TAK-279 (TYK2 inhibitor)
Investor Call on Phase 2b Psoriasis Data

March 18th, 2023 ET / March 19th, 2023 JST

Better Health, Brighter Future

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AGENDA

Today's Topics

1. **Efficacy and safety results from the randomized, double-blind, placebo-controlled phase 2b trial of TYK2 inhibitor NDI-034858* in moderate-to-severe psoriasis**

Graham Heap, MBBS, PhD
Vice President Global Program Leader, R&D

2. Q&A Session

Panelists

Andy Plump
President, R&D

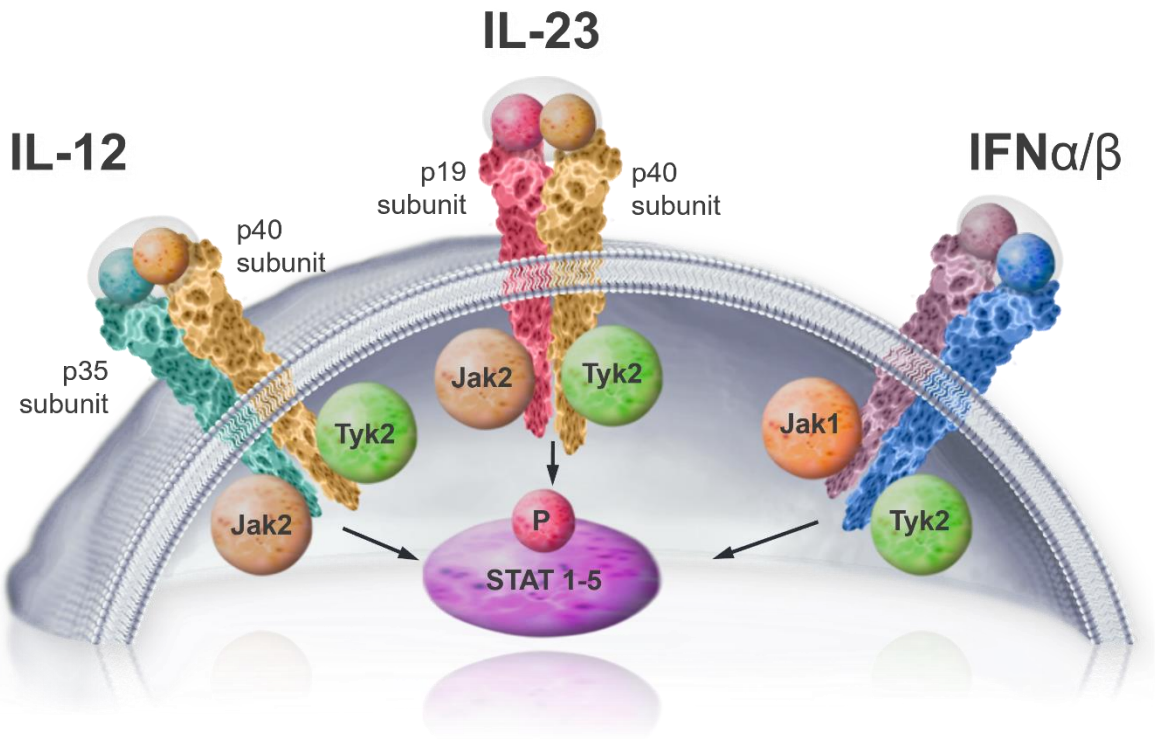
Uthra Sundaram
Executive Vice President & Head of Global Product & Launch Strategy, Global Portfolio Division

Graham Heap
Vice President Global Program Leader, R&D

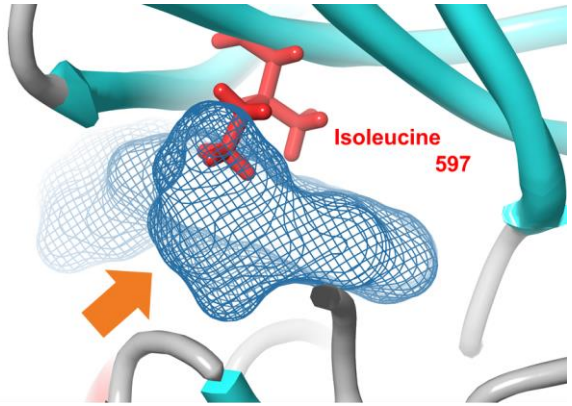
*NDI-034858 now known as TAK-279

Mechanism of action of NDI-034858 (TAK-279)

TYK2 is a key component of the JAK–STAT signaling pathway. Increased activation of proinflammatory enzymes in this pathway is associated with several autoimmune diseases, including psoriasis



TAK-279 is a highly selective oral allosteric TYK2 inhibitor



TAK-279

Prohibited from Binding
in JAK1 Allosteric (JH2) Pocket

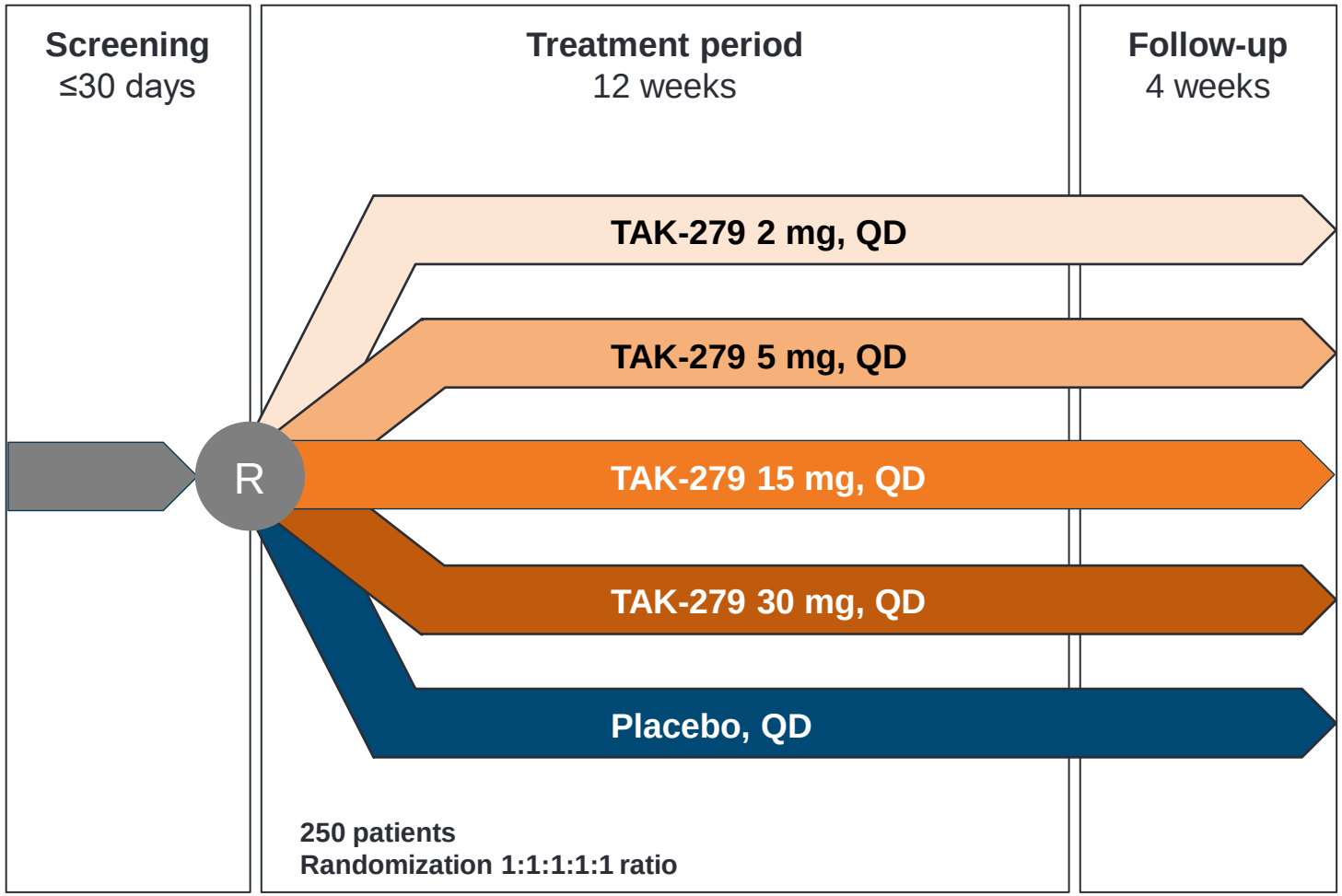
TAK-279 is excluded from the allosteric binding pocket of JAK1 owing to a single amino acid difference from TYK2

TYK2–JH2 binding K_d	0.034 nM
JAK1–JH2 binding K_d	5000 nM
Biochemical selectivity (fold)	1,470,588

Nimbus proprietary structure based computational modeling

JAK, Janus kinase; K_d dissociation constant; IFN, interferon; IL, interleukin; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase

Study design: NCT04999839 (US, Canada)



Key eligibility criteria

- Age 18–70 years
- Plaque psoriasis for ≥6 months
  - PASI ≥12
  - PGA ≥3
  - BSA ≥10%
- Candidate for phototherapy or systemic therapy

Primary endpoint:

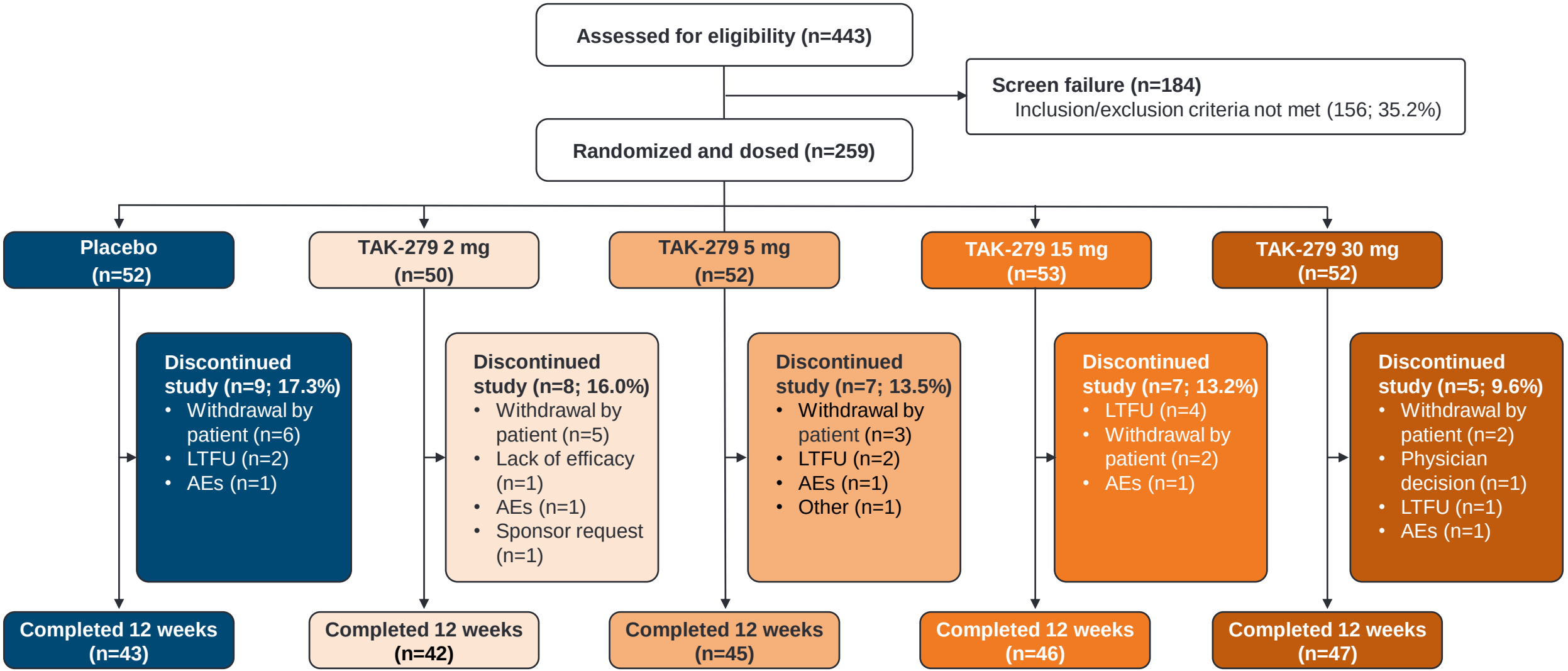
- PASI 75 at Week 12

Secondary endpoints:

- PGA 0/1 at Week 12
- PASI 90 at Week 12
- PASI 100 at Week 12
- Change from baseline in DLQI at Week 12

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; QD, once daily; R, randomization
NCT04999839: https://clinicaltrials.gov/ct2/show/NCT04999839

Study disposition



AE, adverse event; LTFU, lost to follow-up

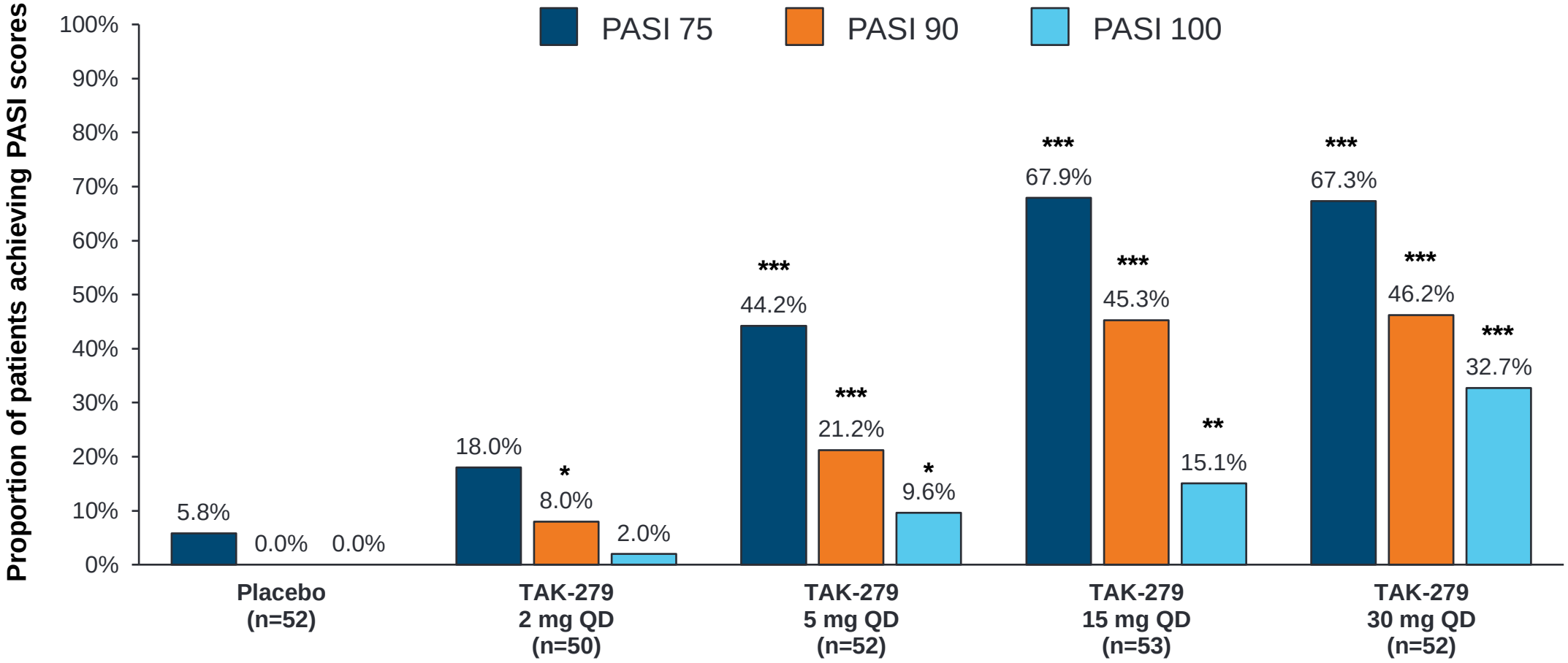
Demographics and baseline disease characteristics

	Placebo (n=52)	TAK-279 2 mg QD (n=50)	TAK-279 5 mg QD (n=52)	TAK-279 15 mg QD (n=53)	TAK-279 30 mg QD (n=52)
Age, years, mean (SD)	48.8 (12.7)	45.8 (14.2)	45.1 (13.6)	46.2 (13.0)	48.5 (11.4)
Male, n (%)	31 (59.6)	38 (76.0)	41 (78.8)	34 (64.2)	33 (63.5)
Race, n (%) White Asian Black/African American Other	 44 (84.6) 5 (9.6) 2 (3.8) 1 (1.9)	 43 (86.0) 3 (6.0) 4 (8.0) 0	 40 (76.9) 7 (13.5) 4 (7.7) 1 (1.9)	 46 (86.8) 2 (3.8) 3 (5.7) 2 (3.8)	 42 (80.8) 3 (5.8) 4 (7.7) 3 (5.8)
Weight, kg, mean (SD)	88.4 (15.8)	93.9 (16.7)	90.4 (18.7)	92.7 (16.8)	90.0 (18.3)
BMI, kg/m^2, mean (SD)	31.3 (5.1)	31.2 (5.2)	30.5 (5.7)	32.0 (4.9)	30.4 (5.4)
Psoriasis duration, years, mean (SD)	12.7 (10.5)	13.8 (10.8)	14.8 (10.7)	17.6 (14.6)	17.4 (11.1)
PASI score, mean (SD)	18.3 (8.1)	18.4 (6.8)	18.6 (6.1)	15.5 (4.5)	17.6 (6.2)
PGA score, mean (SD) 3 (moderate), n (%) 4 (severe), n (%)	3.2 (0.4) 41 (78.8) 11 (21.2)	3.4 (0.5) 30 (60.0) 20 (40.0)	3.3 (0.5) 34 (65.4) 18 (34.6)	3.2 (0.4) 40 (75.5) 13 (24.5)	3.2 (0.4) 42 (80.8) 10 (19.2)
BSA, mean (SD)	21.3 (13.6)	24.9 (15.5)	22.6 (12.1)	18.3 (10.3)	22.2 (14.3)
DLQI score, mean (SD)	12.4 (7.0)	10.3 (6.2)	12.8 (7.5)	11.9 (7.1)	12.5 (6.9)
Bioexperienced, n (%)	8 (15.4)	8 (16.0)	8 (15.4)	9 (17.0)	8 (15.4)

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; QD, once daily; SD, standard deviation

Patients achieving PASI 75, 90 or 100 at Week 12

NRI analysis

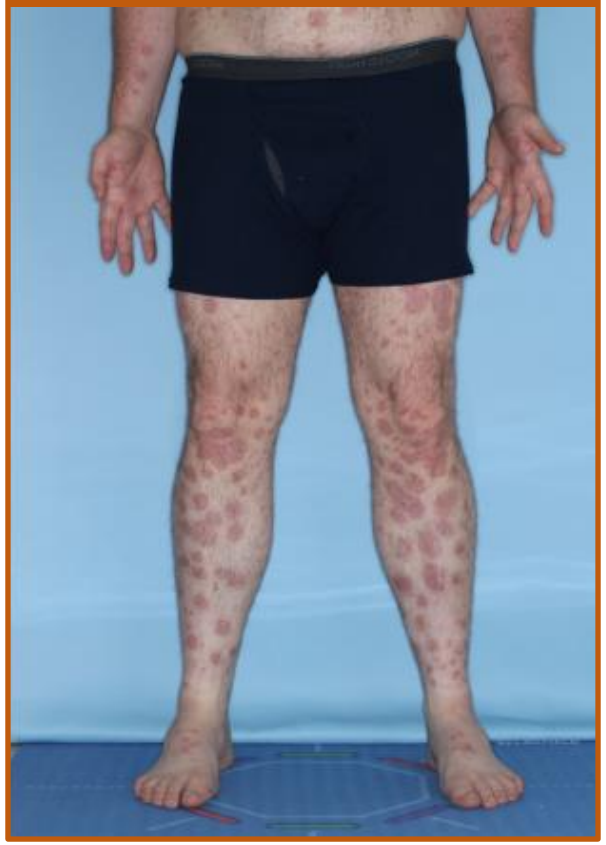


p values from a Cochran-Mantel-Haenszel test, with prior biologic treatment included as a stratification factor, comparing the proportion of patients in the treatment group versus placebo. For secondary endpoints (PASI 90 and PASI 100), p values are nominal: *p<0.05; **p<0.005 ***p<0.001
Modified intent-to-treat (mITT) analysis set: all patients who were randomized and received at least one dose of study treatment
CI, confidence interval; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; QD, once daily

Representative PASI 100 response with TAK-279 30 mg QD

Baseline

Week 4

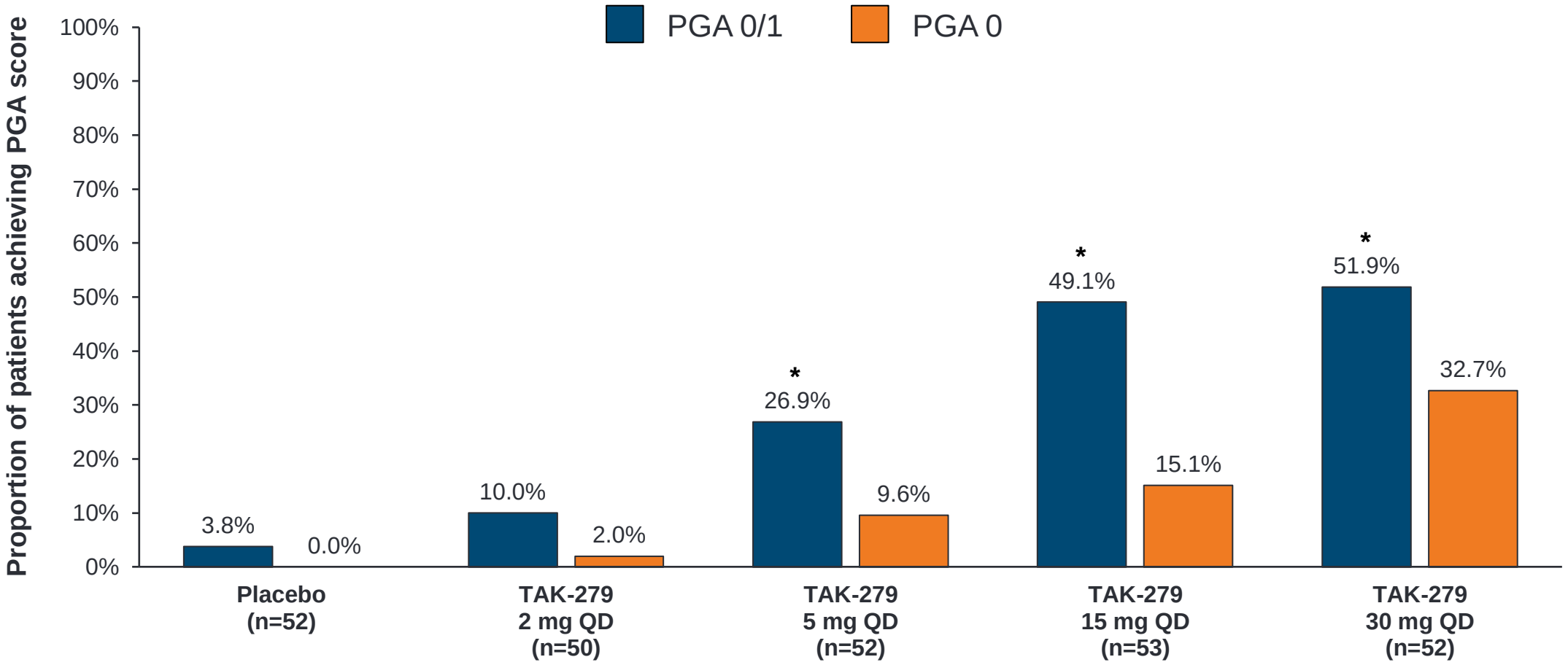


Week 12

PASI, Psoriasis Area and Severity Index; QD, once daily

Patients achieving PGA 0/1 or PGA 0 at Week 12

NRI analysis



p values from a Cochran-Mantel-Haenszel test, with prior biologic treatment included as a stratification factor, comparing the proportion of patients in the treatment group versus placebo. For secondary endpoints (PGA 0/1), p values are nominal: *p≤0.001; PGA 0: post hoc analysis
Modified intent-to-treat (mITT) analysis set: all patients who were randomized and received at least one dose of study treatment
NRI, non-responder imputation; PGA, Physician's Global Assessment; QD, once daily

Safety summary

	Placebo (n=52)	TAK-279 2 mg QD (n=50)	TAK-279 5 mg QD (n=52)	TAK-279 15 mg QD (n=53)	TAK-279 30 mg QD (n=52)
Deaths	0	0	0	0	0
Serious adverse events	0	0	0	1 (1.9)	0
Adverse events	23 (44.2)	31 (62.0)	28 (53.8)	28 (52.8)	31 (59.6)
Adverse events leading to discontinuation[a]	1 (1.9)	1 (2.0)	1 (1.9)	1 (1.9)	2 (3.8)
Most frequent adverse events[b]					
COVID-19	1 (1.9)	6 (12.0)	4 (7.7)	6 (11.3)	7 (13.5)
Acne	0	0	1 (1.9)	3 (5.7)	2 (3.8)
Acneiform dermatitis	0	0	1 (1.9)	1 (1.9)	3 (5.8)
Diarrhea	1 (1.9)	3 (6.0)	1 (1.9)	1 (1.9)	0

[a]Adverse events leading to drug discontinuation and early termination in 5 patients included:
- CPK increased (30 mg)
- pericardial effusion and pleural effusion (15 mg)
- tachycardia and syncope (5 mg)
- lymphocyte count decreased (2 mg)
- atrial fibrillation (placebo)

One additional patient (30 mg) permanently discontinued study drug due to an adverse event of hypertensive urgency, but remained on study.
No patients discontinued owing to COVID-19

[b]AEs reported by ≥3 patients in any treatment group (events elicited by laboratory testing are not included)
Number of patients (percent)

CPK, creatine kinase; QD, once daily

Common terminology criteria for adverse events Grade ≥3

Treatment-emergent laboratory shifts CTCAE Grade ≥3[a,b]	Placebo (n=52)	TAK-279 2 mg QD (n=50)	TAK-279 5 mg QD (n=52)	TAK-279 15 mg QD (n=53)	TAK-279 30 mg QD (n=52)
Neutropenia	1 (2)	1 (2)	0	0	1 (2)
Lymphopenia	1 (2)	1 (2)	0	0	0
Anemia	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0
CPK elevation	1 (2)	0	0	1 (2)	1 (2)
ALT elevation	0	0	0	0	0
AST elevation	0	0	0	0	0
Creatinine elevation	0	0	0	0	0
Cholesterol elevation, Wk 12	0	0	0	0	0
Triglyceride elevation, Wk 12	1 (2)	1 (2)	0	1 (2)	1 (2)
Worsening of proteinuria	0	0	0	0	0

[a]Post-hoc analysis, percent rounded up to nearest integer
[b]Treatment-emergent and ≥1 grade increase from baseline
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine kinase; CTCAE, common terminology criteria for adverse events; QD, once daily; Wk, week

Conclusions

- **Primary endpoint (PASI 75 response at Week 12) achieved with TAK-279 doses ≥5 mg**
  - **68% of patients on 15 mg QD and 67% of patients on 30 mg QD achieved PASI 75**
- Secondary endpoints also achieved with TAK-279 at doses ≥5 mg
  - Greater proportion of patients achieved PASI 100 or PGA 0 at the highest dose of TAK-279
  - At 30 mg QD dosing, 33% of patients achieved clear skin
- Generally low rates of TEAEs: COVID-19, acne, acneiform dermatitis and diarrhea were the most common TEAEs
  - One patient with two SAEs at Day 35, 10 days after last administration of 15 mg dose (not related)
  - Few patients with TEAEs leading to treatment discontinuation (1–2 per treatment group)
- Overall, efficacy with safety findings from this phase 2b study support further larger studies of TAK-279 in psoriasis

PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event

ANTICIPATED NEXT STEPS FOR TAK-279

Potential for Best-in-Class Oral Treatment Option for Psoriasis

- High selectivity for TYK2 over JAKs (1,470,588-fold vs. JAK1)
- Potent TYK2 inhibition with well tolerated, once daily oral dosing
- Robust efficacy in Ph2b Psoriasis study, including 33% of patients on 30mg achieving clear skin at 12 weeks (PASI 100 / PGA 0)

Psoriatic Arthritis *Phase 2b Readout*	Initiate Psoriasis *Phase 3* [1]	Initiate IBD, SLE *Phase 2*	Initiate Other Indications *Phase 2*
FY23	FY23	FY23	FY24 and beyond

Potential for Psoriasis regulatory filing in FY25-27 timeframe

1. Phase 3 study design of Psoriasis to be finalized with regulatory input

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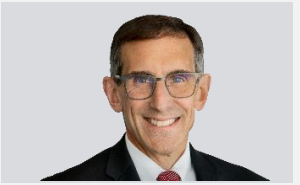
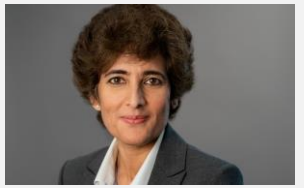


Andy Plump
President, R&D



Uthra Sundaram
Executive Vice President & Head of Global Product & Launch Strategy, Global Portfolio Division

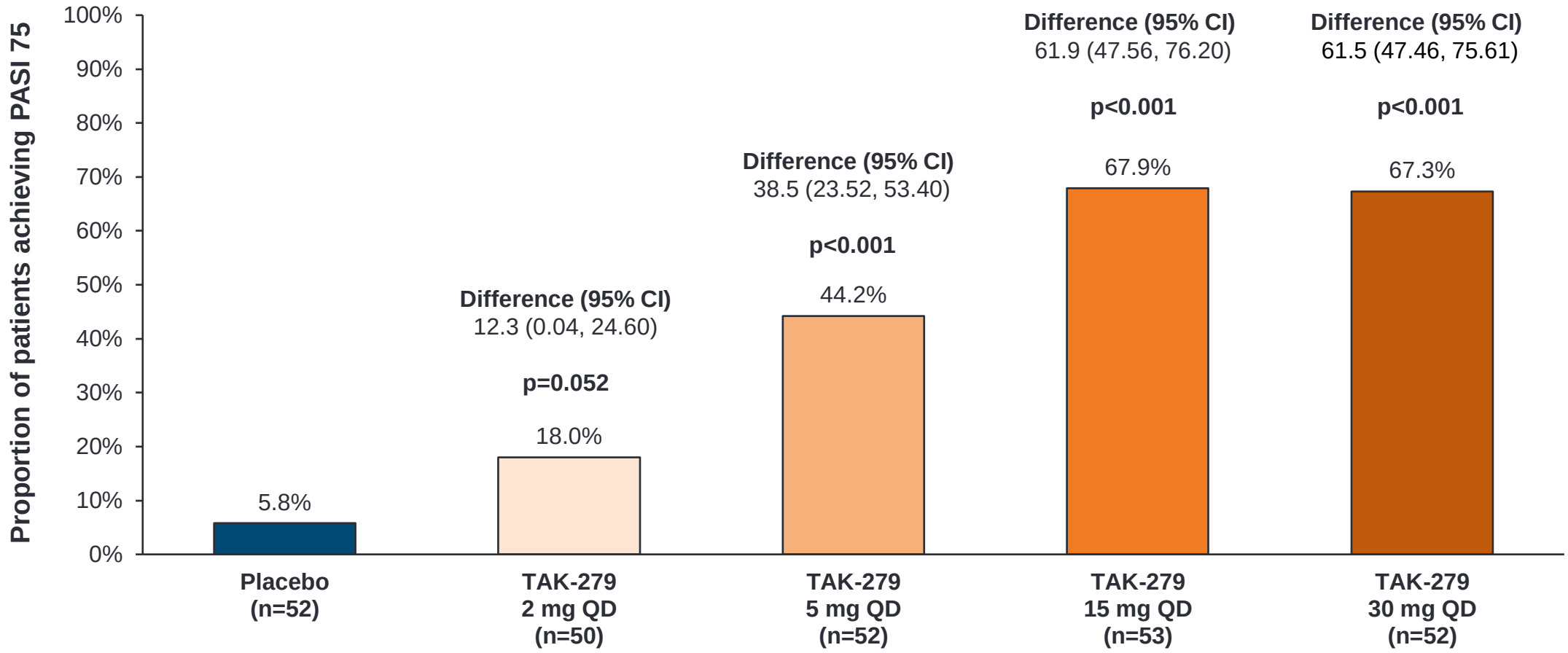
Graham Heap
Vice President Global Program Leader, R&D

APPENDIX

Additional Slides from the AAD Presentation

Primary endpoint: PASI 75 at Week 12

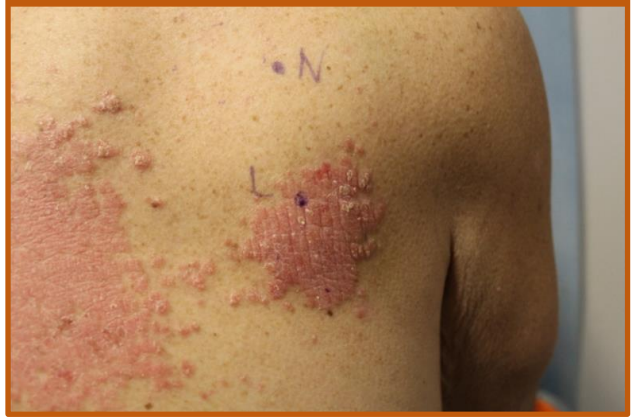
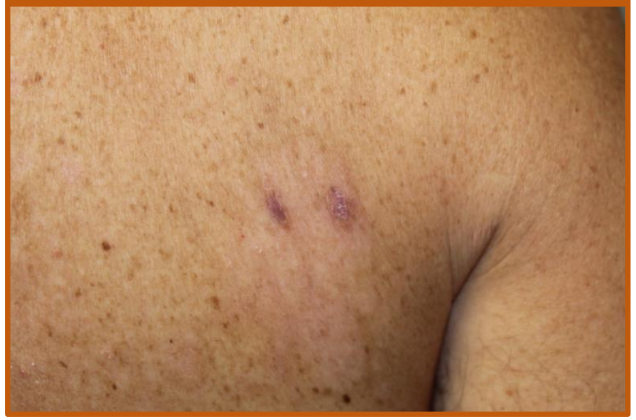
NRI analysis



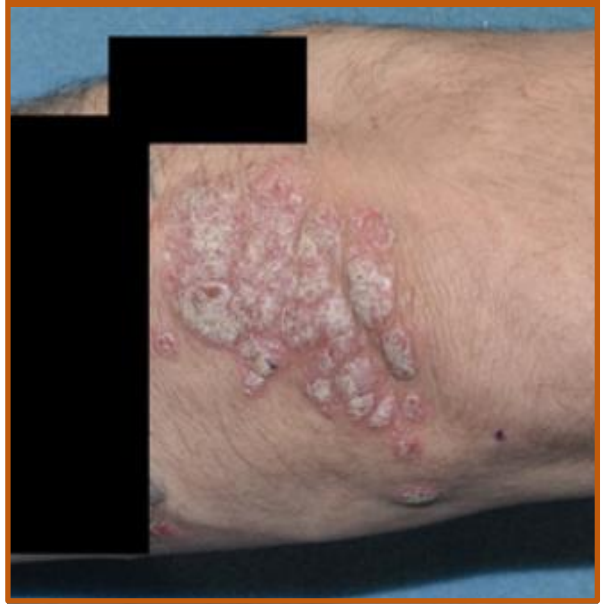
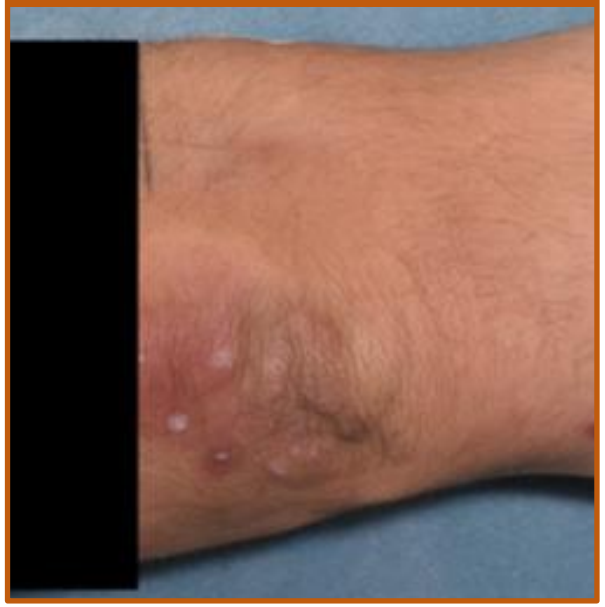
p value from a Cochran-Mantel-Haenszel test, with prior biologic treatment included as a stratification factor, comparing the proportion of patients in the treatment group versus placebo
Modified intent-to-treat (mITT) analysis set: all patients who were randomized and received at least one dose of study treatment
CI, confidence interval; NRI, non-responder imputation; QD, once daily

Representative PASI 75 and PASI 90 responses with TAK-279 30 mg QD

PASI 75 response

Baseline	Week 12
	

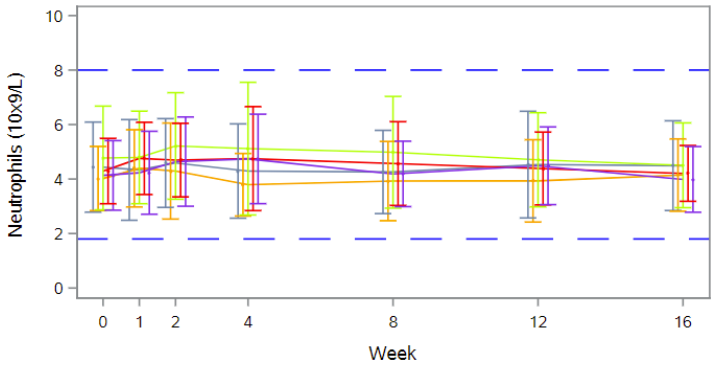
PASI 90 response

Baseline	Week 12
	

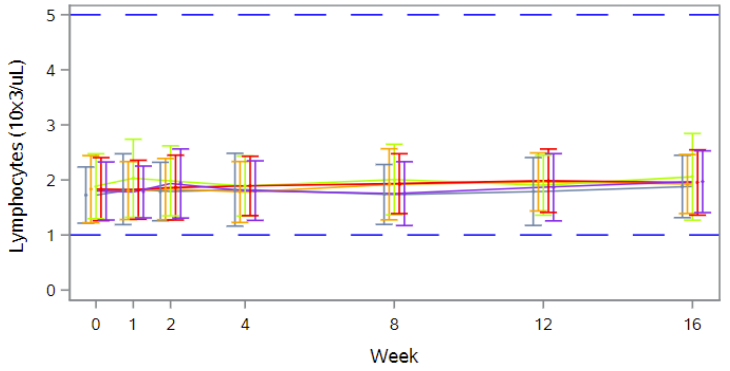
PASI, Psoriasis Area and Severity Index; QD, once daily

Hematological parameters and CPK

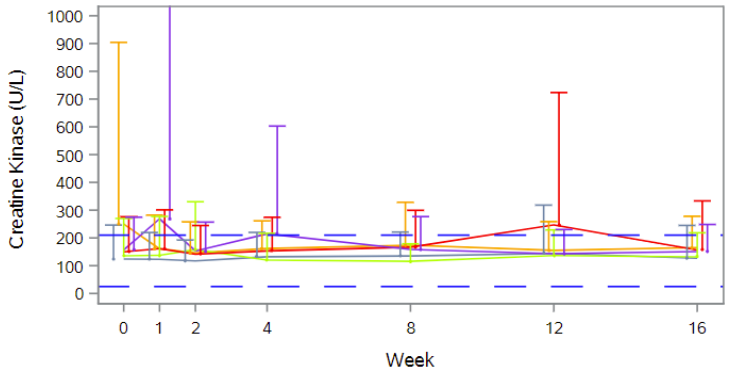
Neutrophil count (ANC)
Reference range 1.8–8.0 (10^9/L)



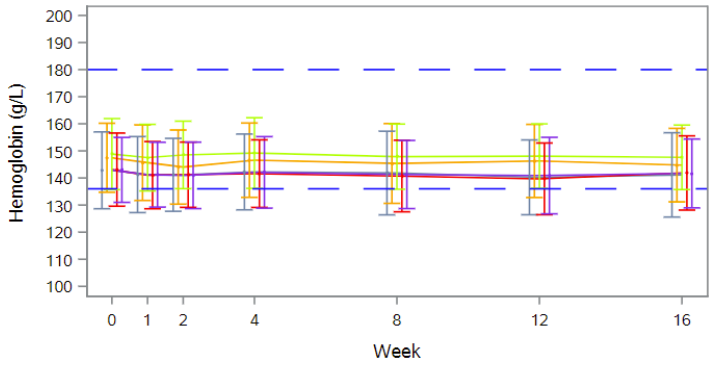
Lymphocyte count (ALC)
Reference range 1.0–5.0 (10^9/L)



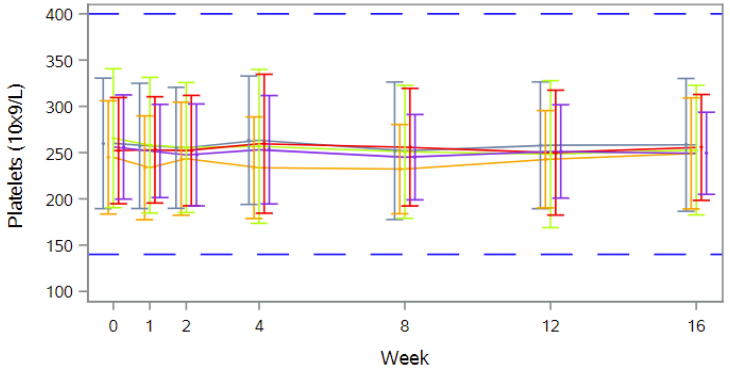
Creatine kinase (CPK)
Reference range 25–210 (U/L)

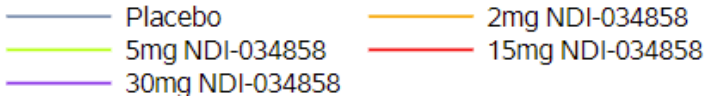


Hemoglobin
Reference range 136–180 (g/L)



Platelets
Reference range 140–400 (10^9/L)



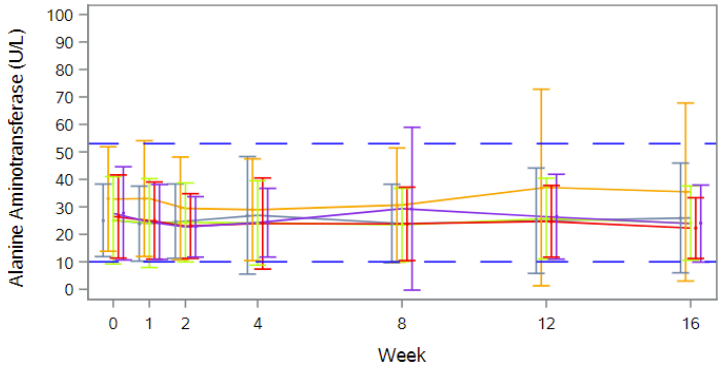


- Mean lab values and changes from baseline **do not reveal adverse trends in cell counts**
- CPK shows some variability at 15 mg and 30 mg with large error bars

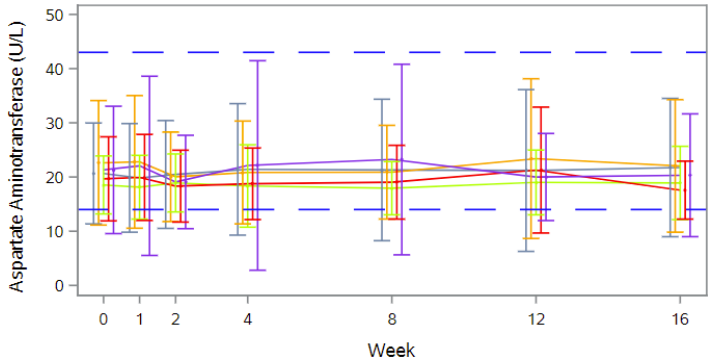
Data are mean ± standard deviation

Hepatic and renal parameters

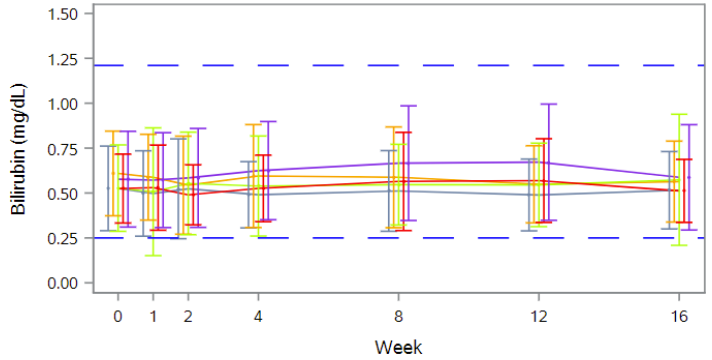
Alanine aminotransferase (ALT)
Reference range 10–53 U/L



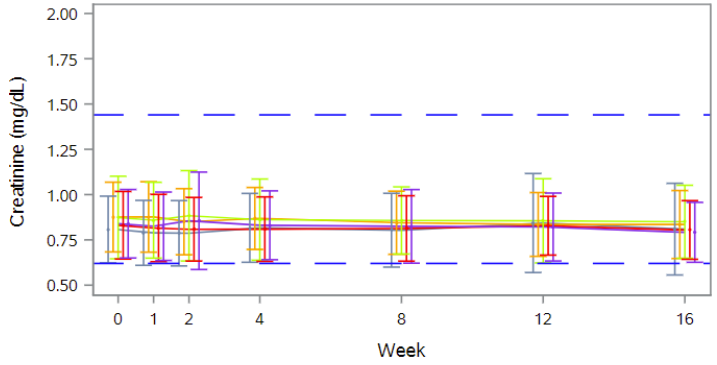
Aspartate aminotransferase (AST)
Reference range 14–43 U/L



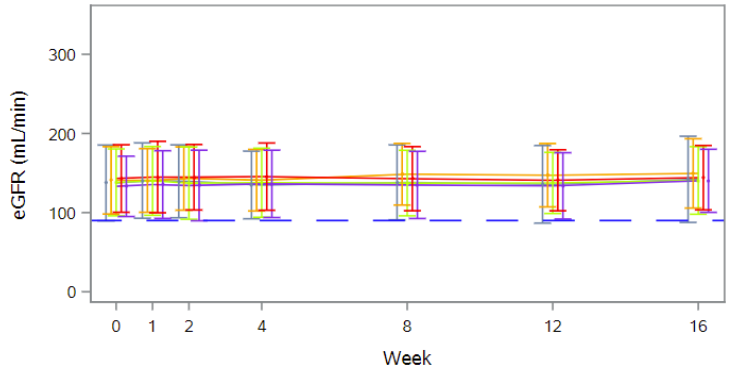
Bilirubin (total)
Reference range 0.25–1.21 mg/dL

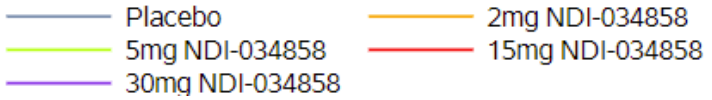


Creatinine
Reference range 0.62–1.44 mg/dL



Estimated glomerular filtration rate (eGFR)
Normal range >90 mL/min/1.73 m^2



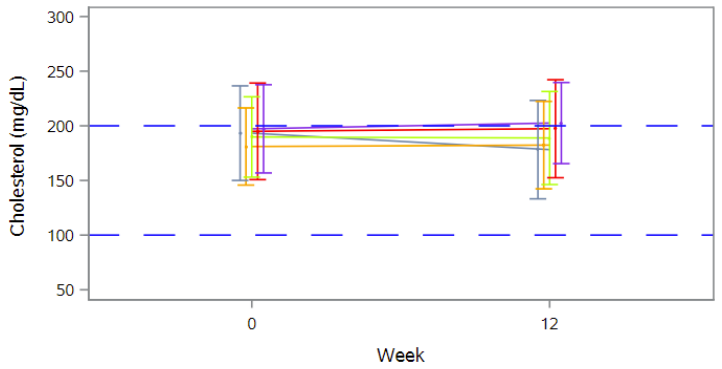


- Mean lab values and changes from baseline **do not reveal adverse trends for liver enzymes, creatinine or eGFR**

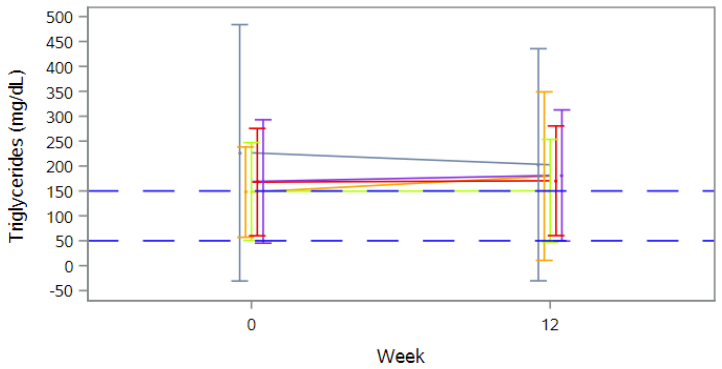
Data are mean ± standard deviation

Lipid parameters

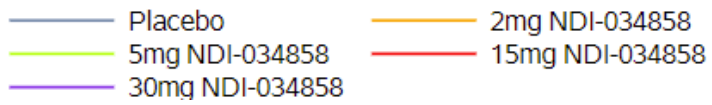
Cholesterol (total)
Reference range 100–200 mg/dL



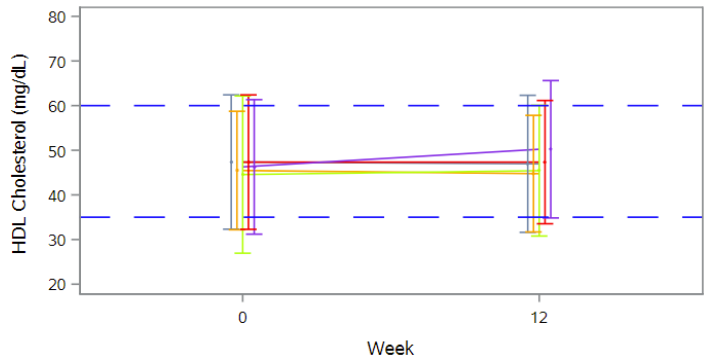
Triglycerides
Reference range 50–150 mg/dL



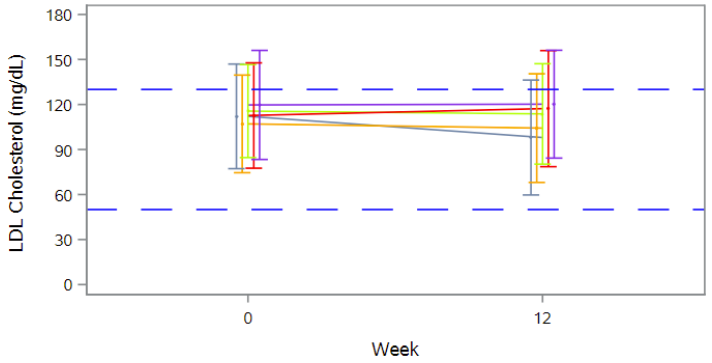
- Mean lab values and changes from baseline **do not reveal adverse trends in cholesterol, HDL, or LDL**
- Triglyceride elevation **is minimal**



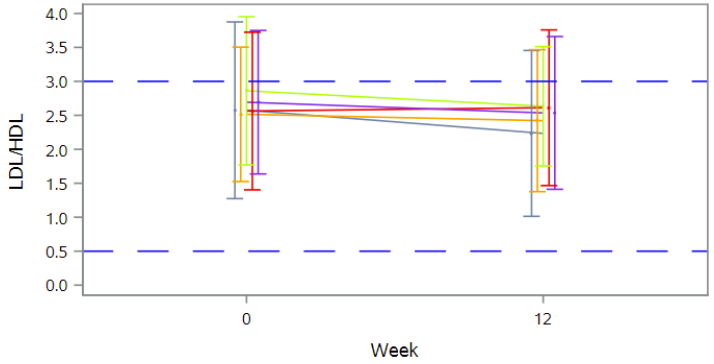
HDL cholesterol
Reference range 0.91–1.55 mmol/L



LDL cholesterol
Reference range 50–130 mg/dL



LDL/HDL ratio
Reference range 0.5–3.0



Data are mean ± standard deviation
HDL, high-density lipoprotein; LDL, low-density lipoprotein

Better Health, Brighter Future