

Tofacitinib tissue exposure correlates with endoscopic outcome

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Disclosures S Vermeire

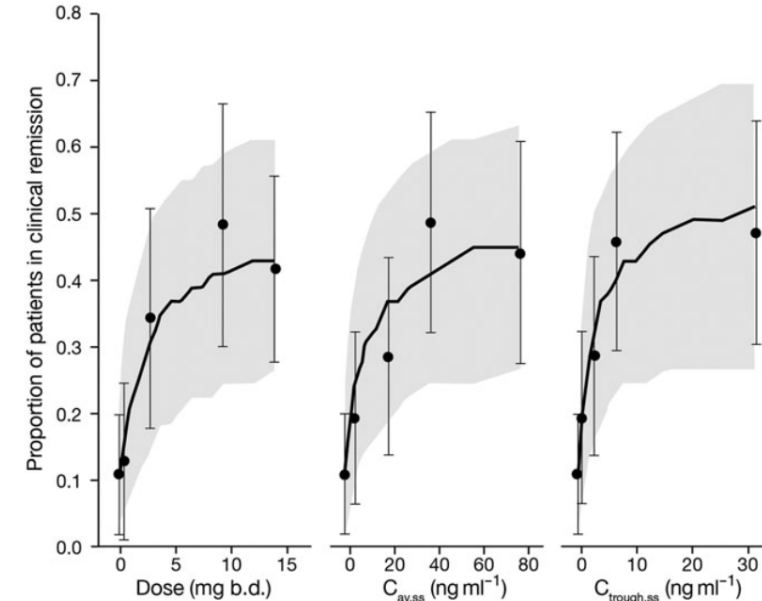
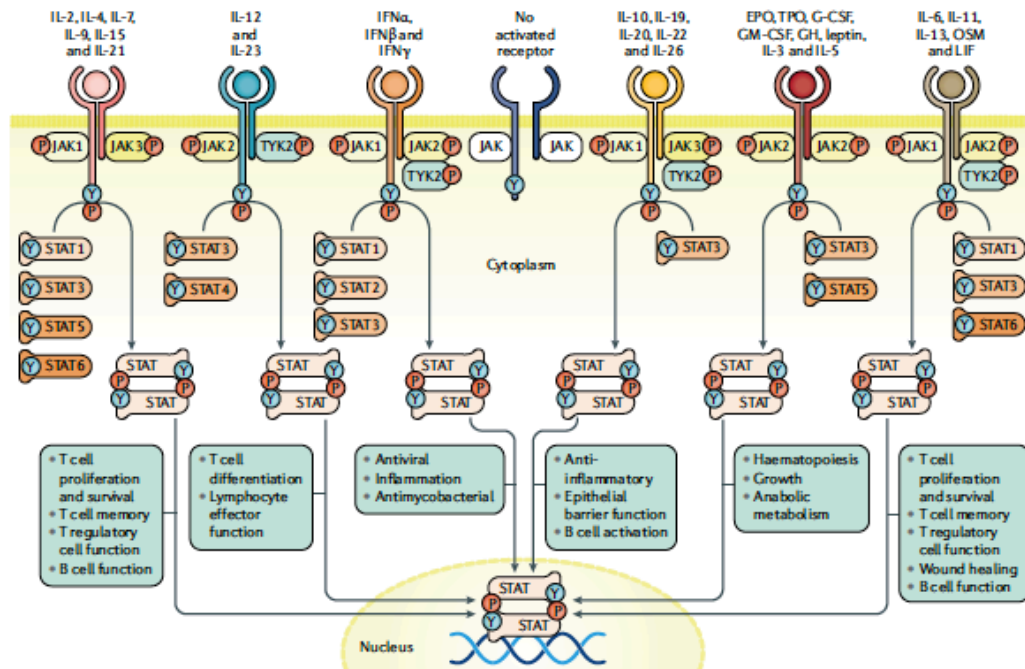
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Introduction

- **Tofacitinib** is the **1st** in class Janus Kinase (JAK) inhibitor, approved for moderate-to-severely active ulcerative colitis

- In contrast to monoclonal antibodies, very **little** is **known** about its **pharmacokinetic – pharmacodynamic profile**

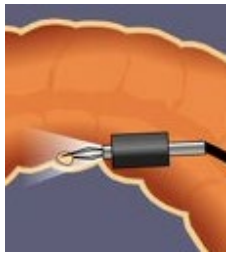


Aim

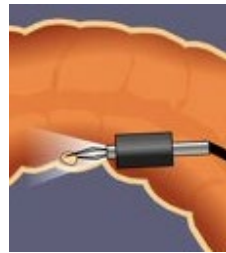
To assess **pharmacokinetic-pharmacodynamic changes** in UC patients treated with **tofacitinib (TFC)**, with a **focus on STAT3 phosphorylation**

Methods

- Prospective
- 30 consecutive UC patients
- active endoscopic disease (Mayo endoscopic subscore 2 or 3)
- tofacitinib 10mg BID induction



Week 0

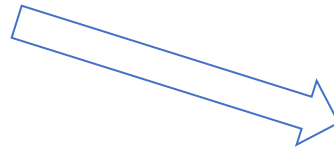
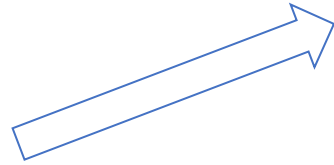
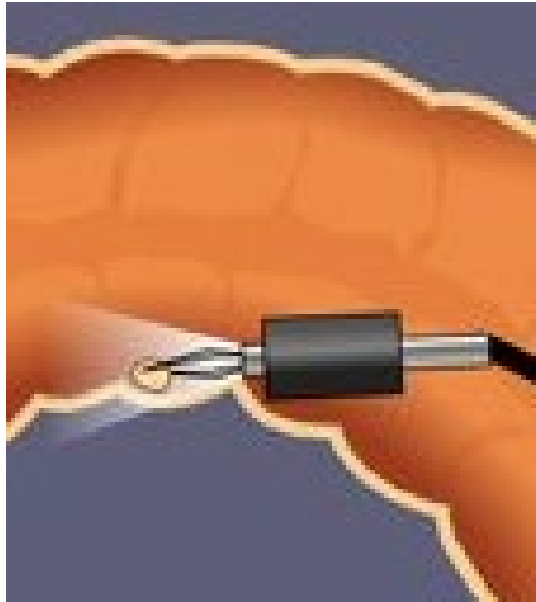


Week 8 - 16

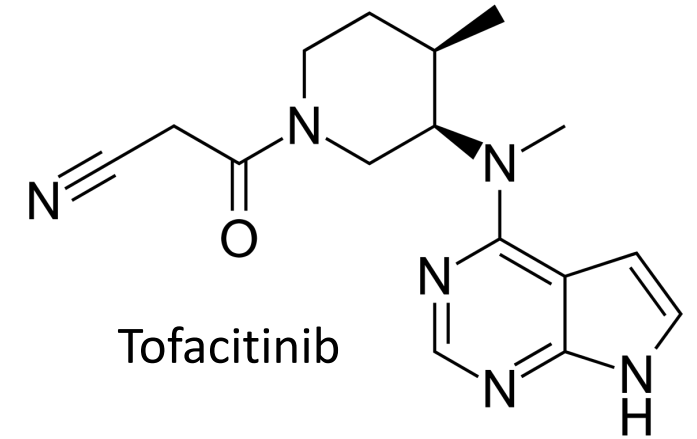


Endoscopic improvement / response :
Mayo endoscopic sub-score 0-1

Methods



Mass spectrometry



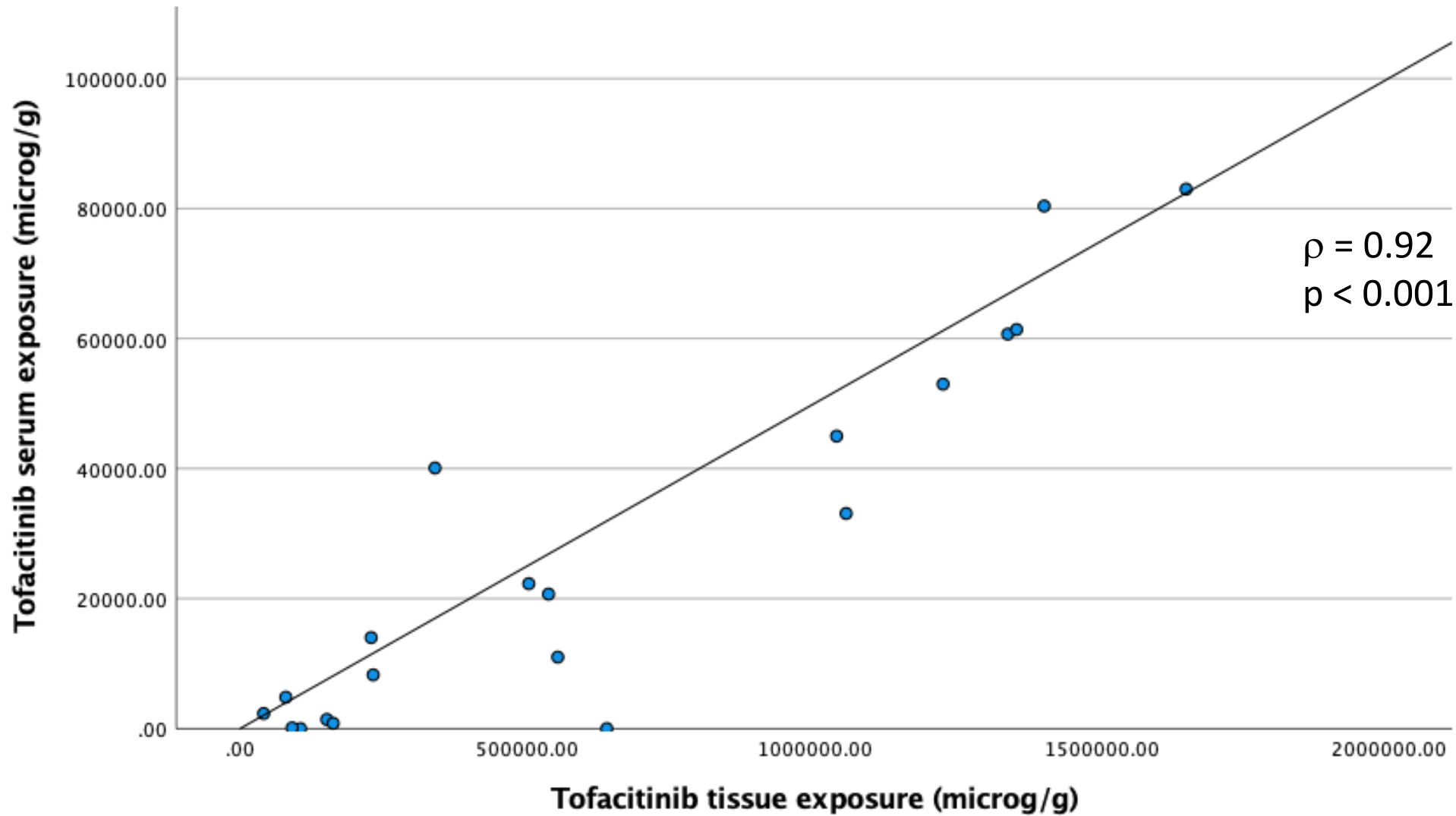
**Ultrasensitive luminescent
oxygen channelling**



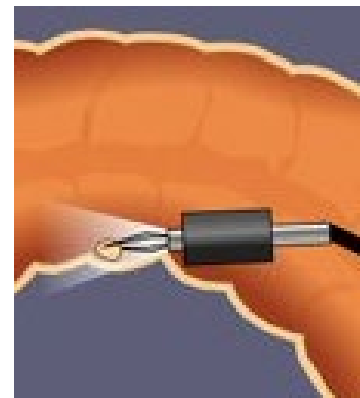
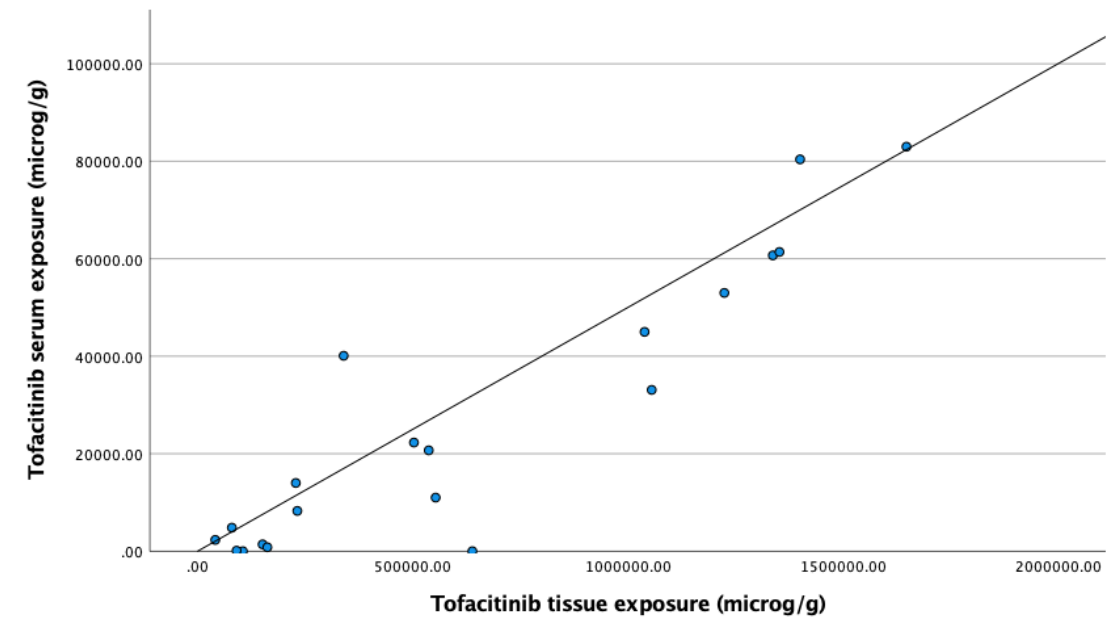
Patient col

Sex, women, n (%)	17 (56.7)
Age at initiation of tofacitinib, y, median [IQR]	47.1 (28.2 – 53.7)
Disease duration, y, median [IQR]	7.5 (3.1 – 15.4)
Faecal calprotectin, mg/g, median [IQR]	1718.6 (1446.8 – 1800)
Serum albumin, g/L, median [IQR]	41.7 (40.8 – 44.2)
Partial Mayo score, median [IQR]	10.0 (9.0 – 11.0)
Endoscopic scoring	
- Mayo endoscopic sub-score, median [IQR]	3.0 (2.0 – 3.0)
- Ulcerative colitis index of severity, median [IQR]	5.0 (4.0 – 6.0)
Histologic scoring Nancy index, median [IQR]	3.0 (3.0 – 3.0)
Disease extent, n (%)	
- Proctitis E1	4 (13.3)
- Left-sided colitis E2	14 (40.0)
- Extensive colitis E3	12 (46.7)
Concomitant medication, n (%)	
- Corticosteroids	
• Topical	7 (23.3)
• Systemic	8 (26.7)
- Immunomodulators	0 (0.0)

Tofacitinib tissue and serum exposure correlate significantly (Pk)



Tofacitinib tissue exposure is > 30-fold higher than serum exposure

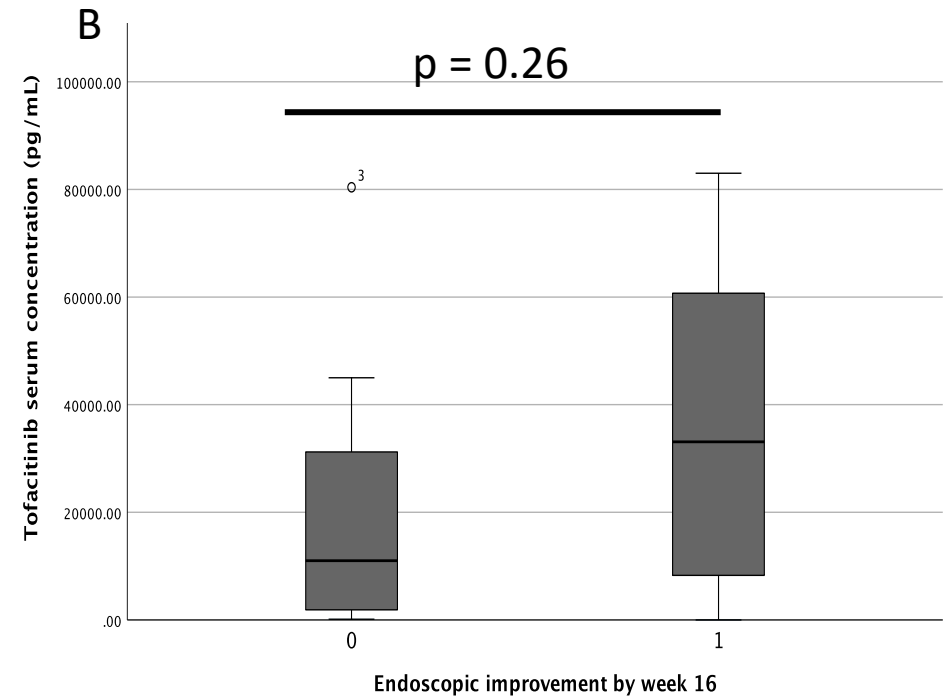
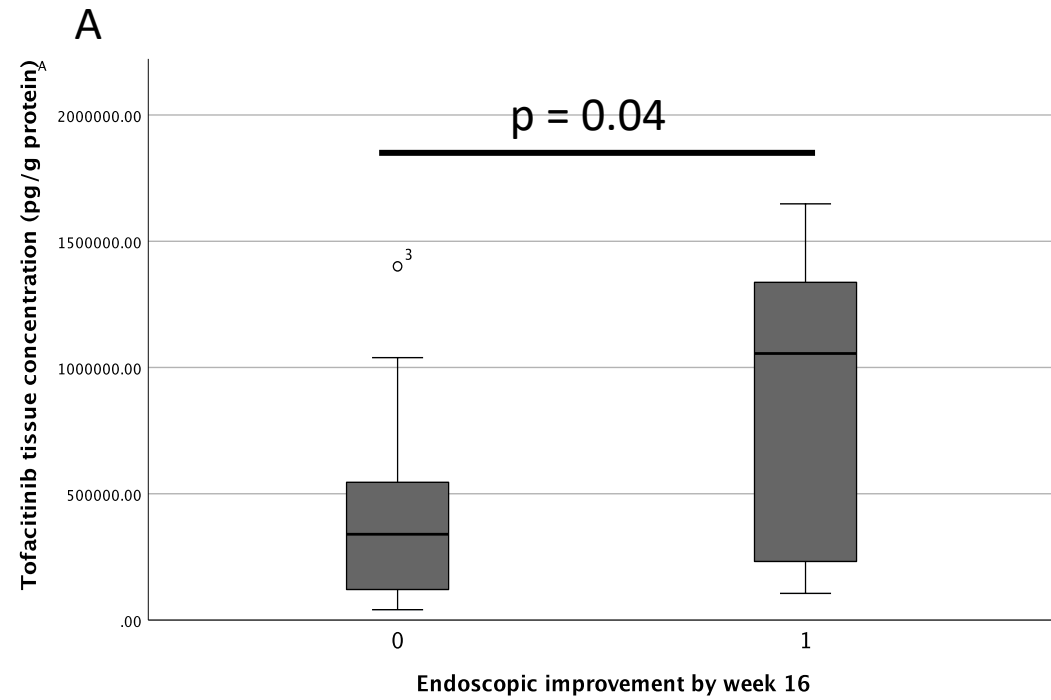


520.19 ng/g



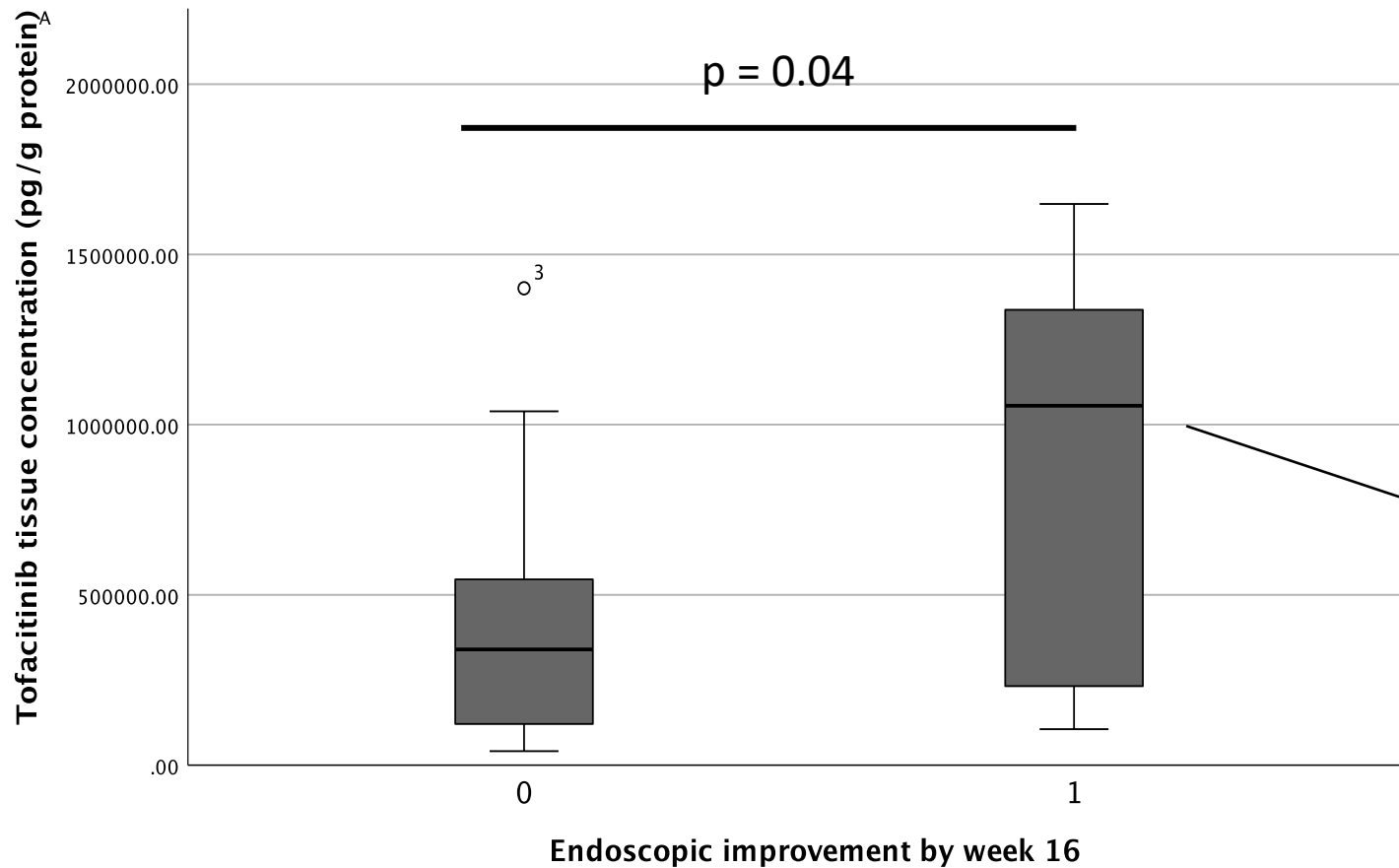
17.35 ng/g

A Pk-PD relationship in tissue, but not in serum



Therapeutic consequences of high tissue exposure

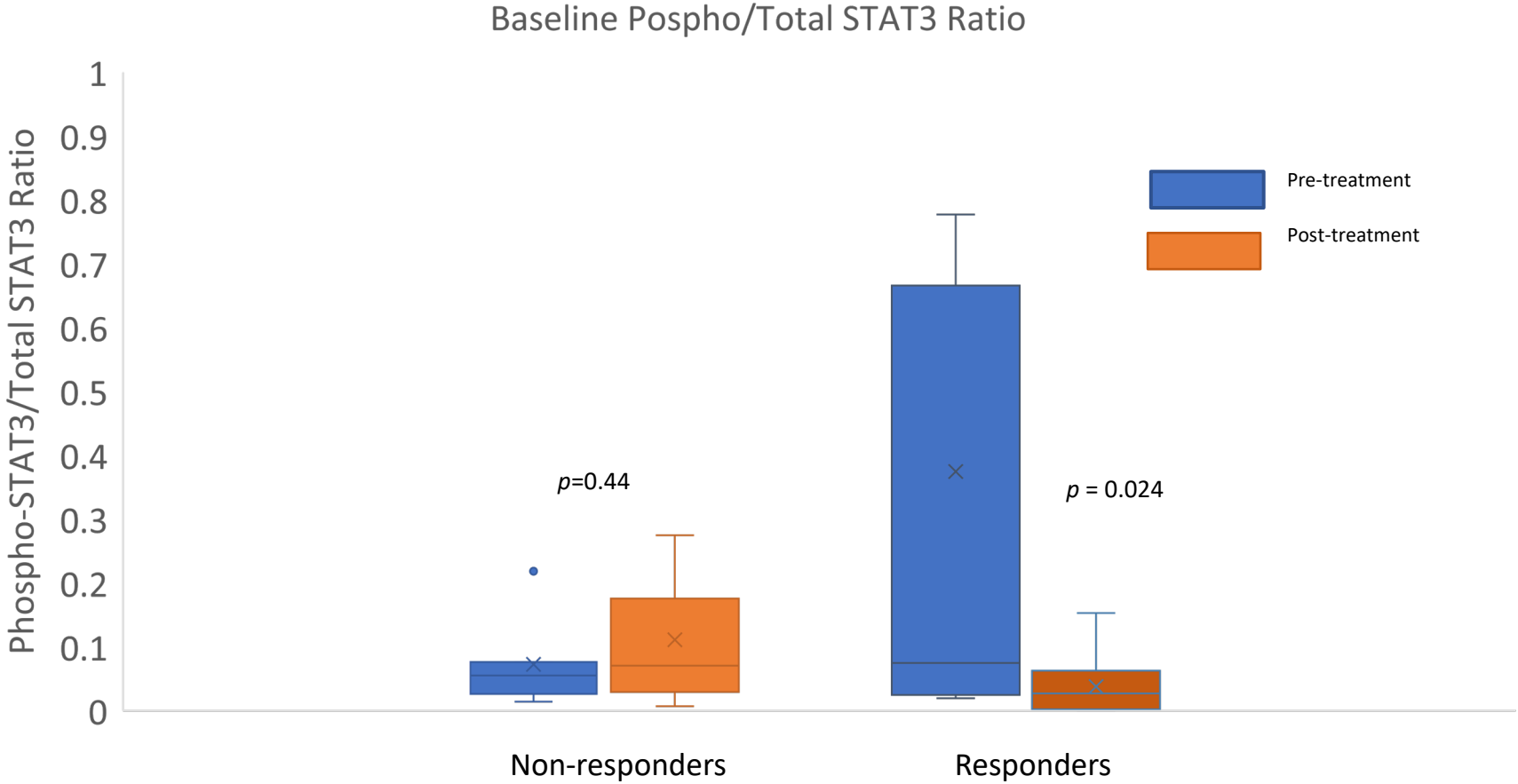
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IC 90 : 823 ng/g

1 055 ng/g

Phosphorylated STAT3/STAT3, a useful predictive or monitoring marker



Conclusions

- We demonstrated a **mucosal exposure-response relationship** with tofacitinib in UC
- **pSTAT3/STAT3 ratio** is a potential **molecular marker to track response**, directly linked to the MOA of tofacitinib
- An increased local dose of tofacitinib could potentially lead to improved efficacy without compromising safety



PGN-600: UC induction trial with 'topical, soluble' tofacitinib

Longitudinal monitoring of STAT3 phosphorylation and histologic outcome of tofacitinib therapy in patients with ulcerative colitis

