Oral IL-23 Receptor Peptide Antagonist JNJ-2113:
The Journey from De Novo Discovery to Phase 3 Clinical Development Program

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

14th Drug Discovery Strategic Summit
San Francisco, CA, USA
*October 18, 2023*

Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, product candidates, capital resources, potential markets for our product candidates, our plans related to potential future collaboration arrangements, the impact on our business or product candidates of actions or determinations of the U.S. Food and Drug Administration ("FDA"), enrollment in our clinical trials, any potential impact on our business related to COVID-19, our potential receipt of milestone payments and royalties under our Collaboration Agreement with Janssen Biotech, Inc., are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potentially" "predict," "should," "will" or the negative of these terms or other similar expressions.

The forward-looking statements made in this presentation involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These forward-looking statements are subject to risks and uncertainties, including those discussed in Protagonist's filings with the Securities and Exchange Commission, including in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of most recently filed periodic reports on Form 10-K and Form 10-Q and subsequent filings and in the documents incorporated by reference therein. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation concerns products that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration. They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Nothing contained in this presentation is, or should be construed as, a recommendation, promise or representation by the presenter or Protagonist or any director, employee, agent or advisor of Protagonist. This presentation does not purport to be all inclusive or to contain all the information you may desire.
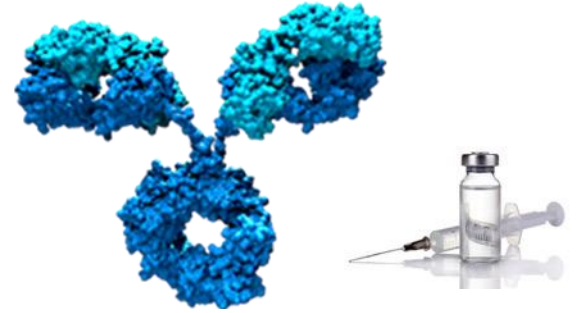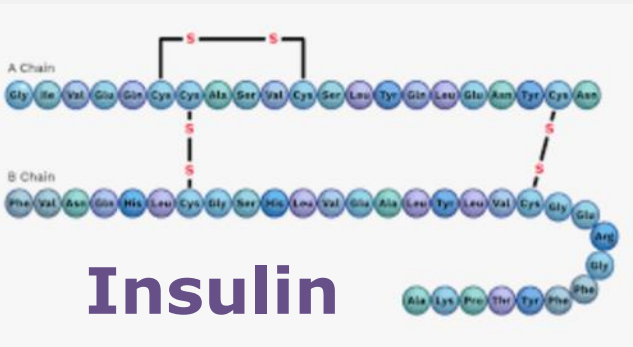
Peptides
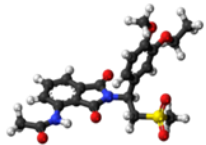
**Small Molecule
MW <0.5 Kd**
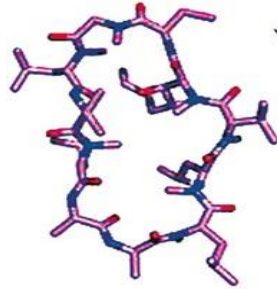
**Peptide
MW ~1-5 Kd**

**Biologics
MW ~100-300 Kd**

Insulin

once weekly
mounjaro®
(tirzepatide) injection 0.5 mL
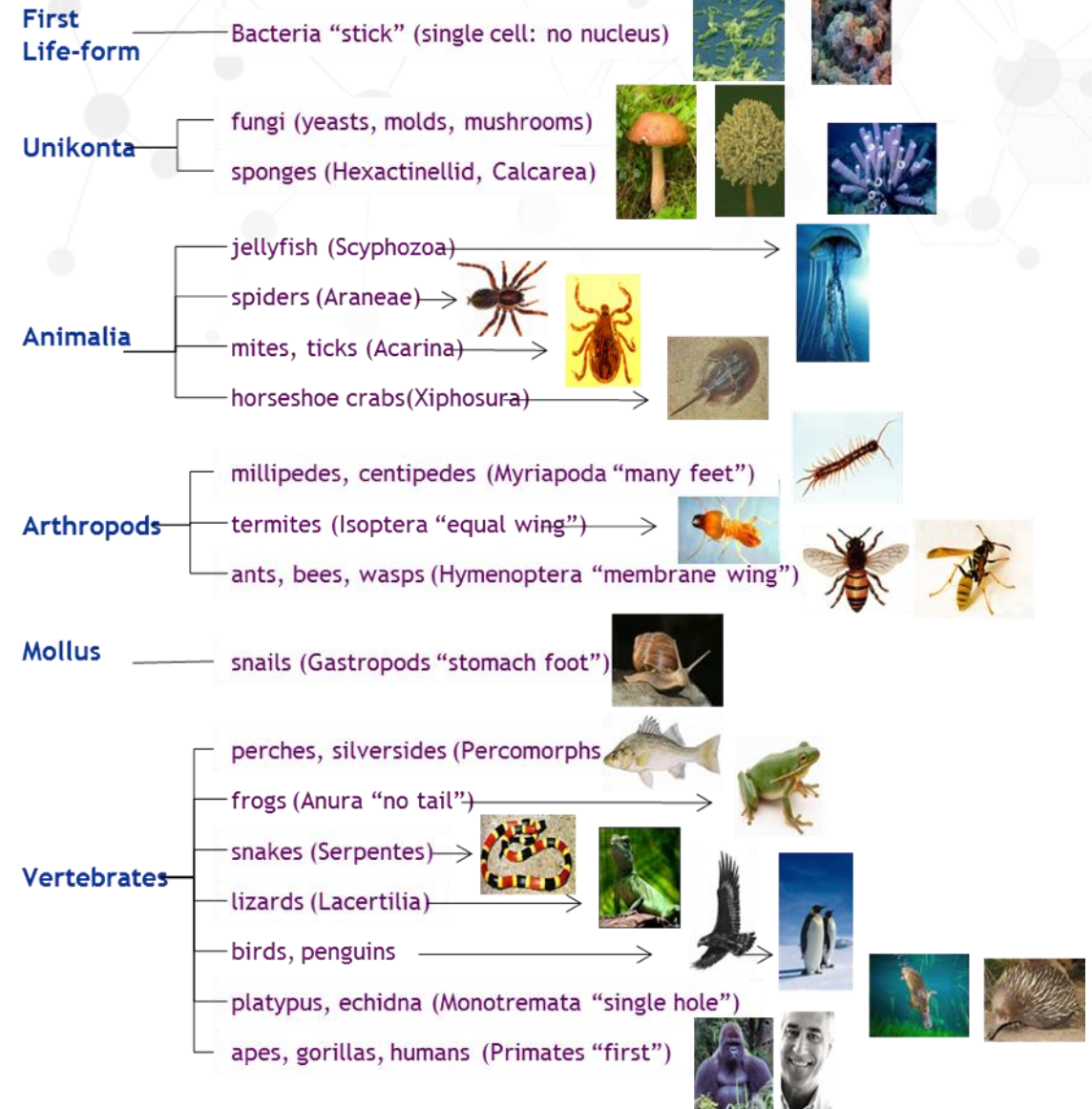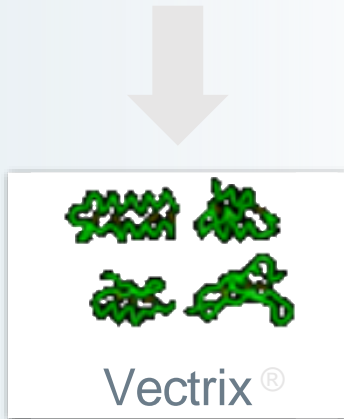2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

ONCE-WEEKLY
wegovy™
semaglutide injection **2.4 mg**

Protagonist
Therapeutics

Peptides-based De Novo Drug Discovery

Where to Start?

Mother Nature: Disulfide Rich Peptides (DRPs)

- Immense scaffold **diversity**
- Multiple recognition surfaces
  - Biologics like **potency** and specificity
- Rigid, constrained, knotted
  - Small molecule-like **stability**

Vectrix ®

First Life-form —— Bacteria "stick" (single cell: no nucleus)

Unikonta —— fungi (yeasts, molds, mushrooms)
—— sponges (Hexactinellid, Calcarea)

Animalia —— jellyfish (Scyphozoa)
—— spiders (Araneae)
—— mites, ticks (Acarina)
—— horseshoe crabs (Xiphosura)

Arthropods —— millipedes, centipedes (Myriapoda "many feet")
—— termites (Isoptera "equal wing")
—— ants, bees, wasps (Hymenoptera "membrane wing")

Mollus —— snails (Gastropods "stomach foot")

Vertebrates —— perches, silversides (Percomorphs)
—— frogs (Anura "no tail")
—— snakes (Serpentes)
—— lizards (Lacertilia)
—— birds, penguins
—— platypus, echidna (Monotremata "single hole")
—— apes, gorillas, humans (Primates "first")

Protagonist Therapeutics

Peptides-based Medicine

Injectable Peptides vs. Injectable Antibodies

1 Computational
Vectrix, Clusters

Vectrix®   Clusters

2 Phage Libraries
Hits

3 Peptide Chemistry
SAR, Leads

IL-6 Peptide Antagonists
Collaboration with Ironwood Pharmaceuticals (2011-14)
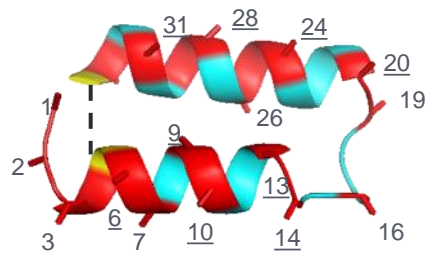
ZDC Scaffold
PN-1484
IC_{50} ~10 μM

>1400 peptides

3 years

PN-2921
$IC_{50} = 0.4$ nM

PEG
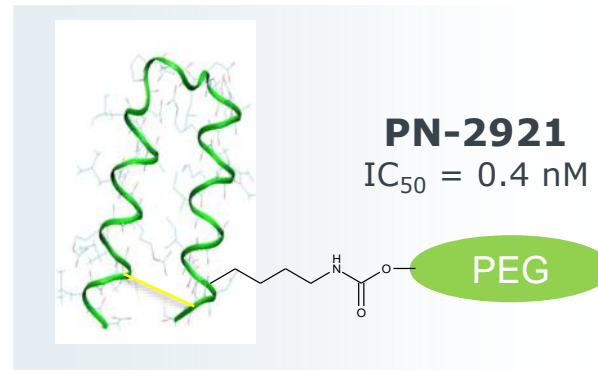
ACTEMRA®
tocilizumab

IL-6R antagonist
Castleman's disease

Protagonist
Therapeutics

Oral Peptides

The Holy Grail

Cyclosporine

Linaclotide

C18 diacid-isoGlu-(1PEG2)2
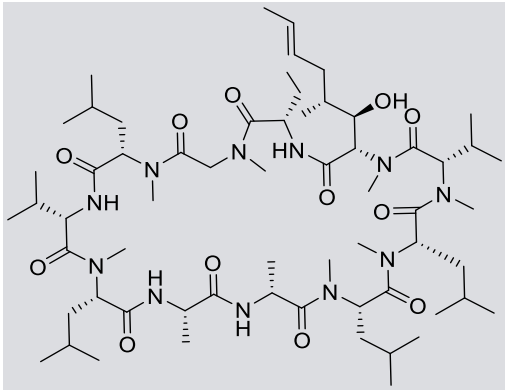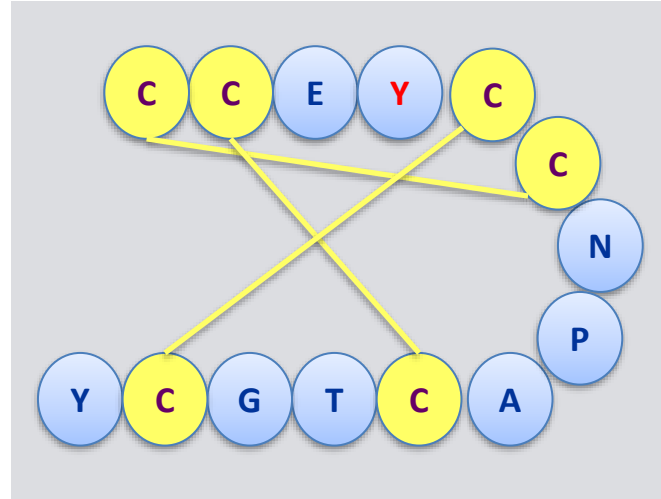
Semaglutide
Rybelsus®: oral, diabetes
Ozempic®: sc, diabetes
Wegovy®: sc, Obesity

Peptide Technology Platform

Towards Oral Peptides

Potency

1 Computational
Vectrix, Clusters

Vectrix ®   Clusters

2 Phage Libraries
Hits

3 Peptide Chemistry
SAR, Leads

Stability

4 Oral Stability
Peptidomimetics
GI & Microbial
Assays

5 Gut-Restricted
Targeted GI
absorption &
delivery

6 Systemic Availability
Formulation
SAR, Transport

Protagonist
Therapeutics

Peptides-based Medicine

Inflammation & Immunomodulatory Diseases
Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, IBD (Crohn's, UC)

Injectable Antibody Drugs

HUMIRA® adalimumab

TNF

Entyvio® vedolizumab

α4β7-Integrin

Stelara ustekinumab
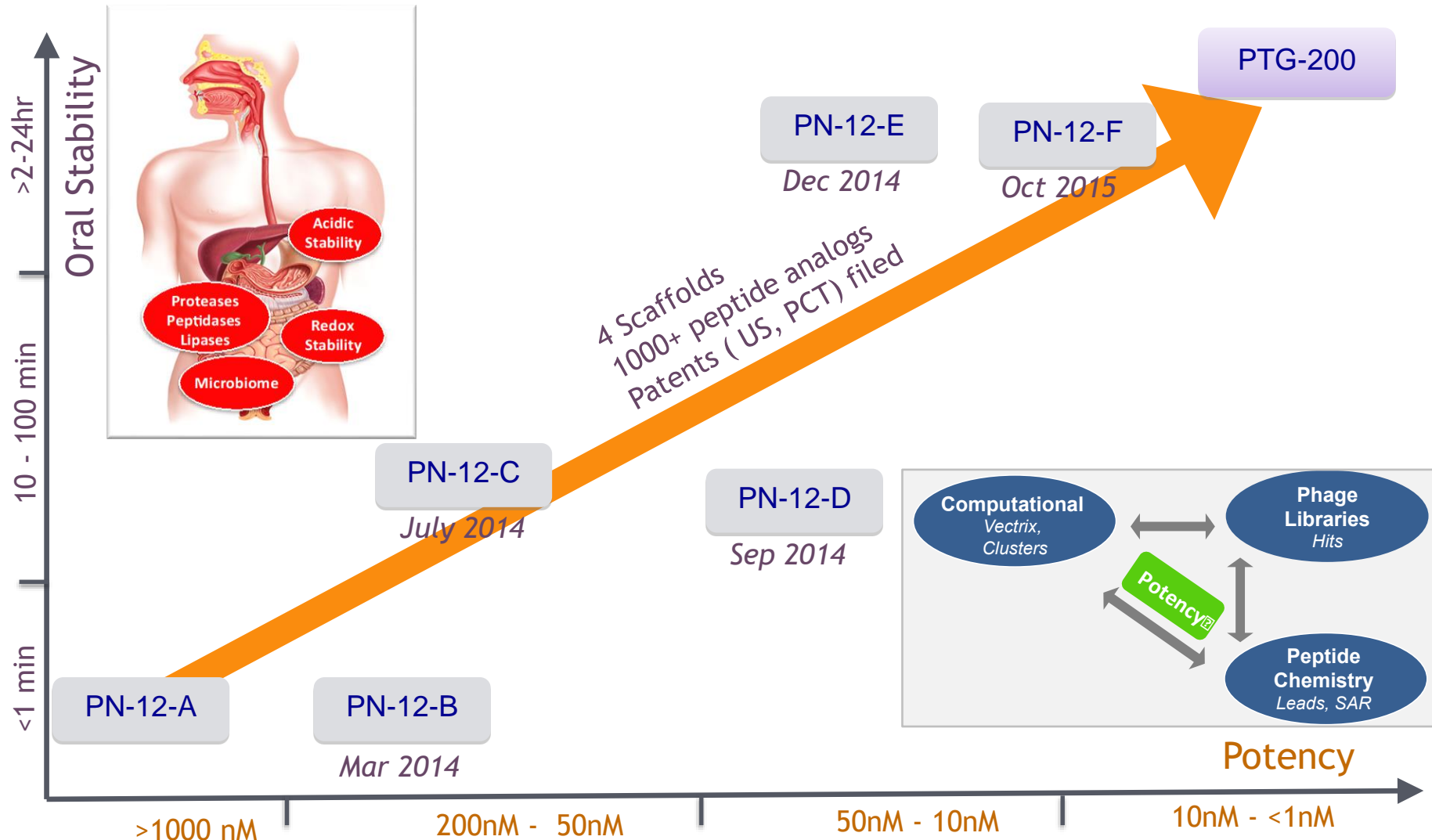
IL-12/23

Tremfya® (guselkumab)

IL-23

Protagonist Oral Peptide Discovery Programs

Oral α4β7-integrin antagonist

Oral IL-23 receptor antagonist

Protagonist Therapeutics

PTG-200: Potent, Selective and Stable IL-23R Antagonist

Potency → Selectivity → Stability
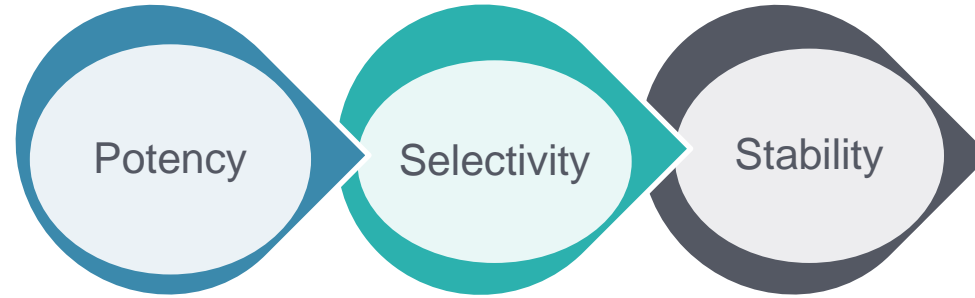
Peptide	ELISA (nM)			Cell assay (nM)			Selectivity (ELISA, nM)		Stability ($t_{1/2}$, hr)		
	Hu	Cyno	Rat	Hu DB Cell (pSTAT3)	Hu NK cell	Rat (Spleen)	IL-12 Rβ1	IL-6/ IL-6R	SIF*	SGF*	HIF*
PTG-200	**2.0**	**2.0**	**2.0**	**0.6**	**2.2**	**18.3**	**>100,000**	**>100,000**	**12**	**6**	**24**

*SIF: simulated intestinal fluid
*SGF: simulated gastric fluid
*HIF: human intestinal fluid

Protagonist Therapeutics

PTG-200: Gut-Restricted, High GI Content, Orally Stable

Gut-restricted Peptide with excellent Gastro-intestinal exposure

PK *Gut-restricted*

Minimal systemic exposure

GI-Exposure

Plasma

Peyer's Patch

Small Intestine
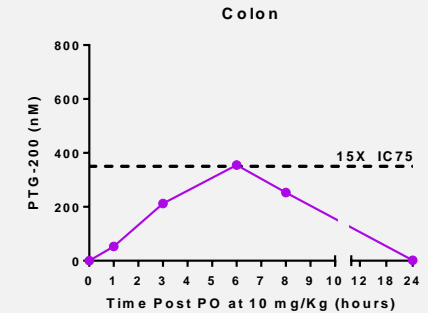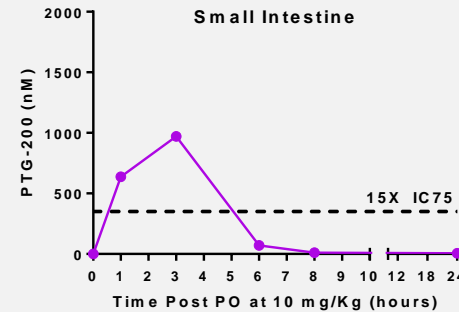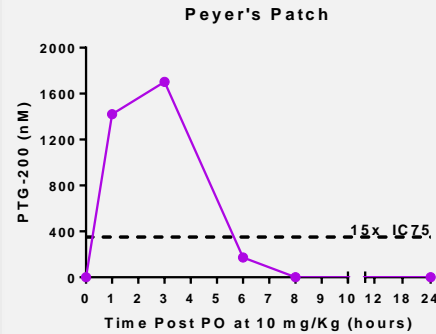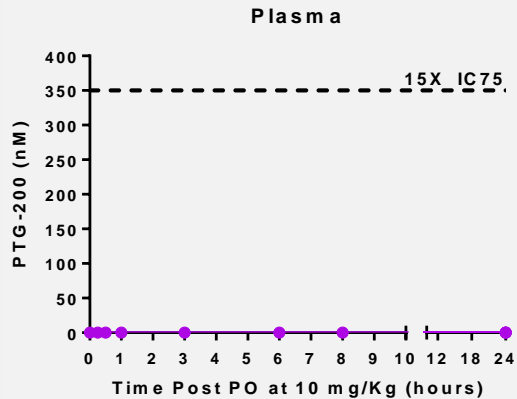
Colon

PTG-200: Pre-Clinical POC in Acute Colitis Rat Study

Dose-dependent Reduction in Ulcerations

- Dose-dependent attenuation of disease parameters
  - Body weight change
  - Colon macroscopic score
  - Colon weight/length ratio
  - Histopathology

- Reduction in IL-23 directed cytokine/disease biomarkers

Vehicle/Disease   Anti-IL-23p19   28 mpk/day   61 mpk/day

Protagonist Therapeutics

12

Protagonist-Janssen Oral, IL-23R Antagonist Collaboration

2017-Present

Collaboration overview

- Initiated in **2017** with I&I market leader **Janssen Biotech**[1]
- 1st generation development candidate: **PTG-200**
- Joint discovery & development efforts
  - Protagonist responsible for pre-clinical and Phase 1 studies
  - Janssen responsible for further development
- Earned $112.5M in upfront & milestones; eligible for up to $855M in future milestones
- Upward-tiering 6-10% royalties

Significant market potential for oral IL-23R antagonist

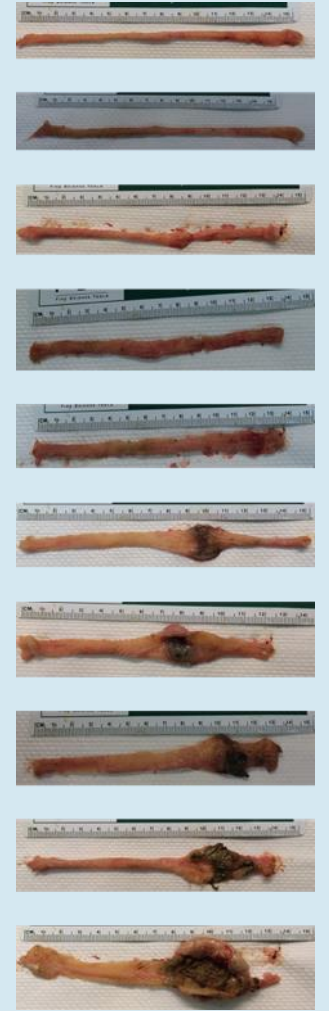- Potential indications include **psoriasis, psoriatic arthritis, IBD (ulcerative colitis, Crohn's disease)**[1]

Oral agents expected to contribute to market growth

- Substantial portion of patients untreated with current standard of care
- Despite strong efficacy, biologics associated with safety concerns, loss of response, inconvenient administration, highlighting the need for safe and effective oral options[2,3]

1. **Stelara® generated $9.7B in sales, and Tremfya® generated $2.7B in sales in 2022, per Johnson & Johnson 2022 Annual Report**
2. Levin, E. et al. *J Dermatol Treat*; 25(1); 78-82; 3. Piragine E., et al. *J Clin Med 2022*; 11(6); 1506

Protagonist Therapeutics

Protagonist Therapeutics

1st and 2nd Generation Oral IL-23 Receptor Antagonist Peptides

PTG-200

PN-235 Now JNJ-2113

2nd Generation

- Good potency (~2 nM) and selectivity
- Adequate oral stability
- Gut-restricted activity
- 2017-18: Ph1 study
- 2019-21: Ph2 Crohn's study
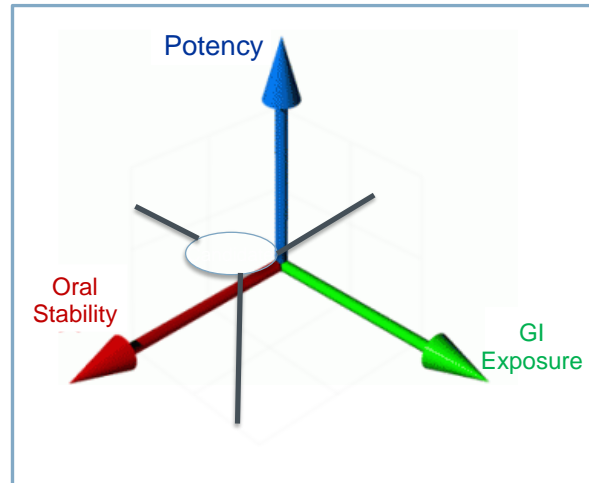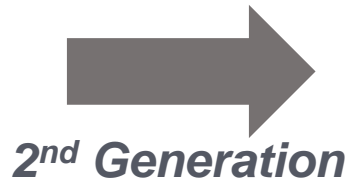
- **>1000-fold more potent** vs. PTG-200
- Excellent oral stability
  - >20% fecal recovery after 24h in cynos
- **Systemically active**
- Pre-clinical POC
  - Rat TNBS colitis model
  - Rat skin inflammation model
- 2020-21: Ph1 study
- **2022-23: Ph2b Psoriasis study**
- 2023: Initiation of Ph3 psoriasis studies
- 2023: Initiation of Ph2b UC study

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

	Screening	Treatment	Safety Follow-up
	(Up to 4 Weeks)*	(Weeks 0-16)	(4 Weeks)

Randomize

1. 25 mg QD & Placebo
2. 50 Mg QD & Placebo
3. 100 mg QD & Placebo
4. 50 mg BID & Placebo
5. 100 mg BID & Placebo
6. Placebo

LTE (FRONTIER 2)

or

4 weeks safety follow-up

Week 0
Randomize

Week 16
Primary Endpoint
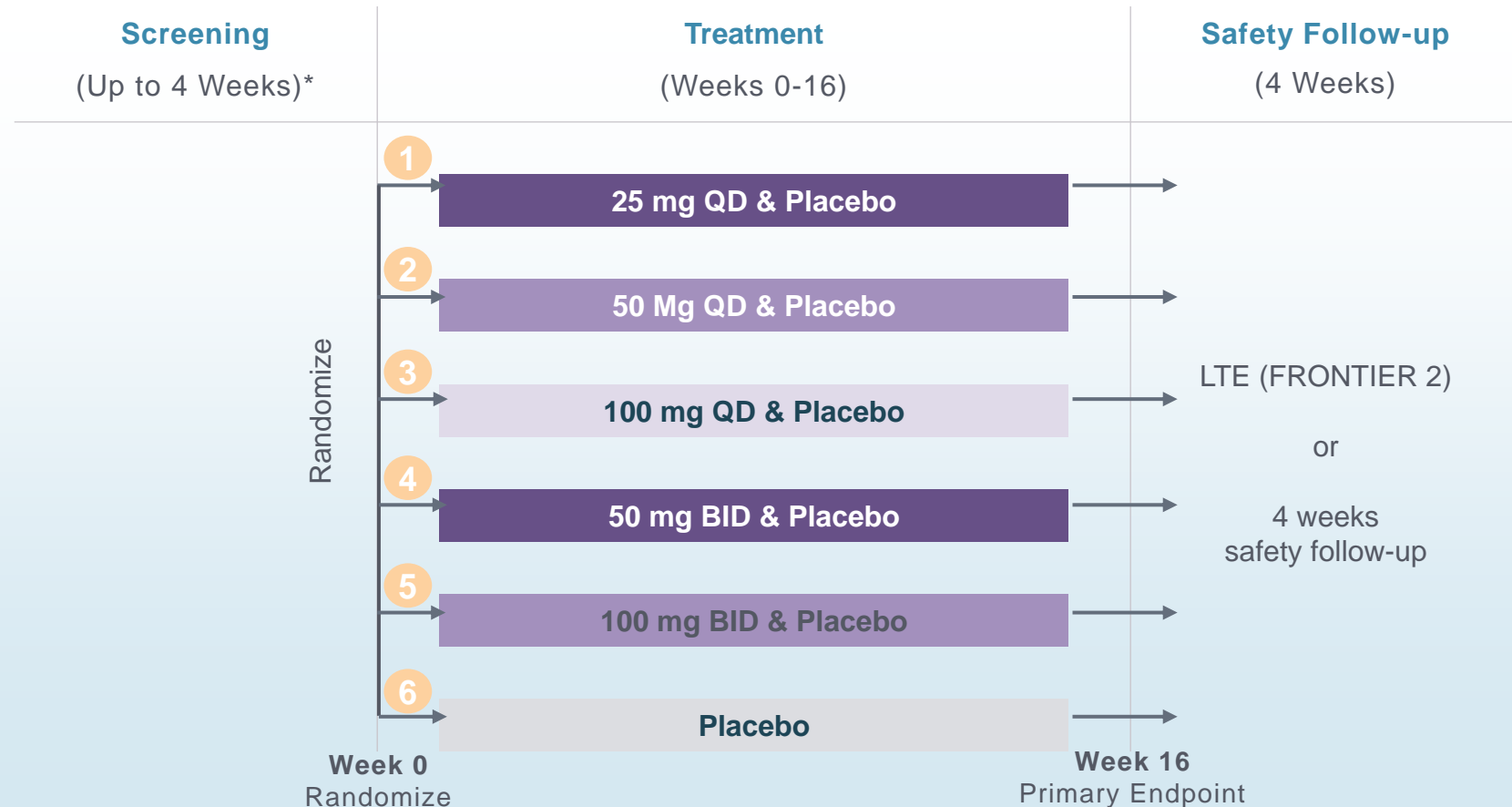
JNJ-2113 Phase 2B Frontier 1 Data

Dose Response

Bar chart showing % response rate for various doses:

Dose	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
25 mg daily (n= 43)	37.2%	25.6%	11.6%
25 mg twice daily (n= 41)	51.2%	26.8%	9.8%
50 mg daily (n=43)	58.1%	51.2%	25.6%
100 mg daily (n=43)	65.1%	46.5%	23.3%
100 mg twice daily (n=42)	78.6%	59.5%	40.5%
Placebo	9.3%	2.3%	0.0%
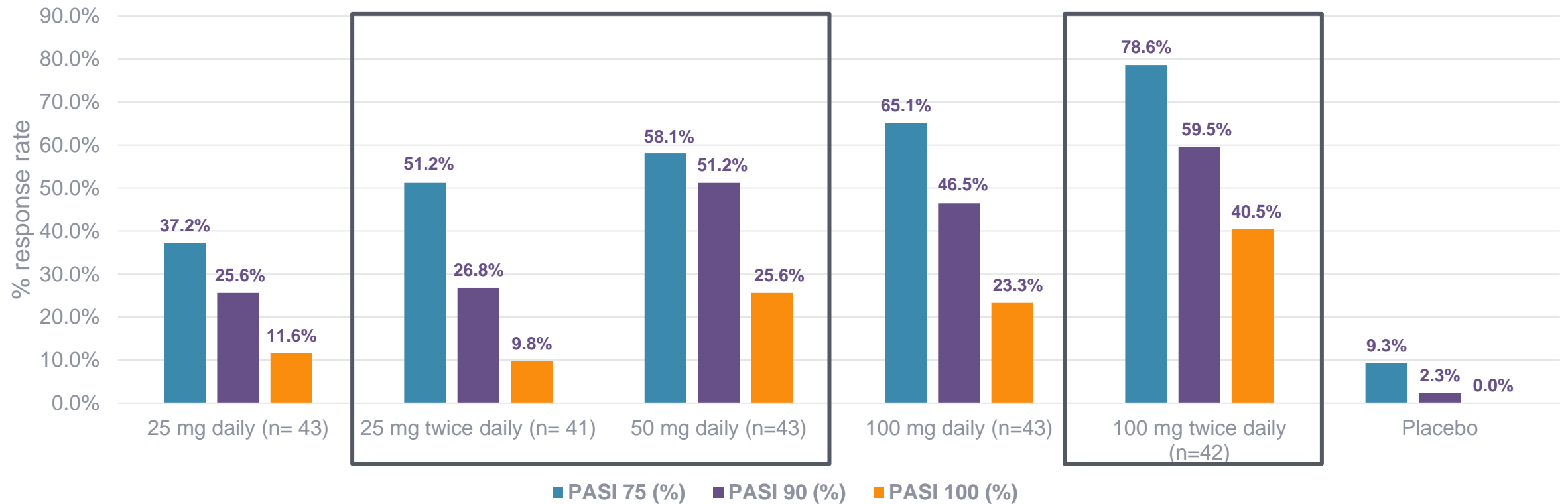
- Clear, linear dose-response
- Once daily dosing appears more efficacious in comparison to twice daily dosing

Protagonist Therapeutics

Cross-Study Comparison of JNJ-2113 to Clinically Relevant Phase 2 Benchmarks[1]

PASI 75 chart (% response rate):
- JNJ-2113: 79%
- Oral agents: Otezla 41%, Sotyktu 69%, TAK-279 67%
- Injectable antibodies: Stelara 67%, Tremfya 81%

PASI 90 chart:
- JNJ-2113: 60%
- Oral agents: Otezla 11%, Sotyktu 44%, TAK-279 46%
- Stelara 44%, Tremfya 57%

PASI 100 chart:
- JNJ-2113: 41%
- Oral agents: Otezla NR, Sotyktu 9%, TAK-279 33%
- Stelara 16%, Tremfya 29%

Legend:
- JNJ-2113 (IL-23R)[2]
- Otezla (PDE4)[3]
- Sotyktu (TYK2)[4]
- TAK-279 (TYK2)[5]
- Stelara (IL-12/23)[6]
- Tremfya (IL-23)[7]

1. Cross trial (not head-to-head) comparisons
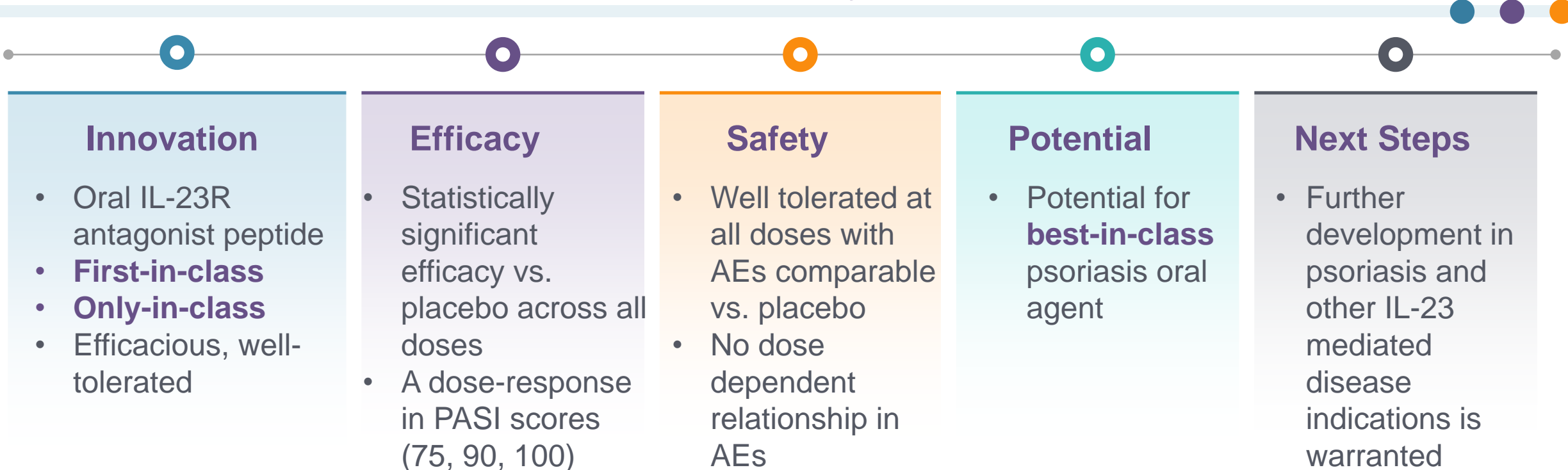2. JNJ2113 100 mg bid dose. Wk 16 endpoint (Placebo: PASI 75: 9.3%, PASI 90: 2.3%, PASI 100: 0%)
3. Otezla 30 mg qd approved dose. Week 16 primary endpoint. Papp K et al. Lancet 2012; 380: 738–46. (Placebo: PASI 75: 5.7%, PASI 90: 1.1%, PASI 100: NR)
4. Sotyktu 3 mg bid dose (6 mg qd dose approved). 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 wkly 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%)

Protagonist Therapeutics

JNJ-2113 (formerly PN-235):

Conclusions from Phase 2b FRONTIER 1 Psoriasis Study and Next Steps

Innovation

- Oral IL-23R antagonist peptide
- **First-in-class**
- **Only-in-class**
- Efficacious, well-tolerated

Efficacy

- Statistically significant efficacy vs. placebo across all doses
- A dose-response in PASI scores (75, 90, 100)

Safety

- Well tolerated at all doses with AEs comparable vs. placebo
- No dose dependent relationship in AEs

Potential

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

Next Steps

- Further development in psoriasis and other IL-23 mediated disease indications is warranted

JNJ-2113 is a first-, and only-in-class <u>oral</u> IL-23 receptor antagonist peptide with a potential for best-in-class oral psoriasis agent

Protagonist Therapeutics

JNJ-2113

Multiple Clinical Studies with Multiple Shots on Goal

Study	Phase 1	Phase 2	Phase 3	Key Milestones
NCT04621630	Ph1 in NHVs			• Ph1 PK study in NHVs in Australia
NCT05062200	Ph1 in NHVs			• Ph1 in healthy Japanese/Chinese participants
NCT05703841	Ph1 in NHVs			• Ph1 study in healthy adult Chinese participants
FRONTIER 1	Ph2b in Psoriasis			• 255-patient psoriasis study completed
FRONTIER 2	Ph2b in Psoriasis			• LTE study of FRONTIER 1
SUMMIT	Ph2a in Psoriasis			• 90-patient psoriasis delayed release formulation
ICONIC-LEAD	Ph3 in Psoriasis			• **Oct '23**; PASI90 & IGA 0/1
ICONIC-TOTAL	Ph3 in Psoriasis			• **Oct '23**; special areas IGA 0/1
Planned	New Psoriasis studies			• New psoriasis studies planned
ANTHEM-UC	Ph2 in UC			• **Initiated Oct '23**

Protagonist Therapeutics

janssen ⫝

Protagonist Therapeutics

Peptides-based Medicine

Innovation

- Validated peptide technology platform
- Two phase 3 assets
  - **JNJ-2113: Oral, IL-23R antagonist peptide in Ph3 study in psoriasis**
  - *Rusfertide: Hepcidin mimetic injectable peptide (qw) in **ph3 study in polycythemia vera***

Resilience

- IL-6 antagonist program: **Injectable peptide vs injectable antibody**
- IL-23 receptor antagonist program
  - 1st Generation **PTG-200**: **Oral, gut-restricted peptide**
  - 2nd Generation **JNJ-2113**: **Oral, systemically available peptide** in Ph3 study in psoriasis

Differentiation

- **JNJ-2113**: **First-in-class, only-in-class, oral,** IL-23 receptor antagonist
- *Rusfertide: First-in-class* erythrocytosis specific agent

Protagonist
Therapeutics

Thank you