September 13, 2016
UPDATE - Alert - UpdatesPlus-Rheumatoid Arthritis Gilead reports start of FINCH program evaluating filgotinib in rheumatoid arthritis

FINCH 1 study of filgotinib now listed on clinicaltrials.gov

- Over the past few weeks Gilead and Galapagos have gradually been releasing details of FINCH. As previously reported this program comprises three studies of JAKi, filgotinib
- FINCH 2 (bDMARD-ir) and FINCH 3 (MTX-naïve) have previously been listed on clinicaltrials.gov. Both have been the focus of previous alerts (see below)
- The final study of the program, FINCH 1 has now been listed. The study is a 52wk placebo- and Humira-controlled study in combination with MTX in an expected 1,650 MTX-ir patients
- Galapagos has previously described the study in a press release. The primary endpoint is ACR20 at week 12. The study will also include radiographic assessment at weeks 24 and 52. We understand that the study is powered to compare filgotinib to both placebo and Humira. No further information was provided in the clinicaltrials.gov entry

Comments: All studies in the FINCH program have now been disclosed. A summary of the studies is shown below with competing SELECT (ABT-494) and Lilly's baricitinib programs (this is also attached to this mail as a ppt). It seems that studies of ABT-494 and baricitinib in the cDMARD naive setting focus on patients with early disease and biomarkers suggestive of highly active progressive disease. For example the median duration of disease in RA-BEGIN was ≈2mo, while in SELECT-EARLY patients must be RF+ and ACPA+ (or just one with erosions). In the cDMARD-ir setting patients enrolled to RA-BEAM had established disease of 10yr duration. If the same is true for RA-BUILD Lilly may be in a position where they are targeting very early disease or well established disease but not in between. As previously discussed, FINCH 3 includes an early population but also includes patients with more established disease but who have yet to receive a cDMARD. This may allow Gilead/Galapagos to target those patients living in areas where time to diagnosis is relatively slow. These patients are more likely to have bone erosion than those living in areas where patients are rapidly triaged and initiated on therapy. This is of interest as there is some evidence that JAKi may promote bone healing. If FINCH 1 is able to enroll a broad range of MTX-ir patients in terms of disease advancement filgotinib may enjoy use across the pre-biologic spectrum. One apparent gap in the FINCH development program is a monotherapy arm. This contrasts with SELECT which includes SELECT-MONOTHERAPY. This could be an issue especially as increasingly companies target the 30-40% of patients unwilling or unable to use MTX

FINCH 3 study of filgotinib now listed on clinicaltrials.gov

- As reported last week the FINCH program designed to evaluate Filgotinib in rheumatoid arthritis has opened (see below)
- FINCH 2 a placebo controlled study in bDMARD-ir patients was listed on clinicaltrials.gov
- FINCH 1 (Humira and placebo controlled in MTX-ir patients) and FINCH 3 (placebo controlled in MTX-naive patients) were still to be listed
- FINCH 3 has now been listed. This study will compare filgotinib+MTX to MTX
- The primary endpoint is ACR20 at week 24. As described for FINCH 2 (below), ACR rates will be determined from day 1, potentially allowing the identification of fast efficacy onset characteristic of the JAKi class. The primary efficacy endpoint is expected to be reached Feb 2020
- Radiographic progression will also be assessed both at 24wks and 52wks
- We had originally commented that the study will enroll patients with early rheumatoid arthritis but will not be limited to this population
- Prior to listing it was not clear if patients who are MTX naive but who have previously been exposed to another cDMARD can be enrolled to FINCH 3. It has now been disclosed that patients will be excluded if they have previously received a csDMARD for longer than 3 months

Comments: The current ACR definition of early rheumatoid arthritis is a "duration of disease/symptoms of <6 months, where "duration" denotes the length of time the patient has had symptoms/disease". Based on the exclusion criteria FINCH 3 is expected to enroll a combination of patients with **1)** early disease receiving a csDMARD (but for <3 months) or still to receive a csDMARD (in practice and based on the guidelines early rheumatoid arthritis would initially be treated with a csDMARD; **2)** those with established disease who have been diagnosed within the current norms (ie approx 6 months) but failed to reach a target response to a first csDMARD (guidelines suggest that disease should be evaluated after 3 months of treatment to determine if a target has been reached and if it hasn't switching should be considered) or **3)** those with established disease and delayed diagnosis. Of note a 2011 paper reported that the mean time from symptom onset to diagnosis was 6 months in Europe. The DANBIO registry suggests more rapid diagnosis in Denmark (approx 3 months), while theAUDIT registry suggest a delay of 12 months in Catalonia. The MARI study suggests a delay in Italy as well. FINCH 3 could therefore support the use of filgotinib in both early rheumatoid arthritis and as a first or second line treatment of established disease. In Northern Europe we would expect patients to be enrolled with early or limited established disease following initial failure of first line csDMARD. In Southern Europe and developing regions patients could be enrolled with established disease but prior to initiation of a csDMARD (ie first line). While economics could prevent this if approved it should be noted that delay to treatment is associated with increased radiographic damage. On the other hand blocking the IL-6/JAK1 axis has been suggested to halt or reverse radiographic damage. Hence the first line use of a JAK1i may offer significant hope of bone salvage/repair in the delayed diagnosis cohort. We note that Abbvie is not investigating ABT494 in this established rheumatoid arthritis csDMARD naive population offering Gilead/Galapagos a potential advantage

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Gilead reports start of FINCH program evaluating filgotinib in rheumatoid arthritis

- Gilead is developing, under license from Galapagos, selective JAK1 inhibitor filgotinib
- The companies believe that due to this selectivity, the safety of filgotinib may be superior to competing JAKis
- In particular the risk of anemia or infection is suggested to be lower than with less selective JAKis
- Galapagos has now announced that the Phase 3 rheumatoid arthritis program, FINCH has been initiated in rheumatoid arthritis (see below for overview alongside Abbvie's competing SELECT program for ABT494)
- Dosing will be at 100 mg and 200 mg qd in females and males. This is important because the FDA initially limited dosing to 100mg in males in earlier rheumatoid arthritis studies due to preclinical suggestions of possible testicular AEs
    - **FINCH 1** is a 52wk placebo- and Humira-controlled study in combination with MTX in an expected 1,650 MTX-ir patients. The primary endpoint is ACR20 at week 12. The study will also include radiographic assessment at weeks 24 and 52. We understand that the study is powered to compare filgotinib to both placebo and Humira
    - **FINCH 2** is a 24wk placebo-controlled study in an expected 423 bDMARD-ir patients. The primary endpoint is ACR20 at week 12. Dosing will be on background cDMARD. The design of this study has now been uploaded to clinicaltrials.gov. The study is currently recruiting and expected to reach its primary end point in June 2018. Secondary endpoints are typical and as expected however it is of note that measures with be from day 1. While the frequency of assessment is unclear this could allow the rapid onset of efficacy in Phase 2 studies to be leveraged
    - **FINCH 3** is a 52wk study in an expected 1,200 MTX-naïve patients. Filgotinib will be administered in combination with MTX, as well as monotherapy. The primary endpoint is ACR20 at week 24. Radiographic progression will also be assessed. We understand that the study will enroll patients with early rheumatoid arthritis but will not be limited to this population. It is not clear if patients who are MTX naive but who have previously been exposed to another cDMARD can be enrolled to FINCH 3 or FINCH 1

Comments: Abbvie has already opened its SELECT program investigating competing JAK inhibitor ABT494 in five Phase 3 studies. The programs are compared below. Abbvie is investigating ABT494 in early rheumatoid arthritis in a monotherapy setting in SELECT-EARLY. Gilead is also looking at the MTX-naive setting (FINCH 3). This study appears to cover a broader population offering the potential advantage of treating MTX-naive patients who have relatively well established disease as well as early disease. The number of patients with established disease not

yet treated with MTX would be expected to be limited unless this includes patients previously treated with hydroxychloroquine, leflunomide and/or sulfasalazine. If such patients are being investigated filgotinib could gain a competitive advantage supporting its broader use prior to MTX. The determination of efficacy from day 1 in FINCH 2 is potentially important. JAKis appear to have a fast onset of action across indications including rheumatoid arthritis. It is unclear in efficacy is being determined so early in the SELECT program. If not Gilead could potentially establish a further competitive advantage

Dr Jon Goldhill
Pharma Information & Reports Ltd