Clinical, Endoscopic, Histologic and Biomarker Activity Following Treatment with the Gut-Selective, Pan-JAK Inhibitor TD-1473 in Moderately-to-Severely Active Ulcerative Colitis

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Conflict of Interest

- **William Sandborn**: Consulting fees from AbbVie, Akros Pharma, Allergan, Ambrx Inc., Amgen, Ardelyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Conatus, Cosmo Technologies, Escalier Biosciences, Ferring, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, MedImmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic Research Trust or HART), Salix, Seattle Genetics, Seres Therapeutics, Shire, Sigmoid Biotechnologies, Takeda, Theradiag, Theravance Biopharma Ireland Limited, Tigenix, Tillotts Pharma, UCB Pharma, Vascular Biogenics, and Vivelix; research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, and Celgene/Receptos; payments for lectures/speakers bureau from AbbVie, Janssen, and Takeda; and holds stock/stock options in Escalier Biosciences, Oppilan Pharma, Precision IBD, Progenity, and Ritter Pharmaceuticals
- **Julian Panes**: Consulting fees from AbbVie, Arena, Boehringer Ingelheim, Celgene, GoodGut, GSK, Janssen, MSD, Nestlé, Oppilan, Pfizer, Takeda, Theravance Biopharma US, Inc., and TiGenix. Unrestricted research grants from AbbVie and MSD
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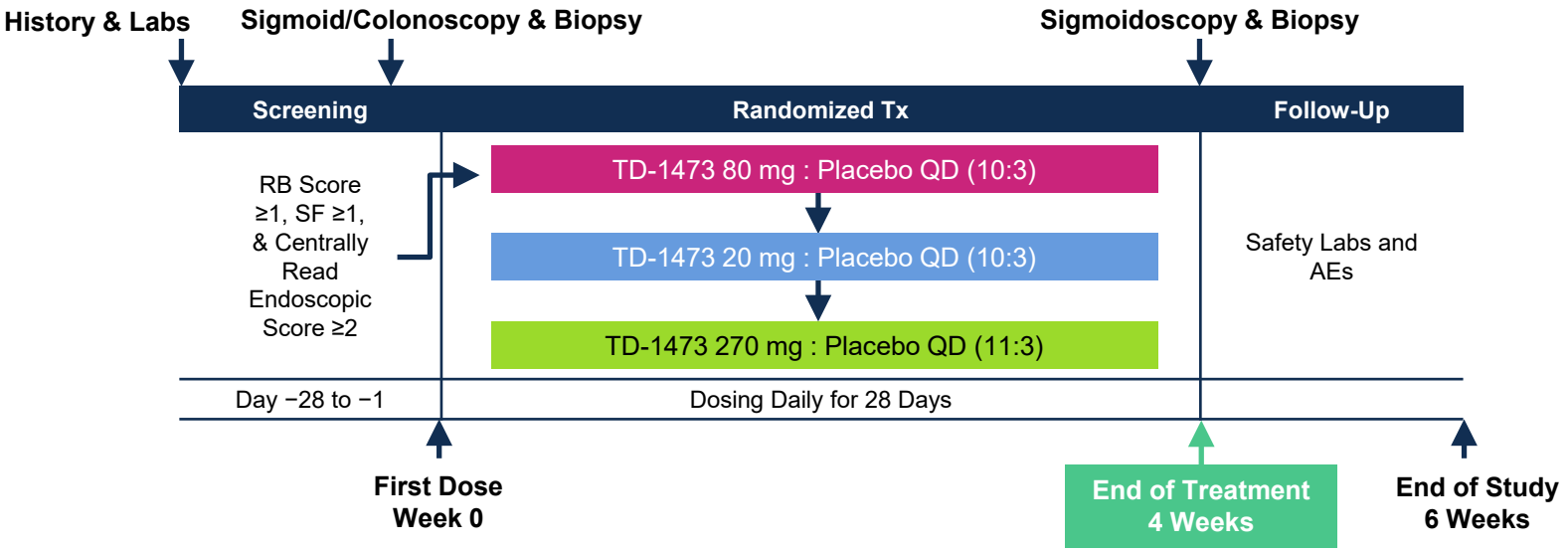
- **David Boyle**: Nothing to disclose
- **Deanna Nguyen and Richard Graham**: Employees of Theravance Biopharma US, Inc. and shareholders of Theravance Biopharma, Inc
- **Brian Ferslew**: Former employee of Theravance Biopharma US, Inc. and shareholder of Theravance Biopharma, Inc
- **Brihad Abhyankar**: Employee of Theravance Biopharma Ireland Limited and shareholder of Theravance Biopharma, Inc

TD-1473 Phase 1b 4-Week Exploratory Study in Patients with Ulcerative Colitis (UC)

TD-1473 is an **oral, once-daily, potent pan-JAK (JAK1, 2, 3, Tyk2) inhibitor** designed to act selectively in the gut to treat IBD with minimal systemic exposure



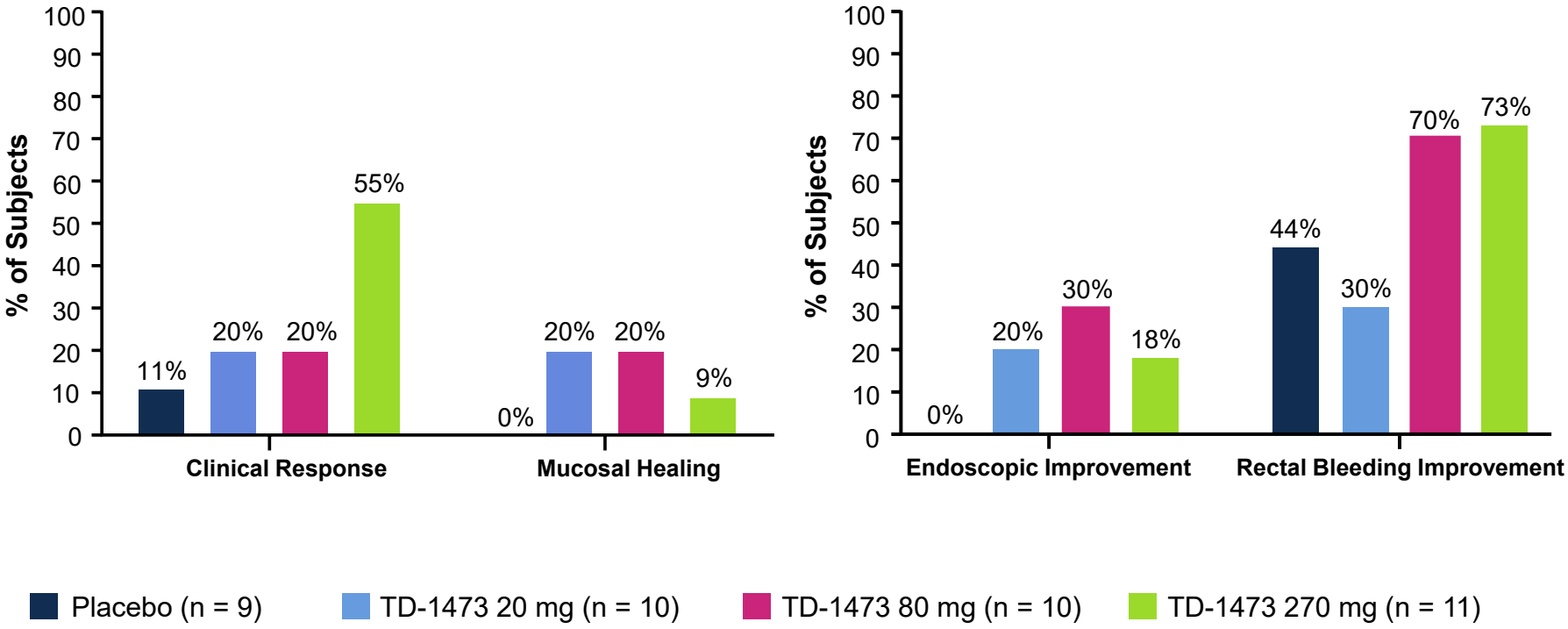
Objective: Assess the clinical & molecular effects of TD-1473 in subjects with moderately-to-severely active UC

Patient population: Moderately-to-severely active UC intolerant or refractory to conventional therapy or biologics

Endoscopy and histology (Robarts Histologic Index**) were centrally read**
Colonic tissue biomarker protein levels (by ELISA) and transcriptomics (by RNAseq) were measured at baseline and at Day 28

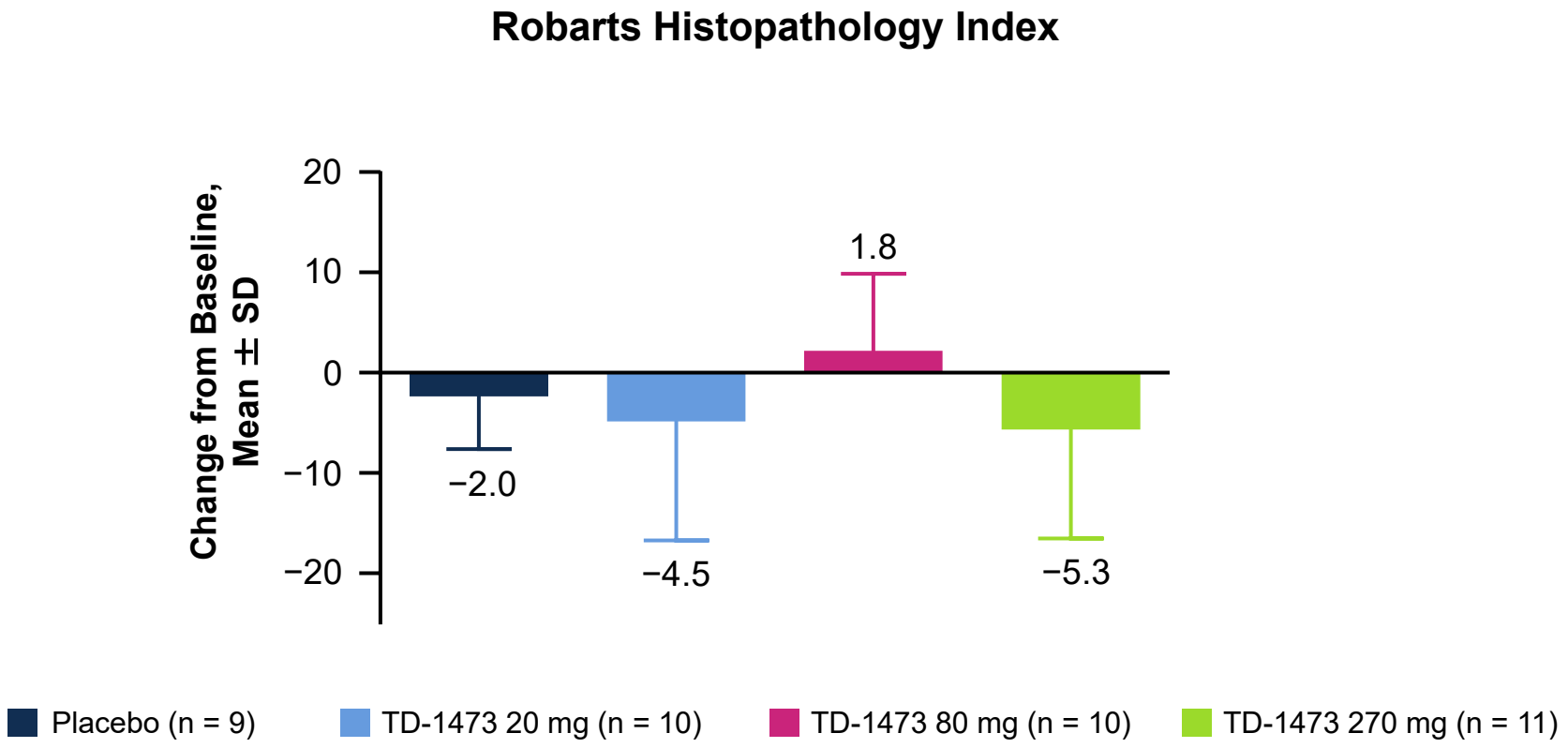
QD, once daily; RB, rectal bleeding; Tx, treatment; SF, stool frequency; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Trends for Higher Rates of Clinical Response, Mucosal Healing, and Improvement in Endoscopy & Rectal Bleeding after 4 Weeks of Treatment with TD-1473



tMS clinical response, ↓ total Mayo score of ≥3 points and ≥30%, with ↓ rectal bleeding subscore by ≥1 or an absolute rectal bleeding subscore of ≤1; mucosal healing, endoscopic subscore of ≤1; improvement: reduction by ≥ 1 point

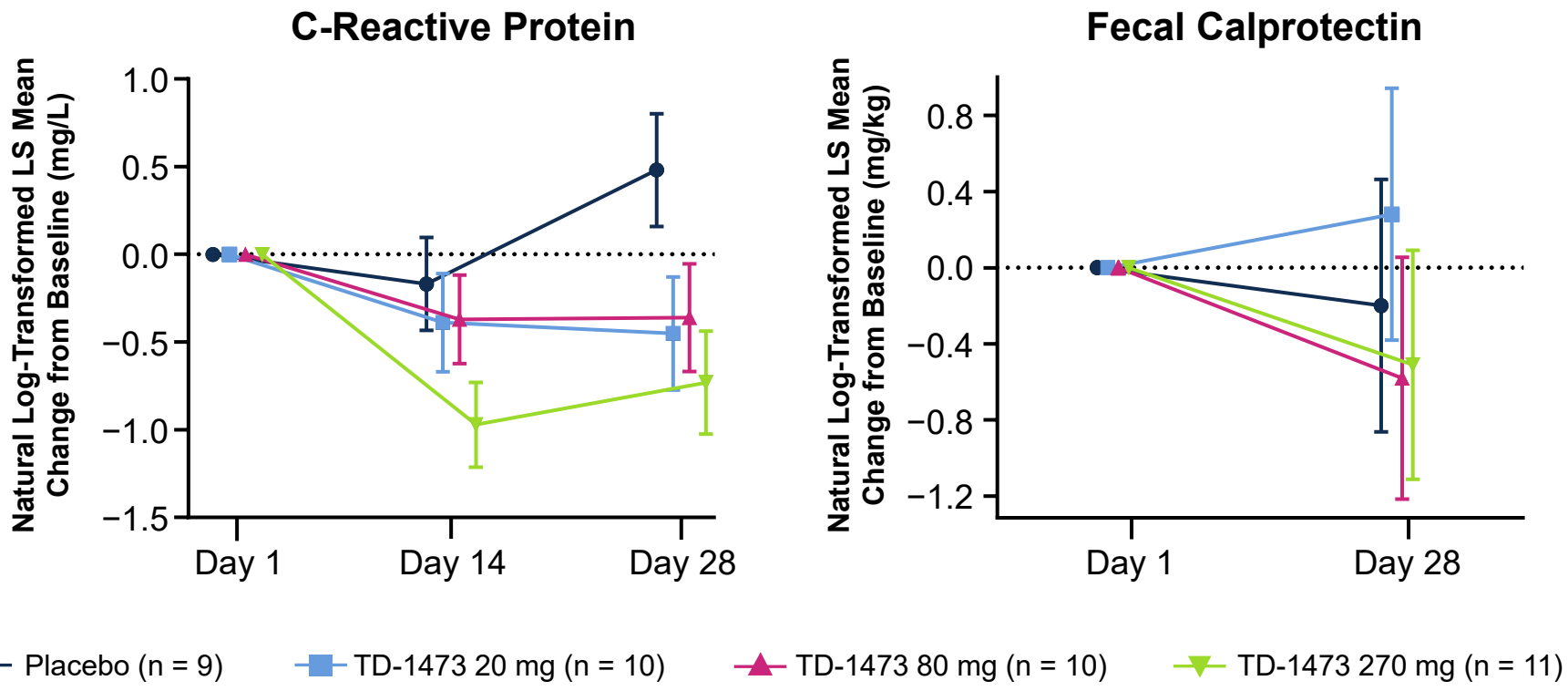
Reductions in Histologic Activity after 4 Weeks of Treatment with TD-1473



- Higher reductions in RHI for TD-1473 20 mg and 270 mg compared to placebo

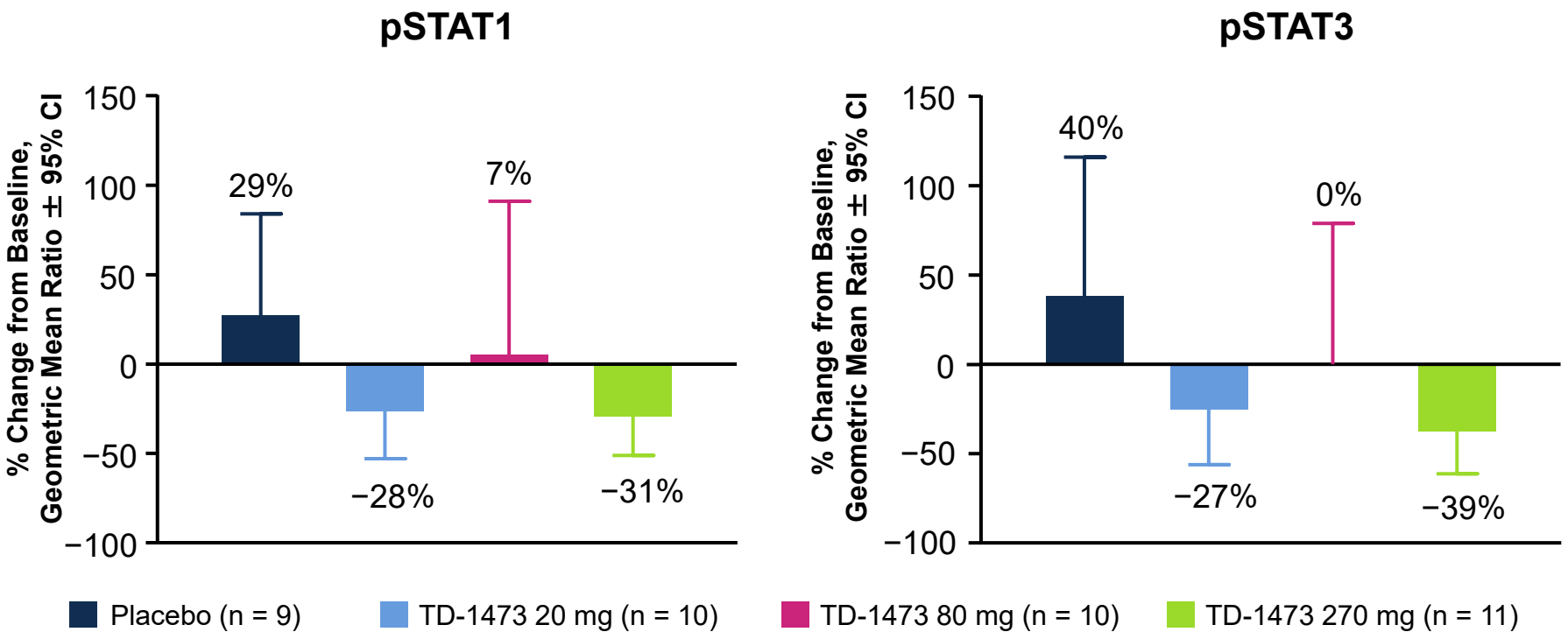
RHI, Robarts Histopathology Index; SD, standard deviation

Trends for Reductions in Disease Surrogate Biomarkers with TD-1473 Treatment



CRP, C-reactive protein; LS, least-squares.

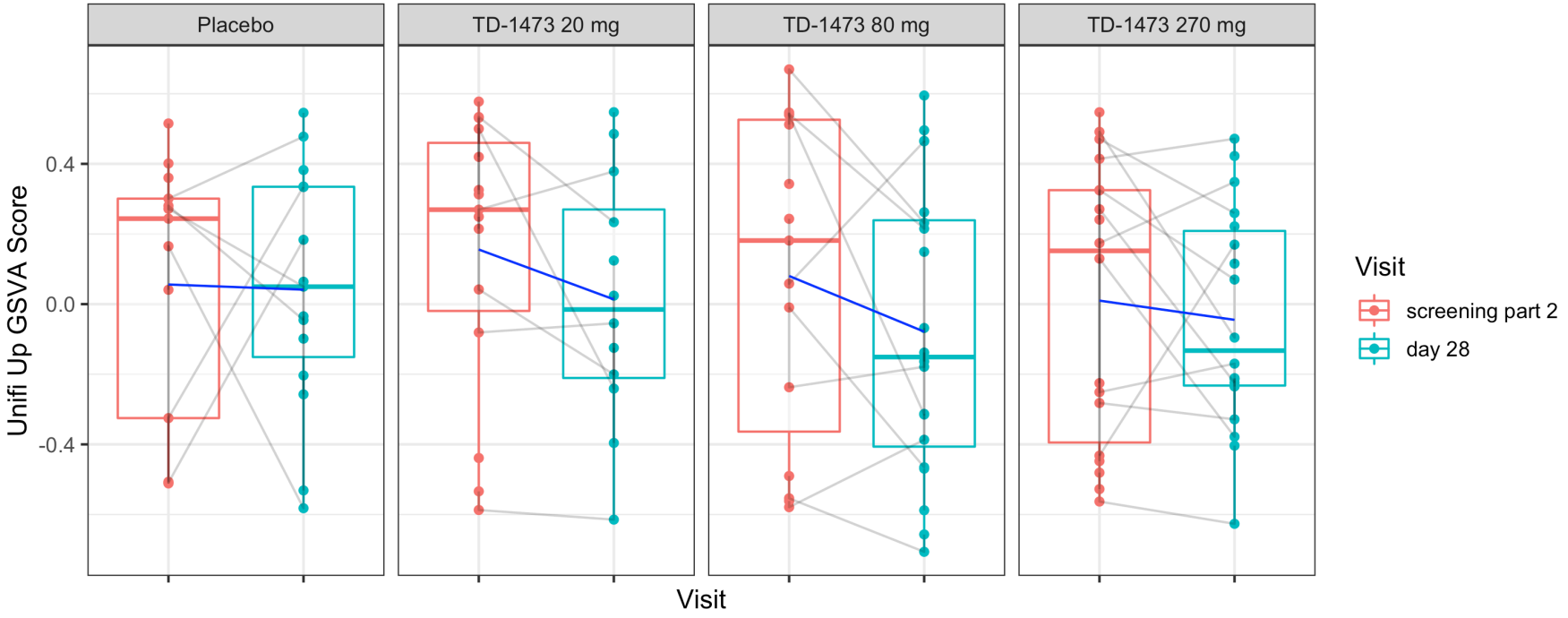
Trends for Higher Reductions in Activated STAT Protein Levels after 4 Weeks of Treatment with TD-1473



- Phosphorylated (p)-STAT is a downstream regulatory protein in the JAK-STAT signaling pathway
- Higher reductions in pSTAT1 and pSTAT3 levels for TD-1473 20 mg and 270 mg compared to placebo

CI, confidence interval; pSTAT, phosphorylated signal inducer and activator of transcription.

TD-1473 Reduces Transcript Levels of Genes Upregulated in Active Inflammation



- Colonic tissue RNA profiling demonstrated trends in reductions in expression levels of upregulated UC disease profile genes* with TD-1473 treatments at all doses compared to placebo

*Gene list includes S100A12, MMP7, IDO1, SOCS1. For details, please refer to Li *et al.*, ECCO 2019. A-1714

Conclusions

This translational medicine study demonstrated clinical and molecular activity, as evidenced by the totality of data, after 4 weeks of TD-1473 treatment:

- Trends for higher rates of relevant clinical outcomes and for higher reductions in disease surrogate biomarkers, relative to placebo
- Histologic and pSTAT assessments demonstrated trends for reduction at 20 mg and 270 mg, suggesting modulation of JAK signaling
- RNA expression profiling data are consistent with local modification of the UC-transcriptomics signature by TD-1473

These signals of clinical and biomarker activity, which are suggestive of localized target engagement, led to the decision to initiate a Phase 2 POC Study in CD and Phase 2b/3 Induction and Maintenance Studies in UC

UC, ulcerative colitis.