EFFECTS OF FILGOTINIB ON CIRCULATING CYTOKINES

INTRODUCTION
A Phase 2 study of filgotinib (FIL), a Janus Kinase (JAK) 1-selective inhibitor, in moderate-to-severe Crohn’s disease (CD); FITZROY demonstrated significantly higher clinical remission rates compared to placebo at 10 weeks (Vermeire S. Lancet. 2017;389(10066):266–275), and an early decrease in systemic and mucosal inflammation biomarkers, which was more pronounced in endoscopic responders (Roblin X. ECCO, Vienna, Austria, 2018). We investigated the baseline (BL) correlation of whole-blood transcriptome pathway activities with clinical disease indices and circulating cytokines. The effect of FIL on changes in disease-related pathways in responders and nonresponders was also explored.

METHODS
PAXgene blood samples were collected from 104 patients with CD at BL and Week 10 (W10). RNA was sequenced (Illumina HiSeq 2500) after globin depletion (ThermoFisher GlobinClear). Differential gene expression analysis was performed using limma R package and hallmark pathway activity scores were calculated using single sample gene set enrichment analysis. All correlations were performed using the Spearman method.

RESULTS
At BL, pathways with activity scores positively correlated with Simple Endoscopic Score for Crohn’s disease (SES-CD) were immune (IL-6/JAK/STAT3, inflammatory response), metabolic, and reactive oxygen species (ROS). These were also positively correlated with markers of systemic inflammation (CRP, SAA, IL-6, and OSM) and epithelial turnover (IL-22, C4M2, and C3M). Ten weeks of FIL treatment led to significant decreases of these pathways in endoscopic responders (50% reduction in SES-CD), whereas there were no significant changes following placebo treatment. While interferon (IFN) response pathway scores showed weak correlation (rho < 0.2) with SES-CD at BL, they were significantly reduced by FIL treatment, particularly in FIL responders.

CONCLUSIONS
In whole blood, inflammation, metabolic and ROS pathways were reduced by FIL in endoscopic responders at W10, while reductions in IFN response pathways were observed in all patients regardless of endoscopic response.

Abstract P117 Table 1

<table>
<thead>
<tr>
<th>pSTAT</th>
<th>BL MDA</th>
<th>W10 change</th>
<th>Ep</th>
<th>Non-Ep</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FIL</td>
<td>PBO</td>
<td>P</td>
<td>FIL</td>
</tr>
<tr>
<td>pSTAT1</td>
<td>Low</td>
<td>Worsen</td>
<td>0.168</td>
<td>0.348</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Improve</td>
<td>0.436</td>
<td>0.286</td>
</tr>
<tr>
<td>pSTAT3</td>
<td>Low</td>
<td>Worsen</td>
<td>0.115</td>
<td>0.375</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Improve</td>
<td>0.449</td>
<td>0.241</td>
</tr>
</tbody>
</table>
segments were used to classify segments as low or high molecular disease activity (MDA). Agreement between endoscopy/histology and MDA was evaluated by Cohen’s kappa coefficient (%) and% agreement.

**Results** In segments with BL GHAS activity subscore ≥2, Ep (10–30%) and non-Ep (25–35%) MDA were elevated and correlated to histologic activity. Table 1 shows the effect of FIL on MDA in the intestinal mucosa: significantly fewer low BL MDA segments showed MDA worsening, and significantly more high BL MDA segments showed MDA improvement (pSTAT3 only) with FIL vs. PBO. Agreement for MDA and endoscopy was fair to moderate (κ 0.3–0.5), and for MDA and histology was moderate to good (κ 0.4–0.8).

**Conclusions** FIL improved JAK1-related MDA within the mucosa of pts with CD. Agreement between MDA and clinical indices was highest with histology.

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**P118**

**POSITIVITY THRESHOLDS OF TOTAL INFlixIMAB AND ADALIMUMAB ANTI-DRUG ANTIBODY ASSAYS AND IMPACT IN CLINICAL PRACTICE**

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**Introduction** Anti-drug antibodies can affect biopharmaceutical pharmacokinetics by increasing or decreasing drug clearance. Drug-tolerant (total), unlike drug-sensitive (free), antibody assays permit antibodies to be measured in the presence of drug.

We aimed to confirm the positivity threshold of our total anti-tumour necrosis factor (TNF) antibody ELISA assays in healthy volunteers and to use this threshold to report the prevalence of clearing and transient antibodies in patients treated with infliximab and adalimumab.

**Methods** Serum was obtained from 498 anti-TNF-naïve healthy adults recruited to the Exeter 10,000 study and tested for total anti-drug antibodies to infliximab and adalimumab. We used bootstrapping to calculate the 80% one-sided lower confidence interval [CI] of the 99th centile recommended by the FDA to define assay thresholds.

We used paired drug and anti-drug antibody levels derived from our national therapeutic drug monitoring service to report the distribution of clearing (antibody positive, drug negative) vs non-clearing (antibody positive, drug positive) antibodies. In patients with at least two test results, antibodies were classified as transient (single positive test with subsequent negative test) or persistent (at least two positive tests).

**Results** The 80% one-sided lower CI of the 99th centile titre for total anti-drug antibody to infliximab and adalimumab were 8.7 AU/mL and 5.9 AU/mL, respectively.

Using these thresholds, at the time of last testing, of 7,428 and 4,043 patients treated with infliximab and adalimumab; 21.1% and 8.3% had clearing antibodies and 27.9% and 20.0% had non-clearing antibodies, to infliximab and adalimumab, respectively.

Amongst patients with at least two tests, most developed persistent antibodies. Irrespective of anti-TNF drug, or threshold used, less than 10% patients developed transient antibodies.

Across both our national TDM cohort and the PANTS study, there were significant associations between anti-drug antibody and drug levels (figure 1). In PANTS, higher anti-drug antibody levels were associated with poorer outcomes at weeks 14 and 54.

**Conclusions** We report lower positivity thresholds for the IDK-monitor® total anti-TNF antibody ELISA assays than the manufacturer, in particular, for adalimumab. Transient antibody formation is uncommon: most patients develop persistent anti-drug antibodies that lead to drug clearance.

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**Abstract P118 Figure 1** Relationship between adalimumab drug and anti-drug antibody levels in national TDM cohort

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**P119**

**RISK OF FURTHER SURGERY AND ADHERENCE TO COLONOSCOPY GUIDELINES FOLLOWING RIGHT HEMICOLECTOMY FOR CROHN’S DISEASE**

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**Introduction** The risk of further surgery following right hemicolectomy (RH) for Crohn’s disease (CD) is high (~40%). Recent guidelines advise colonoscopy 6–12 months following RH to reduce the risk of further surgical intervention through medical therapy. We examined the risk of further surgery and use of colonoscopy following index RH.

**Methods** Hospital Episode Statistics were used to identify subjects with CD and RH between 2007 and 2016 in England. Adherence to post resection colonoscopic assessment guidance and risk of further surgery at the same site were investigated. Cox regression models examined the risk factors associated with further surgery and funnel plots demonstrated the colonoscopy practice of providers.

**Results** 12,230 CD subjects (55% female, median age 36 (IQR 26–49) years) had a RH during the study period. 1,367 (11%) had further surgery at the anastomotic site during follow up. 40% of Index surgery and 50% of further surgery was performed during an elective admission. 9% (747/8,293) of those with 5 year at follow up had further surgery as and 17% (366/2,163) of those with 10 years at follow up. Age over 54 compared to 18–24 years had a reduced risk of further surgery (adjusted Hazard ratio 0.81 (95%CI 0.67–0.97), 17% (366/2,163) of those with 5 year at follow up had further surgery as and 17% (366/2,163) of those with 10 years at follow up. Age over 54 compared to 18–24 years had a reduced risk of further surgery (adjusted Hazard ratio 0.81 (95%CI 0.67–0.97),