Filgotinib

Filgotinib (**GLPG0634**) is a drug which is currently under investigation for the treatment of rheumatoid arthritis (RA) and Crohn's disease. It was developed by the Belgian biotech company Galapagos NV.

1 Mechanism of action

Filgotinib is a Janus kinase inhibitor with selectivity for subtype JAK1 of this enzyme. It is considered a promising agent as it inhibits JAK1 selectively. Less selective JAK inhibitors (e.g. tofacitinib) are already being marketed. They show long-term efficacy in the treatment of various inflammatory diseases. However, their lack of selectivity leads to dose-limiting side effects.[1] It is thought that inhibition of all JAK isoenzymes is beneficial in rheumatoid arthritis. However, pan-JAK inhibition might also lead to unwanted side effects that might not outweigh its benefits. This is the rationale for the development of newer and more selective inhibitors like filgotinib.

The signal transmission of large numbers of proinflammatory cytokines is dependent on JAK1. Inhibition of JAK2 may also contribute to the efficacy against RA. Nonetheless it is thought that JAK2 inhibition might lead to anemia and thrombopenia by interference with erythropoietin and thrombopoietin and granulocyte-macrophage colony-stimulating factor. Therefore, one might prefer to choose a more selective JAK1 inhibitor as a primary therapeutic option. Filgotinib exerts a 30-fold selectivity for JAK1 compared to JAK2.[2] It is however still to be seen to what extent JAK2 inhibition should be avoided.

2 Clinical trials

The efficacy of filgotinib is currently studied in a phase2b program (DARWIN trial 1, 2) with involvement of 886 rheumatoid arthritis patients and 180 Crohn's disease patients.

2.1 Phase 1 study

It was shown in phase 1 studies that the pharmacokinetics of filgotinib metabolism is independent of hepatic CYP450 enzymatic degradation. The drug metabolism is however mediated by carboxylesterases. There is no interference reported with the metabolism of methotrexate nor with any of the investigated transport proteins.[3]

2.2 Phase 2 study: Proof of concept (2011)

In November 2011 Galapagos released the results of their phase 2 study (identification: NCT01384422, Eudract: 2010-022953-40) in which 36 RA patients were treated who showed a suboptimal clinical response to methotrexate treatment.[4] Three groups of twelve patients were treated either with 200 mg filgotinib in a single dose, 200 mg divided in two doses or placebo. The primary end-point was the ACR20 score, which monitors improvements in the symptomatology of the patient. After the scheduled 4 weeks of treatment, 83% of the respondents showed an improved ACR20-score. Half of the treated patients showed a complete (or near complete) remission of the disease. There were no reports of anemia nor changes in lipidemia. The company stated in their press release that filgotinib is the first selective JAK1 inhibitor that shows clinical efficacy. As a result of this study, the company stated that "GLPG0634 shows one of the highest initial response rates ever reported for rheumatoid arthritis treatments".[5]

2.3 DARWIN 1 trial

The DARWIN 1 trial is a 24-week double blind placebo-controlled trial with 599 rheumatoid arthritis patients enrolled. All participants have moderate to severe RA and showed an insufficient response to standard methotrexate treatment. The trial compares three dosages of filgotinib as a once or twice per day regimen.[6] During the trial all participants remain on their methotrexate treatment. According to the company, the results of this trial are expected in July 2015.[7]

2.4 DARWIN 2 trial

The DARWIN 2 trial is a double blind placebo-controlled trial with 280 rheumatoid arthritis patients enrolled who show an insufficient response to standard methotrexate treatment. This trial, in contrast to the previous DARWIN 1 trial, methotrexate is discontinued. Therefore, this trial investigates filgotinib as a monotherapy.[8] The recruitment of DARWIN trial 2b ended in November 2014.[9] Preliminary results are expected in the second

quarter of 2015 and a full completion of the study is expected in the third quarter of 2015.

2.5 DARWIN 3 trial

Patients who complete DARWIN 1 and 2 will be eligible for DARWIN 3.

3 Time line

- June 2011: results of first phase 2 trial
- November 2014: initiation of DARWIN 1 and 2 trials
- April 2015: expected date of DARWIN 1 trial results
- June 2015: expected date of DARWIN 2 trial results

4 References

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[2] Van Rompaey, L; Galien, R; Van der Aar, E; Clement-Lacroix, P; Van der Aar, E; Nelles, L; Smets, B; Lepescheux, L; Cristophe, T; Conrath, K; Vandeghinste, N; Vayssiere, B; De Vos, S; Fletcher, S; Brys, R; Van't Klooster, G; Feyen, J; Menet, C (2013-10-01). "Preclinical characterization of GLPG0634, a selective inhibitor of JAK1 for the treatment of inflammatory diseases". *J Immunol*. 191(7). doi:10.4049/jimmunol.1201348.

[3] Florence, Namour; Julie, Desrivot; Van der Aa, Annegret; Tasset, Chantal; van 't Klooster, Gerben (2014). "Phase 1 and Phase 2 Data Confirm That GLPG0634, a Selective JAK1 Inhibitor, Has a Low Potential for Drug-Drug Interactions". *Meeting Abstracts*. 2014 ACR/ARHP Annual Meeting. American College of Rheumatology. 1481.

[4] "Safety and Preliminary Efficacy of GLPG0634 in Methotrexate-refractory Active Rheumatoid Arthritis Patients".

[5] "Galapagos' GLPG0634 shows excellent efficacy and safety in rheumatoid arthritis Phase II study" (PDF) (Press release). Retrieved 2015-02-26.

[6] "Dose-finding Study of GLPG0634 as add-on to Methotrexate in Active Rheumatoid Arthritis Patients (DARWIN1)".

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[9] "Galapagos completes recruitment for Darwin 2 monotherapy study with GLPG0634 (filgotinib) in RA" (Press release). Galapagos NV. Retrieved 2015-02-26 – via GlobeNewswire.

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