POS1079

Pharmacodynamic Response of JNJ-77242113 in Serum and Skin of Patients with Moderate-to-Severe Psoriasis: 1-Year Results from FRONTIER 1 & 2

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Key Takeaways

- **In patients with moderate-to-severe plaque PsO, the first and only targeted oral peptide JNJ-77242113:**
  - **Selectively blocked IL-23-driven inflammation and induced a dose-related PD response, with rapid and sustained reduction of serum biomarkers of the IL-23 pathway and PsO disease severity, through 1 year of treatment**
  - **Attenuated skin inflammation with robust reduction in PsO-relevant disease biomarkers**
- **Tape-strip skin protein analysis recapitulates disease biology and can be leveraged to characterize tissue treatment response in PsO patients**

Background

Psoriasis (PsO) is a chronic, immune-mediated, skin disease[1] associated with the interleukin (IL)-23/IL-17 axis

IL-23 pathway inhibition via monoclonal antibodies has demonstrated clinical efficacy and safety in patients with moderate-to-severe PsO[2]

JNJ-77242113

- First and only targeted oral peptide that inhibits IL-23 signaling by binding to the IL-23 receptor
- Showed superior clinical efficacy vs placebo (PBO) through 1 year of FRONTIER 1 & 2 in patients with moderate-to-severe plaque PsO[3,4]
- Induced strong pharmacodynamic (PD) responses in serum and skin through Week 16[3,5,6]

Objectives

Evaluate effect of JNJ-77242113 on PD responses in:

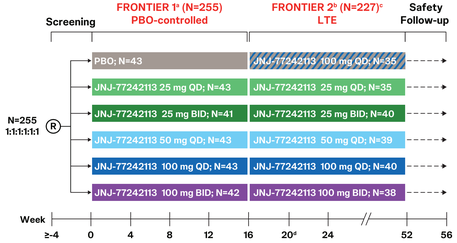
- Serum through 1 year of FRONTIER 1 & 2
- Skin through Week 16 of FRONTIER 1, including relationships with clinical response, via minimally invasive tape-strip skin sampling

Methods

FRONTIER 1 & FRONTIER 2 Study Designs

Key inclusion criteria:

- Moderate-to-severe plaque PsO
  - ≥18 years old
  - PASI ≥12
  - IGA ≥3
  - BSA ≥10%
- Diagnosed with PsO, with or without psoriatic arthritis, for ≥6 months
- Candidate for phototherapy or systemic therapy



[a]NCT05223868. [b]NCT05364554. [c]At Week 16, 227 participants from FRONTIER 1 entered FRONTIER 2 LTE study. [d]Final safety follow-up for participants who did not enter the LTE. Those not participating in the LTE completed 4 weeks of safety follow-up to complete the FRONTIER 1 study. **BID**=Twice daily, **BSA**=Body surface area, **IGA**=Investigator's Global Assessment, **LTE**=Long-term extension, **PASI**=Psoriasis Area and Severity Index, **PBO**=Placebo, **PsO**=Psoriasis, **QD**=Once daily, **R**=Randomization

Assays and Analyses

Systemic PD Response Weeks 0-52

Targeted proteomic assays:

- Beta defensin (BD)-2 (upregulated in PsO; marker of disease activity[7]), IL-22, IL-17A, IL-17F, and IL-23
- Linear mixed effect model to analyze treatment*time interaction, baseline serum levels, and subject random effect

Broad proteomics:

- Olink® Explore HT (5400+ proteins)

Tape-Strip Skin PD Response Weeks 0-16

Targeted proteomic assay: BD-2

- Unpaired t-test for BD-2 levels in lesional vs non-lesional skin
- Correlation of BD-2 levels and Psoriasis Area and Severity Index (PASI) scores

Broad proteomics:

- Olink® Explore HT (5400+ proteins)

Transcriptome analysis and gene set variation analysis (GSVA) for the following gene sets:

- IL-23 pathway: includes genes involved in the IL-23 pathway
- Meta-analysis derived transcriptome of PsO (MAD)-5 and MAD-3[8]: include genes upregulated in PsO lesional skin

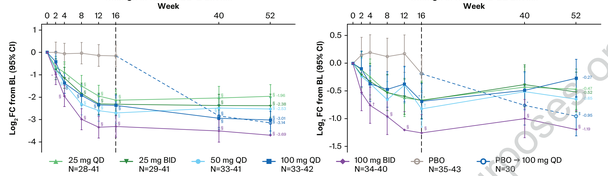
Results

Participants had established, moderate-to-severe plaque PsO

	PBO (N=43)	JNJ-77242113 25 mg QD (N=43)	JNJ-77242113 25 mg BID (N=41)	JNJ-77242113 50 mg QD (N=43)	JNJ-77242113 100 mg QD (N=43)	JNJ-77242113 100 mg BID (N=42)	JNJ-77242113 All (N=212)	All Groups (N=255)
Demographics								
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)
Female	42%	26%	27%	37%	26%	29%	29%	31%
White	86%	70%	66%	72%	81%	71%	72%	74%
Asian	12%	28%	17%	21%	16%	21%	21%	19%
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)
Characteristics								
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 (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)
Psoriatic BSA, %	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)	88%	70%	80%	84%	81%	71%	77%	79%
Severe (4)	12%	30%	20%	16%	19%	29%	23%	21%
Medication use at baseline								
Phototherapy[a]	44%	40%	37%	56%	49%	33%	43%	43%
Biologics[b]	16%	16%	32%	26%	21%	21%	23%	22%
Systemics[c]	79%	77%	80%	81%	79%	74%	78%	78%

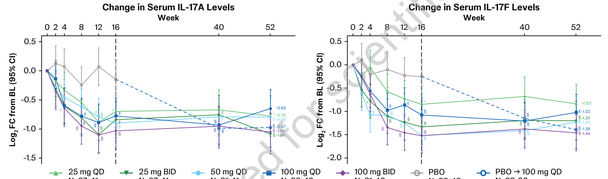
Data shown are mean (SD), unless otherwise indicated. [a]Includes PUVA or UVB. [b]Includes etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, efalizept, efalizumab, natalizumab, certolizumab pegol. [c]Includes conventional nonbiologic systemic therapies, novel nonbiologic systemic therapies, 1,25-vitamin D3 and analogues, phototherapy, and biologics. **BID**=Twice daily, **BSA**=Body surface area, **IGA**=Investigator's Global Assessment, **PASI**=Psoriasis Area and Severity Index, **PBO**=Placebo, **PsO**=Psoriasis, **PUVA**=Psoralen plus ultraviolet A, **QD**=Once daily, **SD**=Standard deviation, **UVB**=Ultraviolet B, **yrs**=Years

JNJ-77242113 drove strong sustained reductions in serum BD-2 and IL-22 levels



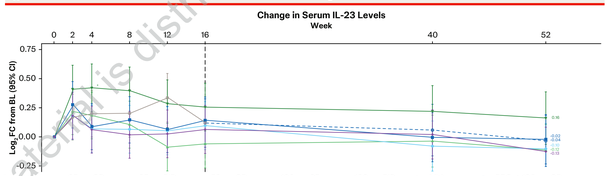
Nominal *p<0.05; †p<0.01; ‡p<0.001; §p<0.0001 for Log_2 FC from BL. **BD**=Beta defensin, **BID**=Twice daily, **BL**=Baseline, **CI**=Confidence interval, **FC**=Fold change, **IL**=Interleukin, **PBO**=Placebo, **QD**=Once daily

JNJ-77242113 drove sustained reductions in serum IL-17A and IL-17F levels



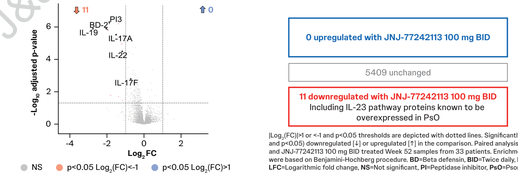
Nominal *p<0.05; †p<0.01; ‡p<0.001; §p<0.0001 for Log_2 FC from BL. **BID**=Twice daily, **BL**=Baseline, **CI**=Confidence interval, **FC**=Fold change, **IL**=Interleukin, **PBO**=Placebo, **QD**=Once daily

JNJ-77242113 treatment did not induce changes in serum IL-23 levels



Nominal *p<0.05; †p<0.01; ‡p<0.001; §p<0.0001 for Log_2 FC from BL. **BID**=Twice daily, **BL**=Baseline, **CI**=Confidence interval, **FC**=Fold change, **IL**=Interleukin, **PBO**=Placebo, **QD**=Once daily

JNJ-77242113 selectively inhibited IL-23–driven inflammation in serum



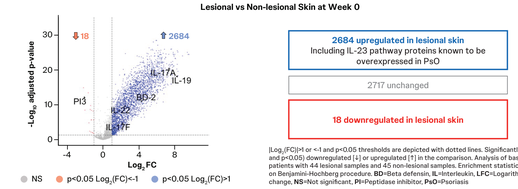
0 upregulated with JNJ-77242113 100 mg BID

5409 unchanged

11 downregulated with JNJ-77242113 100 mg BID
Including IL-23 pathway proteins known to be overexpressed in PsO

[Log_2(FC)]>1 or <-1 and p<0.05 thresholds are depicted with dotted lines. Significantly (+/- 1LFC and p<0.05) downregulated [↓] or upregulated [↑] in the comparison. Paired analysis of baseline and JNJ-77242113 100 mg BID treated Week 52 samples from 33 patients. Enrichment statistics were based on Benjamini-Hochberg procedure. **BD**=Beta defensin, **BID**=Twice daily, **IL**=Interleukin, **LFC**=Logarithmic fold change, **NS**=Not significant, **PI**=Peptidase inhibitor, **PsO**=Psoriasis

Lesional skin tape-strips are enriched for PsO-relevant proteins



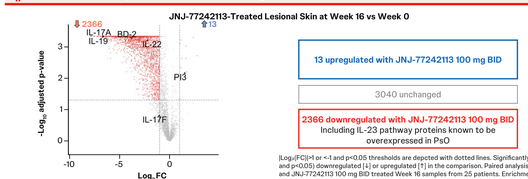
2684 upregulated in lesional skin
Including IL-23 pathway proteins known to be overexpressed in PsO

2717 unchanged

18 downregulated in lesional skin

[Log_2(FC)]>1 or <-1 and p<0.05 thresholds are depicted with dotted lines. Significantly (+/- 1LFC and p<0.05) downregulated [↓] or upregulated [↑] in the comparison. Analysis of baseline Week 0 patients with 44 lesional samples and 45 non-lesional samples. Enrichment statistics were based on Benjamini-Hochberg procedure. **BD**=Beta defensin, **IL**=Interleukin, **LFC**=Logarithmic fold change, **NS**=Not significant, **PI**=Peptidase inhibitor, **PsO**=Psoriasis

PsO-associated proteins were downregulated in JNJ-77242113-treated lesional skin at Week 16



13 upregulated with JNJ-77242113 100 mg BID

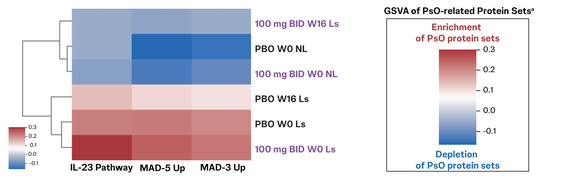
3040 unchanged

2366 downregulated with JNJ-77242113 100 mg BID
Including IL-23 pathway proteins known to be overexpressed in PsO

[Log_2(FC)]>1 or <-1 and p<0.05 thresholds are depicted with dotted lines. Significantly (+/- 1 LFC and p<0.05) downregulated [↓] or upregulated [↑] in the comparison. Paired analysis of baseline and JNJ-77242113 100 mg BID treated Week 16 samples from 25 patients. Enrichment statistics were based on Benjamini-Hochberg procedure. **BID**=Twice daily, **BD**=Beta defensin, **IL**=Interleukin, **LFC**=Logarithmic fold change, **NS**=Not significant, **PI**=Peptidase inhibitor, **PsO**=Psoriasis

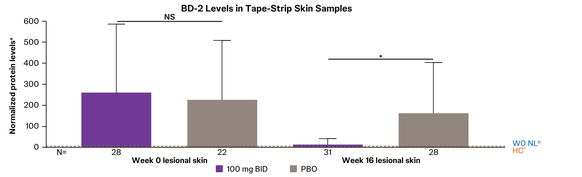
JNJ-77242113 robustly attenuated skin inflammation

- At Week 16, JNJ-77242113-treated lesional skin clustered with non-lesional samples



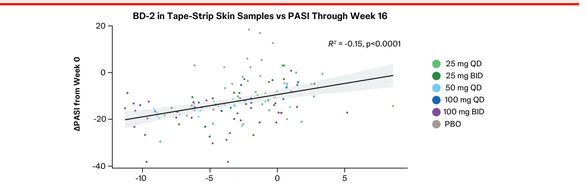
[a]Average GSVA scores per treatment/time point shown. Analysis of 25 Week 16 lesional samples and 25 Week 0 non-lesional samples. **BID**=Twice daily, **GSVA**=Gene set variation analysis, **IL**=Interleukin, **Ls**=Lesional, **MAD**=Meta-analysis derived transcriptome of PsO, **NL**=Non-lesional, **PBO**=Placebo, **PsO**=Psoriasis, **W**=Week

JNJ-77242113 reduced BD-2 in lesional skin to levels seen in non-lesional and healthy skin



*p<0.05 based on unpaired t-test. [a]BD-2 pg/mL; Total µg/mL. [b]Average of 100 mg BID and PBO non-lesional skin at Week 0. [b]HC skin tape-strip samples were obtained from sponsor healthy donor program at J&J (Protocol NOCOMPOUNDNAP1001). **BD**=Beta defensin, **BID**=Twice daily, **HC**=Healthy controls, **NL**=Non-lesional, **NS**=Not significant, **PBO**=Placebo, **W**=Week

BD-2 reductions in skin correlated with improved PASI scores



Gray region represents 95% CI for regression line. **BD**=Beta defensin, **BID**=Twice daily, **CI**=Confidence interval, **PASI**=Psoriasis Area and Severity Index, **PBO**=Placebo, **QD**=Once daily

PRESENTED AT: European Alliance of Associations for Rheumatology (EULAR) 2025; Barcelona, Spain: June 11–14, 2025. **REFERENCES: 1.** Armstrong, AW. *JAMA.* 2020;323:1945–60. **2.** Vu, A. *Expert Opin Biol Ther.* 2022;22:1489–502. **3.** Bissonnette, R. *N Engl J Med.* 2024;390:510–21. **4.** Ferris, LK. Oral presentation 5675B, AAD Annual Meeting: March 8-12, 2024; San Diego, CA, USA. **5.** Pinter, A. Abstract #810. EADV Congress; October 11-14, 2023; Berlin, Germany. **6.** Krueger, J. Abstract #LB938. SID Annual Meeting; May 15-18, 2024; Dallas, TX, USA. **7.** Kolbinger, F. *J Allergy Clin Immunol.* 2017;139:3:923–32.e8. **8.** Tian, S. *PLoS One.* 2012;7:e44274.

ACKNOWLEDGEMENTS: Medical writing support was provided by JSS Medical Research, Inc, under the direction of the authors in accordance with Good Publication Practice guidelines (*Ann Intern Med.* 2022;175:1298-1304). Sponsored by Johnson & Johnson. Layout design and reformatting for this encore presentation was provided by Ganesh Karpe of SIRO Medical Writing Pvt Ltd, Thane, Maharashtra, India (funded by Johnson & Johnson). **DISCLOSURES: KE:** Speaker's fees from, and/or advisory board member: AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Hexal, Janssen, Leo, Novartis, Pfizer, Sanofi, Sitryx, and UCB. Co-founder and shares of Dermagnostix and Dermagnostix R&D. **LKF:** Investigator: AbbVie, Acelyrin, Amgen, Apogee, Arcutis, Aristea, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, DermTech, Eli Lilly, Galderma, GRAIL, Incyte, Janssen, Leo Pharma, Moberg, Mobius, Novartis, Regeneron, SkinAnalytics, Takeda, and UCB; Consultant: AbbVie, Amgen, Apogee, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, DermTech, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, and Takeda; Speaker: AbbVie, Arcutis, Boehringer Ingelheim, Bristol Myers Squibb, and Regeneron. **JK:** Consultant/honoraria: AbbVie, Actelis, Allergan, Almirall, Amgen, Arena, Aristea, Asana, Aurigene, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Escalier, Galapagos, Janssen, MoonLake, Nimbus, Novartis, Pfizer, Sanofi, Sienna, Sun, Target-Derm, UCB, Valeant, and Ventyx. **APa:** Investigator: AbbVie, Applied Pharma Research, Biomedics, Dermavant, Eli Lilly, Incyte, Janssen, Krystal, Regeneron, Timber, and UCB; Consultant: AbbVie, Abeona, Apogee, Arcutis, Asian, BioCryst, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Incyte, Johnson and Johnson, Krystal Biotech, LEO, Mitsubishi Tanabe, Nektar, Primus, Procter and Gamble, Regeneron, Sanofi, Seanergy, TWI Biotech, and UCB; Data Safety Monitoring Board member: AbbVie, Abeona, and Galderma. **APe:** Advisor, received speaker's honoraria, received grants, and/or participated in clinical trials: AbbVie, Almirall Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Galderma, GSK, Hexal, Janssen-Cilag GmbH, Klinge Pharma, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering-Plough, Tigercat Pharma, UCB Pharma, and Zorlig Pharma. **AK, DS, SB, DR, DH, KP, CHC, EC, CD, PN, DW, ML, BM, MM, TO, DRa, YWY:** Employees of Johnson & Johnson; employees may own stock/stock options in Johnson & Johnson. **JM:** Consultant of: AbbVie, Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Incyte, Janssen, Leo, Novartis, Pfizer, Sanofi-Regeneron, Sun, and UCB; grant/research support from: AbbVie, Amgen, Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Incyte, Janssen, Leo, Novartis, Pfizer, Sanofi-Regeneron, Sun, and UCB. **RB:** Advisory Board Member, consultant, speaker and/or investigator for and received honoraria and/or grants: AbbVie, Alumis, Arcutis, Amgen, Bausch Health, Boston, BMS/Celgene, Dermavant, Eli Lilly, Janssen, LEO Pharma, Nimbus, Novartis, Pfizer, Regeneron, UCB, VentyxBio, and Xencor; employee and shareholder of Innovaderm Research. Previously presented at the 10th International Congress Psoriasis from Gene to Clinic; London, UK; December 5-7, 2024.