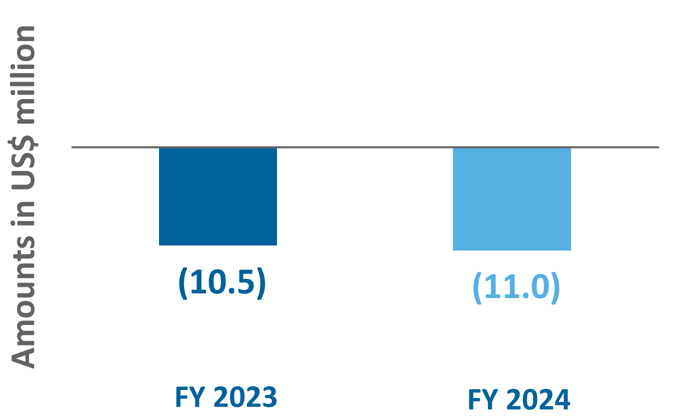
OpEx development



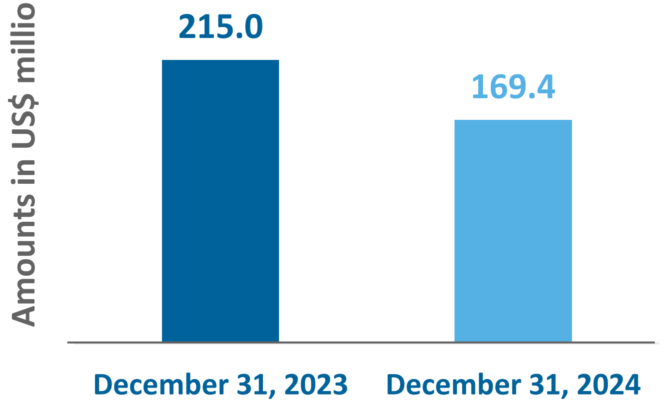
Adjusted (Non-GAAP) Operating profit (loss)*



Net profit (loss)



Overall cash and marketable securities**



* Operating profit (loss) for 2023 excludes milestone payments for Joenja® (US$10.5 million) and gain on sale of Priority Review Voucher to Novartis (US$21.3 million).

** US$30.4 million of the US$45.6 million decrease in overall cash and marketable securities is due to convertible bond refinancing.

Abliva acquisition completed

Acquisition Terms

- Acquisition through a public tender offer under Swedish Takeover Act and Nasdaq Stockholm Takeover Rules
- Offer price of SEK 0.45 in cash for each share in Abliva AB, totalling approximately $66.1M USD *

Financial Details

- Acquisition of shares with available cash
- KL1333 in-licensed by Abliva from Yungjin Pharm, which is entitled to milestone and royalty payments **

Timing

- Announced ownership exceeding 90% on February 20 and initiated delisting activities
- Initiated compulsory acquisition procedure for remaining Abliva shares
- Abliva application for delisting was approved on March 3 and last day of trading will be March 17

Transaction illustrates our strategy of developing a high-value pipeline

*Based on an exchange rate of 0.0911 SEK / USD from 13 December 2024

**Worldwide rights, excl. Japan and South Korea primarily for the treatment of genetic mitochondrial disease; single-digit to low double-digit royalties on net sales, plus development and commercial milestone payments

2025 Financial guidance

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Revenue and operating expenses:

	FY 2025 Guidance	Notes
Total Revenues	**US$315 - 335 million**	6 - 13% growth
Operating Expenses (pre-Abliva impact)	**Flat vs. FY 2024**	
Operating Expenses (Abliva-related)	**~US$30 million**	Preliminary estimate including R&D and non-recurring transaction and integration costs

Financial impact of Abliva acquisition:

- Available cash and future cash flows expected to cover KL1333 development and pre-launch costs and current pipeline investments.
- Business combination - substantially all value concentrated in a single asset, KL1333.
- Following delisting as expected in March 2025, the acquisition would be reflected in our financial statements beginning with the current quarter. At this point we expect the US$66.1M acquisition price to be allocated to the fair value of the acquired identifiable assets and liabilities, with any excess to be recorded as goodwill.

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- Pediatrics label expansion

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2025 guidance: US$315 - 335 million

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Appendix

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 Burden[1-4]
- 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.

Heterogeneous, evolving symptomology can often lead to missed diagnoses

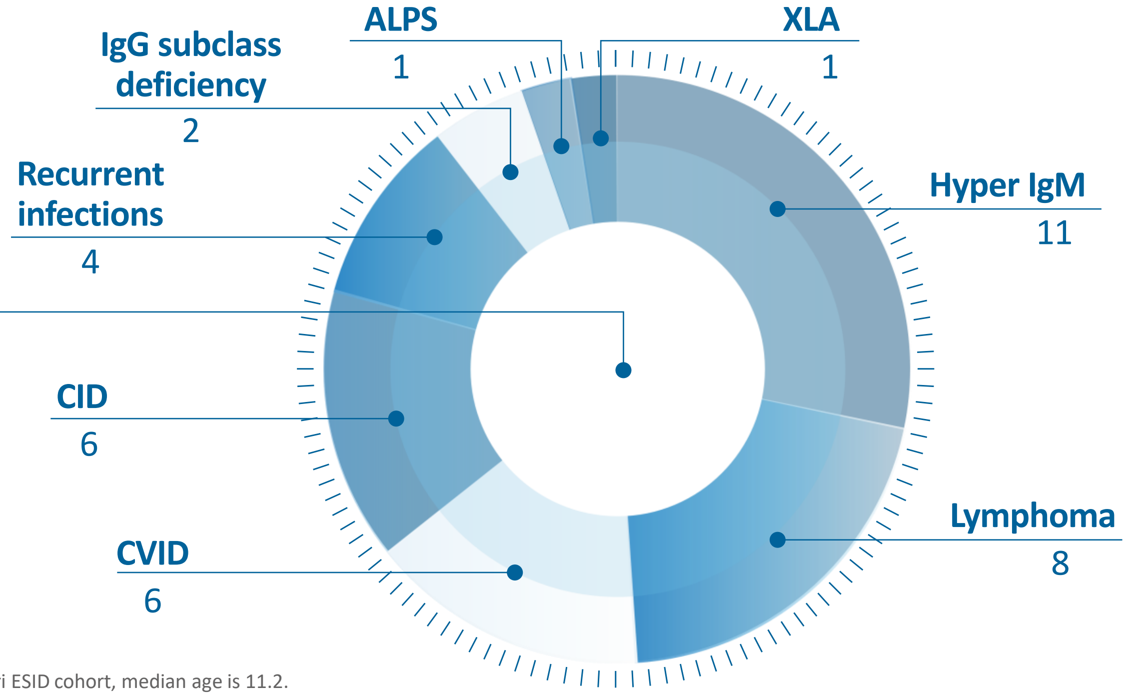
Timeline of the most common pathologies* seen in APDS[1-4]

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

<1 year (range, 1 month-10 years)	3 years (range, 1-6 years)	5 years (range, 1-18 years)	10.5 years (range, 6-15 years)	11.2 years† (range, 18 months-39 years)	18 years (range, 1.5-40 years)
Sinopulmonary infections	Benign lymphoproliferation	Enteropathy	Autoimmunity	Bronchiectasis	Malignancy

Cytopenias, arthritis, or other dysregulation‡

APDS has often been diagnosed as another PI or condition, causing delays in diagnosis[1]



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.

Management for APDS[1,2] prior to Joenja®

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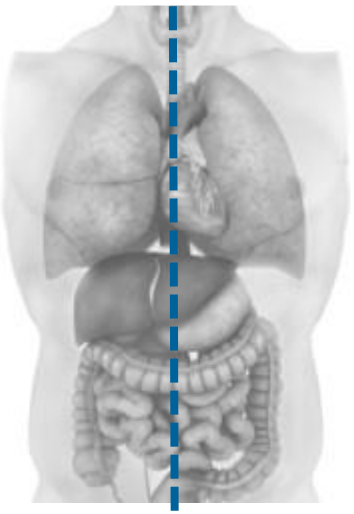
Immune Deficiency

- 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.

Joenja® clinical trial designs

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 Evaluation[3]

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 log^{10}-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.

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

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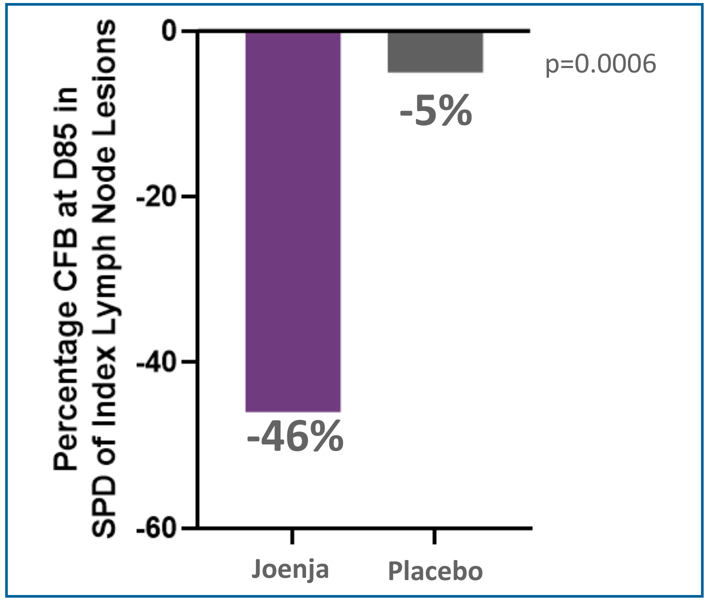
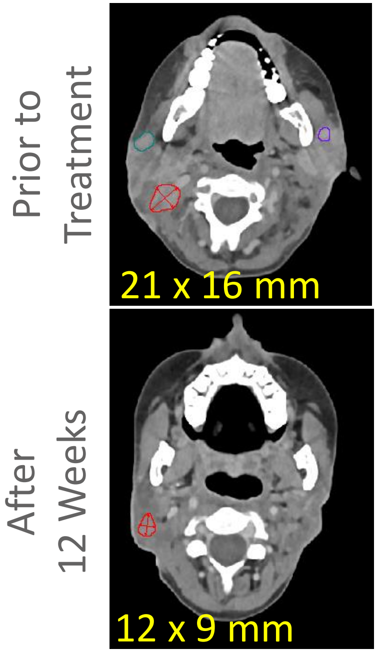
At 12 weeks Joenja® decreased lymphadenopathy and increased naïve B cells

Immune Dysregulation

Change from baseline in index nodes*

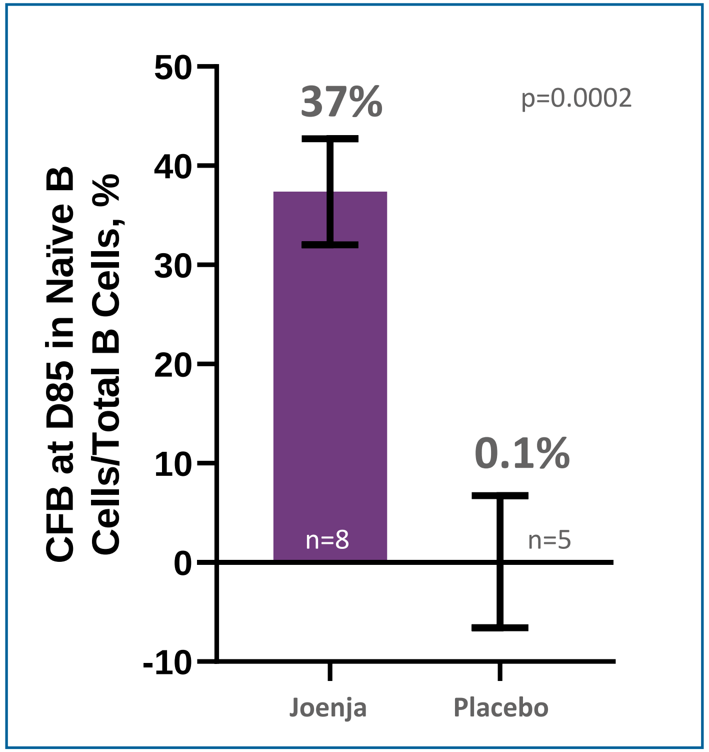
Log_{10}-transformed SPD of index lesions	Joenja (n=18)	Placebo (n=8)
Baseline mean (SD)	3.03 (0.42)	3.05 (0.39)
Change from baseline, LS mean (SE)	-0.27 (0.04)	-0.02 (0.05)
Difference vs placebo (95% CI)		-0.25 (-0.38, -0.12)





Immune Deficiency

Change from baseline in 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

Joenja® significantly reduced splenomegaly

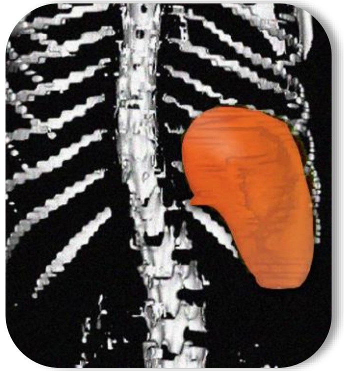
Secondary endpoint: Significant reductions in spleen size by 2D and 3D analysis compared to placebo

- 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

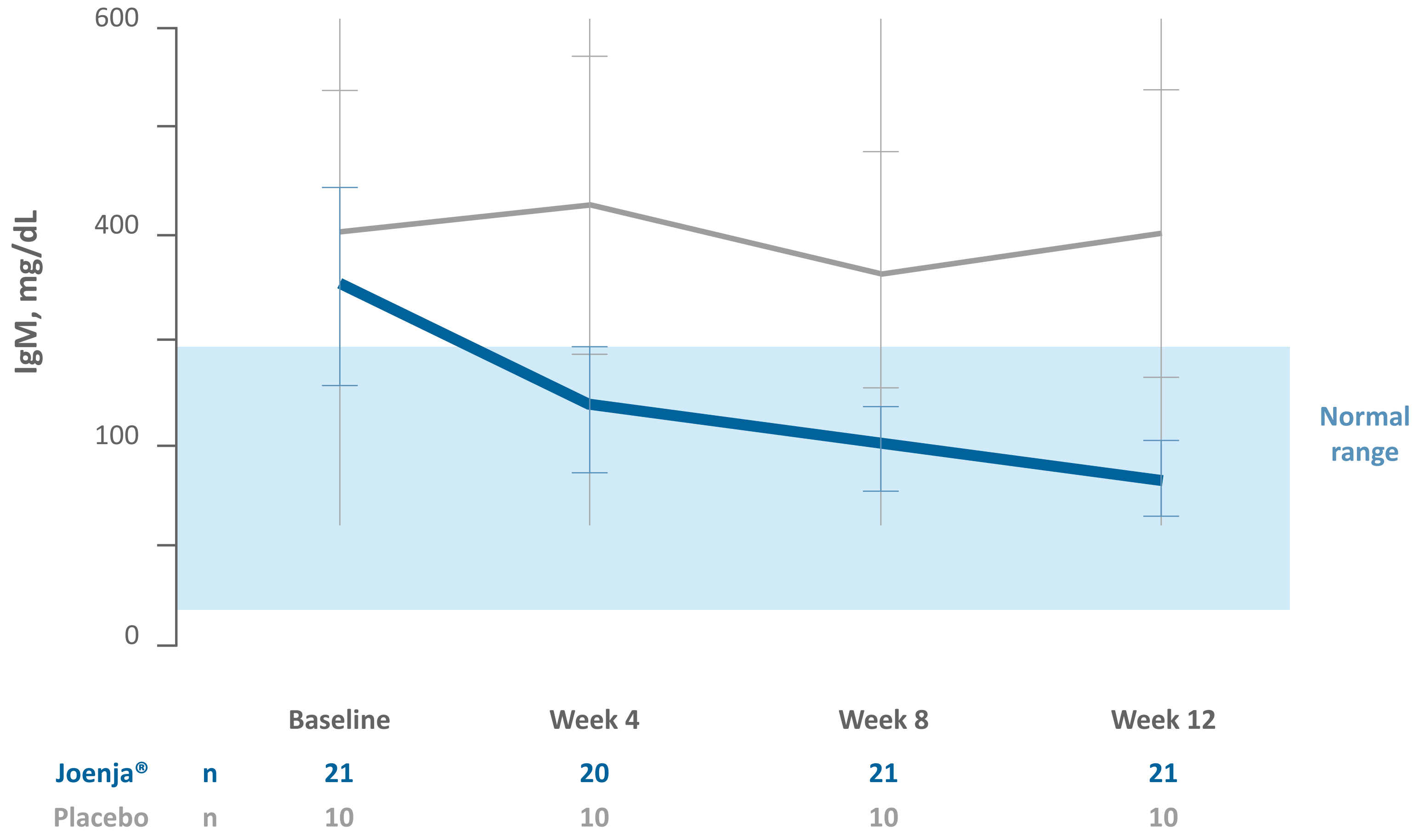
Actual patient images of a 17-year-old male. As individual results vary, images may not be representative of all patients.

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 endpoint 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

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

Joenja® safety profile

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

Open-label Extension Study[3]

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 trials[2]

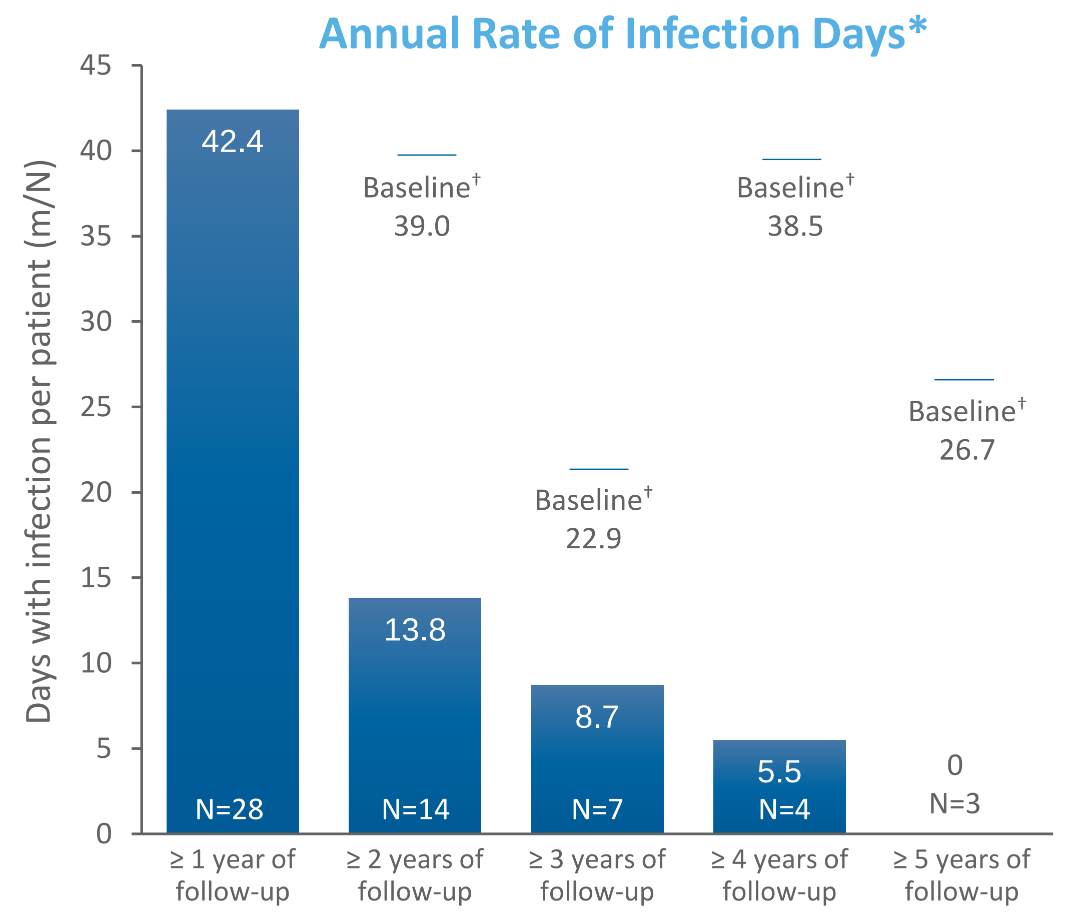
- 38 patients had a **median exposure of ~2 years**
- 4 patients had **>5 years of exposure**

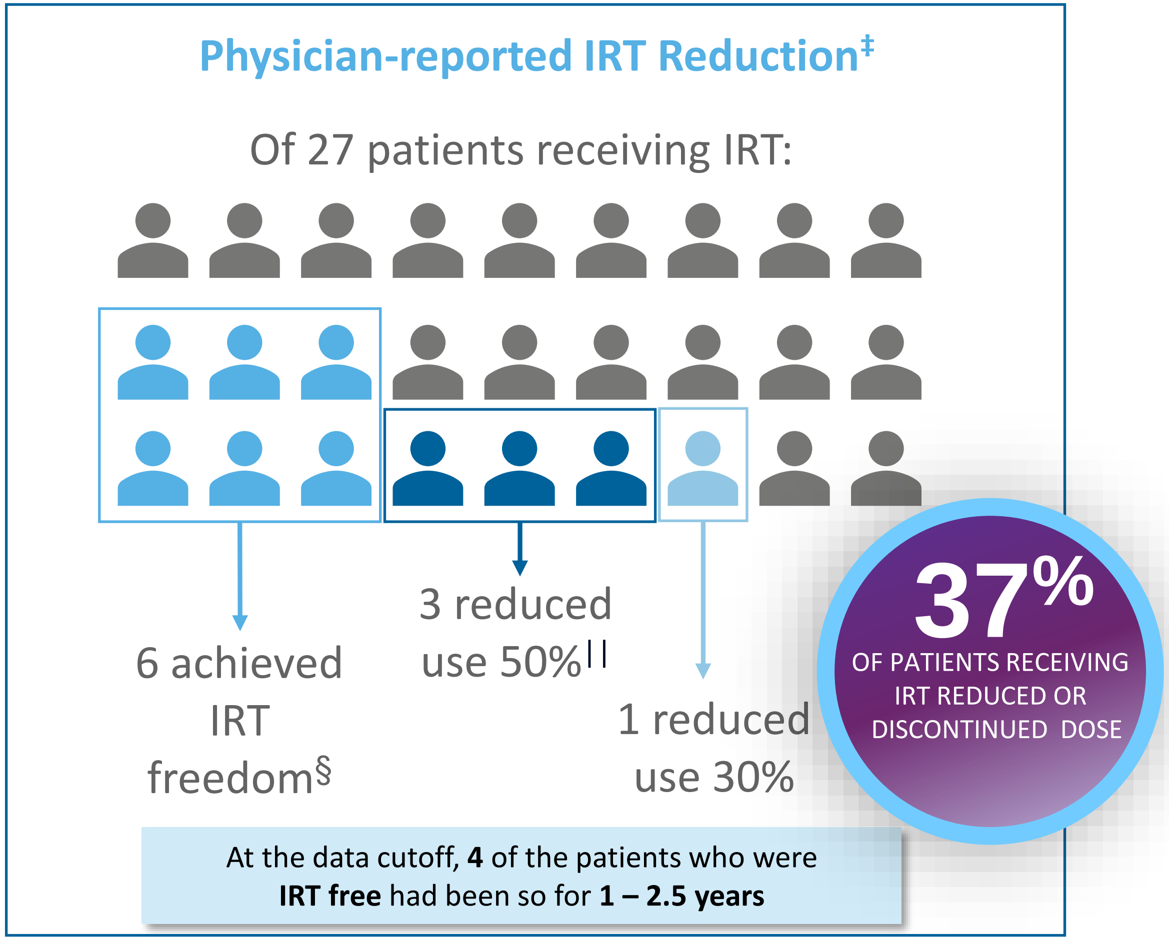
A patient with multiple occurrences of an AE is counted only once in the AE category. Only AEs occurring at or after first drug intake are included.
*Includes dermatitis atopic and eczema. †Includes tachycardia and sinus tachycardia.
AEs, adverse events; **ALT**, alanine aminotransferase; **AST**, aspartate 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 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.

IRT, immunoglobulin replacement therapy; **m**, number of infection days; **N**, number of patients in follow-up category.

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

VUS by the numbers

VUSs frustrate patients and doctors, limiting diagnosis of genetic diseases such as APDS

~1,200

Pharming is aware of **~1,200 US patients** harboring *PIK3CD/R1* VUSs

- This figure will continue to grow over time
- VUS are identified at ~4x the rate of likely pathogenic/pathogenic (LP/P) variants
- Similar VUS frequencies expected worldwide
- Published literature, which includes more than 1.5 million patients, showed that 20% of reclassified VUSs are upgraded to LP/P
- Pilot study in 25 VUS patient samples - findings consistent with APDS identified in 5 patients (20%) including patient preparing for enrollment

No systemic initiatives exist to resolve *PIK3CD/R1* VUSs, yet these patients remain a significant opportunity to identify incremental patients with APDS

Given importance of PI3Kδ in B & T cells, immune dysregulation in PIDs can occur via alterations in PI3Kδ signaling

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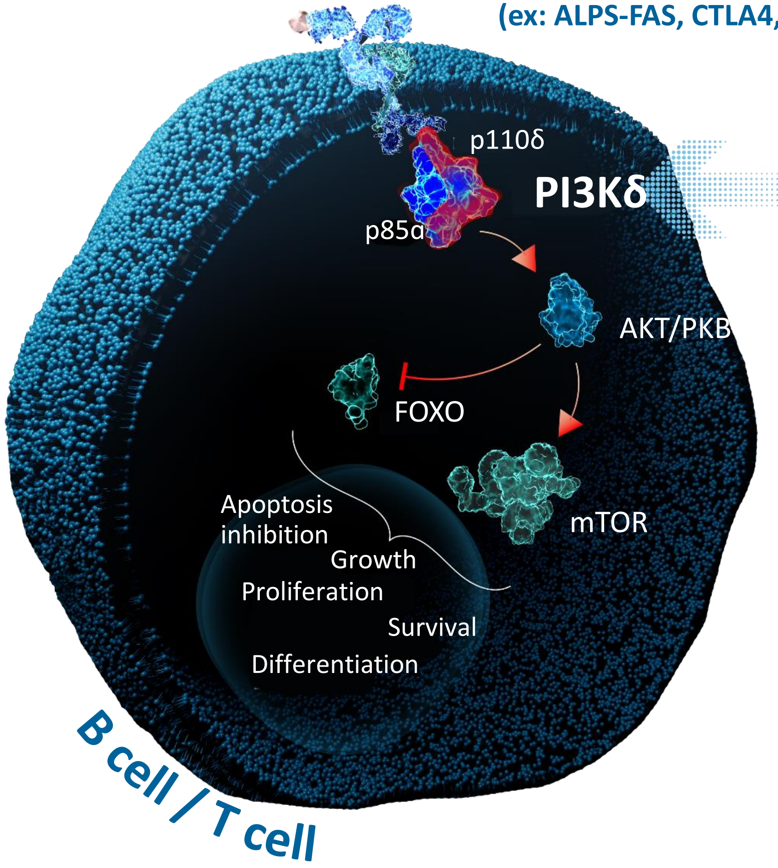
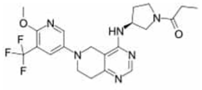
Altered PI3Kδ signaling can occur in multiple PID genetic disorders beyond APDS

(ex: ALPS-FAS, CTLA4, NFKB1, PTEN) [1-4]



leniolisib



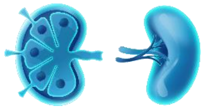
Note: Illustration does not include all steps in the signaling pathway.

High unmet medical need

- no approved therapies other than Joenja® (leniolisib) for APDS:

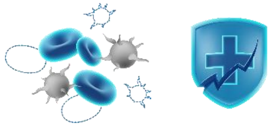
SOC immunosuppressives (e.g. rapamycin) have limited efficacy and significant tolerability concerns

Clinical manifestations, disease onset and severity similar to APDS [5-10]



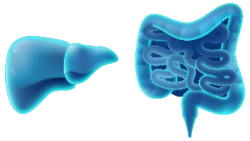
Lymphoproliferation

- 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

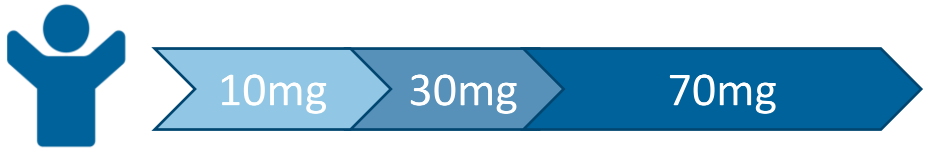
Lymphoma

FOXO, forkhead box O; mTOR, mammalian target of rapamycin; PI3Kδ, phosphoinositide 3-kinase delta; PKB, protein kinase B.

1. Volkl et al. Blood 2016; 128(2):227-238. 2. Tsujita, et al. J Allergy Clin Immunol. 2016;138(6):1872-80. 3. Rowshanravan B, et al. Blood. 2018;131(1):58-67. 4. Additional unpublished collaborator data. 5. Bride K & Teachey D. F1000Res. 2017;6:1928 6. Kuehn HS, et al. Science 2014; 345:1623-27. 7. Lorenzini T, et al. J Allergy Clin Immunol. 2020:146:901-11. 8. Eissing, et al. Transl Oncol. 2019;12(2):361-3672. 9. Coulter TI, et al. J Allergy Clin Immunol. 2017;139(2):597-606. 10. Schwab C, et al. J Allergy Clin Immunol. 2018;142(6):1932-1946.

PIDs linked to PI3Kδ signaling – Phase II study design

Phase II proof of concept clinical trial – single arm, open-label, dose range-finding study (N=12)



- Patients with PIDs linked to PI3Kδ signaling, e.g. ALPS-FAS[1], CTLA4 haploinsufficiency[2], NFKB1 haploinsufficiency[3], PTEN deficiency[4] (treatable population ~7/million)
- Primary: Safety & Tolerability
- Secondary/Exploratory: PK/PD, efficacy measures
- 10/30/70 mg: 4/4/12 wks treatment, respectively
- Pick Best Dose regimen for Phase III

NIH 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)

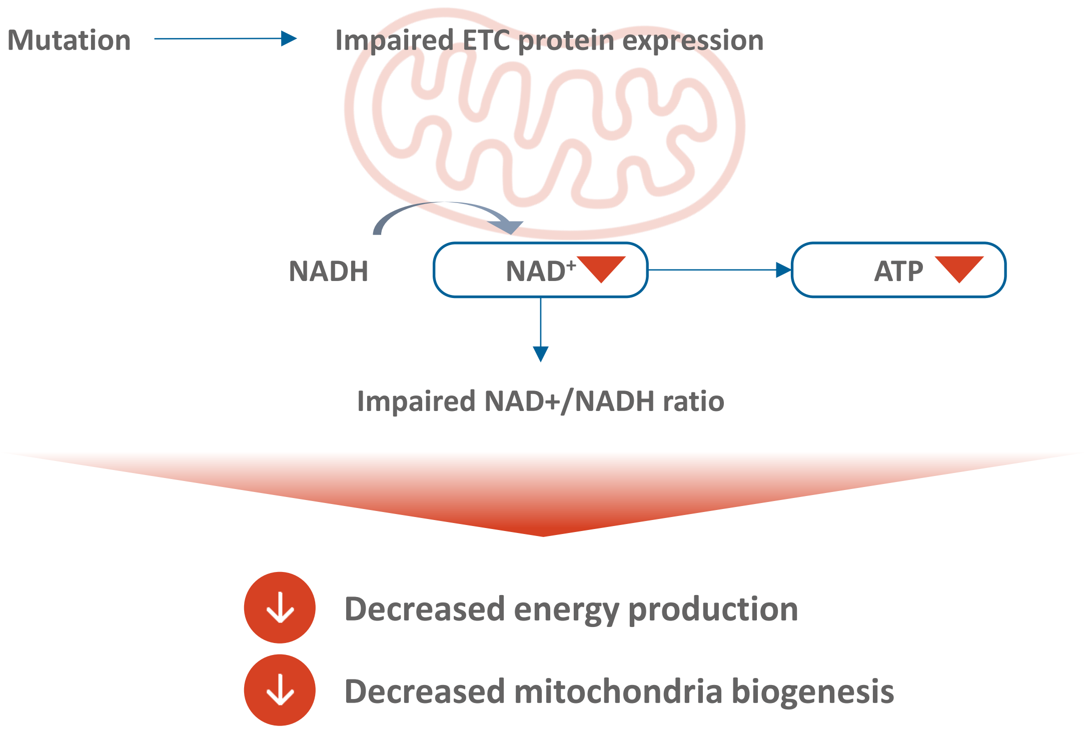
1. Bride K & Teachey D. F1000Res. 2017;6:1928. ; Rao VK & Oliveria JB. Blood 2011; 118(22):5741-51.
2. Kuehn HS, et al. Science 2014; 345:1623-27. ; Schwab C, et al. J Allergy Clin Immunol. 2018;142(6):1932-1946.
3. Lorenzini T, et al. J Allergy Clin Immunol. 2020:146:901-11.
4. Eissing M, et al. Transl Oncol. 2019;12(2):361-367. ; Tsujita, et al. J Allergy Clin Immunol. 2016;138(6):1872-80.

Dysfunctional mitochondria produce less ATP

Primary Mitochondrial Disease (PMD)

- Mitochondria, often described as the “powerhouses” of cells, are crucial for energy production
- Mitochondrial diseases are a group of genetic disorders characterized by dysfunctional mitochondria due to mutations in mitochondrial (mtDNA) or nuclear DNA
- The abnormal NAD^+/NADH ratio results in decreased ATP production, contributing to organ dysfunction and disease deterioration
- For patients this means symptoms of severe fatigue and muscle weakness – symptoms which patients report as the most troublesome*

Dysfunctional Mitochondria



*Voice of the Patient Report, United Mitochondrial Disease Foundation, 2019.

NAD: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide + hydrogen; ETC: Electron transport chain.

Heavy patient burden with no approved therapies

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Presentation and Diagnosis

- Patients present to their primary care doctor and then often get referred to a neurologist for musculoskeletal issues
- Either the neurologist or a referral to a metabolic geneticist will result in a diagnosis
- Many patients are diagnosed at academic centers specializing in mitochondrial disease
- A combination of routine lab tests and genetic testing available from major testing labs help to diagnose patients

Impact

- Patients heavily burdened in their daily lives including symptoms like severe fatigue, myopathy, and metabolic dysfunction
- Impact on QoL including loss of job, loss of independence, depression/anxiety
- Primary mitochondrial diseases lead to a three-to-four-decade reduction in life-expectancy

Treatment

- No approved treatment options
- Patients are limited to using vitamins, supplements, and physical therapy

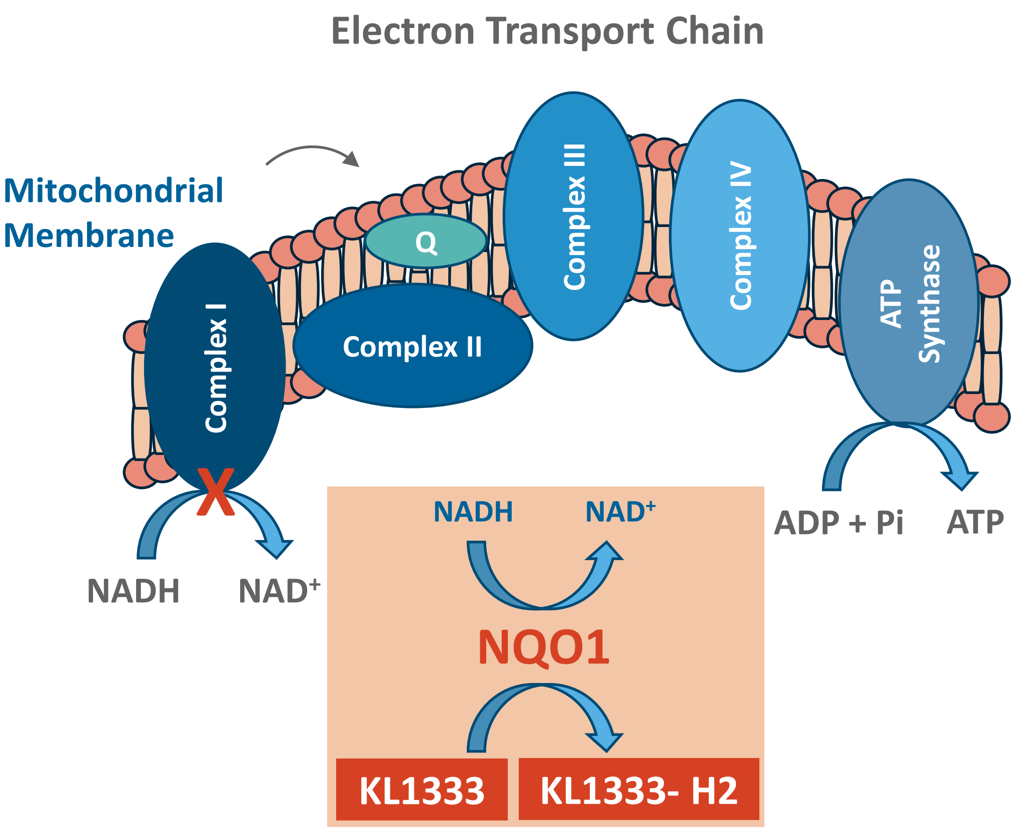
" On the worst days I will be crying in frustration because going to the kitchen seems equivalent to climbing a mountain and just trying to process what others are saying to me involves all the energy and concentration that I have."

United Mitochondrial Disease Foundation, Voice of the Patient Conference, 2019

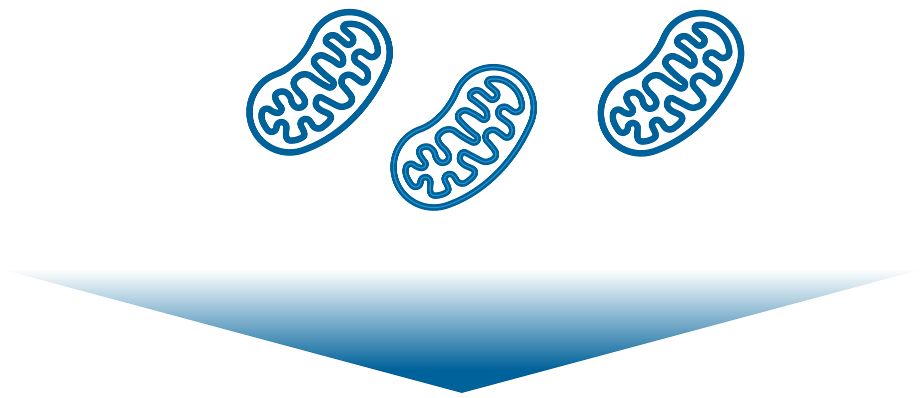
KL1333 corrects the underlying pathophysiology

KL1333 normalizes conversation of NADH to NAD+ via NQO1

Normalizes the NAD^+/NADH Ratio



Restored Energy Metabolism



- ↑ Restored energy regulation and improved ETC function
- ↑ Stimulation of mitochondria biogenesis
- ↑ Overall resulting in symptom reduction and expected disease modification

KL1333: First-in-disease small molecule with unique MOA

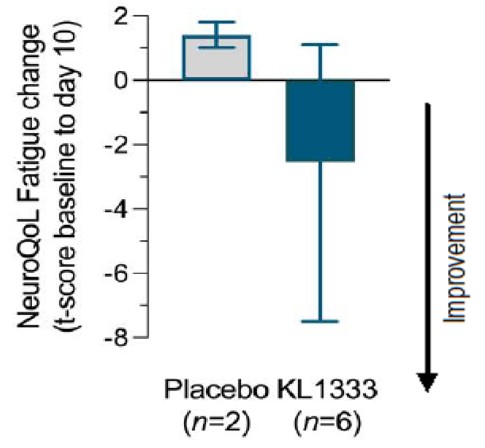
Attributes	Outcomes
- Directly increases the NAD+/NADH ratio via NQO1 - Unique MoA works upstream from all competing MoA in PMD - Oral, small molecule, BID dosing - Favourable safety profile - Favourable IP protection - Orphan Drug Designation in US & EU and FDA Fast Track - Potential first-in-disease with registrational clinical study	- Improved energy regulation and ETC function - Stimulation of mitochondria biogenesis - Fatigue reduction - Increased exercise capacity

Phase 1b demonstrated significant activity vs. placebo

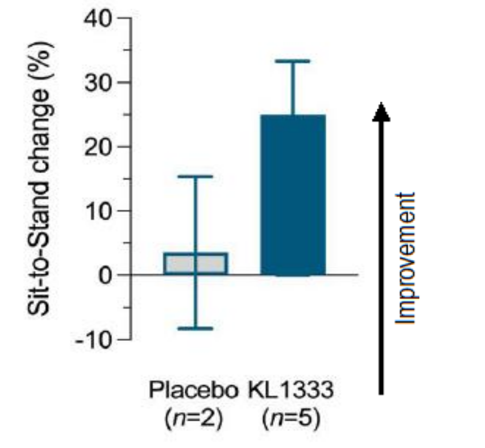
The placebo-controlled Phase 1b study demonstrated that KL1333 reduced patients' fatigue and myopathy after only 10 days, 50 mg/day

- KL1333 demonstrated efficacy in the phase 1b placebo-controlled portion with patients diagnosed with mtDNA mitochondrial disease
  - Fatigue reduction (NeuroQoL fatigue change)
  - Muscle function improvement (30 seconds sit-to-stand)
- KL1333 showed efficacy signals after 10 days using 50 mg/day
- Mitochondrial patients have increased lactate levels and increasing the concentration of KL1333 resulted in an improved lactate/pyruvate ratio, reflecting target engagement
- No serious adverse events reported

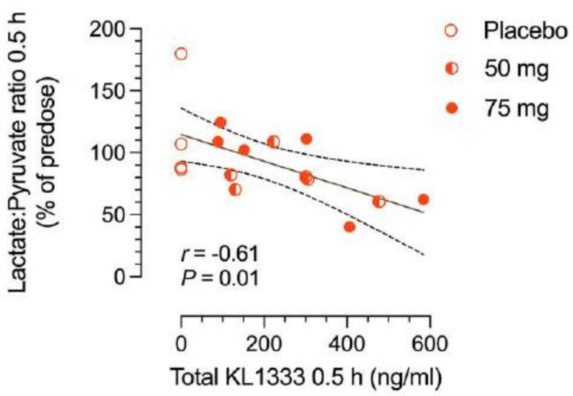
Fatigue Reduction
Changes from baseline to day 10



Muscle Function Improvement
Changes from baseline to day 10



Lactate:Pyruvate Ratio
Changes from baseline to day 10



Source: Pizzamiglio C et al., Optimizing rare disorder trials: a phase 1a/1b randomized study of KL1333 in adults with mitochondrial disease, Brain, 2024.

Pivotal study design based on regulatory and patient advocacy input

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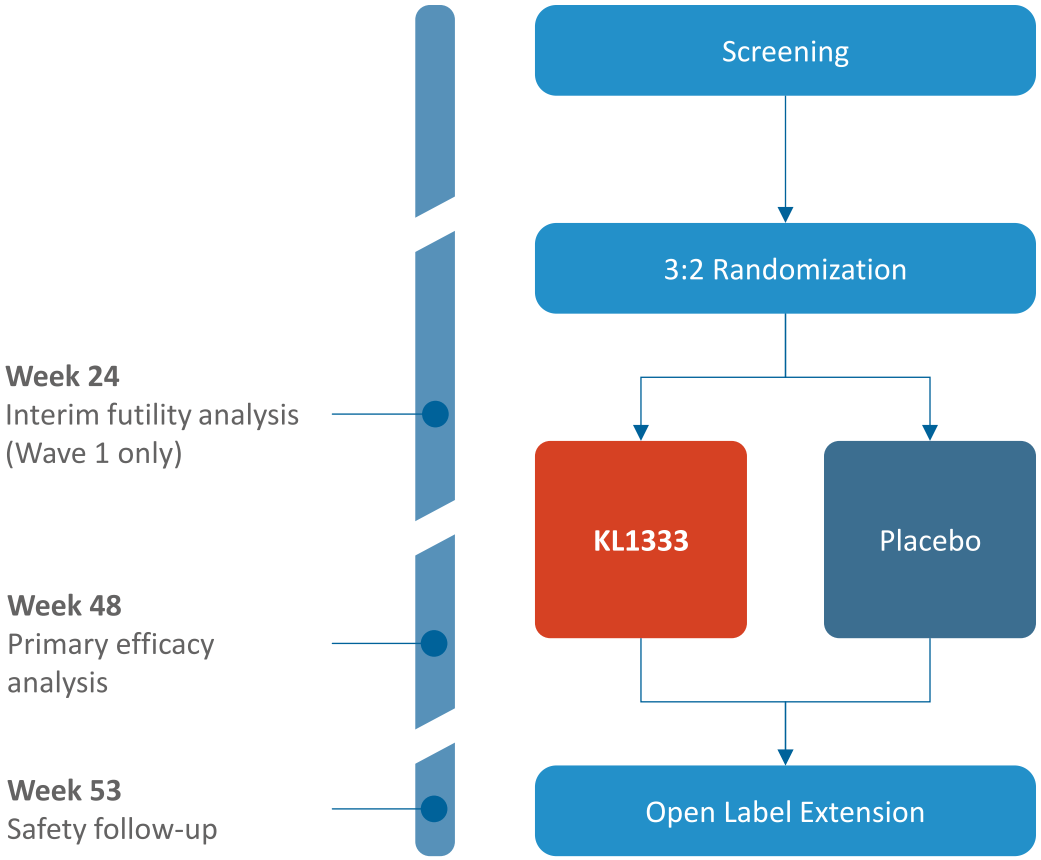
Regulatory Feedback

- Both FDA and EMA accepted study as registrational
- FDA said achieving one of the two endpoints would be sufficient for filing
- Conducted regular and detailed discussions with the FDA to facilitate alignment

Study Design

- **Methodology**
  - Randomized, double-blind, parallel-group, placebo-controlled pivotal study
- **Patients Included**
  - Adult PMD patients with mtDNA mutations* with fatigue and myopathy
- **Primary Endpoints**
  - Fatigue using the PROMIS Fatigue Mitochondrial Disease Short Form
  - Muscle weakness using the 30 second Sit-to-Stand test

Study Schematic



*Most prevalent mtDNA disorders include m.3243A>G associated MELAS-MIDD spectrum disorders, single large scale mtDNA deletion associated KSS-CPEO spectrum disorders, other multisystemic mtDNA-related disease (including MERRF)

Significant revenue opportunity for KL1333

PMD Prevalence
1 per 4,300[1]
US 78,200; EU4 and UK 76,400

Diagnosed mtDNA
9.6 per 100,000[2]
US 32,300; EU4 and UK 31,600

FALCON Trial Inclusion Criteria*
51%
US 16,500; EU4 and UK 16,100

>30,000 diagnosed mtDNA mitochondrial disease patients addressable in the US, EU4 and UK

*mtDNA mutations including m.8344A>G MELAS-MIDD, MERRF, KSS-CEPO, large scale mtDNA deletions

[1] Gorman, G.S. et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015 May;77(5):753-9.
[2] Gorman, G.S. et al. Mitochondrial Diseases. Nat. Rev. Vol 2, 1-22 (2016).

Majority of patients diagnosed and treated in US Centers of Excellence or academic institutions

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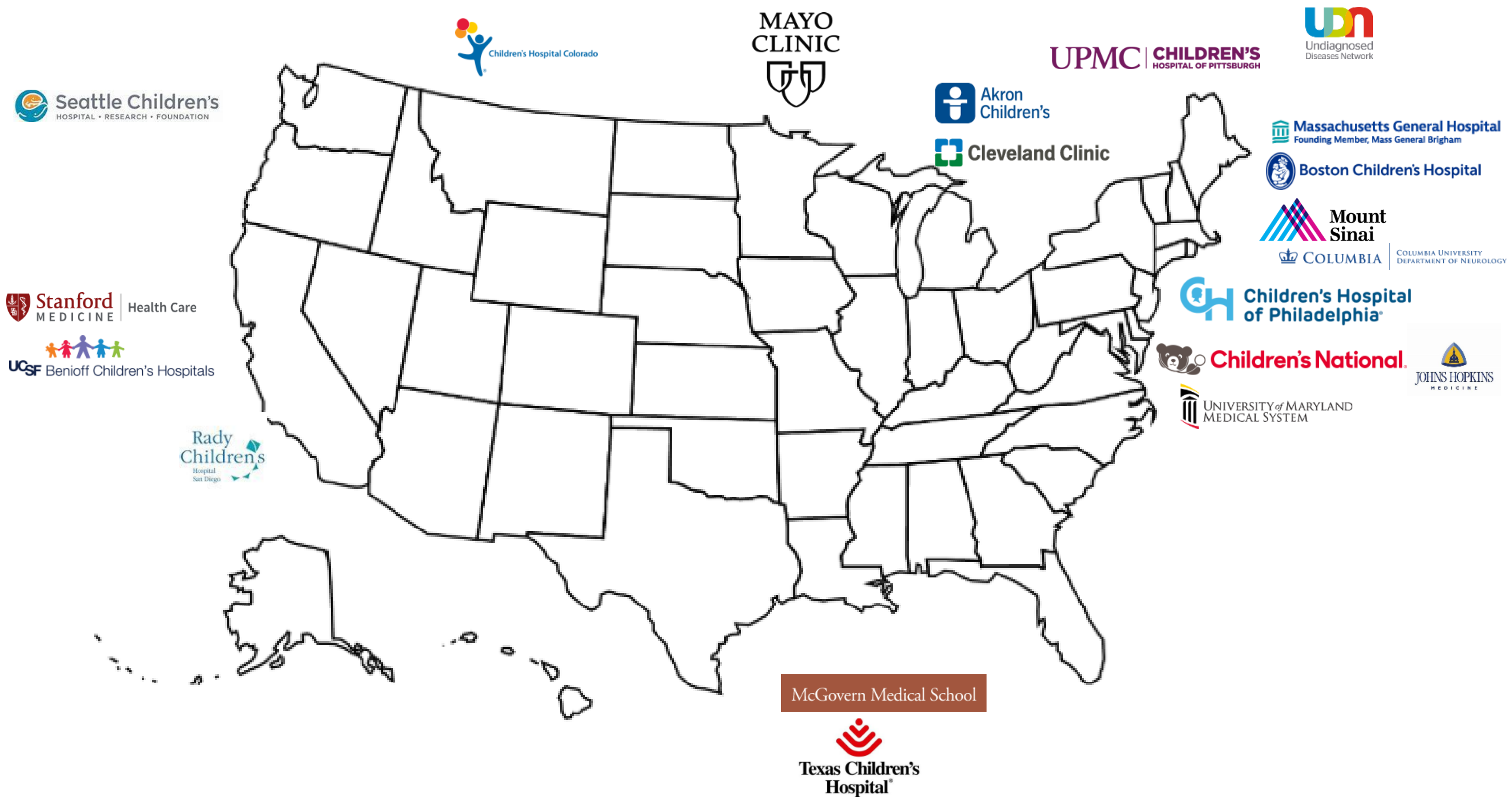

Mitochondrial Care Network – Centers: www.mitonetwork.org/centers

Other programs focus on different patient population or failed with different MOA

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Previous programs failed due to old mechanisms of action or evaluating the wrong endpoints

Asset	Type	MOA / ROA	Stage	Patient Group	Comments
ABLIVA **KL1333**	Small molecule	NAD+/NADH modulator Oral	Pivotal	mtDNA mutations (e.g., mtDNA deletion, m.8344A>G, MELAS-MIDD, MERRF, KSS-CEPO)	▪ Ongoing potentially registrational phase 2 study ▪ FALCON pivotal study reported positive 24w interim analysis
Stealth BIOTHERAPEUTICS **Elamipretide**	Peptide	Cardiolipin stabilizer Subcutaneous	Phase 3	nDNA mutations	▪ nDNA represents about 20% of PMD patients ▪ In discussions with FDA for ultra rare Barth syndrome
Tisento THERAPEUTICS **Zagociguat**	Small molecule	Guanylate cyclase stimulator Oral	Phase 2b ready	MELAS	▪ Completed open-label MELAS phase 2a ▪ Phase 2b trial planned with focus on fatigue, myopathy and cognition
KHONDRION **Sonlicromanol**	Small molecule	Redox modulator Oral	Phase 3 ready	mtDNA mutation (MELAS-MIDD)	▪ Phase 2a study in m.3243A>G patients showed predominantly neutral results across multiple endpoints ▪ Phase 2b study failed primary endpoint, positive changes in post-hoc analyses and open-label extension
Reneo **Mavodelpar**	Small molecule	PPARδ agonist Oral	NA	mtDNA in the interventional trial and extended to include nDNA in the OLE	Phase 3 failed to achieve primary endpoint of 12-minute walk test
astellas **Boicedelpar**	Small molecule	PPARδ agonist Oral	NA	Mixed population of mtDNA and nDNA	Phase 2 program using 6-minute walk test terminated