Jefferies Global Healthcare Conference

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June 8, 2022

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Product Portfolio

Addressing Unmet Needs in Multiple Indications with Multi-Billion Dollar Market Potential

Programs	Candidates	Study	Phase 1	Phase 2	Phase 3	Key Milestones
HEMATOLOGY & BLOOD DISORDERS						
		POLYCYTHEMIA VERA (PV)				
		VERIFY	**PV Ph3 trial**			• ~250 patient, randomized, double-blind, placebo-controlled study • Patient screening underway
Hepcidin Mimetic	**Rusfertide (PTG-300)**	REVIVE	PV Ph2 PoC trial			• 60+ patient enrollment completed • Updates at 2022 ASCO & EHA
		PACIFIC	PV Ph2 elevated HcT (>48%) trial			• 16 patients completed 16-week study and continuing in OLE
		HEREDITARY HEMOCHROMATOSIS (HH)				
		300-06	HH Ph2 PoC trial			• 16 patient study completed • Clinical PoC established
INFLAMMATORY & IMMUNOMODULATORY DISEASES						
Oral GI Restricted α4β7-Integrin Antagonist	**PN-943**	IDEAL	**Ulcerative Colitis (UC) Ph2 trial**			• 159 patient study; topline data announced 4/2022 • Efficacy signals with 150 mg bid dosing • Ph3 planning & partnership efforts underway
Oral IL-23R Antagonist	**PN-235** JNJ-77242113	FRONTIER-1	**Psoriasis Ph2b PoC trial**		janssen	• 240 patient FRONTIER-1 psoriasis study • 80 patient SUMMIT study with new formulation • Phase 1 NHV study (Japanese & Chinese) • IBD Ph2 Initiation expected in 2023
		SUMMIT	**Psoriasis Ph2b PoC trial**			

Protagonist Therapeutics

Rusfertide for Polycythemia Vera

Continued Progress with Three Clinical Studies

Ph3 VERIFY, Ph2 REVIVE, Ph2 PACIFIC

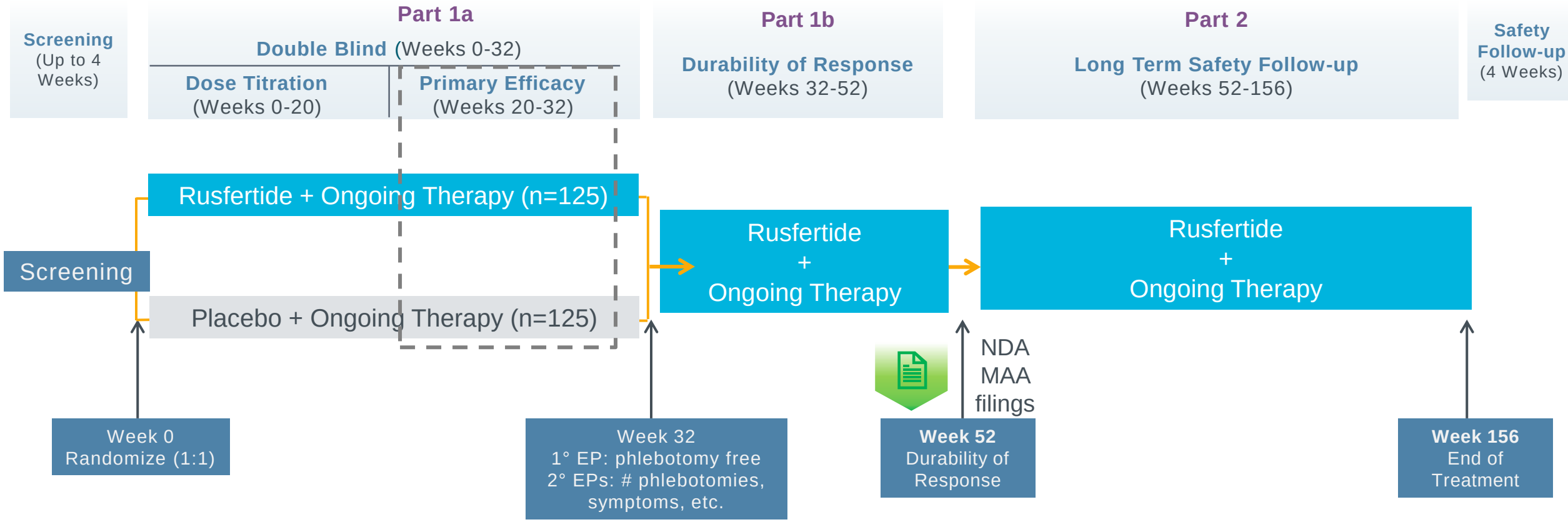
- Phase 3 **VERIFY** Study:
  - FDA and CHMP (EU) have approved the Phase 3 VERIFY study design
  - Major agreements in place for US NDA
    - Non-clinical studies including two-year rat carcinogenicity study
    - Non-clinical and clinical pharmacology studies
    - Chemistry, Manufacturing and Controls plan
- Phase 2 **REVIVE** Study:
  - Clinical updates presented at ASH 2021, ASCO 2022, and EHA 2022
    - Most recent Phase 2 data, presented at ASCO 2022, demonstrates the effects of dosing interruption and resumption
  - Enrollment complete; post-hold re-enrollment rate of >85%
- Phase 2 **PACIFIC** Study:
  - High hematocrit (HcT >48%) 16-week study completed; subjects in OLE
- Orphan Drug designation, Fast Track status*

*The Company voluntarily withdrew its Breakthrough Therapy Designation in June 2022 following correspondence with FDA. Protagonist retains its Fast Track status for rusfertide in PV. All clinical studies in PV are proceeding as planned, with no further changes.

Protagonist Therapeutics

Randomized, Double-blind, Placebo-Controlled Phase 3 PV Study (VERIFY)

VERIFY Study of N~250 subjects



The Phase 3 study design capitalizes on the successful outcome to date of the 60-plus patient open-label Phase 2 REVIVE Study

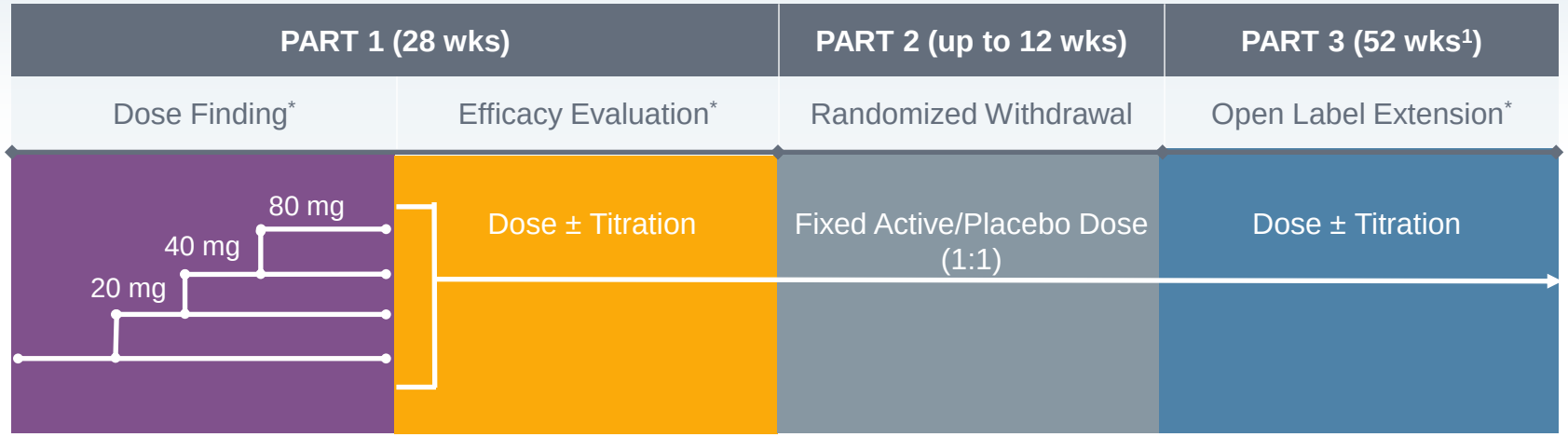
In consultation with the U.S. Food and Drug Administration, Protagonist has implemented a set of rigorous safety monitoring procedures in all ongoing clinical studies, including cancer surveillance measures (augmented dermatological examinations) and stopping rules.

Protagonist Therapeutics

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

GOAL: Maintain Hematocrit <45%

Clinical 'Proof-of-Concept' Study with Add-On



- **Titrate every 4 weeks to maintain hematocrit < 45%*
- *[1]OLE increased from 52 weeks to 3 years*

ELIGIBILITY REQUIREMENTS:

- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- Rusfertide (PTG-300) doses of 10-80 mg administered subcutaneously weekly added to prior standard therapy

KEY ENDPOINTS:

Safety
Maintain Hematocrit <45%
Reduction in Phlebotomies
Symptom Scores: MPN-SAF TSS, PGI-C

Protagonist Therapeutics

Baseline Characteristics of Study Participants in REVIVE Study

Characteristics (n = 70)

AGE	
Range	27-77 years (Mean = 57.3 yrs)
GENDER	
Females	21 (30.0%)
Males	49 (70.0%)
RISK	
Low	29 (41.4%)
High	41 (58.6%) [Age based – 37.1%, Thrombotic events – 21.4%]
DURATION SINCE PV DIAGNOSIS	
<1 yr	14 (20.0%)
1 - <3 yrs	24 (34.3%)
3 - <5 yrs	11 (15.7%)
≥5 yrs	21 (30.0%)

THERAPIES	
PHL only	34 (48.6%)
PHL + HU	21 (30.0%)
PHL + IFN	8 (11.4%)
PHL + RUX	3 (4.3%)
PHL +Multiple Agents	4 (5.7%)
NUMBER OF PHL IN 28 WEEKS PRIOR	
2-3	14 (20.0%)
4-5	38 (54.3%)
≥6	18 (25.7%)
Median	4.79
DAYS BETWEEN PHLEBOTOMIES	
Median	34

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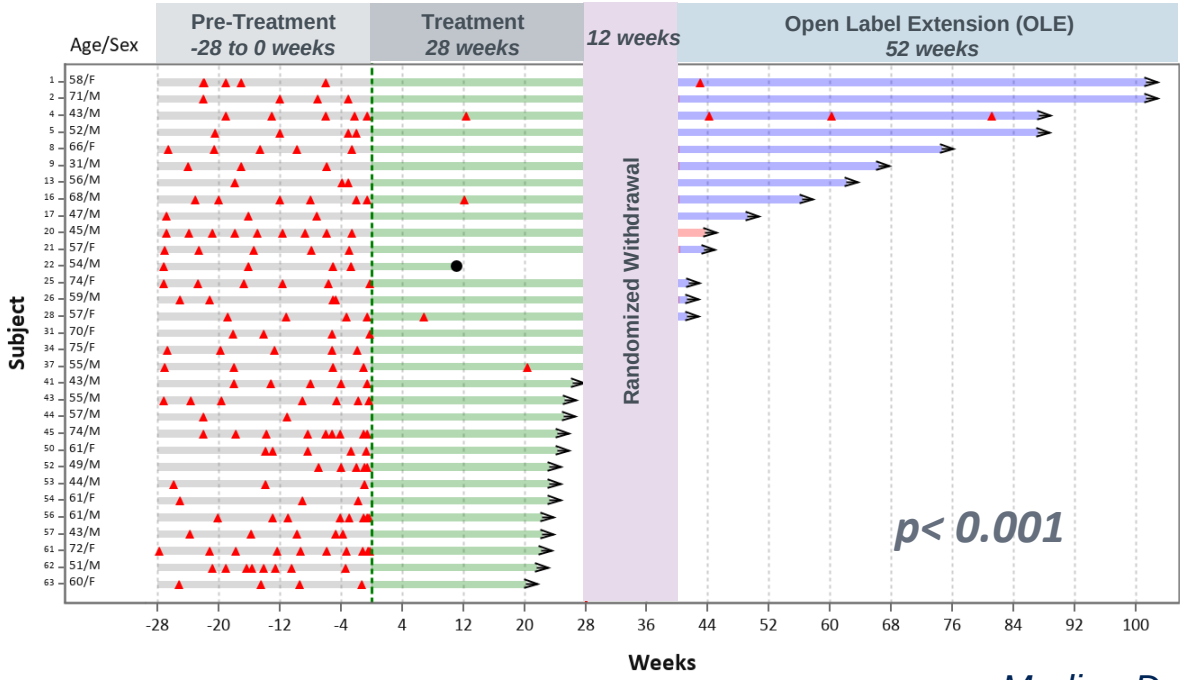
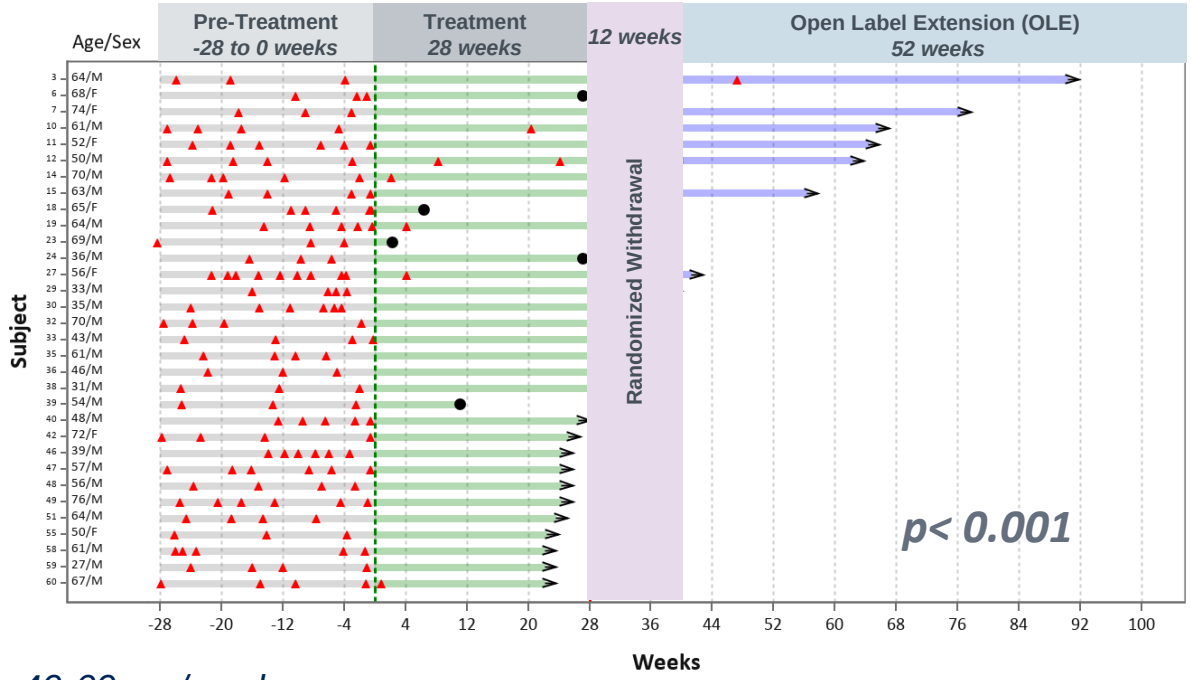
Enrollment complete. Data as of March 10, 2022, and as presented at ASCO June 2022

Effect of Rusfertide on Phlebotomy Frequency in REVIVE Study

Phlebotomy only (N=31, 49%)



Phlebotomy + cytoreductive (N=32, 51%)



Median Dose 40-60 mg/week

During the first 28 weeks of treatment, **84% of patients did not require a phlebotomy**

14% required one and 2% required two phlebotomies.

Screening — Part 1 – Dose Finding — Part 2– Blinded Withdrawal — Part 3 – Open Label Extension

▲ Phlebotomy ● Last dose on study

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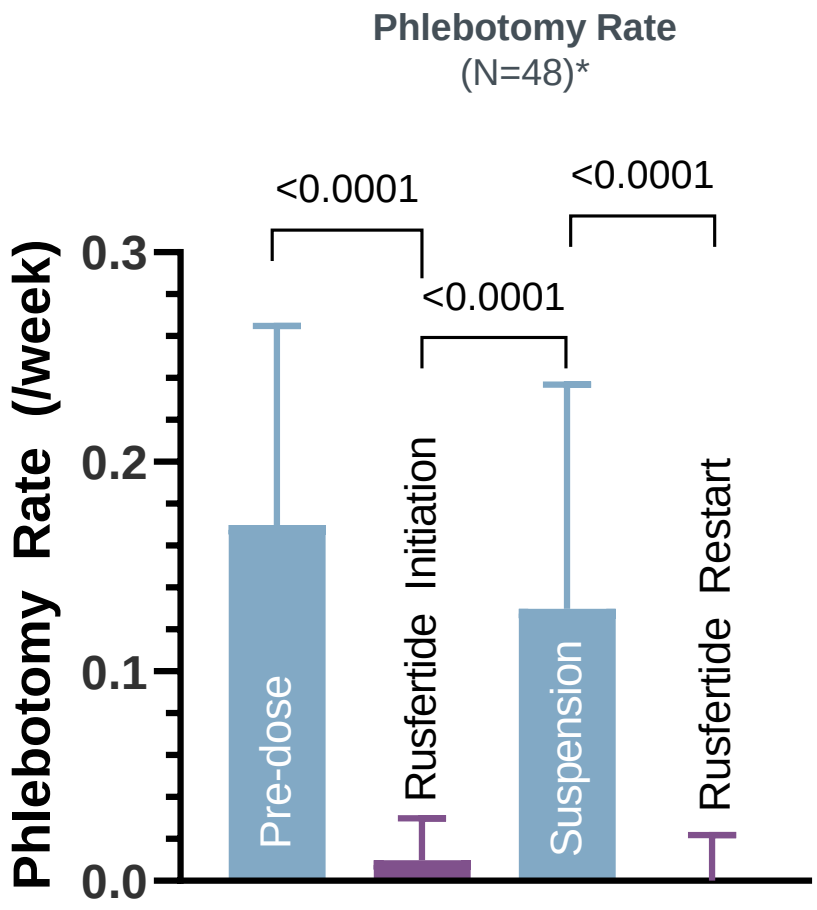
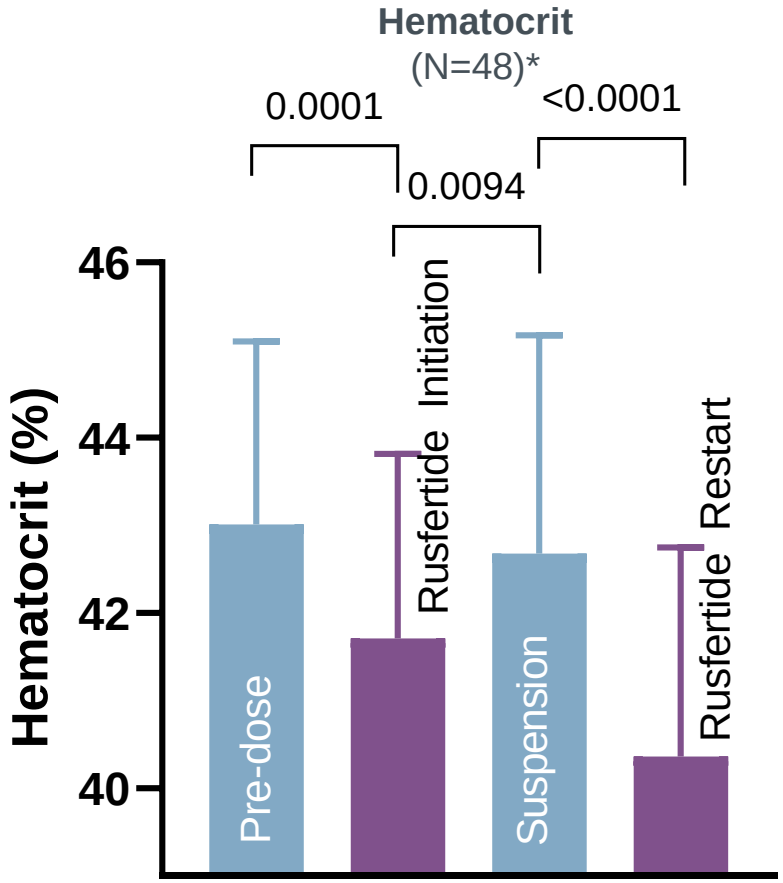
Data as of September 30, 2021
Updated charts to be provided at EHA 2022

Rusfertide Treatment Suspension Leads to Loss of Effect

Restarting Rusfertide Treatment Restores Therapeutic Benefits





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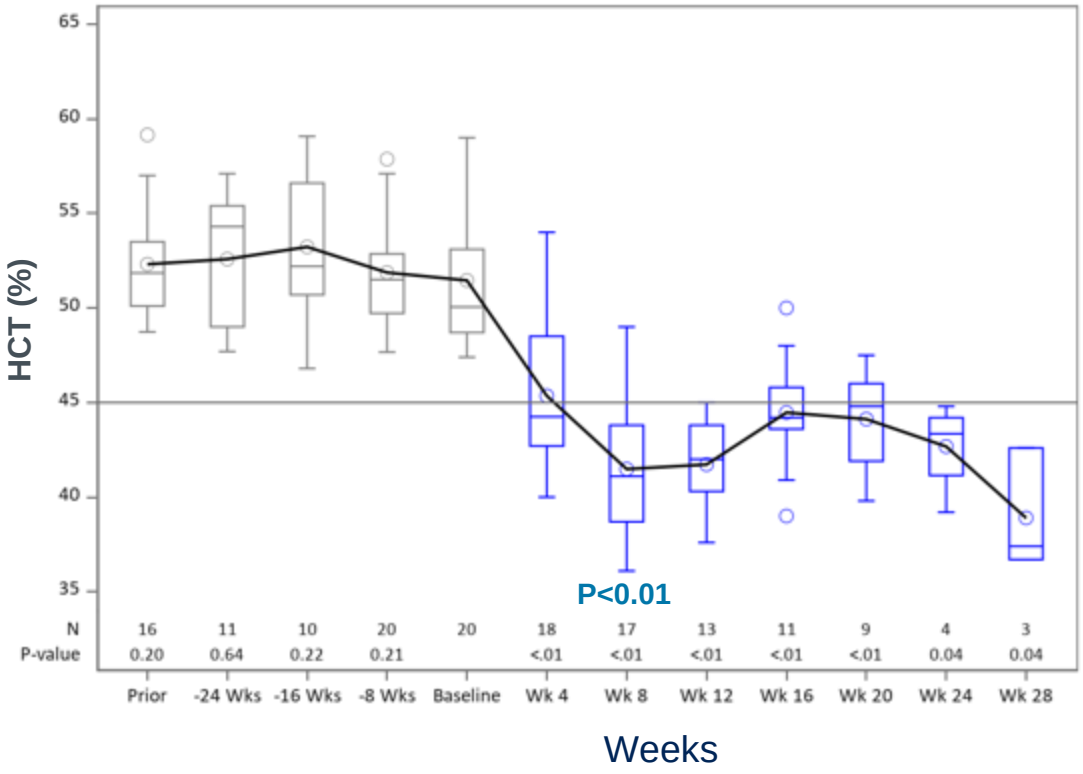
*Subjects with complete restart data

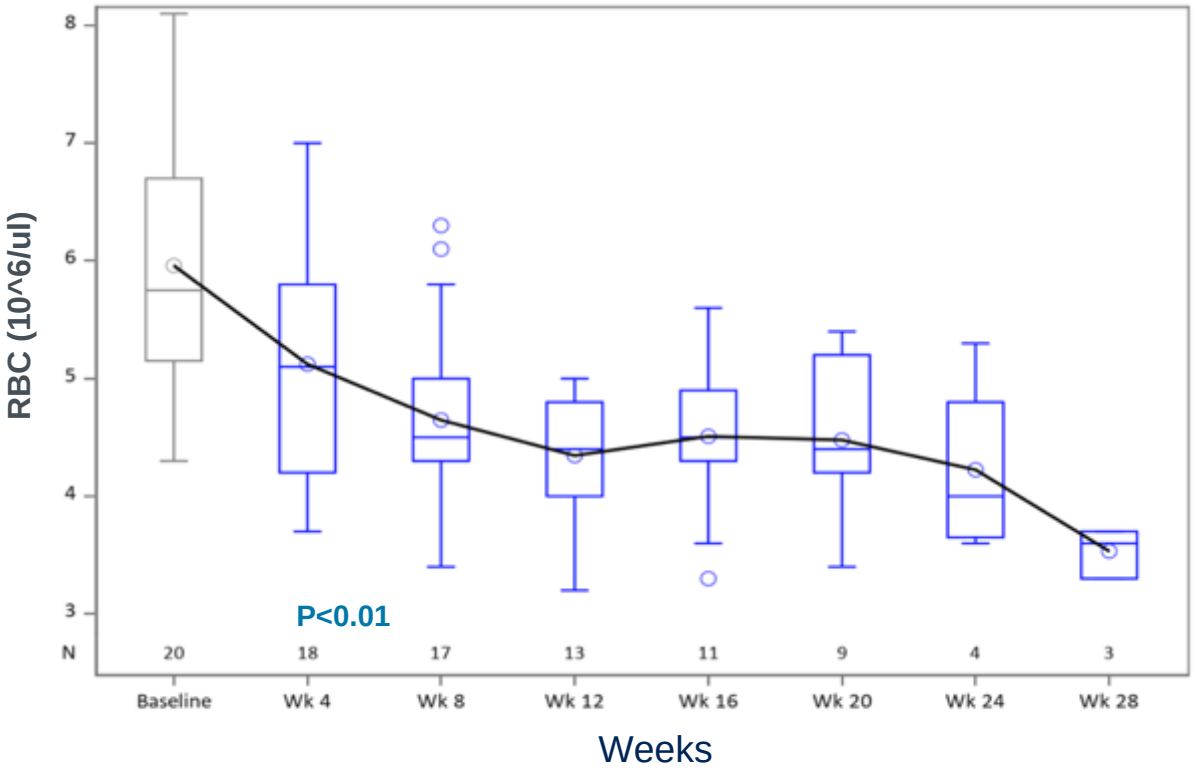
Data as of April 21, 2022

PACIFIC Study in PV Patients with High (>48%) Baseline Hematocrit (n=20)

Rapid HCT Control with Rusfertide



Rapid RBC count reduction with Rusfertide



Screening Rusfertide MEAN

Data as of September 30, 2021
Updated charts to be provided at EHA 2022

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Adverse Events Following Rusfertide in Patients with PV

Combined Summary of Events: REVIVE and PACIFIC Studies

System Organ Class Preferred term	AE n (%)
Total number of Subjects	*90*
General disorders and administrative site conditions	77 (85.6)
Fatigue	19 (21.1)
Skin and subcutaneous tissue disorders	37 (41.1)
Pruritis	19 (21.1)
Hyperhidrosis	9 (10.0)
Nervous system disorders	35 (38.9)
Headache	18 (20.0)
Dizziness	14 (15.6)
Gastrointestinal disorders	32 (35.6)
Nausea	13 (14.4)
Diarrhea	11 (12.2)
Musculoskeletal and connective tissue disorders	32 (35.6)
Arthralgia	17 (18.9)
Infections and infestations	23 (25.6)
Investigations	22 (24.4)
Blood and Lymphatic Disorders	20 (22.2)
Anemia	11 (12.2)
Metabolism and nutrition disorders	17 (18.9)
Respiratory, thoracic and mediastinal disorders	16 (17.8)
Injury, poisoning and procedural complications	13 (14.4)
Psychiatric disorders	11 (12.2)
Vascular disorders	9 (10.0)

Treatment-emergent AEs with more than 10% incidence

Most treatment related AEs were Grade 1 or 2

- Injection site reaction (ISRs) were most common and associated with 33% of injections. All ISRs were transient, and no patient discontinued due to an ISR
- **SAEs** include aneurysm of popliteal artery, atrial fibrillation, chest pain, hydrocephalus, gastroenteritis, syncope
  - 5 subjects with cancer events (basal cell carcinoma, squamous cell carcinoma, melanoma, AML)
- No grade 3 events related to rusfertide; one grade 4 event possibly related to rusfertide (asymptomatic and fluctuating thrombocytosis)
- 2 withdrawals due to possibly related AE - both asymptomatic thrombocytosis
- No clinically significant laboratory abnormalities
- No Anti Drug Antibody (ADA) response was noted in any patient

Data as of March 10, 2022, and as presented at ASCO

Clinical Studies of Rusfertide in Polycythemia Vera

Summary of VERIFY, REVIVE and PACIFIC Studies

- Patient screening has been initiated in Phase 3 VERIFY study with enrollment completion expected in 1H 2023
- Enrollment completed in Phase 2 REVIVE and PACIFIC studies, dosing ongoing
- PV patients requiring frequent phlebotomy ± cytoreductives have been treated with rusfertide for >18 months, with subjects remaining essentially phlebotomy free
  - Rapid, sustained and durable hematocrit control without clinically meaningful increase in WBC or platelet counts
  - Robust efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon or ruxolitinib
  - In high hematocrit PACIFIC study, rusfertide induction therapy with twice weekly dosing achieves rapid hematocrit control (<45%) without phlebotomy
  - Rusfertide dosing was interrupted and led to loss of effect (increased phlebotomy rate, increase in HCT and RBC). Rusfertide restart restored therapeutic benefits
    - ➢ Following the re-activation of all sites, >85% of patients returned to the study after dosing interruption
- Rusfertide treatment with or without cytoreductives appears to be well tolerated
    - ➢ Randomized, placebo-controlled Phase 3 VERIFY study to refine understanding of the safety profile.

Hereditary Hemochromatosis (HH)

Disease Prevalence and Treatment

- HH is an inherited iron overload disorder characterized by excessive iron absorption, due to deficiency of hepcidin
  - Hepcidin deficiency leads to increased circulating transferrin saturation (TSAT) and toxic non-transferrin bound iron (NTBI), and ultimately, iron accumulation in organs such as the liver, pancreas, heart, and bone
  - Therapeutic phlebotomy to reduce iron loading is standard treatment for HH. While phlebotomy is effective, it does not target the biological mechanism, and may actually exacerbate the underlying issue
- If untreated, iron overload can cause hepatomegaly, diabetes mellitus, skin hyperpigmentation, cardiomyopathy, diastolic dysfunction, heart failure, cirrhosis, etc.

Prevalence in million+ patients in US; clinical disease in ~100K subjects

Excessive iron accumulation in heart, liver, pancreas, skin, joint tissues & joint pain

Phlebotomy is the only therapeutic option; no approved drugs

Unmet need in specific sub-populations

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Source: Porter JL, Rawla P. Hemochromatosis. (Updated 2020 Jun 18], https://www.ncbi.nlm.nih.gov/books/NBK430862/

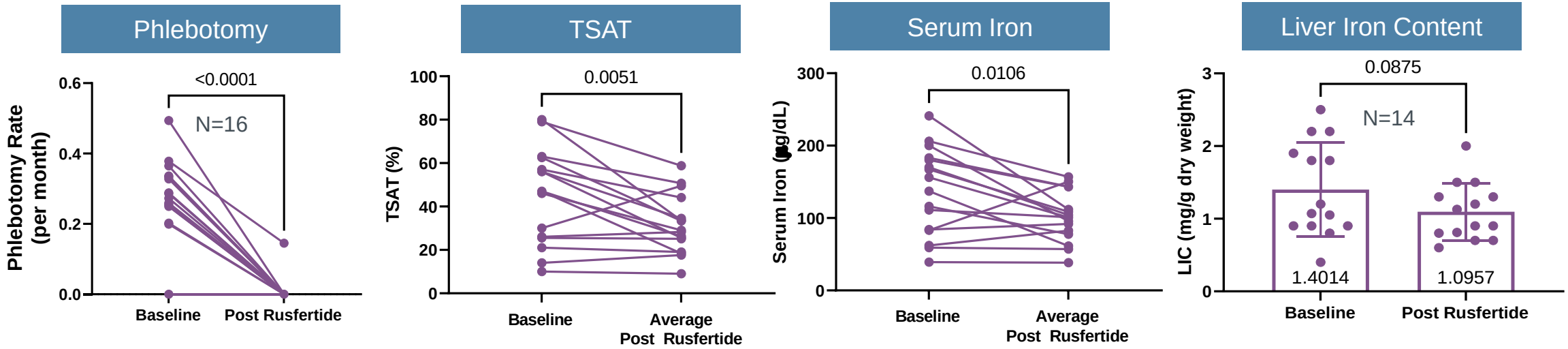
Phase 2 Study in Hereditary Hemochromatosis

Clinical PoC Achieved

SCREENING	MONTH 1	MONTH 2	MONTH 3	MONTH 4	MONTH 5	MONTH 6

Pre-study Phlebotomy and Liver MRI

- Six-month, open-label study in 16 HH patients in maintenance phase of iron depletion
- Stable pre-study phlebotomy for ≥6 months; requiring ≥3 phlebotomies/12 months or ≥4 phlebotomies/15 months
- Study endpoints included safety, reduction in phlebotomies, serum iron, TSAT, transferrin, ferritin, liver iron content by MRI, adverse events



Well tolerated; all treatment-emergent AEs were Grade 1 or 2

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Potential Utility of Rusfertide in Hereditary Hemochromatosis (HH)

HH Arthropathy (joint pain) is a Common and Persistent Phlebotomy Resistant[1] Symptom

- Chronic arthropathy occurs in 24-81% of patients with HH [2,3,4]
  - Joint pain is an early manifestation of the disease and in many is the cause for first diagnosis of HH
  - X-ray/MRI imaging combined with validated joint pain and function scoring instruments
- Persistent arthropathy can diminish QoL and yield high healthcare utilization and costs [4,7]
  - Up to 16% of HH patients undergo joint replacement surgery
- Iron accumulation in joints may be associated with increased oxidative stress, disrupted matrix metabolism, and cartilage degeneration, which contribute to the development of arthropathy [3,5,6]
- **Arthropathy correlates with iron overload and is associated with elevated age, ferritin, and TSAT [2,3]**

1 Richette, P. "Musculoskeletal Complications of Hereditary Hemochromatosis: A Case-Control Study", J Rheumatology, 2010

2 Whalen, N. "Association of Transferrin Saturation with the Arthropathy of Hereditary Hemochromatosis", Clinical Gastroenterology Hepatology, 2017

3 Carroll, GJ. "Hereditary Hemochromatosis is characterized by a clinically definable arthropathy that correlates with iron load", Arthritis & Rheumatism, 2011

4 Nguyen, C. "Bone and joint complications in patients with hereditary hemochromatosis: a cross-sectional study of 93 patients," Ther Adv Musculoskel Dis, 2020

5 Carroll, GJ. "Characteristics of the Arthropathy Described in Hereditary Hemochromatosis", Arthritis Care & Research, 2012

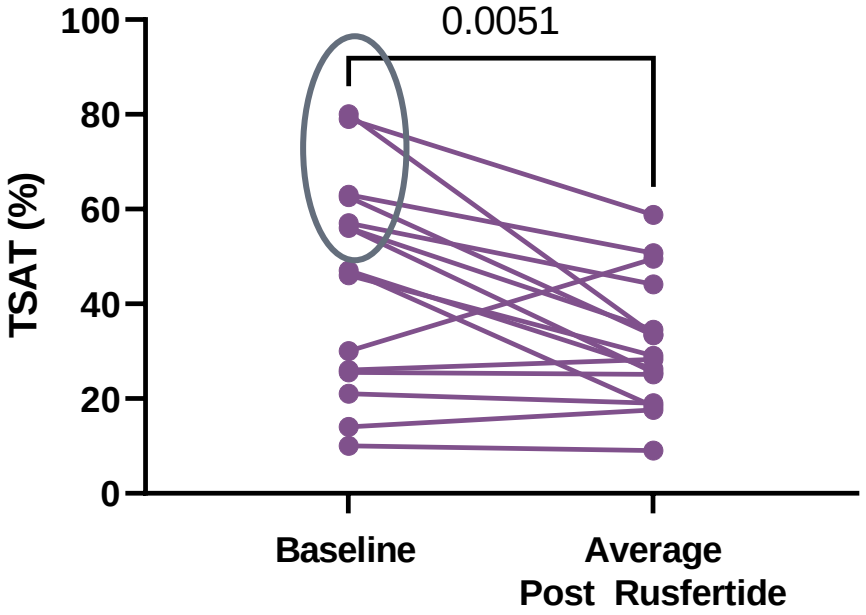
6 Karim, A. "The role of disrupted iron homeostasis in the development and progression of arthropathy", 2022

7 Sahinbegovic, E. "Musculoskeletal Disease Burden of Hereditary Hemochromatosis", Arthritis & Rheum, 2010

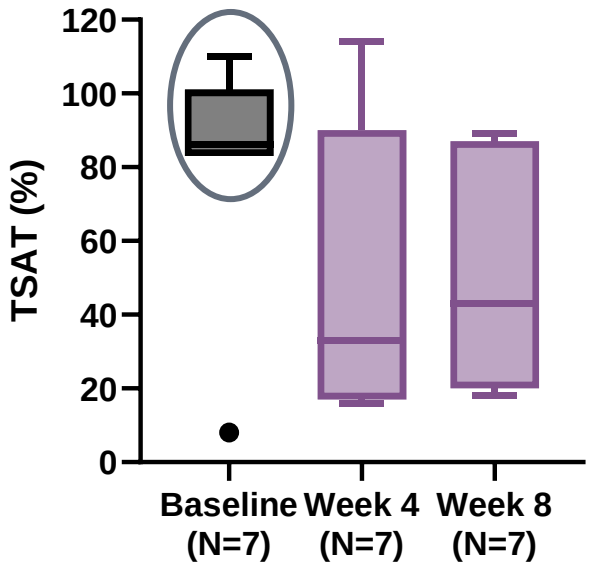
Potential Utility of Rusfertide in Treating HH Arthropathy

Rusfertide Treatment Leads to Rapid and Persistent Control of TSAT

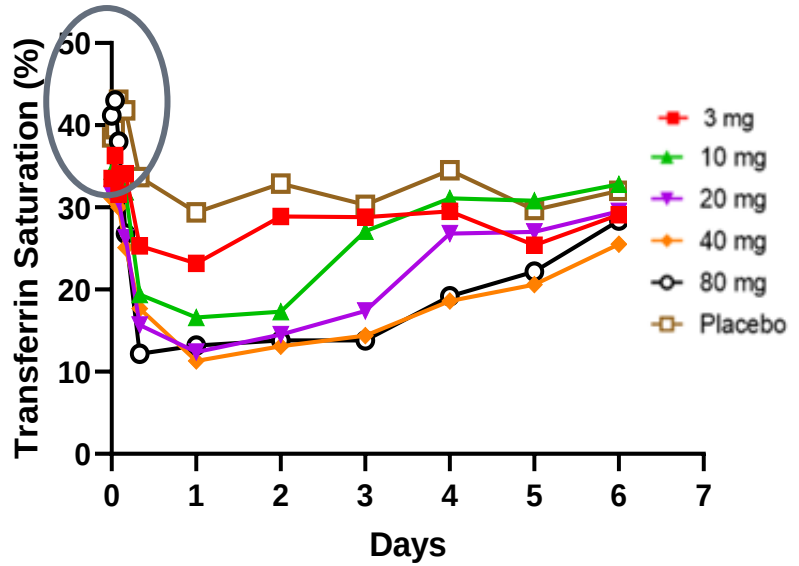
Hereditary Hemochromatosis (HH)



TD β Thalassemia



Healthy Subjects



- **Next Steps**
  - Design a Phase 2 clinical PoC study to demonstrate potential utility of Rusfertide in treating iron overload and reducing joint pain in phlebotomy resistant, HH arthropathy patients

Protagonist Therapeutics

IBD: Paradigm Shift Toward Targeted Oral and Combination Therapy

A Growing Multi-Billion Dollar Market

2019: ~ $14B sales[1] → **2029: projected ~ $24B sales[1]**

Historical IBD Treatment Paradigm

TNF mAbs dominated IBD Therapy

- Injectable TNF mAbs – Blockbusters
  - Humira® & Remicade®
- Significant room for improvement
  - Low response rates / loss of response
  - Safety concerns - black box warnings

Emerging IBD Treatment Paradigm

Injectable mAbs with safer MOAs

- α4β7 integrin: Entyvio® (~ $4B sales 2020)
- IL-12/IL-23: e.g., Stelara®

Oral Targeted Therapy for IBD

Protagonist: *mAb Validated Pathways*

- **PN-943[2]** (α4β7 integrin)
- **IL-23Rs**

Other Oral Approaches: *New Targets*

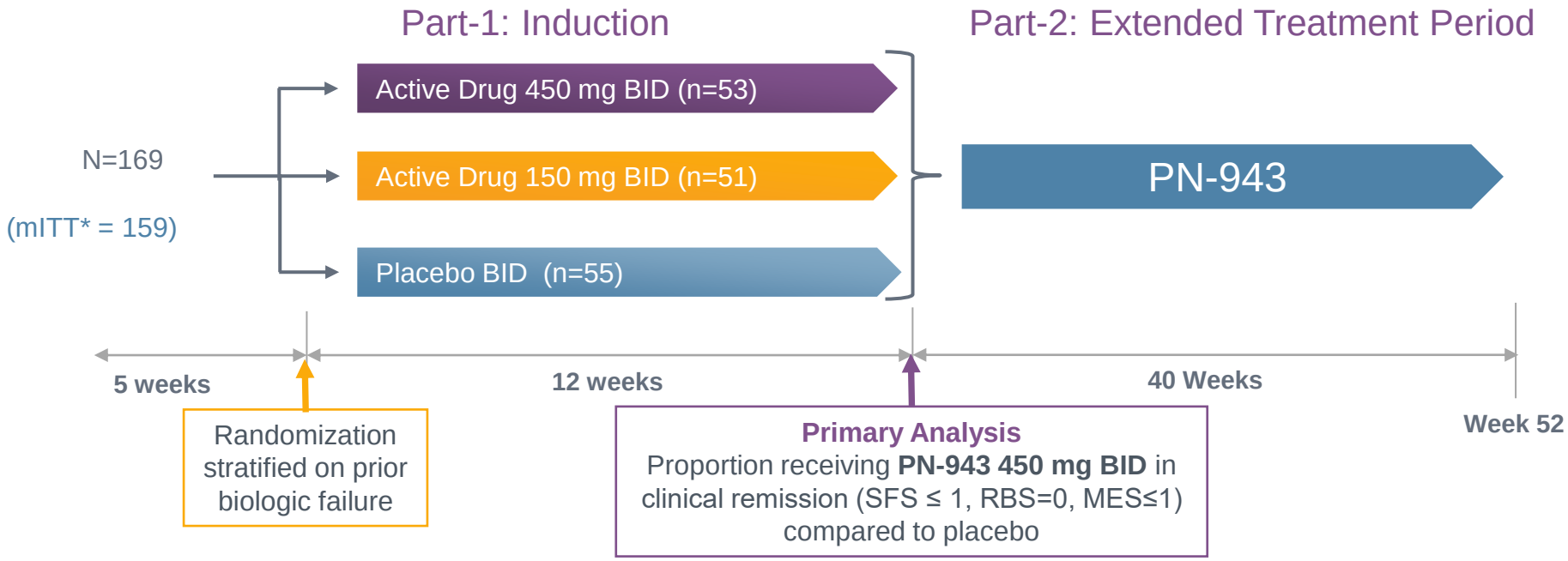
- S1P1: e.g., Zeposia®
- JAK*: e.g., Xeljanz®, Rinvoq®

**black box warnings*

Potential Future of IBD
Oral Combo Therapy

[1] GlobalData: Global Drug Forecast and Market Analysis to 2029; 7 Major Markets: US, EU5, JP
[2] Investigational product candidate, not approved

IDEAL: PN-943 Phase 2 UC Study Design



Eligibility:

- Adults with moderate-severe UC: 3-Component Mayo Score 5-9 points
- Failed at least 1 UC medication (5-ASA, steroids, immunomodulators or one biologic)
- Stable dose steroids, prednisone equivalent ≤ 20 mg/day
- Stable dose immunomodulators
- One prior biologic exposure (anti-TNF or anti-IL-12/23) allowed; prior vedolizumab excluded

*All ITT patients excluding 10 from Russia and Ukraine who did not complete Week 12 assessments prior to March 3, 2022

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The Outcome of Phase 2 IDEAL Study Will Inform Phase 3 decisions

- **Phase 2 data in UC with various candidates spanning different mechanism of actions**
  - Large confidence intervals, influenced by study design, duration, size, demographics, & criteria
  - Phase 2 outcomes (10-20% delta) has generally predicted efficacy in Phase 3

Historical Ph2, Ph3, and Approval Data in UC				
Candidate	**MoA**	**Clinical Remission Delta**		**Approval**
		Phase 2	**Phase 3**	
Vedolizumab (Entyvio®)[1]	α4β7 integrin	19%	11.5%	✓
Ozanimod (Zeposia®)[2]	S1P	10%	12.4%	✓
Upadacitinib (Rinvoq®)[3]	JAK	19.6%	21/29.5%	✓*(black box)*

*Cross trial comparisons complicated by different inclusion criteria, patient populations, primary endpoint definitions, timing of primary endpoint, phase of clinical development

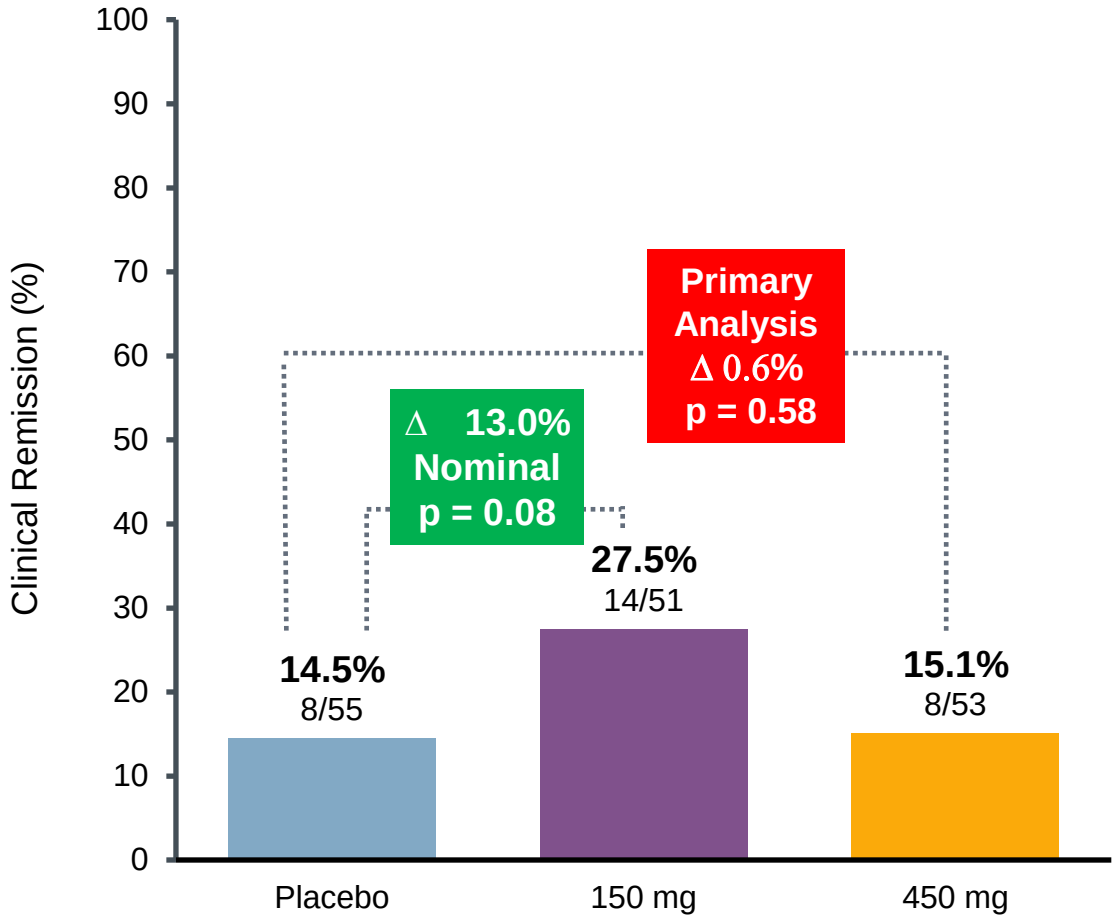
- **Phase 2 data will provide specific guidance for Phase 3 program on:**
  - Go/No-go decision ✓
  - Dose selection ✓
  - Powering of registrational primary and secondary endpoints ✓

1. Feagan, B. G., Greenberg, G. R., Wild, G., Fedorak, R. N., Paré, P., McDonald, J. W., ... & Vandervoort, M. K. (2005). Treatment of ulcerative colitis with a humanized antibody to the α4β7 integrin. *New England Journal of Medicine*, *352*(24), 2499-2507; Feagan, B. G., Rutgeerts, P., Sands, B. E., Hanauer, S., Colombel, J. F., Sandborn, W. J., ... & Parikh, A. (2013). Vedolizumab as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*, *369*(8), 699-710.
2. Sandborn, W. J., Feagan, B. G., Wolf, D. C., D'Haens, G., Vermeire, S., Hanauer, S. B., ... & Olson, A. (2016). Ozanimod induction and maintenance treatment for ulcerative colitis. *New England Journal of Medicine*, *374*(18), 1754-1762; Sandborn, W. J., Feagan, B. G., D'Haens, G., Wolf, D. C., Jovanovic, I., Hanauer, S. B., ... & Danese, S. (2021). Ozanimod as induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*, *385*(14), 1280-1291.
3. Danese, S., Vermeire, S., Zhou, W., Pangan, A., Siffledeen, J., Hébuterne, X., ... & Pannaccione, R. (2021). OP24 Efficacy and safety of upadacitinib induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from the phase 3 U-ACHIEVE study. *Journal of Crohn's and Colitis*, *15*(Supplement_1), S022-S024.; Vermeire, S., Danese, S., Zhou, W., Pangan, A., Greenbloom, S., D'Haens, G., ... & Panaccione, R. (2021). OP23 Efficacy and safety of upadacitinib as induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from phase 3 U-ACCOMPLISH study. *Journal of Crohn's & Colitis*, *15*(Suppl 1), S021.

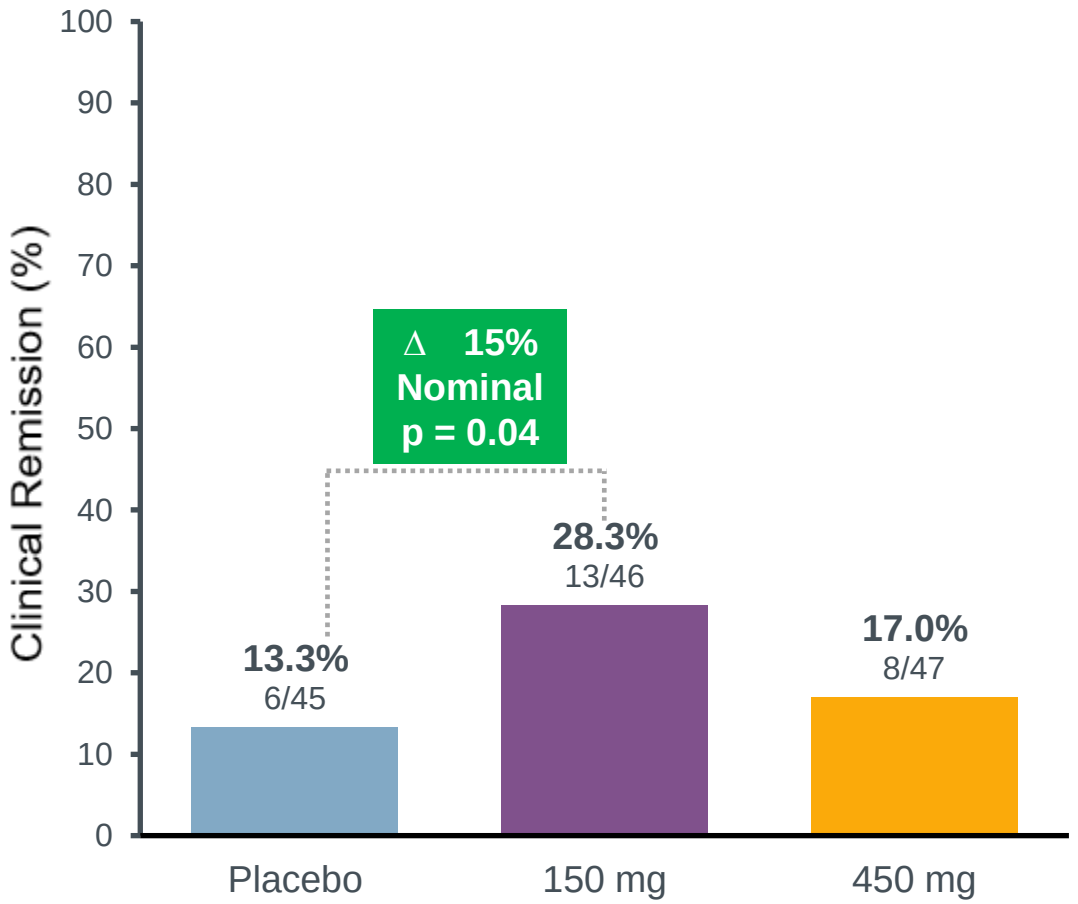
Protagonist Therapeutics

Clinical Remission at Week 12 - mITT

Modified ITT Population



Biologic Naïve and Biologic-Exposed-Non-Failure Patients



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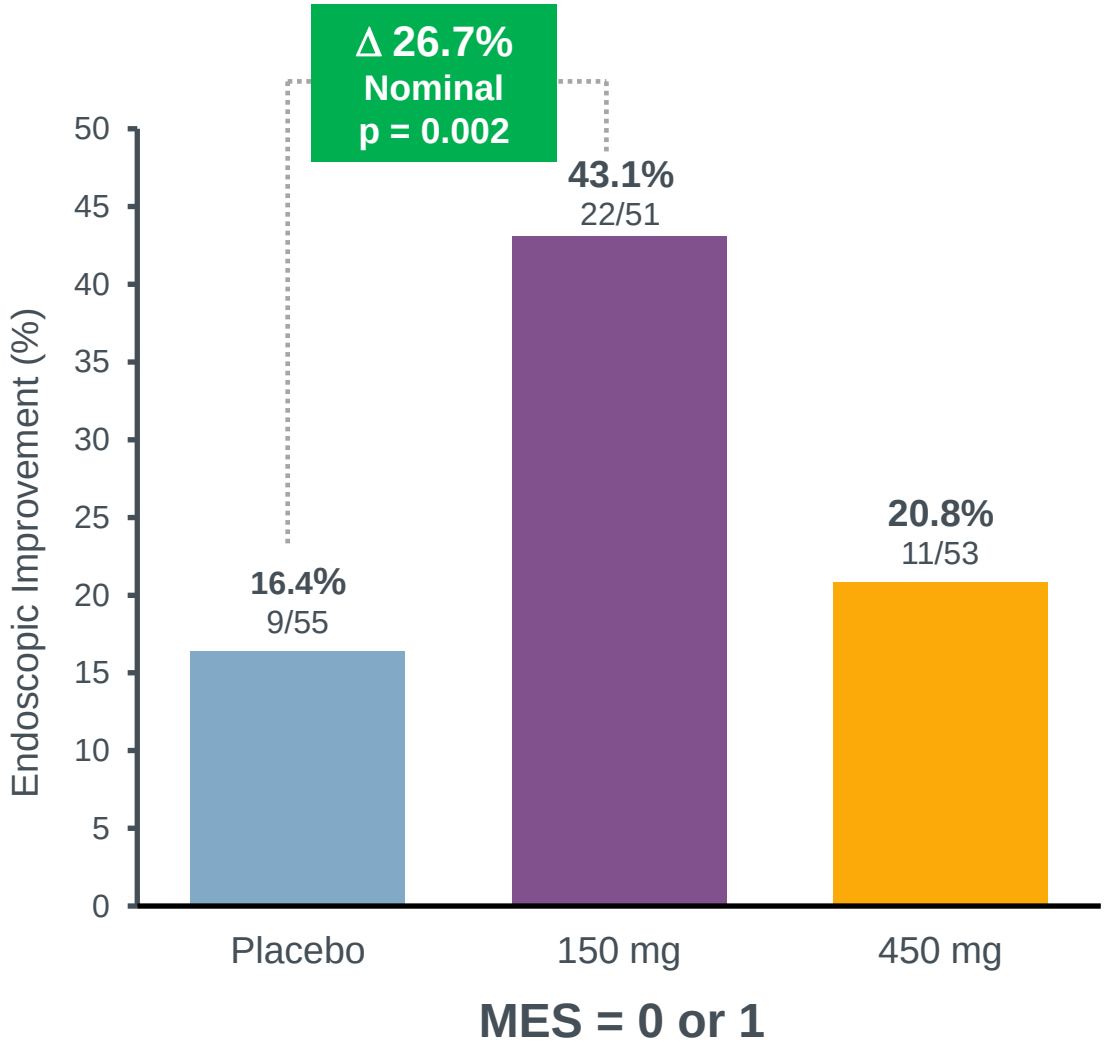
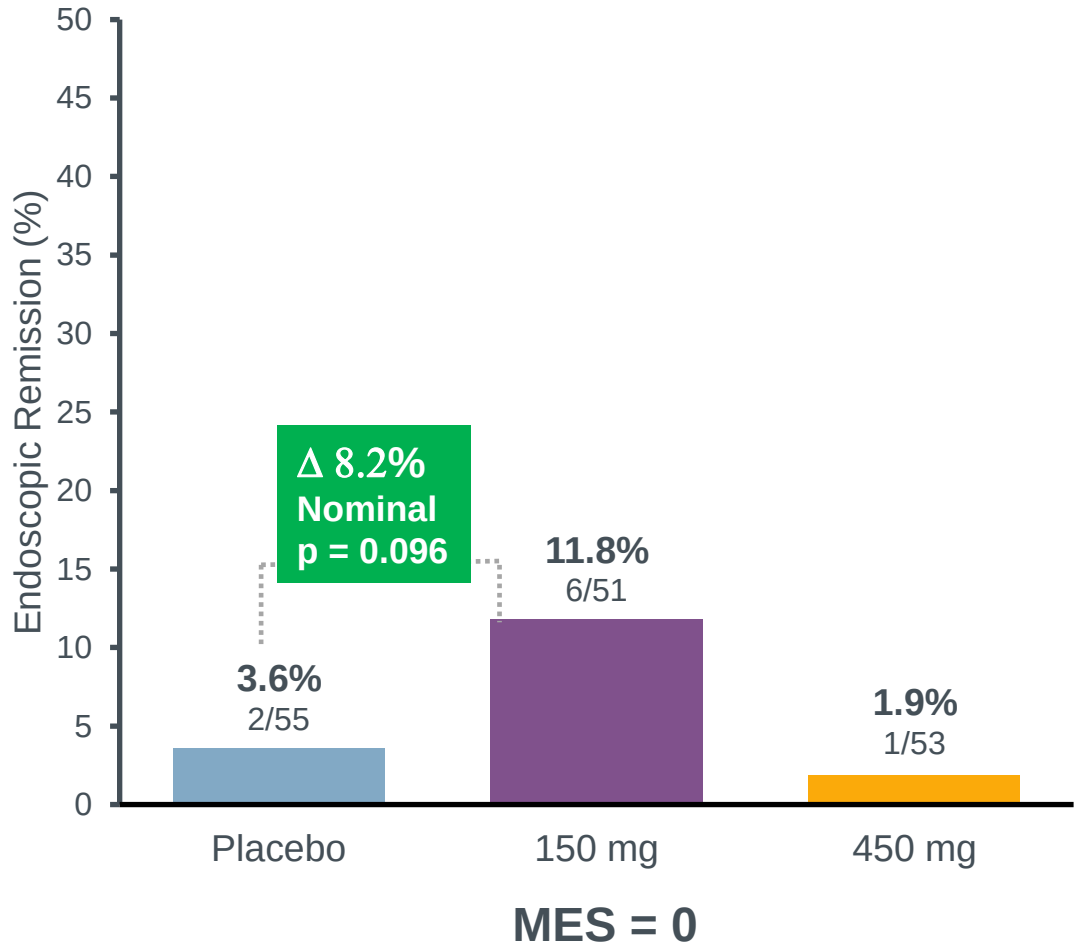
Data as presented at DDW, May 2022

Endoscopic Improvement and Remission at Week 12 - mITT

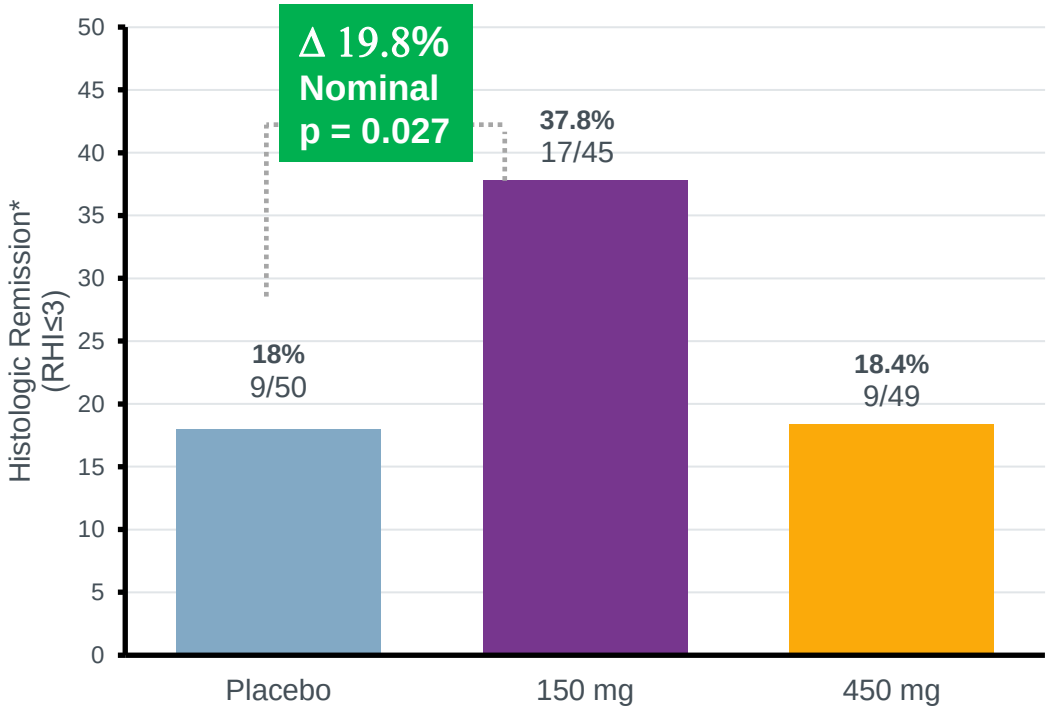


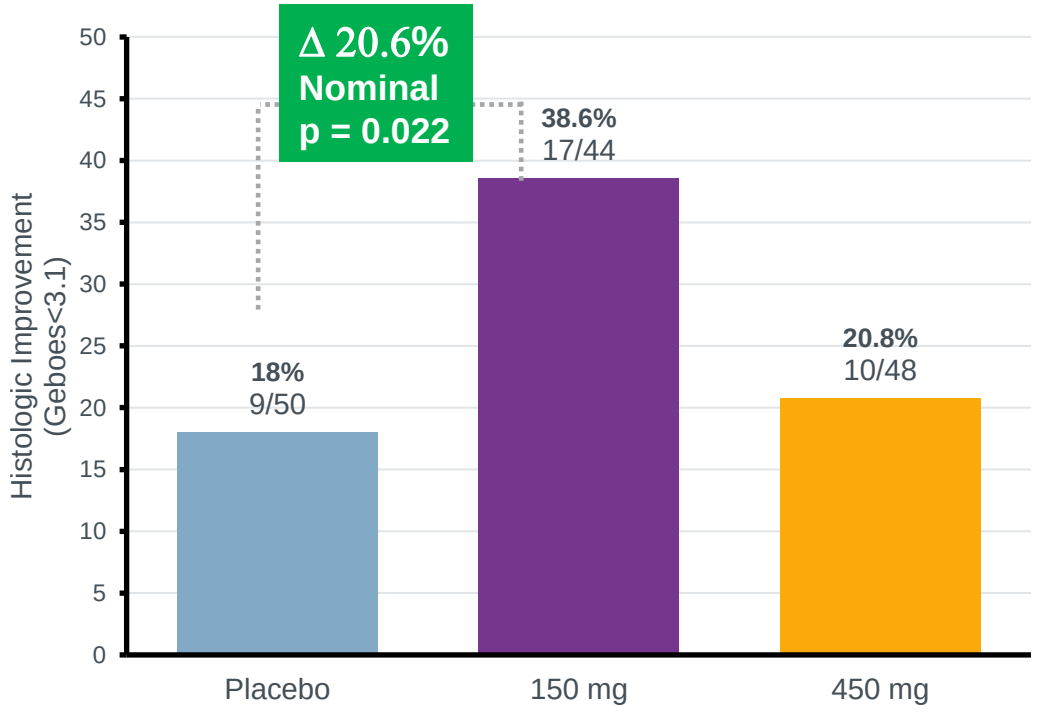


Protagonist Therapeutics

Data as presented at DDW, May 2022

Histologic Remission and Improvement[1] at Week 12 - mITT





*post hoc analysis

[1]patients who are below the baseline improvement/remission criteria are excluded

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Data as presented at DDW, May 2022

Conclusions and Next Steps

IDEAL Study

Summary of Results

- No treatment effect for primary endpoint (clinical remission at week 12, PN-943 450 mg BID vs placebo)
- Clinical remission in 27.5% of PN-943 150 mg BID group vs 14.5% in placebo (Δ 13%, nominal p = 0.08) for mITT analysis
  - Δ in Biologic-Non-Failure population 15% (nominal p = 0.04)
- Very good concordance with efficacy across multiple key secondary endpoints including histologic and endoscopic remission/improvement at the 150 mg BID dose
- No significant safety signals detected
- 40-week maintenance extension study (Part 2) ongoing; data expected in 2023

Next Steps

- Ph3 registrational study design
- Identifying a potential partner

The IDEAL study supports further development of PN-943 in UC registrational trials

Oral, IL-23 Receptor Specific Peptide Antagonist: PN-235

Janssen Partnership

Objective

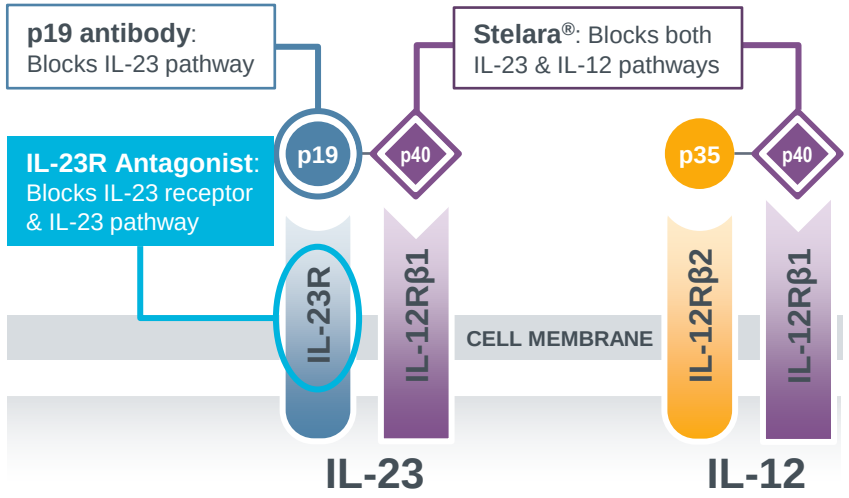
- Extend the Stelara® franchise and transition from injectable to oral targeted therapy
  - Stelara approved for psoriasis, psoriatic arthritis, Crohn's, UC
  - ~$7.7B total global sales in 2020

Terms

- May 2017: Partnership initiated
- $112.5M in upfront and development milestones received to date
- Eligible for about additional $875M in milestones, up to double digit royalties, US co-detailing rights
  - Study initiation milestones: $25M (psoriasis, received April 2022)

Status

- Focus on the PN-235 candidate, with its superior potency and PK/PD profile, for IBD and non-IBD indications
  - **PN-235 (JNJ-77242113):** Ph1 completed in 2021
  - ***Advancing in psoriasis indication in 240 patient Ph2b FRONTIER 1 study, 80 patient Ph2 SUMMIT study, 27 patient Ph1 study in Japanese/Chinese NHVs***
  - ***Ph2 study initiations in IBD indications expected in 2023***



Stelara® is a key Janssen franchise

- ~$7.7B total global sales in 2020

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Financial Highlights

Financial Resources Forecast Extends Through Full Year 2024*

$305.3M	2024	48.7M
CASH & SECURITIES as of March 31, 2022	**CASH & SECURITIES** provide financial resources forecast through full year 2024*	**SHARES OUTSTANDING** as of April 29, 2022

**Based on our current operating plan and expenditures. These estimates may change as new events occur and additional information is obtained.*

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Upcoming Catalysts in 2022 and Beyond

Significant Opportunities to Unlock and Capture Value in the 12-24 Months Ahead

Products	Anticipated Events in 2022				2023
	Q1	Q2	Q3	Q4	
Rusfertide	1 • **VERIFY:** Ph3 250 patient PV study initiation 2 • **REVIVE:** Ph2 PV study • **PACIFIC:** Ph2 PV study	ASCO EHA		ASH	• Ph3 enrollment completion (1H) • Ph2 randomization results (Q1)
	3 • **HH** clinical PoC achieved; opportunity in phlebotomy resistant HH arthropathy sub-population				
PN-943		4 • **IDEAL: Topline results reported** DDW	**Partnering efforts**		
PN-235 janssen	5 • Ph2 initiation –$25M milestone • **Plaque psoriasis: Ph2b FRONTIER 1 (240 patients); Ph2 SUMMIT (80 patients)**				• Ph2 study results • IBD study initiation ($10M milestone)
Discovery and Pre-Clinical	6 • Nomination of **new development candidate** – new target for new indication(s)				• **Oral hepcidin** mimetic candidate

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Thank you