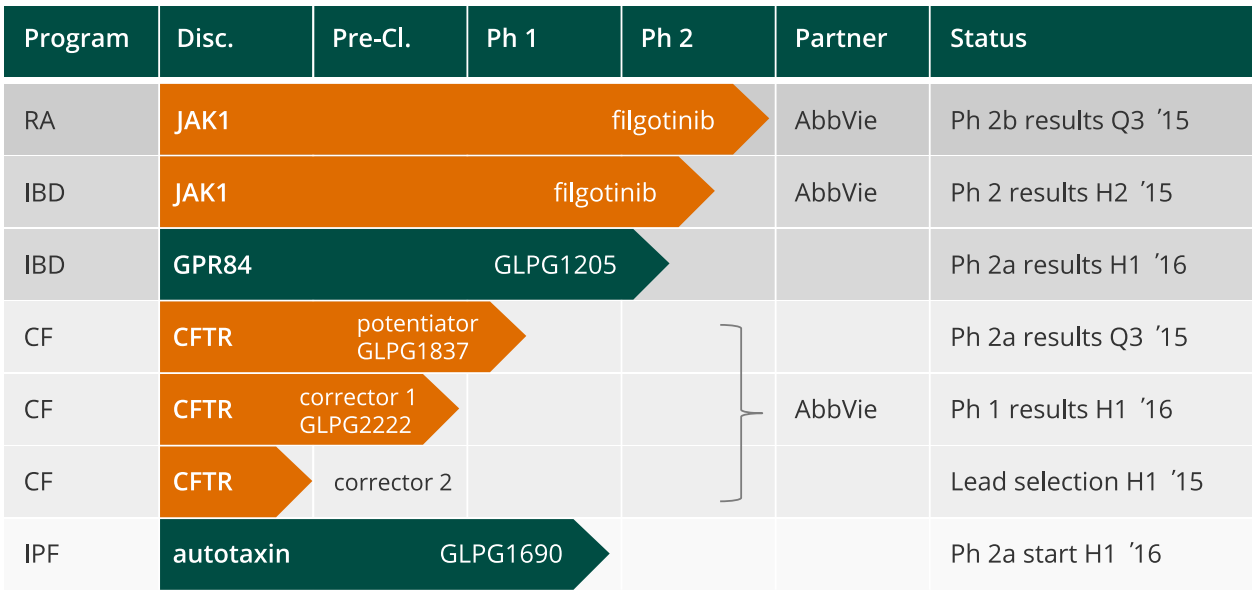
R&D

Research & Development

I get very passionate about my work, and I believe in what I do. I like having the freedom to create, improvise and do new exciting research. My job challenges me every day in different ways.

Dr Christel Menet
Director Medicinal Chemistry

The Galapagos pipeline



Novel, proprietary target discovery platform

Galapagos' target discovery platform provides a significant and substantial competitive advantage in its 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

Galapagos' product candidates in Phase 2 clinical development, filgotinib and GLPG1205, both act on targets whose role in the specific disease were discovered by Galapagos using its discovery platform and are proof of success of this approach. Filgotinib acts on JAK1 and could confirm potential for a best-in-class profile in rheumatoid arthritis and Crohn's disease clinical trials. GLPG1205 acts as a GPR84 inhibitor which has shown activity in an inflammatory bowel disease animal model and is currently being tested in a Phase 2 ulcerative colitis trial.

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.

Galapagos' approach to target discovery is unique as its discovery platform focuses on target identification using primary human cells, which provides a good system to study the effect that a protein might have on the disease in the human body. Moreover, Galapagos concentrates its efforts on so called "drugable" proteins and utilizing high throughput screening technology to screen these protein targets efficiently in human cells. This discovery approach may increase the chances of success in bringing new mode of action drugs to the market. Since 2009, Galapagos has generated 22 pre-clinical candidates using the discovery platform, of which 16 have novel modes of action. Of these, 10 have entered the clinic, of which seven have novel modes of action.

In order to study proteins in human cells, Galapagos takes 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 adenoviruses Galapagos works with have been engineered to act as a shuttle vehicle, allowing the delivery of specific pieces of DNA into human cells. Additionally, these viruses 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. Galapagos has 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, that specifically interferes with the mRNA of the protein it was designed for. By using these viruses, Galapagos 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. Galapagos has built a collection with these adenoviruses, now in excess of 20,000 viruses, that addresses over 6,000 drugable genes.

Galapagos' 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.

In addition to its pipeline of molecules in the clinic, Galapagos has 25 different discovery programs which are advancing toward clinical development. In addition to additional targets and molecules in RA, IBD, and CF programs, Galapagos is exploring new modes of action in osteoarthritis, metabolic diseases, fibrosis and immune inflammation.

Filgotinib program in rheumatoid arthritis

The RA market and limitations of current treatments

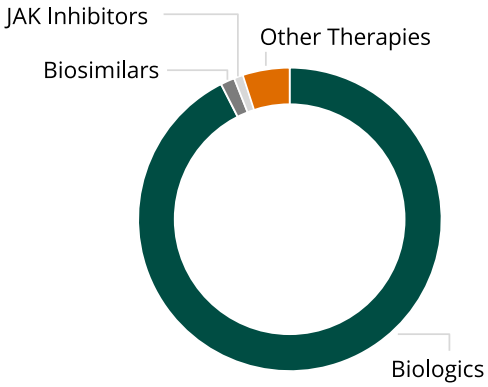
RA is a chronic autoimmune disease, characterized by inflammation and degeneration of the joints. It affects almost 1% of the adult population worldwide, with onset typically between the ages of 30 and 50 years, and with a high prevalence in women. Patients suffer from pain, stiffness, and restricted mobility due to a persistent inflammation of multiple joints, which ultimately results in irreversible damage of the joint cartilage and bone. As RA develops, the body's immune cells perceive the body's own protein as foreign and cells called lymphocytes react to this protein. The reaction then causes the release of cytokines, which are chemical messengers that trigger more inflammation and joint damage. The inflammation may spread to other areas in the body, ultimately causing not only joint damage but also chronic pain, fatigue, and loss of function. Inflammation has also been linked to heart disease and the risk of having a heart attack. RA nearly doubles the risk of having a heart attack within the first 10 years of being diagnosed, according to the ACR.

The primary goals in the treatment of RA are to control inflammation and slow or stop disease progression. Initial therapeutic approaches relied on disease-modifying anti-rheumatic drugs, or DMARDS, such as methotrexate and sulphasalazine. These oral drugs work primarily to suppress the immune system and, while effective in this regard, the suppression of the immune system leads to an increased risk of infections. These drugs are also associated with side effects including nausea, abdominal pain, and serious lung and liver toxicities. Further, because these drugs often take on average from 6-12 weeks to take effect, rheumatologists may also couple them with over-the-counter pain medications or non-steroidal anti-inflammatory drugs, or NSAIDs, to treat the pain and inflammation. Despite their serious shortcomings, DMARDS are still considered first-line therapies.

The development of monoclonal antibodies and biologics represented a significant advance in RA treatment. Biologic therapies involve the use of antibodies or other proteins produced by living organisms to treat disease. In some people with arthritis, the TNF protein is present in the blood and joints in excessive amounts, thereby increasing inflammation, along with pain and swelling. Biologic therapies have been developed to address this overproduction of TNF by disrupting communication between the body's immune cells. Thus, they block the production of TNF or are designed to attach to and destroy the body's immune B-cells, which play a part in the pain and swelling caused by arthritis. Anti-TNFs are currently the standard of care for first- and second-line biologic therapies for RA patients who have an inadequate response to DMARDS. Since anti-TNF drugs function through a suppression of the immune system, they also lead to a significant increase in the risk of infections. In addition, all approved anti-TNFs need to be delivered by injection or intravenously, which is inconvenient and painful for some patients, and in some cases self-injection can be particularly difficult for patients who suffer joint pain and damage from RA.

Not all patients achieve sufficient clinical response or maintain clinical response to anti-TNFs over time, resulting in a need to switch or cycle to a new therapy to control their disease. Approximately one-third of RA patients do not adequately respond to anti-TNFs. In addition, anti-TNFs are associated with low rates of disease remission and the response to these agents is not typically durable. In more than 30% of this population, alternative treatment approaches are needed. A significant number of patients treated with an anti-TNF will be cycled to their second and third anti-TNF within 24 months of anti-TNF therapy initiation. A prospective cohort study of RA patients from a UK national register of new anti-TNF treatments showed that, within 15 months of treatment, 12% cycle to a second anti-TNF due to inefficacy, and 15% cycle to a second anti-TNF due to toxicity. Ultimately, 30% of patients need an alternative to anti-TNF treatment. Therapeutic cycling is a serious issue for patients because the efficacy of each successive drug is not known typically for several months, which contributes to progression of disease and continued irreversible structural joint damage. For RA patients who fail or for whom anti-TNFs are contraindicated, the oral agent JAK inhibitors and biologics with distinct mechanisms are in development.

2013 RA Worldwide Market: $15.6B



Despite these limitations, the global market for RA therapies is large and growing rapidly. The market for RA therapies across the 10 main healthcare markets was $15.6 billion in 2013 and is expected to grow in excess of $19 billion by 2023, according to a December 2014 GlobalData PharmaPoint report. Injectable, biological therapies are the largest component of this market.

However, despite the prevalence of biologics in the treatment of RA, there continues to be a considerable unmet need with regard to efficacy, including sustained efficacy, safety, and convenience of use with these existing first line treatments.

The potential of JAK inhibitors

The family of JAKs is composed of four tyrosine kinases, JAK1, JAK2, JAK3 and Tyk2 that are involved in the JAK signaling pathway, which regulates normal hematopoiesis, or blood making, inflammation and immune function. Dysregulation of the JAK signaling pathway has been associated with a number of diseases, including RA, psoriasis and other chronic inflammatory diseases. Accordingly, the JAK family has long been an area of interest for drug developers working in these areas.

A growing body of clinical data suggests that the level of selectivity of a JAK therapeutic is highly correlated to its efficacy and safety profile. For example, JAK1 is known to interact with the other JAKs, among others, to transduce cytokine-driven pro-inflammatory signaling, which leads to inflammation in human tissues. Therefore, inhibition of JAK1 is believed to be of therapeutic benefit for a range of inflammatory conditions as well as for other diseases driven by JAK-mediated signal transduction. In contrast, inhibition of the other three kinases (JAK2, JAK3, and TYK2) may not

be required for the anti-inflammatory effect, whereas their inhibition may contribute to side effects. For example, inhibition of JAK2 has been linked to anemia, and inhibition of JAK3 to immunosuppression. Non-selective JAK inhibitors have been shown to increase LDL cholesterol. Therefore, the desired efficacy and safety profile of any JAK inhibitor may be directly linked to the selectivity of the product.

In November 2012, Xeljanz was approved by the FDA as the first and only JAK inhibitor for RA approved for commercial sale in the United States. Xeljanz is intended for the treatment of adult patients with RA who have had an inadequate response to, or who are intolerant of, methotrexate. Xeljanz is a small molecule suitable for oral administration and has strong binding affinity for JAK3 and JAK1, and weaker affinity for JAK2. The safety and effectiveness of Xeljanz were evaluated in seven clinical trials in adult patients with moderately to severely active RA. In all of the trials, patients treated with Xeljanz experienced improvement in clinical response and physical functioning compared to patients treated with placebo. However, the use of Xeljanz has been associated with a range of side effects, including anemia (reduced hemoglobin levels) and elevations in both liver enzyme and lipid levels. For example, in controlled clinical trials for Xeljanz, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure, including a 15% increase in LDL cholesterol in the Xeljanz 5 mg twice daily arm, the approved dosage in the United States. Xeljanz was not approved in Europe. Accordingly, there continues to be a significant unmet medical need in RA and other inflammatory diseases for an orally administered approach with a more favorable side effect profile.

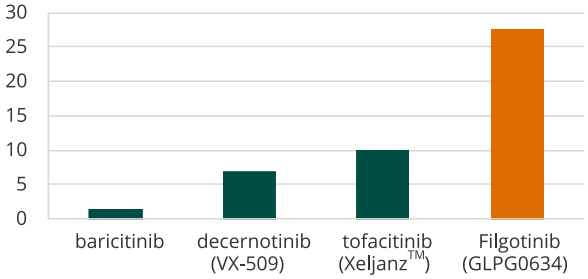
Galapagos' filgotinib program for RA

Due to its high selectivity for JAK1, filgotinib may have the potential to offer an improved side effect profile and improved efficacy in RA patients as compared to other JAK inhibitors which are less selective for JAK1. Filgotinib is currently being evaluated in three ongoing Phase 2b trials, which are referred to collectively as DARWIN, in patients with moderate to severe RA who have an inadequate response to methotrexate (MTX) a common first line treatment for RA. Galapagos expects topline results from 12 weeks of treatment in the DARWIN trials (DARWIN 1 and 2) in April 2015 and final results from 24 weeks of treatment in July 2015. In addition, Galapagos is conducting DARWIN 3, a long-term follow-up trial that allows patients to remain on filgotinib treatment. Of the patients who have completed DARWIN 1 and DARWIN 2, 98% of eligible patients has elected to participate in the DARWIN 3 follow-up trial.

In an in-house human whole blood assay, Galapagos demonstrated that filgotinib was more selective for JAK1 than any other known compound that is either approved for sale or in clinical development, with a 30-fold selectivity for JAK1 over JAK2. Galapagos anticipates that the high selectivity of filgotinib for JAK1 may allow for efficacy equal to or better than that of other approved RA therapies, with an improved safety profile due to less selectivity for JAK2 and JAK3.

Selectivity of JAK Inhibitors in RA

Ratio JAK1/JAK2 in Human Whole Blood Assay



Moreover, filgotinib may have the potential to be used as a once-daily therapy, thereby potentially improving ease of administration and patient compliance. Filgotinib has the potential to be used safely with concomitant medications, an important feature for this patient population since many of these patients are on other therapies to address co-morbities or other diseases.

Through the extensive DARWIN clinical programs, Galapagos aims to demonstrate the following clinical and product benefits of filgotinib for the treatment of RA:

- Safety: That filgotinib will be well tolerated, will show absence of treatment-induced anemia, will show no increase of LDL/HDL balance and will result in an overall lower infection rate as compared to other approved RA therapies.
- Efficacy: That filgotinib will enable rapid onset of action with durable efficacy equal to or better than approved biologics and approaches such as anti-TNFs.
- Convenience: That filgotinib will enable oral, once-daily dosing.

- Combination with other therapies: That filgotinib will be able to be safely combined with other therapies commonly prescribed to RA patients, due to its lack of drug-drug interactions.

Filgotinib is currently being evaluated in three ongoing Phase 2b trials in patients with moderate to severe RA and who have demonstrated an inadequate response to MTX. DARWIN 1 and DARWIN 2 are dose finding trials. DARWIN 3 is a long-term follow-up trial that allows patients to roll-over from DARWIN 1 and 2 trials and remain on treatment. These global Phase 2b trials are fully recruited. Topline results after 12 weeks of treatment in the DARWIN studies are expected in April 2015 and final results after 24 weeks of treatment for these studies are expected in July 2015.

Galapagos has an exclusive collaboration agreement with AbbVie to develop and commercialize filgotinib. Under this agreement, Galapagos is responsible for the advancement of three Phase 2 trials in RA and CD. If AbbVie determines that the first two of these trials (DARWIN 1 and 2) meet certain specified criteria, AbbVie will be deemed to have in-licensed the compound. If the specified criteria are not met, AbbVie has the opportunity to elect to in-license the compound following our delivery of the final data package from these trials. Should AbbVie in-license these programs, AbbVie will assume sole responsibility for Phase 3 clinical development, global manufacturing and commercialization of filgotinib. Galapagos retains an option to exercise certain co-promotion rights in the Netherlands, Belgium and Luxembourg, and Galapagos will be entitled to potential future regulatory and commercial milestone payments and royalties on global commercial sales across all approved indications for this compound, if any.

Galapagos research in inflammatory bowel disease (IBD)

Galapagos is also researching inflammatory bowel disease (IBD): filgotinib in Crohn's disease (CD) and GLPG1205 in Phase 2 addressing a novel target in ulcerative colitis (UC). IBD is a group of inflammatory conditions in the colon and small intestine including CD and UC.

CD and limitations of current treatments

CD is an IBD causing chronic inflammation of the gastrointestinal, or GI, tract with a relapsing and remitting course. The prevalence estimates for CD in North America range from 44 cases to 201 cases per 100,000 persons. In Europe, prevalence varies from 37.5 cases to 238 cases per 100,000 persons, according to a January 2014 GlobalData PharmaPoint report. The disease is slightly more common in women, with a peak incidence at the age of 20 to 40 years. The cause of CD is unknown; however, it is believed that the disease may result from an abnormal response by the body's immune system to normal intestinal bacteria.

The disease is characterized by inflammation that may affect any part of the GI tract from mouth to anus, but most commonly the distal small intestine and proximal colon, causing a wide variety of symptoms including anemia, abdominal pain, diarrhea, vomiting, and weight loss. The characteristic inflammatory response of CD is focal transmural inflammation, frequently associated with granuloma formation, which may evolve to progressive damage over time.

Treatment of CD will depend on severity of the disease. The main goal of treatment is to stop the inflammation in the intestine, prevent flare-ups and keep patients' disease in remission. While mild to moderate symptoms may respond to an antidiarrheal medicine, antibiotics, and other medicines to control inflammation, severe symptoms are often treated with anti-TNF agents. Anti-TNF agents, however, do not work for all patients, and, in patients who do find therapeutic benefit, they can lose their effect over time as a result of relapse. Anti-TNF agents have also demonstrated side effects arising from long term suppression of the immune system including increased rate of infections. Unlike in RA, few biologics have been approved in CD and, as such, caregivers have a more limited number of available treatments. To date, there are no oral therapies approved for CD.

The market for CD therapies, across the 10 main healthcare markets, was approximately $3.2 billion in 2012 and is estimated to exceed $4.1 billion in 2022, according to a January 2014 GlobalData PharmaPoint report, driven primarily by use of anti-TNF agents.

The potential of JAK inhibitors for the treatment of CD

As with RA, dysregulation of the JAK-STAT signaling pathway has been associated with CD. Accordingly, drugs with high selectivity for JAK1 and less selectivity for JAK2 and JAK3 could be attractive candidates for development in CD. By inhibition of JAK1 but not JAK2, unwanted effects such as anemia may be prevented. Complications surrounding anemia are of particular importance to IBD patients, who frequently experience fecal blood loss. There continues to be a significant unmet medical need in CD treatment for an oral, highly selective JAK1 inhibitor that allows for the efficacy benefits of a highly selective JAK1 inhibitor with a more favorable side effect profile driven by less selectivity to JAK2 and JAK3.

Filgotinib is currently in Phase 2 clinical development for CD and has shown favorable activity in pre-clinical models for IBD. Galapagos expects to complete recruitment for FITZROY, our Phase 2 trial in CD with filgotinib, in 2015. Galapagos expects topline results from 10 weeks of treatment in the CD trial in the second half of 2015, followed by the 20 weeks data in Q1 2016. Filgotinib is being developed under an exclusive collaboration agreement with AbbVie, under which Galapagos expects a licensing decision by AbbVie in the second half of 2015.

UC and limitations of current treatments

UC is an IBD causing chronic inflammation of the lining of the colon and rectum. Unlike CD, UC involves damaging inflammation of only the colon and rectum. The disease often presents in young adulthood. In patients with moderate to severe UC the symptoms include frequent loose bloody stools, anemia, abdominal pain, fever, and weight loss.

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 likely could be achieved by a new mechanism of action.

The ultimate aim in the treatment of UC is to change the natural course of the disease by slowing down or halting its progression, thus avoiding surgery or hospitalization. The current standard treatment for mild-to-moderate UC is 5-aminosalicylates, or 5-ASA. Given either orally or rectally, these drugs work to decrease inflammation in the lining of the intestines. For patients who do not respond to 5-ASA, other treatment options include corticosteroids, immunomodulators, biological therapies, such as anti-TNF agents, and cyclosporin. Surgery may be necessary for patients with refractory UC. The global market for UC therapies was approximately $4.2 billion in 2012, and is estimated to grow to $6.7 billion in 2022, driven primarily by use of biological therapies, according to a September 2014 GlobalData PharmaPoint report.

Over the last decade, changes in UC treatment strategies, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for patients. Although the introduction of anti-TNF agents has changed the treatment of refractory patients dramatically, only one-third or fewer patients will achieve long-term remission, and many of those patients will eventually lose their response. In addition, anti-TNF agents have known side effects including increased risk of infections. As such, the medical need in this patient segment is still considered to be significant.

Galapagos' clinical program for GLPG1205 for UC

GLPG1205 is a selective inhibitor of GPR84, a novel target for inflammatory disorders. GPR84 is a protein involved in the regulation of macrophages, monocytes, and neutrophils in the human immune system and is overexpressed in inflammatory disease patients. GPR84 antagonists such as GLPG1205 present a novel mode of action for the treatment of inflammatory diseases. GLPG1205 targets diseases associated with up-regulation of GPR84 on inflammatory leukocytes, such as IBD and neuro-inflammatory disease, i.e., multiple sclerosis, through once-daily oral dosing. Galapagos identified GPR84 as playing a key role in inflammation, using its target discovery platform and determined in a pre-clinical IBD model that GLPG1205 prevents colitis disease progression. GLPG1205 is fully proprietary, where Galapagos retains all development and commercial rights.

Galapagos initiated ORIGIN, a 60-patient 12-week Phase 2a clinical trial of GLPG1205 in UC and the first patients received treatment in early 2015. The Phase 2a clinical trial is a multi-center, randomized, double-blind, placebo-controlled, exploratory proof-of-concept trial with two parallel 12 weeks of treatment groups in subjects with moderate to severe UC.

Galapagos programs in cystic fibrosis

The unmet need in CF

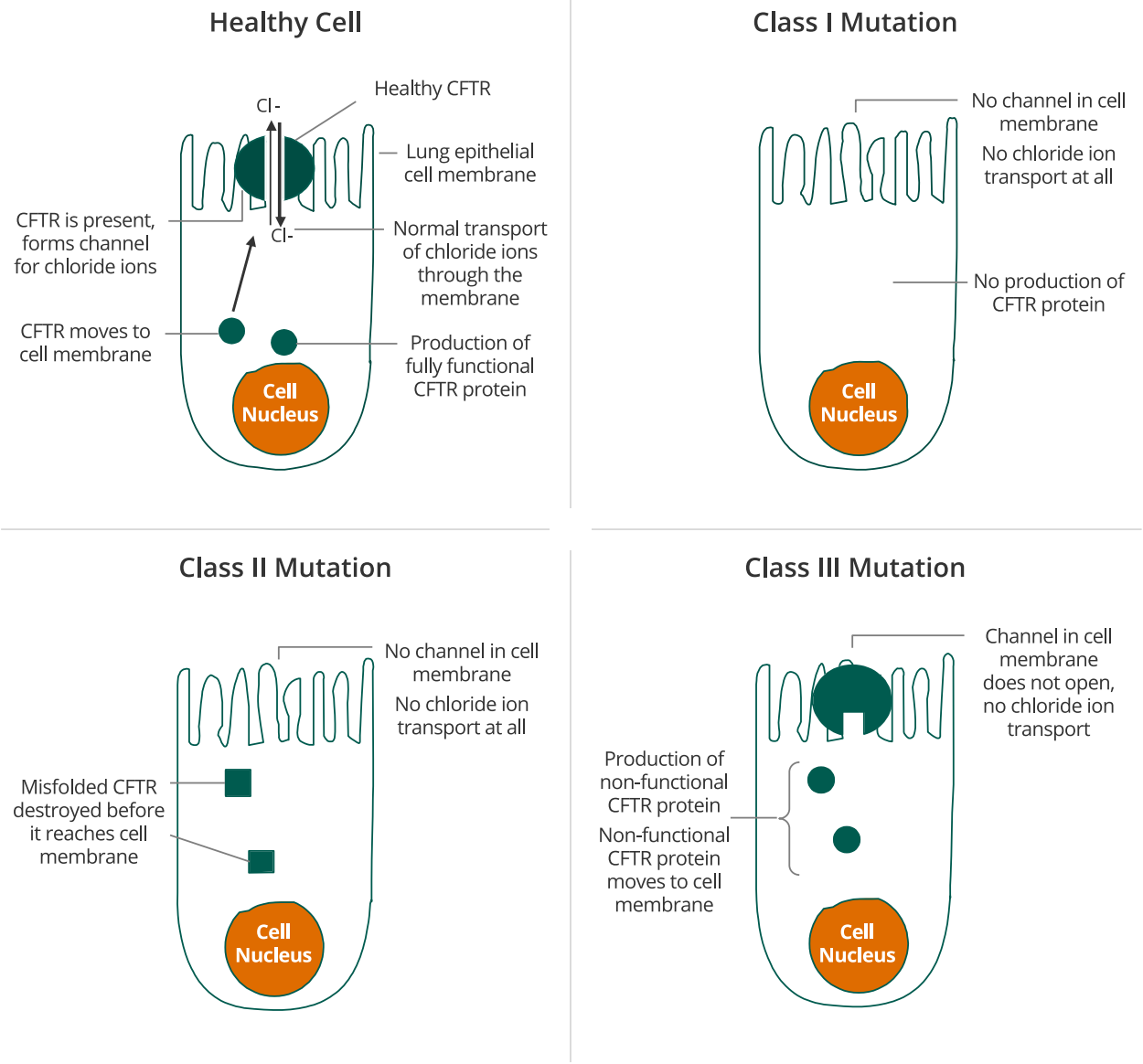
CF is an area of significant unmet medical need for which Galapagos is developing a three-product combination therapy.

CF is a rare, life-threatening, genetic disease that affects approximately 80,000 patients worldwide. CF is a chronic disease that affects the lungs and digestive system. CF patients, with significantly impaired quality of life, have an average lifespan approximately 50% shorter than the population average, with the median age of death at 37. There currently is no cure for CF. CF patients require lifelong treatment with multiple daily medications, frequent hospitalizations and ultimately lung transplant, which is life-extending but not curative. In the United States, a CF patient on average incurs approximately $50,000 per year, or $1,350,000 over his or her lifetime, in outpatient expenses alone and substantial additional costs for frequent hospitalizations. Kalydeco, the only approved therapy for the underlying cause of CF, adds approximately $300,000 of additional costs per year.

CF is caused by a mutation in the gene for the CFTR protein, which results in abnormal transport of chloride across cell membranes. Transport of chloride is required for effective hydration of epithelial surfaces in many organs of the body. Normal CFTR channel moves chloride ions to outside of the cell. Mutant CFTR channel does not move chloride ions, causing sticky mucous to build up on the outside of the cell. CFTR dysfunction results in dehydration of dependent epithelial surfaces, leading to damage of the affected tissues and subsequent disease, such as lung disease, malabsorption in the intestinal tract and pancreatic insufficiency.

Individuals who carry two copies of a defective CFTR gene, referred to as homozygous, are typically affected by CF and show symptoms of the disease. Individuals who carry one copy of a defective CFTR gene are called carriers. Carriers are typically unaffected by CF and show no symptoms of the disease. Individuals who carry one copy each of two different defective CFTR genes are referred to as heterozygous. They are typically affected by CF and show symptoms of the disease. Today, the majority of CF patients are diagnosed at birth through newborn screening and approximately 92% of diagnosed patients have been genotyped. There are more than 1,900 known mutations in the CFTR gene. Mutations in the CFTR gene can be classified into six classes according the mode by which they disrupt the synthesis, traffic and function of CFTR, as described in the diagram below.

CF Mutations



Source: Adapted from [Proesmans et al., 2008]

The two most prevalent mutations in the CFTR gene are Class II and Class III, including the F508del mutation and the G551D mutation, respectively. In Class II patients, insufficient CFTR reaches the membrane, about 50% of the patients have the F508del mutation on both alleles, the so-called homozygotes. For clinical trials, these patients form a homogenous group. The other 50% of the patients, have the F508del mutation on one allele only and carry another mutation on the second allele, they are called the heterozygotes. Also this other mutation impairs the correct processing of CFTR. As the group is less homogenous, clinical trials have proven to be more difficult. The F508del mutation is sometimes called a "processing" mutation because it results in a defect in the CFTR protein in which the CFTR protein does not reach the surface of cells in sufficient quantities. The G551D mutation, a Class III mutation, is sometimes called a "gating" mutation because it results in a defect in the CFTR protein in which the defective CFTR protein reaches the surface of a cell but does not efficiently transport chloride ions across the cell membrane. Most therapeutic approaches under development

for CF target the defects caused by one or both of these mutations. Given the prevalence of the F508del mutation, a compound that corrects the effect of the F508del mutation can, beside for patients with Class II mutations only, also be used for combination therapy approaches in heterozygous patients with Class I and Class III mutations.

The potential of CFTR modulators (potentiators and correctors) for the treatment of CF

There is no cure for CF, and to date, all but one of the therapies approved to treat CF patients have been designed to treat the symptoms rather than address the underlying cause of the disease. The market for CF therapies, across the six main healthcare markets, exceeded $1 billion in 2012 and is to exceed $5 billion in 2018 according to a July 2014 GlobalData OpportunityAnalyzer report, primarily driven by introduction of disease modifying treatments. To treat the symptoms of disease, such as CF-associated malnutrition, diabetes, lung disease and systemic inflammation, an aggressive combination of specific therapies is required. To address the cause of the disease, the primary focus has been on a class of drugs known as CFTR modulators.

Kalydeco, marketed by Vertex, is currently the only approved therapy to address the cause of CF. Kalydeco is an orally-administered CFTR potentiator for the treatment of patients two years of age and older with CF who have the Class III (G551D) gating mutation in their CFTR gene. Kalydeco is designed to keep the CFTR protein channels on the cell surface open longer in order to increase the flow of salt and water into and out of the cell. However, this treatment is limited to the subset of patients who suffer from the Class III and other gating mutations of the CFTR gene. Class III mutations occur in only a small percentage of patients with CF (3%).

In contrast, the Class II F508del mutation affects close to 90% of all CF patients. In these patients, CFTR is not expressed at the cell surface and cannot be potentiated by drugs like Kalydeco (that can only function if CFTR is already present in the cell membrane). Small molecule corrector approaches aim to transport the non-functional Class II CFTR protein to the cell membrane. Other companies currently developing small molecule correctors include Vertex, Pfizer, Flatley Laboratories, Genzyme, Targeted Genetics and Bayer. To date, however, there are no approved corrector molecules on the market.

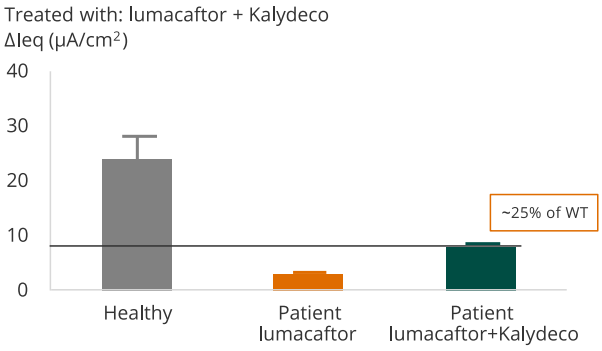
The Class I mutations affect approximately 7% of all CF patients. This mutation shortens the length of the CFTR protein and leads to complete loss of CFTR function. To date, there are no approved molecules on the market to treat this mutation.

Lumacaftor (VX-809), which is being developed by Vertex, is a small molecule corrector being studied in patients with two copies (homozygous) of the Class II (F508del) mutation in their CFTR gene for use in combination with Kalydeco. In June 2014, Vertex announced that its two Phase 3 clinical trials of lumacaftor, when used in combination with Kalydeco in CF patients homozygous for the Class II (F508del) mutation, showed statistically significant improvement in the trial's primary endpoint of improved lung function, compared to placebo. Vertex also showed statistically significant reductions in pulmonary exacerbations in the pooled analysis of both studies. Other signs of clinical improvement were either limited or not statistically different from placebo.

Despite the approval of Kalydeco and the pending approval of Kalydeco/lumacaftor combinations, there is need for better therapies with improved pulmonary function. 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.

Galapagos believes that restoration of CFTR function in cellular assays may be predictive of clinical outcomes. Specifically, review of Vertex patient and cellular data has shown strong correlation as reflected in the diagram below.

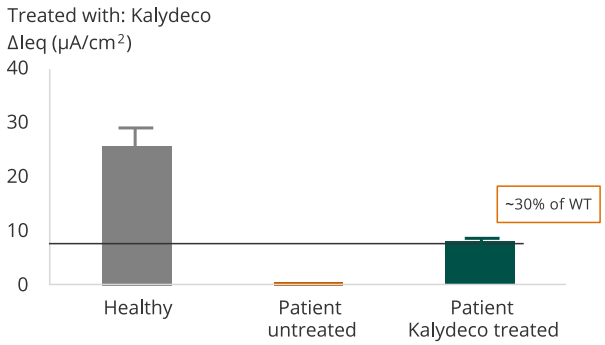
F508del – Homozygous for F508del



In the case of patients with F508del mutation, the administration of Kalydeco and lumacaftor combination resulted in approximately 20% restoration of normal, or wild-type, CFTR. The clinical outcome reflected in Vertex's Phase 3

trial and primary endpoint was that 46% of patients showed an FEV1 improvement of greater than or equal to 5%. Forced expiratory volume (FEV1) levels are a measurement of the volume of air that can be forcibly blown out in one second after full inspiration.

G551D – Heterozygous G551D with F508del



Further, as reflected in the diagram above, for patients with G551D mutation, the administration of Kalydeco resulted in approximately 30% restoration of wild-type CFTR. The clinical outcome reflected in Vertex' Phase 3 trial and primary endpoint was that 75% of patients showed an FEV1 improvement of greater than or equal to 5%.

Galapagos believes these studies demonstrate that cellular models can be used to identify novel molecules to treat Class II and Class III mutations and select those combinations that can restore wild-type CFTR to greater than 50%, a threshold that may need to be achieved to lead to disease remission in patients.

Galapagos' programs in CF

Galapagos has an exclusive collaboration agreement with AbbVie to discover, develop and commercialize novel CF modulators. AbbVie and Galapagos are working collaboratively, contributing technologies and resources to develop and commercialize oral drugs that address the main mutations in CF patients, including Class II and Class III.

Galapagos' CF modulators may have the potential to offer important advantages compared to currently approved therapies as well as other therapies under development:

- disease modifying activity in Class II/III mutations in CF
- regaining greater than 50% of CFTR activity, important for achieving compelling clinical efficacy
- improved risk/benefit compared to standard of care
- small molecules allowing for oral administration
- adequate safety for chronic use, including pediatric application
- no adverse interactions with drugs commonly taken by CF patients, including antibiotics and anti-inflammatory drugs
- effective in homo- & heterozygous patients

Galapagos may be well positioned in CF due to its:

- robust portfolio of CF modulators, including prolific chemistry with multiple binding modes to modulate CFTR
- unique assay cascade, including primary cells from CF patients, for screening of candidate drugs that modulate the CFTR protein
- expertise in working since 2008 with a broad discovery platform containing highly relevant disease assays starting from cells from CF patients
- collaborative partnership with AbbVie, which is an expert in combination therapies and committed to the CF field

Galapagos novel modulator combinations for treating CF

Galapagos is developing novel oral corrector-potentiator combinations for the treatment of CF patients with the Class II F508del mutation, including both homozygous and heterozygous patients. The aim is to develop multiple correctors and multiple potentiators for patients with this mutation, and Galapagos has been successful in identifying multiple candidates in each focus area thus far.

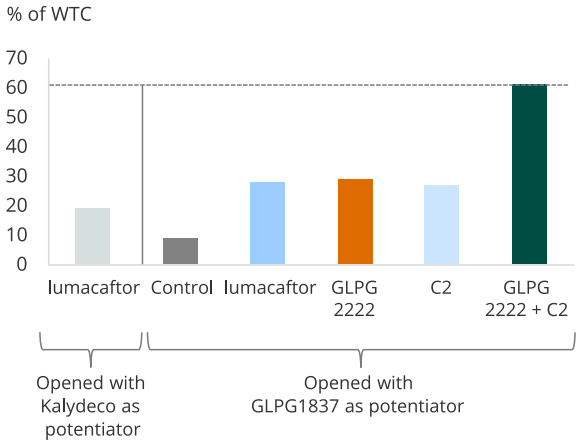
Therapies that restore CFTR function through a combination of correctors and potentiators improve hydration of the lung surface and subsequent restoration of mucociliary clearance. Galapagos is focused on increasing the percentage of wild-type CFTR restored to greater than 50%. A potentiator/corrector combination restoring more than 50% of healthy function CFTR may have a substantially positive impact on the quality of life of Class II patients and may reverse disease.

Galapagos has identified multiple series of novel corrector molecules that enhance the restoration of CFTR in combination with novel potentiator GLPG1837. Based on pre-clinical data, potentiator GLPG1837 may have the potential to offer a superior efficacy and safety profile compared to Kalydeco, important for Class III positioning, but also

important for forming the potentiator component of superior combination therapies for Class II mutation patients as well. As reflected below, Galapagos' triple combination therapy of GLPG1837 plus corrector candidate GLPG2222 plus other molecules from our other corrector series show up to 60% restoration of wild-type CFTR function in pre-clinical tests, compared to the 20% demonstrated by the Kalydeco/ lumacaftor combination. In addition, Galapagos' triple combination therapy could offer the ability to combine with antibiotics and other therapies often prescribed to CF patients, and these molecules appear to have the potential for no drug-drug interaction liabilities, important for CF patients who use multiple medications like antibiotics.

The diagram below is a pre-clinical evaluation of Class II homozygous primary cells.

Galapagos in-house pre-clinical evaluation of various compounds in lung epithelial cells from Class II mutation patients



Lumacaftor and Kalydeco achieve approximately 20% wild-type restoration on average in this assay. The other bars show potentiator GLPG1837 in combination with lumacaftor, with GLPG2222, and with another corrector candidate, or a combination of GLPG2222 and another corrector candidate, all tested in this assay in the same donor cells. These compounds may make a clinical difference for heterozygous Class II patients. Based on pre-clinical data, potentiator GLPG1837, in combination with GLPG2222 plus other molecules from the C2 corrector series showed a 60% restoration of wild-type, as shown in the diagram above.

Galapagos' IPF program

With GLPG1690, Galapagos discovered a novel mode of action targeting autotaxin, with potential application in idiopathic pulmonary fibrosis. GLPG1690 completed a Phase 1 first-in-human trial. The randomized, double-blind, placebo controlled, single center trial was conducted in at least 40 healthy volunteers in Belgium. In the first part of the trial, single ascending doses were evaluated. In the second part, the new compound was administered daily for 14 days. GLPG1690 proved to be safe and well-tolerated over a wide dose range in healthy volunteers. Engagement of the autotaxin target was confirmed using a relevant biomarker. GLPG1690 displayed a favorable pharmacokinetic and pharmacodynamic profile. The data shown in Phase 1 encourage Galapagos to explore a Phase 2 study design in IPF, to be filed before end 2015. GLPG1690 is wholly owned by Galapagos.