



## COMPANY OVERVIEW

**Dinesh V. Patel, Ph.D.**  
President & CEO

March 11, 2024

# Forward-looking Statements

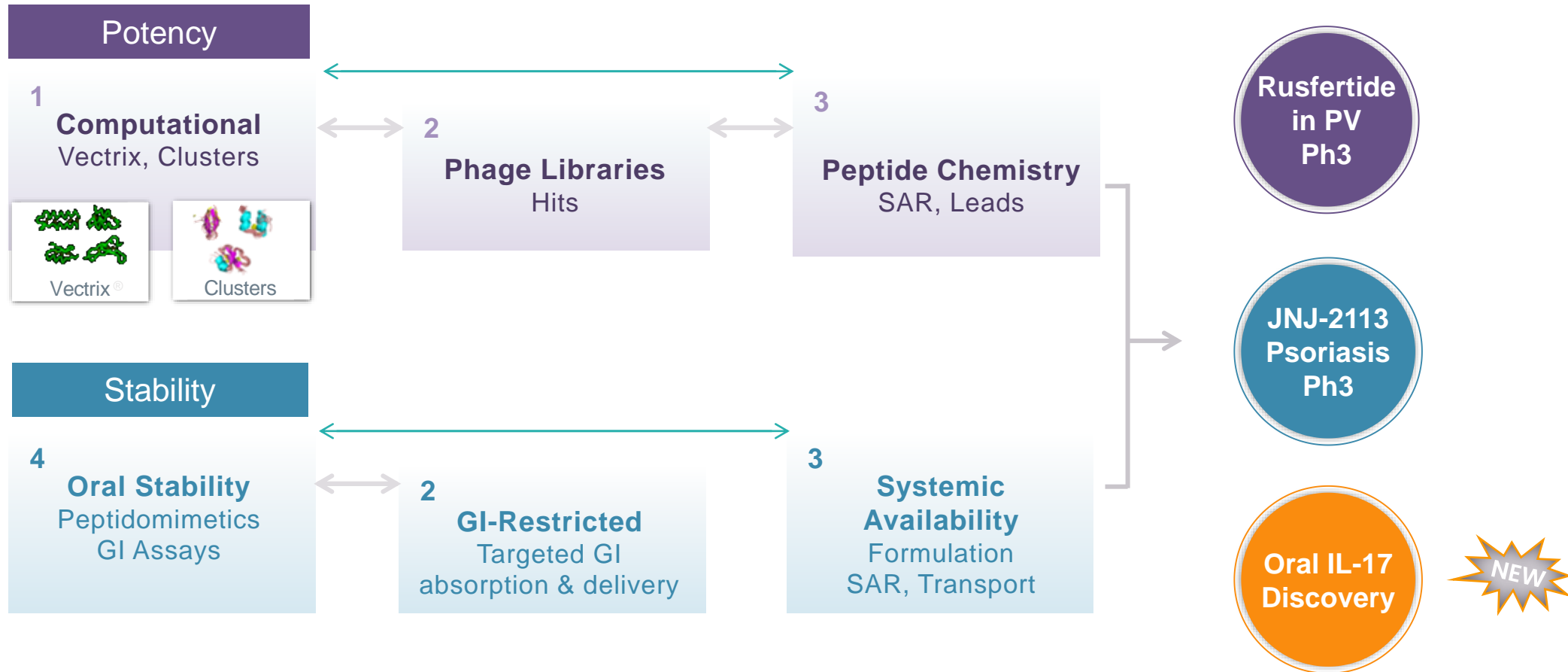
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# Core Competency Remains our Focus

## Expertise in Peptide-based Medicines



# Product Pipeline: Multiple Assets with Multi-Billion Dollar Market Potential

		Disc./Pre-Clinical	Phase 1	Phase 2	Phase 3	Key Milestones
HEMATOLOGY	  <b>RUSFERTIDE</b>	<b>Polycythemia Vera (PV)</b>				
		<b>VERIFY Ph3, n~250</b>				• Enrollment completion by end of 1Q 24
		<b>REVIVE Ph2, n=70, 40 wk study + 3 yr OLE</b>				• Completed; OLE ongoing
		<b>THRIVE LTE</b>				• For REVIVE patients on years 3-5
		<b>PACIFIC Ph2 Elevated Hct (&gt;48%), n=20</b>				• Completed
I & I	  <b>JNJ-2113</b> <b>Oral IL-23R</b> <b>Peptide</b> <b>Antagonist</b>	<b>Psoriasis</b>				
		<b>FRONTIER 1 &amp; 2 Ph2b, n~255</b>				• Completed
		<b>ICONIC-LEAD Ph3, n~600</b>				• Primary: PASI 90 & IGA 0/1; completion ~ Nov '24 <sup>1</sup>
		<b>ICONIC-TOTAL Ph3 in special areas of psoriasis, n~300</b>				• Primary: IGA 0/1; completion ~ Nov '24 <sup>2</sup>
		<b>ICONIC- ADVANCE 1 Ph 3, n~750</b>				• JNJ-2113 vs. deucravacitinib; completion ~ Mar '25 <sup>3</sup>
		<b>ICONIC- ADVANCE 2 Ph 3, n~675</b>				• JNJ-2113 vs. deucravacitinib; completion ~ Apr '25 <sup>4</sup>
		<b>Ulcerative Colitis (UC)</b>				
DISCOVERY	 <b>Discovery</b>	<b>Oral IL-17</b>				• Oral peptide development candidate by EOY <sup>6</sup>
		<b>HEME</b>				• Leads in heme program
		<b>Metabolic</b>				

1 See [clinicaltrials.gov NCT06095115](https://clinicaltrials.gov/ct2/show/study/NCT06095115)

2 See [clinicaltrials.gov NCT06095102](https://clinicaltrials.gov/ct2/show/study/NCT06095102)

3 See [clinicaltrials.gov NCT06143878](https://clinicaltrials.gov/ct2/show/study/NCT06143878)

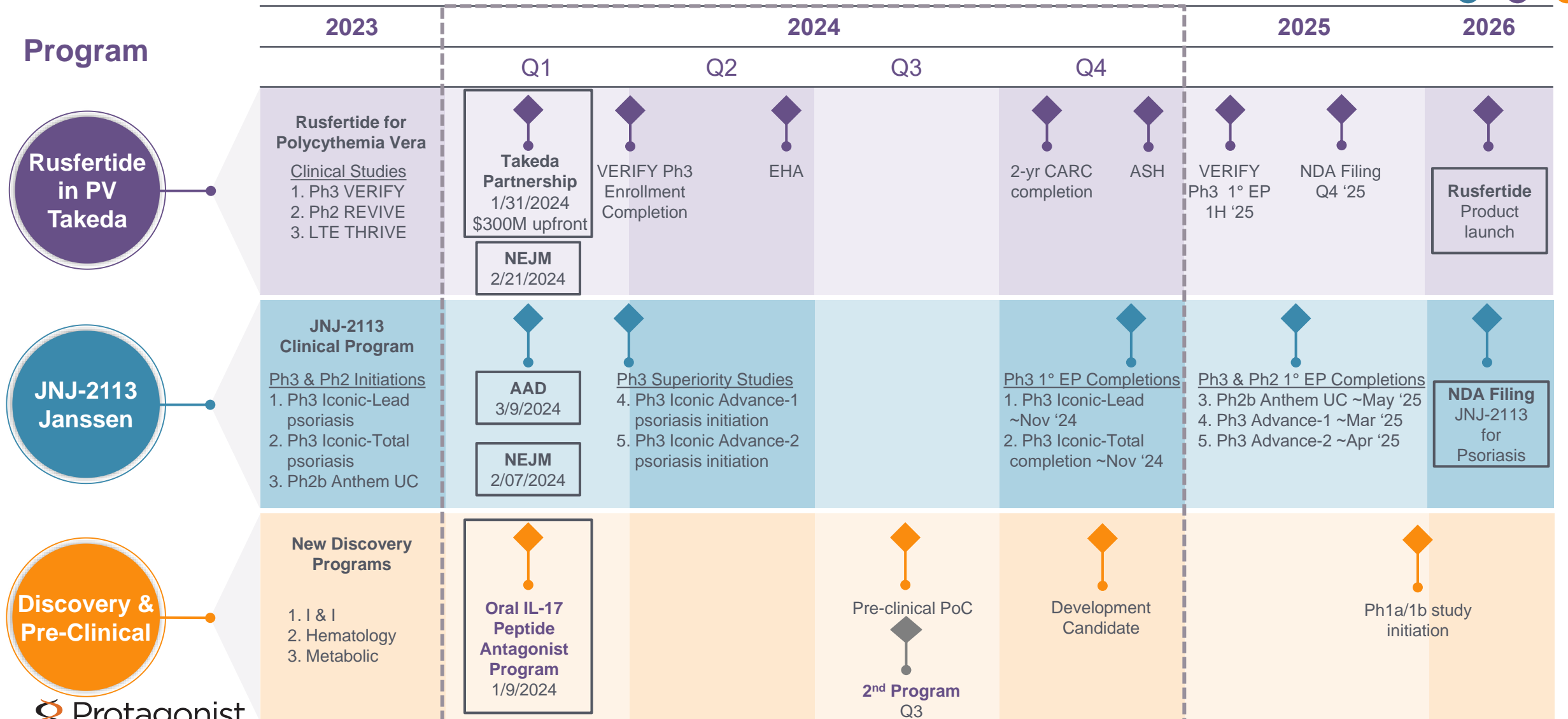
4. See [clinicaltrials.gov NCT06220604](https://clinicaltrials.gov/ct2/show/study/NCT06220604)

5. See [clinicaltrials.gov NCT06049017](https://clinicaltrials.gov/ct2/show/study/NCT06049017)

6. Development Candidate: ready for IND enabling studies

# Major Catalysts Ahead

## A Transformative Path Forward for Protagonist, from Discovery to Development to Commercialization





# Rusfertide

## Hepcidin Hormone Mimetic

Addressing Unmet Needs in  
Polycythemia Vera



# Rusfertide

## Takeda and Protagonist Collaboration, Jan 31, 2024

- Co-development and Co-commercialization partnership with 50:50 profit/loss share in US
  - Takeda has exclusive Ex-US global rights
  - Protagonist responsible for R&D through Phase 3 completion and NDA filing
  - Takeda responsible for pre-commercial activities
  - Up-front payment of \$300M
- Protagonist has the right to remain (**OPT-IN**) in the US 50:50 profit share, or to **OPT-OUT** post-NDA filing

Scenario	Total	Upfront	Payable Opt-Out	Potential Milestones	Royalty Rates	Comment
OPT-IN	\$630M	\$300M	-	\$330M	10-17%	<ul style="list-style-type: none"><li>• 50:50 US profit/loss share</li><li>• Royalties on Ex-US net sales</li></ul>
OPT-OUT	\$1,675M	\$300M	\$400M	\$975M	14-29%	<ul style="list-style-type: none"><li>• No US profit/loss share</li><li>• Royalties on Worldwide net sales</li></ul>

# Rusfertide Publication in *NEJM*, 2024<sup>1</sup>

- Phase 2 REVIVE study investigating rusfertide in PV published in *The New England Journal of Medicine* on 21 February 2024
- REVIVE met the primary efficacy endpoint and achieved a clinically and statistically significant response in maintaining hematocrit control <45%
- Rusfertide associated with lower disease-related symptoms in patients with moderate to severe symptoms at baseline (assessed by the MPN-SAF)
- Most common adverse events were grade 1-2 injection site reactions; no grade 4 or 5 adverse events were reported
- Phase 3 VERIFY study is ongoing to evaluate rusfertide in patients with PV

## Results of REVIVE Phase 2 Study

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

### Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera

M. Kremyanskaya, A.T. Kuykendall, N. Pemmaraju, E.K. Ritchie, J. Gotlib, A. Gerds, J. Palmer, K. Pettit, U.K. Nath, A. Yacoub, A. Molina, S.R. Saks, N.B. Modi, F.H. Valone, S. Khanna, S. Gupta, S. Verstovsek, Y.Z. Ginzburg, and R. Hoffman, for the REVIVE Trial Investigators\*

<sup>1</sup>Kremyanskaya et al. *New Engl J Med*;2024;390:723-35.



# Polycythemia Vera

## Disease Background

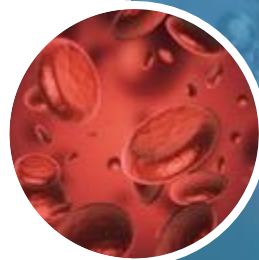
**Myeloproliferative neoplasm characterized by excessive production of red blood cells (RBCs)<sup>1</sup>**

- Elevated hematocrit (Hct) is a hallmark of the disease, indicating overproduction of RBCs<sup>2</sup>

**Serious, chronic disease associated with increased thrombotic and cardiovascular risks<sup>1-3</sup>**

**Rare disease with ~100,000 diagnosed and treated patients in US<sup>1</sup>**

- Diagnosed commonly in individuals 50-70 years of age
- Median survival ~20 years



Treatment goal is to control

# HCT < 45%

to minimize TEs, CV events and death<sup>3</sup>

# The Unmet Need in PV is Three-Fold

## Inconsistent Hct Control, Iron Deficiency, and Symptom Burden

### Inconsistent Hct Control



- Maintaining Hct <45% is critical, as uncontrolled Hct is associated with ~4 times higher rate of death from cardiovascular causes or thrombotic events<sup>2</sup>
- Real-world data shows that 78% of patients have uncontrolled Hct with tests  $\geq 45\%$ <sup>1</sup>

### Iron Deficiency



- Most patients with PV are iron deficient due to depleted bone marrow iron levels<sup>3</sup>
- Some treatments exacerbate disease-related symptoms by inducing iron deficiency<sup>3,4</sup>
- There is no pharmaceutical option with RBC-specific mechanism

### Symptom Burden



- Patients have burdensome symptoms, including fatigue and concentration problems<sup>5</sup>
- 84% of patients report fatigue, and 23% report spending full days in bed because of symptoms<sup>6</sup>
- PV impacts reported activities of daily living and productivity<sup>5</sup>

# Hydroxyurea is the Gatekeeper to Other Agents in PV

» HU, used alone or in combination with phlebotomy, is the most common 2<sup>nd</sup> and 3<sup>rd</sup> line PV therapy<sup>1</sup>

- » Many patients require high doses of HU, but still experience inadequate Hct control
- 60% of patients receiving HU require  $\geq 1,000\text{mg}$  daily<sup>1</sup>
  - 35% of patients receiving HU experience Hct  $\geq 45\%$ <sup>2</sup>
  - Some patients may be intrinsically resistant to HU, making even high doses  $\geq 2,000\text{mg}$  ineffective<sup>2</sup>

- » HU is associated with potentially serious side effects and adverse events<sup>3</sup>
- Myelosuppression may lead to anemia, leukopenia, and thrombocytopenia, especially at high doses
  - Long-term use of HU can cause secondary leukemias and skin cancers

**Sub-optimal efficacy and safety of HU illustrates an unmet need for PV patients with elevated Hct that cannot be managed without frequent phlebotomies**

# Marketed Agents for PV are Cytoreductive Therapies

## No Approved Medications That Specifically Target Red Blood Cells and Hematocrit



### Interferon

Pegasys®, Besremi®

Interferons have long been used off-label in PV treatment; Besremi is the first interferon product approved for PV<sup>1</sup>

Slow onset of action, with average time to response of **1.2 to 1.4 years**<sup>2</sup>

Failed to show noninferiority to HU at 12 months in the PROUD-PV study<sup>3</sup>

Black box warning for serious neuropsychiatric, autoimmune, ischemic, and infectious disorders<sup>2</sup>



### Ruxolitinib

Jakafi®

Only approved for hydroxyurea-resistant or intolerant patients<sup>4</sup>

Improves splenomegaly, a potential marker of disease progression<sup>5</sup>

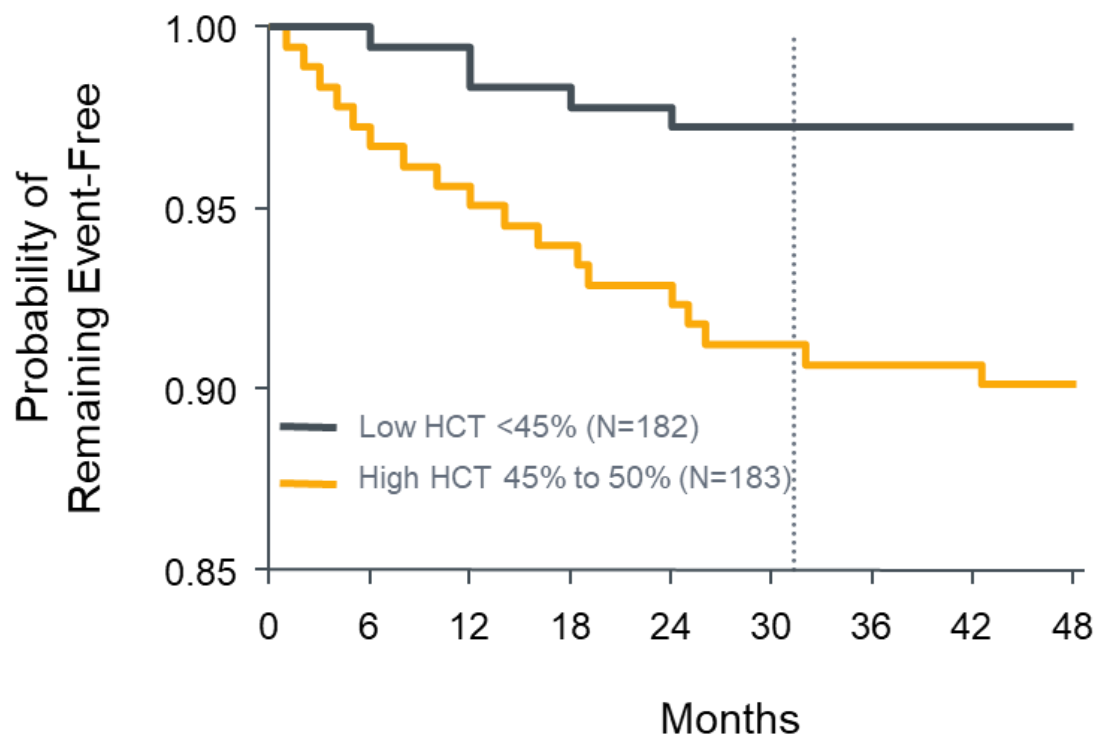
Potential serious side effects include thrombocytopenia, neutropenia, and anemia<sup>4</sup>

**23%** of patients were found to have discontinued ruxolitinib within a mean of **2 years** post treatment initiation<sup>6</sup>

# Increased Hematocrit is Associated with Increased Morbidity and Mortality

## Current Treatment Options are Inadequate

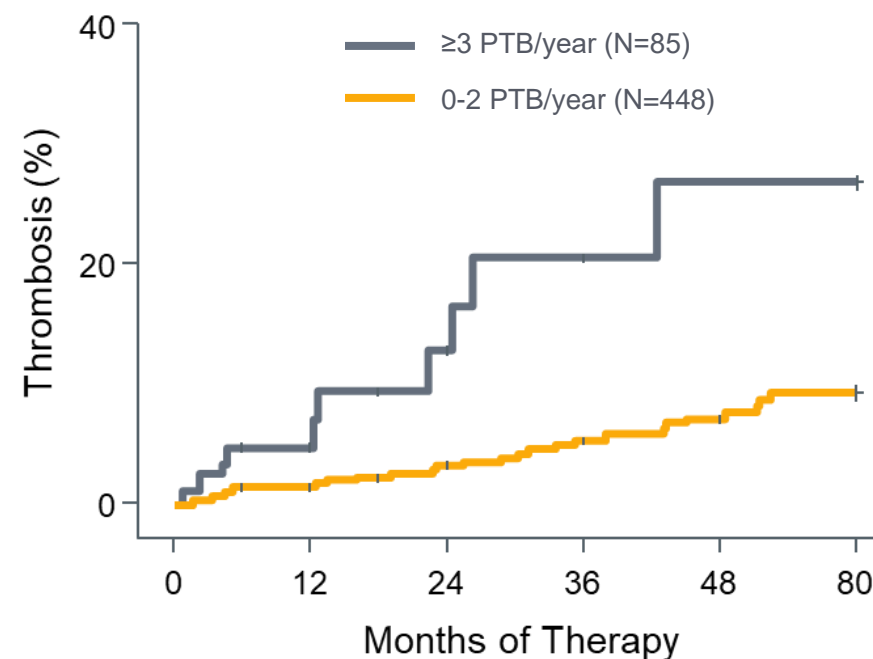
### Elevated Hematocrit Contributes to ~4x Increased Risk of CV Death and Major Thrombosis



Marchioli, R. et al., *N Engl J Med.* 2013;368(1):22-33.

### Phlebotomy, Even with Concomitant Cytoreductive Therapy, Is Inadequate in Reducing Thrombotic Risk

All HU-treated ( $P<0.0001$ )



Alberto Alvarez-Larran et al. *Haematologica* 2017; 102:103-109



# Thromboembolic Events are Associated with PV

- In observational studies, **patients with PV had higher rates of TEs** compared to matched controls (14.3 vs 4.9/1000 patient years)<sup>1-3</sup>
- In a retrospective analysis of US electronic health records contained in the Optum® MarketClarity database, TEs were evaluated in 20,000+ PV patients (date range: 2007-2019)<sup>4</sup>
  - Approximately **25% of PV patients experienced post-index TEs**
  - TE incidence was highest among event-based high-risk patients (50.2%), followed by age-based high-risk (25.0%) and low-risk patients (13.3%)

Parameter	Total cohort	Event-based high-risk	Age-based high-risk	Low-risk
Total	N=20,089	n=3256	n=9924	n=6909
Any TE, n (%)	5035 (25.1)	1634 (50.2)	2480 (25.0)	921 (13.3)

- In PV patients with 5 years of follow-up data, high-risk patients had a greater risk of death than event-based low risk patients (37% vs 8.5%, respectively)
- **These data suggest that thrombotic risk reduction should be an area of focus across all PV risk groups**

# Burden of Treatment Impacts Treatment Strategy

## Guidelines Use Risk to Govern Treatment Strategy, but Treatment Burden Has Real-World Significance

### Risk Stratification



- NCCN guidelines characterize PV patients as low- or high-risk, defined as:
  - Low-risk: age <60 years without history of TE
  - High-risk: age ≥60 years and/or history of TE
- Physicians often do not adhere to guidelines for low- and high-risk patients because this stratification is not comprehensive
- Other critical aspects of care, such as perceived **treatment burden**, influence one's treatment strategy

### Treatment Burden



- **Treatment burden** is the impact of patient's therapy regimen on overall wellbeing
- Factors influencing treatment burden include:
  - Physical impacts (side effects, pain, inconvenience of therapy)
  - Psychological impacts (emotional burden, fear of complications)
  - Financial impacts
- According to HCP research, frequent PHL (≥3 in 6 months) and adverse events had the most significant impact on treatment burden

# Identifying PV Patients with Moderate Treatment Burden



Defining the “moderate treatment burden” population using current market treatments and trends is the key to understanding rusfertide's market opportunity

## Key indicators of suboptimal control for a PV patient

### Phlebotomy Frequency



A high frequency of phlebotomies indicates the intervention is not working to maintain Hct  $\leq$ 45%

Frequent phlebotomies may exacerbate iron deficiency and related symptoms<sup>1</sup>

### Dosing of Hydroxyurea



High doses of HU (1-2 g/day) can indicate difficult-to-control PV, especially when used in combination with phlebotomy

Potential serious side effects and adverse events, including leukemic transformation and skin malignancies<sup>2</sup>

### Thrombotic Events



Occurrence of thrombotic events following treatment initiation can be an indicator of the ineffectiveness of the treatment – an example of a sub-optimally controlled PV patient

# Rusfertide for Polycythemia Vera

## Successful Phase 2 Completion and Phase 3 Enrollment Nearing Completion

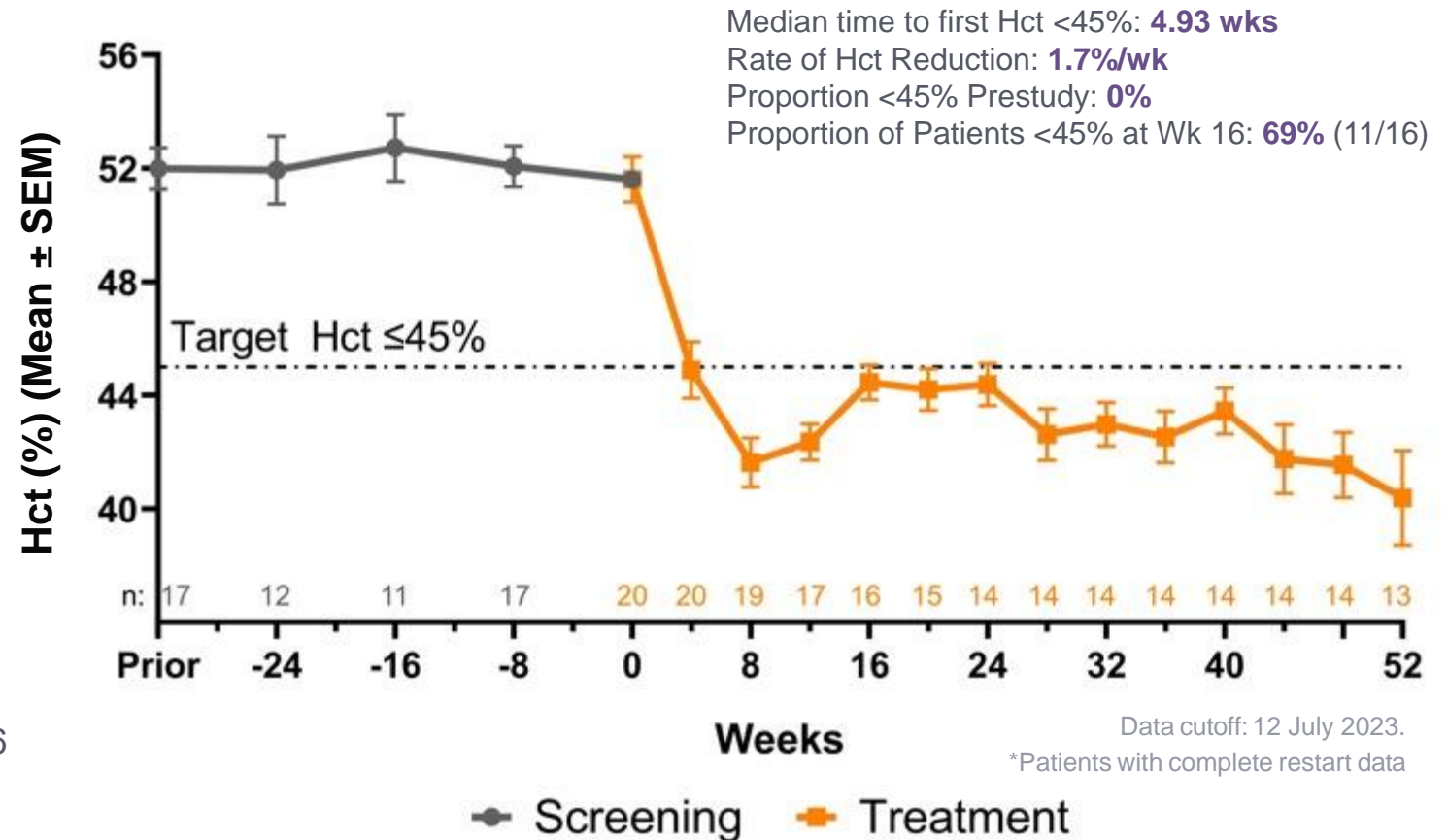
- Phase 2 **REVIVE** Study (n=70):
  - Randomized withdrawal data presented at EHA 2023<sup>1</sup> as a late breaker oral; data published in *NEJM*<sup>2</sup>
    - Full Analysis Population: 69% responder rate (vs. 19% placebo; p=0.0003)
    - Randomized Population: 60% responder rate (vs. 17% placebo; p=0.002)
  - Long-term extension data presented at ASH 2023<sup>3</sup>
    - Durable hematocrit control through 2.5 years
- Phase 2 **THRIVE** Study (n≈50):
  - Long-term extension study (for REVIVE patients on study years 3-5)
- Phase 2 **PACIFIC** Study (n=20)<sup>4</sup>:
  - High hematocrit (Hct >48%); 52-week open-label study completed in Q2 2023
- Phase 3 **VERIFY** Study (n≈250)<sup>5</sup>:
  - Enrollment completion expected in 1Q 2024
  - Primary endpoint essentially same as Phase 2; statistical powering geared for proving secondary endpoints
  - Secondary endpoints include multiple symptom improvement metrics

Rusfertide has **Orphan Drug** designation and **Fast Track** status for PV

# Clinical Study of Rusfertide in PV Patients with High Hematocrit (>48%)<sup>1,2</sup>

## Rapid Hematocrit Control <45% Was Achieved

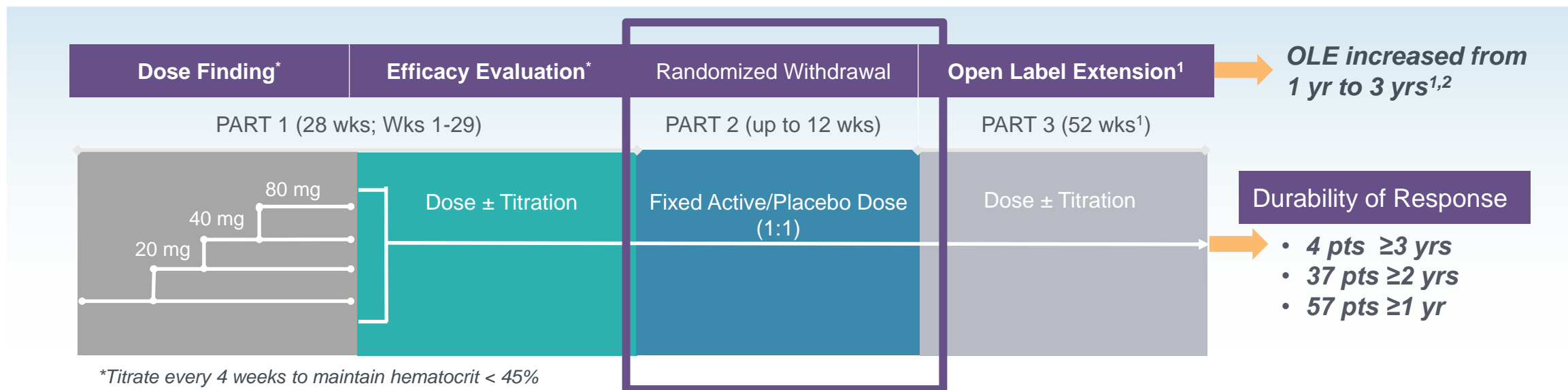
- Open-label, 1 year study in PV patients who are newly diagnosed or for whom current treatment is not sufficient to control hematocrit (Hct)
- Patients met WHO criteria for PV diagnosis
  - Baseline Hct > 48%
  - History of  $\geq 3$  Hct values > 48% in prior 28 wks or  $\geq 5$  Hct values in prior year
  - Phlebotomy alone or with concurrent cytoreductive therapy
  - Initiated rusfertide treatment without prestudy phlebotomy
- Clinical endpoints
  - Proportion of subjects with Hct < 45% at week 16
  - Time to first Hct < 45%
  - Safety





# Phase 2 **REVIVE** Study of Rusfertide in PV Patients (n=70)

## Randomized Withdrawal Design



### STUDY HIGHLIGHTS:

- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- Rusfertide (PTG-300) administered s.c. weekly, added to prior standard therapy
- Key endpoints: Safety, Hct<45%, freedom from phlebotomy, symptom scores

# Baseline Characteristics

Characteristics (n = 70)

## AGE

Range	27-77 years (Median, 58)
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## GENDER

Females	21 (30.0%)
Males	49 (70.0%)

## RISK

Low	30 (42.9%)
High	40 (57.1%) [Age based – 37.1%, Thrombotic events – 20.0%]

## DURATION SINCE PV DIAGNOSIS

≤1 yr	14 (20.0%)
1 - ≤3 yrs	23 (32.9%)
3 - ≤5 yrs	11 (15.7%)
>5 yrs	22 (31.4%)

## CONCURRENT THERAPIES

PHL only	37 (52.9%)
PHL + HU	18 (25.7%)
PHL + IFN	8 (11.4%)
PHL + JAK inhibitor	5 (7.1%)
PHL + Multiple Agents	2 (2.9%)

## NUMBER OF PHL IN 28 WEEKS PRIOR

2	1 (1.4%)
3	13 (18.6%)
4	26 (37.1%)
≥5	30 (42.9%)
Median	4 (2.9)

## WEEKS BETWEEN PHLEBOTOMIES IN 28 WEEKS PRIOR

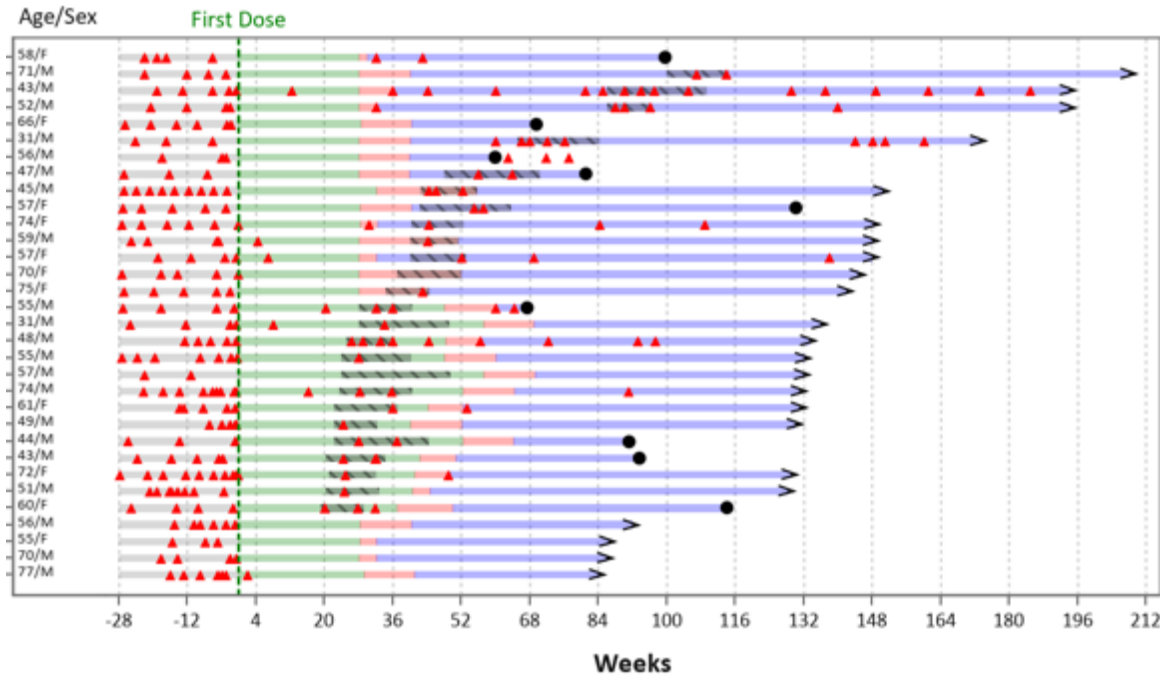
Median	5.5
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# REVIVE: Durability of Rusfertide Efficacy

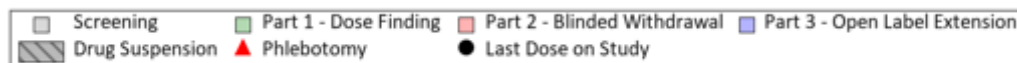
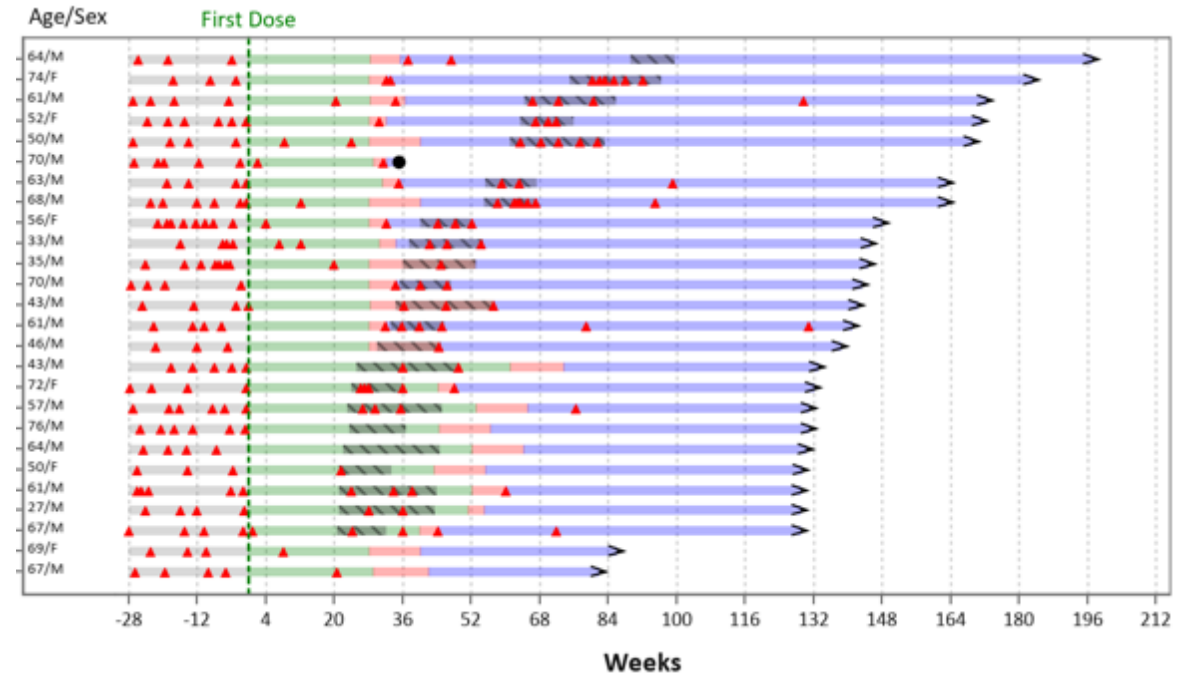
## Significant Reduction in Therapeutic Phlebotomy

- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with cytoreductive therapy, respectively

### Phlebotomy Only (n=32)



### Phlebotomy + Cytoreductive Therapy (n=26)



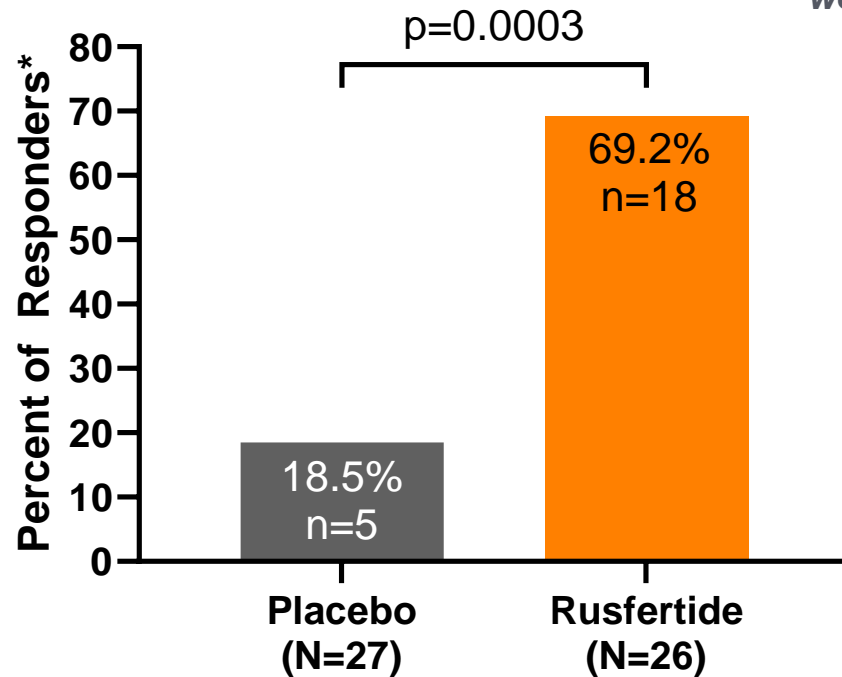
# Part 2: Blinded Randomized Withdrawal Period, Weeks 29-41

## Rusfertide Met Primary Efficacy Endpoint in Prespecified Full Analysis and Randomized Populations

### Full Analysis Population<sup>1</sup>

Highly Significant Efficacy in Rusfertide Arm vs. Placebo in Prespecified Primary Efficacy Endpoint

*\*Patient defined as a responder if they had hematocrit control, did not undergo phlebotomy, and completed the 12-week trial regimen during Part 2*

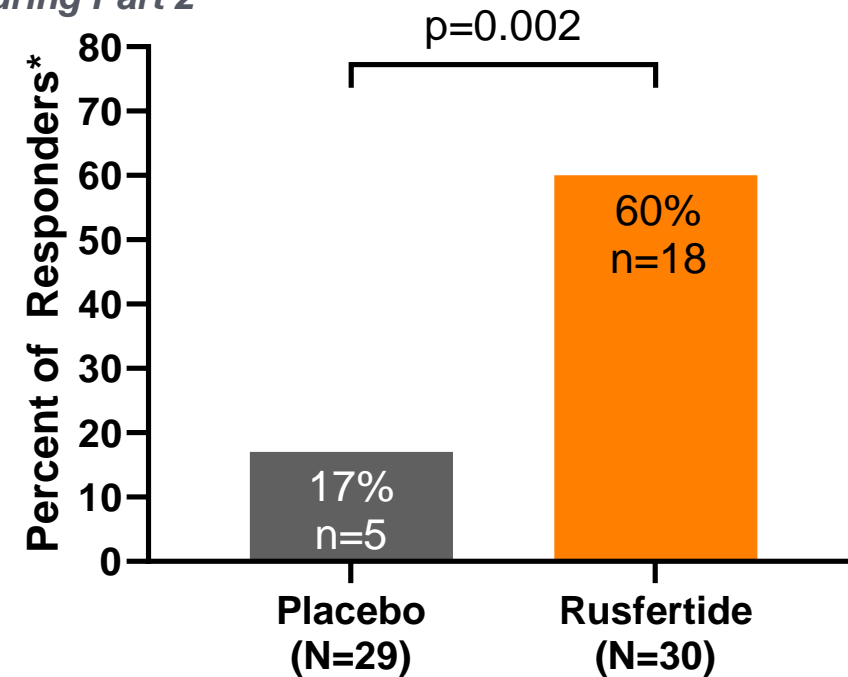


- **69.2% of patients** (18 out of 26) responded to rusfertide

– Full analysis population excludes 6 patients (4 in the rusfertide arm; 2 in the placebo arm) who discontinued early and did not complete Part 2

### Randomized Population<sup>2</sup>

Highly Significant Efficacy in Rusfertide Arm vs. Placebo in Sensitivity Analysis

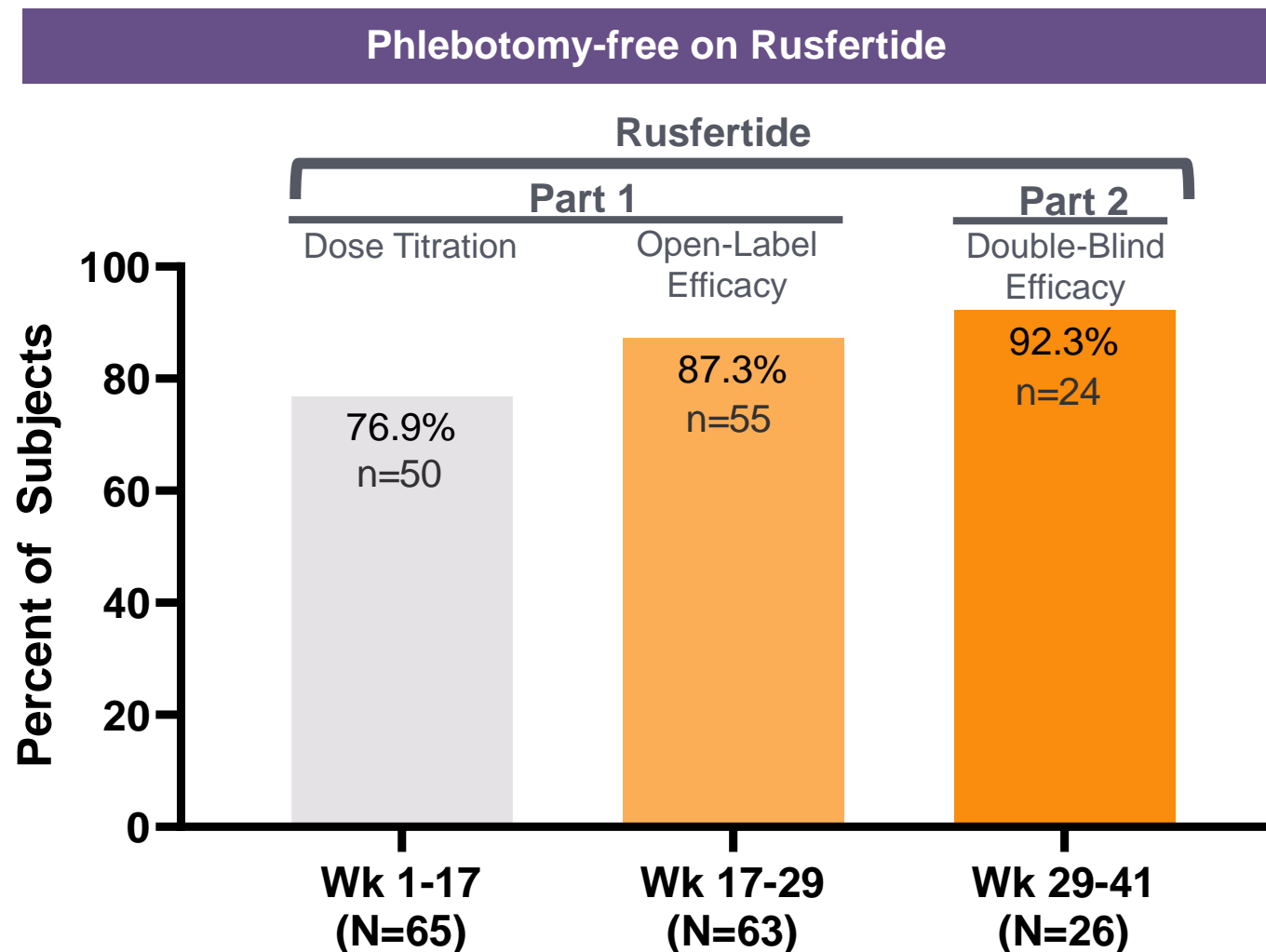


- **60% of patients** (18 out of 30) responded to rusfertide

– Randomized population includes 6 patients (4 in the rusfertide arm; 2 in the placebo arm) who discontinued early and did not complete Part 2

# Phase 2 REVIVE Study: Part 1 and 2

## Consistent Effects on Freedom from Phlebotomy

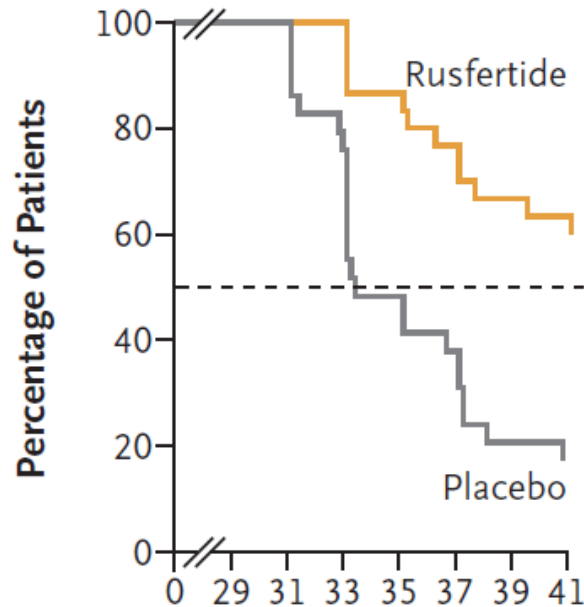




# Phase 2 REVIVE Study: Time to Event Analysis in Randomized Population

Rusfertide Associated With Delayed Time to Loss of Response, Phlebotomy Eligibility, and First Hct  $\geq 45\%$

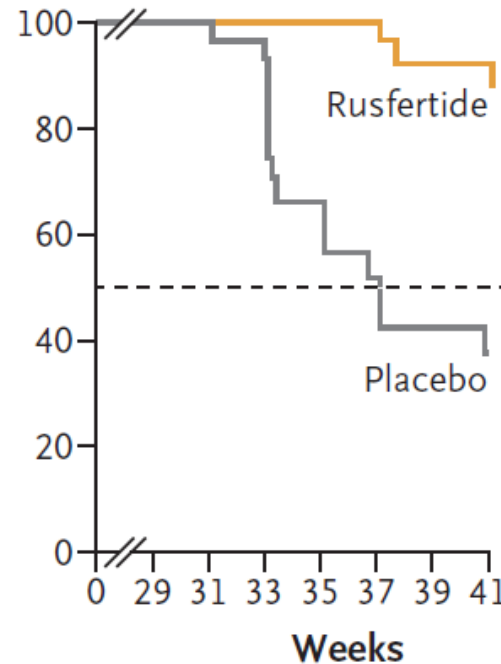
## Time to Loss of Response



**No. of Patients**

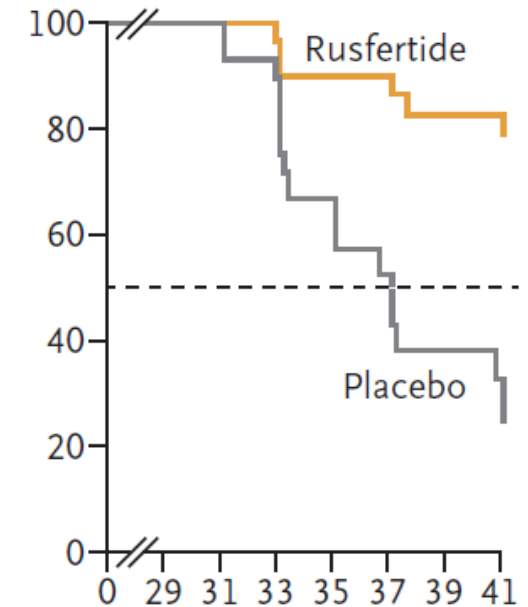
Rusfertide	30	30	26	25	21	20	15
Placebo	29	25	22	12	9	6	5

## Time to Phlebotomy Eligibility



Rusfertide	30	30	30	30	22	20	15
Placebo	29	28	25	12	9	9	5

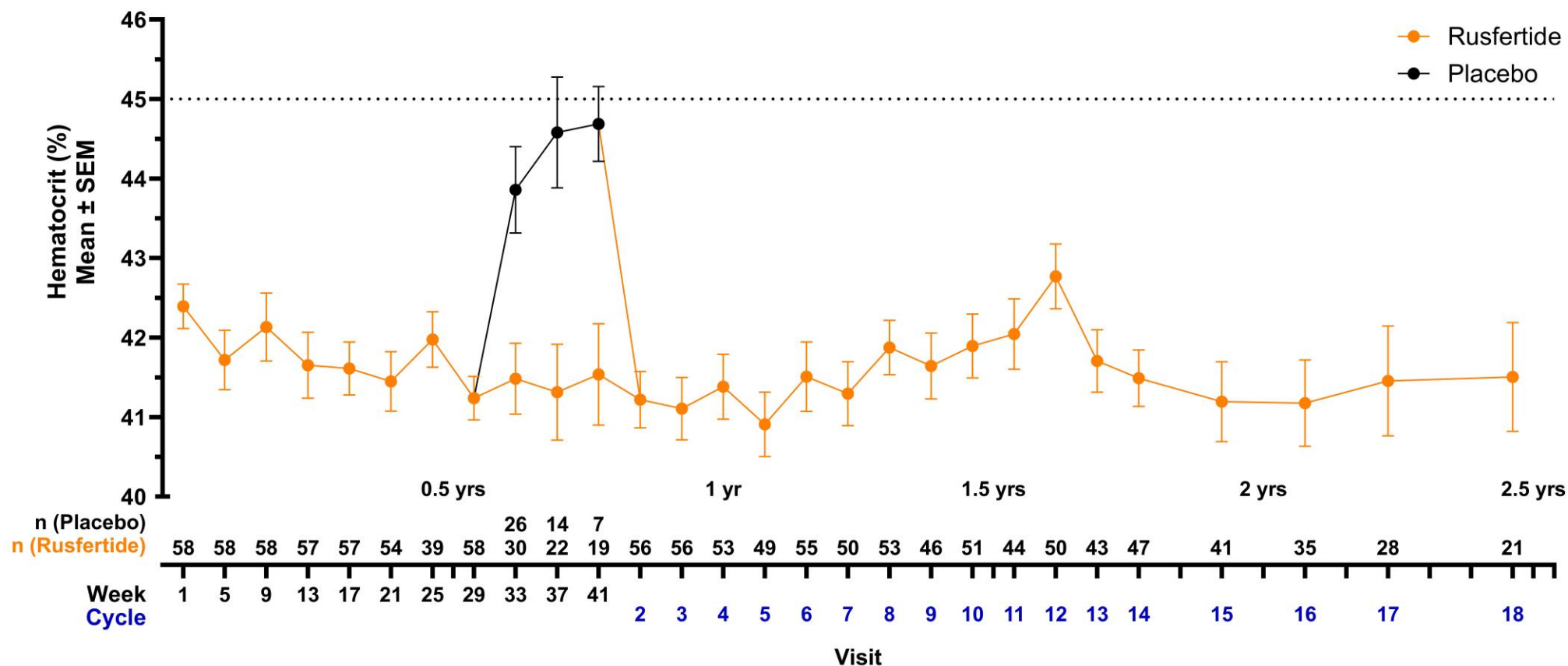
## Time to First Hct $\geq 45\%$



Rusfertide	30	30	29	27	22	20	15
Placebo	29	27	25	12	9	7	3

# Rusfertide Provided Durable Control of Hematocrit Through 2.5 Years

## REVIVE Part 3: Open-Label Extension (OLE)

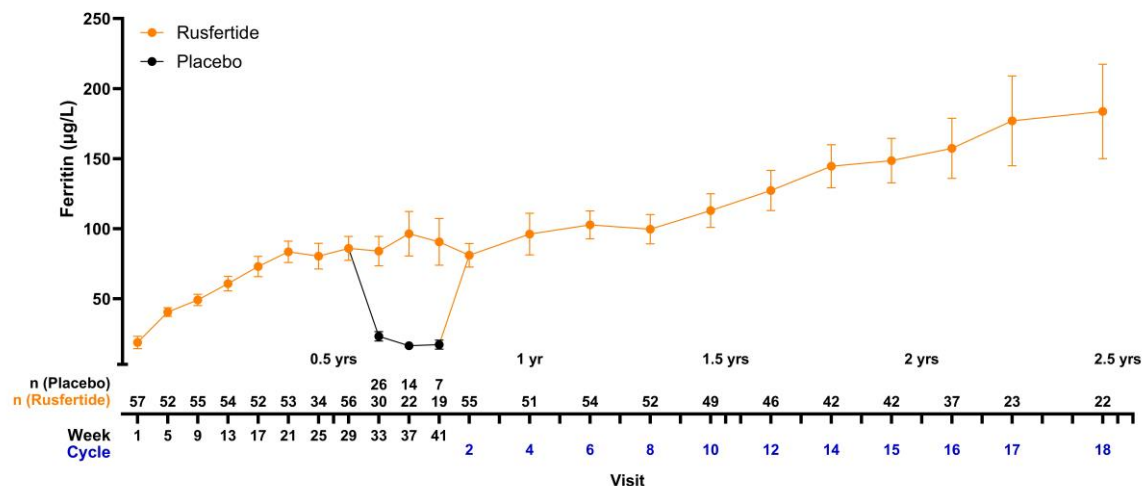


- Rusfertide treatment resulted in consistent maintenance of hematocrit <45%

# Phase 2 REVIVE Study: Symptom Improvement

## Improvement in Ferritin Levels and Symptoms

### Serum Ferritin (Central) Data (Mean $\pm$ 1 SEM)<sup>1</sup>

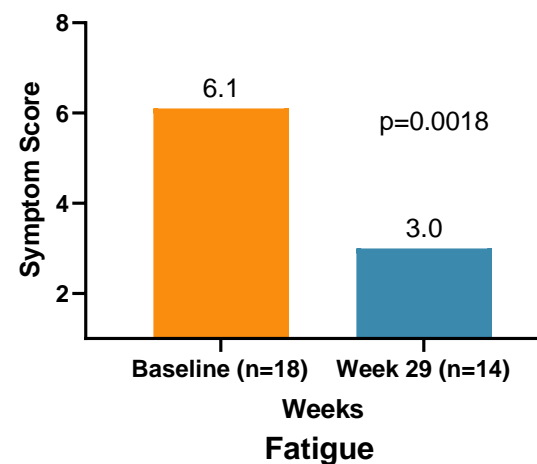


- Prior to enrollment, iron-related parameters were consistent with systemic iron deficiency
- Rusfertide resulted in normalization of serum ferritin levels over 2.5 years

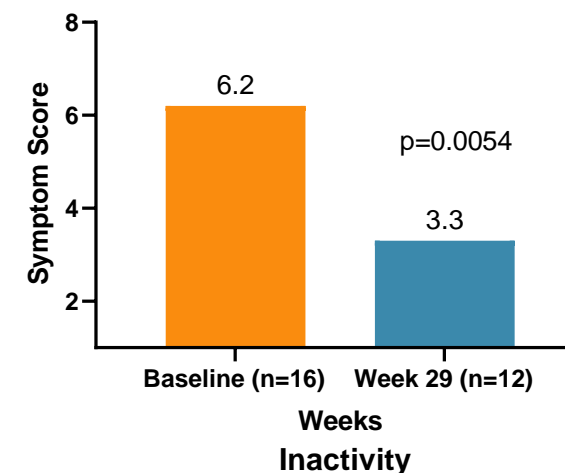
<sup>1</sup>Adapted from Ritchie EK, et al. Durability of Hematocrit Control in Polycythemia Vera with the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results from the Revive Study. *Blood*. 2023;142 (Supplement 1): 745.

### Symptom Improvements in Part 1 (28 Weeks)<sup>2</sup>

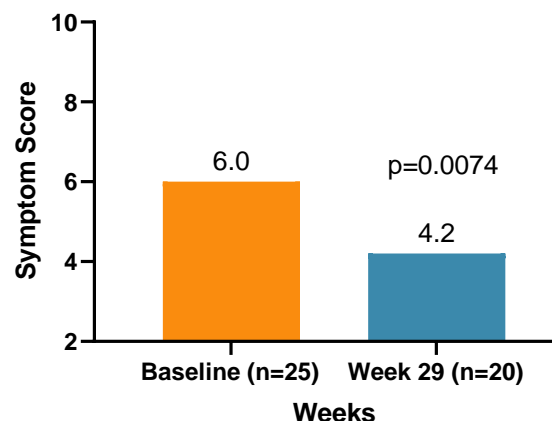
#### Problems with Concentration



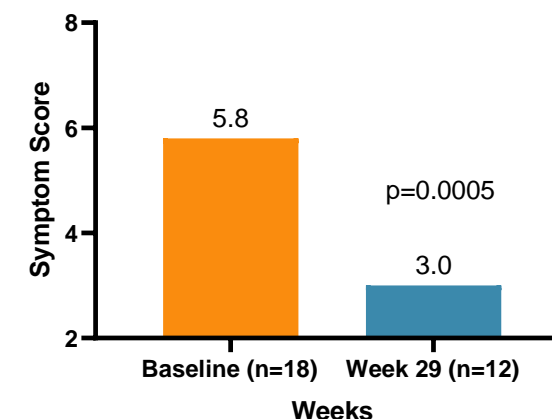
#### Itching



#### Fatigue



#### Inactivity



Individual symptoms assessed using MPN-SAF; p-values are based on paired comparisons

<sup>2</sup>Adapted from Kremyanskaya et al. EHA2023; Abstract LB2710.

# Phase 2 REVIVE Study: Safety and Exposure

## Rusfertide Was Generally Well Tolerated

Summary of Reported TEAEs (Any Grade) by Preferred Term Noted at $\geq 10\%$	N=70
Patients with at least 1 TEAE	70 (100.0)
Injection site erythema	46 (65.7)
Injection site pain	28 (40.0)
Injection site pruritus	28 (40.0)
Fatigue	23 (32.9)
Injection site mass	21 (30.0)
Arthralgia	19 (27.1)
Pruritus	19 (27.1)
Injection site swelling	18 (25.7)
COVID-19	17 (24.3)
Dizziness	17 (24.3)
Headache	16 (22.9)
Nausea	16 (22.9)
Anemia	15 (21.4)
Injection site irritation	14 (20.0)
Injection site bruising	11 (15.7)
Diarrhea	10 (14.3)
Dyspnea	10 (14.3)
Hyperhidrosis	10 (14.3)
Injection site warmth	10 (14.3)

- **70 subjects were enrolled in the rusfertide REVIVE study**
  - 57 subjects (81.4%) have exposure  $\geq 1$  yr
  - 51 subjects (72.9%) have exposure  $\geq 1.5$  yrs
  - 37 subjects (52.9%) have exposure  $\geq 2$  yrs
  - 11 subjects (15.7%) have exposure  $\geq 2.5$  yrs
  - 4 subjects (5.7%) have exposure  $\geq 3$  yrs
  - Overall, the median duration of exposure to rusfertide was 105.4 weeks (range, 3-182 weeks)
- **Rusfertide was generally well tolerated**
  - A majority of TEAEs were Grade 1 or 2
    - Overall, 77.1% of TEAEs had a maximum grade of 2
    - Overall, 21.4% of TEAEs were grade 3
    - No Grade 4 or 5 TEAEs
  - The most common TEAEs were injection site reactions, which were localized and grade 1-2 in severity and decreased in incidence

# REVIVE: Serious Adverse Events

## No New Safety Signals

- Overall, 14 patients (20.0%) experienced an SAE\*
  - There were 3 cases of basal cell carcinoma
  - There was 1 case each of atrial fibrillation, myocardial infarction, anogenital dysplasia, constipation, non-cardiac chest pain, gastroenteritis, sepsis, lung adenocarcinoma, malignant melanoma, malignant melanoma (Stage I), acute myeloid leukemia (Part 2; placebo arm), squamous cell carcinoma (Part 2; placebo arm), ischemic stroke, syncope, transient ischemic attack, peripheral artery aneurysm, and peripheral vascular disorder
- The nature of the SAEs observed is consistent with comorbidities anticipated in the PV population, including vascular events and skin cancer

*\*Most SAEs were assessed as being unrelated to rusfertide by the investigators*

Data cutoff: 17 October 2023

# Prevalence of Second Cancers in PV

## Second Cancers

- One large population-based study found that **patients with MPNs had a 60% higher risk of developing second non-hematologic cancers** compared to matched controls<sup>1</sup>
  - **Skin cancers were among the most prevalent second cancers** (2.8-fold increase in risk of non-melanoma skin cancer vs. matched controls)
- In a retrospective analysis of US electronic health records contained in the Optum® MarketClarity database, the post-index period prevalence of second cancers was evaluated in 20,000+ PV patients (date range: 2007-2019)<sup>2</sup>
  - **35.7%** of patients had **at least one second cancer** in the post-index period; **the highest rates were observed for skin cancers**
    - **9.1%** of patients had **any form of skin cancer**
    - **8.3%** of patients had **non-melanoma skin cancer**
    - **1.4%** of patients had **melanoma**
  - Patients treated with hydroxyurea had nearly **2×** the rate of skin cancers compared to patients treated with phlebotomy alone
- **Given these data<sup>1,2</sup>, patients with PV appear to have high rates of second cancers, including skin cancers**

# Rusfertide Summary

## An Investigational Injectable Hepcidin Mimetic for Treatment of Polycythemia Vera



- PV patients requiring frequent phlebotomy  $\pm$  cytoreductives have been treated with rusfertide for **>2 years** in the **REVIVE** study, with subjects remaining essentially phlebotomy free
  - Rapid, sustained and durable hematocrit control
  - Robust efficacy in all categories of patients
  - Rusfertide dosing was interrupted and led to loss of effect; restart restored therapeutic benefits
  - Positive improvements in symptom scores
  - 53 patients, 1:1 randomization part 2 of the study completed

- Rapid Hct control (<45%) without phlebotomy in high Hct (>48%) **PACIFIC** study
- 
- Rusfertide treatment with or without cytoreductives appears to be well tolerated
    - Safety update presented at ASH in December 2023; no new safety signals observed<sup>1</sup>
- 
- ~250 patient, randomized, placebo-controlled Ph3 **VERIFY** study to confirm efficacy and safety
    - Execution underway, enrollment completion by 1Q 2024



# Phase 3 Study **VERIFY** (NCT05210790): Rusfertide vs Placebo in Patients With PV

## Pathway to Potential Registration in the USA and Europe

Phase 3 VERIFY study design capitalizes on the successful outcome to date of the Phase 2 REVIVE Study

### Key Eligibility:

- ✓ Age ≥18 years
- ✓ Meet revised 2016 WHO criteria for diagnosis of PV
- ✓ ≥3 phlebotomies due to inadequate Hct control in 28 weeks before randomization OR ≥5 phlebotomies due to inadequate Hct control within 1 year prior to randomization

**N≈250**

### Part 1A: Double-Blind

**Dose Titration**  
(Weeks 0-20)

**Primary Efficacy**  
(Weeks 20-32)

Placebo + phlebotomy ±  
cytoreductive therapy (n≈125)

Rusfertide + phlebotomy ±  
cytoreductive therapy (n≈125)  
*Starting dose: 20 mg SC Q1W*

CRT may be decreased or stopped but not increased

### Part 1B: Open-Label

**Durability of Response**  
(Weeks 32-52)

Rusfertide +  
ongoing therapy

### Part 2: Open-Label

**2 Year Long-Term Safety Follow-Up**  
(Weeks 52-156)

Rusfertide +  
PV therapy

Dose of CRT may be changed or new CRT  
may be initiated

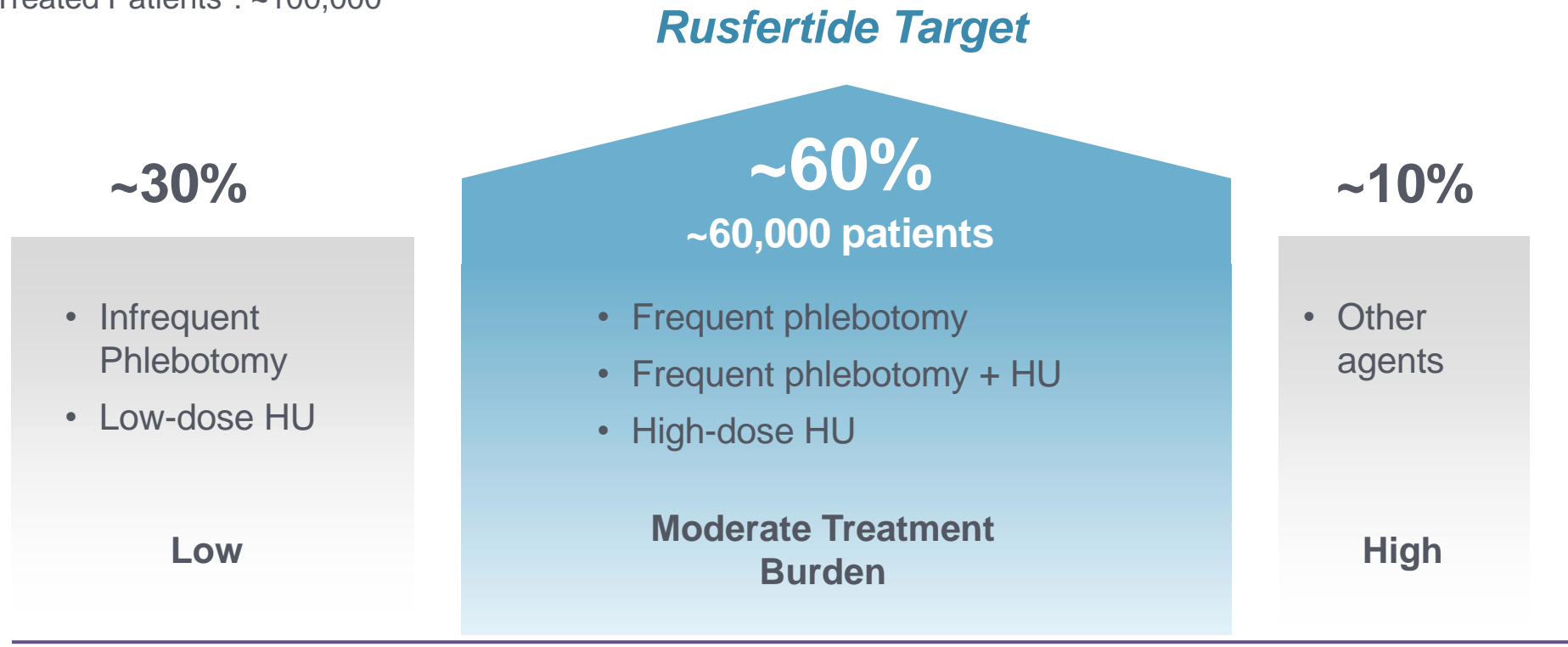
### Key Endpoints:

- Proportion of patients achieving response (defined as absence of phlebotomy eligibility; measured between Weeks 20-32)
- Mean number of phlebotomies (Weeks 0-32)

# Potential Commercial Positioning for Rusfertide

## Potential Therapy of Choice for Patients with Moderate Treatment Burden

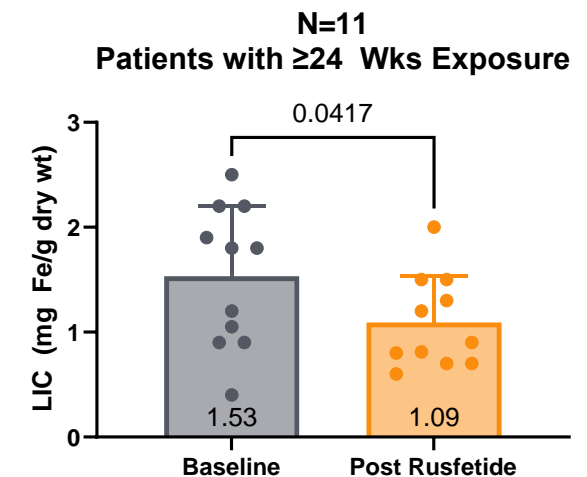
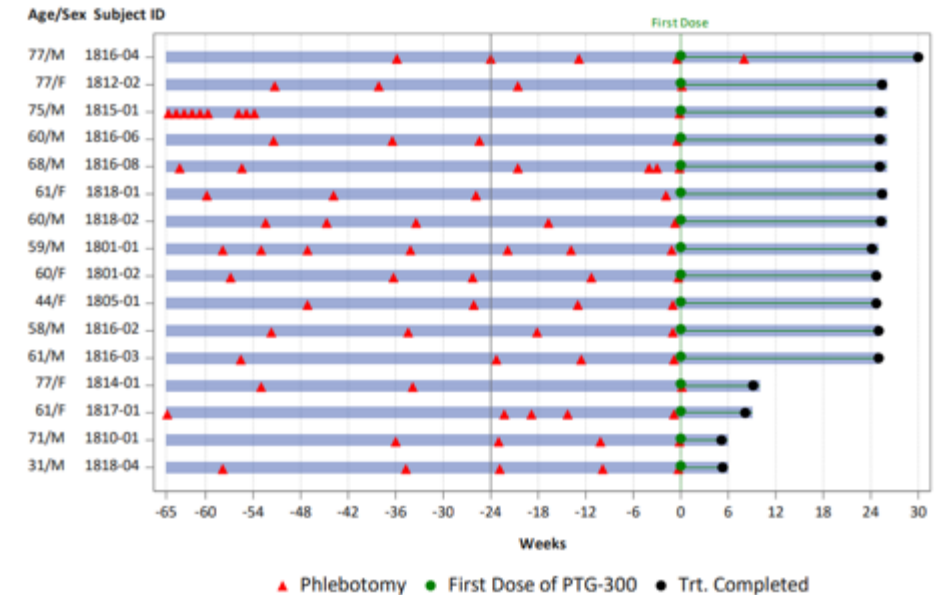
Prevalent Patients in US<sup>1</sup>: ~160,000  
Diagnosed & Treated Patients<sup>2</sup>: ~100,000



# Clinical Study of Rusfertide in Patients with Hemochromatosis

## Control Serum Iron and Reduce Phlebotomies

- Open-label, 24-week proof-of-concept study in patients with hemochromatosis
- Eligibility
  - Adults with HFE-related hemochromatosis.
  - History of  $\geq 3$  phlebotomies in 12 months or  $\geq 4$  phlebotomies in 15 months
- Clinical endpoints
  - Number of phlebotomies
  - Liver Iron Concentration (LIC) by MRI
- Manuscript published in *Lancet Gastroenterol Hepatol* in December 2023<sup>1</sup>
  - Rusfertide treatment rapidly reduced and suppressed serum iron and TSAT.
  - Essential elimination of phlebotomies and stable LIC.
  - Rusfertide was generally well tolerated





# **JNJ-2113: Oral IL-23 Receptor Antagonist Peptide**

Targeted Investigational Therapy for  
Psoriasis & Other IL-23 Mediated Diseases



# Protagonist-Janssen Oral, IL-23R Antagonist Collaboration



## Collaboration overview

- Initiated in 2017 with I&I market leader Janssen Biotech<sup>1</sup>
- JNJ-2113 (formerly PN-235) jointly discovered using Protagonist's proprietary peptide discovery platform
  - Protagonist completed pre-clinical and first Phase 1 study
  - Janssen responsible for further development and commercialization

## Comprehensive JNJ-2113 Phase 3 registrational program (ICONIC) in psoriasis

- Four Phase 3 studies
- PASI 90 highlighted as high-bar primary endpoint to reflect the modern clinical goal of durable, symptom-free remission
- Two head-to-head trials vs. deucravacitinib
- All psoriasis trials to be conducted with single dose of JNJ-2113 at 200 mg once-daily

## Phase 2b study in ulcerative colitis ongoing (ANTHEM)

## JNJ-2113 highlighted as first- and best-in class targeted oral IL-23 peptide antagonist<sup>2</sup>

- "Unprecedented potential" from JNJ-2113 across multiple indications: IBD, plaque psoriasis, psoriatic arthritis, IBD
- PTGX positioned as delivering "transformational science" and a source of "best innovation" alongside two other JNJ partners
- "Potential peak year sales for JNJ-2113 across indications: **\$5B+**"

# JNJ-2113 Market Potential<sup>1</sup>

## Big Opportunity for a safe and effective oral, once daily medication

- **50-70%** of patients (~5 million in G8) living with psoriatic and IBD conditions and are eligible for advanced therapies, and yet aren't receiving them

### Reasons eligible patients avoid using advanced treatments<sup>2</sup>

**30%** Method of administration

**75%** Overall risk/benefit profile

### Market growth expected to be driven by orals<sup>4</sup>

Patients on injectables who would switch to an oral with similar safety & efficacy<sup>3</sup>

**75%**

**~5M** Eligible patients not receiving advanced therapy

### Growing Market for Oral Treatment Options<sup>5</sup>

WW market Size 2030 est. (7-yr CAGR) <sup>1</sup>	PsO	~\$35B (4-6%)
	PsA	~\$8B (4-6%)
	CD	~\$19B (2-4%)
	UC	~\$13B (7-9%)

Combination of advanced efficacy and trusted safety in a preferred oral formulation could unlock a large market share

# JNJ-2113: Oral, IL-23R Peptide Antagonist

## Preclinical, Phase 1 and Phase 2b Data Supportive of a Robust Clinical Development Program<sup>1</sup>



### Highly Potent Oral IL-23R Antagonist

- **Picomolar potency**  
Similar or better target affinity vs. IL-23 mAbs

### High Oral Stability

- >24hr half-life in feces (human, cyno, and rat)
- >25% fecal recovery after 24hrs in cynos

### Pre-clinical Proof-of-Concept

- Rat ear skin inflammation model
- Rat TNBS colitis model

### Phase 1 studies in NHVs

- PD based PoC: Inhibition of IL-23 biomarkers

### Phase 2b FRONTIER1 study in Psoriasis

- Potential for best-in-class oral agent for psoriasis

Protagonist – JNJ Innovative Medicines Discovery & Development Partnership



# JNJ-2113 FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

A Phase 2b multicenter, randomized, placebo controlled, dose-ranging study to evaluate the efficacy and safety of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis

## Adult Patients with PP

N=255

### Eligibility

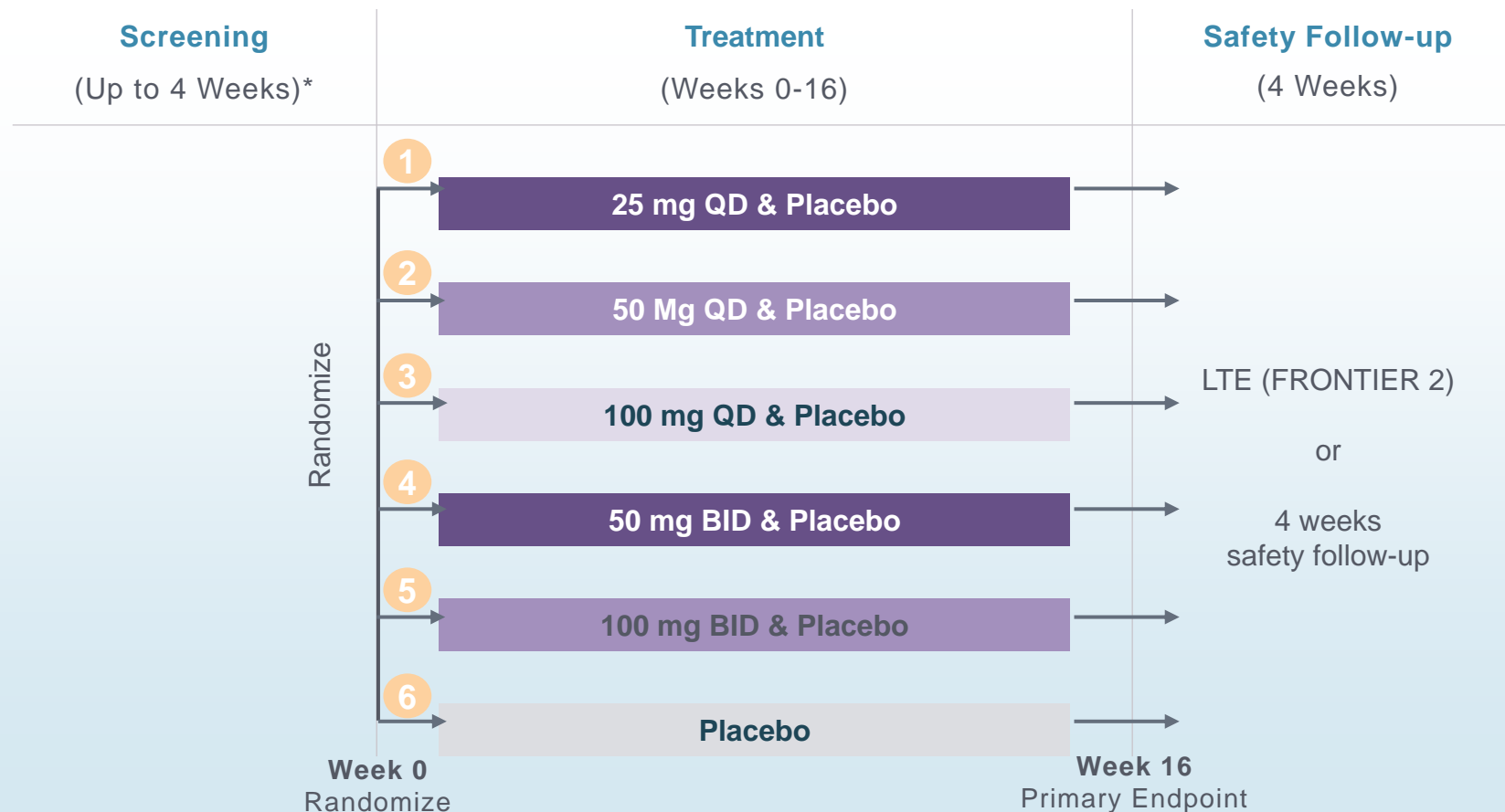
- Moderate – Severe PP

### Inclusion

- BSA  $\geq 10\%$
- PASI  $\geq 12$

### Primary endpoint

- PASI  $\geq 75$  at Week 16



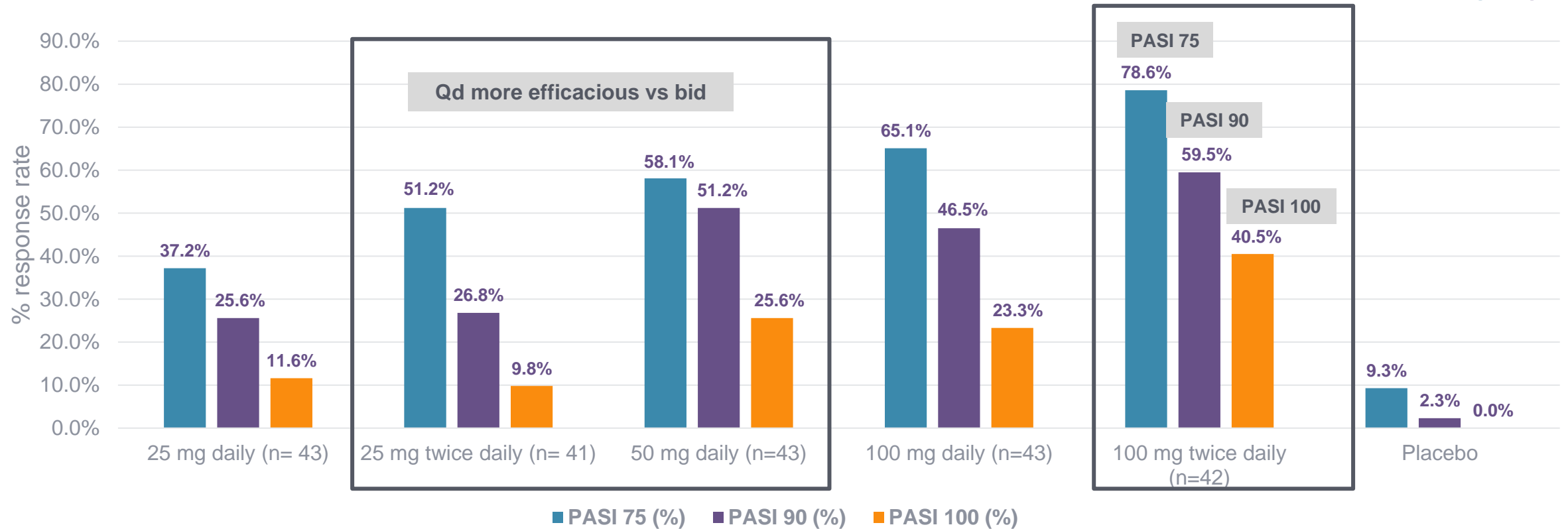
# Demographics and Disease Characteristics at Baseline

	Placebo	JNJ-77242113						Total
		25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID	Combined*	
Full analysis set	43	43	43	41	43	42	212	255
Age (yrs)	43.9 (14.70)	44.5 (12.72)	45.1 (11.08)	45.7 (11.91)	44.7 (14.11)	42.0 (11.34)	44.4 (12.24)	44.3 (12.65)
Weight (kg)	92.1 (24.66)	89.0 (19.42)	87.6 (19.23)	90.8 (22.12)	85.4 (22.49)	88.5 (16.94)	88.2 (20.03)	88.9 (20.87)
BMI (kg/m <sup>2</sup> )	31.2 (7.61)	30.0 (7.25)	29.3 (5.97)	30.2 (6.72)	28.8 (7.39)	30.0 (5.40)	29.6 (6.55)	29.9 (6.75)
PsO disease duration (yrs)	17.9 (14.37)	15.5 (11.76)	21.5 (11.16)	18.1 (11.82)	19.5 (13.34)	16.7 (13.78)	18.3 (12.48)	18.2 (12.79)
Age at diagnosis (yrs)	26.1 (15.55)	29.1 (15.56)	23.7 (11.57)	27.7 (13.73)	25.3 (15.08)	25.5 (15.26)	26.2 (14.31)	26.2 (14.50)
PASI total score	18.99 (5.341)	18.90 (5.272)	19.23 (5.082)	18.46 (5.838)	18.42 (6.873)	20.33 (6.509)	19.07 (5.938)	19.05 (5.831)
IGA score, n (%)								
Severe (4)	5 (11.6%)	13 (30.2%)	7 (16.3%)	8 (19.5%)	8 (18.6%)	12 (28.6%)	48 (22.6%)	53 (20.8%)
Moderate (3)	38 (88.4%)	30 (69.8%)	36 (83.7%)	33 (80.5%)	35 (81.4%)	30 (71.4%)	164 (77.4%)	202 (79.2%)
Previous Psoriasis Medications/Therapies, n (%)								
Phototherapy**	19 (44.2%)	17 (39.5%)	24 (55.8%)	15 (36.6%)	21 (48.8%)	14 (33.3%)	91 (42.9%)	110 (43.1%)
Biologics†	7 (16.3%)	7 (16.3%)	11 (25.6%)	13 (31.7%)	9 (20.9%)	9 (21.4%)	49 (23.1%)	56 (22.0%)
Systemics‡	34 (79.1%)	33 (76.7%)	35 (81.4%)	33 (80.5%)	34 (79.1%)	31 (73.8%)	166 (78.3%)	200 (78.4%)

BID=Twice daily; BMI=Body mass index; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; PsO=Psoriasis; PUVA=Psoralen plus ultraviolet A; QD=Daily; UVB=Ultraviolet B. Data shown are mean (SD), unless otherwise indicated. \*Includes all JNJ-77242113 treatment columns. \*\*Includes PUVA or UVB. †Includes etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, certolizumab pegol. ‡Includes conventional nonbiologic systemics, novel nonbiologic systemics, 1,25-vitamin D3 and analogues, phototherapy, biologics.

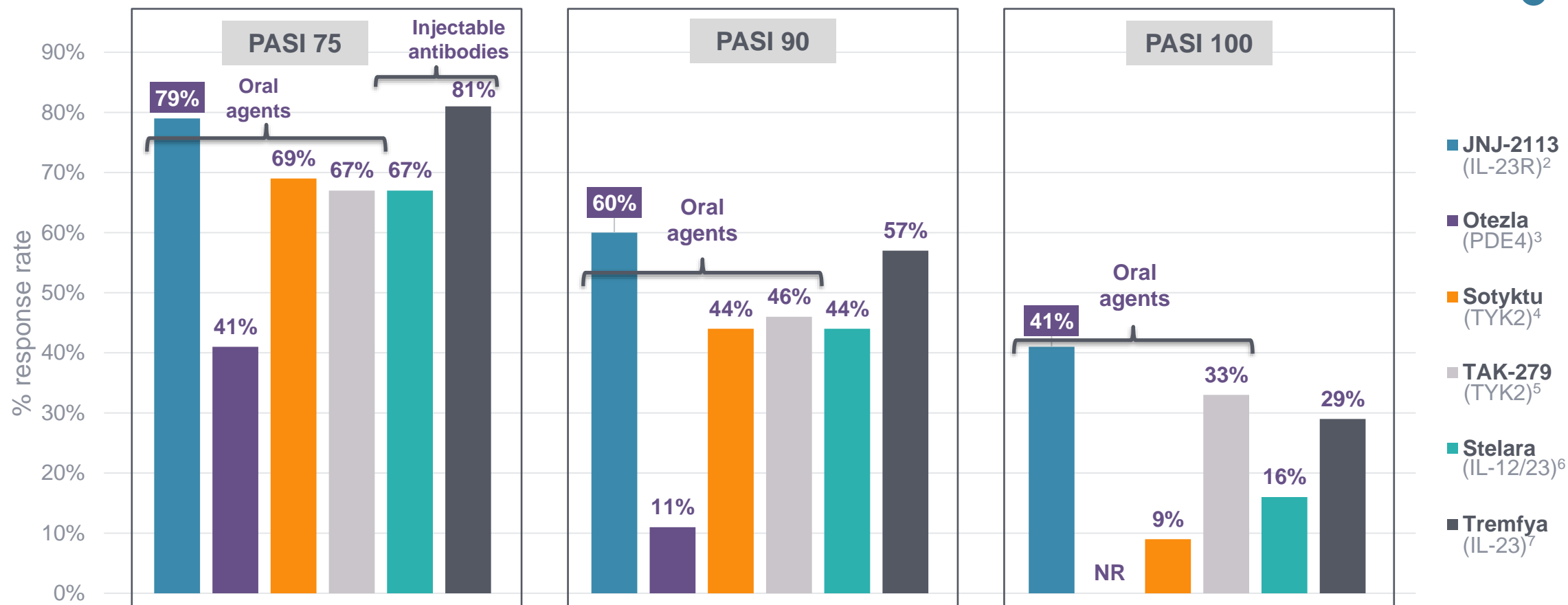
# JNJ-2113 Phase 2B Frontier 1 Data

## Dose Response



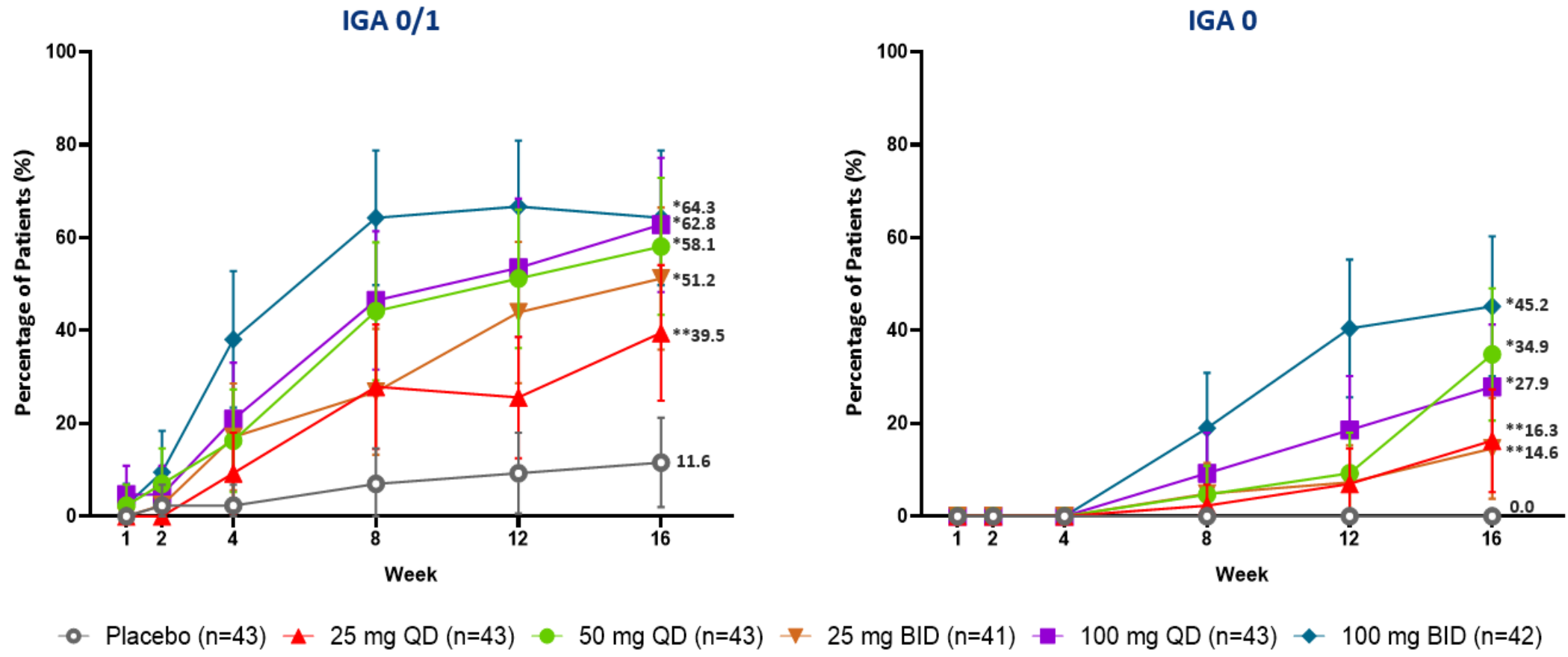
- 200 mg once daily oral dose selected for all four phase 3 psoriasis studies
- PASI 90 as a high-bar primary endpoint in these phase 3 studies

# Cross-Study Comparison of JNJ-2113 to Clinically Relevant Phase 2 Benchmarks<sup>1</sup>



1. Cross trial (not head-to-head) comparisons
2. JNJ2113 100 mg bid dose. Wk 16 endpoint (Placebo: PASI 75: 9.3%, PASI 90: 2.3%, PASI 100: 0%)
3. Otezla 30 mg qd approved dose. Week 16 primary endpoint. Papp K et al. Lancet 2012; 380: 738–46. (Placebo: PASI 75: 5.7%, PASI 90: 1.1%, PASI 100: NR)
4. Sotyktu 3 mg bid dose (6 mg qd dose approved). Wk 12 primary endpoint. Papp K et al. N Engl J Med 2018; 379:1313-1321. (Placebo: PASI 75: 7%, PASI 90: 2%, PASI 100: 0%)
5. TAK-279 30 mg qd dose (Expected phase 3 dose). Wk 12 primary endpoint. AAD 2023. (Placebo: PASI 75: 5.8%, PASI 90: 0%, PASI 100: 0%)
6. Stelara 45 mg wklly x 4 (~approved 90 mg week 0 and 2 approved dose). Wk 12 primary endpoint. Krueger et al. N Engl J Med 2007;356:580-92. (Placebo: PASI 75: 2%, PASI 90: 2%, PASI 100: 0%)
7. Tremfya 200 mg wk 0, 4, then q 8 wks (approved dose 100 mg wk 0, 4 then q 8 wks). Wk 16 primary endpoint. Gordon KB et al. N Engl J Med 2015;373:136-44. (Placebo: PASI 75: 5%, PASI 90: 2%, PASI 100: 0%)

# Proportion of Patients Achieving IGA 0/1 and IGA 0 (95% CI) Through Week 16



Non-responder imputation  
\*nominal  $p < 0.001$  vs placebo; \*\*nominal  $p < 0.01$  vs placebo. p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category ( $\leq 90$  kg,  $> 90$  kg). Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

# Number of Patients With $\geq 1$ TEAE With Frequency of $\geq 5\%$ of Preferred Terms in Any Treatment Group Through End of Study by System Organ Class and Preferred Term

	Placebo	JNJ-77242113					
		25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID	Combined*
Safety analysis set, n	43	43	43	41	43	42	212
Avg duration of follow-up (weeks)	15.03	15.70	15.75	16.20	16.07	15.81	15.90
Patients with $\geq 1$ AE, n (%)	22 (51.2%)	20 (46.5%)	26 (60.5%)	20 (48.8%)	19 (44.2%)	26 (61.9%)	111 (52.4%)
System organ class/Preferred term, n (%)							
Infections and infestations	12 (27.9%)	15 (34.9%)	17 (39.5%)	14 (34.1%)	7 (16.3%)	11 (26.2%)	64 (30.2%)
COVID-19	5 (11.6%)	5 (11.6%)	3 (7.0%)	8 (19.5%)	3 (7.0%)	4 (9.5%)	23 (10.8%)
Nasopharyngitis	2 (4.7%)	1 (2.3%)	8 (18.6%)	3 (7.3%)	1 (2.3%)	2 (4.8%)	15 (7.1%)
Upper respiratory tract infection	1 (2.3%)	3 (7.0%)	0	0	0	2 (4.8%)	5 (2.4%)
Gastrointestinal disorders	5 (11.6%)	3 (7.0%)	6 (14.0%)	4 (9.8%)	4 (9.3%)	7 (16.7%)	24 (11.3%)
Diarrhoea	1 (2.3%)	2 (4.7%)	4 (9.3%)	2 (4.9%)	1 (2.3%)	1 (2.4%)	10 (4.7%)
Nervous system disorders	1 (2.3%)	0	3 (7.0%)	2 (4.9%)	3 (7.0%)	2 (4.8%)	10 (4.7%)
Headache	1 (2.3%)	0	1 (2.3%)	1 (2.4%)	3 (7.0%)	1 (2.4%)	6 (2.8%)
Respiratory, thoracic and mediastinal disorders	1 (2.3%)	1 (2.3%)	1 (2.3%)	0	3 (7.0%)	2 (4.8%)	7 (3.3%)
Cough	0	1 (2.3%)	1 (2.3%)	0	3 (7.0%)	1 (2.4%)	6 (2.8%)

AE=Adverse event; BID=Twice daily; QD=Daily; TEAE=Treatment-Emergent Adverse Events. \*Includes all JNJ-2113 treatment columns.

Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

# JNJ-2113 FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

## Safety Summary



The proportion of patients experiencing 1 or more AEs was comparable between JNJ-77242113 groups and the placebo group

- Most frequently reported AEs were COVID-19 and nasopharyngitis
- There was no evidence of dose-dependent increase in the occurrence of AEs across the JNJ-77242113 treatment groups



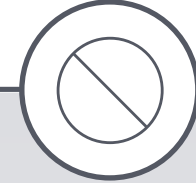
There were three serious AEs that occurred in FRONTIER-1 (n=1 each: suicide attempt, COVID-19, infected cyst; all on active drug and assessed as not related to study intervention by investigators).

No dose-dependent relationship was observed.



A low number of laboratory abnormalities occurred during the study and were comparable between placebo and JNJ-77242113 groups.

There was no evidence of a dose-dependent increase in the occurrence of abnormalities.

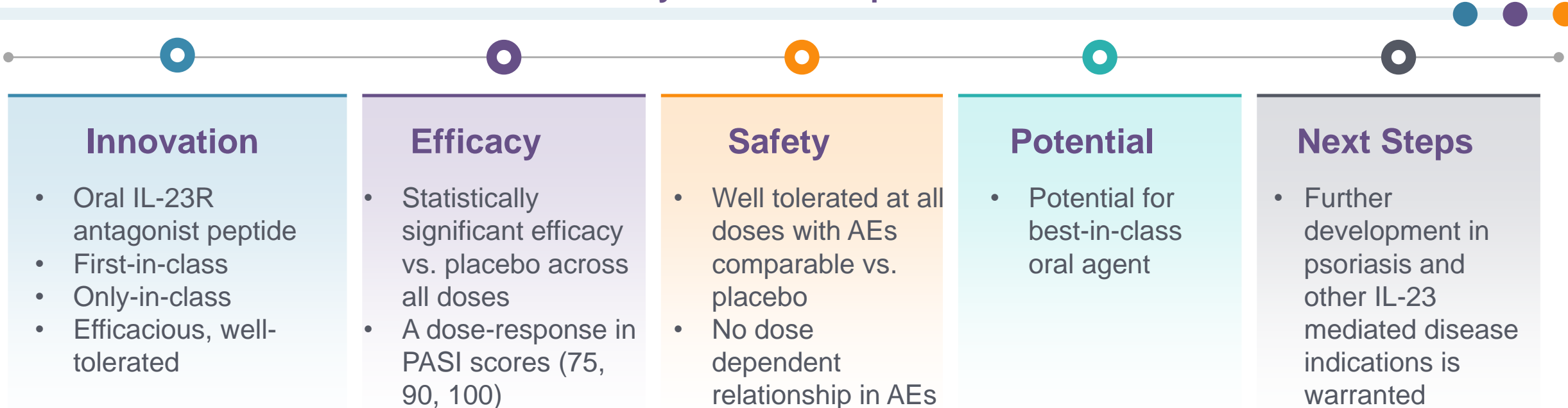


There were no deaths, MACE, or malignancies during the study.



# JNJ-2113 (formerly PN-235)

## Conclusions from Phase 2b Psoriasis Study and Next Steps



### Next Steps

- Registrational program (ICONIC) with four phase 3 studies in psoriasis
  - Two head-to-head trials with deucravacitinib
- PASI 90 highlighted as a high-bar primary endpoint
- **200 mg oral once-daily dosing in all four phase 3 studies**

**JNJ-2113 is a potential best, first-, and only-in-class oral IL-23 receptor antagonist**

# JNJ-2113 Publication in NEJM, 2024

- Patients were randomized to doses of 25 mg qd, 25 mg bid, 50 mg qd, 100 mg qd, or 100 mg bid or placebo
- Results demonstrate a dose-dependent Psoriasis Area and Severity Index score (PASI-75) response in patients treated with JNJ-2113 versus placebo at Week 16 (primary endpoint), with 79% of patients achieving a PASI-75 response in the highest dose group (100 mg twice daily)
- Secondary endpoints results consistent with primary evaluation
  - Highest dose of JNJ-2113 showed 59.5% of patients achieving PASI-90, and 40.5% of patients achieving a PASI-100 at Week 16
  - At the highest dose, 64.3% of patients achieved an Investigator Global Assessment (IGA) score of 0/1 and 45.2% of patients achieved a score of 0, with IGA responses showing separation between JNJ-2113 and placebo groups as early as Week 4
  - Significant improvements were observed across key Patient-Reported Outcomes
- JNJ-2113 is currently being studied in
  - the ICONIC program, which includes four Phase 3 studies for moderate-to-severe psoriasis
  - ANTHEM-UC, phase 2b study in moderate-to-severe ulcerative colitis

## Results of FRONTIER-1 Phase 2b Study

*The* NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

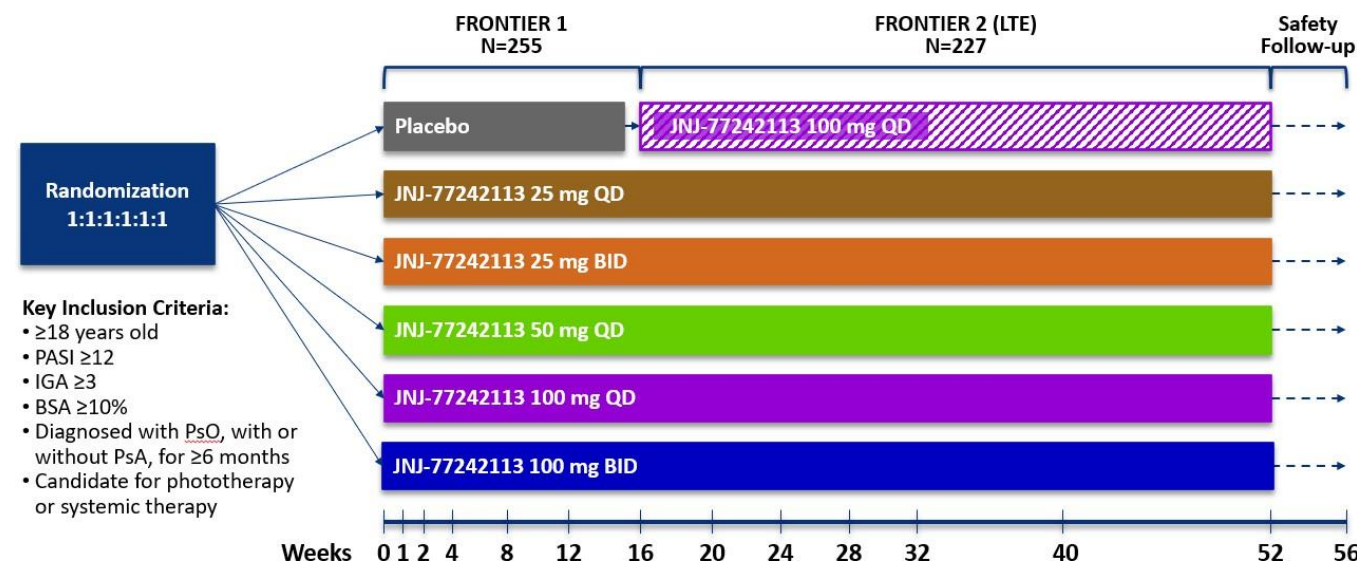
### An Oral Interleukin-23–Receptor Antagonist Peptide for Plaque Psoriasis

Robert Bissonnette, M.D., Andreas Pinter, M.D., Laura K. Ferris, M.D., Ph.D.,  
Sascha Gerdes, M.D., Phoebe Rich, M.D., Ronald Vender, M.D.,  
Megan Miller, M.P.H., Yaung-Kaung Shen, Ph.D., Arun Kannan, Ph.D.,  
Shu Li, Ph.D., Cynthia DeKlotz, M.D., and Kim Papp, M.D., Ph.D.

# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## Study Design and Methods

- In FRONTIER 2, patients randomized to a JNJ-77242113 dosing group in FRONTIER 1 continued treatment through Week 52
- Patients from the FRONTIER 1 PBO group crossed over to JNJ-77242113 100 mg daily (QD) at Week 16 (PBO→100 mg QD)
- Efficacy endpoints (dichotomous and continuous endpoints utilized NRI and MMRM, respectively):
  - All JNJ-77242113-randomized patients
  - 35 PBO →100 mg QD patients
  - Scalp-specific Investigator's Global Assessment (ss-IGA): assessed in patients with an ss-IGA  $\geq 2$  at baseline
- Adverse events: assessed in patients who entered the LTE and received  $\geq 1$  dose of JNJ-77242113 treatment



# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## Results

- FRONTIER 2 evaluated FRONTIER 1 participants with moderate-to-severe plaque PsO who entered the LTE

FRONTIER 1 Baseline Characteristics	PBO	JNJ-77242113						Total
		25 mg QD	25 mg BID	50 mg QD	100 mg QD	100 mg BID	Combined <sup>a</sup>	
Full analysis set, n	43	43	41	43	43	42	212	255
Age (yrs)	43.9 (14.7)	44.5 (12.7)	45.7 (11.9)	45.1 (11.1)	44.7 (14.1)	42.0 (11.3)	44.4 (12.2)	44.3 (12.6)
Weight (kg)	92.1 (24.7)	89.0 (19.4)	90.8 (22.1)	87.6 (19.2)	85.4 (22.5)	88.5 (16.9)	88.2 (20.0)	88.9 (20.9)
PsO disease duration (yrs)	17.9 (14.4)	15.5 (11.8)	18.1 (11.8)	21.5 (11.2)	19.5 (13.3)	16.7 (13.8)	18.3 (12.5)	18.2 (12.8)
PASI total score (0-72)	19.0 (5.3)	18.9 (5.3)	18.5 (5.8)	19.2 (5.1)	18.4 (6.9)	20.3 (6.5)	19.1 (5.9)	19.0 (5.8)
BSA, % (0-100)	26.1 (15.7)	21.1 (9.3)	20.9 (11.9)	23.9 (13.6)	20.5 (13.7)	24.2 (12.6)	22.1 (12.3)	22.8 (13.0)
IGA (%), moderate (3)/severe (4)	88.4/11.6	69.8/30.2	80.5/19.5	83.7/16.3	81.4/18.6	71.4/28.6	77.4/22.6	79.2/20.8
PSSD Symptom Score (0-100)	47.3 (20.7)	59.0 (23.6)	51.9 (24.0)	53.9 (24.5)	43.0 (21.3)	55.9 (26.3)	52.7 (24.4)	51.8 (23.8)
PSSD Sign Score (0-100)	62.9 (16.6)	69.5 (16.5)	64.1 (18.9)	64.7 (19.4)	60.4 (18.6)	66.3 (19.1)	65.0 (18.6)	64.6 (18.3)
ss-IGA, at least mild (≥2) <sup>b</sup>	81.4	86.0	80.0	93.0	93.0	87.8	88.1	87.0
Prior Biologics <sup>c</sup> (%)	16.3	16.3	31.7	25.6	20.9	21.4	23.1	22.0

PSSD=PsO symptoms and signs diary.

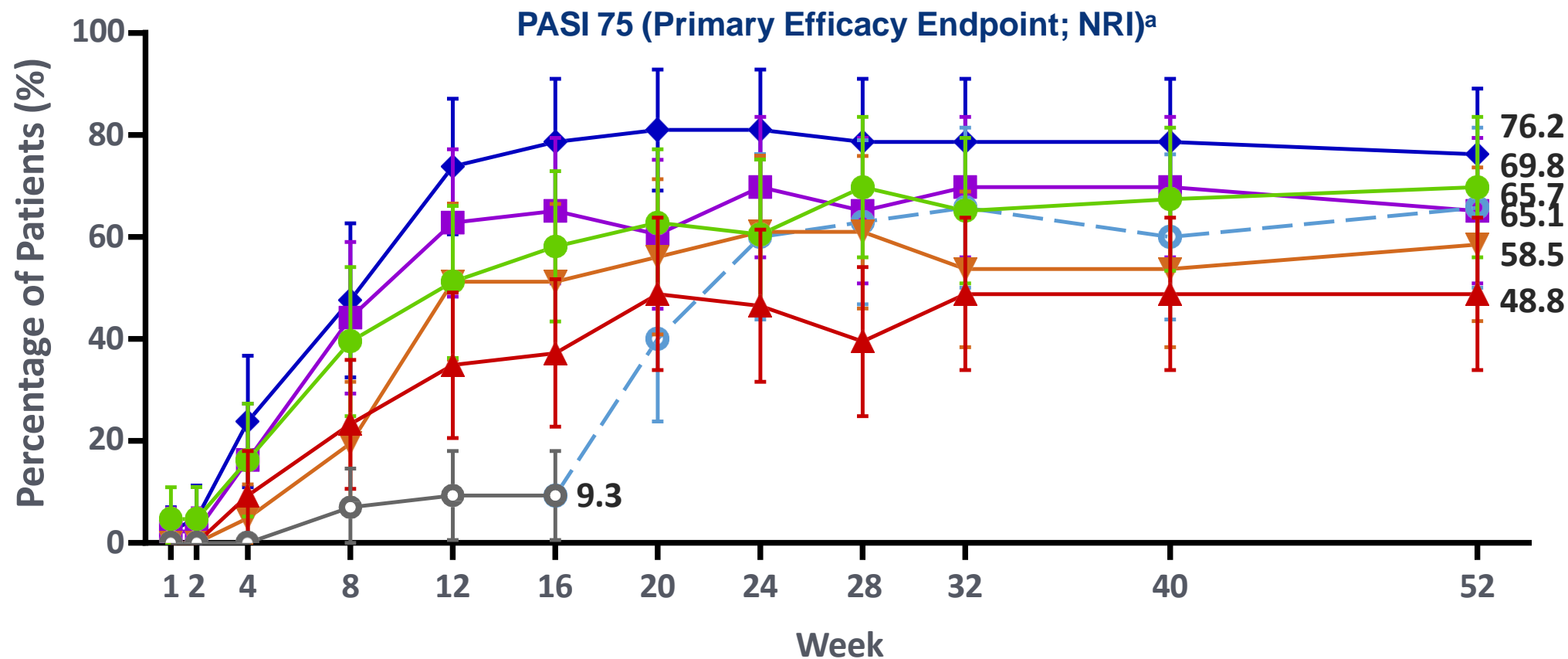
Data shown are mean (SD), unless otherwise indicated.

<sup>a</sup>Includes all JNJ-77242113 treatment columns. <sup>b</sup>25 mg BID, n=40; 100 mg BID, n=41; Combined, n=210; Total, n=253. <sup>c</sup>Includes etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, certolizumab pegol.

# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## PASI 75 response rates at Week 16 were maintained through Week 52

- Among patients who crossed over from PBO→100 mg QD at Week 16, PASI 75 response rates rapidly converged with those of JNJ-77242113-randomized patients

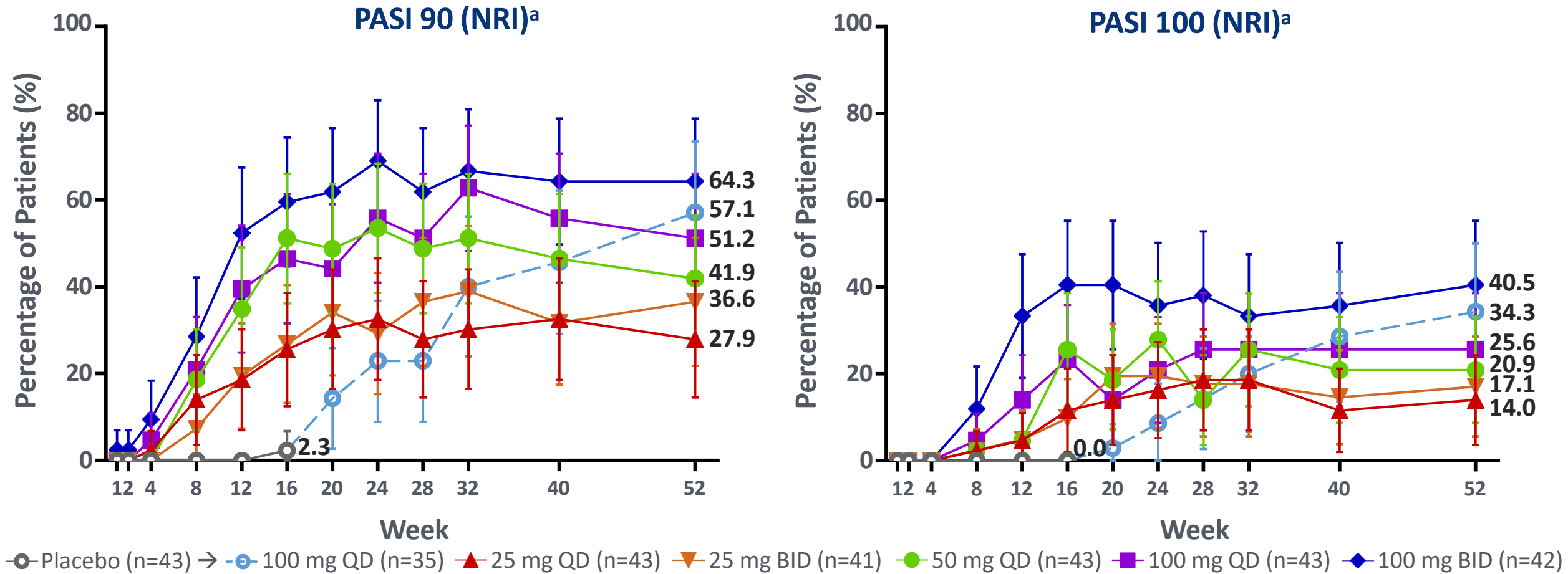


● Placebo (n=43) → ● 100 mg QD (n=35) ▲ 25 mg QD (n=43) ▼ 25 mg BID (n=41) ● 50 mg QD (n=43) ■ 100 mg QD (n=43) ◆ 100 mg BID (n=42)

# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## PASI 90 and PASI 100 response rates

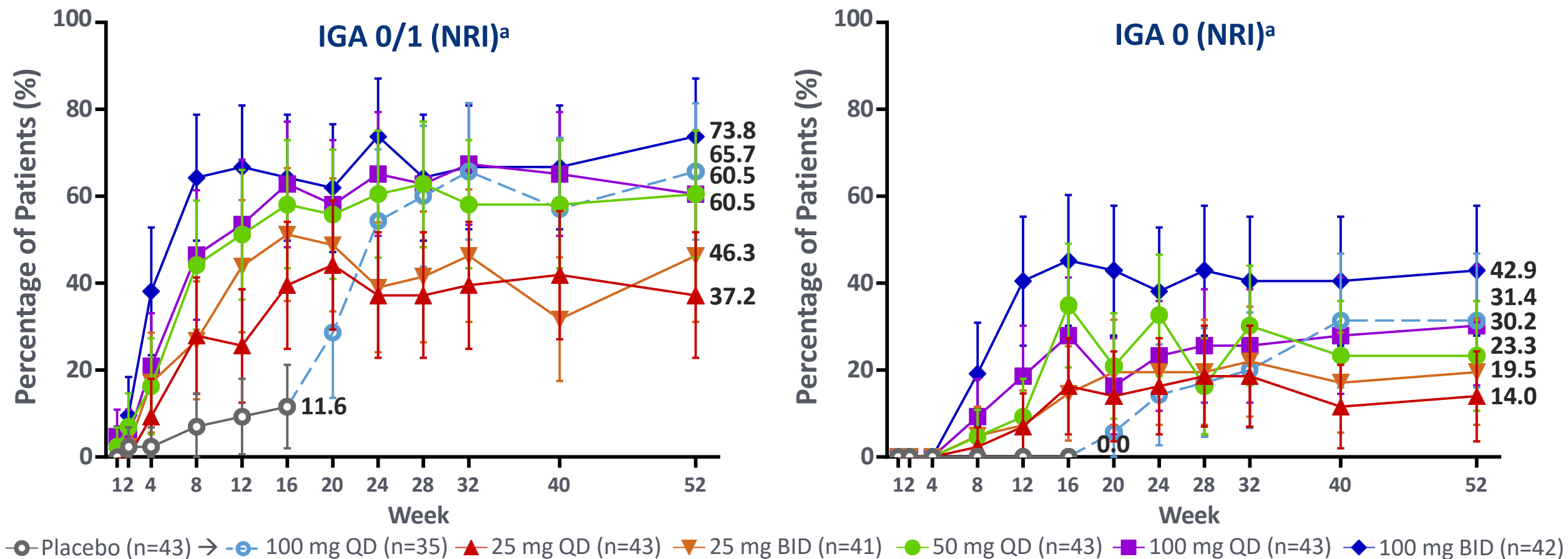
- PASI 90 and PASI 100 response rates were generally maintained from Week 16 through Week 32



# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## IGA 0/1 and IGA 0 response rates

- IGA 0/1 and IGA 0 response rates were generally maintained from Week 16 through Week 52

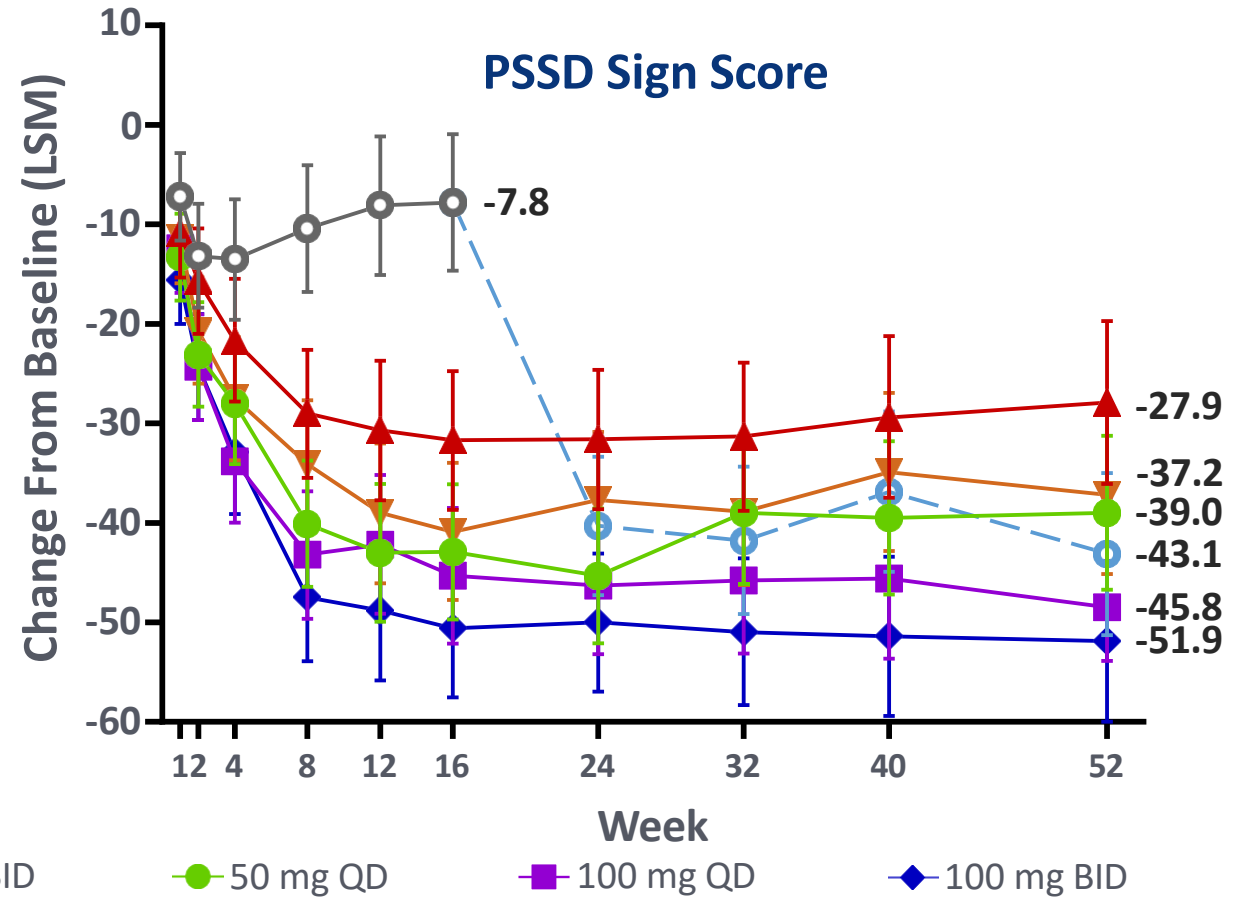
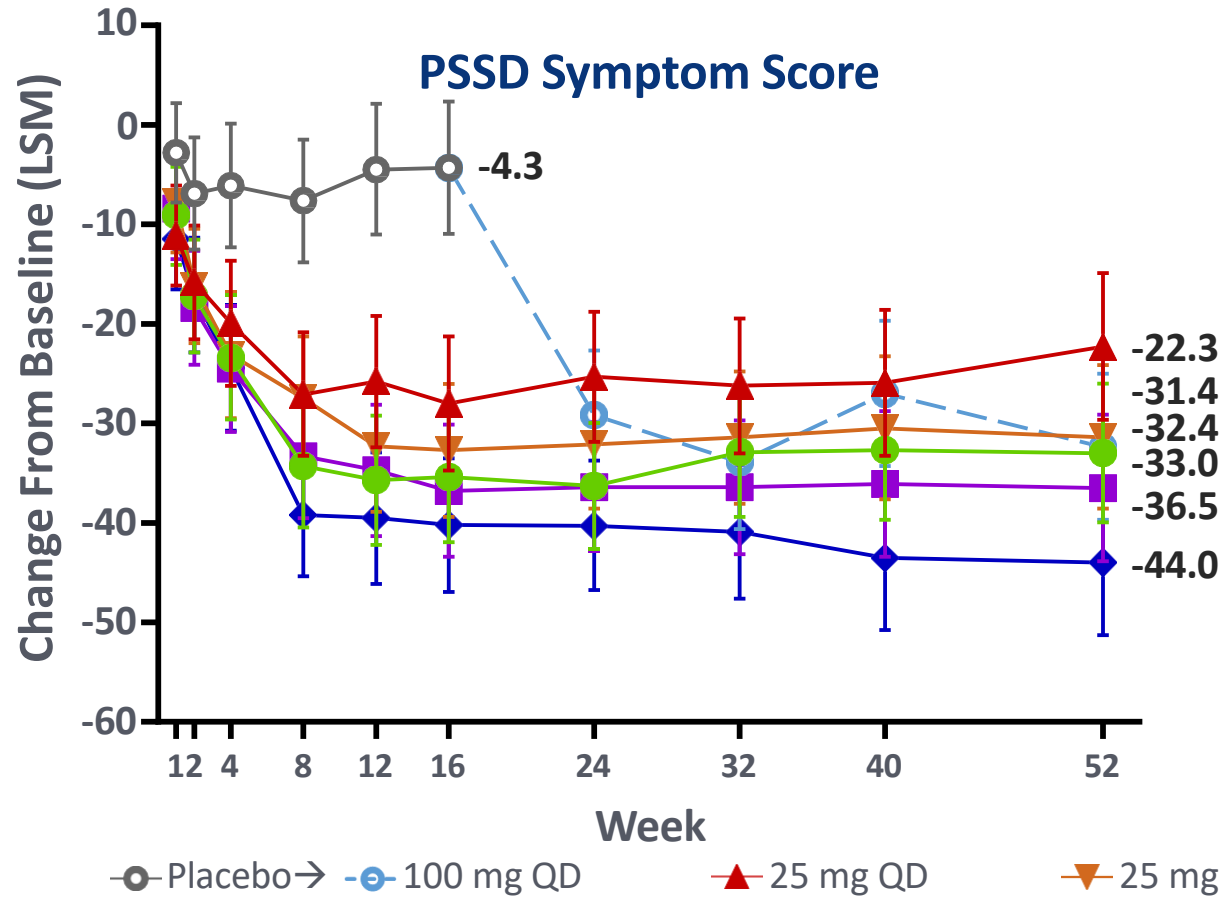




# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## Changes from baseline in PSSD symptom and sign scores

- Improvements in Psoriasis Symptoms and Signs Diary (PSSD) scores at Week 16 were generally maintained through Week 52



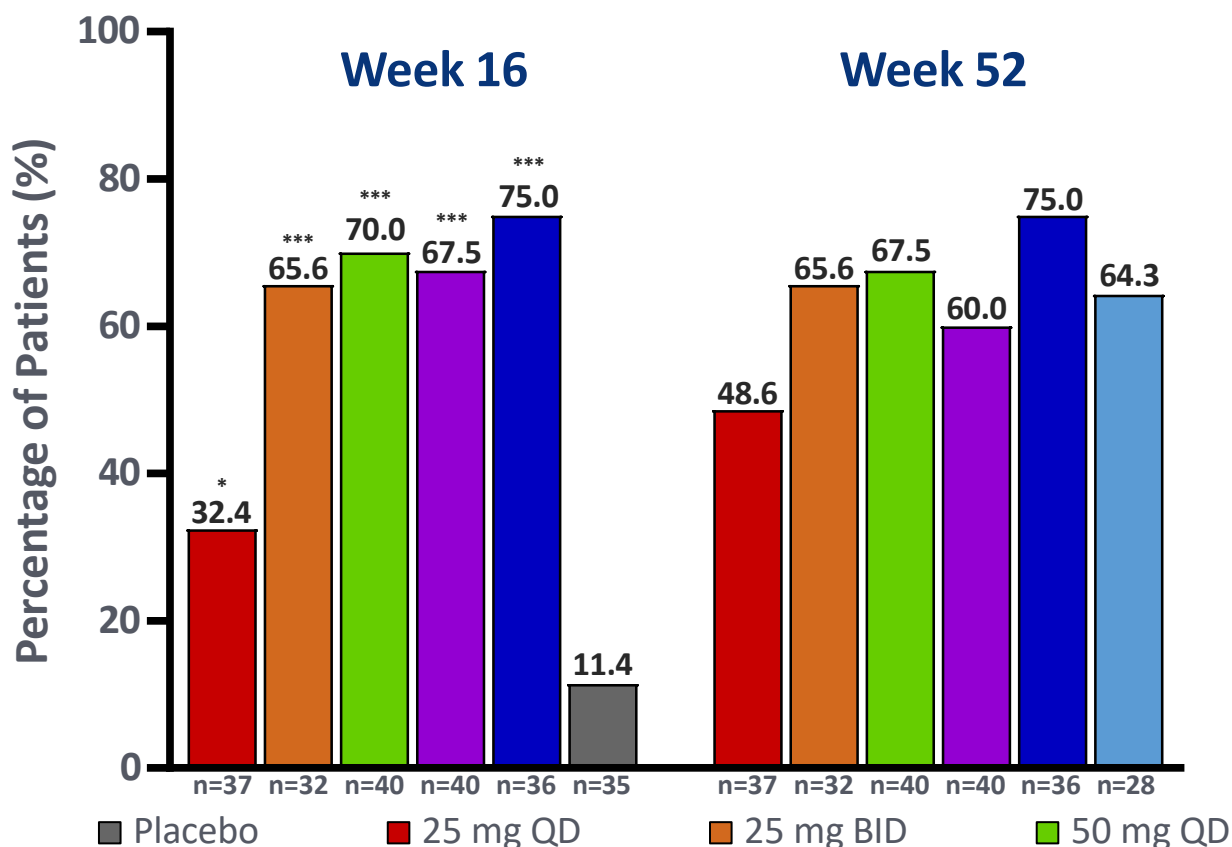
Least Squares Means (LSM) are based on the Mixed Models for Repeated Measures (MMRM) model with treatment group, visit, treatment group by visit interaction, baseline weight category ( $\leq 90$  kg,  $>90$  kg), baseline weight category by visit interaction, baseline PSSD symptom/sign score, and baseline PSSD symptom/sign score by visit interaction as covariates. Zero change was assigned after patients discontinued study agent due to lack of efficacy/worsening of PsO or initiated a prohibited PsO treatment. Missing data was handled by MMRM under missing at random assumption.

# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

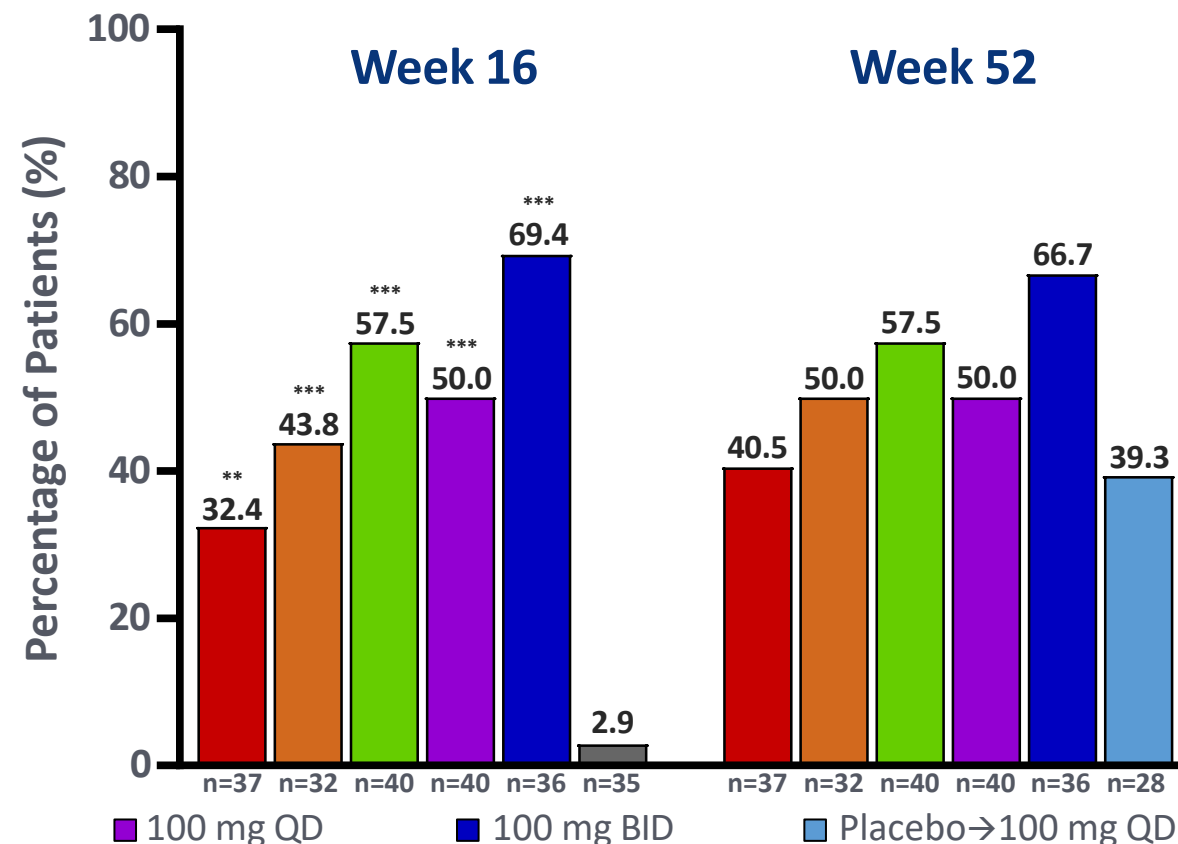
## Scalp-specific (ss)-IGA 0/1 and ss-IGA 0 Response Rates

- In patients who crossed over from PBO→100 mg QD at Week 16, ss-IGA 0/1 and ss-IGA 0 response rates substantially increased by Week 52

ss-IGA 0/1<sup>a,b</sup> (NRI)<sup>c</sup>



ss-IGA 0<sup>a</sup> (NRI)<sup>c</sup>



# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

Patients With  $\geq 1$  TEAE With Frequency  $\geq 5\%$  of Preferred Terms in Any Treatment Group From Week 16 Through Week 56

	Placebo → 100 mg QD						
		25 mg QD	25 mg BID	50 mg QD	100 mg QD	100 mg BID	Combined <sup>a</sup>
Analysis set: LTE Safety analysis set, n	35	35	40	39	40	38	227
Avg duration of follow-up (weeks)	37.8	36.6	35.0	38.4	35.9	38.6	37.0
Patients with $\geq 1$ AE, n (%)	23 (65.7)	18 (51.4)	27 (67.5)	19 (48.7)	27 (67.5)	19 (50.0)	133 (58.6)
Nasopharyngitis	9 (25.7)	3 (8.6)	6 (15.0)	7 (17.9)	11 (27.5)	5 (13.2)	41 (18.1)
Upper respiratory tract infection	4 (11.4)	6 (17.1)	3 (7.5)	3 (7.7)	2 (5.0)	4 (10.5)	22 (9.7)
COVID-19	2 (5.7)	1 (2.9)	1 (2.5)	3 (7.7)	2 (5.0)	3 (7.9)	12 (5.3)
Headache	0	2 (5.7)	3 (7.5)	0	3 (7.5)	0	8 (3.5)
Influenza	1 (2.9)	0	3 (7.5)	1 (2.6)	1 (2.5)	1 (2.6)	7 (3.1)
Urinary tract infection	2 (5.7)	1 (2.9)	1 (2.5)	1 (2.6)	0	2 (5.3)	7 (3.1)
Alanine aminotransferase increased	2 (5.7)	1 (2.9)	0	1 (2.6)	0	2 (5.3)	6 (2.6)
Bronchitis	1 (2.9)	1 (2.9)	1 (2.5)	3 (7.7)	0	0	6 (2.6)
Hypertension	1 (2.9)	0	2 (5.0)	1 (2.6)	1 (2.5)	1 (2.6)	6 (2.6)
Aspartate aminotransferase increased	1 (2.9)	1 (2.9)	0	1 (2.6)	0	2 (5.3)	5 (2.2)
Arthralgia	1 (2.9)	0	0	1 (2.6)	2 (5.0)	0	4 (1.8)
Meniscus injury	0	1 (2.9)	2 (5.0)	0	0	0	3 (1.3)
Sinusitis	0	0	2 (5.0)	1 (2.6)	0	0	3 (1.3)
Vomiting	0	0	0	0	2 (5.0)	0	2 (0.9)

# JNJ-2113 FRONTIER 2 Long-term Extension, Dose-Ranging Study

## Safety Summary



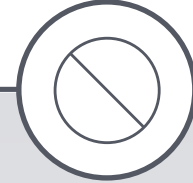
- 59% experienced  $\geq 1$  AEs
- Rates of GI-related AEs did not increase in patients receiving JNJ-77242113 during the LTE (6% JNJ-77242113 combined group)
- FRONTIER 1 Week 16: 12% PBO vs 11% JNJ-77242113 combined group



- The most common AEs were nasopharyngitis (18.1%), upper respiratory tract infection (9.7%), and COVID-19 (5.3%)
- No evidence of dose-dependent increase in the occurrence of AEs



- 4% experienced serious AEs through Week 52
- All serious AEs were considered not related to study intervention by investigators



- No deaths occurred during the LTE

# JNJ-2113

## Multiple Clinical Studies with Multiple Shots on Goal

Study	Phase 1	Phase 2	Phase 3	Key Milestones
NCT04621630	Ph1 in NHVs			• NHVs in Australia; completed
NCT05062200	Ph1 in NHVs			• Adult Japanese/Chinese participants; completed
NCT05703841	Ph1 in NHVs			• Healthy adult Chinese participants; completed
FRONTIER 1	Ph2b in Psoriasis, n~255			• Completed
FRONTIER 2	Ph2b in Psoriasis			• Long term extension; completed
SUMMIT	Ph2a in Psoriasis, n~90			• Delayed release formulation; Completed
ICONIC-LEAD	Ph3 in Psoriasis, n~600			• PASI 90 & IGA 0/1; completion ~Nov '24*
ICONIC-TOTAL	Ph3 in Psoriasis, n~300			• Special areas IGA 0/1; completion ~Nov '24*
ICONIC-ADVANCE 1	Ph3 in Psoriasis, n~750 pts			• Superiority study vs. deucravacitinib; completion ~Mar '25
ICONIC-ADVANCE 2	Ph3 in Psoriasis, n~675 pts			• Superiority study vs. deucravacitinib; completion ~Apr '25
ANTHEM-UC	Ph2b in UC, n~240 Pts			• Completion ~May '25

# Milestones Status and Outlook

## 2024 and Beyond

**\$172.5M\***

in upfront and development milestones have been achieved

**\$795M**

amount of total future development and sales milestones for which Protagonist remains eligible

**Royalty**

**6% to 10%**  
upward tiering  
**10% at ≥ \$4B net sales**

### Upcoming Potential Milestones

1 <sup>st</sup> indication	Ph3 1° end point achieved	\$115M**
	NDA filing	\$35M**
	NDA approval	\$50M**
2 <sup>nd</sup> indication	Ph3 initiation	\$15M**

\* Includes \$60 million in milestones achieved in Q4 2023

\*\* \$215M potential milestones NOT included in current cash runway forecast



# Discovery Pipeline Financial Outlook

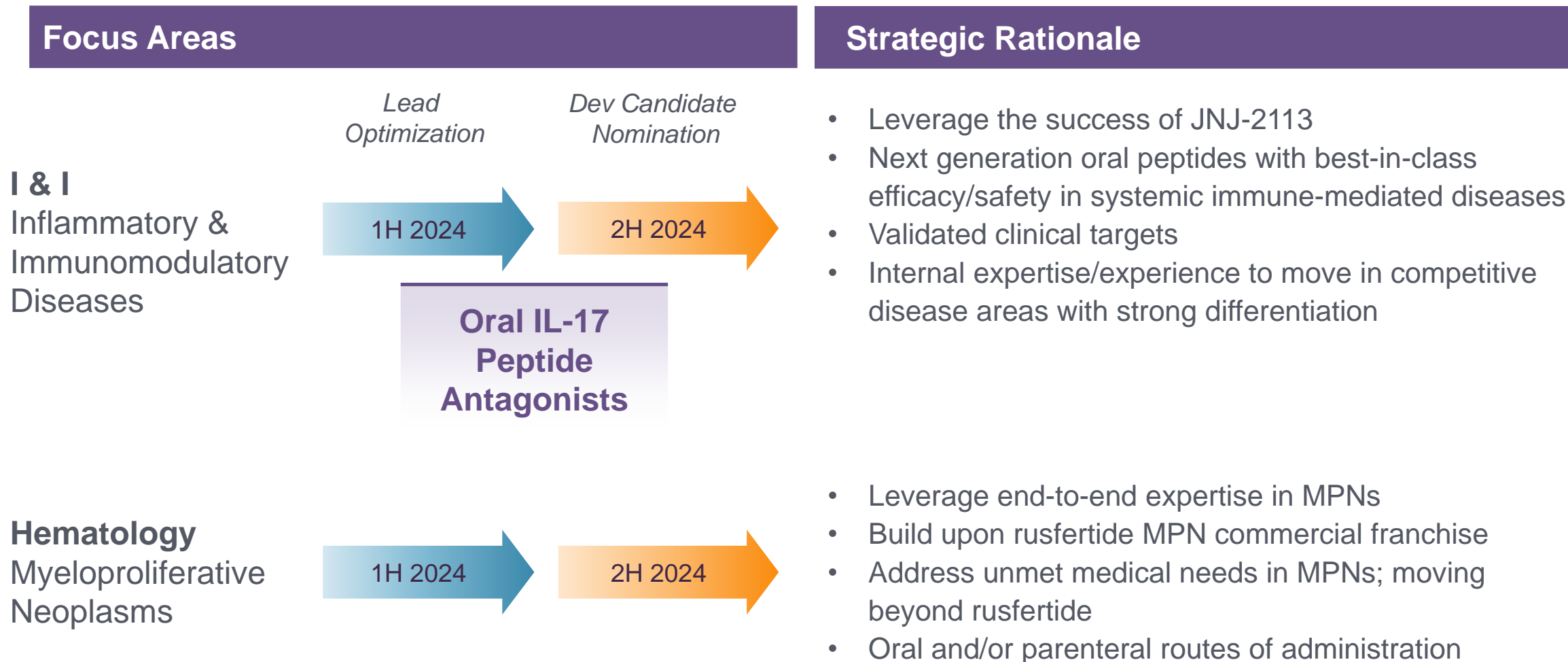
2024 is a year of pipeline execution and strategic evolution for Protagonist





# Discovery Pipeline

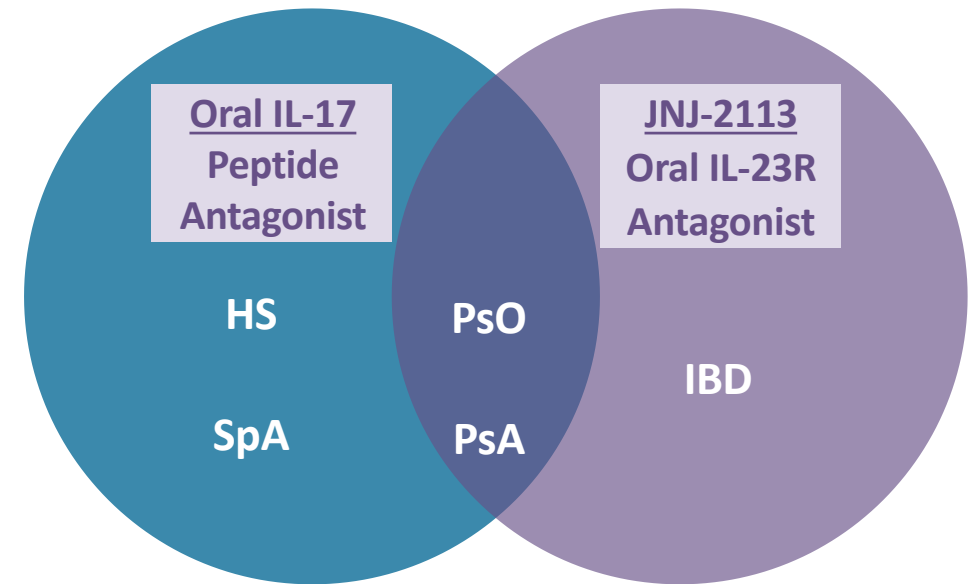
## Leveraging Our Successes to Address Major Unmet Medical Needs and Create Value



# Oral IL-17 Peptide Antagonists

## New Discovery Program

- IL-17 inhibitors expected to lead the I&I space
  - Global sales expected to increase significantly from ~\$29B (2021) to >\$50B (2031) for IL-17 mediated indications<sup>1</sup>
  - IL-23 and IL-17 inhibitors expected to have significant PsO (~80%) and PsA (~60%) market share by ~2035<sup>2</sup>
- Leveraging our oral peptide technology platform
- Target product profile (TPP)
  - Oral peptide, first-in-class
  - Similar/better potency vs. approved mAbs<sup>3</sup>
  - Tri-specific (IL-17 AA, AF & FF)
- Development candidate in 2024<sup>4</sup>



HS: Hidradenitis Suppurativa  
SpA: Spondyloarthritis  
PsO: Plaque Psoriasis  
PsA: Psoriatic Arthritis  
IBD: Inflammatory Bowel Diseases (Crohn's and Ulcerative Colitis)

# Financial Highlights

## Financial Resources Forecast Extends Through Q4 2027

CASH,  
CASH EQUIVALENTS &  
MARKETABLE SECURITIES

**\$341.6M**

as of  
December 31, 2023

CASH RUNWAY  
FORECAST

**Q4 2027**

- **Includes \$300M** expected upfront from Takeda\*
- **Excludes** all future potential milestones from JNJ and Takeda

SHARES  
OUTSTANDING

**~57.7M**

as of  
December 31, 2023

Thank you

# 65<sup>th</sup> American Society of Hematology Annual Meeting & Exposition

Accepted Abstracts

# 65th ASH Annual Meeting and Exposition (2023)

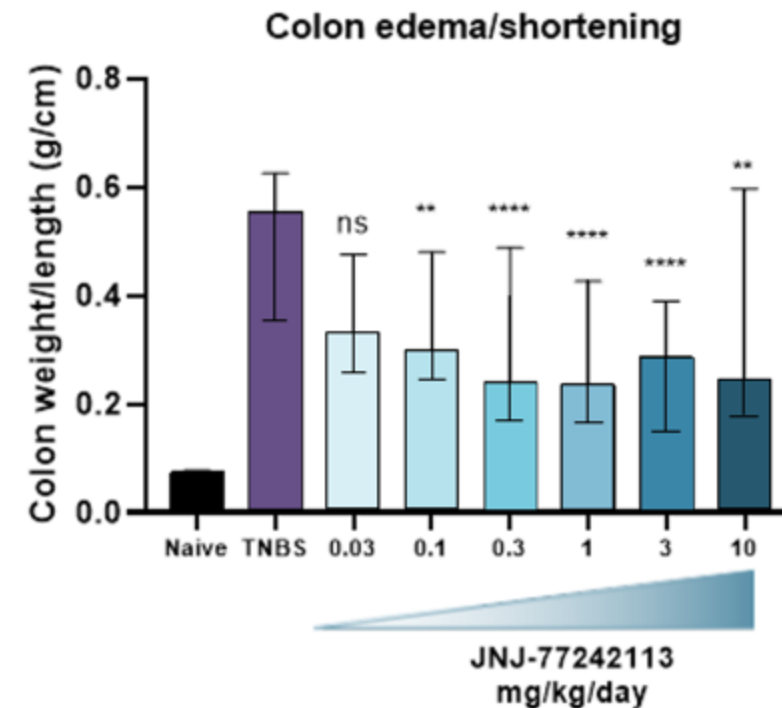
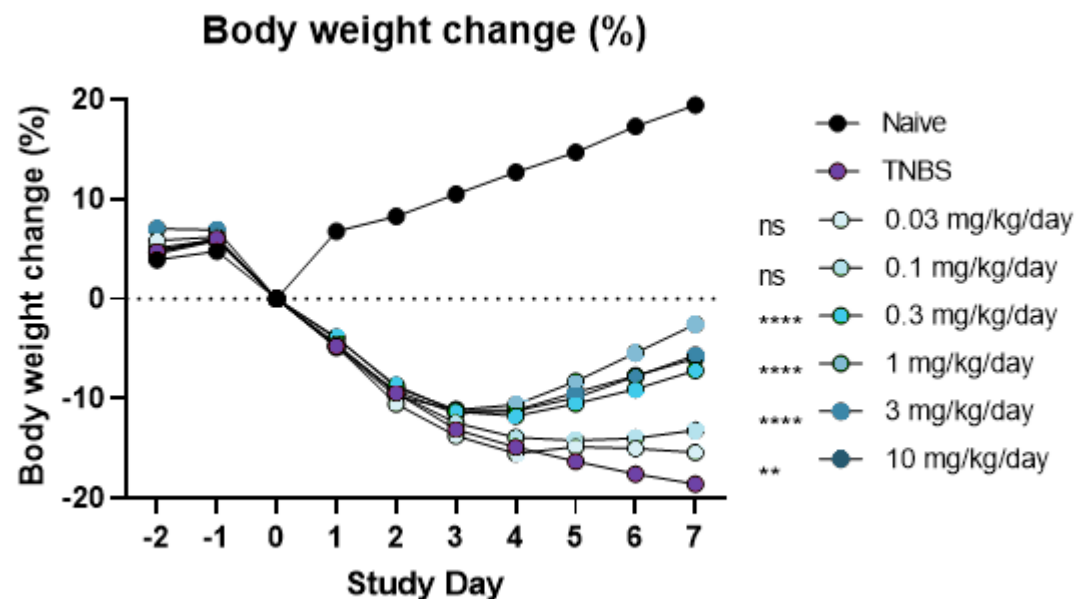
## Company-Sponsored Abstracts



Day	Time (PST)	Type	Location	Presentation/Abstract Title	Abstract Number	Presenting Author	Abstract URL
<b>Oral Presentations</b>							
Sat 9 Dec	10:30 AM	Oral	Marriott Marquis San Diego Marina, Pacific Ballroom Salons 18-19	Real-World Analysis of Thromboembolic Event Rates in Patients in the United States with Polycythemia Vera	137	Kuykendall	<a href="https://ash.confex.com/ash/2023/webprogram/Paper180309.html">https://ash.confex.com/ash/2023/webprogram/Paper180309.html</a>
Mon 11 Dec	10:30 AM	Oral	San Diego Convention Center, Ballroom 20CD	Durability of Hematocrit Control in Polycythemia Vera with the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results from the Revive Study	745	Ritchie	<a href="https://ash.confex.com/ash/2023/webprogram/Paper178253.html">https://ash.confex.com/ash/2023/webprogram/Paper178253.html</a>
<b>Poster Presentations</b>							
Sat 9 Dec	6:00 PM	Poster	San Diego Convention Center, Halls G-H	Prevalence of Second Cancers in Patients with Polycythemia Vera (PV): A Retrospective Analysis of US Real-World Claims Data	3190	Pemmaraju	<a href="https://ash.confex.com/ash/2023/webprogram/Paper180045.html">https://ash.confex.com/ash/2023/webprogram/Paper180045.html</a>
Sat 9 Dec	6:00 PM	Poster	San Diego Convention Center, Halls G-H	Iron Restricted Erythropoiesis Under Hepcidin Mimetic Treatment (PN23114) Improved Disease Parameters in a Mouse Model for Sickle Cell Disease	1117	Taranath	<a href="https://ash.confex.com/ash/2023/webprogram/Paper182472.html">https://ash.confex.com/ash/2023/webprogram/Paper182472.html</a>
Sun 10 Dec	6:00 PM	Poster	San Diego Convention Center, Halls G-H	Rusfertide Improves Markers of Iron Deficiency in Patients with Polycythemia Vera	3208	Ginzburg	<a href="https://ash.confex.com/ash/2023/webprogram/Paper178334.html">https://ash.confex.com/ash/2023/webprogram/Paper178334.html</a>

# Pre-Clinical PoC 1: Rat TNBS-Induced Colitis Model

## Orally Dosed JNJ-2113 Attenuates Weight Loss and Colon Inflammation



- Statistically significant effects seen beginning at doses of 0.1 to 0.3 mg/kg/day
- Although exposure in plasma and skin was much lower than GI tissues, exquisite potency of JNJ-2113 indicated potential for systemic activity beyond the GI tract

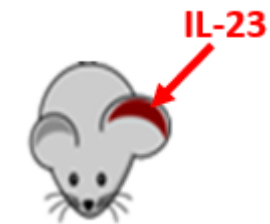
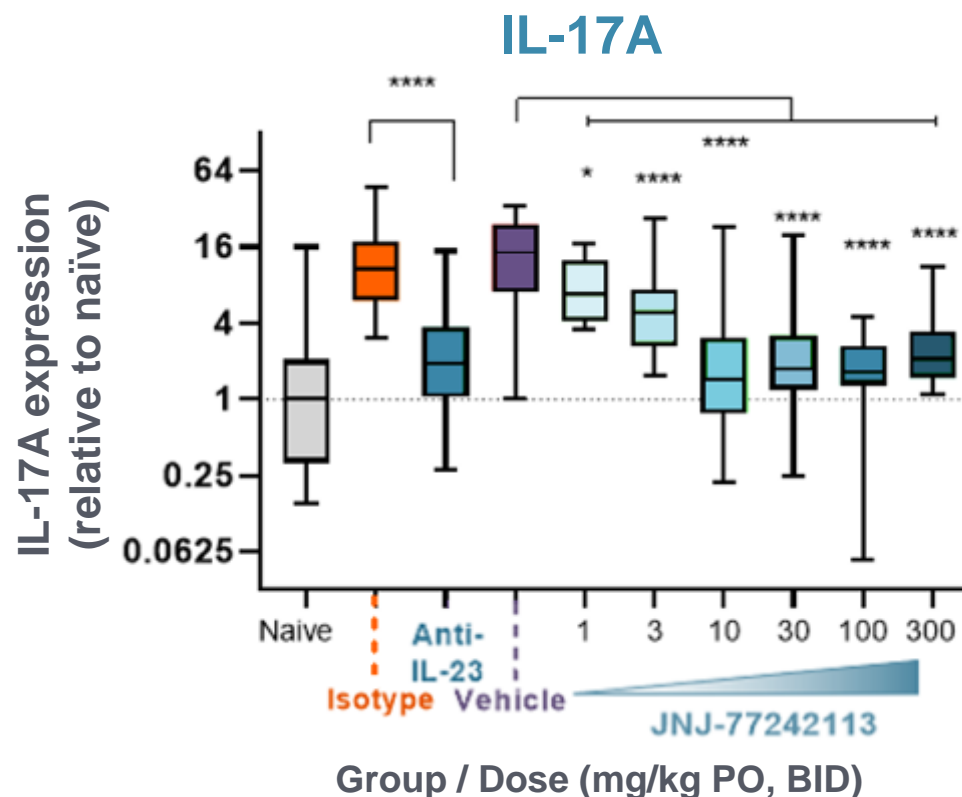
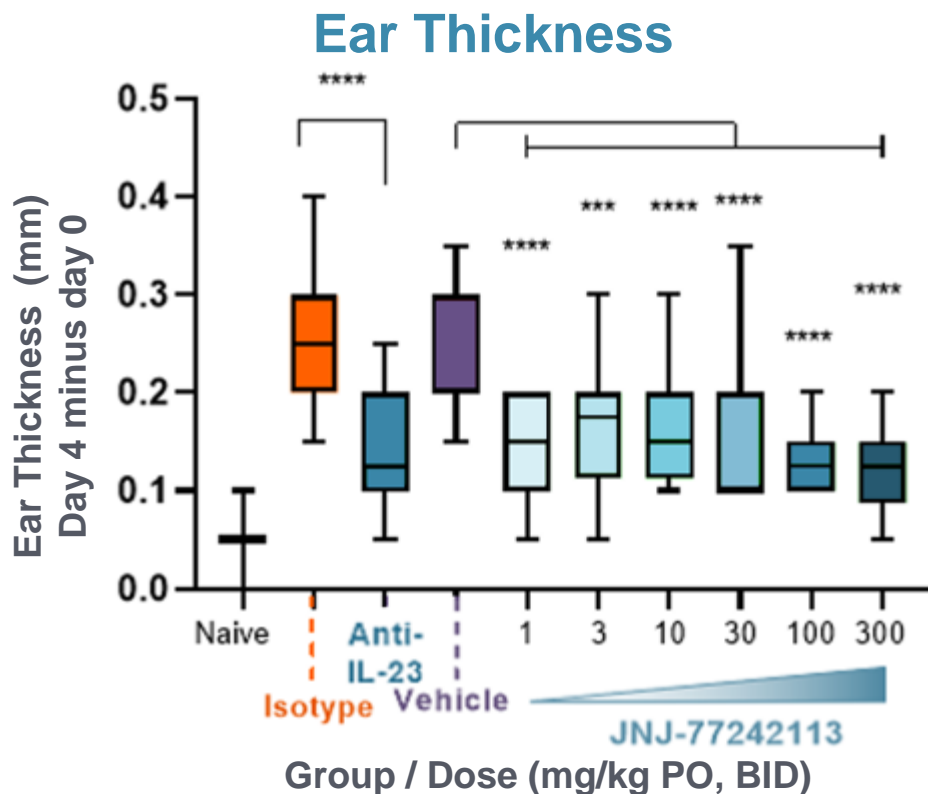
GI=Gastrointestinal; TNBS=Trinitrobenzenesulfonic acid.

ns=not significant, \*\*p <0.01, \*\*\*\*p <0.0001. Graph on right represents median and interquartile range. Data combined from three studies.



# Pre-Clinical PoC 2: Rat IL-23 Induced Skin Inflammation Model

## Orally Dosed JNJ-2113 Achieves Inhibition Equivalent to Anti-IL-23 Antibody



- Doses  $\geq 1$  mg/kg BID reduced inflammation and cytokine induction (IL-17A, IL-17F and IL-22)
- Doses  $\geq 10$  mg/kg BID showed equivalent inhibition to an anti-IL-23 antibody

BID=Twice daily. Anti-IL-23 and isotype control dosed intraperitoneally on days -1 and 3.

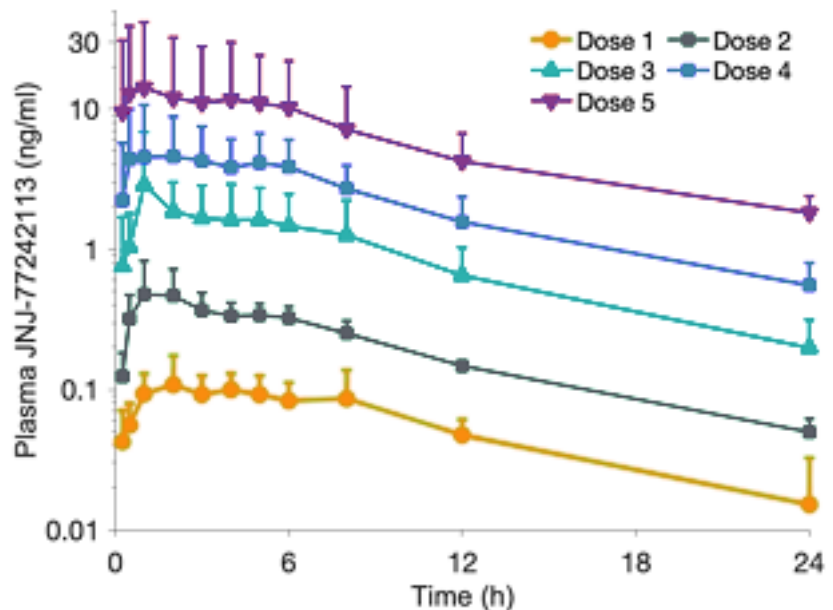
ns=not significant, \* $p < 0.05$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ . Boxes depict median and interquartile ranges; bars depict minima and maxima. Data combined from three experiments.

Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

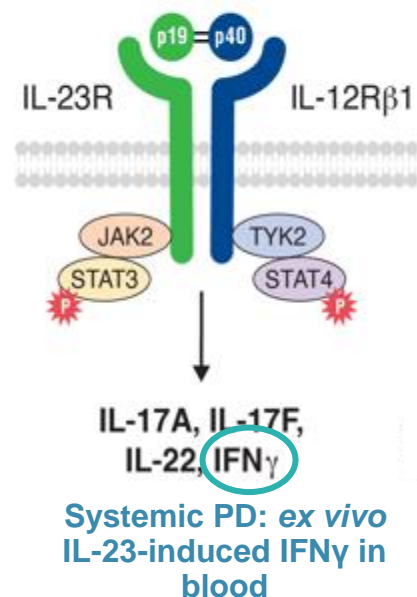
# Phase 1 Study of JNJ-2113 in Healthy Volunteers

## Safety, Pharmacokinetics, Systemic Pharmacodynamics

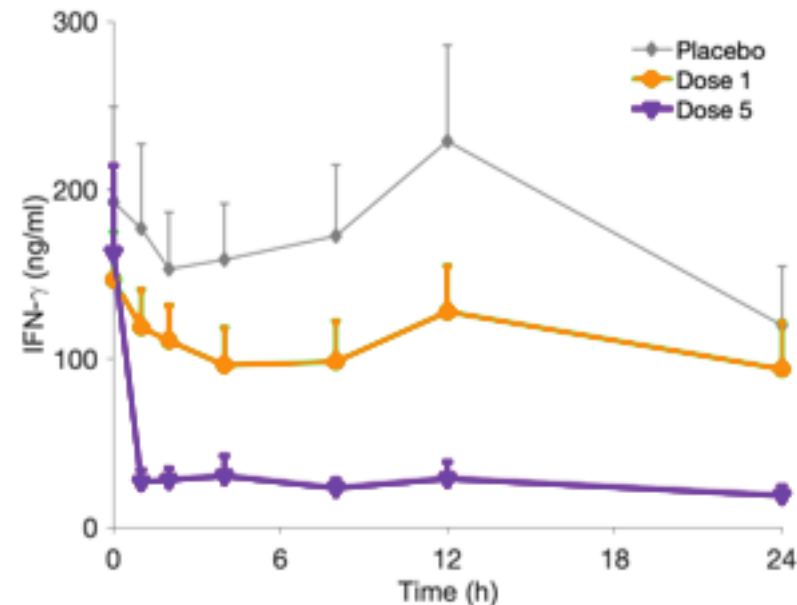
### Human PK Profile<sup>†</sup> Supports Pathway Coverage



### IL-23



### Robust Systemic PD Activity with Oral Dosing



- Demonstrated PoC for systemic PD activity of orally dosed JNJ-2113 in humans
- Single and multiple oral doses were safe and generally well tolerated with no safety signal of concern

PD=Pharmacodynamic; PK=Pharmacokinetic; PoC=Proof of Concept.

PK data represent mean + SD.

<sup>†</sup>Phase 1 conducted under fasted conditions.

# ICONIC-LEAD: JNJ-2113 Phase 3 Study in Moderate to Severe Plaque Psoriasis

## A Study of JNJ-77242113 in Adolescent and Adult Participants with Moderate to Severe Plaque Psoriasis

n=600 (2:1 randomization)

### Eligibility:

#### Mod/Severe PsO

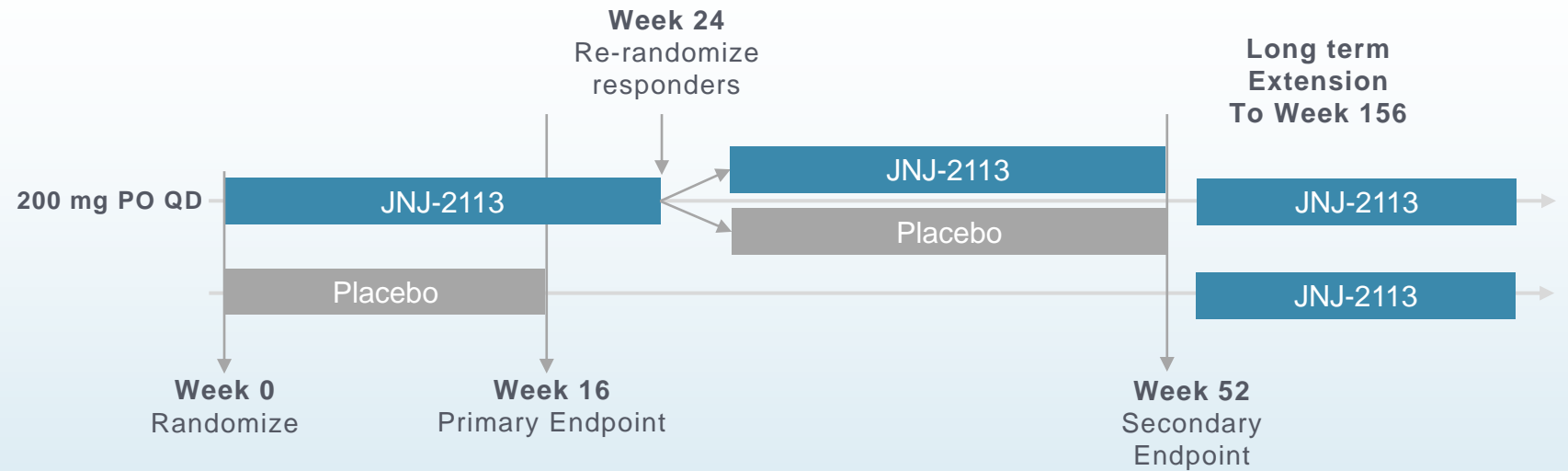
- IGA  $\geq 3$
- PASI  $\geq 12$
- BSA  $\geq 10\%$
- Age:  $\geq 12$

### Primary endpoint:

- IGA 0/1 Week 16
- PASI 90 Week 16

Study Start Date: 10/12/23

Estimated Primary Completion: 11/19/24



# ICONIC-TOTAL: JNJ-2113 Phase 3 Study in Plaque Psoriasis Involving Special Areas

## A Study of JNJ-77242113 for the treatment of Participants with Plaque Psoriasis Involving Special Areas (Scalp, Genital, and/or Palms of the Hands and the Soles of the Feet)

n=300 (2:1 randomization)

### Eligibility:

#### Special Areas and Low BSA Mod-Severe

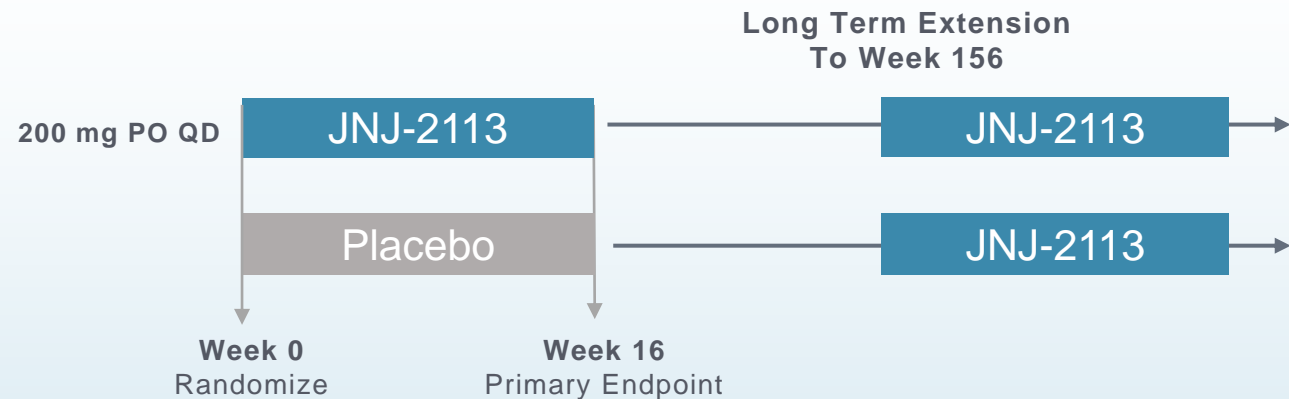
- IGA $\geq$ 2 + BSA  $\geq$  1% + mod/severe special area (ss-IGA $\geq$ 3 or sPGA of genitalia $\geq$  3 or hf-IGA $\geq$ 3) OR
- IGA $\geq$ 3, BSA 5-10%
- Failed Topicals
- Age:  $\geq$  12

### Primary endpoint:

- IGA 0/1 Week 16

Study Start Date: 10/12/23

Estimated Primary Completion: 11/5/24



# ICONIC-Advance 1: JNJ-2113 Phase 3 Study in Moderate to Severe Plaque Psoriasis (Head-to-Head Versus Deucravacitinib)

## A Study of JNJ-77242113 in Adolescent and Adult Participants with Moderate to Severe Plaque Psoriasis

2:1:2 randomization  
2113/placebo/deucra, n=750\*

### Eligibility:

#### Mod/Severe PsO

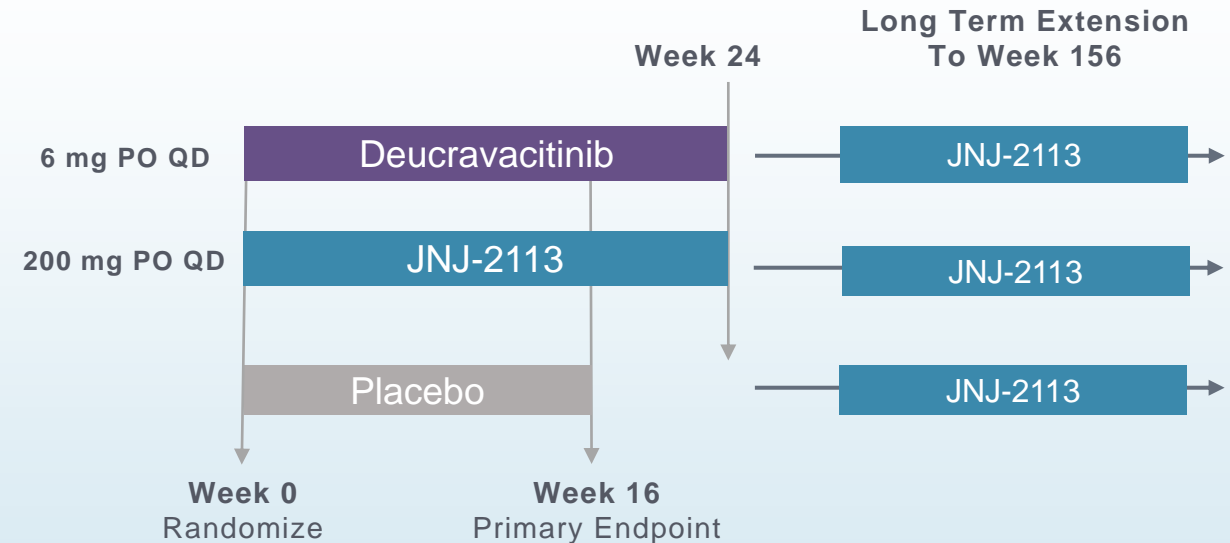
- IGA  $\geq 3$
- PASI  $\geq 12$
- BSA  $\geq 10\%$
- Age:  $\geq 18$

### Primary endpoint:

- IGA 0/1 Week 16
- PASI 90 Week 16

Estimated Study Start Date: 2/9/24

Estimated Primary Completion: 3/13/25



\*Study powered for JNJ-2113 superiority to placebo and deucravacitinib

# ICONIC-Advance 2: Second JNJ-2113 Phase 3 Study in Moderate to Severe Plaque Psoriasis (Head-to-Head Versus Deucravacitinib)

## A Study of JNJ-77242113 in Adolescent and Adult Participants with Moderate to Severe Plaque Psoriasis

4:1:4 randomization  
2113/placebo/deucra, n=675\*

### Eligibility:

#### Mod/Severe PsO

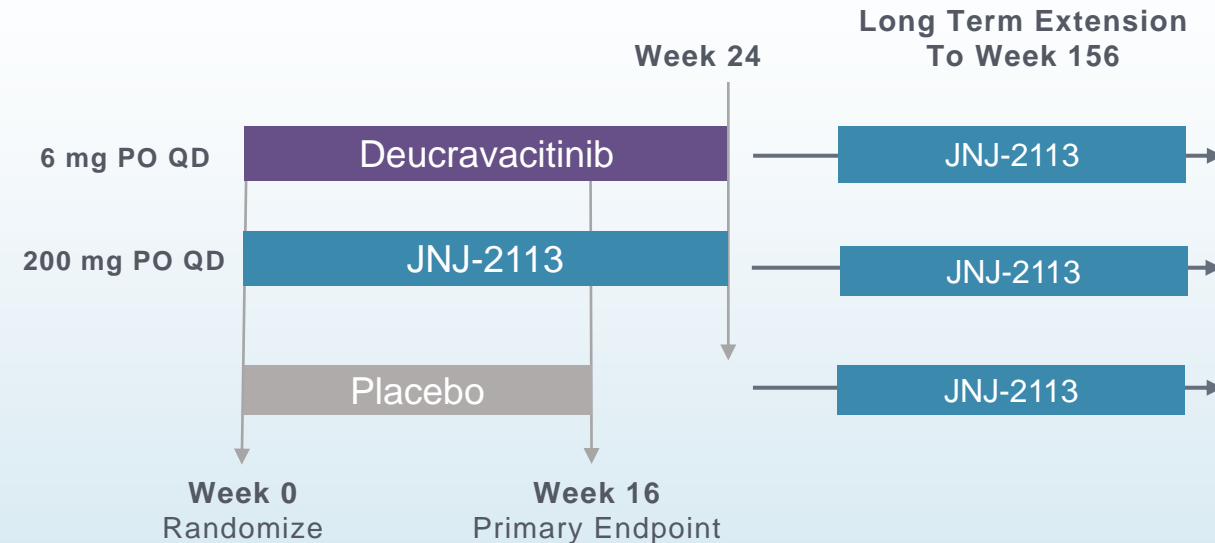
- IGA  $\geq 3$
- PASI  $\geq 12$
- BSA  $\geq 10\%$
- Age:  $\geq 18$

### Primary endpoint:

- IGA 0/1 Week 16
- PASI 90 Week 16

Estimated Study Start Date: N/A

Estimated Primary Completion: N/A



\*Study powered for JNJ-2113 superiority to placebo and deucravacitinib

# ANTHEM-UC: JNJ-2113 Phase 2b Study in Moderate to Severe Ulcerative Colitis

## A Study of JNJ-77242113 in Participants With Moderately to Severely Active Ulcerative Colitis (ANTHEM-UC)

### Adult Patients with UC

n~240

#### Eligibility:

- 18 years of age or older
- Moderately to severely active UC as per the modified Mayo score
- Demonstrated inadequate response to or intolerance of conventional therapy and/or advanced therapy

#### Primary endpoint:

- Clinical Response (Modified Mayo score) at Week 12

Study Start: 10/9/23

Estimated Primary Completion: 5/27/25

