R&D

Research & Development

Evi Narinx

Project Manager Development Operations

The Galapagos pipeline

We are a clinical-stage biotechnology company specialized in the discovery and development of medicines with novel modes of action, addressing disease areas of high unmet medical need. Our pipeline comprises programs ranging from discovery to Phase 3 clinical trials in inflammation, cystic fibrosis, fibrosis, osteoarthritis and other indications. Our highly flexible platform is applicable across many therapeutic areas. Our clinical stage programs include: filgotinib, which is currently in Phase 3 clinical trials in rheumatoid arthritis (RA), Crohn's disease (CD), and ulcerative colitis (UC); our cystic fibrosis (CF) portfolio of drugs aimed at a triple combination therapy for 90% of CF patients, for which we plan to initiate patient clinical trials by mid-2017; GLPG1690, our fully proprietary autotaxin inhibitor, which is concluding a Phase 2a trial for idiopathic pulmonary fibrosis (IPF); GLPG1972 for osteoarthritis (OA), which is expected to be dosed in a Phase 1b trial in U.S. patients in 2017; and MOR106, which is currently being dosed in atopic dermatitis (AtD) patients in a Phase 1b trial. Except for our CF program, these programs are derived from our proprietary target discovery platform.

We have collaborations with Gilead for filgotinib, with AbbVie for CF, with Servier for GLPG1972, and with MorphoSys for MOR106. The following table summarizes key information on our lead development programs as of the date of this annual report:

Area	Pre-clinical	Ph 1	Ph 2	Ph 3
RA	JAK1 filgotinib			
CD	JAK1 filgotinib			
UC	JAK1 filgotinib			
Sb & Fist. CD	JAK1 filgotinib			
CF	Potentiators '3067	'2451	'1837	
CF	C1 '2222			
CF	C2 '2737			
IPF	Autotaxin '1690			
OA	'1972			
AtD	MOR106			
IPF	'2938			
AtD	'2534			

partnered

Proprietary target discovery platform

Our target discovery platform provides a significant and substantial competitive advantage in our portfolio of novel mode of action medicines as it:

- closely mimics the *in vivo* situation through the use of primary human cell with relevant trigger and readout for a specific disease phenotype;
- identifies the optimal point to intervene in a disease pathway by knocking down of a given protein in these assays;
- enables us to rapidly analyze all of the drugable genome and select pharmaceutically tractable protein targets directly by their ability to regulate key disease biology.

Our product candidate filgotinib acts on a target whose role in the specific disease was discovered by us using our discovery platform and we believe is a proof of success of this approach. Filgotinib acts on JAK1, and we believe has potential for a best-in-class profile in Phase 3 clinical trials in RA, CD, and UC.

The human genome is made up of tens of thousands of genes which code for the proteins that make up the human body. Nearly all chronic diseases and disorders are caused by a disruption in the normal function of certain proteins. The main goal of pharmaceutical companies is to design drugs that alter the activity of these proteins so that normal function returns and the cause of the disease is minimized or eliminated. One of the main obstacles in discovering new drugs is to understand exactly which of the body's thousands of proteins play a key role in a particular disease. Once these proteins are discovered, they become targets for drug design. Finding these targets is one of the critical steps in the drug discovery process. Our approach to target discovery is unique as our discovery platform focuses on target identification using primary human cells, which we believe provides a good system to study the effect that a protein might have on the disease in the human body.

In order to study proteins in human cells, we take advantage of the distinctive properties of adenoviruses. Adenovirus is the virus that causes the common cold and has the capability to infect almost every type of human cell. The viruses that Galapagos works with have been made replication incompetent, meaning they do not replicate in the human cell they infect, and so do not interfere with the processes in the cell. We engineered the viruses to carry small pieces of DNA, specific for individual human genes. When the virus enters the cell, this DNA piece leads to the production of a short sequence of RNA that is processed in the cell to become "short interfering RNA", or siRNA, which specifically interferes with the mRNA of the protein it was designed for. By using these viruses, we can cause the cells to block, or "knock-down," the production of a certain protein, mimicking what a small molecule drug does in the human body. We built a collection with these adenoviruses, now in excess of 20,000 viruses, that addresses over 6,000 drugable genes.

Our drug discovery research is based on the targets discovered using this technology. Once a target is validated, it is tested against large collections of chemical small molecules to identify chemical structures that interact with the target and block or activate protein production. These chemical structures are then optimized to obtain "drug-like" characteristics followed by testing of the drug candidate in the clinic.

We believe that this discovery approach may increase the chances of success in bringing new mode of action drugs to the market. Since 2009, Galapagos has generated 32 pre-clinical candidates of which 24 have novel modes of action. Of these, 15 have entered the clinic, 11 with novel modes of action.

In addition to our pipeline of molecules in the clinic, we have multiple discovery programs which are advancing toward clinical development. Further to targets and molecules in RA, IBD, and CF, we are exploring new modes of action in OA, metabolic diseases, fibrosis, Hepatitis B virus, and immune inflammation.

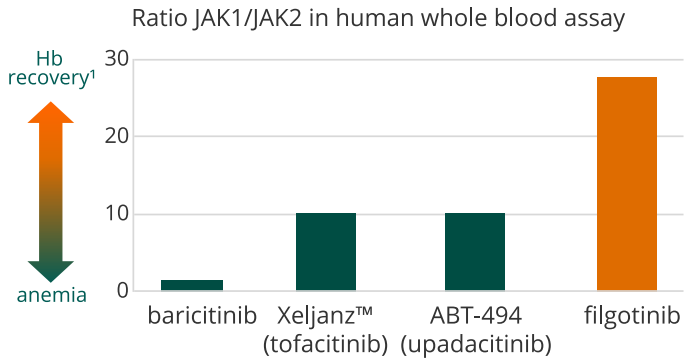
Filgotinib is a selective JAK1 inhibitor, potentially best-in-class

Based on results from our Phase 2 trials, we believe that filgotinib is a promising candidate for the treatment of RA, CD and potentially other inflammatory diseases. We are party to an exclusive Collaboration Agreement with Gilead to develop and commercialize filgotinib in multiple diseases. Under the terms of the collaboration, Gilead is primarily responsible for development and seeking regulatory approval of the licensed product. We are required to use commercially reasonable efforts as requested by Gilead to assist Gilead with certain development activities. Gilead initiated Phase 3 clinical programs in RA and CD, and a Phase 2b/3 program in UC in 2016.

Our filgotinib program in RA

RA is a chronic autoimmune disease that affects 2.9 million patients (of which approximately 1.5 million are being treated with biologics) in the U.S. and Europe. RA is characterized by inflammation and degeneration of the joints. Patients suffer from pain, stiffness, and restricted mobility due to a persistent inflammation of multiple joints, ultimately resulting in irreversible damage of the joint cartilage and bone. According to GlobalData, sales of RA therapeutics across the 10 main healthcare markets was USD 19.5 billion in 2015, with the current market being dominated by injectable, biological therapies. Biologics, mostly TNF therapies, need to be injected and often lose their effect over time, so there continues to be a considerable unmet need with regard to efficacy, safety, and convenience of use with existing treatments.

New oral therapies that target the Janus kinase, or JAK, signalling pathway are emerging to treat inflammatory diseases; JAK inhibitors, however, are associated with a range of side effects, including aberrations in low-density lipoprotein, or LDL, cholesterol and red blood and NK cell counts. Filgotinib, however, as so far not shown any of these side effects in Phase 2 clinical trials. In a human whole blood assay we demonstrated that filgotinib, with a 30-fold selectivity for JAK1 over JAK2, was more selective for JAK1 than any other compound known to us to be either approved for sale or in clinical development. We believe the high selectivity of filgotinib for JAK1 over JAK2 and JAK3, may allow for a positive efficacy profile, with an improved safety profile.

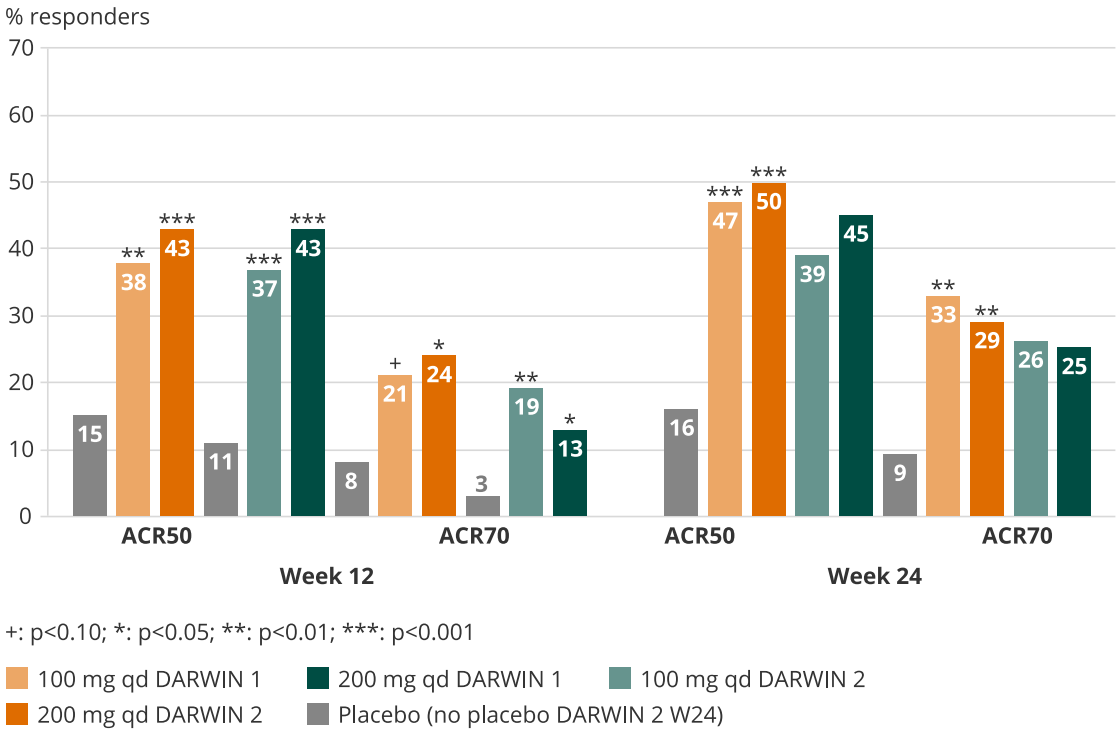


[1] A Pardanani, et al, Leukemia (2013) 27, 1322-1327

Our clinical program for filgotinib for RA

Clinical trials to date have shown that filgotinib is well-tolerated, with atherogenic index improvement and absence of anemia, and shows strong activity in treating RA. On top of this, we believe its once-a-day oral dosage and its low risk for drug-drug interactions make it convenient for patient use.

We reported final 24 weeks' data from DARWIN 1 and DARWIN 2 Phase 2b dose-range finding clinical trials in 2015. Both trials were double-blind, placebo-controlled for 24 weeks of treatment in patients with moderate to severe rheumatoid arthritis who showed an inadequate response to methotrexate. DARWIN 1 (594 patients) evaluated filgotinib as an addition to methotrexate, as once- and twice-daily administration (qd and bid dosing, respectively) at three daily dose levels. DARWIN 2 (283 patients) evaluated filgotinib as once-daily monotherapy administration (qd dosing) at three dose levels. Both trials achieved the primary endpoints (ACR20). Below are the ACR50 and ACR70 scores at 12 and 24 weeks for 100 and 200 mg qd in both DARWIN 1 and DARWIN 2:



+: p<0.10; *: p<0.05; **: p<0.01; ***: p<0.001

100 mg qd DARWIN 1 | 200 mg qd DARWIN 1 | 100 mg qd DARWIN 2
200 mg qd DARWIN 2 | Placebo (no placebo DARWIN 2 W24)

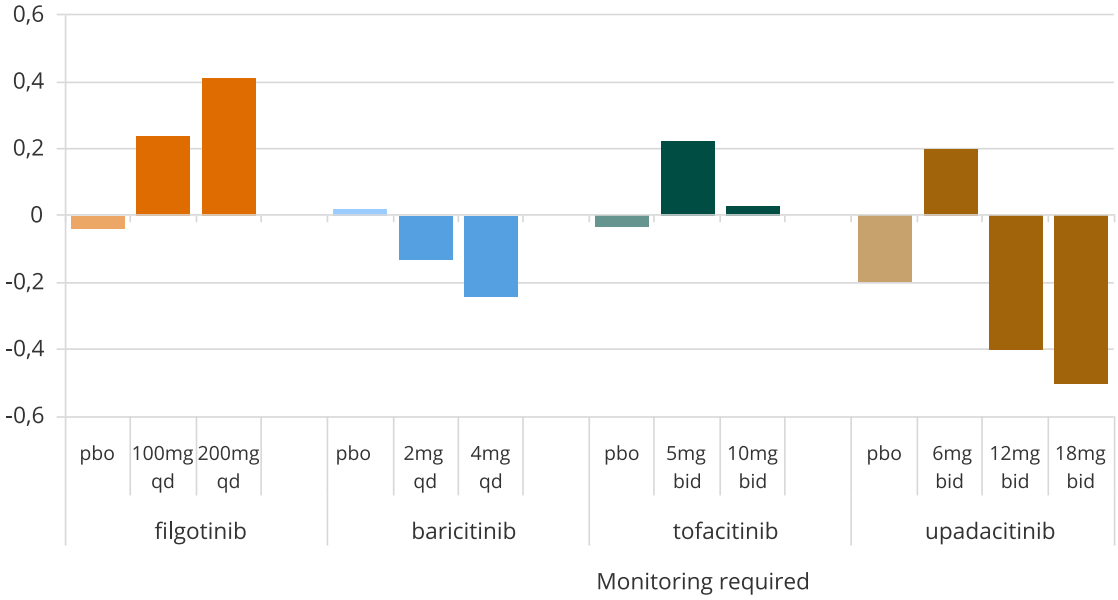
Overall, there was no statistically relevant difference between the once-daily and twice-daily dosing regimens in DARWIN 1. Both trials showed a rapid onset of activity, as of week one for ACR and DAS28(CRP) responses. In DARWIN 1 (200 mg bid) and in DARWIN 2 (100 mg qd) up to 50% of the patients reached low disease activity or remission. The 100 mg and 200 mg qd doses achieved similar levels of activity overall.

Safety data in both trials was similarly promising. In dose groups including placebo in both studies, 3.9% of patients stopped treatment during the trial for safety reasons. In DARWIN 1 patients reporting serious (2.5% overall) and non-serious treatment-emergent adverse events were evenly spread over the dose groups including placebo. Serious infections were reported in six patients, including one death on active treatment in the second half of the trial and for which the Data Safety Monitoring Board did not see a reason to pause or change the trial. No opportunistic infections were reported. Herpes zoster infection occurred in five patients, equally spread over placebo and filgotinib groups. In DARWIN 2 a higher discontinuation rate for safety was observed for placebo (5.6%) during the first 12 weeks of the trial compared to filgotinib treated patients (2.5%) up to week 24. Similar incidence of serious and non-serious treatment-emergent adverse events was reported, evenly spread over the dose groups including placebo. A higher rate of infections was observed in filgotinib (19% over 24 weeks) compared to placebo (10% up to week 12), with serious infections remaining limited (1.4% of filgotinib patients). No malignancies, tuberculosis, major adverse cardiac events, opportunistic infections, or deaths were reported in DARWIN 2.

On the basis of pre-clinical findings, males in the U.S. were restricted by the FDA to the 100 mg dose for DARWIN 1 and 2. Male reproductive hormones consequently were monitored in male patients taking 200 mg in DARWIN 1 and 2 outside the U.S. No clinically significant changes or discontinuations were observed for male reproductive hormones in either trial.

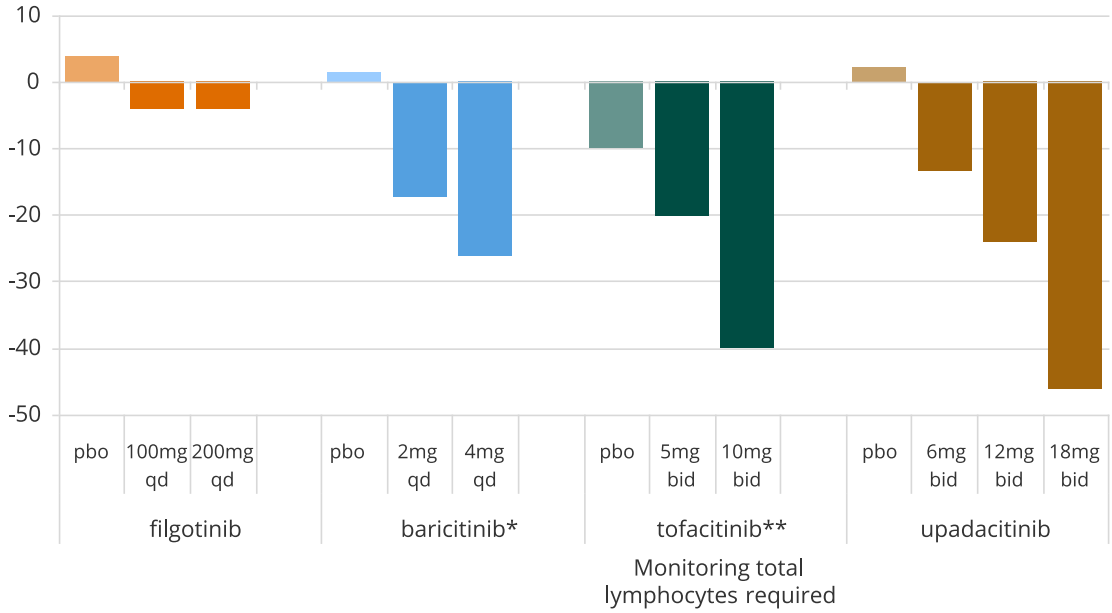
Consistent with its selective JAK1 inhibition, filgotinib treatment led to an improvement in hemoglobin (DARWIN 1 up to 0.5 g/dL, or a 4% increase from baseline, DARWIN 2 up to 0.4 g/dL, or 3.6% increase from baseline). In DARWIN 1, all lipid fractions including HDL and LDL increased, with the largest percentage increase in HDL, while in DARWIN 2 similar increases in LDL and HDL were maintained. Neutrophil levels remained stable after initial decline to mid-normal range at week four. Neither lymphocytes nor liver enzymes were impacted by treatment with filgotinib in either study.

Filgotinib's improvement in hemoglobin shown in DARWIN 1 and 2 potentially differentiates it when compared to impact on hemoglobin shown by other JAK inhibitors in RA trials:



Note: data from separate RA studies not conducted by the Company. **filgotinib** – Westhovens et al, and Kavanaugh et al, ARD 2016; **baricitinib** – Dougados et al, Annrheumdis 2016, RA-BUILD; **tofacitinib** – FDA AdComm briefing document May 2012; **upadacitinib** – Genovese et al A&R 2016 BALANCE 2.

Filgotinib's lack of impact on natural killer (NK) cells shown in DARWIN 1 and 2 potentially differentiates it when compared to the impact on NK cells shown by other JAK inhibitors in RA trials:



Note: data from separate RA studies not conducted by the Company. **filgotinib** – Westhovens et al, and Kavanaugh et al, ARD 2016; **baricitinib** – *Dougados et al, Annrheumdis 2016, RA-BUILD and Tanaka EULAR 2016 abstract RA-BEAM; **tofacitinib** – Van Vollenhoven abstract 2013, ** median CFB at W6; **upadacitinib** – Genovese et al A&R 2016 BALANCE 2.

Of the patients who have completed DARWIN 1 and DARWIN 2 and were eligible to continue, approximately 98% elected to participate in the DARWIN 3 follow-up trial. DARWIN 3 is a multi-center, open-label, long-term follow-up safety and efficacy trial of subjects who have completed either DARWIN 1 or DARWIN 2. All subjects have started the trial at the same dose level, either at 200 mg once per day or at 100 mg twice per day (except for males in the U.S. sites of these trials who receive a maximum daily dose of 100 mg), depending on the regimen administered during the preceding trial, with DARWIN 1 subjects continuing to use filgotinib in combination with MTX.

FINCH Phase 3 program with filgotinib in RA

In August 2016, our collaboration partner Gilead initiated the FINCH global Phase 3 program investigating the efficacy and safety of 100 mg and 200 mg filgotinib once daily, in RA patient populations, ranging from early stage to biologic-experienced patients:

FINCH 1 is a 52-week, randomized, placebo- and adalimumab-controlled trial in combination with methotrexate (MTX) in an expected 1,650 patients who have had inadequate response to MTX. The primary endpoint is ACR20 at week 12. The study will also include radiographic assessment at weeks 24 and 52.

FINCH 2 is a 24-week, randomized, placebo-controlled trial in an expected 423 patients who are on conventional disease-modifying anti-rheumatic drugs (cDMARD), and have had an inadequate response to biological treatment. The primary endpoint is ACR20 at week 12.

FINCH 3 is a 52-week, randomized trial in an expected 1,200 MTX-naïve patients to study filgotinib in combination with MTX, as well as monotherapy. The primary endpoint is ACR20 at week 24. Radiographic progression will also be assessed.

Gilead will perform a single dedicated male patient safety study concurrent to all Phase 3 programs. This study is expected to include RA, CD, and UC patients.

Inflammatory bowel disease

Our filgotinib program in inflammatory bowel disease (IBD)

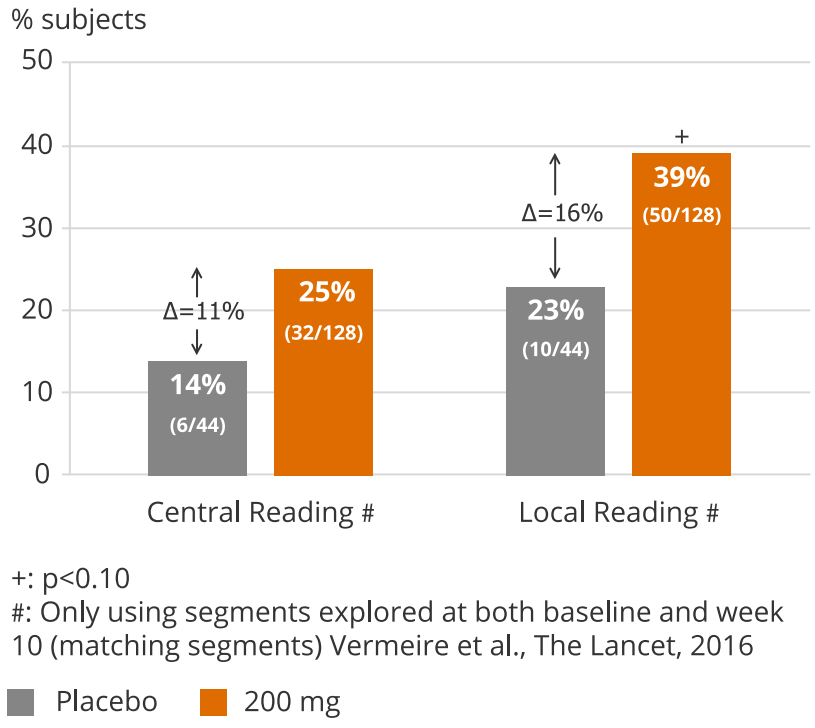
IBD includes CD and UC. We observed high activity and a favorable safety profile in a Phase 2 trial with filgotinib in CD. The profile we saw with filgotinib in this CD patient trial leads us to believe the candidate drug may show activity and tolerability in UC patient studies as well. IBD affects approximately 2 million patients (of which approximately 0.5 million are being treated with biologics) in the U.S. and Europe, and the market for IBD therapies is approximately $9 billion today, according to GlobalData. Current treatments are dominated by anti-TNF agents, with new biologic agents gaining some ground in second line treatment.

CD is an IBD of unknown cause, resulting in chronic inflammation of the gastrointestinal (GI) tract with a relapsing and remitting course. Today, only 10% of CD patients achieve prolonged clinical remission. There are currently no highly effective oral therapies approved for CD and, similar to RA, treatment is dominated by injectable, biologic treatments including anti-TNF therapies. Anti-TNF agents have improved the management of CD; however, not all patients respond to these drugs, and secondary loss of response is reported in up to 50% of patients per year in placebo-controlled trials. There continues to be a considerable unmet need with these existing treatments. Dysregulation of the JAK signaling pathway has also been associated with CD, and we believe that filgotinib, with its high selectivity for JAK1, is a highly attractive candidate for the treatment of CD. By inhibiting JAK1 but not JAK2, unwanted effects such as anemia may be prevented. This absence of anemia is of particular importance to IBD patients, who frequently experience fecal blood loss.

Increased activity and focus from pharmaceutical companies has led to more clinical trials of oral therapies in CD. AbbVie is conducting a Phase 2 trial with upadacitinib (pan-JAK inhibitor) which should read out in 2017. Celgene announced Phase 1b results with GED-0301 (SMAD-7), which showed early activity but limited endoscopic improvement. Celgene is also investigating ozanimod (S1P 1 and 5 receptor modulator) in Phase 2 in CD, with topline results expected in 2017. After two Phase 2 trials, Pfizer announced Xeljanz (pan-JAK inhibitor) will not be developed further in CD.

Our clinical program with filgotinib in CD

Our FITZROY Phase 2 trial (174 patients) evaluated filgotinib once-daily versus placebo in patients with moderate to severely active CD and mucosal ulceration. Patients recruited were either anti-TNF naïve or anti-TNF failures. FITZROY was the first trial in CD to require endoscopic confirmation of lesions at entry, and also to include a placebo control on endoscopy. The trial comprised two parts, each of 10 weeks duration: the first part investigated the safety and efficacy of filgotinib 200 mg once daily versus placebo, while the second part of the study investigated continued treatment through 20 weeks in an observational exploratory design. The FITZROY trial achieved the primary endpoint of clinical remission at 10 weeks: the percentage of patients achieving a Crohn's Disease Activity Index (CDAI) score lower than 150 was statistically significantly higher in patients treated with filgotinib (47%) versus patients receiving placebo (23%). The share of patients achieving 100-points clinical response (60%) also was significant versus those receiving placebo (41%). Improvement in quality of life, histopathology, endoscopy assessment and biomarkers of inflammatory activity were also observed at week 10. Overall mean change in histopathology scores at week 10 for patients treated with filgotinib (-3.5) versus placebo (-0.6) was significantly different, confirming the clinical responses in the tissues of patients. More patients on filgotinib showed >50% improvement in SES-CD (endoscopy) scores versus placebo patients at week 10:



Vermeire et al., The Lancet, 2016

Clinical responses were maintained from week 10 to week 20. Non-responders in the placebo arm from the first ten weeks received filgotinib 100mg in the second ten weeks and showed improvement in clinical remission during the second part of the trial.

Overall, in the FITZROY study at 20 weeks of treatment, filgotinib demonstrated a favorable safety profile consistent with the DARWIN studies in RA. An increase in hemoglobin was also observed in FITZROY, without difference between filgotinib and placebo. No clinically significant changes from baseline in neutrophils or liver function tests were observed.

Gilead initiated a Phase 3 trial (DIVERSITY) with filgotinib in CD in November 2016. The DIVERSITY Phase 3 trial investigates efficacy and safety of 100 mg and 200 mg filgotinib once-daily compared to placebo in patients with moderately to severely active disease including those with prior antibody therapy failure. Gilead will recruit approximately 1,300 patients from the U.S., Europe, Latin America, Canada, and Asia/Pacific regions. Men and women in the DIVERSITY trial will be randomized to receive placebo, 100 mg or 200 mg filgotinib. In the U.S., males may receive 200 mg if they failed at least one anti-TNF and vedolizumab, a monoclonal anti-integrin antibody marketed by Takeda.

In March 2017, Gilead initiated two additional Phase 2 studies with filgotinib in Crohn's disease: small bowel and fistulizing Crohn's disease.

Our clinical program with filgotinib in UC

UC is an inflammatory bowel disease resulting in ulcerations and inflammation of the colon and rectum. Unlike CD, UC involves damaging inflammation of only the colon and rectum. Although the introduction of anti-TNF biologics has improved the treatment of some patients, only 33% of patients will achieve long-term remission, and many patients lose their response to treatment over time. The medical need for improved efficacy is high and could likely be achieved by a new mechanism of action.

Increased activity and focus from potential competitors has led to more clinical trials of oral therapies in UC. Pfizer showed activity with Xeljanz (pan-JAK inhibitor) in Phase 3 UC trials and has filed for approval. AbbVie is conducting a Phase 2 trial with upadacitinib (pan-JAK inhibitor) which should read out in 2017. Celgene is investigating ozanimod (S1P 1 and 5 receptor modulator) in Phase 3 and GED-0301 (SMAD-7) in Phase 2 in UC.

Gilead initiated the SELECTION Phase 2b/3 trial in UC with filgotinib in December 2016. SELECTION investigates efficacy and safety of 100 mg and 200 mg filgotinib once-daily compared to placebo in patients with moderately to severely active disease including those with prior antibody therapy failure. Gilead will recruit approximately 1,300 patients from the U.S., Europe, Latin America, Canada, and Asia/Pacific regions. The SELECTION Phase 2b/3 trial in ulcerative colitis will include a futility analysis, serving as the Phase 2b part of this integrated Phase 2b/3 study. Men and women in SELECTION will be randomized to receive placebo, 100 mg or 200 mg filgotinib. In the U.S., males may receive 200 mg if they failed at least one anti-TNF and vedolizumab.

Our CF program

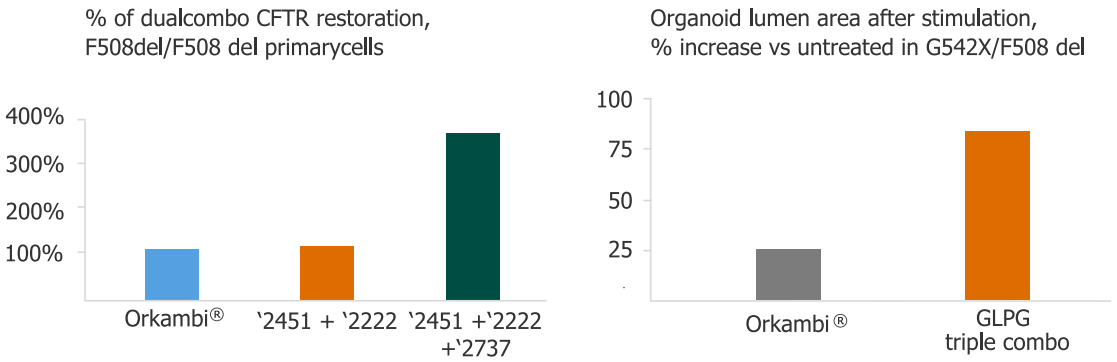
CF is a rare, life-threatening, genetic disease affecting the lungs and the digestive system, impacting approximately 80,000 patients worldwide with approximately 30,000 patients in the United States. CF patients carry a defective cystic fibrosis transmembrane conductance regulator, or CFTR, gene and are classified based on their specific mutation of the CFTR gene. The Class II mutation is present in approximately 90% of CF patients, with Orkambi®[3] being the only approved therapy for the underlying cause of CF in this mutation. Kalydeco is a disease-modifying treatment for Class III mutations, representing 4% of total CF patients. The market for CF therapies is robust and growing. According to Vertex Pharmaceuticals, approximately 9,000 patients were treated with Vertex therapies in 2016, and this they expect to grow to approximately 75,000 patients by 2024. Combined sales of Kalydeco and Orkambi were approximately $1.7 billion in 2016.

Despite the approval of Kalydeco and Orkambi, there is need for better therapies to improve pulmonary function for the majority of the patient population. Though many pediatric patients have normal lung function at the time of diagnosis, physicians generally believe that earlier treatments can have downstream benefits for the patient by slowing the deterioration in lung function.

[3] Orkambi is marketed by Vertex Pharmaceuticals

Two types of disease-modifying CFTR modulators have the current focus of CF drug developers. Potentiator molecules aim to restore the flow of ions through an activated CFTR by influencing the channel's opening. Corrector molecules aim to overcome defective protein processing by restoring proper folding of CFTR and allowing for increased cell surface expression. In order to improve CFTR function meaningfully for the largest patient group with Class II, and Class III/IV, and other mutations, we believe a combination of medicines will be required, comprising a potentiator and two novel corrector (which we refer to as C1 and C2) molecules.

In pre-clinical cellular assay studies, we consistently observed that combinations of potentiator, C1, and C2 correctors restore close to healthy CFTR function in lung epithelial cells and organoids cultured from Class II patients, both homozygous and heterozygous for F508del, respectively:



These results are suggestive of a compelling therapeutic option for these patients. We believe that our CF combination therapy may address the unmet need in both homozygous and heterozygous Class II patients, based on these *in vitro* results.

We aim to evaluate a once-daily, oral, triple combination CF therapy in patients starting in mid-2017, with additional trials with novel CF compounds initiating throughout 2017. We have developed a portfolio of lead and follow-on compounds from which to select the best potentiator and corrector molecules for our triple combination therapy:

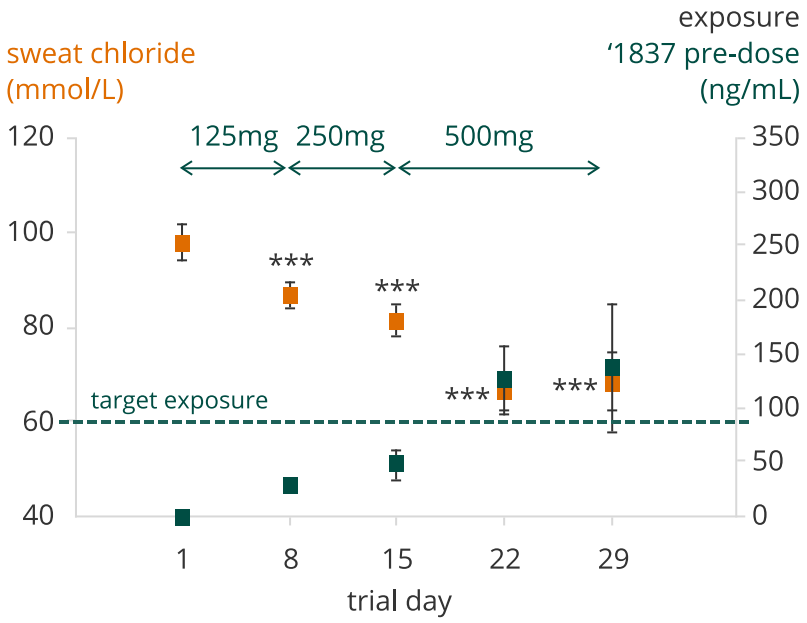
Pre-clinical	Ph1	Ph2	Status	
potentiator '1837			Ph2 results:	✓
potentiator '2451			Ph1 with '2222:	✓
potentiator '3067			Ph1 start:	✓
C1 corrector '2222			Ph2 start:	✓
C1 corrector '2851			Ph1 start:	H2 '17
C2 corrector '2737			Ph1 with '2222/'2451:	H1 '17
C2 corrector '3221			Ph1 start:	H2 '17

Our clinical program for CF

Our most advanced candidate drug for CF, potentiator GLPG1837, was the first potentiator since Kalydeco to show comparable results in G551D patients in the SAPHIRA 1 Phase 2a trial in late 2016.

SAPHIRA 1 was an open-label study of three doses of GLPG1837 in 26 patients with the G551D mutation. Of these patients, 25 patients were on stable Kalydeco treatment at screening and agreed to a one week washout prior to the start of dosing GLPG1837. One patient was naïve to Kalydeco. All subjects received GLPG1837 125 mg bid (twice-daily) for 7 days, immediately followed by 250 mg bid for 7 days and subsequently by 500 mg bid for 14 days.

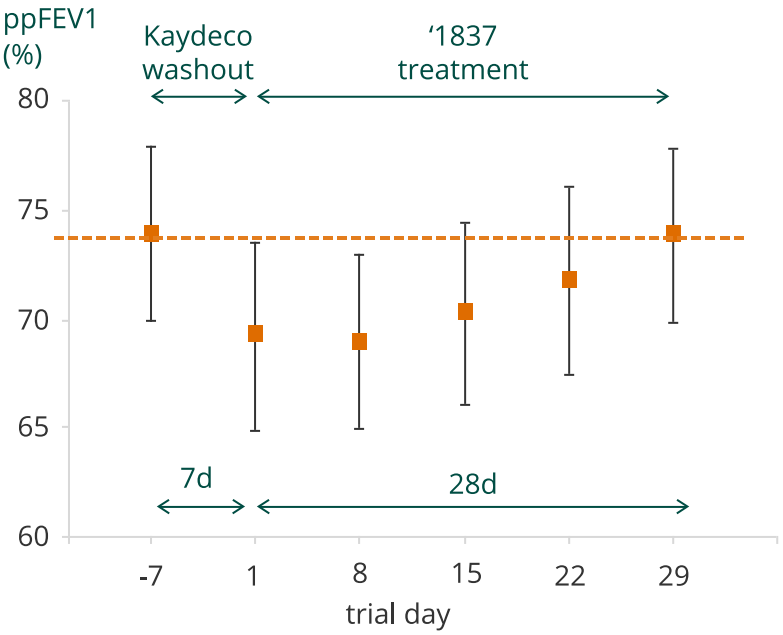
A statistically significant dose dependent decrease in sweat chloride concentration was observed. At the 500 mg bid dose, sweat chloride decreased from a mean value of 98 mmol/L at baseline to 66 mmol/L ($p < 0.0001$). For those patients exceeding the predicted target concentration, sweat chloride changed from a mean value of 94 mmol/L at baseline to 52 mmol/L. Below is an illustration of the changes in sweat chloride at increasing pre-dose exposures of GLPG1837 in blood plasma from SAPHIRA 1 in G551D patients who had washed out of Kalydeco prior to being treated with GLPG1837:



*** p<0.001

All '1837 exposure measurements are taken pre-dose escalation, except for days 22 and 29 in which there is no escalation. Here '1837 concentration measurements are taken prior to intake of first daily dosis.

25 patients were on stable treatment with Kalydeco prior to this study. For these patients, mean percent predicted FEV1 (ppFEV1) levels were 74% at screening (prior to Kalydeco washout). The one week wash-out resulted in a 5.4% mean decrease in absolute ppFEV1. At the end of treatment with GLPG1837, the ppFEV1 levels returned to the Kalydeco pre-washout levels. The figure below illustrates this restoration of ppFEV1 to screening levels, after washout and treatment with GLPG1837 in SAPHIRA 1:



Overall GLPG1837 was well tolerated in SAPHIRA 1, with observed treatment emergent adverse events being predominantly mild or moderate, and typical for a CF patient population. One patient dropped out of the study due to an increase in non-cardiac creatine phosphokinase.

We believe that SAPHIRA 1 represents a clinical validation of our *in vitro* systems, reinforcing our confidence in our approach to get to a triple combination therapy.

We initiated a Phase 1 trial for a second potentiator candidate GLPG2451 in May 2016. Follow-on potentiator GLPG3067 is currently in Phase 1. GLPG1837 has a twice-daily dosing profile, while GLPG2451 has potential for once-daily dosing.

We reported that GLPG2222, the first early binding (C1) corrector, showed favorable safety and tolerability in Phase 1 trials in healthy volunteers in June 2016. GLPG2222 was tested in single ascending doses up to 800 mg, and in multiple ascending doses up to 600 mg qd for 14 days in a double-blind, randomized, placebo-controlled study. The candidate drug was shown to be well-tolerated and no emerging safety signals observed in the dose range studied. Absorption of GLPG2222 was rapid and favorable. Pharmacokinetics of GLPG2222 support once-daily dosing regimens to be explored in further development. We believe GLPG2222 is well positioned for selection for the first triple combination therapy in 2017 and will be further explored in the clinic throughout the year to improve our understanding of dosing for the triple combination, including a Phase 2 trial on top of Kalydeco in Class III mutation patients initiated in January 2017. We dosed the first healthy volunteer with a combination of GLPG2451 and GLPG2222 in February 2017. Follow-on C1 corrector GLPG2851 will enter Phase 1 trials in 2017.

We initiated a Phase 1 trial for our first late binding (C2) corrector GLPG2737, the final component needed for a triple combination therapy, in November 2016. Topline results from this trial are expected in Q2 2017. We are developing follow-on C2 correctors which are expected to enter Phase 1 in 2017.

Our IPF programs

IPF is a chronic, relentlessly progressive fibrotic disorder of the lungs that typically affects adults over the age of 40. According to GlobalData, IPF affects approximately 109,000 patients in the U.S. and Europe and, as such, we have received orphan designation for our product candidate GLPG1690 in this indication from European authorities and we intend to seek orphan designation in the U.S. for our product candidates in IPF. The clinical prognosis of patients with IPF is poor, as the median survival at diagnosis is 2–4 years. Currently, no medical therapies have been found to cure IPF. The medical treatment strategy aims to slow disease progression and improve quality of life. Lung transplantation may be an option for appropriate patients with progressive disease and minimal comorbidities.

Regulatory agencies have approved Esbriet®[4] and Ofev®[5] for the treatment of mild to moderate IPF. Both Esbriet and Ofev have been shown to slow the rate of functional decline in IPF and are gaining ground as the standard of care worldwide. Combined sales of both drugs reached $1.1 billion in 2016, with 74% of global revenues being in the U.S. These regulatory approvals represent a major breakthrough for IPF patients; yet neither drug improves lung function, and the disease in most patients on these therapies continues to progress. Moreover, the adverse effects associated with these therapies are considerable (e.g., diarrhea, liver function test abnormalities with Ofev, nausea and rash with Esbriet). Therefore, there is still a large unmet medical need as IPF remains a major cause of morbidity and mortality. GlobalData estimates global sales of approved IPF drugs will grow to nearly $2.4 billion in 2022.

GLPG1690 is a potent and selective inhibitor of autotaxin (ATX) and is fully proprietary to us. We identified ATX as a potential target for IPF, after finding the target using an inflammation assay in our target discovery platform. Pharmacology and translational studies published by other parties since then suggest that ATX may also play a role in metabolic disease, arthritic pain, oncology, and lung disease. We evaluated GLPG1690 in a pre-clinical lung fibrosis model (bleomycin-treated mice) and observed effects on reducing the fibrotic score, numerically favoring GLPG1690 over Esbriet.

GLPG1690 completed a Phase 1 first-in-human trial in February 2015. In this trial, GLPG1690 was shown to be well-tolerated in up to 1000 mg daily dose and demonstrated a favorable pharmacokinetic profile. Moreover, in this trial GLPG1690 demonstrated the ability to reduce plasma lysophosphatidic acid (LPA) levels on a sustained basis, implying ATX engagement.

We are currently finalizing a Phase 2a trial (called FLORA) in IPF patients. FLORA is fully recruited and we expect topline results in the second half of 2017. This randomized, placebo-controlled double-blind trial includes up to 24 patients with IPF from 17 centers in Europe and evaluates treatment with 600 mg of GLPG1690 for 12 weeks. Primary objectives are to assess safety, tolerability, and pharmacokinetics and pharmacodynamics of GLPG1690 in IPF patients. Target engagement will be measured by LPA in plasma and bronchoalveolar lavage fluid, both at baseline and through 12 weeks of treatment. Secondary objectives include the evaluation of lung function, changes in disease biomarkers and quality of life.

In June 2016, we nominated a second candidate drug, GLPG2938, with an undisclosed novel mechanism of action aimed at IPF. This candidate is expected to enter Phase 1 trials in 2017.

[4] Esbriet (pirfenidone) is marketed by Roche.
[5] Ofev (nintedanib) is marketed by Boehringer Ingelheim.

Our OA program

Sometimes called degenerative joint disease or degenerative arthritis, OA is the most common chronic condition of the joints. OA can affect any joint, but it occurs most often in the small joints of the fingers, knees, hips, lower back and neck, and the bases of the thumb and big toe.[6] According to GlobalData, OA will be the fourth leading cause of disability by the year 2020. There are limited data on the total prevalence of OA. GlobalData estimates that diagnosed cases will grow from approximately 117 million cases in 2016 to approximately 131 million cases by 2024, with cases affecting hand, knee, and hip in that order of prevalence.

In normal joints, a firm, rubbery material called cartilage covers the end of each bone. Cartilage provides a smooth, gliding surface for joint motion and acts as a cushion between the bones. In OA, the cartilage breaks down, causing pain, swelling and problems moving the joint. As OA worsens over time, bones may break down and develop growths called spurs. Bits of bone or cartilage may chip off and float around in the joint. In the body, an inflammatory process occurs and cytokines (proteins) and enzymes develop that further damage the cartilage. In the final stages of OA, the cartilage wears away and bone rubs against bone leading to joint damage and more pain.[6]

Although OA occurs in people of all ages, it is most common in people older than 65. Common risk factors include obesity, previous joint injury, overuse of the joint, and weak thigh muscles. One in two adults will develop symptoms of knee OA during their lives. One in four adults will develop symptoms of hip OA by age 85. Current treatments for OA include weight loss, physical therapy, pain and anti-inflammatory medicines, and surgery, all of which address only the symptoms of the disease. There are currently no disease-modifying therapies available for OA, with drug sales for OA patients amounting to approximately $4 billion in generic painkillers in 2016.

GLPG1972 has a novel mode of action with potential application in OA, and was discovered by us under our collaboration agreement with Servier, a French pharmaceutical company.

In June 2016, we announced that GLPG1972, a first-in-class candidate drug aimed at treating OA, was shown to be safe and well tolerated in healthy human volunteers in a Phase 1 first-in-human trial. In this trial, dosing with GLPG1972 reduced a cartilage breakdown biomarker by up to 60% in these volunteers within two weeks. In 2017, we intend to conduct a Phase 1b patient clinical trial of GLPG1972 in the U.S., where we retained full commercial rights. Additional data resulting from the ongoing non-clinical program expected in the second quarter of 2017 will enable our collaboration partner Servier to decide on the exercise of the option to license the compound for further development into OA patient trials outside the U.S.

[6] From website of the Arthritis Foundation (arthritis.org)

Our AtD programs

Atopic dermatitis (AtD), is a chronic pruritic (itching) inflammatory skin disease that most frequently starts in early childhood, often persists into adulthood, but may also have an adult onset. According to GlobalData, sales of AtD therapies in the 7 major healthcare markets may reach $4 billion in 2016, with 35 million patients diagnosed with the disease and 10 million patients being treated in those markets. The main features of AtD are the impairment of the skin barrier and dysfunction of the immune system accompanied with dry skin and severe pruritus that is associated with cutaneous hyperactivity to various environmental stimuli. The pruritus (itching) may lead to sleep loss, anxiety, depression and impaired social life and is therefore considered as highest therapeutic need in AtD. Generic drugs are the approved standard of care, including immunomodulators cyclosporine and mycophenolate mofetil and topical treatments. There are disease-modifying biologics in development.

MOR106 is a human monoclonal antibody designed to selectively target IL-17C. IL-17C is a target discovered by us and has been shown to be distinct from other members of the IL-17 cytokine family, playing an important and pro-inflammatory role in certain skin disorders. MOR106 potently inhibits the binding of IL-17C to its receptor and thus inhibits its biological activity.

MOR106 arises from a discovery and co-development alliance between Galapagos and MorphoSys, in which both companies contribute their core technologies and expertise.

We are currently evaluating MOR106 in a randomized, double-blind, placebo-controlled Phase 1 trial, with the aim to evaluate safety and tolerability. As secondary endpoints, the trial will assess pharmacokinetics and potential immunogenicity of MOR106.

The first part of the trial was conducted in a single center in 56 healthy volunteers, evaluating single ascending doses (SAD) as intravenous infusion compared to placebo. MOR106 showed favorable safety and PK results when administered to healthy volunteers in the ongoing trial. Subsequently an investigation was started of multiple ascending doses (MAD) compared to placebo in approximately 24 patients with moderate to severe AtD in several European centers. Topline results of the complete trial, including the MAD part in patients and further results from the SAD part in healthy volunteers, are expected in the second half of 2017.

In June 2016, we nominated a second candidate drug for AtD, GLPG2534, with an undisclosed novel mechanism of action aimed at atopic dermatitis and which is different from the target of MOR106. This small molecule candidate is fully proprietary to us and is expected to enter Phase 1 trials in 2017.