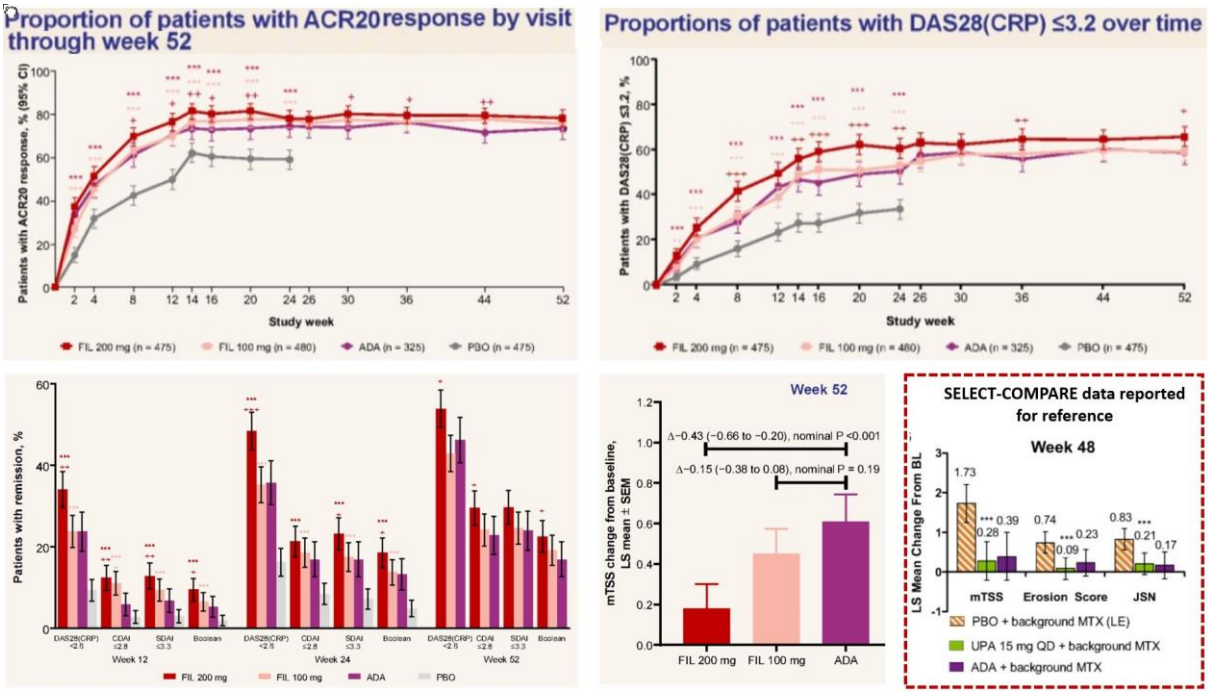
Description:

EULAR 2020: New data presented from the FINCH program including 52wk results and an integrated safety analysis

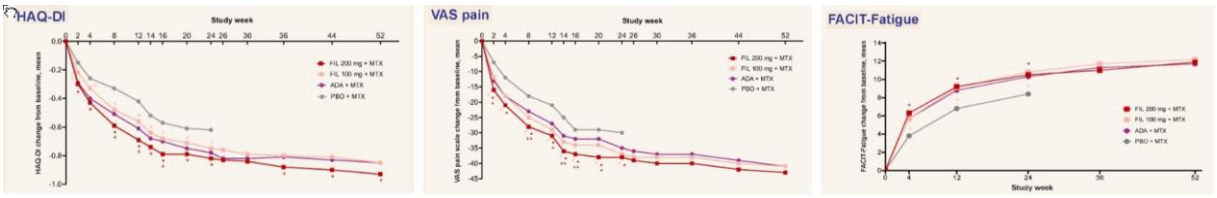
- We complete our review of EULAR with a look at filgotinib data (all EULAR information distributed through our alerts will be collated into a report shortly)
- Gilead announced in Aug that the EMA had accepted filgotinib's MAA in the EU. US filing was announced at the end of 2019 using a priority review voucher. We therefore expect approval in the EU and US around Aug 2020 with Gilead and Galapagos launching soon thereafter. Filing was supported by the FINCH program
- **FINCH 1** (MTX-ir) was reported in Mar 2019 and then as a late breaker at EULAR 2019. The same data were presented at ACR 2019
- The study randomized MTX-irs to filgotinib, placebo or adalimumab on background MTX. The primary endpoint ACR20 for superiority over placebo was met, with efficacy observed from 2wk. All secondary efficacy endpoints comparing filgotinib to placebo were met
- Non-inferiority to Humira was also met on the DAS28-CRP LDA endpoint although superiority was not statistically significant. Consequently, statistics on all subsequent endpoints on the hierarchy could only be described nominally. Of note filgotinib demonstrated nominal significance with regards to superiority of Humira on the arguably more important stringent DAS28-CRP remission measure
- 52wk data were presented at EULAR 2020 (**THU0198**). Discontinuation rates were low with ≈90% patients completing the study. Response rates on the primary endpoints (ACR20 and DAS28-CRP LDA) were maintained over the 52wk period but failed to diverge from Humira responses (see below). We note however that the response to Humira continued to be higher than in the SELECT-COMPARE study of Rinvoq
- Various remission rates were also reported (see below) and these increased with time in each of the groups such that at 52wk filgotinib was nominally more efficacious than Humira on each measure except SDAI remission. Overall, therefore the trends remain similar over 24wk and 52wk where filgotinib efficacy was similar to Humira on the primary endpoints but nominally greater on the more stringent endpoints
- Radiographic progression was very limited with filgotinib, especially at 200mg and considerably less than with Humira (see below). We note that progression with Humira is similar to that seen in the Olumiant study, RA-BEAM but greater than in SELECT-COMPARE, albeit with considerable variability. Thus, in contrast to clinical responses where Humira seems to produce high degrees of efficacy in FINCH 1, radiographic responses to Humira are more limited and variability in the efficacy of Humira rather than differences between filgotinib and Rinvoq could explain some of the findings

Figure: Summary of key 52wk data in FINCH 1 demonstrating durable effect of filgotinib on background MTX in MTX-irs [Download image]



- Further PRO data were reported from FINCH 1 (**FRI0128**). As with clinical data, efficacy on measures including HAQ-DI, pain and disability was not only rapid, but it was also durable. In fact, efficacy seemed to accrue with time although filgotinib and Humira curves did not separate. Similar to clinical findings the Humira response seems larger than in previous studies and this may again explain the lack of divergence
- Overall, long-term efficacy in FINCH 1 follows the pattern of previously reported early responses with similar, or in the case of radiographic progression, possibly superior efficacy compared to Humira. Only a head to head study will clarify Rinvoq efficacy relative to filgotinib and how the two compare to Humira

Figure: Summary of key PRO data at 52wk in FINCH 1 [Download image]



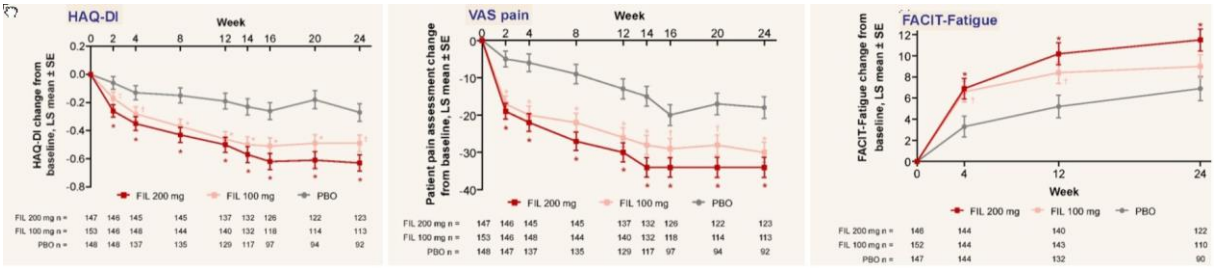
- As indicated above a head to head study would be of use to compare the efficacy of Rinvoq and filgotinib. In the absence of such data MAIC (Matching Adjusted Indirect Comparison) analyses are of use. This approach allows the indirect comparison of two therapies using a common comparator as an anchor. This approach was taken by Gilead and reported in **SAT0142**. The analysis compared filgotinib efficacy in FINCH 1 to Xeljanz efficacy in ORAL STRATEGY using the common Humira comparator as an anchor. Both studies studied MTX-irs on background MTX
- Data were matched based on patient baseline characteristics and filgotinib then compared to Xeljanz relative to Humira responses. As shown below p

values were <0.05 on several measures at 52wk but after adjusting for multiple comparisons significance was not observed. It would be of interest to conduct a similar analysis comparing filgotinib and Rinvoq, but maybe selecting out the most meaningful measures

Figure: Indirect comparison of filgotinib and Xeljanz in MTX-irs [Download image]

- **FINCH 2** was first reported at ACR 2018. The study randomized bDMARD-ir patients to biologic agents. The primary endpoint was ACR20 at 12wk and this was met. Further presentations at EULAR 2019 reported stratification by prior treatment; race/region; and age. Similar data were presented at ACR and at EULAR 2020 efficacy by prior treatment was described again (**THU0204**). Despite FINCH 2 data having been reported on several occasions PROs were to our knowledge reported for the first time at EULAR 2020 (**FRI0139**). Data are summarized below for HAQ-DI, pain and fatigue. Filgotinib improved each of these measures with a rapid response observed

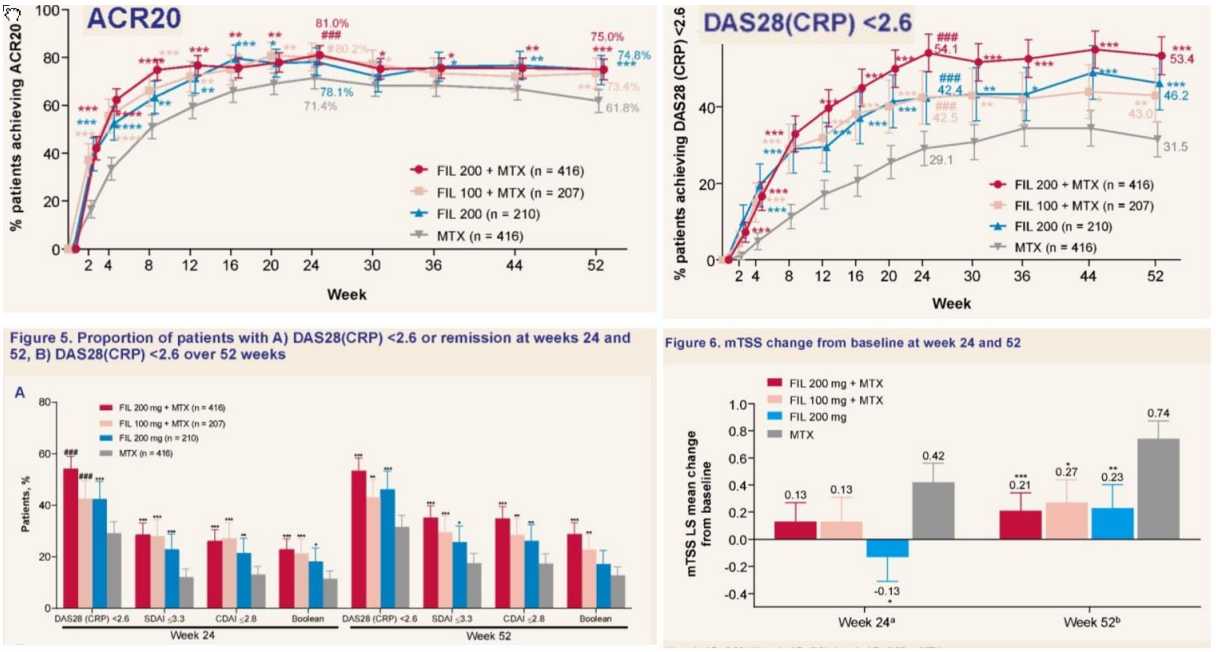
Figure: The effect of filgotinib on PROs in bDMARD-irs [Download image]



- **FINCH 3** was first reported at the same time as FINCH 1 in Mar 2019. The study compared filgotinib to MTX either as a monotherapy or in combination with background therapy in MTX-naïve patients. This compares to the SELECT-EARLY study for upadacitinib. The primary endpoint was ACR20 rates with filgotinib/MTX vs MTX. This was met as were multiple secondary endpoints on the hierarchical analysis
- As a monotherapy filgotinib improved the 24wk ACR20 primary endpoint, but this was only nominal, reflecting an exceptionally high MTX response. This measure was improved in all filgotinib arms vs placebo at all time points except 24wk where monotherapy did not reach significance. All other endpoints can only be considered hypothesis generating as they came after this measure on the hierarchical analysis. This included more stringent endpoints and radiographic progression
- 52wk data were reported at EULAR 2020 (**SAT0158**). Using a NRI analysis all filgotinib arms demonstrated statistically significant improvement over MTX on ACR20 scores (see below). Similar patterns were seen for ACR50 and ACR70. In general efficacy was similar for filgotinib 200mg with or without MTX
- DAS28-CRP remission as well as remission on other measures was also significantly improved at 52wk although in contrast to ACR responses the combination of MTX and filgotinib 200mg was nominally more efficacious

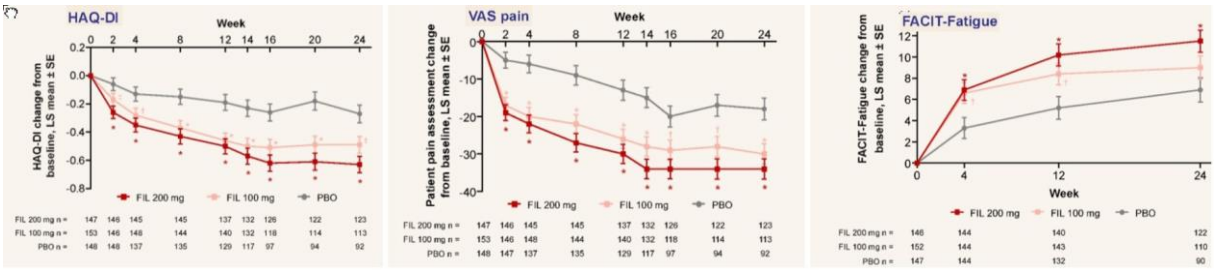
than filgotinib alone (see below). Finally, radiographic progression continued to be inhibited by filgotinib with or without MTX

Figure: Key data from FINCH 3 comparing filgotinib with or without MTX to MTX in MTX-naïve patients [Download image]



- In addition to filgotinib improving clinical measures in MTX-naïve patients, PROs including HAQ-DI, pain and fatigue were each improved and like the more stringent remission endpoints optimal efficacy was seen on a MTX background

Figure: Key PRO data from FINCH 3 [Download image]



- One particularly interesting sub-analysis presented at EULAR 2020 described the efficacy of filgotinib in patients with poor prognostic factors (**THU0188**). These patients, defined as RF+ or ACPA+; hsCRP ≥4mg/mL; DAS28-CRP >5.1 and pre-existing erosions made up 41% of the FINCH 3 cohort. Remission rates were generally similar in this group vs the overall cohort. The effect on radiographic progression (see below) was particularly impressive with mTSS increasing considerably on MTX in those patients with poor prognostic factors but reduced quite dramatically with filgotinib
- Comparison of data from those patients with vs without poor prognostic factors would have been interesting but the findings are nonetheless important as

HCPs may be more likely to prescribe new treatments such as filgotinib in the MTX-naïve setting in those patients with more aggressive disease

Figure: Filgotinib efficacy is maintained in patients with poor prognostic factors in FINCH 3 [Download image]

- As mentioned in our previous Rinvoq alert many of the endpoints employed in clinical trials are composites, yet it is important to demonstrate therapeutic benefit on multiple disease domains. This was reported for 12wk data in both FINCH 1 and FINCH 3 (see below)
- In general, filgotinib efficacy at 200mg in FINCH 1 and at both doses in FINCH 3 favors filgotinib over Humira and MTX monotherapy respectively. This not only offers reassurance on the efficacy of filgotinib but it is also of particular interest to the understanding of FINCH 1 data and particularly why efficacy was not superior to Humira on ACR20 measures at 12wk. On each of the individual measures treatment favors filgotinib vs Humira except the global assessment scores. On the other hand, benefit seems greatest on the hsCRP measure which may be a direct effect of JAK inhibition as described in previous alerts

Figure: Effect of filgotinib on individual components of ACR in both FINCH 1 and FINCH 3 [Download image]

- One central message around filgotinib is its JAK1 selectivity and safety. Given the current climate of VTE concern this may be very important. While safety data from individual studies were reported at EULAR, we focus on an integrated analysis of the FINCH program (**THU0202**) and this is where we complete our review of EULAR 2020. Data were included from 52wk comparisons with Humira or MTX as well as LTE studies. Rates of VTE remain very low and lower than MTX or Humira (see below). The big question now is whether filgotinib can achieve a differentiated label in terms of VTE safety. We suspect this will not be the case given the label language for Rinvoq despite the low rates of VTE in the integrated SELECT database analysis. It would be useful to compare rates with a rheumatoid arthritis population adjusted for baseline characteristics although this approach does not appear to have held sway with the regulators to date
- Serious infection and zoster rates were also similar to those seen with Humira and MTX. This is distinct from the situation with Rinvoq which produced increased rates on both although serious infection was only evident at the 30mg dose of Rinvoq
- Rinvoq produced a clear dose response on serious infection and zoster, and this is reflected in the approval of just the 15mg dose. In contrast there is not a clear dose response for filgotinib supporting approval of both doses and possibly an argument for differing MOAs which could feed into the discussion around not including VTE as a risk

Figure: Selected safety events reported from an integrated analysis of the FINCH program [Download image]

Dr Jon Goldhill
Pharma Information & Reports Ltd
UpdatesPlus/LeadDiscovery

www.leaddiscovery.co.uk
Maddomswood, Whatlington
E Sussex , TN31 5RA
England

Tel: +44 (0)1580 831877