


**CSO Thomas Jonassen**  
**Resomelagon - AP-1189:**  
**Program Overview and**  
**Updates**

# SynAct Pharma – Pipeline overview

Asset	Indication	Pre-clinical	Phase I	Phase IIa	Phase IIb	Phase III
AP1189	Rheumatoid Arthritis Severe treatment-naïve with MTX	Completed			Ongoing	Resolve Part B (Approved in IND)
	Rheumatoid Arthritis DMARD-IR	Completed		Ongoing	Resolve Part B (Approved in IND)	
	Nephrotic syndrome (iMN)	Completed		Ongoing		
	Virus- Induced Respiratory Insufficiency	Completed				
TXP-11	Prevention of organ failures in complicated surgery	Ongoing				
Small Molecules and Peptides	Autoimmune and inflammatory conditions	Ongoing				

 Completed

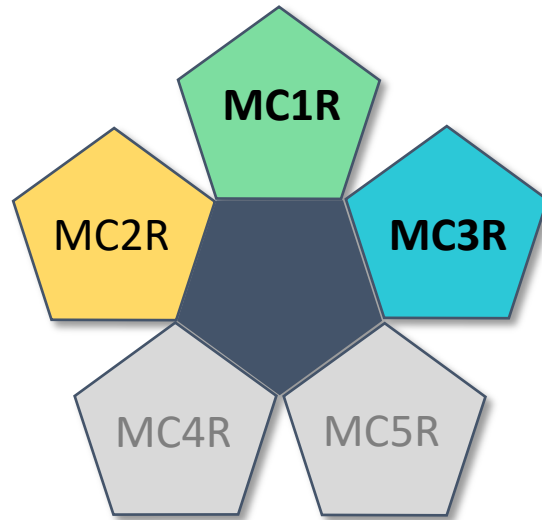
 Ongoing

 Resolve Part B (Approved in IND)

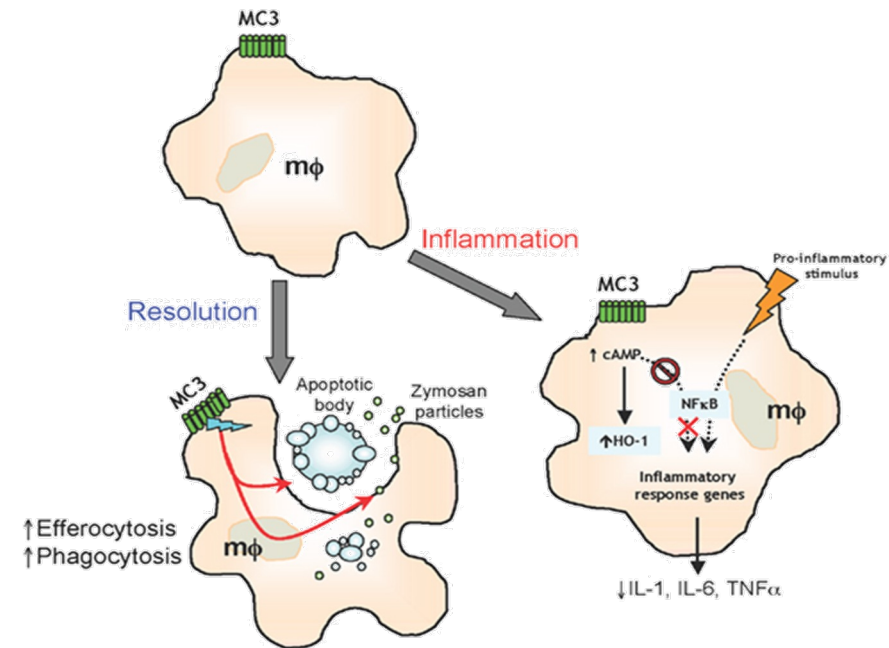
A blurred background image of three scientists in white lab coats working in a laboratory. One scientist in the foreground is looking at a document, while others are visible in the background.

**Resomelagon (AP1189):  
Once-Daily Oral Selective MC1R and MC3R Agonist in Phase 2  
clinical Development for Autoimmune and Inflammatory Diseases**

# SynAct is developing selective melanocortin agonists with both anti-inflammatory and pro-inflammation resolution activity



Steroid dependent effects
 
 Targeted by AP1189 and TXP-11



- Selective stimulation of **melanocortin receptors 1 and 3 (MC1R and MC3R)** present on immune active cells promotes direct immunomodulatory effects
- **Neither AP1189 nor TXP-11 activates MC2R**, present in the adrenal glands, which causes the release of cortisol when stimulated and results in steroid side effects and tolerability issues

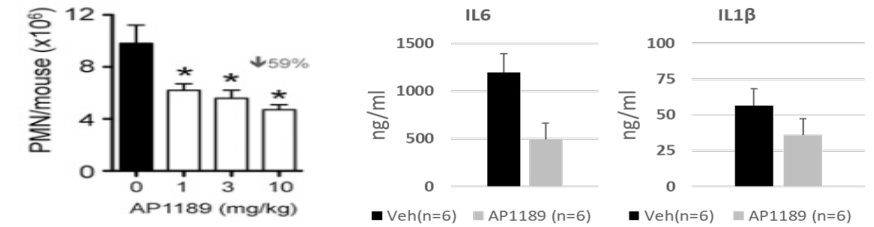
- AP1189 **exhibits anti-inflammatory activity** via MC1R and MC3R stimulation on targets cells – such as lowering the release of pro-inflammatory cytokines
- AP1189 **promotes pro-resolution pathways** following stimulation of MC1R and MC3R on targets cells – such as increasing efferocytosis in macrophages

ACTH: adrenocorticotrophic hormone; MCR: melanocortin receptor

# Lead Program AP1189 – A once-daily oral selective melanocortin agonist

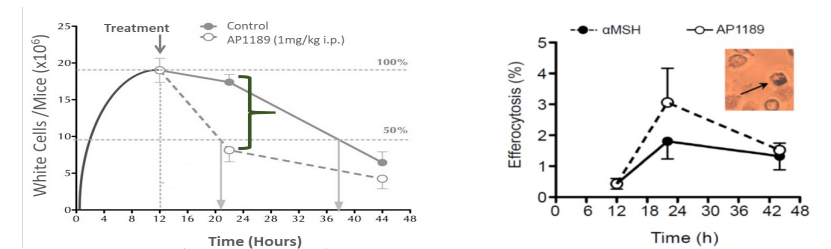
- AP1189 selectively stimulates MC1R and MC3R present on white cells including neutrophils and macrophages
- Reduction but not suppression of cell infiltration and release of pro-inflammatory pathways
- Stimulation of pro-resolving pathways including the ability to stimulate the macrophages' ability to efferocytosis
- As AP1189 is also a biased agonist, the compound will not induce melanogenesis following in vitro stimulation of MC1R

## Administration at disease induction in peritonitis<sup>1</sup>



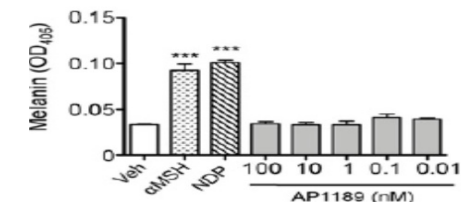
AP1189 inhibits of inflammatory responses

## Therapeutic treatment in peritonitis<sup>1</sup>



AP1189 promotes inflammatory resolution

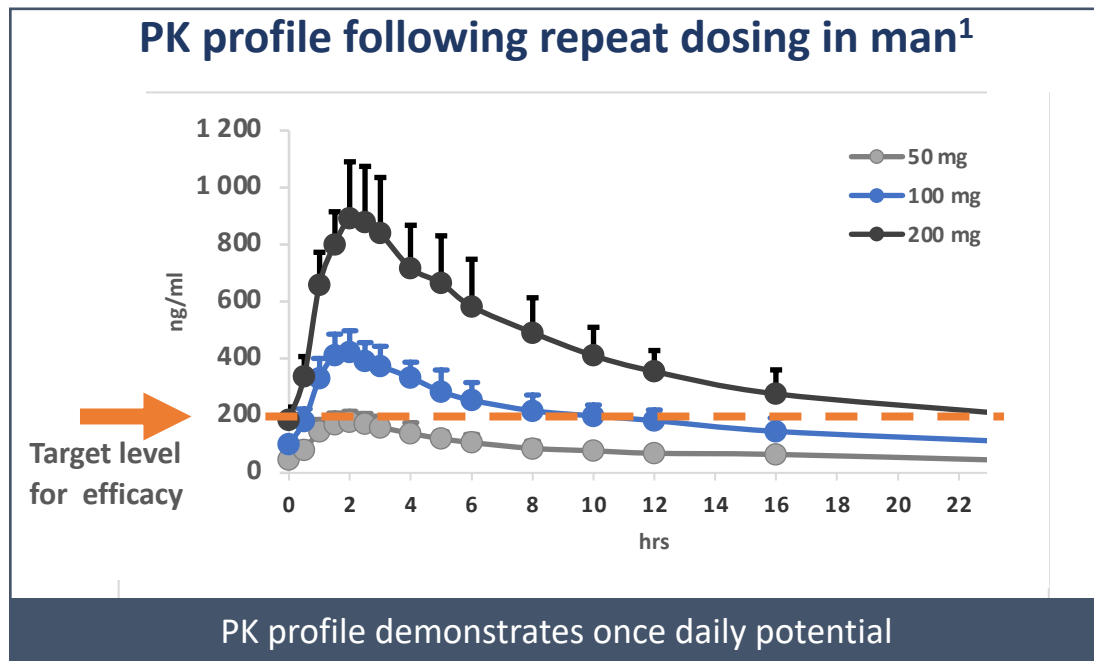
## Melanin production following stimulation of MC1R<sup>1</sup>



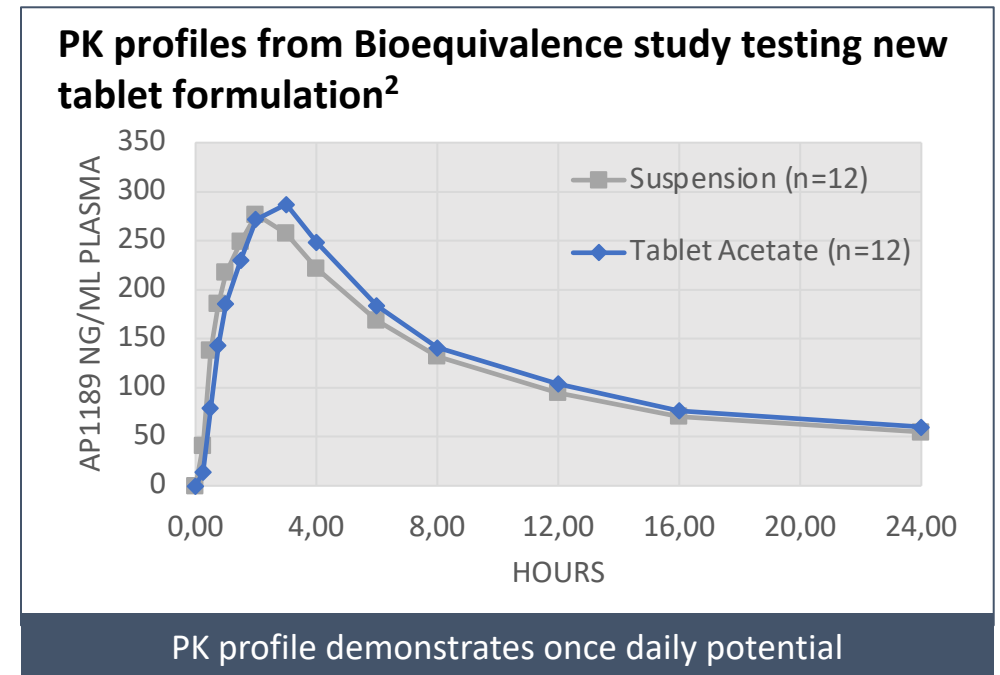
AP1189 does not stimulate melanogenesis

# AP1189 was well tolerated in Phase 1 and Phase 2a studies with pharmacokinetic profile supporting once daily dosing

- Initial clinical development, Phase 1 and Phase 2a, performed with suspension for once daily oral administration was overall well tolerated, no signs of immunosuppression or dose limiting Adverse Events
- Novel immediate release tablet with excellent plasma profile developed and is being dosed in 3 ongoing Phase 2 studies



1. AP1189-CS001 study MAD study



2. AP1189-CS004 bioequivalence study in male volunteers

# Resomelagon (AP-1189)- RA – program



## **The BEGIN Study:**

**A double-blind, multi-centre, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis patients with active joint disease**

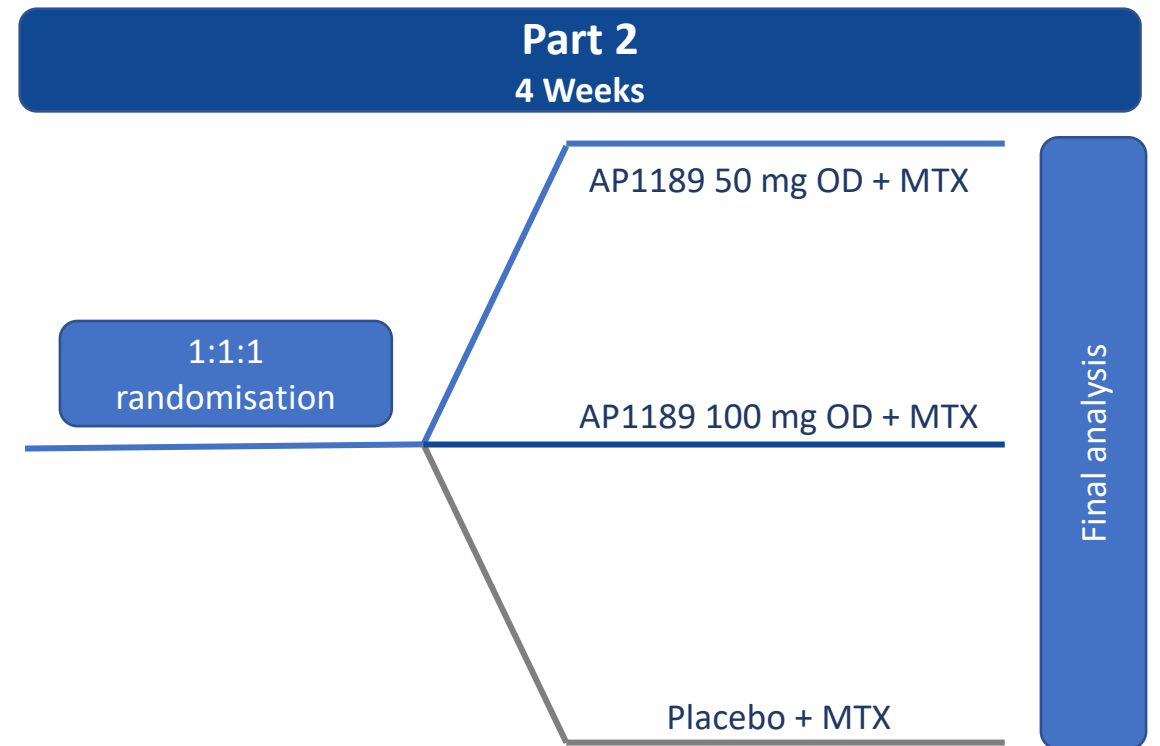
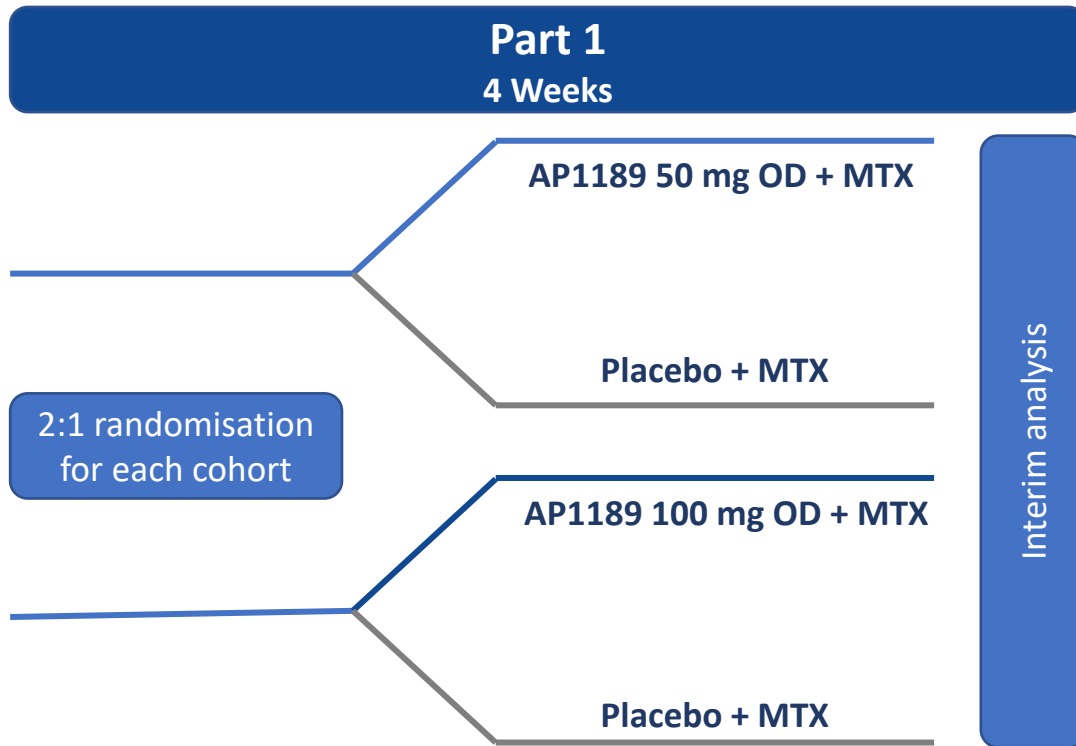
**Completed Q4 2021**





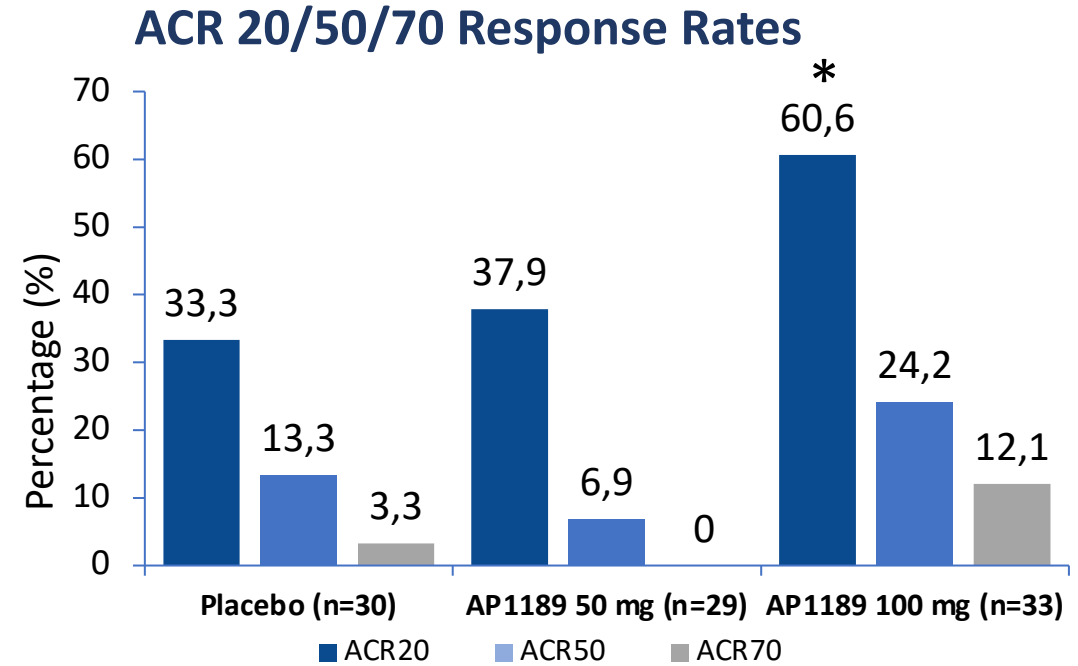
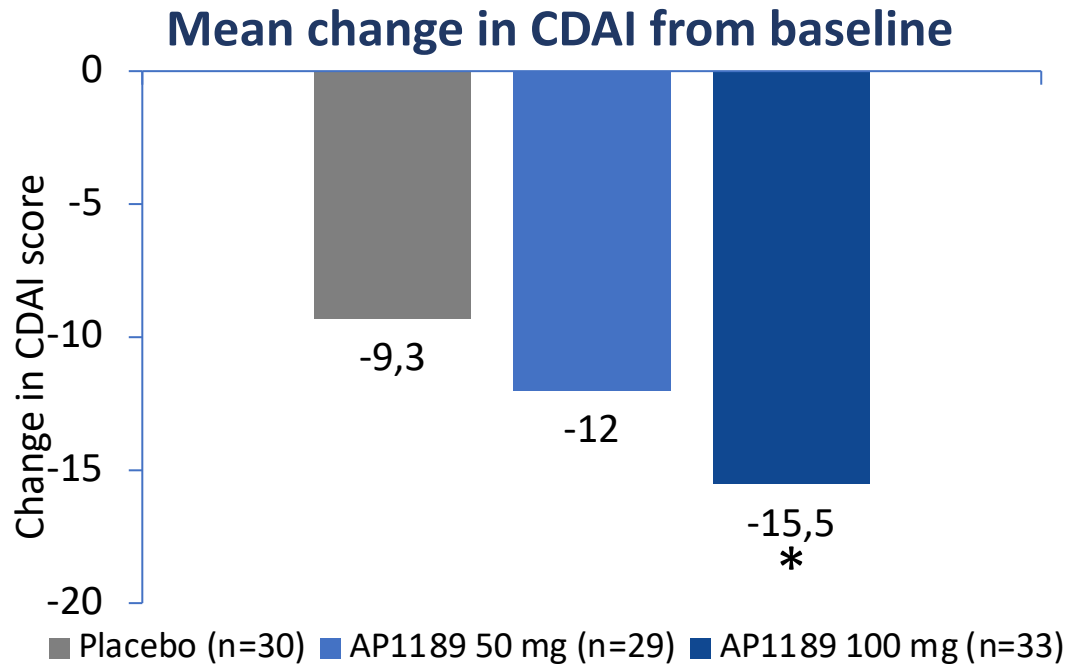
# BEGIN: P2a POC 4-week study of AP1189 + MTX in highly active early RA

Study Population	Primary safety endpoint	Primary efficacy endpoint
Adult patients (aged 18 to 85 years) with severe RA defined as CDAI >22, who are about to begin up-titration with MTX	Safety of AP1189 vs placebo (AEs and SAEs)	<ul style="list-style-type: none"><li>• Mean change in CDAI or</li><li>• % of patients improving from severe (CDAI &gt;22) to at least moderate (CDAI ≤22)</li></ul>



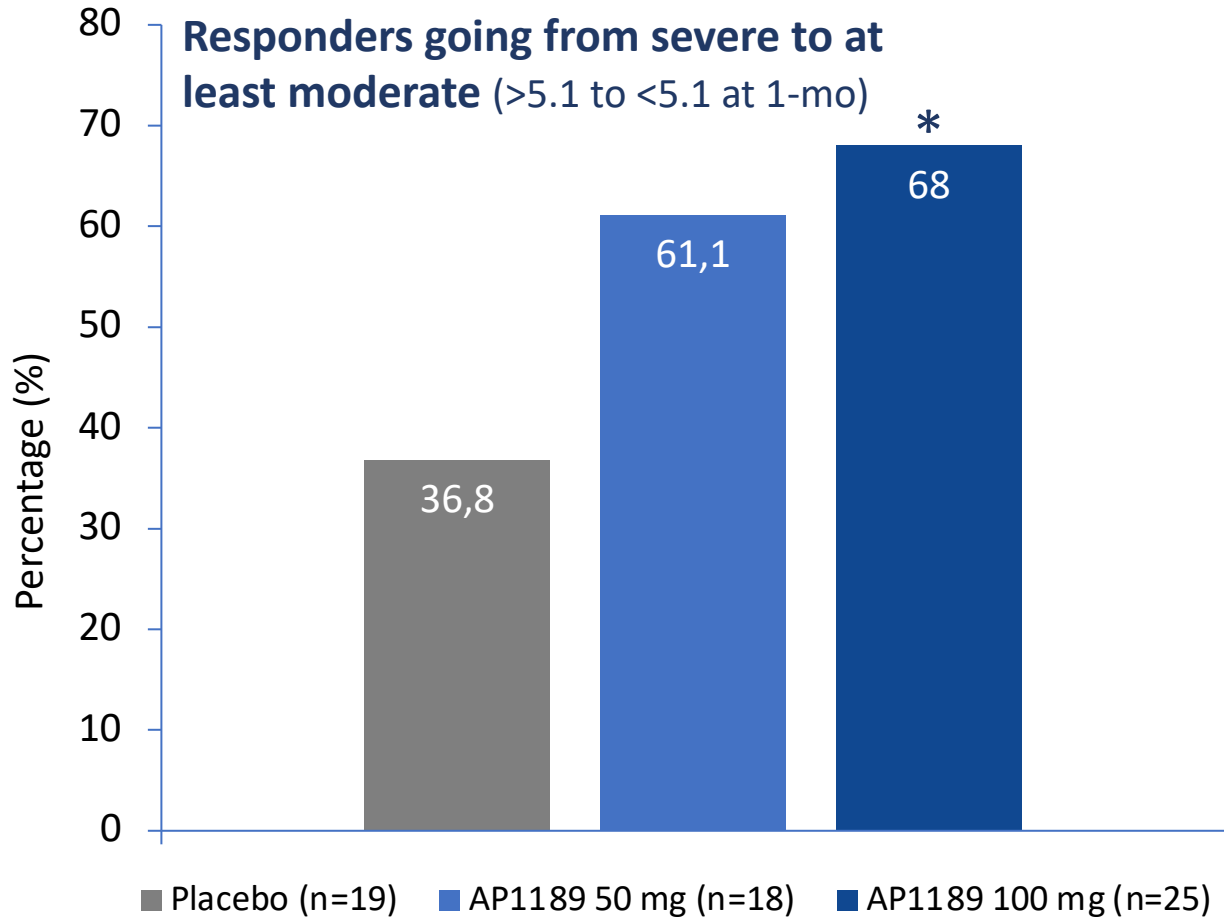
# AP1189 demonstrated significant treatment effects in patients with severe treatment-naïve RA in the 4-week BEGIN P2a clinical trial

Phase 2a study in treatment naïve RA patients with high disease activity (CDAI >22 at randomization) in combination with MTX with 4 weeks treatment

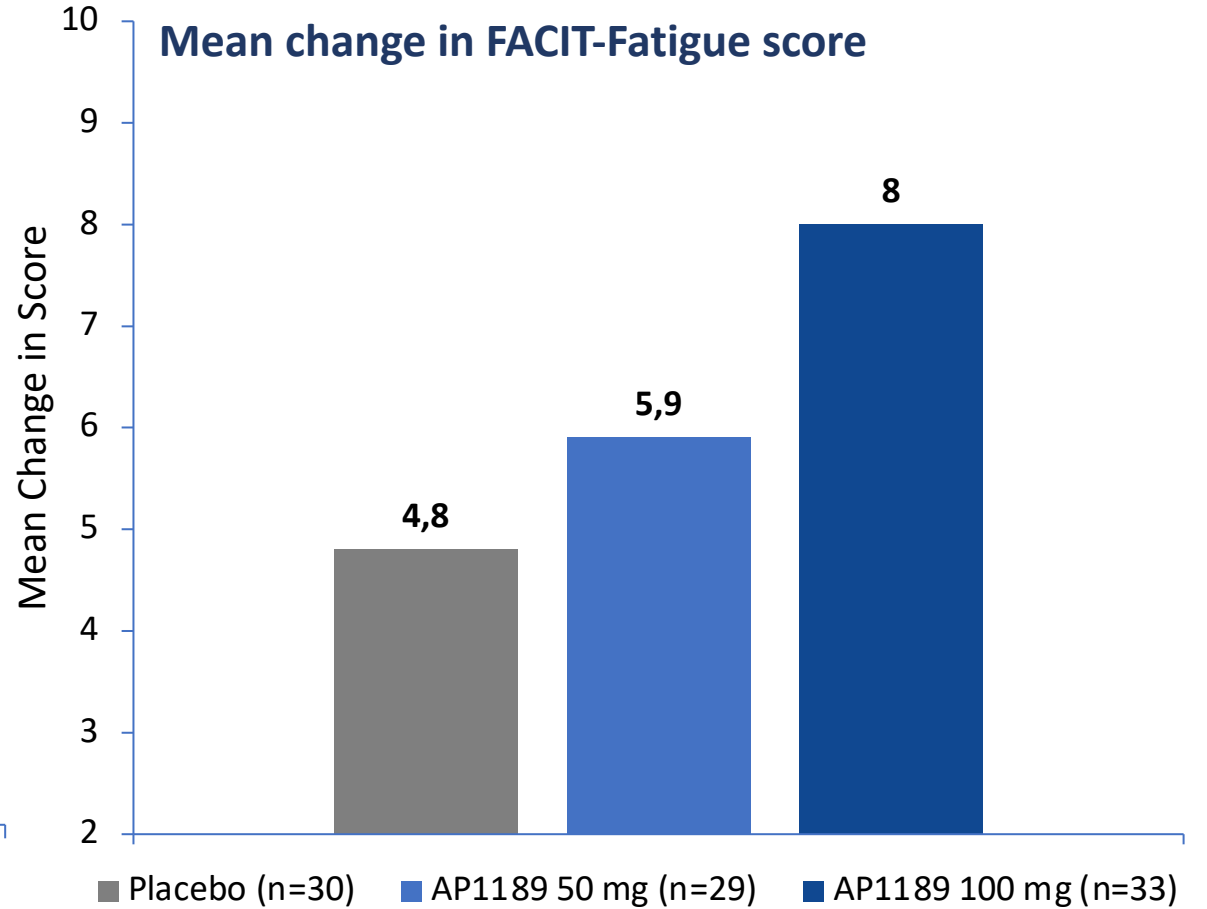


**Mean improvement in CDAI above the minimally important clinical difference (MCID)<sup>+</sup>  
Robust 1-Month ACR20/50/70 response rates for 100mg AP1189**

# Meaningful improvements were also seen in DAS28 (CRP) and FACIT-Fatigue Scores



**Good effects seen with 100mg in patients with very active DAS28 (>5.1) at baseline**



**Mean change in 100mg group is 2x the minimal clinically important difference (MCID)<sup>+</sup>**

# 4-Week daily AP1189 dosing was safe and well tolerated in the BEGIN study

## Adverse Events<sup>1</sup>

Group (n)	Placebo + MTX (34)	AP1189 + MTX		Total (105)
		50 mg (35)	100 mg (36)	
SAEs n	0	0	0	0
AEs n	34	65	53	152
Mild/Mod/Severe	28/4/2	45/20/0	43/10/0	116/34/2
% Mild	82%	69%	81%	76%
Pts with ≥ 1 AE n (%)	17 (50)	20 (57)	20 (56)	57 (54)
Discontinuation n (%)	1 <sup>2</sup> (3)	0 (0)	1 <sup>3</sup> (3)	2 (2)

## AEs >10% of Pts, n

Nausea <sup>4</sup>	7	5	7	19
ALT increase <sup>5</sup>	3	6	0	9
Headache <sup>4</sup>	0	2	5	7

(1) All study AEs; As per protocol safety assessments were conducted at level of all AEs not only treatment-emergent AEs

(2) Baseline ALT>3x upper normal level; patient discontinued from study when levels were read

(3) Onset of herpes zoster; Investigator decided to DC MTX which necessitated study discontinuation

(4) Headache and nausea were transient and occurred more frequently early in dosing period

(5) Laboratory value AEs determined by investigator; 8/10 ALT increases were mild and 3 occurred outside of dosing period

## The EXPAND study

A double-blind, multi-center, randomized, placebo-controlled study of the safety and efficacy of 12 weeks extended treatment with Resomelagon (AP1189) in early rheumatoid arthritis (RA) patients naïve to DMARD treatment –

Recruitment completed in April 2023



# EXPAND STUDY P2b study in previous treatment naive RA patients.

## Recruitment completed in April 2023 -

### Patient Population:

- Previous treatment naïve, eligible for initiation of DMARD treatment (MTX)
- CDAI >22 at baseline – min of 6 swollen and tender joints
- Glucocorticoids only allowed as rescue medicine

Resomelagon (AP1189) 100\* mg, combination with MTX

Placebo, combination with MTX

12 Weeks dosing

### Key Study Parameters

#### Dosing and Duration

- 12 weeks of once-daily dosing of solid tablet AP1189 or placebo- conducted at site in Eastern Europe- Successful completion of recruitment ahead of schedule

#### Study Size and Sites

- Designed to recruit 60 patients per group – actual number randomized is 127

#### Primary Endpoints

- ACR20 response rate at 12 weeks as compared to placebo

#### Secondary Endpoints

- CDAI score; DAS28 score; FACIT-Fatigue; HAQ/RAQoI

#### MRI- SubStudy

- Evaluation of Synovial inflammation using Dynamic Contrast Enhanced MRI Quantification (DEMRIQ)

## The RESOLVE study

A two-part, randomized, double-blind, multi-center, placebo-controlled study of the dose-range, safety and efficacy of 4 and 12 weeks of treatment with AP1189 in adult rheumatoid arthritis (RA) patients with an inadequate response to Methotrexate (MTX) alone

Conducted under and US-IND Recruitment to part A ongoing

# AP1189- Adaptive P2 trial design in DMARD-IR patients

Currently recruiting in US and Europe under an US- IND- Data on part A in H2 2023

Part A – 4 weeks dosing

Part B – 12 weeks dosing

3 dose levels of Resomelagon (AP1189) cont. MTX

Up to 3 dose levels of Resomelagon (AP1189), cont. MTX

Placebo, cont. MTX

Placebo, cont. MTX

## Patient Population:

- >3 mo MTX treatment
- Documented incomplete response or loss of response
- Min of 6 swollen and 6 tender joints and/or increased CRP

## Key Study Parameters

<b>Dosing</b>	<ul style="list-style-type: none"> <li>▪ Once-daily dosing of solid tablet AP1189 or placebo</li> </ul>
<b>Study Size and Sites</b>	<ul style="list-style-type: none"> <li>▪ Part A: 30 pts per group</li> <li>▪ Part B: 75 patients per group</li> </ul>
<b>Primary Efficacy Endpoints</b>	<ul style="list-style-type: none"> <li>▪ ACR20 response rate at 4 Weeks (part A) and 12 weeks as compared to placebo</li> </ul>
<b>Secondary Endpoints</b>	<ul style="list-style-type: none"> <li>▪ CDAI score; DAS28 score; FACIT-Fatigue; HAQ/RAQoI</li> </ul>
<b>MRI- substudy (part B only)</b>	<ul style="list-style-type: none"> <li>▪ Evaluation of Synovial inflammation and potential effects on joint destruction using Dynamic Contrast Enhanced MRI Quantification (DEMRIQ)</li> </ul>



## **Resomelagon (AP1189) Nephrology program –**

### **Exploratory Phase 2 study conducted at Nephrology sites in the Nordic Countries**

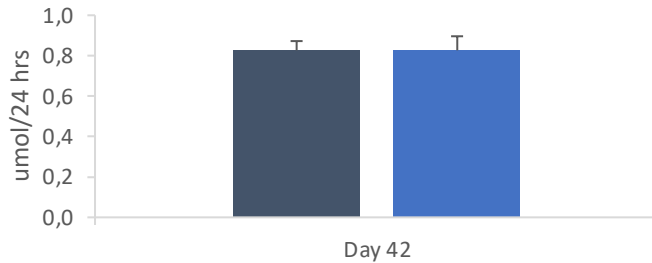
**An exploratory, randomized, double-blind, multicenter, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of AP1189 daily doses versus placebo administered for 12 weeks as an add-on to patients, in ACE inhibitor or angiotensin II receptor blocker treatment, with idiopathic membranous nephropathy and severe proteinuria**

# AP1189 is effective in pre-clinical nephritis models

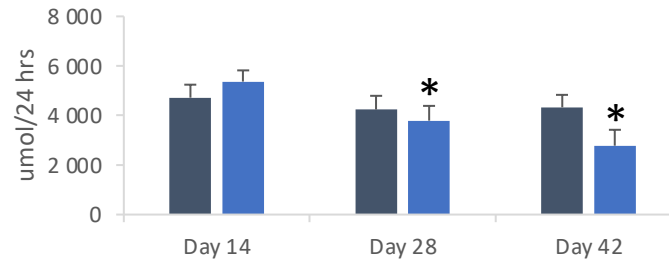
- Vehicle (n=12)
- AP1189 (n=12)

## Membranous nephropathy rat model (passive Heymann Nephritis)

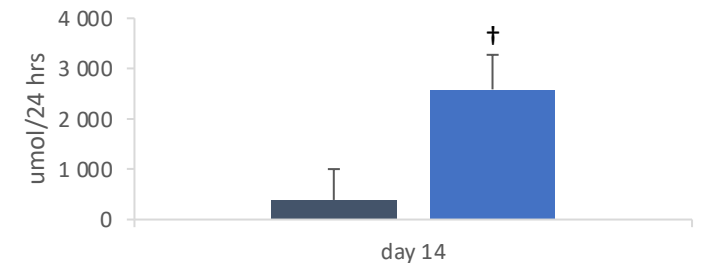
### Creatinine Clearance (ml/min/g KW)



### Albumin excretion rate



### Reduction in AER (day 14-42)

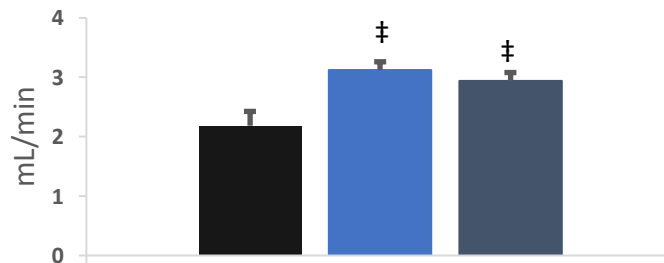


AP1189 showed no effect on creatinine clearance where albumin excretion decreased significantly

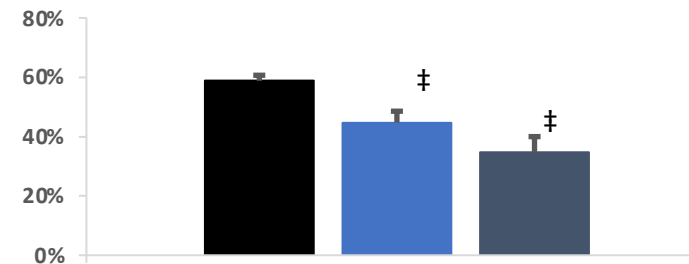
- ACTH (n=6)
- AP1189 20mg/kg (n=8)
- AP1189 40mg/kg (n=8)

## AP1189 vs ACTH in a model of Nephrotic Syndrome

### Creatinine Clearance



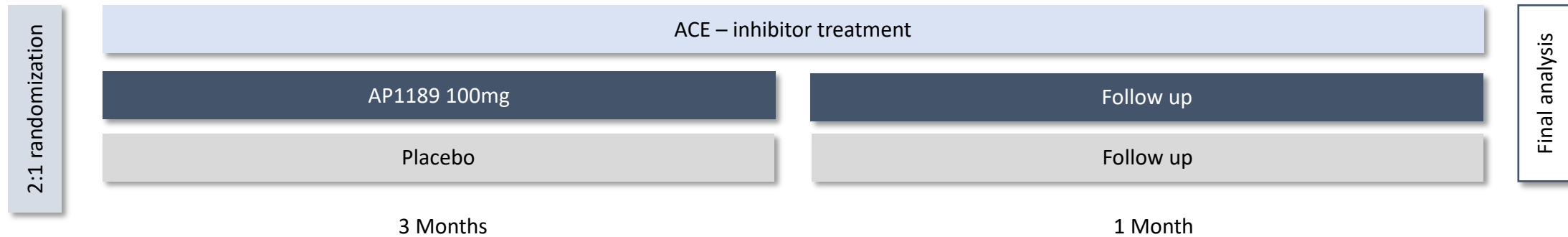
### Fractional Albumin Excretion



AP1189 preserved creatinine clearance and dose-dependently reduced the fractional albumin excretion relative to ACTH

\*p<0.05 vs. Day 14; † p<0.05 vs. vehicle; ‡ p<0.01 vs. ACTH; data from PCT/EP2019/066578. Model adapted from Lindskog et al, J Am Soc Nephrol. 2010; 21:1290-1298

# Ongoing study: CS-003 study – 12 weeks explorative Phase 2a trial in idiopathic membranous nephropathy (iMN) with severe proteinuria



- Dosing is ongoing following approval of major amendment changing from suspension to tablet and dosing extended to 12 weeks.
- The trial resumed in H2 2022 with topline data expected late in 2023

**Thank you**

