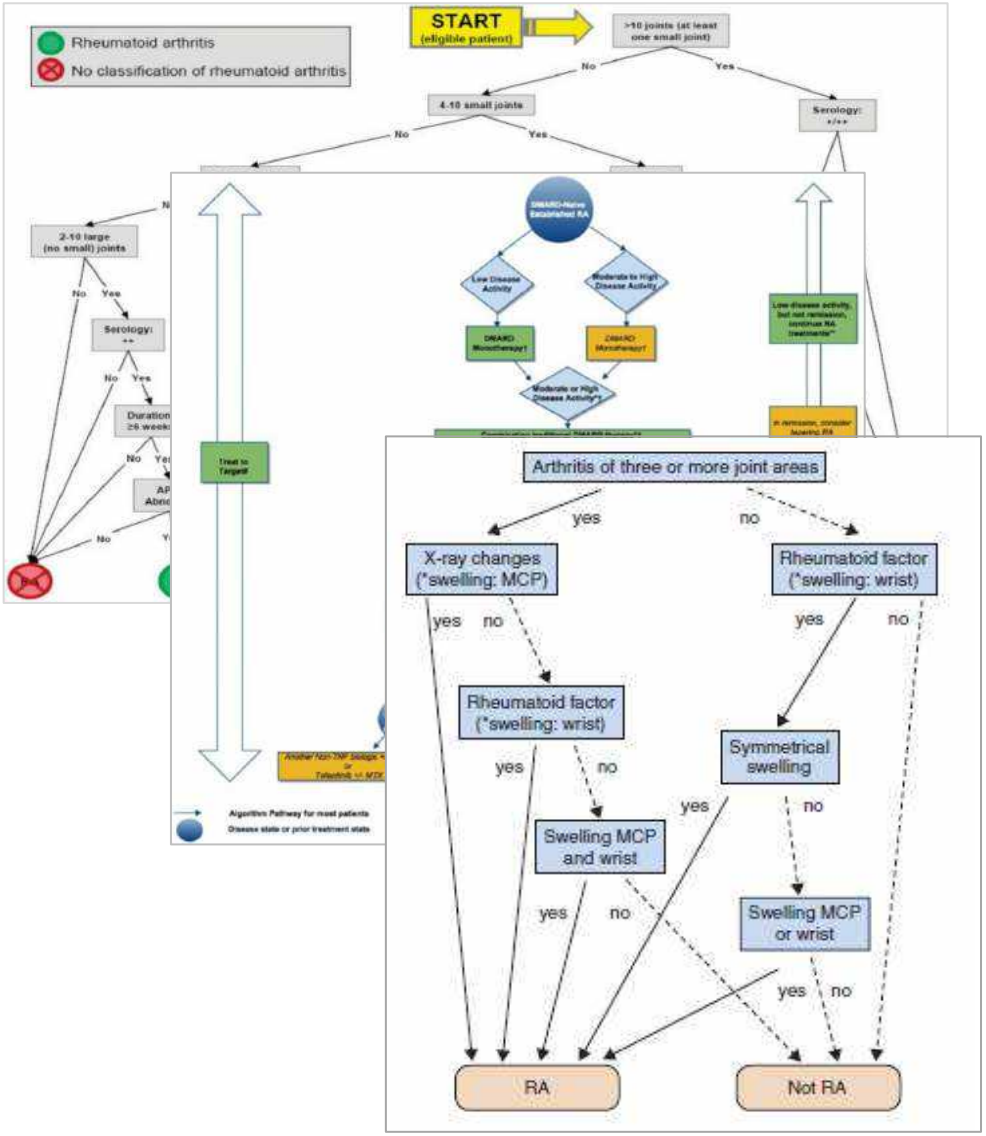
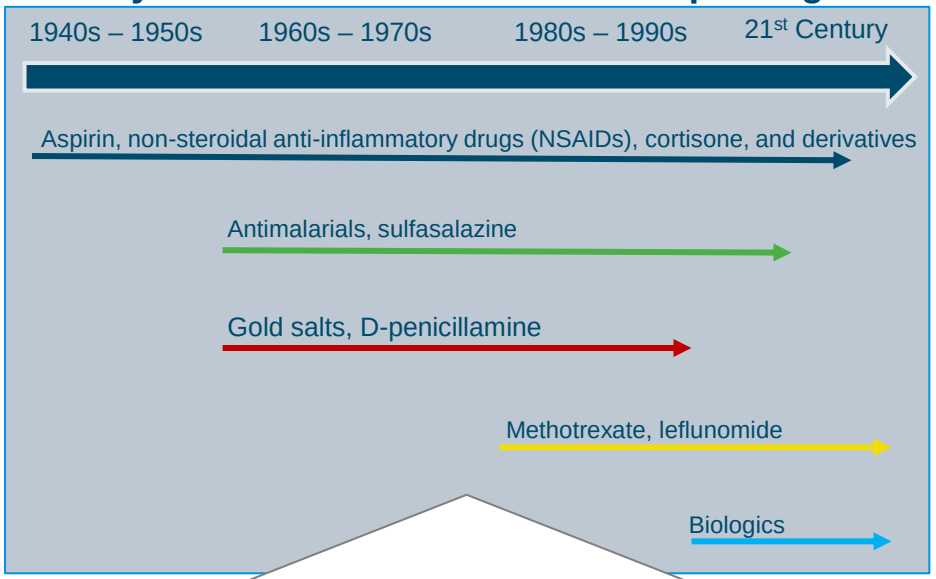
RA diagnosis decision tree

Decades of treatment optimization in rheumatoid arthritis



Ecosystem has settled on treatment paradigm

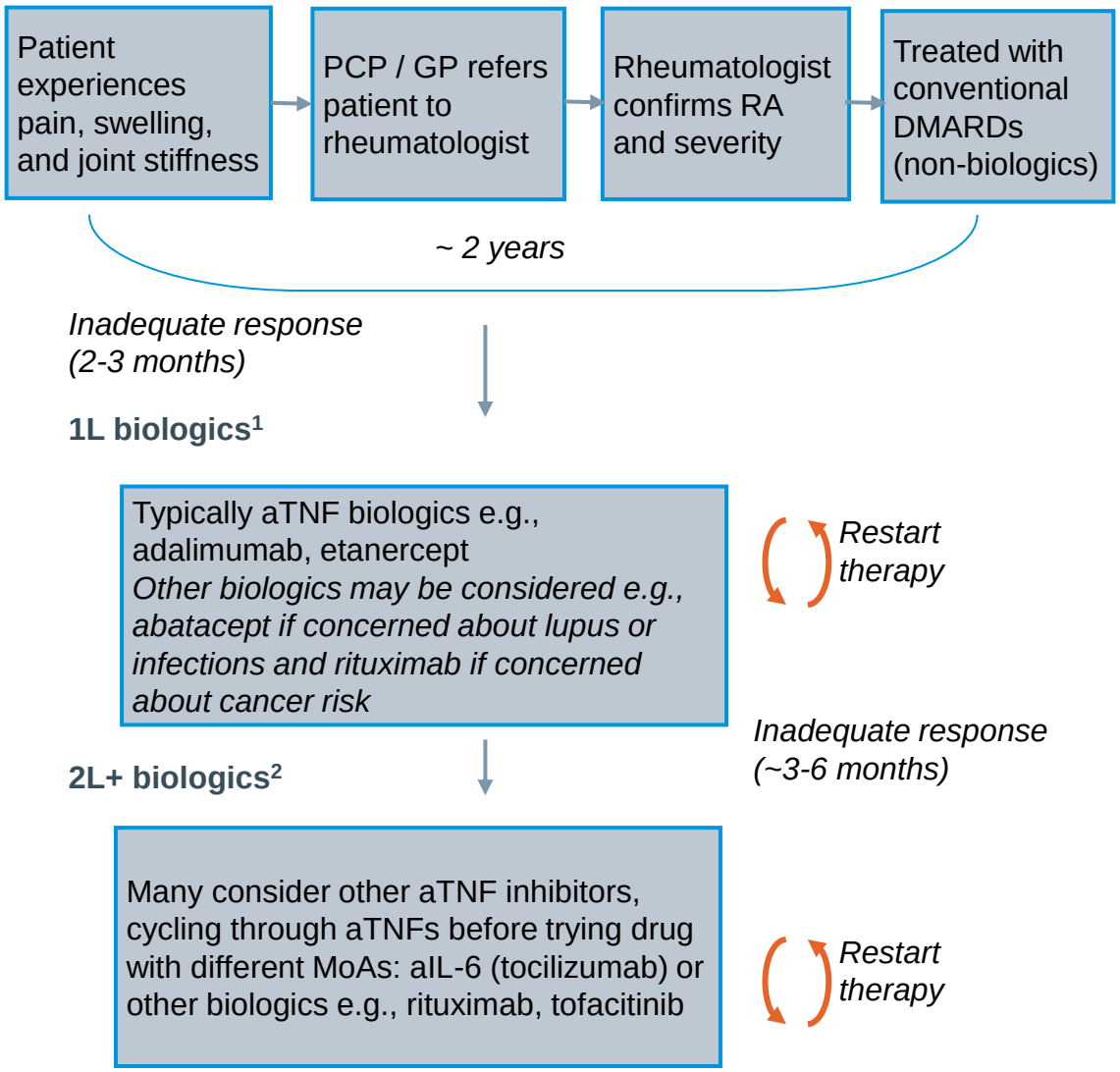


Temporal treatment hierarchy

Early RA	Active RA	Treatment refractory
• DMARDs • Oral combinations	• AntiTNF • AntiIL-6 • Orencia or Rituximab	• Other

Source: Aletaha et al 2010;

Typical RA patient journey starts with cDMARDs and cycles through biologics



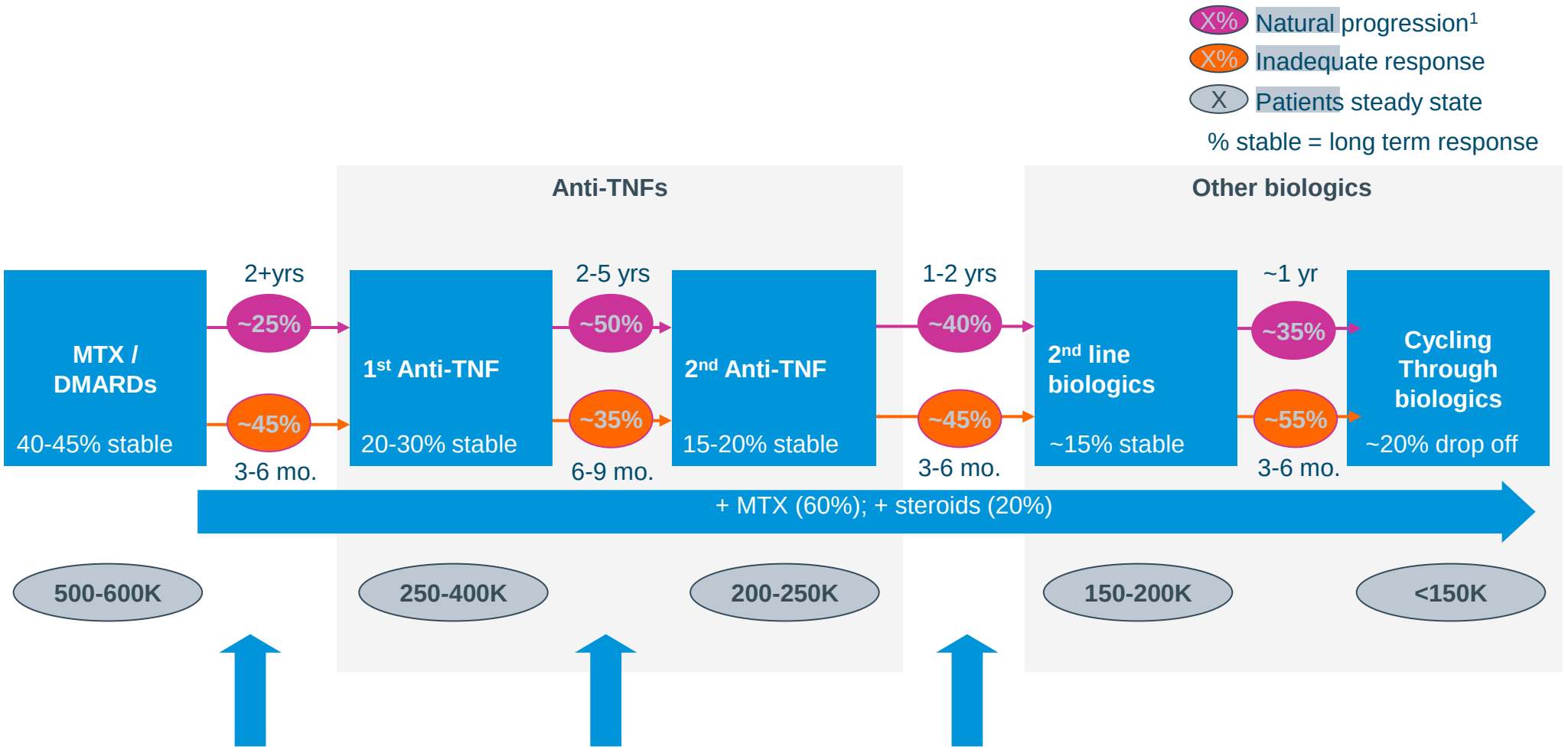
Implications:

- These treatment pathways have been stress tested over millions of person years of patient-doctor experiences
- Regulatory agencies are focused on safety at this point
- Payers are clear on pricing and access; and addicted to rebates
- New entrants have to jump a high hurdle for success

1. Biologics may be offered as a combination treatment with cDMARDs or as monotherapies
2. 2L Biologics or targeted synthetics offered in combination with cDMARDs

Source: Aletaha et al. 2010; Physician interviews

Early Placement In The Therapeutic Funnel Is Critical



Biologics-naïve
- ***Preferred position***
- Largest pool
- Highest likelihood of long term use by patient

1st aTNF failure
- ***With strong trial results, is there potential to play here?***
- Difficult to enter after 1st aTNF failure

2nd aTNF failure
- ***Most likely initial position given current practice***
- Small pool
- Large amount of cycling

1 Consists of patients who meet ACR criteria on therapy and remain on treatment for "average" time
2 Patient population estimates represent U.S. RA patients

Source: Lawrence, Arthritis Rheum (2008); Rendas-Baum, Arthritis Res Ther (2011); Yazici, J Rheumatology (2009); Ruppert-Roth and Finchk Arthritis Res Ther (2009); Bernstein, KOL interviews

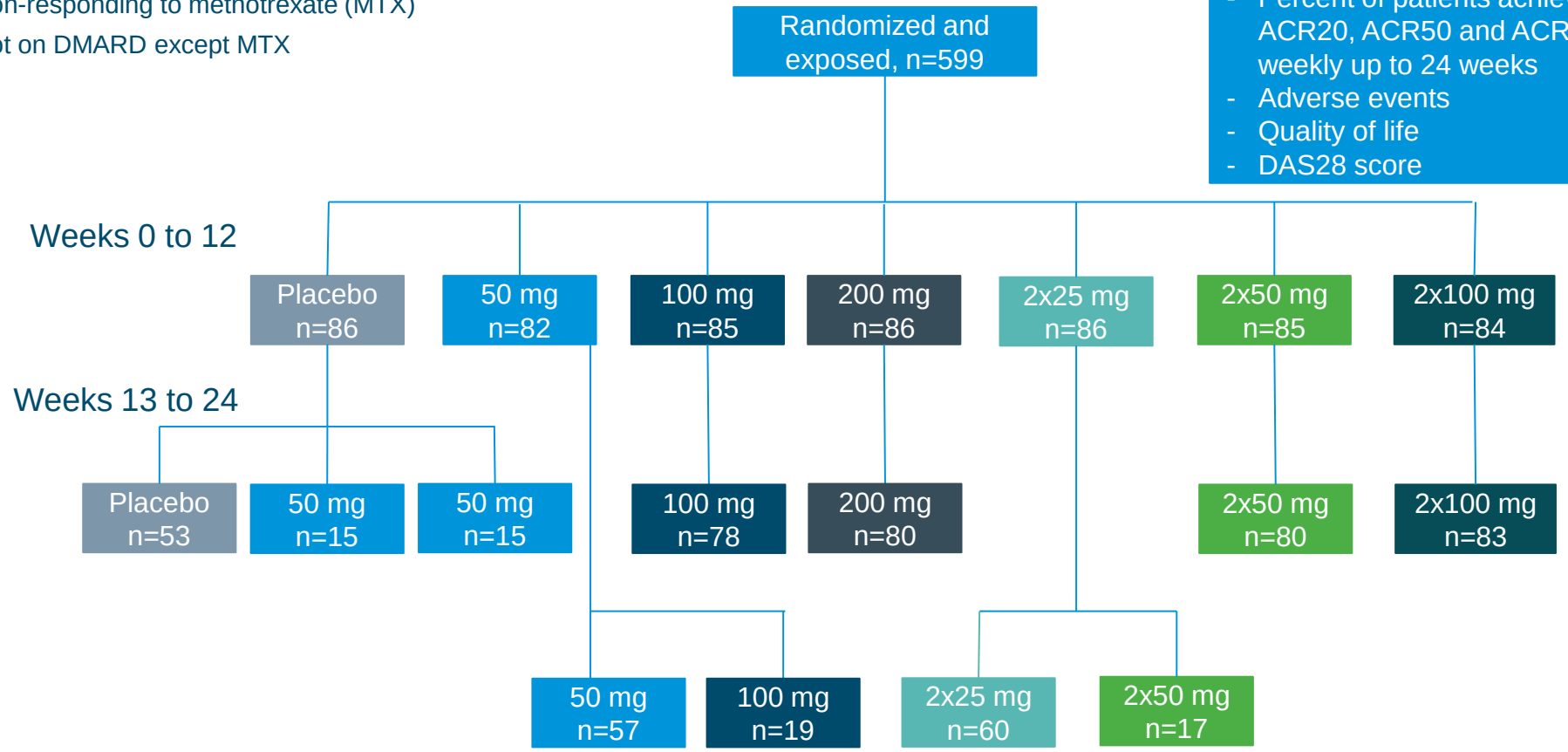
Darwin1 Phase 2 Study: Filgotinib Add-on in MTX non-responding RA

Key Inclusion/Exclusion Criteria

- RA diagnosis of at least 6 months
- Non-responding to methotrexate (MTX)
- Not on DMARD except MTX

Primary Endpoint
- % Patients achieving ACR20 response at 12 weeks

Key secondary endpoints
- Percent of patients achieving ACR20, ACR50 and ACR70, weekly up to 24 weeks
- Adverse events
- Quality of life
- DAS28 score



- RA patients who do not respond to DMARD or MTX make up one of the main patient groups for whom tofacitinib is recommended.
- Darwin1 seeks to show efficacy within this patient population, allowing for non-head-to-head comparisons with other JAK inhibitors.

Source: clinicaltrials.gov; Company Presentations

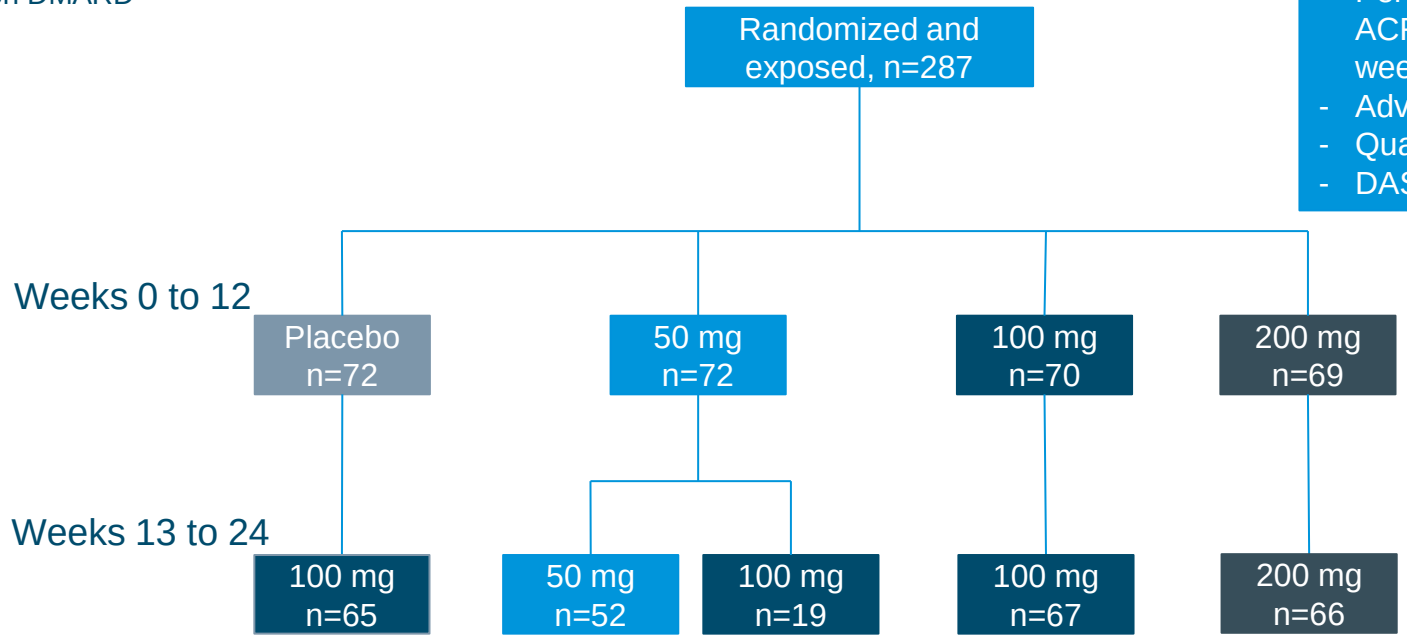
Darwin2 Phase 2 Study: Filgotinib treatment in MTX non-responding RA

Key Inclusion/Exclusion Criteria

- RA diagnosis of at least 6 months
- Non-responding to methotrexate (MTX)
- Not on DMARD

Primary Endpoint
- % Patients achieving ACR20 response at 12 weeks

Key secondary endpoints
- Percent of patients achieving ACR20, ACR50 and ACR70, weekly up to 24 weeks
- Adverse events
- Quality of life
- DAS28 score



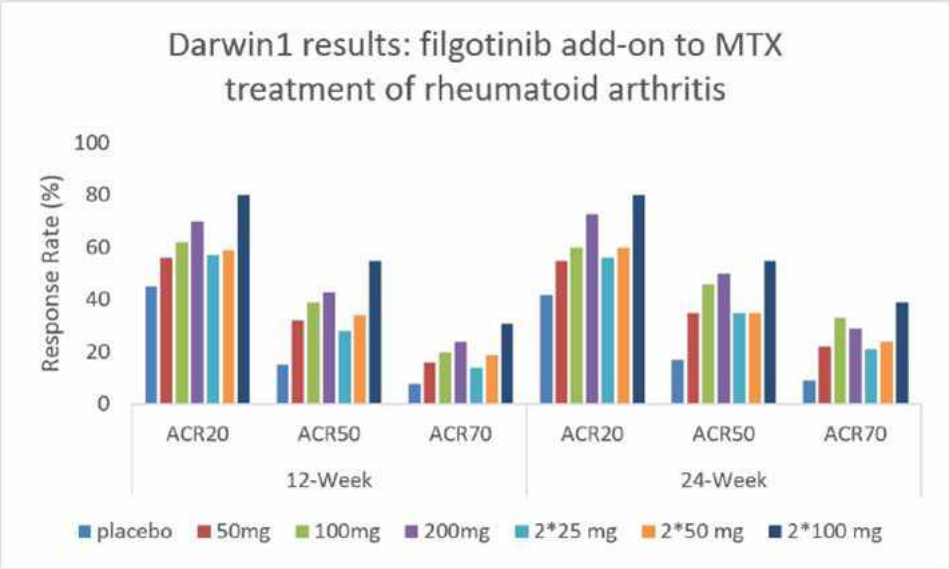
The Phase 2 Darwin trials tested filgotinib in RA patients that would typically be given tofacitinib, a recommended JAK inhibitor for the treatment of RA.

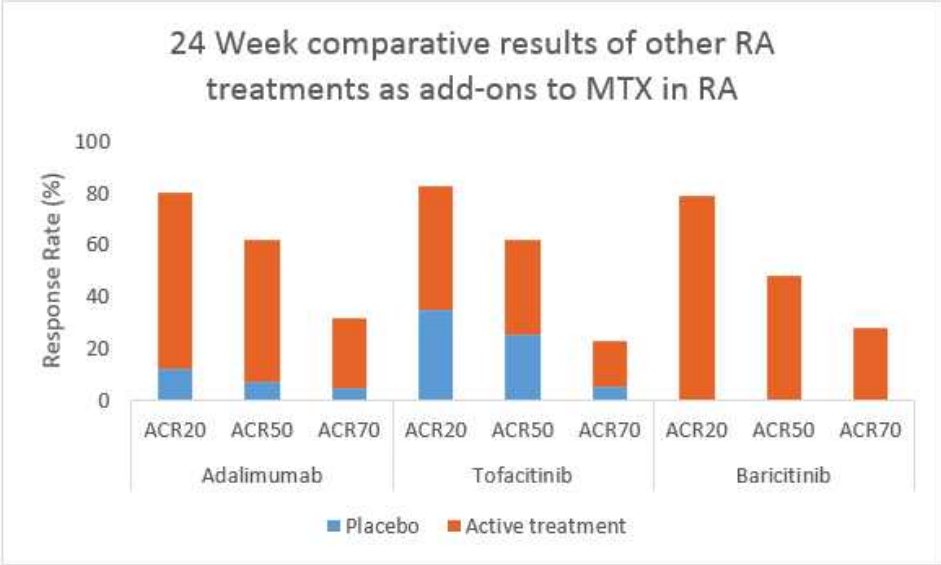
– Like Darwin1, Darwin2 is targeting RA patients for whom the JAK inhibitor tofacitinib is recommended.

Source: clinicaltrials.gov; Company Presentations

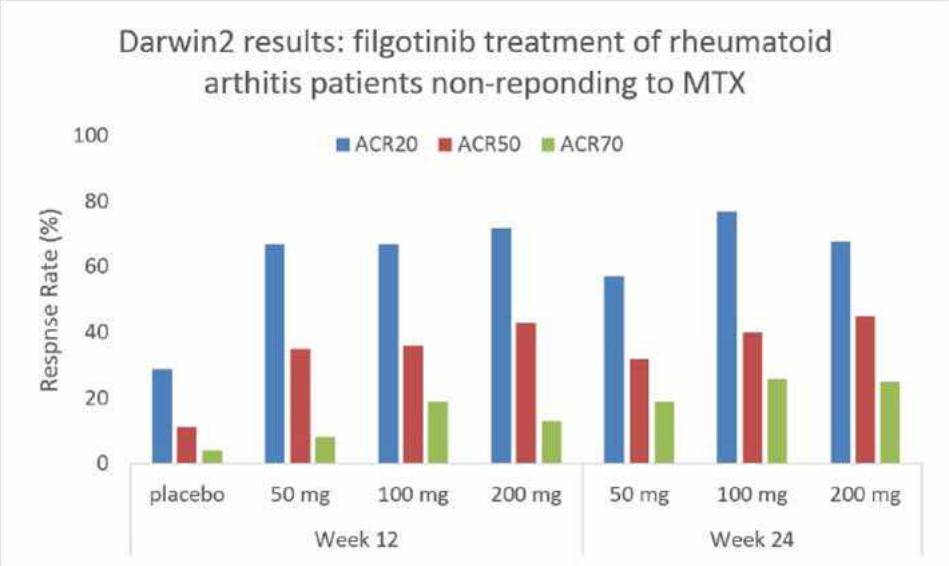
Darwin1 And Darwin2 Results Show Filgotinib's Efficacy Profile Is In Line With Other RA Treatments

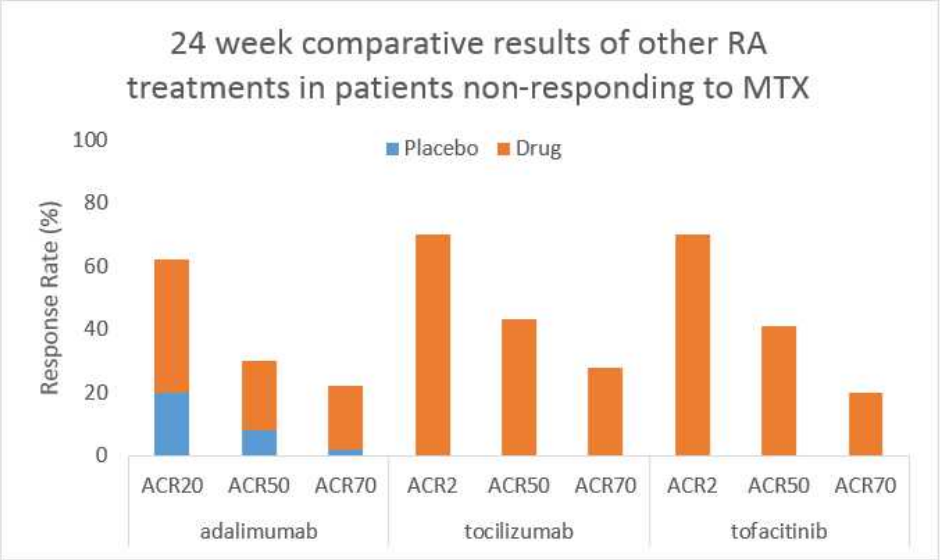
Darwin1 results of filgotinib add-on to MTX show similar efficacy profile to other treatments as add-on therapies to MTX in RA patients not responding to MTX treatment





Darwin2 results of filgotinib monotherapy showed similar efficacy profile to other monotherapies in RA patients not responding to MTX treatment





Source: Company Presentations; van de Putte et al. 2004; Jones et al. 2010; Fleischman et al. 2012; Weinblatt et al. 2003; Keystone et al. 2014; Kremer et al. 2012

Trial Designs For The Three Phase 3 FINCH Trials For Filgotinib In RA

Finch1

52 week study in patients with inadequate response to MTX

1:1:1:1 Randomization
N=1759

Key Inclusion/Exclusion Criteria
- ACR functional class I-III
- Ongoing treatment with MTX
- JAK inhibitor naive

- Filgotinib 200 mg qd
- Filgotinib 100 mg qd
- Adalimumab
- Placebo

Finch2

24 week study in patients with inadequate response to aTNF

Randomization
N=449

Key Inclusion/Exclusion Criteria
- ACR functional class I-III
- Ongoing treatment with 1 or 2 csDMARDs
- JAK inhibitor naive

- Filgotinib 200 mg qd + csDMARD N=147
- Filgotinib 100 mg qd + csDMARD N=153
- Placebo + csDMARD N=148

Finch3

52 week study in MTX naïve patients

1:1:1:1 Randomization
N=1252

Key Inclusion/Exclusion Criteria
- ACR functional class I-III
- Limited or no prior treatment with MTX
- JAK inhibitor naive

- Filgotinib 200 mg qd + MTX
- Filgotinib 100 mg qd + MTX
- Filgotinib 100 mg qd + Placebo
- Placebo + MTX

Primary Endpoint
- % Patients achieving ACR20 response at 12 weeks

Key secondary endpoints
- Percent of patients achieving ACR20, ACR50 and ACR70, day 1 to week 24
- DAS28 score
- Adverse events
- Health assessment questionnaire (HAS)
- European League Against Rheumatism (EULAR) response
- Clinical and simplified diagnostic activity index (CDAI and SDAI)

Expectations of topline results:

Finch1- 1Q19

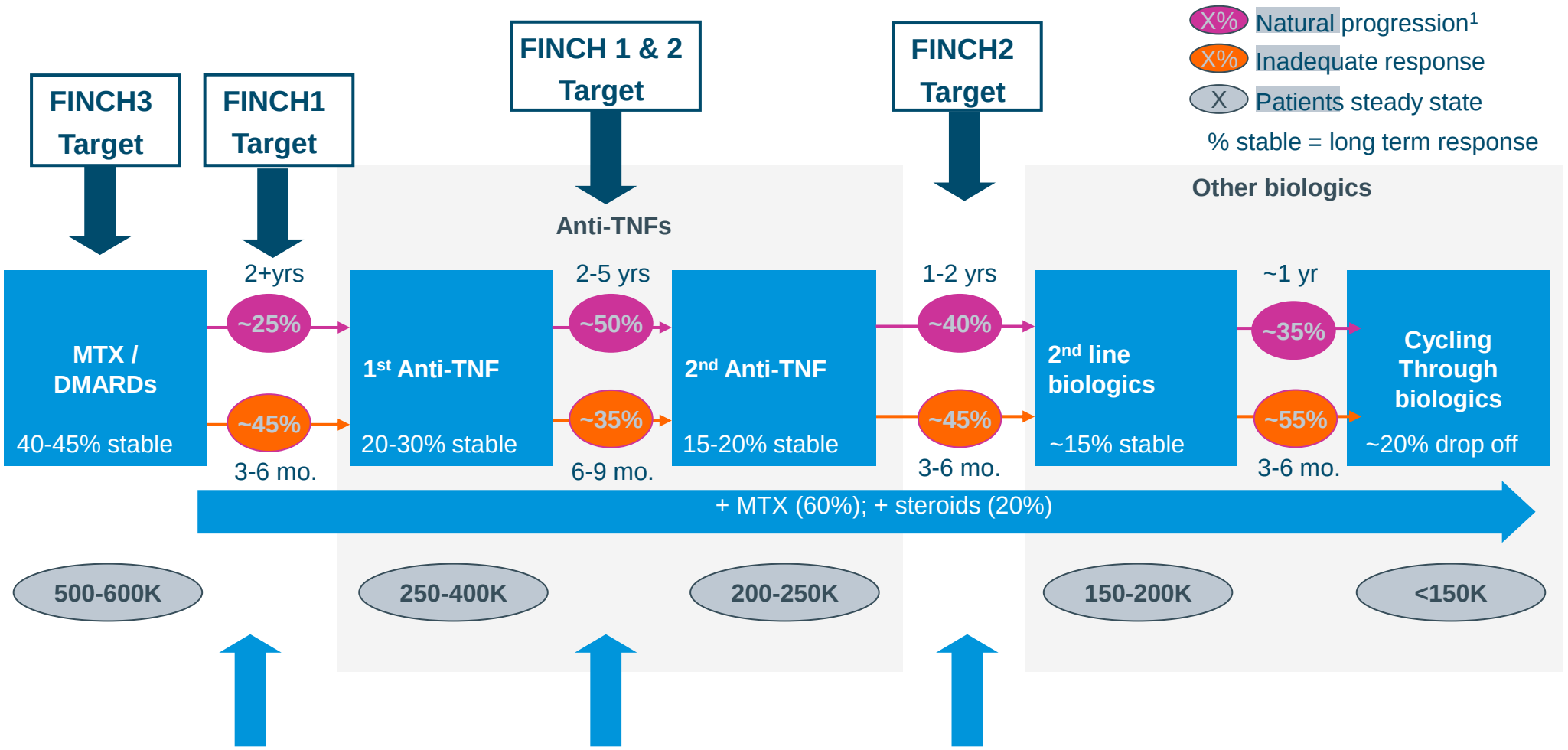
Finch2- Topline released 4Q18

Finch3- 1Q19

The Phase 3 FINCH trials will seek to push filgotinib into earlier lines of treatment for RA compared to the recommended use for other JAK inhibitors.

Source: clinicaltrials.gov; Company Presentations

The FINCH Trials Aim to Place Filgotinib In-Line with Biologics



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1 Consists of patients who meet ACR criteria on therapy and remain on treatment for "average" time
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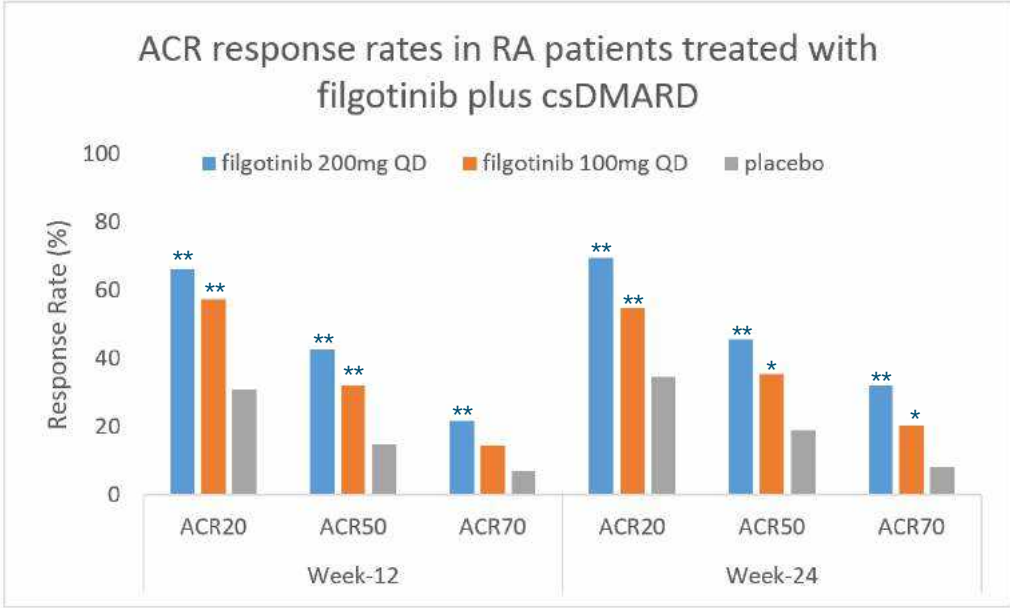
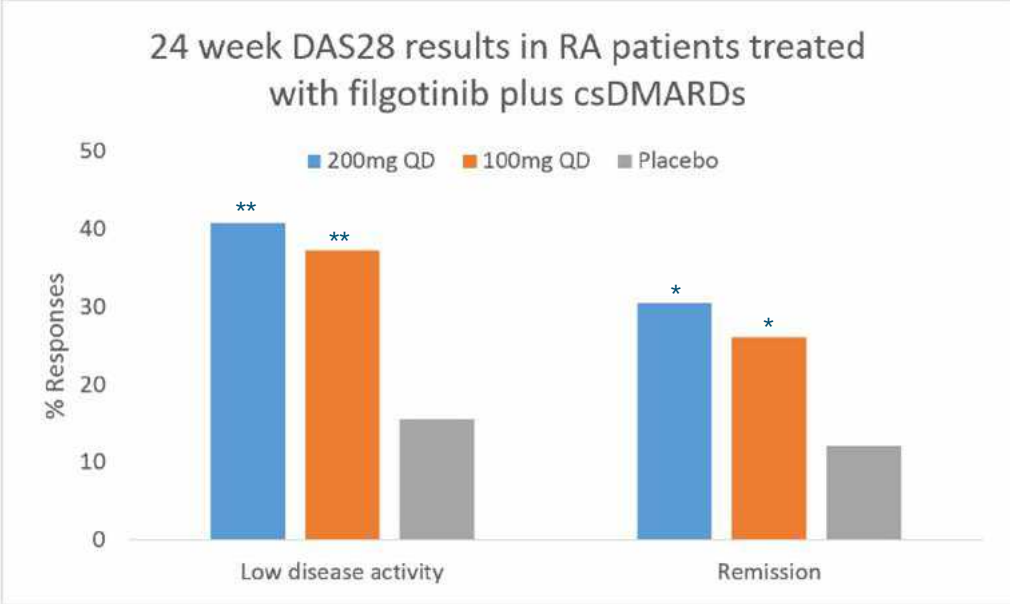
Source: Lawrence, Arthritis Rheum (2008); Rendas-Baum, Arthritis Res Ther (2011); Yazici, J Rheumatology (2009); Rubbert-Roth and Finchk Arthritis Res Ther (2009); Bernstein, KOL interviews

Results of Phase 3 Finch 2 trial

- A significant difference in ACR20, ACR50 and ACR70 response rates versus placebo began as early as week 2 of treatment.
- Response rates began to stabilize at about week 8 and persisted for the remainder of the study.
- Response rates to other drugs in RA patients with inadequate response to aTNF (ACR20/ACR50/ACR70):
  - *10 mg bid tofacitinib plus MTX: 73%/40%/21%
  - 5 mg bid tofacitinib plus MTX: 68%/49%/21%
  - *10 mg bid tofacitinib monotherapy: 51.8%/27.9%/12.4%
  - 5 mg bid tofacitinib monotherapy: 43.4%/24.4%/9.7%
  - 10 mg/kg abatacept: 50.4%/20.3%/10.2%

* Risk of thromboembolism has been associated with 10 mg bid tofacitinib, and so this dosing is no longer available.





Source: Burmester et al. Lancet 2013; Schiff Rheumatology 2010; Charles-Schoeman et al. Clin and Epidem Research 2016; Company presentations.

Filgotinib- Pipeline in a drug

Indication	Pre-IND	Phase 1	Phase 2	Phase 3	NDA	Market (Est. Launch)
Rheumatoid arthritis (RA)	Phase 3 FINCH1, FINCH2, and FINCH3					2020
Ulcerative colitis (UC)	Phase 3 SELECTION1					2021
Crohn's disease (CD)	Phase 3 DIVERSITY1					2021
Psoriatic arthritis (PA)	Phase 2 EQUATOR					
Ankylosing spondylitis	Phase 2 TORTUGA					
Small bowel CD	Phase 2 SBCD					
Fistulizing CD	Phase 2 DIVERGENCE2					
Sjögren's disease	Phase 2					
Cutaneous lupus (CL)	Phase 2					
Lupus nephropathy (LN)	Phase 2					
Uveitis	Phase 2 HUMBOLDT					

Sources: Company reports; SVB Leerink Research

Inflammatory

Crohn's Disease

- ~600,000 U.S. patients
- IBD that can impact the entire gastrointestinal tract
- Chronic inflammation results in:
  - Inflamed mucosa
  - Mucosal in-folding
  - Fissuring
  - Deep ulcerations
  - Anal lesions
  - Occasional Bleeding
  - Abdominal pain
  - Frequent diarrhea
- Mild to moderate CD is initially treated with corticosteroids, DMARDs, and aTNF
- Disease progression towards severely active disease requires more aggressive treatment with drug combinations and corticosteroid drug combinations
- Patients may require surgery in the most severe cases

Ulcerative Colitis

- ~750,000 U.S. patients
- IBD that is typically restricted to the large intestine and rectum
- Chronic UC results in:
  - Inflamed mucosa
  - Goblet cell death
  - Crypt abscesses
  - Superficial ulcerations
  - Anal lesions
  - Frequent Bleeding
  - Occasional pain
  - Frequent diarrhea
- Mild to moderate UC is treated with corticosteroids, DMARDs and aTNF
- In diseases progressing from moderate to severe, JAKis such as tofacitinib can be used
- Patients may require surgery in the most severe cases

Source: John's Hopkins Crohn's Disease overview 2013; John's Hopkins Ulcerative Colitis overview 2013; Shi and Ng 2018; Boyapati et al 2015; Feuerstein and Cheifetz 2017;

Complicating factors in drug development and treatment for IBD

Idiopathic Disease	The idiopathic nature slows identification of effective drug targets
Disease Heterogeneity	Disease heterogeneity makes developing a one-size-fits-all drug difficult
Biomarkers	Lack of specific biomarkers limits effective development of targeted therapies
Patient Responses	High variability in patient dose response
Clouded Efficacy	Many patients on background therapy which makes determining single drug efficacy very difficult
Limited Options	Lack of oral drugs (in CD) increases the treatment burden

Source: SVB Leerink research; Bennike et al. 2014;

Phase 3 Trials for Filgotinib Target Moderately to Severely Active IBD Patients Post-TNFα treatment

Phase 3 DIVERSITY1 (CD)

58 week study

1:1:1 Randomization N=1320

- Filgotinib 200 mg
- Filgotinib 100 mg
- Placebo

Eligibility Criteria

- Adults with moderate to severe CD
- Intolerant, non-responsive or inadequate response to corticosteroids immunomodulators, TNFα antagonists or vedolizumab
- Does not have colitis, symptomatic strictures, severe rectal/anal stenosis, short bowel syndrome

Primary endpoints

1) Clinical remission rates at week 10 by patient reported outcomes (PRO2)
2) Endoscopic response at week 10
3) PRO2 response at week 58
4) Endoscopic response at week 58

Secondary endpoints

1) CDAI clinical remission at weeks 10 and 58
2) Proportion achieving remission by PRO2 and endoscopic response at week 10 and 58
3) Corticosteroid-free remission rate

Patients who meet prespecified eligibility criteria will be enrolled in a follow up Phase 3 extension study (DIVERSITYLYTE)

Phase 2b/3 SIMPLICITY (UC)

24 week study

Randomization N=449

- Filgotinib 200 mg
- Filgotinib 100 mg
- Placebo

Key Inclusion/Exclusion Criteria

- Adults with moderate to severe UC
- Inadequate or loss of response or intolerant to corticosteroids, immunomodulators, TNFα antagonists or vedolizumab
- Does not have CD, or other forms of colitis

Primary endpoints

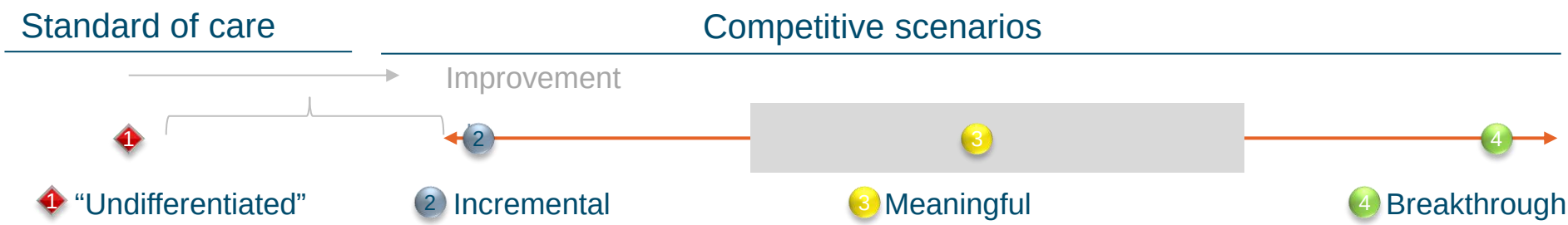
Proportion achieving remission based on components of Mayo Clinic Score (MCS) at weeks 10 and 58

Secondary endpoints

1) Proportion achieving MCS remission at weeks 10 and 58
2) Endoscopic score between 0 and 10 at weeks 10 and 58
3) Histologic remission at weeks 10 and 58

Source: clinicaltrials.gov; Company Presentations

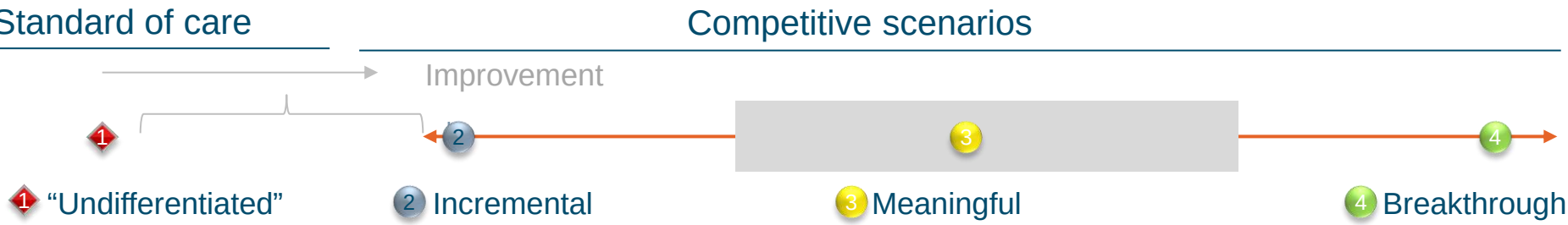
Filgotinib's drug profile in RA places it in potential competition with anti-TNF agents



Efficacy		− ACR20/50/70 response rates: − Monotherapy 50%/25%/10% − Filgotinib + MTX 60%/40%/20%	− ACR20/50/70 response rates: − Monotherapy 60%/30%/10% − Filgotinib + MTX 70%/50%/25%	− ACR20/50/70 response rates: − Monotherapy 70%/40%/20% − Filgotinib + MTX ≥75%/55%/30%
DAS28(CRP) <2.6		- 20-30% remission rate	− 30-40% remission rate	− ≥ 40% remission rate
Safety		− Moderate infection risk − 0.2 thromboembolic events per 100 patient years	− Low risk − < 0.1 thromboembolic events per 100 patient years	− No infection risk − No thromboembolic risk
Commercial probability distribution	17%	35%	45%	3%

Source: Burmester et al. Lancet 2013; Schiff Rheumatology 2010; Charles-Schoeman et al. Clin and Epidem Research 2016; Cohen et al. Clin and Epidem Res 2016; Company presentations.

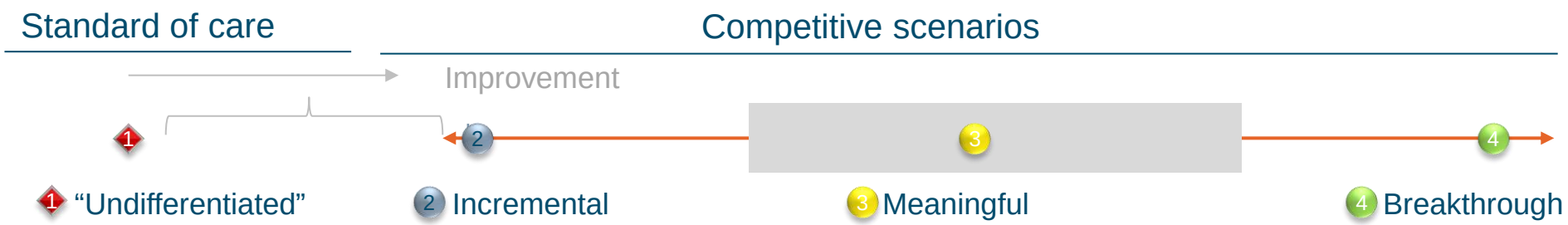
Filgotinib may potentially be the first oral treatment approved to treat CD



Efficacy- PRO2		− 30-40% remission	− 40-50% remission	− ≥ 50% remission
CDEIS Mucosal healing		- 20-25% of patients with mucosal healing	− 30-35% of patients with mucosal healing	− ≥ 45% of patients with mucosal healing
Safety		− Moderate infection risk − 0.2 thromboembolic events per 100 patient years	− Low risk − < 0.1 thromboembolic events per 100 patient years	− No infection risk − No thromboembolic risk
Commercial probability distribution	17%	35%	45%	3%

Source: SVB Leerink research; Rutgeerts et al Gastroenterology 2012; Asgharpour et al. Clin Exp Gastroenterol. 2013; Khanna et al. Inflamm Bowel Dis 2014; Company releases

Although not the first JAK inhibitor approved to UC, filgotinib still carries best-in-class potential



Efficacy- 58 week Mayo Clinic Score (MCS) component remission		− 30-40% remission	− 40-50% remission	− ≥ 50% remission
Mucosal healing		- 25-30% of patients with mucosal healing	− 35-40% of patients with mucosal healing	− ≥ 50% of patients with mucosal healing
Safety		− Moderate infection risk − 0.2 thromboembolic events per 100 patient years	− Low risk − < 0.1 thromboembolic events per 100 patient years	− No infection risk − No thromboembolic risk
Commercial probability distribution	17%	35%	45%	3%

Source: SVB Leerink research;;Berry and Melmed 2018; FDA ADCOM report, tofacitinib ulcerative colitis. Poole et al. 2010; Company releases

Chapter 2

GLPG1690: potential best in care treatment for IPF

Chapter Overview

- Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive and ultimately lethal lung disease hallmarked by a significant continual decline in lung function.
- Pirfenidone and nintedanib, the only two currently approved IPF drugs, combine poor efficacy with burdensome side effects, leaving a significant unmet medical need
- The lysophosphatidic acid (LPA) signaling pathway plays a crucial role in IPF progression and is the target of multiple clinical stage drugs
- GLPG1690 is a first-in-class Autotaxin (ATX) inhibitor entering Phase 3 trials to treat IPF
- ATX operates at the head of the LPA pathway by catalyzing formation of LPA
- If approved, GLPG1890 could potentially become a best-in-care drug, forming the backbone to IPF treatment

Source: Joncour et al. 2017; Desroy et al. 2017; Llona-Minguez et al. 2015; Namour et al. 2016; ; Kihara et al. 2015; Lederer and Martinez 2018; Castelino et al. 2016; Sakai et al. 2013; Oikonomou et al. 2012; Tager et al. 2008; *Cluckers et al. 2017; Palmer et al 2018; Company releases; SVB Leerink Research*

Growing Data Support GLPG1690's Path Forward in IPF

	Why building confidence in GLPG1690	Counter argument
Mechanism	• The LPA1 signaling pathway has been elegantly defined as a driver of IPF in mouse models. • LPA is elevated in bronchoalveolar lavage (BAL) fluid in IPF patients. • The pathway has been well studied and is being targeted by drugs in other disease settings.	• No guarantee preclinical models will translate to the clinic. • Injury induced IPF mouse models are imperfect replications of the actual disease.
Corroborating evidence	• Drugs targeting different parts of the LPA1 signaling pathway have shown evidence of efficacy in the clinic as far as a Phase 2 trial.	• BMS-986020 withdrawn from the clinic due to off-target safety concerns, although we do not expect read-through to GLPG1690.
Imaging data	• Next generation imaging techniques supported and even foretold treatment benefits on FVC in a Phase 2 trial for GLPG1690 in IPF.	• FRI has not been validated as an endpoint by the FDA.
Tolerability and Combinability	• The drug has been well tolerated in clinical trials to date improving its prospects for combinations with current standard of care. Non-clinical research supports potential combinations with standard of care	• No clinical data yet supporting combination efficacy or tolerability in the clinic.
Trial design with biomarker	• Twin Phase 3 trials in combination with local standard of care were carefully designed to be consistent with the FDA's guidance and vision for IPF as combination treated disease.	• Variation in local standard of care could cloud results

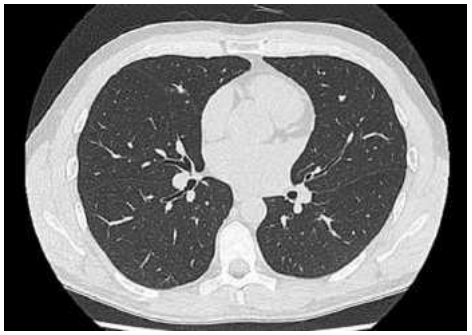
Source: Joncour et al. 2017; Desroy et al. 2017; Llona-Minguez et al. 2015; Namour et al. 2016; ; Kihara et al. 2015; Lederer and Martinez 2018; Castelino et al. 2016; Sakai et al. 2013; Oikonomou et al. 2012; Tager et al. 2008; Cluckers et al. 2017; Palmer et al 2018; Company releases; SVB Leerink Research

What is Idiopathic Pulmonary Fibrosis (IPF)

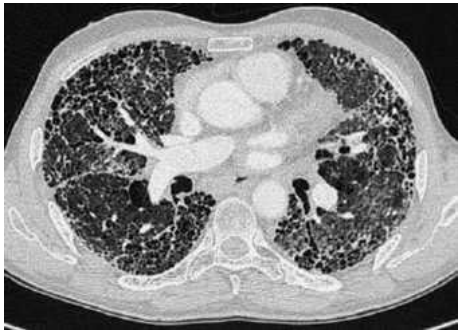
What is Idiopathic Pulmonary Fibrosis?

1) Progressive, debilitating and fatal disease of interstitial lung tissue of unknown cause
2) Results in decline in lung function as measured by
   1) Forced vital capacity (FVC)
   2) diffusing capacity for carbon monoxide (DLco)
3) Leads to reduced capacity for physical activity and increased caregiver burden
4) Irreversible under current care options

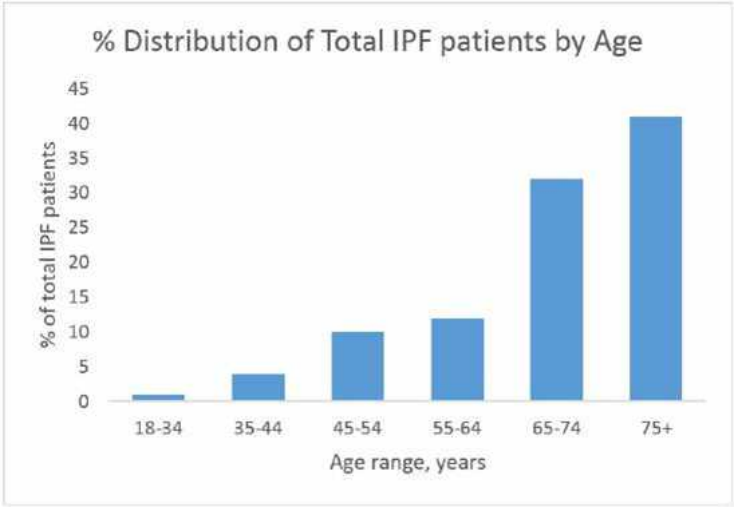
Healthy Lung HRCT Scan



IPF Lung HRCT Scan



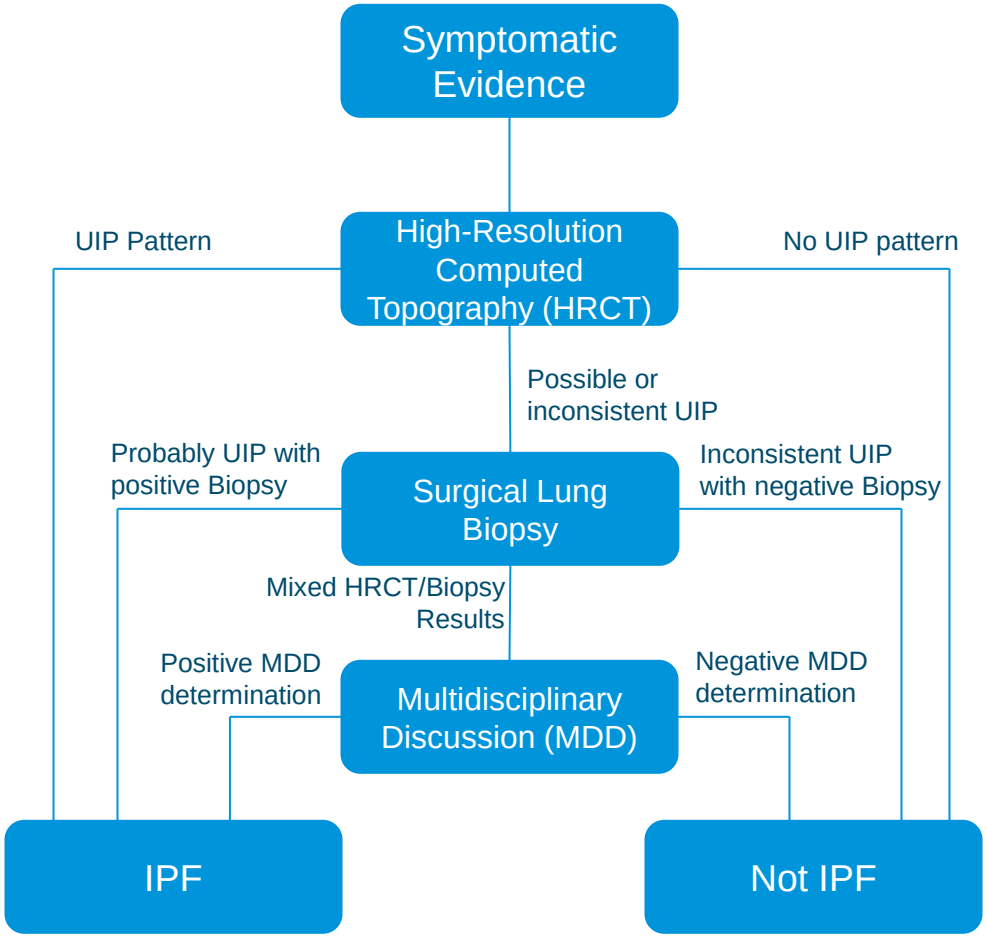
	Total U.S. (range average)	Rates
Prevalence	~120,000	10 to 60 per 100,000 population
Incidence rate	~21,000 per year	3 to 9 per 100,000 population per year
Mortality rate (all cause)	~15,000 per year	9.73 per 100,000 population per year (global)
Median Survival following diagnosis	3.8 years among adults 65+ years	3 to 5 years
Acute exacerbations per year	10% - 20% experience one per year	
Median age at diagnosis	66 years old	



Source: Hutchinson et al. 2015; Hutchinson et al. 2014; Lederer and Martinez. 2018; Raghu et al. 2011; Vancheri et al. 2010

Hindrance of proper IPF diagnosis contributes to disease risk

IPF Diagnosis



Disease Symptoms

1) Dyspnea
2) Dry cough
3) Fatigue
4) Unexplained weight loss
5) Aching muscles and joints
6) Finger clubbing

Disease Diagnosis Issues

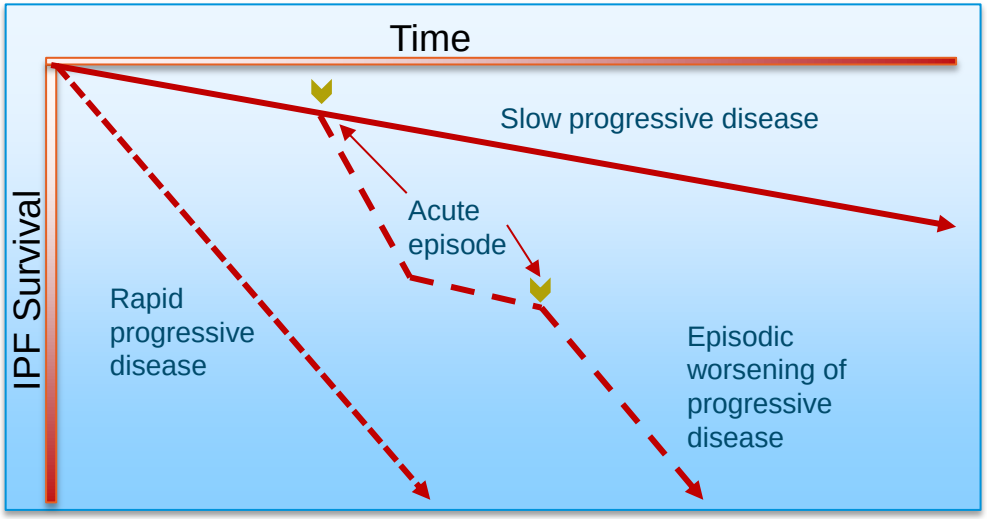
- Misdiagnosis: high overlap of disease symptoms with more common diseases such as cardiovascular disease or chronic obstructive pulmonary disease (COPD)
- Usual interstitial pneumonia (UIP) not always clearly definable using HRCT requiring surgical lung biopsy and multidisciplinary discussion (MDD)
- Absence of identified disease biomarkers

Source: Raghu et al. (2017); Raghu et al. (2011)

Disease progression and lack of treatment place IPF of a level with most cancers

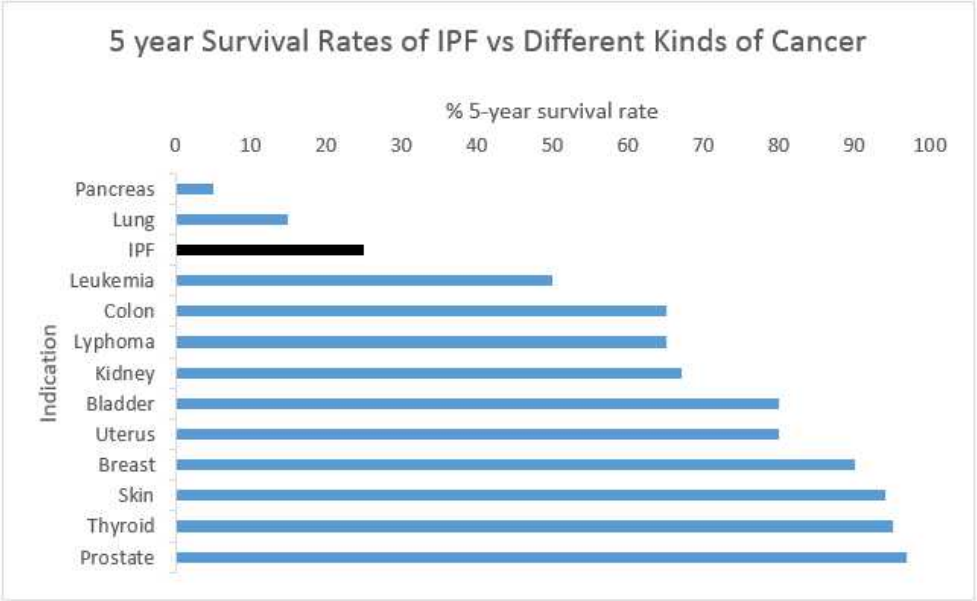
Disease progression can follow one of three courses:

1) Slow progressive disease
2) Slow progressive disease punctuated by acute exacerbations
    1) Exacerbations are often idiopathic in nature
    2) May also arise from other illnesses or comorbidities
3) Rapid progressive disease



Common IPF Comorbidities

1) Emphysema
2) Pulmonary arterial hypertension (PAH)
3) Cardiovascular disease
4) Obesity
5) Sleep apnea



5 year survival rates for IPF are worse than most cancers due to:

1) Late diagnosis after onset of early symptoms
2) Lack of suitable drugs to treat the disease
3) Comorbidities that accelerate disease progression and compound health risks
4) Older patient demographic with a lower fitness baseline

Source: Raghu et al. 2017; Raghu et al. 2011;Vancheri et al. (2010);

MEDACorp Specialists' View on IPF

Key Insights

IPF detection and diagnosis

- IPF is an age related disease that becomes more prevalent in aging populations. As one of many disease that initially present with a cough and shortness of breath, IPF is often misdiagnosed which delays vital early treatment
- Effective diagnosis often requires a multidisciplinary team of physician specialists in order to diagnose due to the degree of variation in early patient symptoms and lung images.
- Next generation imaging techniques may still be several years away from gaining FDA approval, and no biomarkers have yet been identified or validated with the FDA that may improve the diagnosis process

IPF drug efficacy

- The treatment options for IPF patients are limited to two approved drugs, nintedanib and pirfenidone, as well as oxygen. These drugs roughly cut the rate of lung function decline in half.
- These drugs have a very similar therapeutic impact but provide different advantages compared to each other based on safety. Both give patients diarrhea that can be somewhat managed. Pirfenidone makes patients light sensitive where as nintedanib carries some cardiovascular risk.

IPF drug safety

- Because of their similar efficacy, initial prescription choice is dictated by patient lifestyles. The choice to maintain certain quality of life standards often leads the most mild of IPF patients to hesitate in starting drug treatment.
- Treatment options are further limited in the severe disease setting, with patients essentially only receiving supplemental oxygen as palliative care
- The limited use of the approved drugs at the periphery of the disease highlight the high need for more effective drugs to treat IPF with better safety profiles.

Quote

"If caught in the very early stages, it would be a 12 to 14 year disease. But we don't find patients early. It is only after a shortness in breath that we discover them, which is really the last three to five years of life."

- KOL, pulmonologist

"Detecting IPF is very difficult. It is very heterogeneous. A cough may not be prevalent. There is no blood based assay or biomarker approach. And early signs mimic other diseases that touch the lungs. The current gold standard is a multidisciplinary approach."

- KOL, pulmonologist on diagnosing IPF

"IPF is a relentlessly progressive disease. The approved drugs only extend life expectancy from a 3 year survival point to a 5 year survival point, and that is only if we get them on these drugs as early as possible."

- KOL, pulmonologist and IPF specialist

"Right now patients only have two options. Efficacy wise nintedanib and pirfenidone feel equal. The choice really comes down to how the side effect profile impacts the patient's lifestyle."

- KOL on the current standard of care

"Mild patients don't want to start medicine because they feel fine and are active. Why would they want to have diarrhea for a year?"

- KOL on patient compliance issues

"The top 10% of the most severe patients rarely go on the drug. They already can barely breath, and are on oxygen all the time. There is no benefit to handing them these side effects as well."

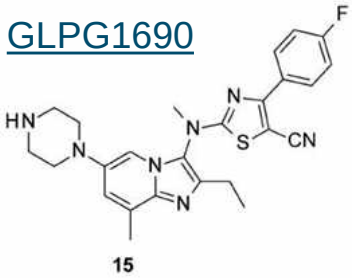
- KOL on patient suitability

Source: MEDACorp specialist KOLs

GLPG's Solution: GLPG1690 selective ATX inhibitor

GLPG1690 mechanism of action

GLPG1690



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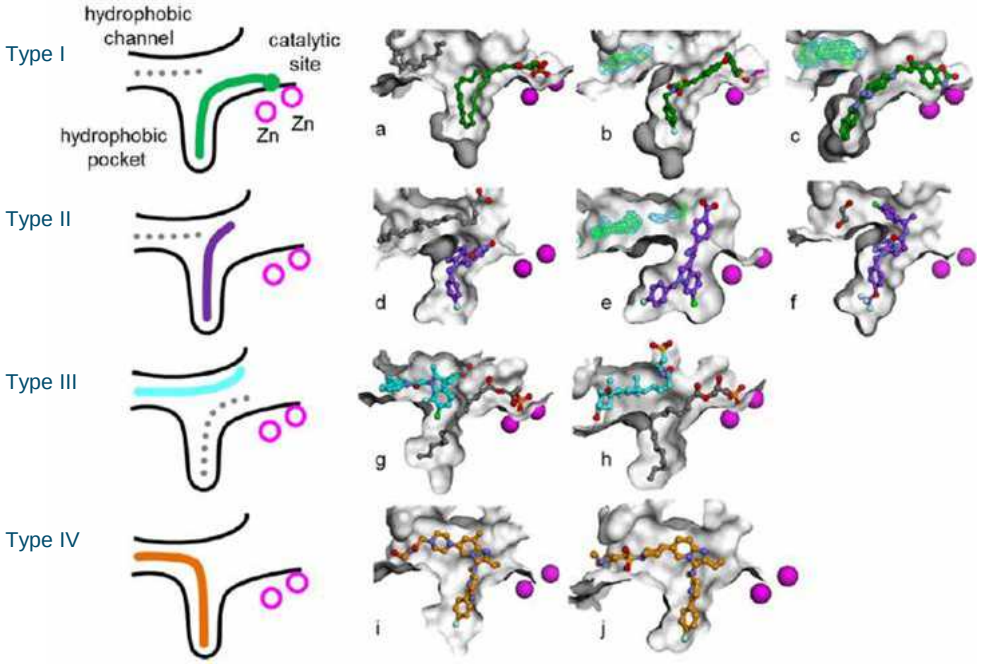
- GLPG1690 is a small molecule inhibitor of autotaxin (ATX) developed using Galapagos' proprietary discovery platform.
- GLPG1690 is an imidazopyridine class molecule that was optimized during discovery to maximize ATX specificity while minimizing off target effects, time-dependent CY3PA4 inhibition, and drug-drug interactions.
- GLPG1690 competitively inhibits ATX:LPC binding by occupying the hydrophobic pocket and hydrophobic channel (Type IV inhibitor) which are required for LPA fatty-acyl chain nesting and transport, respectively.

LPC Competitive Inhibition		LPA 18:2 Inhibition		
ATX LPC	ATX LPC	Mouse plasma assay	Rat plasma assay	Human plasma assay
IC50 = 131 nM	Kv = 15 nM	IC50 = 542 nM	IC50 = 542 nM	IC50 = 242 nM



- Crystallographic structures identified four mechanisms of inhibition within the ATX binding pocket.
- Type I inhibitors mimic LPA substrate by binding to the hydrophobic pocket and catalytic site.
- Type II inhibitors binding within the hydrophobic pocket induced side-chain rearrangement effectively blockading binding pocket access.
- Type III inhibitors bind the hydrophobic channel only, preventing LPA substrate access but not binding within the ATX catalytic region.
- Type IV inhibitors (including GLPG1690) block both the hydrophobic pocket and channel preventing LPA substrate access and binding.

Source: Joncour et al. 2017; Desroy et al. 2017; Llona-Minguez et al. 2015; Namour et al. 2016.

MEDACorp Specialists' View on IPF

Key Insights

Clinical trial design

- Within the U.S. drugs are likely to be developed in clinical trials on a standard of care background due to ethical reasons considering the known benefits current standard of care provides. With this in mind, GLPG1690 is being developed in two Phase 3 trials as add-on therapy to local standard of care.
- Nintedanib and pirfenidone have set an achievable bar that needs to be surpassed either based on improved efficacy or improved safety at a similar efficacy for a drug to be considered an improvement in care. The intermediate target of stopping FVC decline may not impact fibrosis, but would halt deterioration in lung function.

LPA Biology as a source for new drug targets

- The LPA pathway is one of the few pathways to demonstrate a role in fibrosis onset in non-clinical studies. With multiple steps involved in the LPA signaling cascade, the LPA pathway represents a promising set of drug targets.
- The LPA pathway has been implicated in other disease pathologies and has been a point of focus for new drugs in the clinic in these diseases. Autotaxin is a novel drug target that sits at the head of the LPA signaling pathway in IPF models.

Efficacy profiles and market opportunities

- The LPA pathway has demonstrated high potential based on preclinical studies that translated well to the clinic in multiple Phase 2 trials.
- Where other drugs targeting the LPA pathway have demonstrated clinical proof of concept but failed due to drug specific safety concerns, GLPG1690 in a Phase 2 trial displayed a similar proof-of-concept benefit in IPF and was well tolerated by patients.

Quote

"Most trials are starting with patients already on background therapy. It is a practical issue. Why go into a placebo controlled trial with a new drug that might not even work."

- KOL on disruptive injectable insulins

"Stopping FVC decline is not a cure, but if someone did that it would be a huge win. A soft win is the drug is equally as effective as pirfenidone or nintedanib, but without the side effects. This would also push early withholders into taking the drug."

- KOL on disruptive injectable insulins

"LPA has shown exciting proof of concept in preclinical and translational studies. We have high hopes for the Phase 3 study of the autotaxin inhibitor"

- KOL, IPF specialist

"LPA is a classic lipid mediator and pathway that has been under-mined as a drug target, and the autotaxin inhibitor will be an impressive test of the pathway in disease"

- KOL, IPF specialist

"LPA is broadly active across models of fibrosis and is similar to TGFβ in its ubiquitous effects in promoting fibrosis and injury."

- KOL, IPF specialist

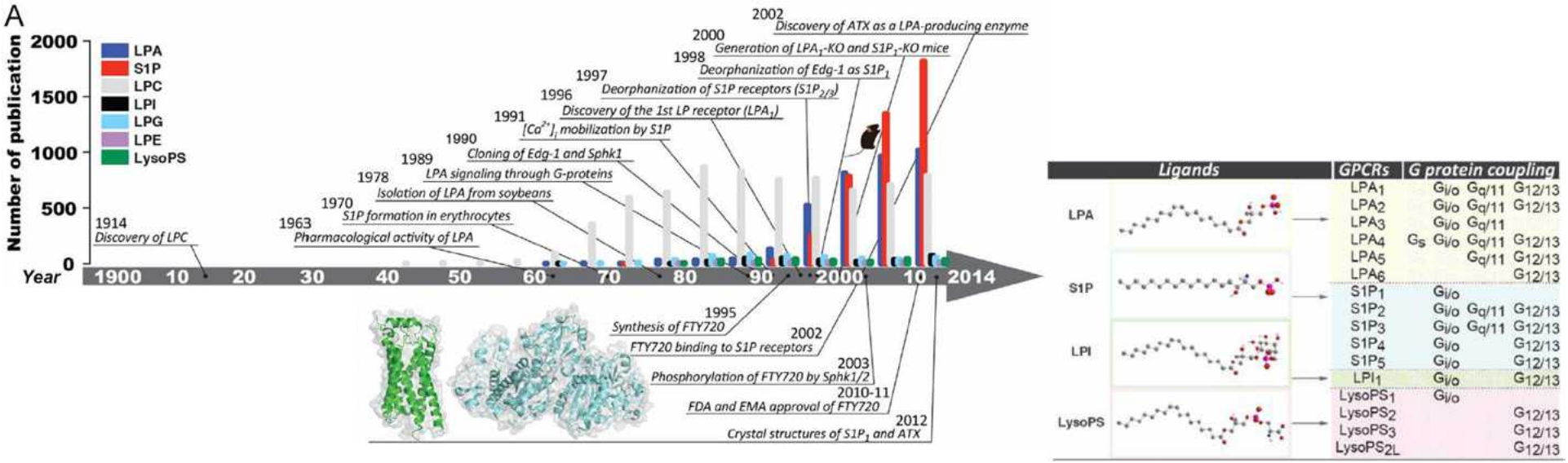
"The small trial GLPG ran showed very clearly that their autotaxin inhibitor was a potent modulator of LPA levels in the human lung."

- KOL, IPF specialist

Source: MEDACorp specialist KOLs.

Lysophospholipid pathway as drug target

Long history of discovery across lysophospholipid pathways and utility for therapeutics

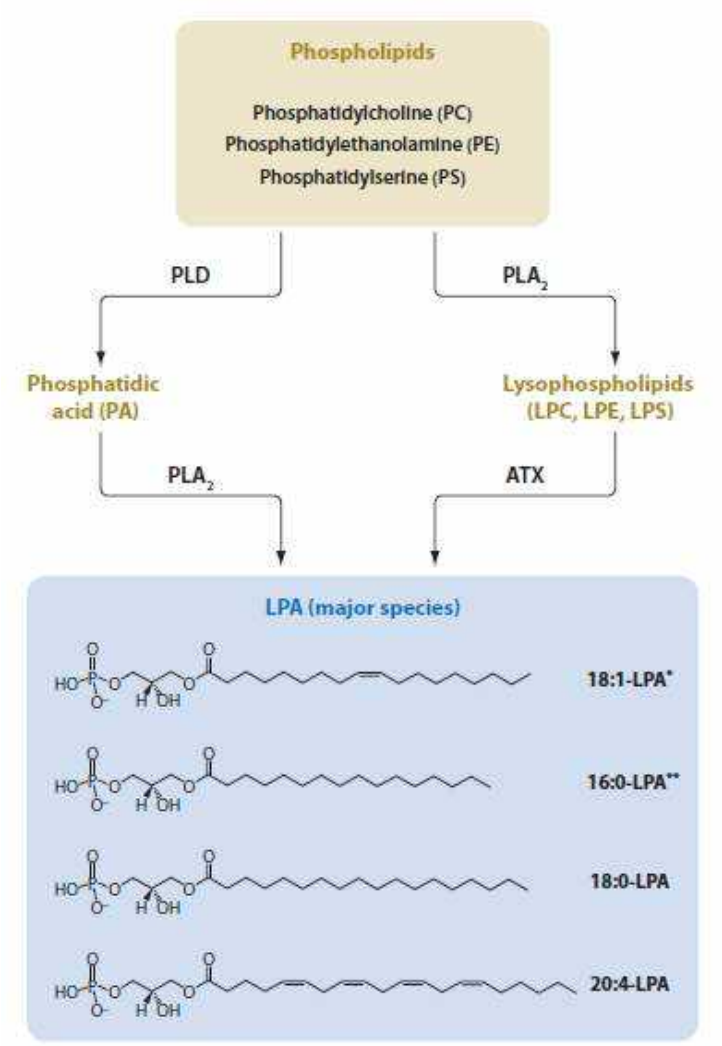


Drugs	Targets	Indication	Stage	Company
SAR100842	LPA1	Systemic sclerosis	Phase 2	Sanofi
BMS-986020	LPA1	IPF	Phase 2 (halted)	Bristol-Myers Squibb
Gilenya (Fingolimod)	S1P1/3/4/5	Relapsing-remitting MS	Approved	
		CIDP	Phase 3	Novartis
BAF312 (Siponimod)	S1P1/5	Secondary progressive MS	Phase 3	
		Polymyositis	Phase 2	
		Active dermatomyositis	Phase 2	Novartis
KRP-203	S1P1	Moderately active refractory ulcerative colitis	Phase 2	
		Hematoligical malignancies	Phase 1	Novartis
Ponesimod	S1P1/5	Relapsing-remitting MS	Phase 2	
		Psoriasis	Phase 2	Actelion
GSK2018682	S1P1	Relapsing-remitting MS	Phase 1	GlaxoSmithKline
RPC1063	S1P1/5	Relapsing-remitting MS	Phase 3	
		Ulcerative colitis	Phase 2	Receptos

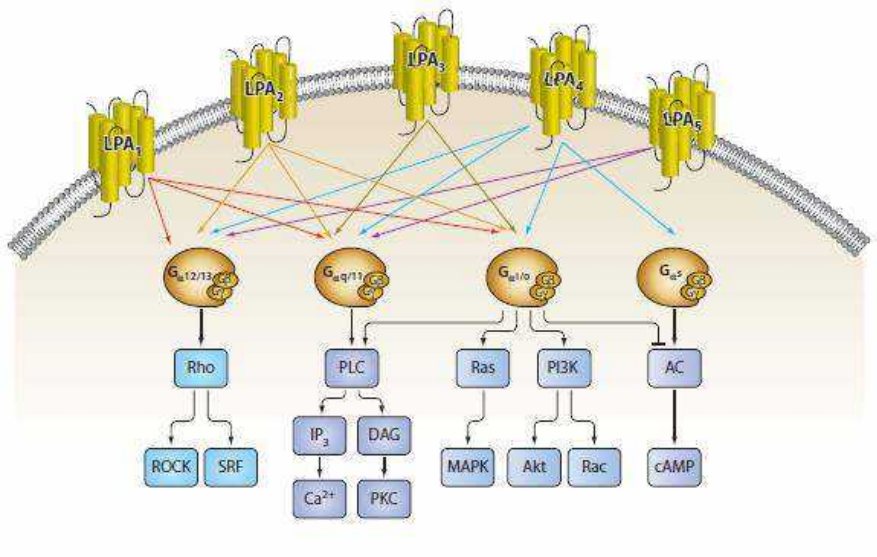
Source: Company Presentations; Kihara et al. 2015; Lederer and Martinez 2018; Desroy et al. 2017; Castelino et al. 2016; Sakai et al. 2013; Oikonomou et al. 2012; Tager et al. 2008.

Pleiotropic signaling of lysophosphatidic (LPA) pathway:

Upstream signaling in generation of LPA



Downstream signaling

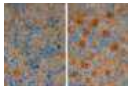


Broad, verified set of important pathobiologies linked to LPA pathway

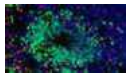
Fibrosis: Lung, Liver and Kidney

Wound healing

Atherosclerosis



Obesity



Neuro-inflammation; Nerve injury

Schizophrenia

Cancer: Ovarian, GI. Lung

Source: Company Presentations; Lederer and Martinez 2018; Desroy et al. 2017; Castelino et al. 2016; Sakai et al. 2013; Oikonomou et al. 2012; Tager et al. 2008.

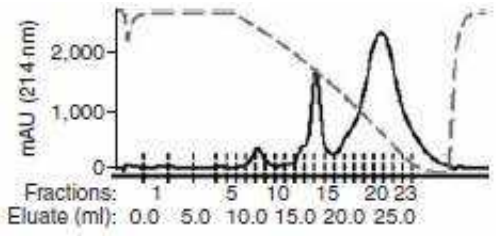
Linking LPA to IPF: an incredible translational journey

nature medicine

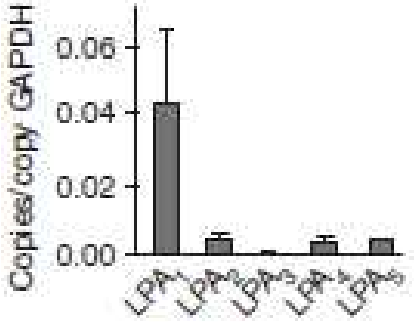
The lysophosphatidic acid receptor LPA_1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak

Andrew M Tager[1,2], Peter LaCamera[1,2,9], Barry S Shea[1,2,9], Gabriele S Campanella[1], Moisés Selman[3], Zhenwen Zhao[4], Vasiliy Polosukhin[5], John Wain[1,6], Banu A Karimi-Shah[1,2], Nancy D Kim[1], William K Hart[1], Annie Pardo[7], Timothy S Blackwell[5], Yan Xu[4], Jerold Chun[8] & Andrew D Luster[1]

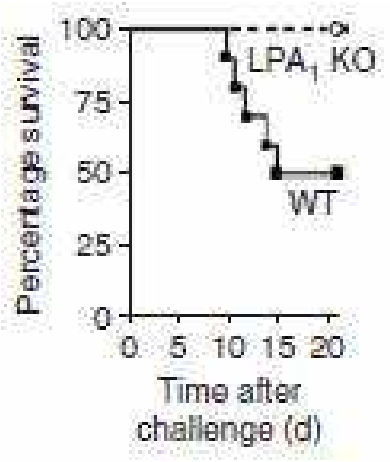
1 Fractionation of chemotactic activity from the lung washings post bleomycin exposure



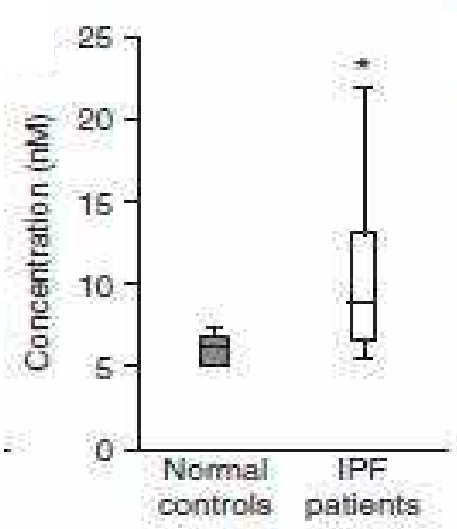
2 Identification of LPA1 activation as the major activity driving fibroblast chemotaxis in fibrotic lung



3 LPA1 receptor KO mice protected against bleomycin induced mortality



4 Elevated levels of LPA in lung washings from patients with IPF

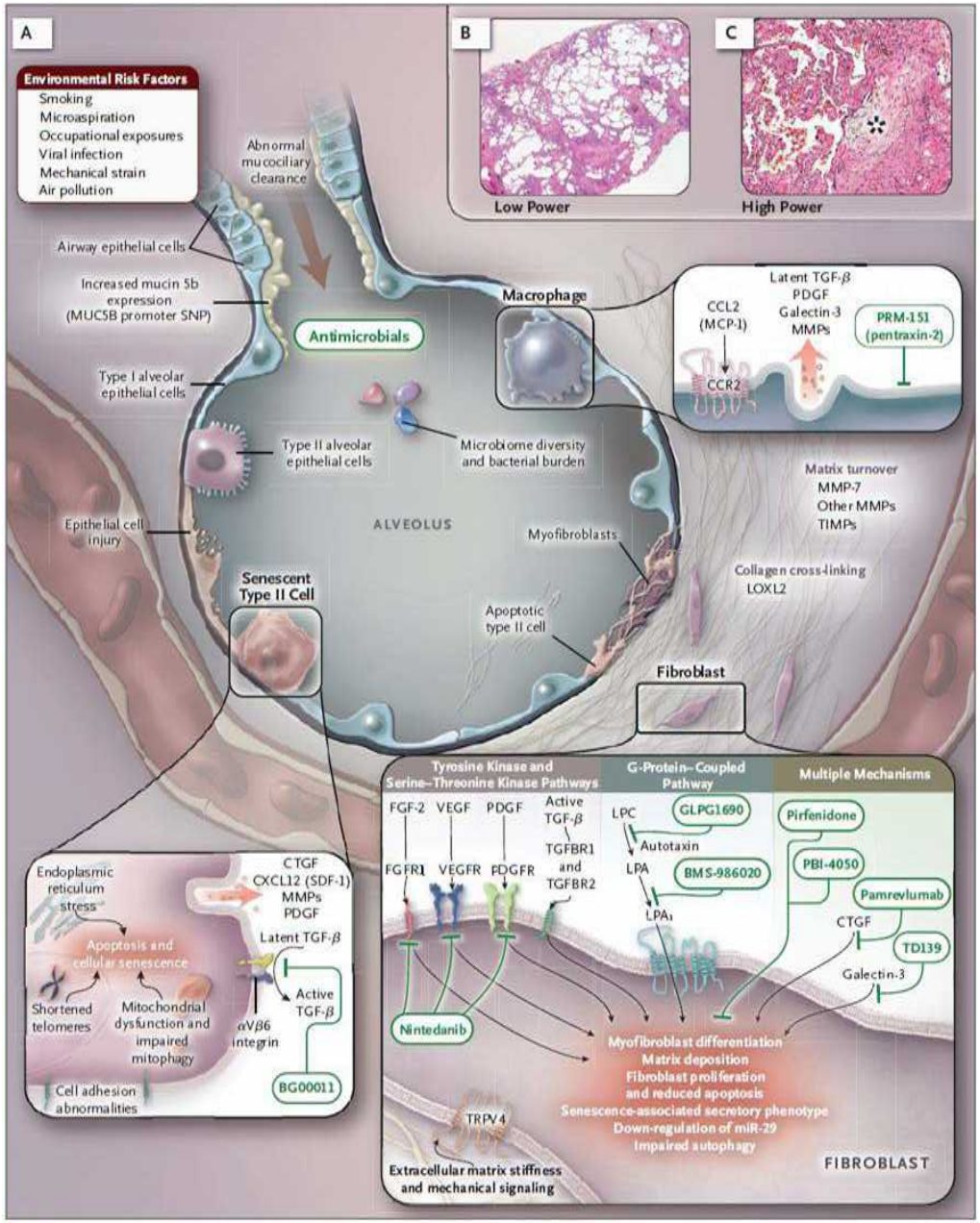


Source: Tager et al. Nature Medicine 2008.

Treating IPF requires astute understanding of its complex pathogenesis

1 Environmental factors coupled with senescent onset in Type II alveolar epithelial cells results in initial tissue insult.

2 Persistent tissue insult drives production of profibrotic signaling molecules that change the phenotypes of nearby cells.



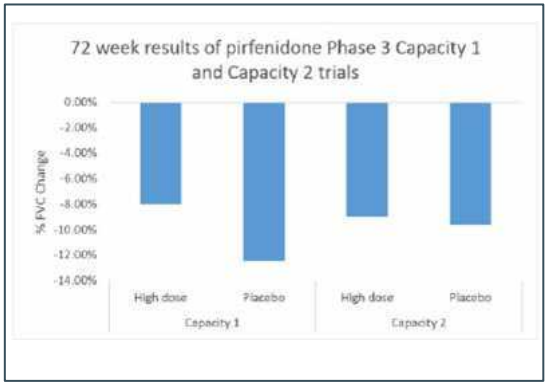
3 Recruitment and engagement of alveolar macrophages further exacerbate conditions by increasing production of profibrotic signaling molecules.

4 Engagement of multiple pathways by profibrotic factors drives fibrosis progression by inducing expression of other profibrotic genes. These signaling pathways comprise significant potential drug targets to treat IPF.

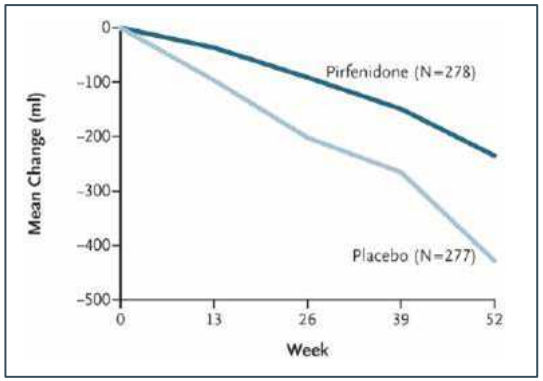
Source: Lederer et al. 2018

Currently approved IPF treatments only delay the inevitable

Pirfenidone phase 3 trials CAPACITY1 AND CAPACITY 2



Pirfenidone phase 3 trial ASCEND



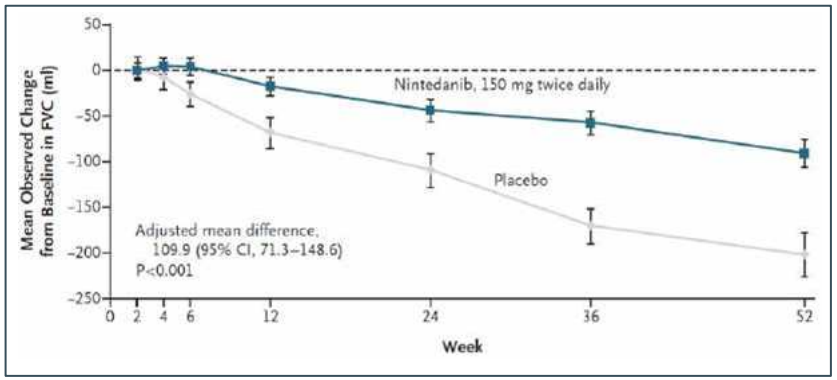
Pirfenidone

- Mechanism is unknown
- Safety: Skin rashes and gastrointestinal issues were the most common side effects. GI issues were milder than those associated with nintedanib.
- The Capacity 1 and Capacity 2 trials gave mixed results with one but not the other showing a significant difference in FVC decline vs placebo.
- The Ascend trial showed a significant difference in FVC at 52 weeks.
- In all three trials, the treat groups continued to show a decline in FVC.
- Patients on pirfenidone

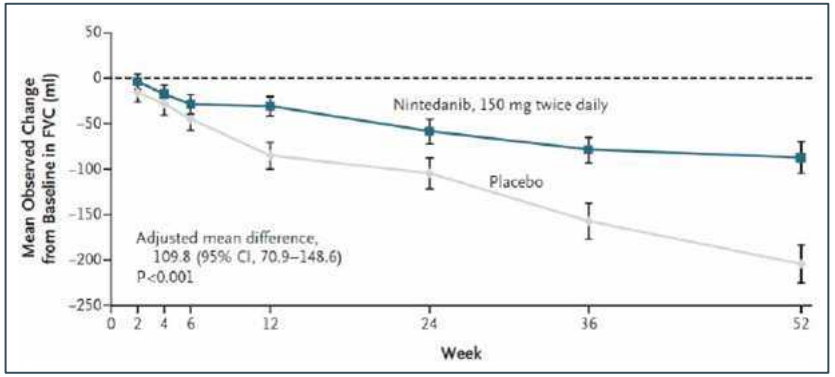
Nintedanib

- TKI inhibitor including VEGFR, FGFR and PDGFR
- Safety: Diarrhea and nausea with Diarrhea being the most common cause of tolerance related change of treatment
- Both Impulse trials showed a significant difference in rate of FVC decline vs placebo
- However, FVC continues to decline.

Nintedanib phase 3 trial IMPULSE 1



Nintedanib phase 3 trial IMPULSE 2



Neither pirfenidone or nintedanib is able to halt or reverse IPF progression leaving IPF patients with a continued unmet medical need

Source: Noble et al. 2011; King et al. 2014; Richeldi et al. 2014; Richeldi et al. 2010.