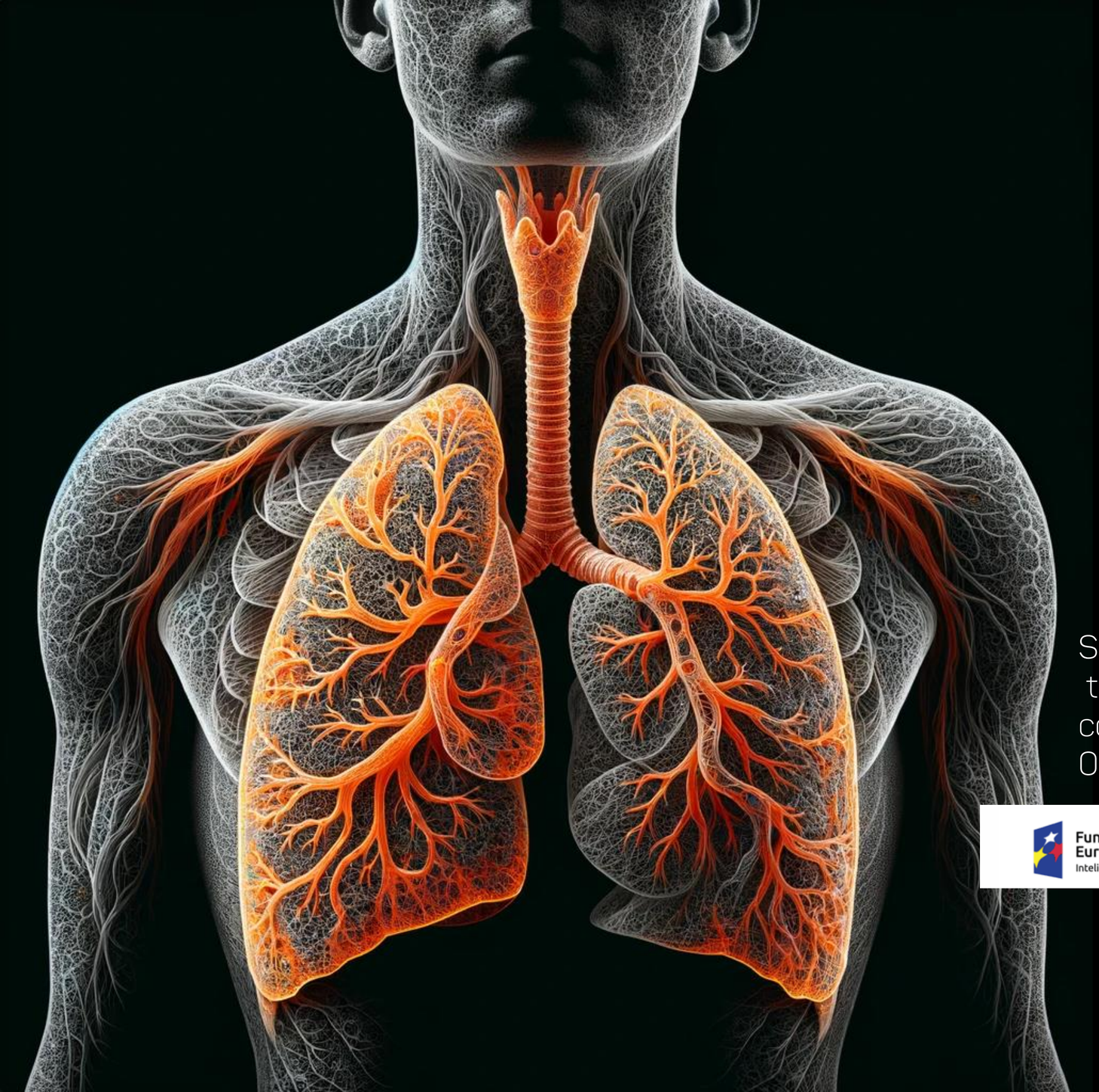


CELON PHARMA

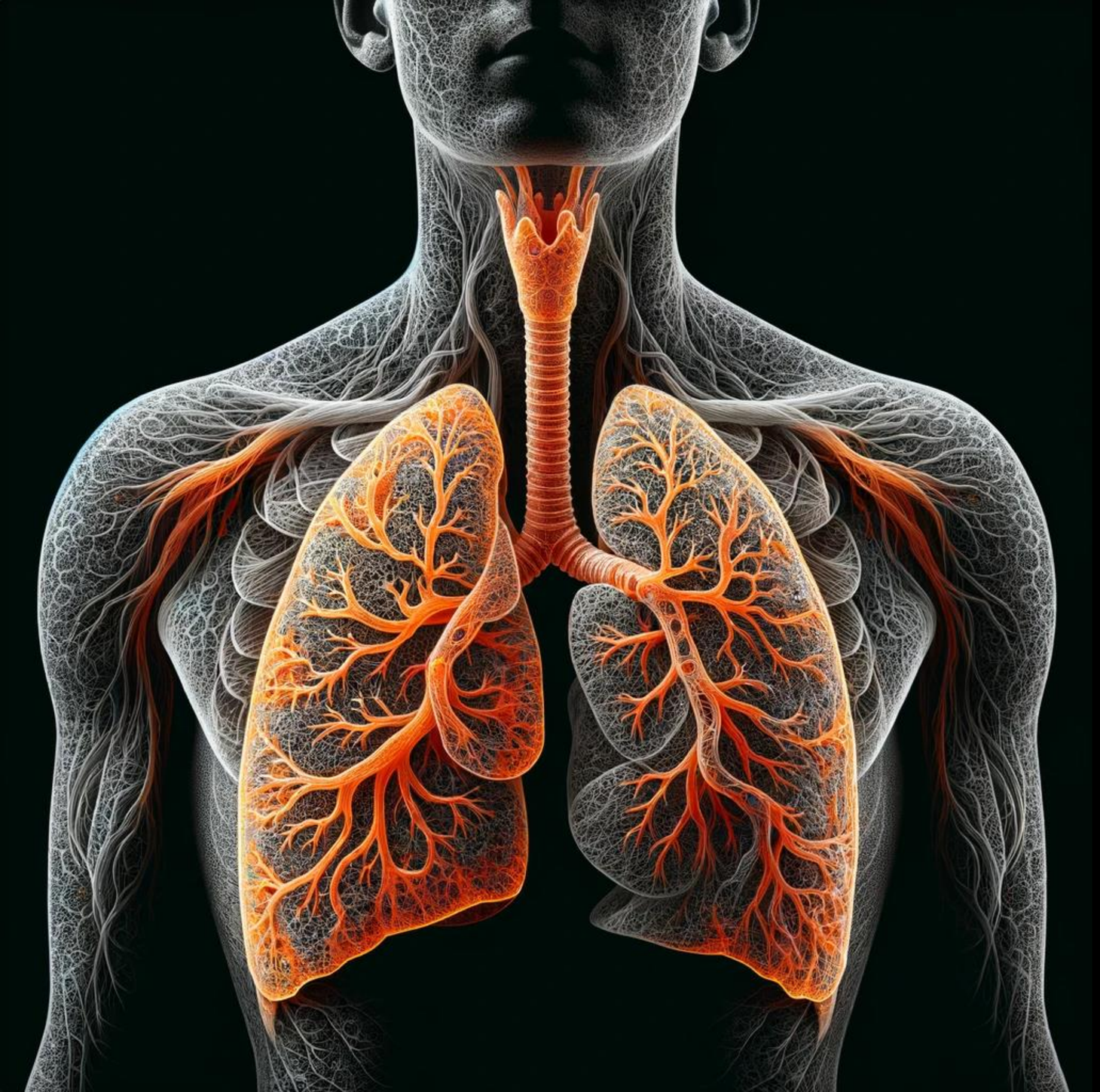
First-in-Class Highly Selective, Potent Dual JAK/ROCK Inhibitor for Debilitating Autoimmune Diseases in Clinical Development, with Proven Clinical Safety and Efficacy

Selective JAK kinase inhibitor in the treatment of immune-related diseases" co-financed under contract no. POIR.01.01.01-00-0382/16.

Fundusze Europejskie Inteligentny Rozwój

NCBR Narodowe Centrum Badań i Rozwoju

Unia Europejska Europejski Fundusz Rozwoju Regionalnego



CELON PHARMA

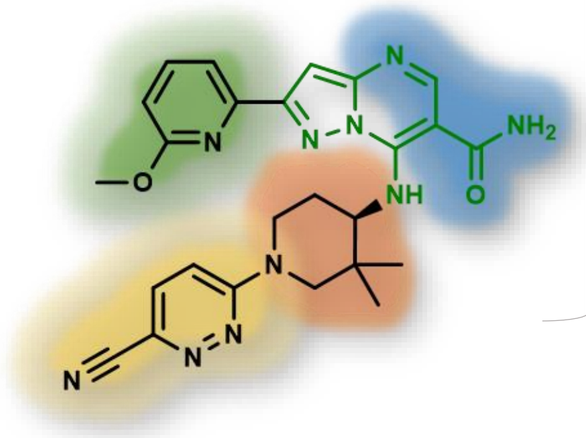
CPL'116

First-in-Class Highly Selective, Potent Dual JAK/ROCK Inhibitor for Debilitating Autoimmune Diseases in Clinical Development, with Proven Clinical Safety and Efficacy

Product	CPL’116
Mechanism of Action	Dual mechanism of action: Janus kinases and Rho-kinases inhibitor (JAK/ROCK)
Route of administration	Oral, small molecule
Features	Safe and well tolerated with no serious AEs; preclinical studies demonstrated anti-inflammatory and anti-fibrotic effect
Indications	Primary: rheumatoid arthritis (RA); potential: plaque psoriasis; interstitial lung disease in RA; idiopathic pulmonary fibrosis; pulmonary arterial hypertension;
Current status	Phase 2 study in RA was successfully completed and confirmed anti-inflammatory efficacy and a well-tolerated profile;
IP	EP3621966B1; US11072619B2
Key Success Factor	New, first-in-class therapeutic applications when anti-inflammatory and anti-fibrotic activity is needed.

CPL’116: First-in-Class Therapy with Anti-inflammatory and Anti-fibrotic Activity Significant Market Opportunity:

Celon's CPL’116 is a novel, orally administered, small molecule, kinase inhibitor, dual: Janus kinases and Rho-kinases inhibitor (JAK/ROCKi).



Anti-inflammatory module

JAK inhibition

- Upadacitinib /Rinvoq/
- Baricitinib /Olumiant/
- Tofacitinib /Xeljanz/

Antifibrotic module

Rho inhibition

- Fasudil /Eril/
- Ripasudil
- Netarsudil

CPL'116: Unique Model of Dual JAK/ROCK Inhibitor

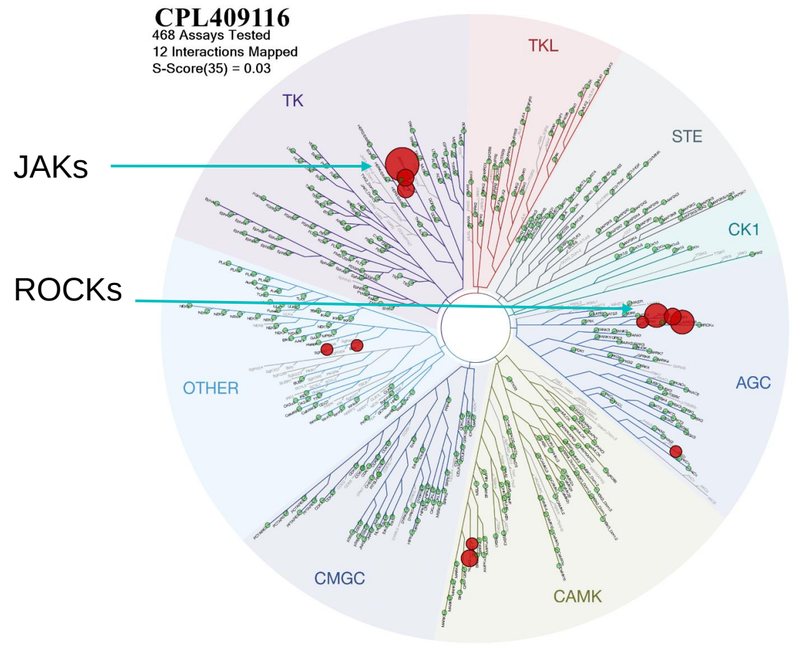
Potent inhibitor of JAKs (JAK1=JAK3>JAK2) and ROCKs kinases with good selectivity:

	IC50 [nM]	
	CPL'116	Tofacitinib
JAK1	0,95	2,46
JAK2	5,36	2,23
JAK3	0,87	1,30
TYK2	63	39

	IC50 [nM]	
	CPL'116	Fasudil
ROCK1	10	4533
ROCK2	5,9	4592

KinomeScan™ for CPL'116 activity towards 403 kinases

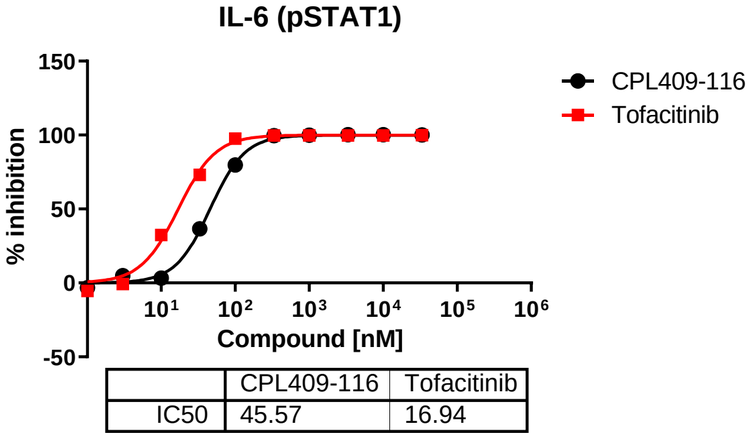
Very high selectivity for JAKs and ROCKs families



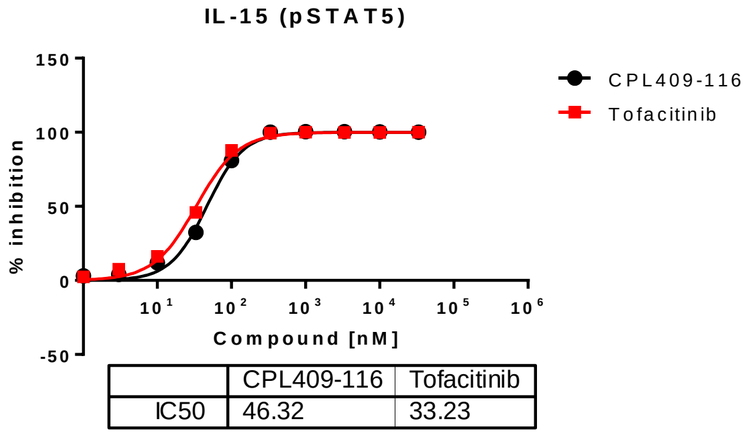
Selectivity Score Type	Numer of Hits	Selectivity Score
1 % of Ctrl	1	0.002
10 % of Ctrl	7	0.017
35 % of Ctrl	12	0.03

Primary Pharmacodynamics – *In vitro* Cell Assays

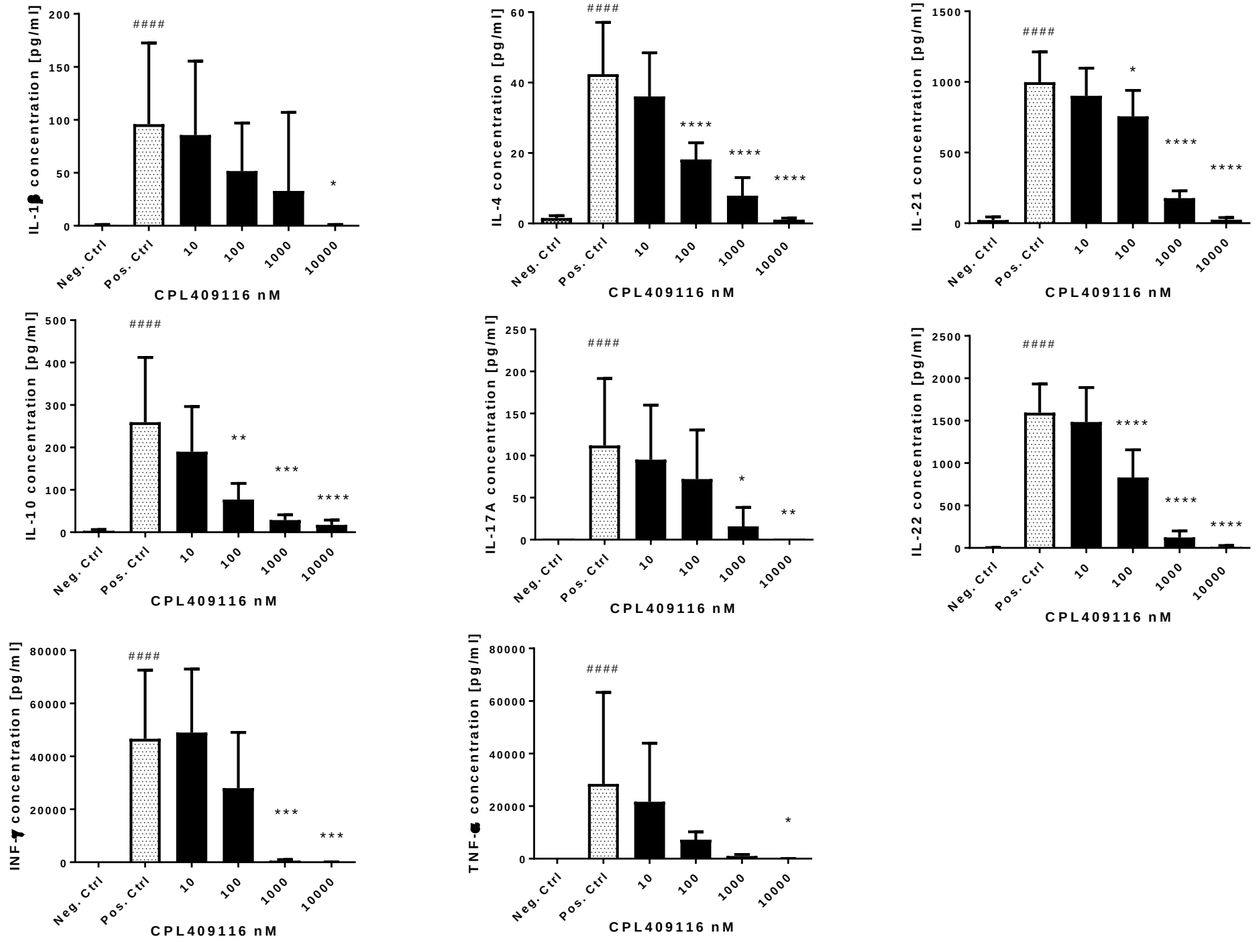
Evaluation of CPL'116 inhibition on cytokine production and STAT pphosphorylation in human PBMC



	CPL409-116	Tofacitinib
IC50	45.57	16.94



	CPL409-116	Tofacitinib
IC50	46.32	33.23

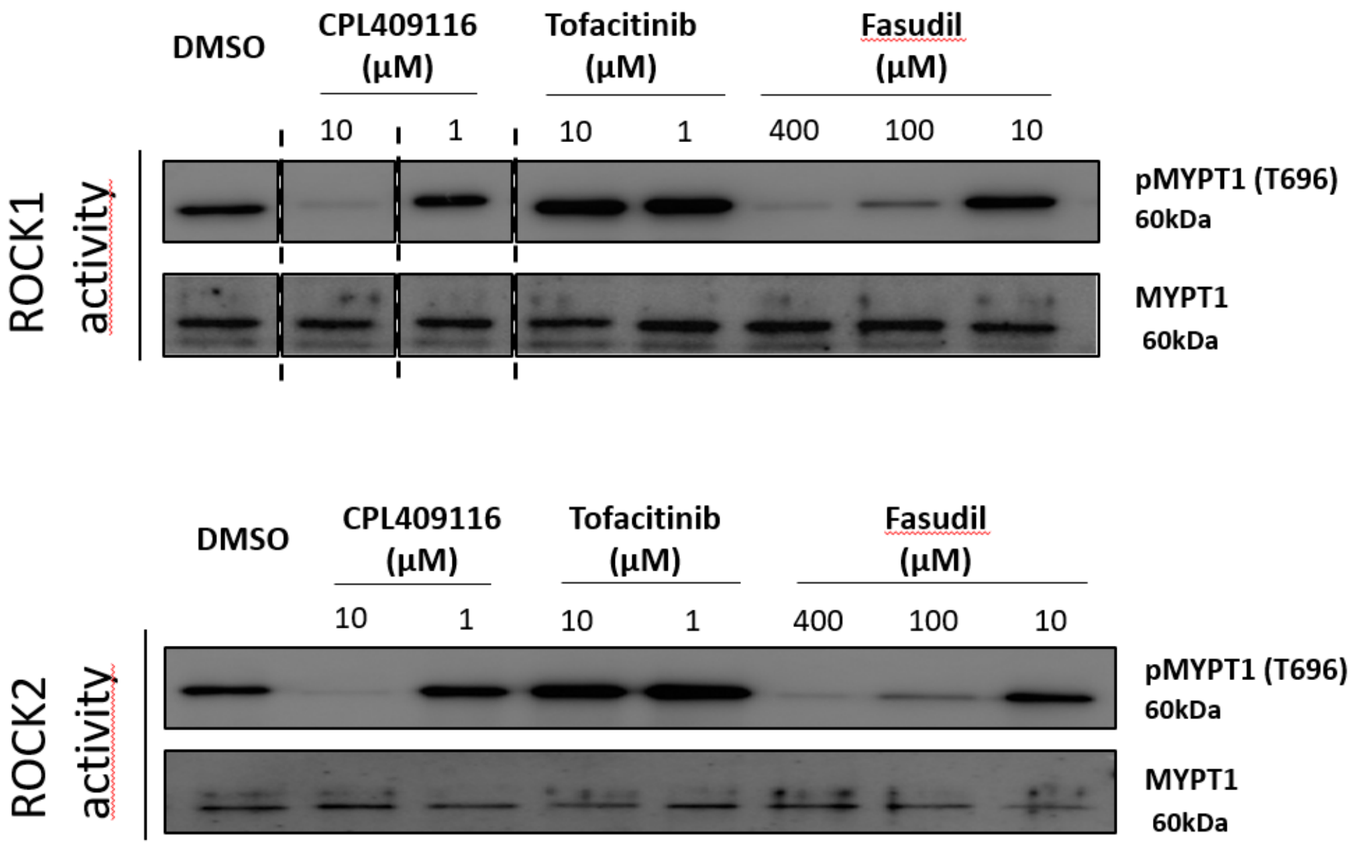


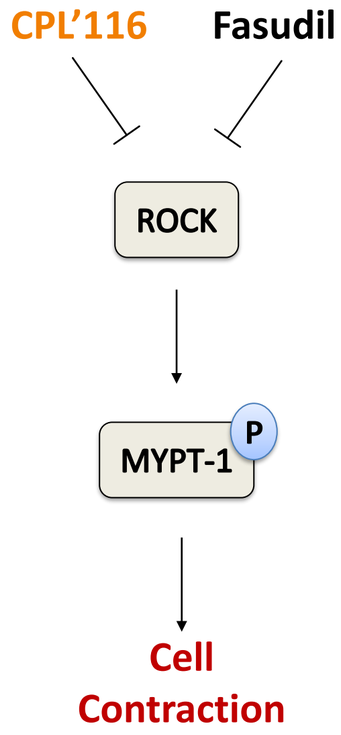
CPL'116 blocks STAT phosphorylation in human PBMC. Human PBMC were stimulated with IL-6 or IL-15 in the presence of range of CPL'116 or tofacitinib concentration. STAT phosphorylation was measured by FACS. IC50 was determined by nonlinear regression.

CPL'116 blocks cytokine production by T cells. Human PBMC were treated with αCD3 and αCD28 for 48 hours. Cytokine concentration in culture supernatants was measured by a Bio-Plex MAGPIX Multiplex Reader. T-test and One-Way Anova were used to determine statistical significance. A value of $p < 0.05$ was considered statistically significant. T-test: #### p<0,0001; One-way ANOVA: *p<0.05, **p<0,01, ***p<0,00 and ****p<0,0001. Error bars represent SEM.

CPL'116 – Potent Inhibitor of Rho-associated Kinases

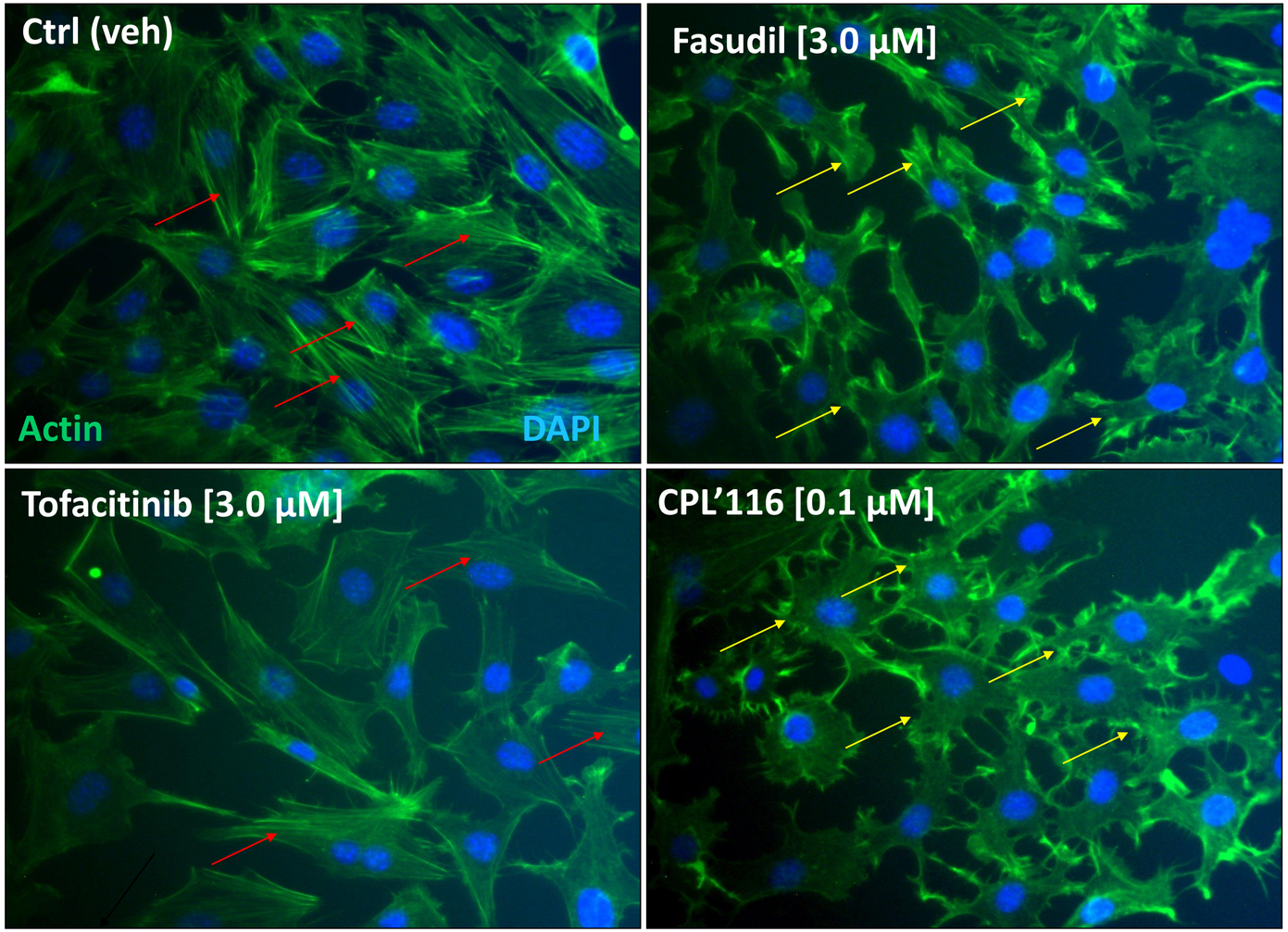
CPL'116, through ROCK inhibition, reduces phosphorylation of MYPT1

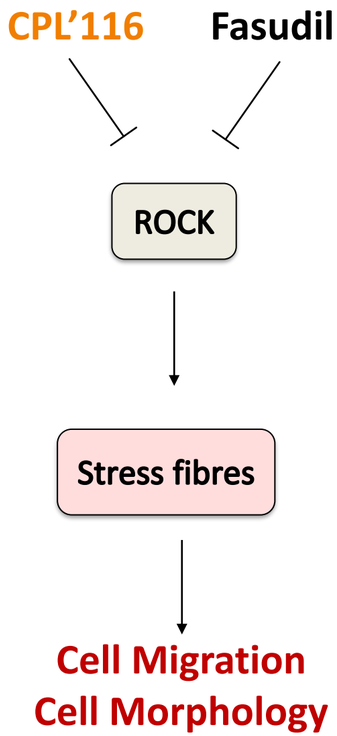




Primary Pharmacodynamics – *In vitro* Cell Assays

CPL'116, through ROCK inhibition, reduces actin stress fibers formation

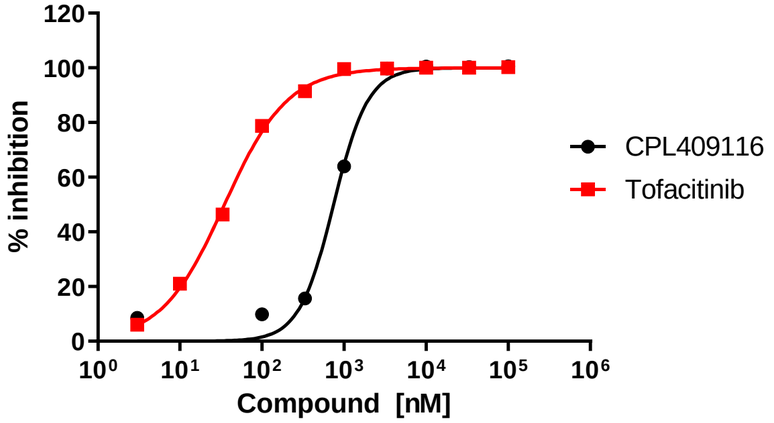




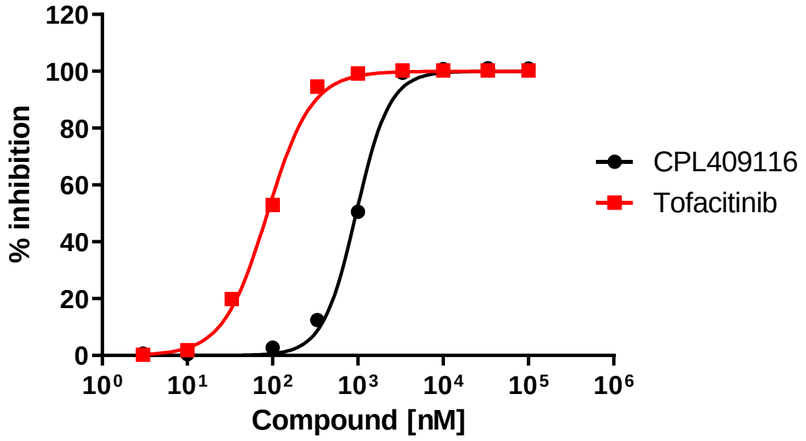
CPL'116 blocks stress fibres formation in mouse fibroblasts.

Primary Pharmacodynamics – Whole Blood Assay

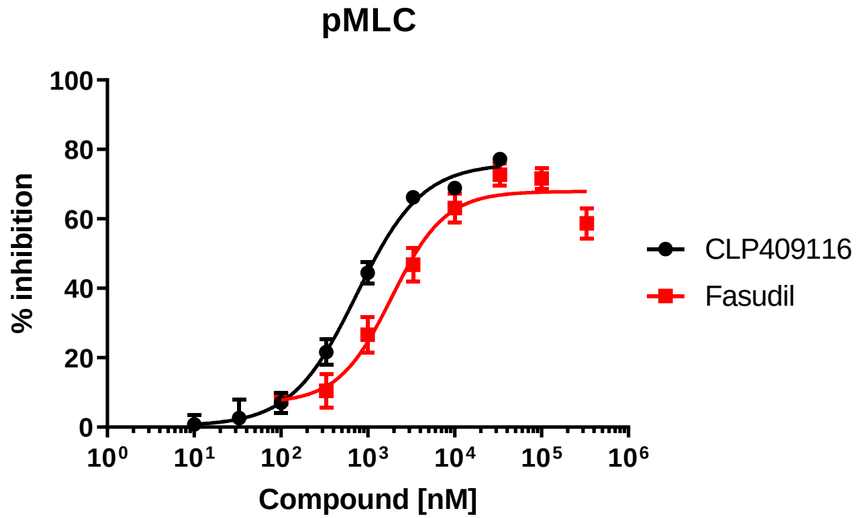
CPL'116 has similar inhibitory activity against JAK and ROCK kinases in Human Whole Blood



	CPL409116	Tofacitinib
IC50	742.3	34.80



	CPL409116	Tofacitinib
IC50	950.1	86.34

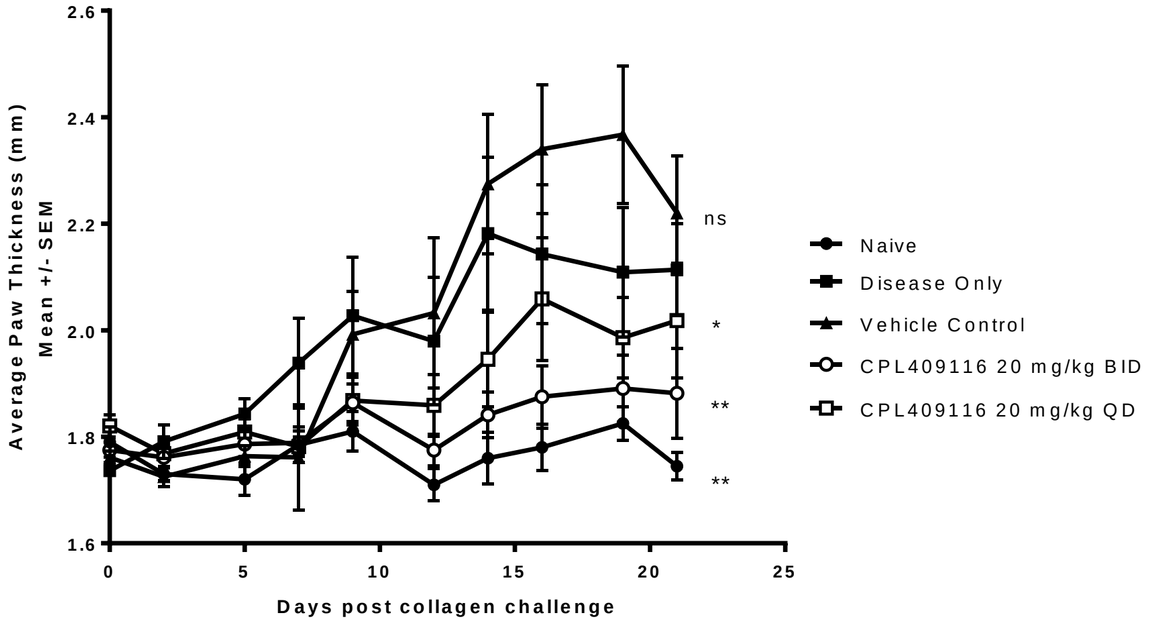


	CLP409116	Fasudil
IC50	742.2	1885

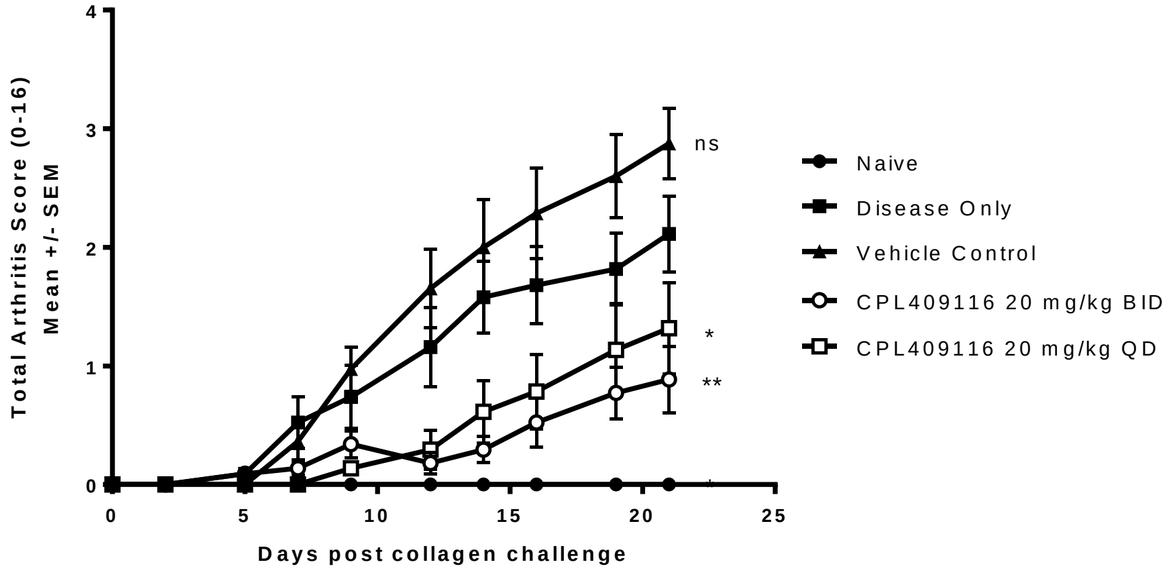
CPL'116 STAT1, STAT5 and MLC phosphorylation in Human Whole Blood. For STAT1 and STAT5 phosporylation HWB was stimulated with IL-6 and IL-15 respectively. Pshosphorylation was measured by FACS. IC50 was determined by nonlinear regression.

Primary Pharmacodynamics – *In vivo* Efficacy

Collagen induced arthritis



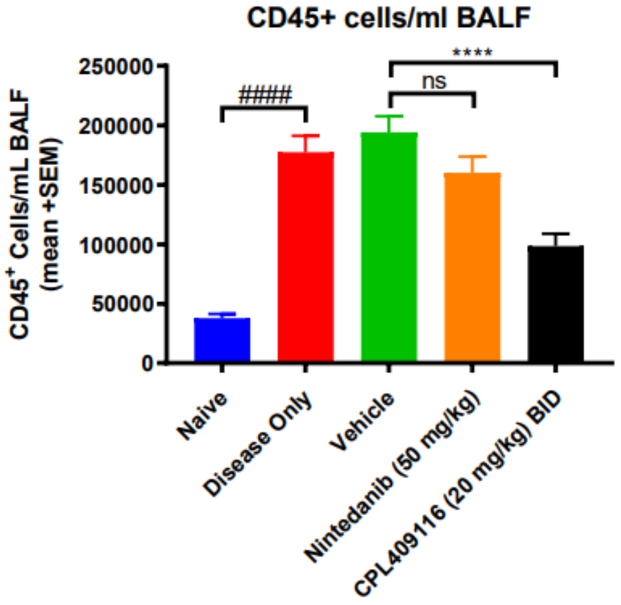
The average thickness of the rear left and rear right paws of each animal. Group means +/- SEM are displayed over time. One-Way Anova was used to determine statistical significance. A value of $p < 0.05$ was considered statistically significant. *p<0.05 and **p<0.01. N=11



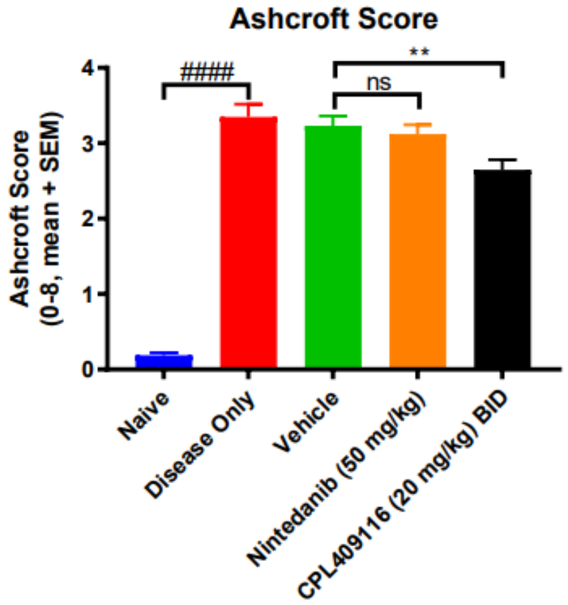
Arthritis clinical score (determined for each animal as the sum of the scores for each paw). Group means +/- SEM are displayed over time. One-Way Anova was used to determine statistical significance. A value of $p < 0.05$ was considered statistically significant. *p<0.05 and **p<0.01. N=11

CPL'116: Activation of Broad Anti-fibrotic Activity in Bleomycin-induced Pulmonary Fibrosis Mouse Model

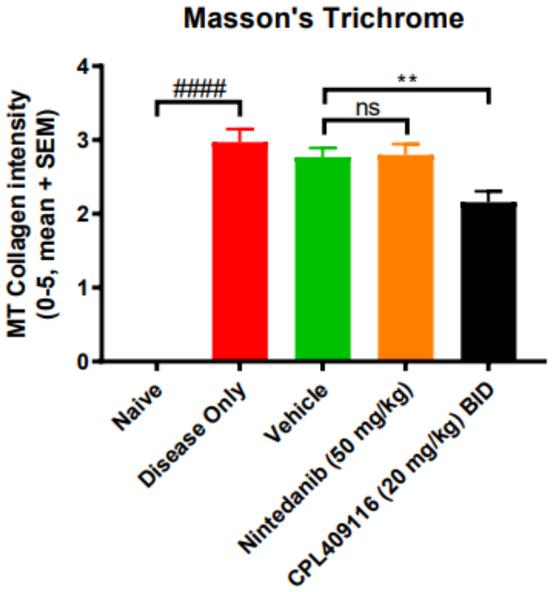
The performed studies showed that CPL'116 blocks immune cells migration to the lungs. There was also decrease in lung fibrosis development observed:



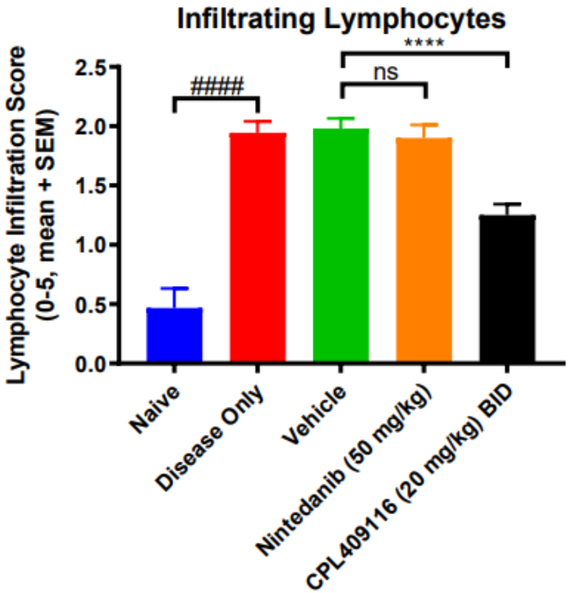
Total CD45+ cells in BALF. Leukocytes (CD45+ cells) were analyzed in bronchoalveolar lavage fluid (BALF) via FACS. Cell infiltration into lung tissue/alveoli is characteristic of inflammation and fibrotic disease.



H&E Histopathology analysis of lung tissue.



Masson's Trichrome histopathological analysis of lung fibrosis: Lung tissue slides were stained with MT to measure collagen fibers in lung tissues.



Lymphocyte and neutrophil infiltration.

CPL’116: Clinical Development Overview

Phase 1

NCT04670757

Q4 2020 – Q3 2021

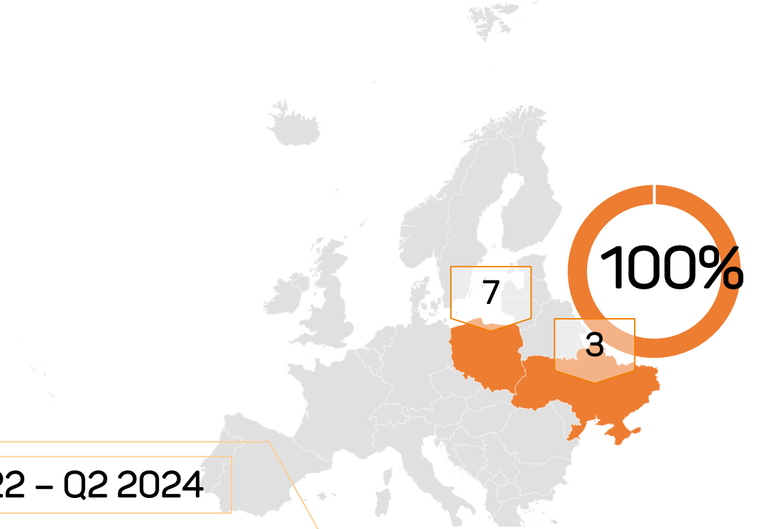
65 healthy volunteers
Safety, PK, PD
SD and MD (2 weeks)

Phase 2
Rheumatoid Arthritis

NCT05374785

Q2 2022 – Q2 2024

106 patients with Rheumatoid Arthritis
3 doses vs placebo
Efficacy, Safety, PK
MD (4 weeks)

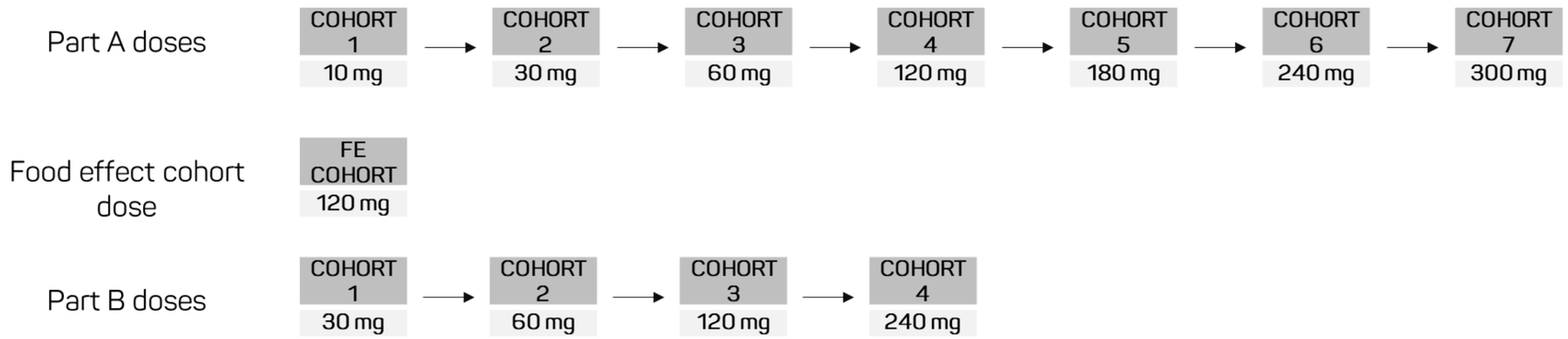


Enrollment: completed
Study readouts: available

CPL’116: Phase 1 Study Design

Safety and Pharmacokinetics of JAK/ROCK Inhibitor in Healthy Volunteers

Open label		Double-blind, placebo-controlled, randomized
Single ascending dose	Dose administered with food	Multiple ascending dose, 2 weeks twice daily administration
Part A	Food effect cohort	Part B
7 cohorts (n=3)	1 cohort (n=12)	4 cohorts (n=8) randomization 3:1



Phase 1: Safety Results

CPL'116 is safe and well tolerated after single and repeated administration in healthy volunteers

Part A:
In total 11 AE's were reported: elevaled bilirubin level, increased leukocyte number, elevated creatine kinase serum level) with **no relation with study drug**

Part B:
In total 43 AE's were reported: **none related with CPL'116**

AE's occurred in >5% of patient in Part B

Adverse event	Overal n= 32	CPL409116			
		30 mg (n=6)	60 mg (n=6)	120 mg (n=6)	240 mg (n=6)
bruise	3 (9,4)	0 (0.0)	0 (0.0)	1 (16.7)	2 (33.3)
diarrhea	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
excessing sweating	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
headache	9 (28,1)	1 (16,7)	0 (0.0	2 (33.3)	4 (66.7)
hematoma	3 (9.4)	0 (0.0)	3 (50)	0 (0.0)	0 (0.0)
increase ALT	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
increase of leucocyte levels	2 (6.3)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
nausea	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)

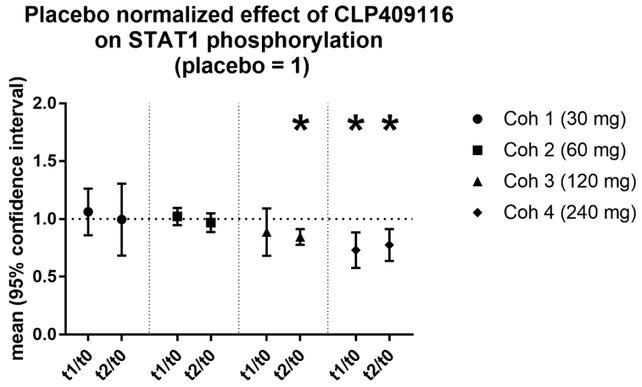
Safety conclusion:

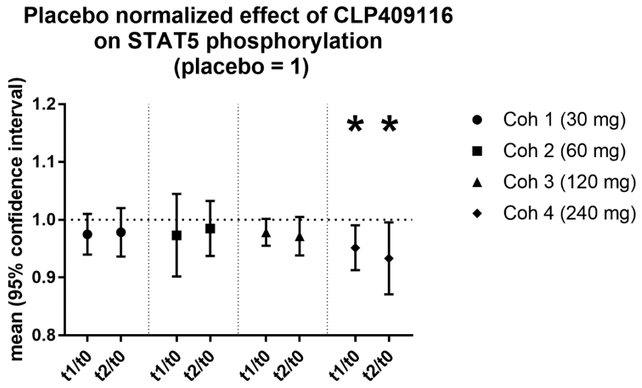
- Generally safe and well tolerated without serious AEs observed
- Most reported AEs were classified as mild to moderate severity
- Frequency of reporting specific symptoms decreased with time from start of the treatment and was highest during firs 4 – 8 days of the study
- Maximal severity of symptoms was usually observed shortly after IMP administration (most frequently 1h after IMP administration) and were transient

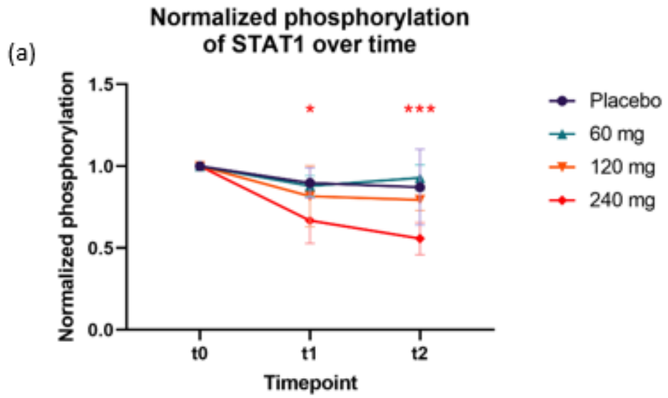
Pharmacodynamic - Phase 1

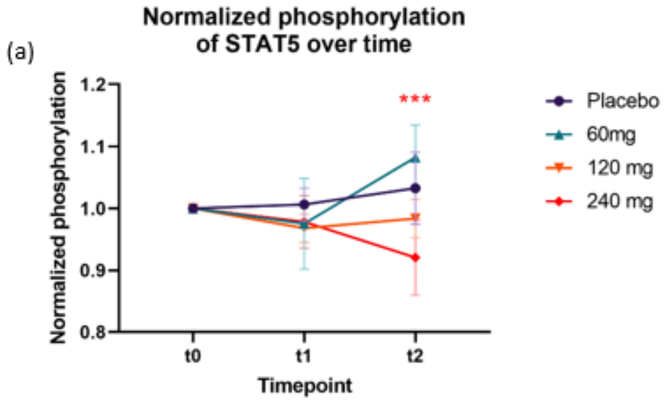
CPL'116 inhibits JAK and ROCK kinases in healthy volunteers

JAK's inhibition

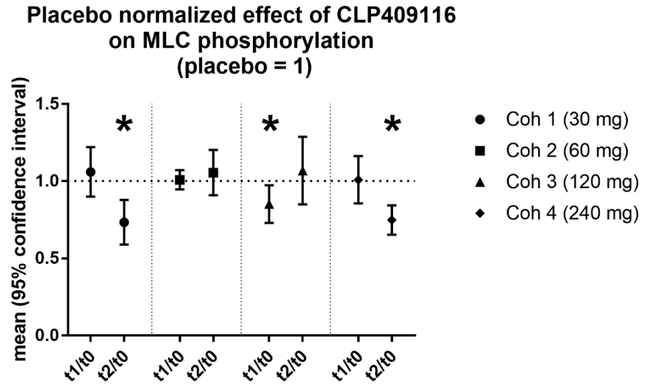


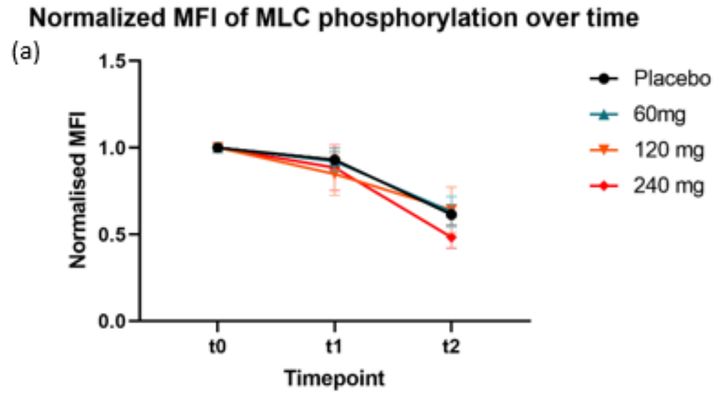






ROCK's inhibition

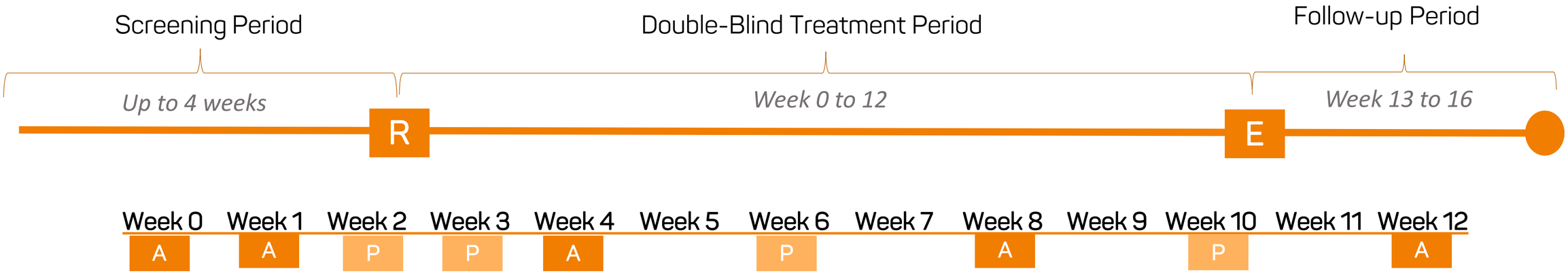




CPL'116 decreased JAKs and ROCKs downstream proteins (STATs and MLC respectively) in human blood of healthy volounteers. Blood samples were collected before (t0) and 2 h after IMP administration on Day 1 (t1) and Day 14 (t2). Statistical signifinace calculated based on t- test (normalisation vs. Placebo; top) and two-way annova (normalized to t0; bottom).

Phase 2 Study Design

A 12-week, Phase 2, multicentre, randomised, double blind, efficacy and safety study comparing CPL'116 to placebo, in combination with methotrexate in participants with active rheumatoid arthritis who have an inadequate response to methotrexate



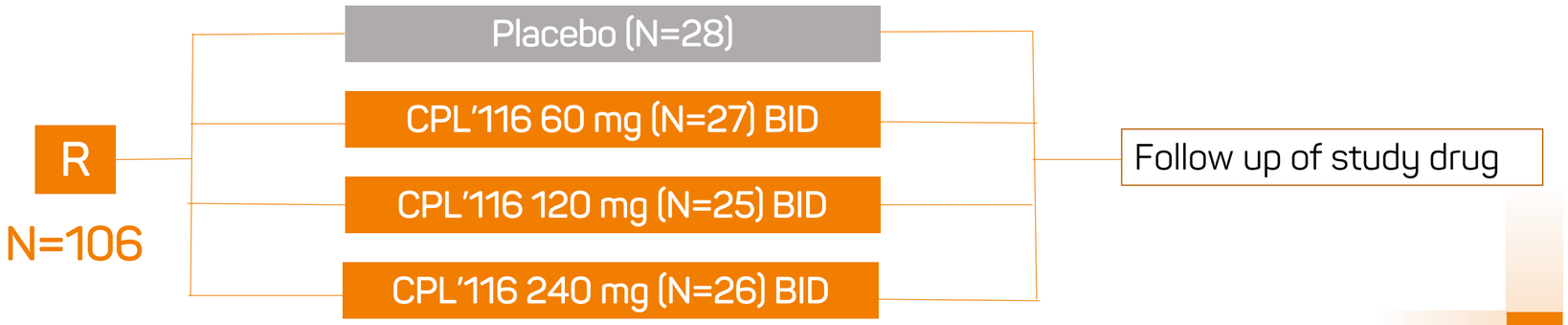
R Randomization

E End of treatment&primary endpoint

End of study

A Ambulatory visit

P Phone call



Clinical Development – Phase 2 Rheumatoid Arthritis

Phase 2 double-blind, randomized, placebo controlled, parallel group efficacy and safety study comparing CPL'116 to placebo in patients with active Rheumatoid Arthritis

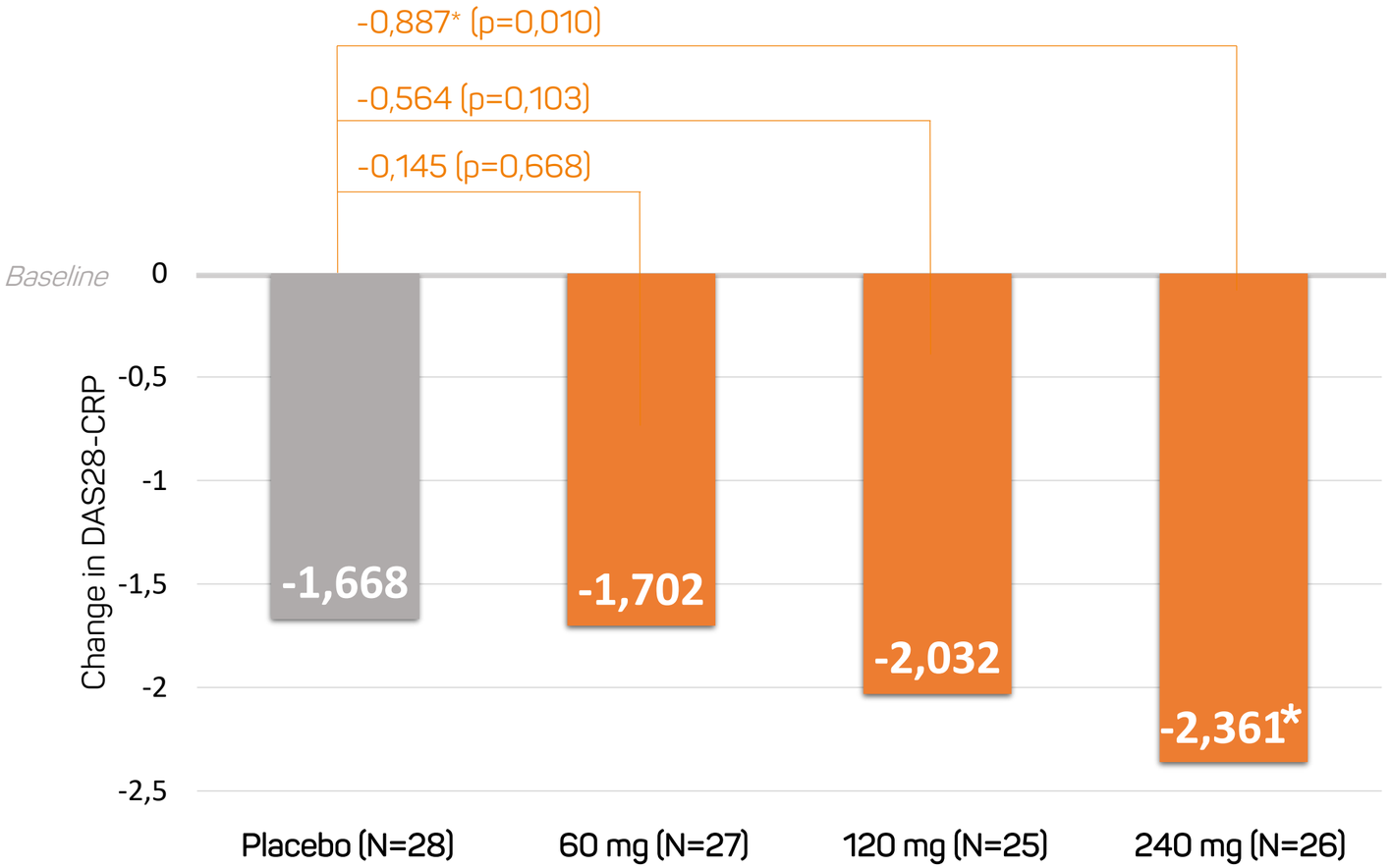
Study overview

Status	Completed	**Objectives**	To determine the efficacy of CPL'116 at 12 weeks, in subjects with active RA who have had an inadequate response to methotrexate (MTX). To determine the effect of CPL'116 at 3 different doses, compared to placebo in subjects with rheumatoid arthritis; To assess dose-response and exposure- response relationship for CPL'116; To evaluate safety and tolerability of CPL'116 administered at doses: 60 mg, 120 mg or 240 mg twice a day for 12 weeks in subjects with RA.
Indication	Rheumatoid Arthritis	**Primary Endpoint**	Change from baseline in Disease Activity Score (DAS)28- C Reactive protein (CRP) at Week 12.
Arms	Double-blind, randomized: 1:1:1:1; CPL'116 (60 mg, 120 mg, 240 mg), placebo	**Key Secondary Endpoints**	Proportion of subjects with DAS28-CRP remission at Weeks 4; 8; 12 and 16; American College of Rheumatology (ACR)20, ACR 50, ACR 70, and ACR 90 responder rates (Weeks 4, 8 and 12); Safety and tolerability of CPL'116: vital signs (blood pressure (BP), pulse and temperature), laboratory tests, Adverse Events (AEs) and Serious Adverse Events (SAEs), 12-lead electrocardiogram (ECG).
		Key Inclusion Criteria	• Be between the ages of 18 and 75 at screening • Meets ACR/EULAR 2010 RA Classification Criteria with a duration of RA disease of ≥6 months at time of screening and participant not diagnosed before 16 years of age. • Must have active disease at both screening and baseline, as defined by having all three:. ≥ 6/68 tender/painful joints (TJC); ≥ 6/66 swollen joints (SJC); DAS28> 3,2. • Must have a C-reactive protein (CRP) measurement ≥7 mg/L at screening.
		Key Exclusion Criteria	• Has had a serious infection (e.g. sepsis, pneumonia, pyelonephritis or any other serious infection as per Investigator's judgement), or has been hospitalized or received intravenous antibiotics for an infection within 3 months prior to Day 1/ baseline. • Any active infection including localized infections within 2 weeks prior to baseline. • History of opportunistic or recurrent (3 or more of the same infection requiring anti-infective treatment in any rolling 12-month period) infection. • Presence of any of the laboratory abnormalities at screening: ALT or AST levels 1.5 x the upper limit of normal (ULN); absolute neutrophil count of <1.5 x 109/L (<1500/mm3); absolute lymphocyte count of <0.75 x 109/L (<750/mm3); absolute white blood cell (WBC) count of < 3.0 x 109/L (<3000/mm3); hemoglobin <9.0 g/dL (90 g/L); thrombocytopenia, as defined by a platelet count <100 x 109/L (<100 000/mm3) at Screening; total bilirubin ≥1.5× the upper limit of normal (ULN). • History of major organ transplant (e.g. kidney, heart, liver, lung) or hematopoietic stem cell/bone marrow transplant. • History of or current moderate to severe congestive heart failure (NYHA class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.

CPL'116 Phase 2: Primary Endpoint

Efficacy based on change in DAS28-CRP scale at week 12

Change from baseline in DAS28-CRP at week 12 by randomized treatment of CPL'116 (Intent to treat set); Overall, N=106:

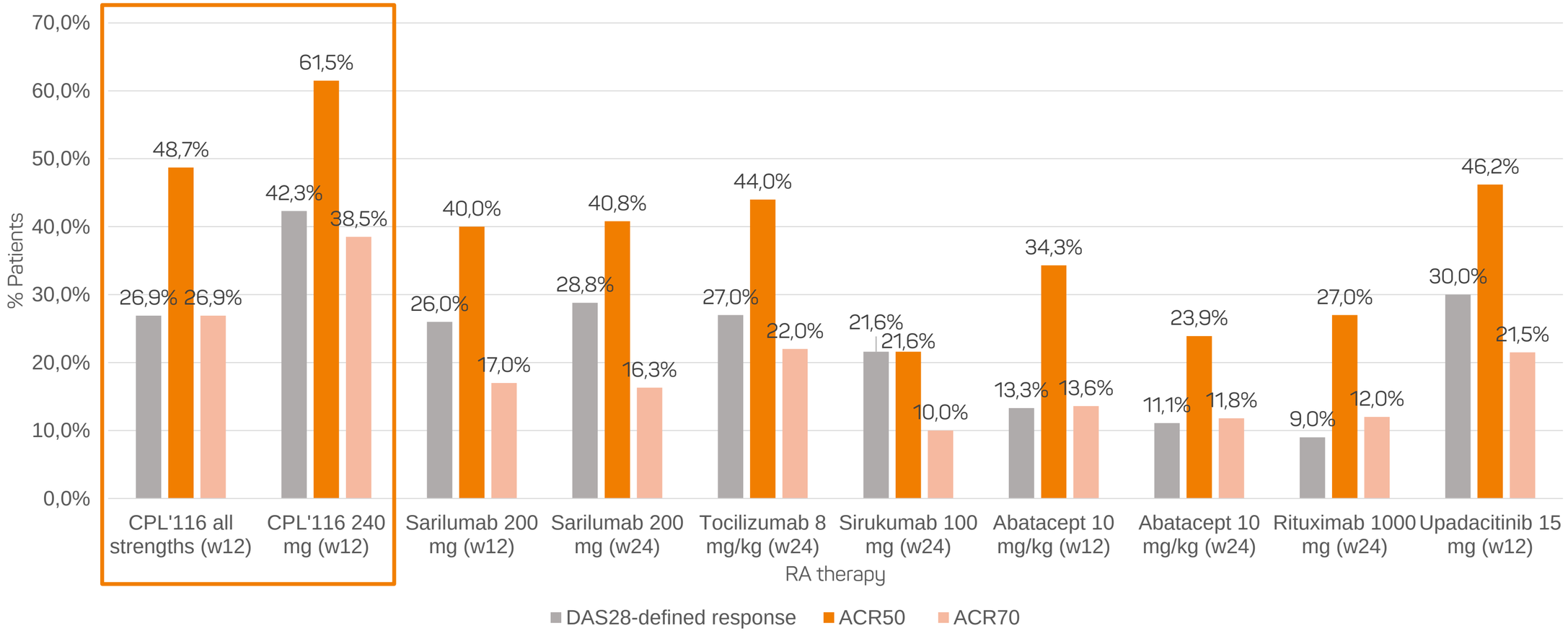


DAS28-CRP difference between Day 1 and Day 85	Placebo, N=28	CPL'116 60 mg, N=27	CPL'116 120 mg, N=25	CPL'116 240 mg, N=26
mean (SD)	-1.668 (1.545)	-1.702 (1.368)	-2.032 (1.030)	-2.361 (1.106)
LS Mean (SE)	-1.496 (0.239)	-1.641 (0.237)	-2.060 (0.243)	-2.383 (0.237)
LS Mean Difference from Placebo (SE)		-0.145 (0.337)	-0.564 (0.343)	-0.887 (0.337)
p-value vs. Placebo		0.668	0.103	0.010
Cohen's D		-0.023	-0.277	-0.516

*Statistically significant

CPL'116 Key Secondary Endpoints – Comparison of Efficacy

Superior Effect of CPL'116 in DAS28-Defined Remission vs. Other RA Therapies



Percentages of patients achieving a response according to the American College of Rheumatology 50% improvement criteria (ACR50), and 70% improvement criteria (ACR70) at week 12 (w12) or week 24 (w24). Disease Activity Score 28-joint assessment for swelling and tenderness (DAS28) - disease remission was defined as DAS28-CRP score <2.6. Indirect comparison.

Source DOI: 10.1002/art.39093; 10.1016/S0140-6736(08)60453-5; 10.1002/art.22025; 10.1136/ard.2007.074773; 10.1056/NEJMoa2008250; 10.1038/s41584-019-0279-6

CPL'116: Safety and Tolerability in Phase 2

Safety profile consistent with drug class

Summary of adverse events by randomized treatment of CPL'116

Category	Overall, N=106	Placebo, N=28	CPL'116		
			60 mg, N=27	120 mg, N=25	240 mg, N=26
Adverse event (AE)	170 (100.0%)	35 (100.0%)	36 (100.0%)	47 (100.0%)	52 (100.0%)
Pre-treatment AE	13 (7.6%)	6 (17.1%)	1 (2.8%)	4 (8.5%)	2 (3.8%)
Serious AE (SAE)	2 (1.2%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (1.9%)
Treatment emergent AE (TEAE)	157 (92.4%)	29 (82.9%)	35 (97.2%)	43 (91.5%)	50 (96.2%)
Treatment emergent SAE (TESAE)	2 (1.2%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (1.9%)
Severe TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Related TEAE	92 (54.1%)	16 (45.7%)	20 (55.6%)	25 (53.2%)	31 (59.6%)
Related severe TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to reduction of dose	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs leading to interruption of dose	1 (0.6%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
TEAE leading to permanent discontinuation of study medication	7 (4.1%)	0 (0.0%)	1 (2.8%)	1 (2.1%)	5 (9.6%)
Related TEAEs leading to permanent discontinuation of study medication	6 (3.5%)	0 (0.0%)	1 (2.8%)	1 (2.1%)	4 (7.7%)
AE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Related TEAE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Targeted medical adverse events	33 (19.4%)	7 (20.0%)	4 (11.1%)	11 (23.4%)	11 (21.2%)

What makes this asset unique?

- Mechanism of Action
- Selective Action with Limited Kinase Binding
- Preclinical Efficacy Demonstrated
- Favorable Pharmacokinetics and Safety Profile
- Positive Phase 2 Trial Results
- Well Tolerated in Human Studies
- Potential for Broad Application

Dual Mechanism of Action in One Capsule

CPL'116's mechanism of action is mainly based on the **inhibition of JAK1 and JAK3,** with less inhibitory activity against JAK2 and TYK2, as well as **Rho-associated kinase (ROCKs)** inhibition.

Anti-inflammatory and Anti-fibrotic Activity

In addition to RA, CPL'116's mechanism of action makes it a potential candidate for **treating a variety of immune-mediated diseases** like rheumatoid arthritis, plaque psoriasis, **interstitial lung disease in RA, idiopathic pulmonary fibrosis,** and pulmonary arterial hypertension.

Strategic Opportunity

First-in-class dual JAK/ROCK inhibitor with broad potential in autoimmune diseases featuring inflammatory and fibrotic components

Target Market Population (7MM) for Orphan Disease Applications

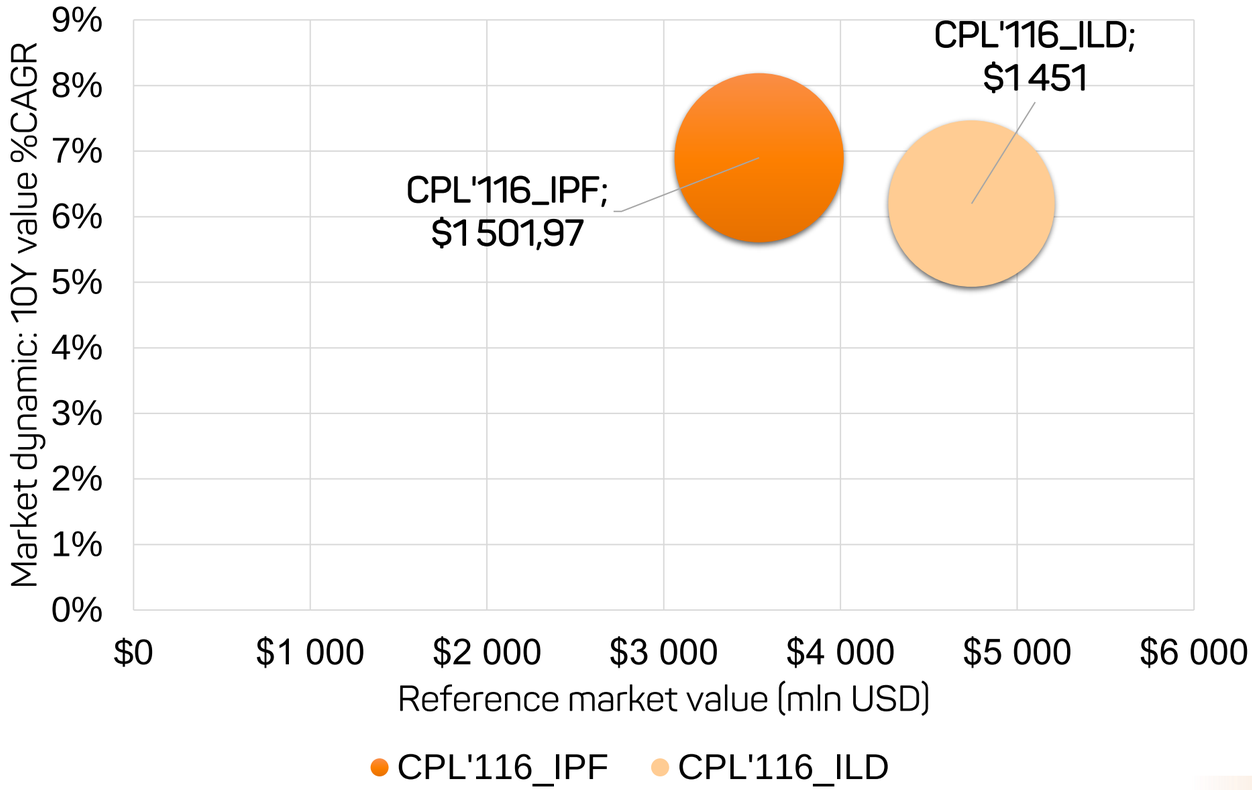
Interstitial Lung Disease in Rheumatoid Arthritis (ILD)

312,8k (2023) +0,7% CAGR

Idiopathic Pulmonary Fibrosis (IPF)

135,3k (2023) +1,7% CAGR

Reference market dynamics vs. market value CPL'116 (bubble size: CPL'116 estimated peak sales in MLN USD, 7MM):



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THANK YOU!