SYNACT PHARMA

INFLAMMATION RESOLUTION

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					
	Rheumatoid Arthritis DMARD-IR					
	Nephrotic syndrome (iMN)					
	Virus- Induced Respiratory Insufficiency					
TXP-11	**Prevention of organ failures in complicated surgery**					
Small Molecules and Peptides	**Autoimmune and inflammatory conditions**					

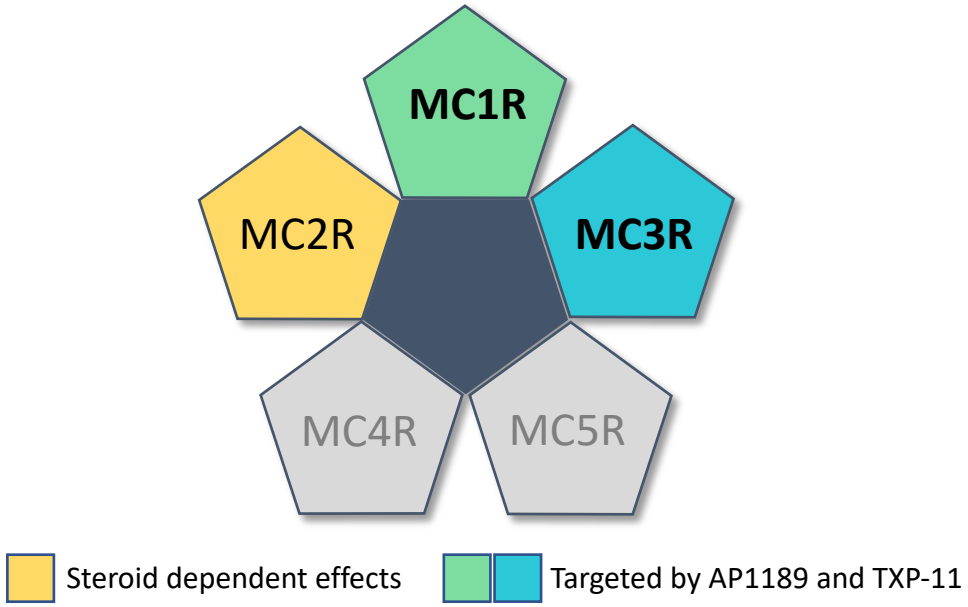
SYNACT PHARMA

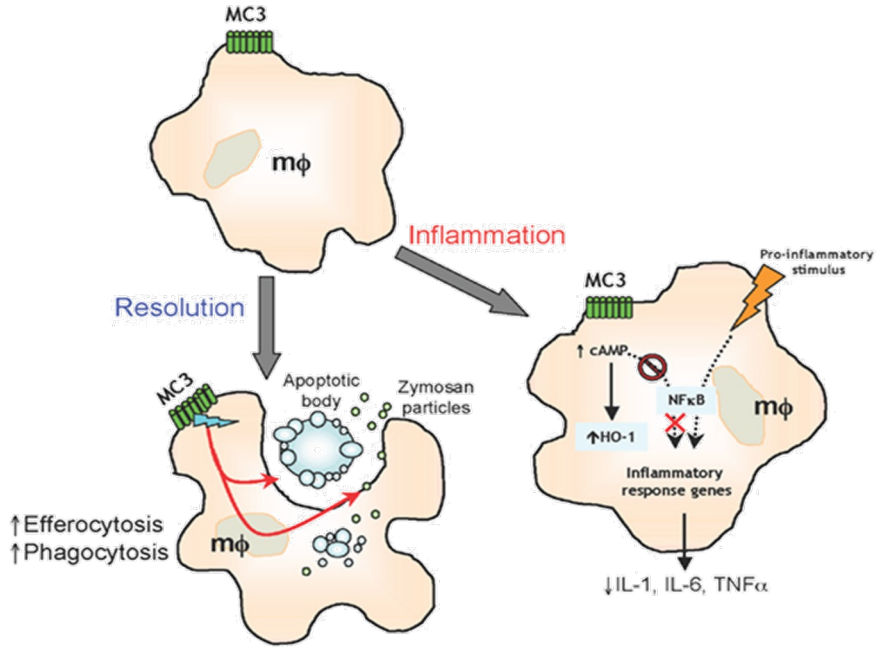
INFLAMMATION RESOLUTION

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





- 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

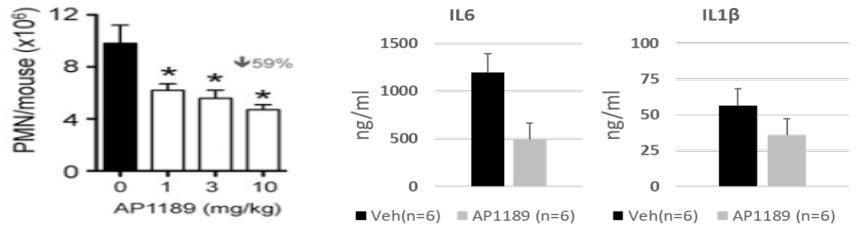
- AP1189 **exbibits anti-inflammatory activity** via MC1R and MC3R stimulation on targets cells – such as lowering the release of pro-inflammatory cytokines
- AP1189 **promotes pro-resolution pathways** following stimulation of MC1R and MC3R on targets cells – such as increasing efferocytosis in macrophages

ACTH: adrenocorticotropic hormone; MCR: melanocortin receptor

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

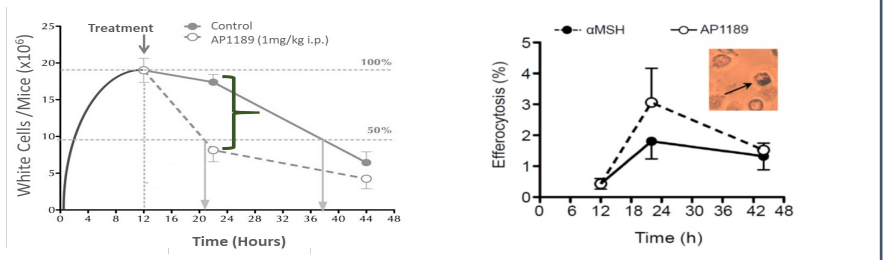
- AP1189 selectively stimulates MC1R and MC3R present on white cells including neutrophils and macrophages
- Reduction but not suppression of cell infiltration and release of pro-inflammatory pathways
- Stimulation of pro-resolving pathways including the ability to stimulate the macrophages' ability 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[1]



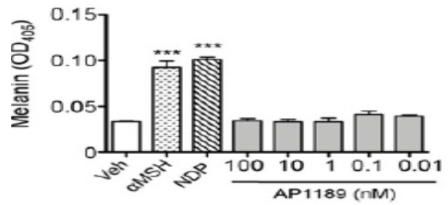
AP1189 inhibits of inflammatory responses

Therapeutic treatment in peritonitis [1]



AP1189 promotes inflammatory resolutionAP1189

Melanin production following stimulation of MC1r[1]



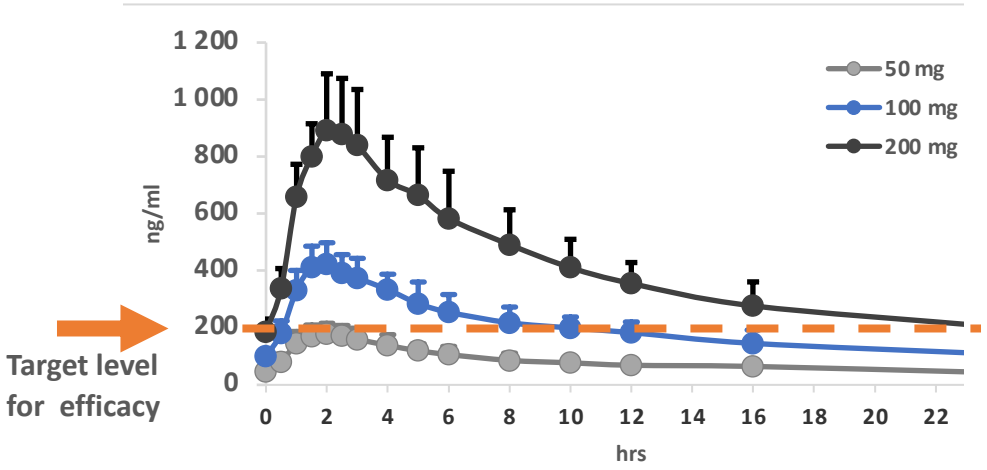
AP1189 does not stimulate melanogenesis

1. Montero-Melendez et al: J Immunol. 194:3381-8, 2015

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

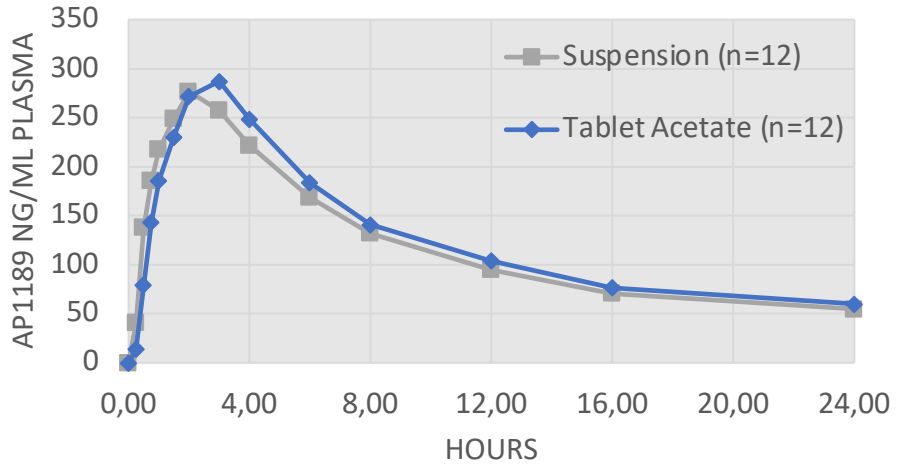
- Initial clinical development, Phase 1 and Phase 2a, performed with suspension for once daily oral administration was overall well tolerated, no signs of immunosuppression or dose limiting Adverse Events
- Novel immediate release tablet with excellent plasma profile developed and is being dosed in 3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

PK profile following repeat dosing in man[1]



PK profile demonstrates once daily potential

PK profiles from Bioequivalence study testing new tablet formulation[2]



PK profile demonstrates once daily potential

1. AP1189-CS001 study MAD study

2. AP1189-CS004 bioequivalence study in male volunteers

SYNACT PHARMA

INFLAMMATION RESOLUTION

Resomelagon (AP-1189)- RA – program

SYNACT PHARMA

INFLAMMATION RESOLUTION

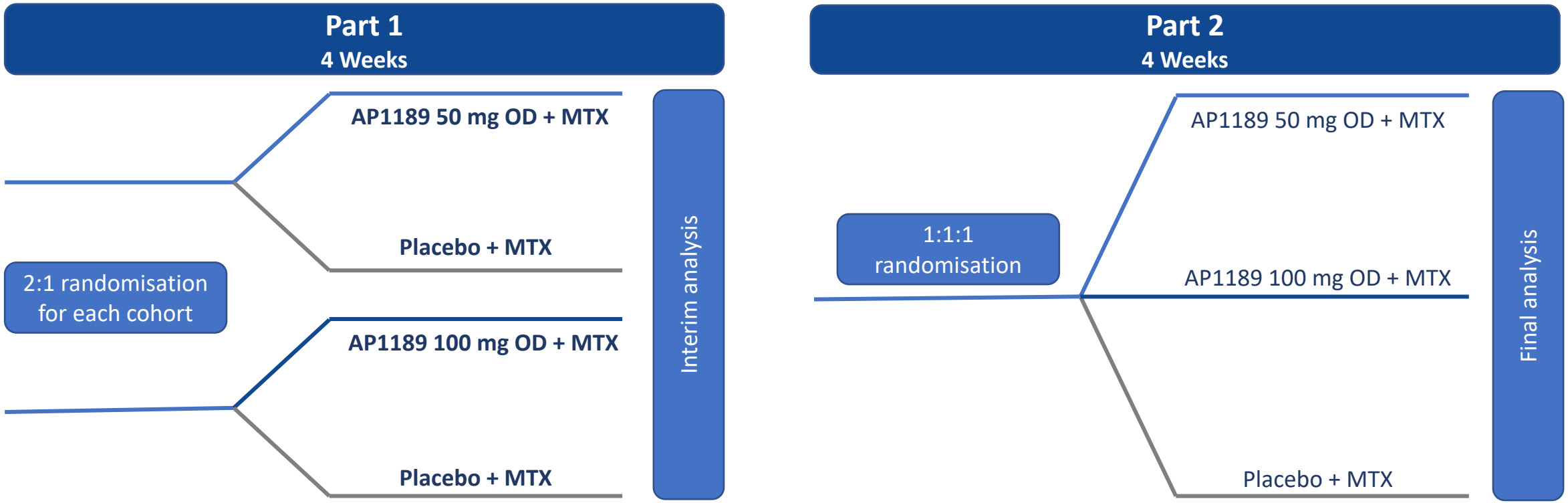
The BEGIN Study:

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

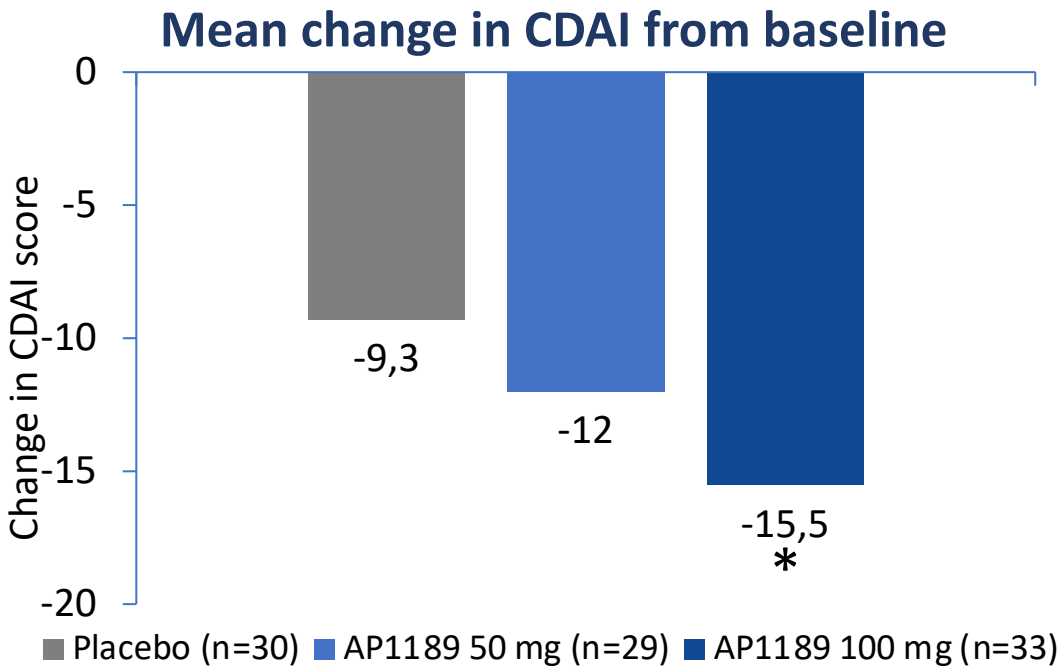
BEGIN: P2a POC 4-week study of AP1189 + MTX in highly active early RA

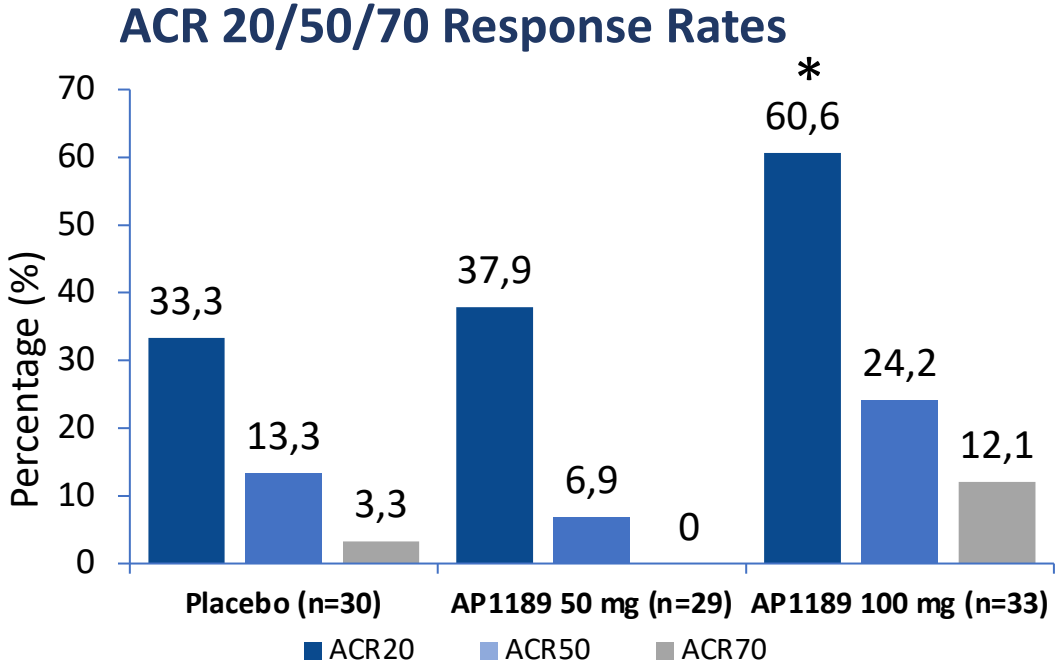
Study Population	Primary safety endpoint	Primary efficacy endpoint
Adult patients (aged 18 to 85 years) with severe RA defined as CDAI >22, who are about to begin up-titration with MTX	Safety of AP1189 vs placebo (AEs and SAEs)	• Mean change in CDAI or • % of patients improving from severe (CDAI >22) to at least moderate (CDAI ≤22)



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 naive RA patients with high disease activity (CDAI >22 at randomization) in combination with MTX with 4 weeks treatment



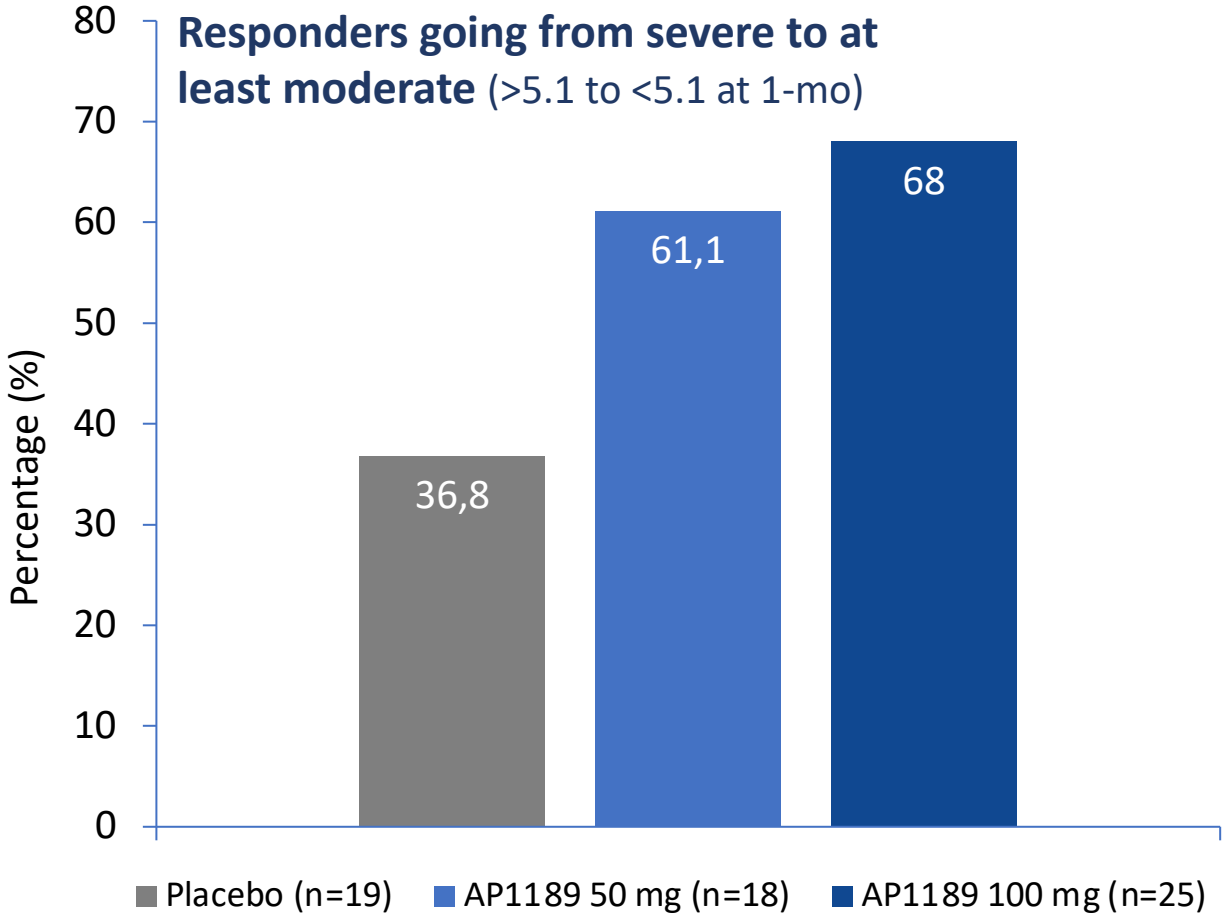


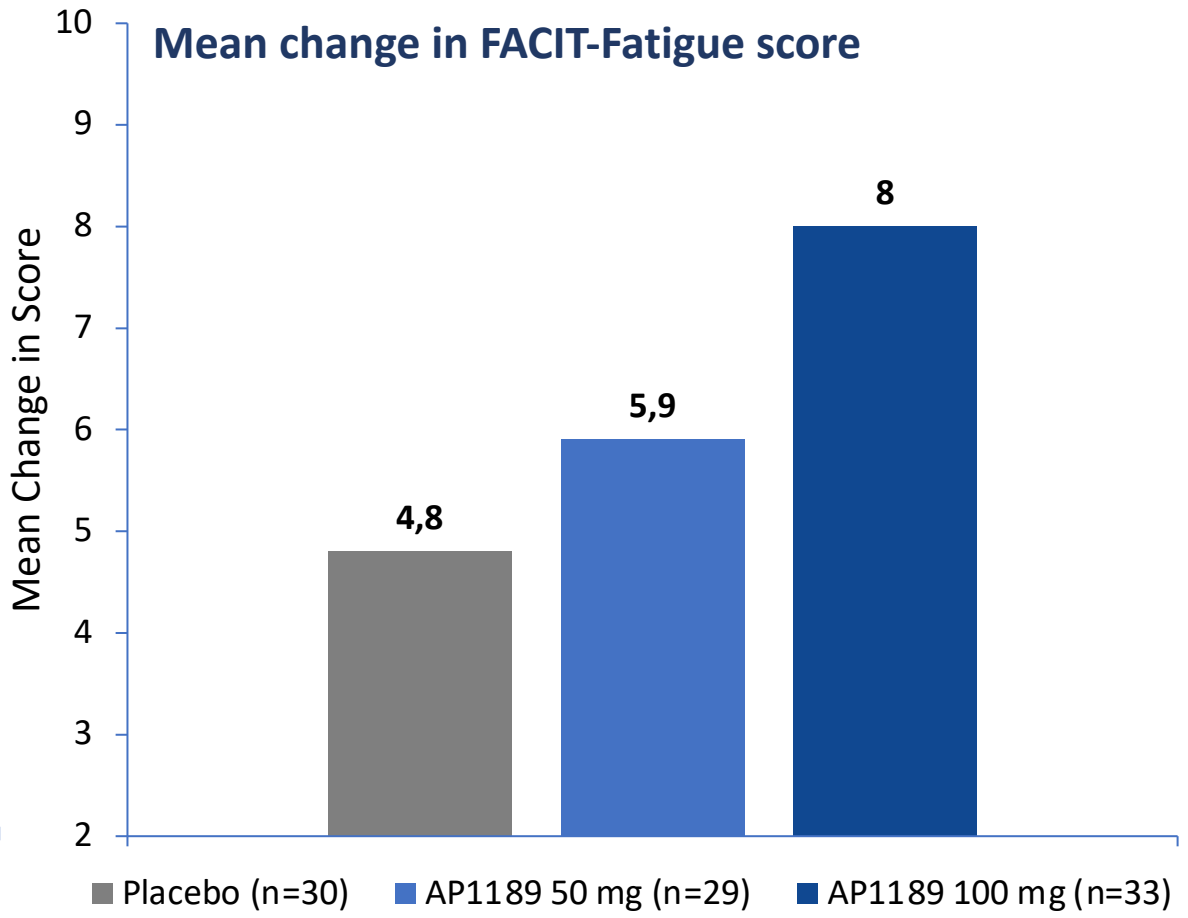
Mean improvement in CDAI above the minimally important clinical difference (MCID)[+]
Robust 1-Month ACR20/50/70 response rates for 100mg AP1189

* = p<0.05 vs placebo

(+) Curtis et. Al *Arthritis Care Res (Hoboken)*. 2015 October; 67(10)

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)⁺

(+) Cella et. Al *The Journal of Rheumatology 2005; 32:5*

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

Adverse Events[1]

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[2] (3)	0 (0)	1[3] (3)	2 (2)
AEs >10% of Pts, n				
Nausea[4]	7	5	7	19
ALT increase[5]	3	6	0	9
Headache[4]	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

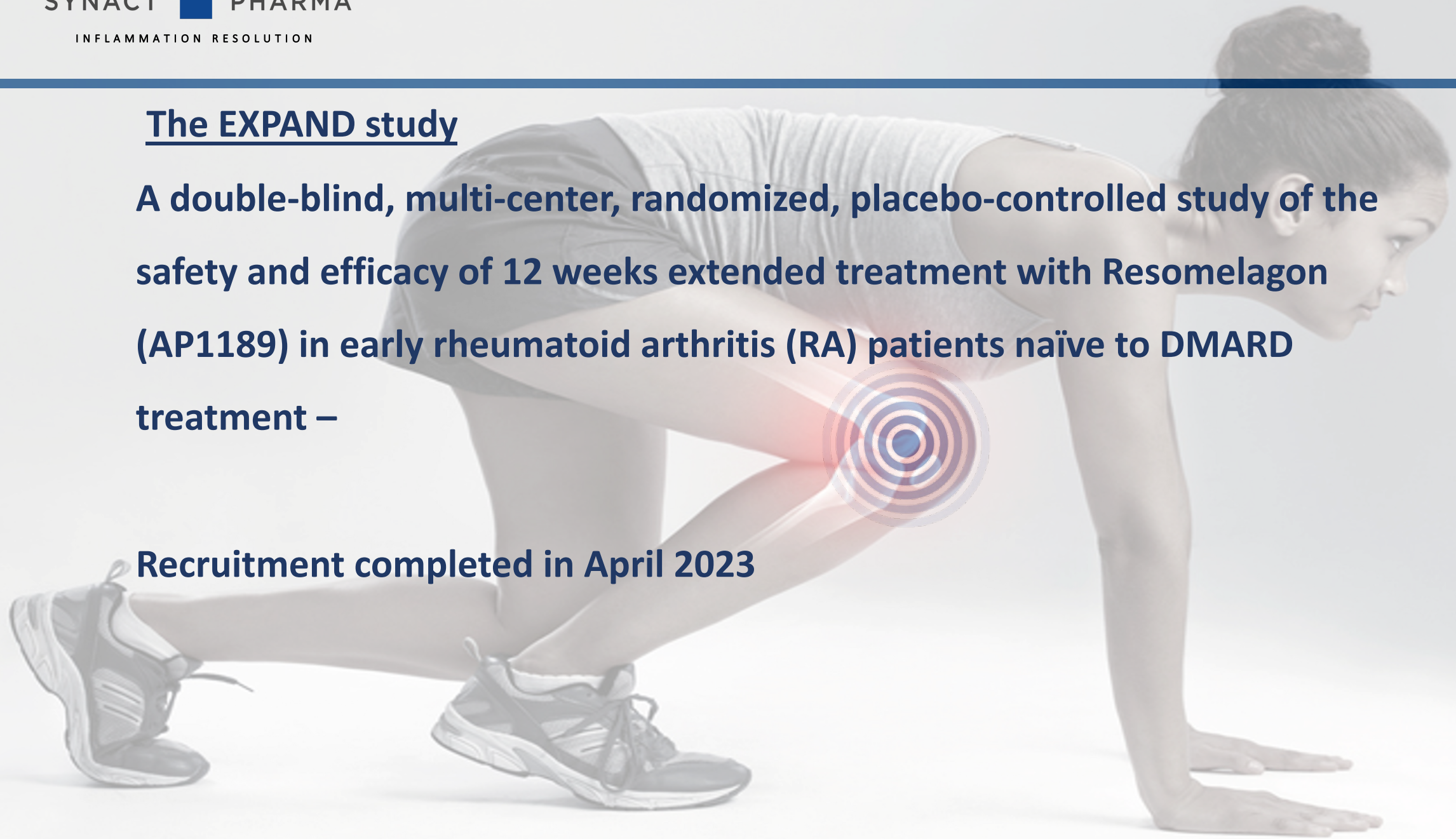
SYNACT PHARMA

INFLAMMATION RESOLUTION

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 –

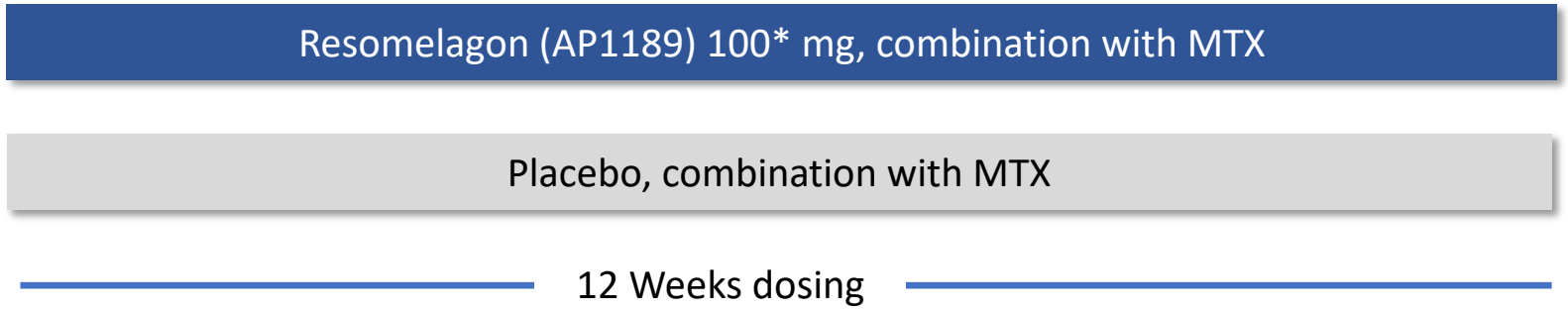
Recruitment completed in April 2023



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

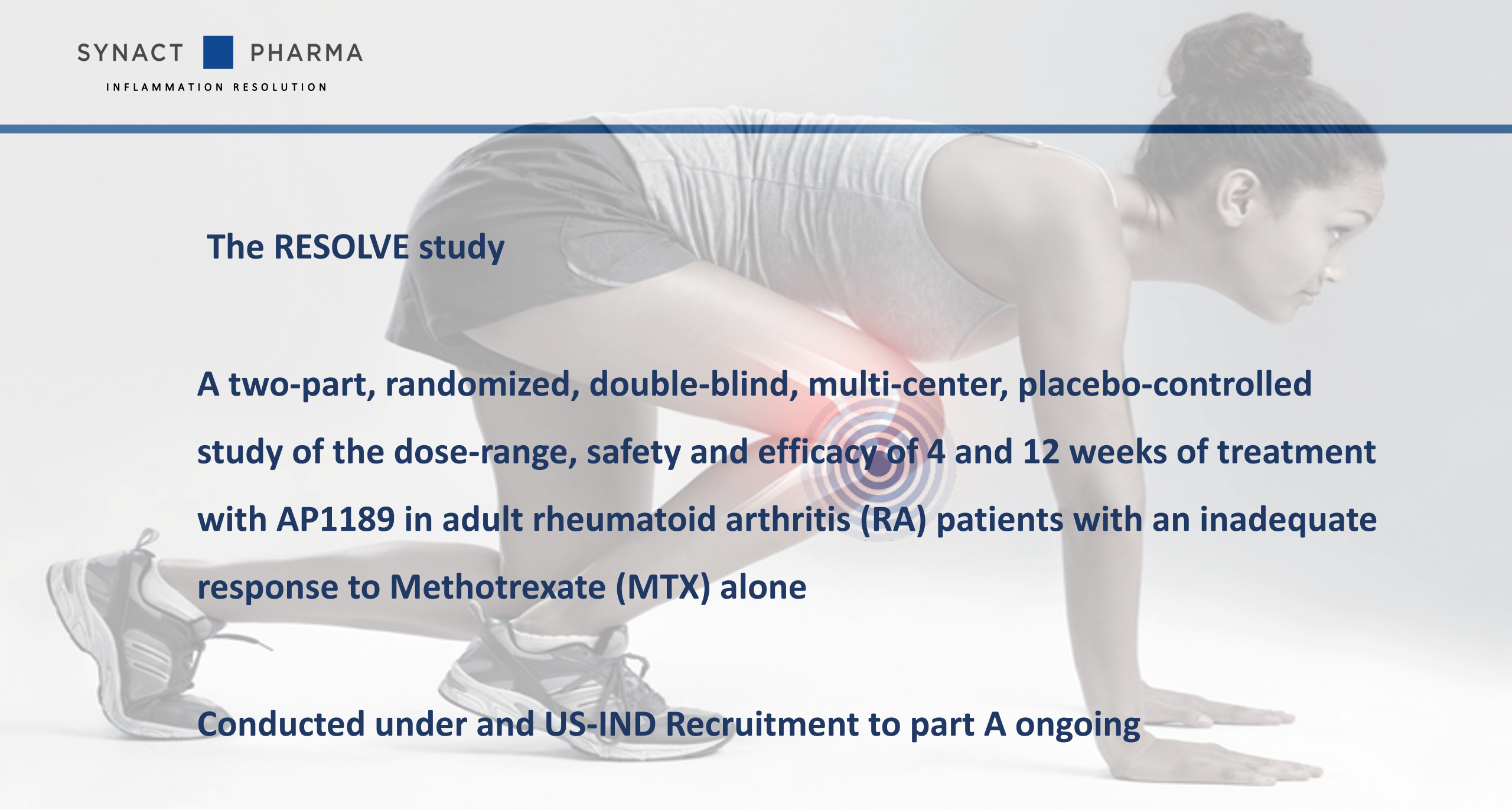


Key Study Parameters	
Dosing and Duration	▪ 12 weeks of once-daily dosing of solid tablet AP1189 or placebo- conducted at site in Eastern Europe- Successful completion of recruitment ahead of schedule
Study Size and Sites	▪ Designed to recruit 60 patients per group – actual number randomized is 127
Primary Endpoints	▪ ACR20 response rate at 12 weeks as compared to placebo
Secondary Endpoints	▪ CDAI score; DAS28 score; FACIT-Fatigue; HAQ/RAQol
MRI- SubStudy	▪ Evaluation of Synovial inflammation using Dynamic Contrast Enhanced MRI Quantification (DEMRIQ)

*:Free base – correspond to 125 mg acetate salt used in the BEGIN study

SYNACT PHARMA

INFLAMMATION RESOLUTION



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

3 dose levels of Resomelagon (AP1189) cont. MTX

Placebo, cont. MTX

Part B – 12 weeks dosing

Up to 3 dose levels of Resomelagon (AP1189), 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	
Dosing	▪ Once-daily dosing of solid tablet AP1189 or placebo
Study Size and Sites	▪ Part A: 30 pts per group ▪ Part B: 75 patients per group
Primary Efficacy Endpoints	▪ ACR20 response rate at 4 Weeks (part A) and 12 weeks as compared to placebo
Secondary Endpoints	▪ CDAI score; DAS28 score; FACIT-Fatigue; HAQ/RAQol
MRI- substudy (part B only)	▪ Evaluation of Synovial inflammation and potential effects on joint destruction using Dynamic Contrast Enhanced MRI Quantification (DEMRIQ)

SYNACT PHARMA

INFLAMMATION RESOLUTION

Resomelagon (AP1189) Nephrology program –

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

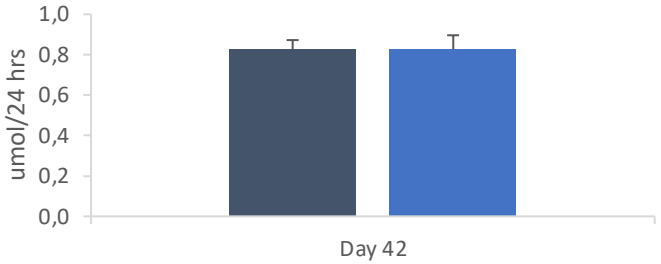
An exploratory, randomized, double-blind, multicenter, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of AP1189 daily doses versus placebo administered for 12 weeks as an add-on to patients, in ACE inhibitor or angiotensin II receptor blocker treatment, with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

AP1189 is effective in pre-clinical nephritis models

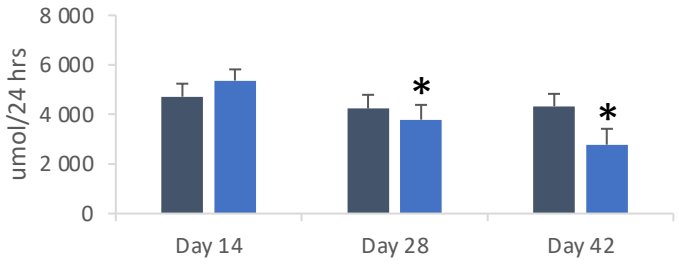
Vehicle (n=12)
AP1189 (n=12)

Membranous nephropathy rat model (passive Heymann Nephritis)

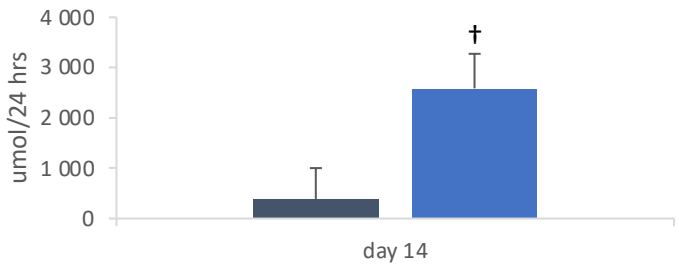
Creatinine Clearance (ml/min/g KW)



Albumin excretion rate



Reduction in AER (day 14-42)

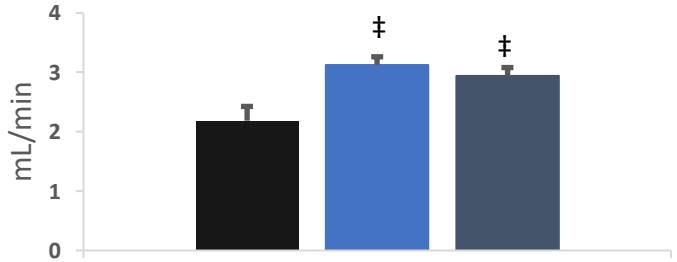


AP1189 showed no effect on creatinine clearance where albumin excretion decreased significantly

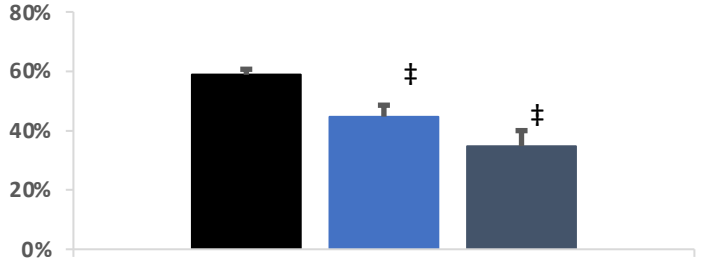
ACTH (n=6)
AP1189 20mg/kg (n=8)
AP1189 40mg/kg (n=8)

AP1189 vs ACTH in a model of Nephrotic Syndrome

Creatinine Clearance



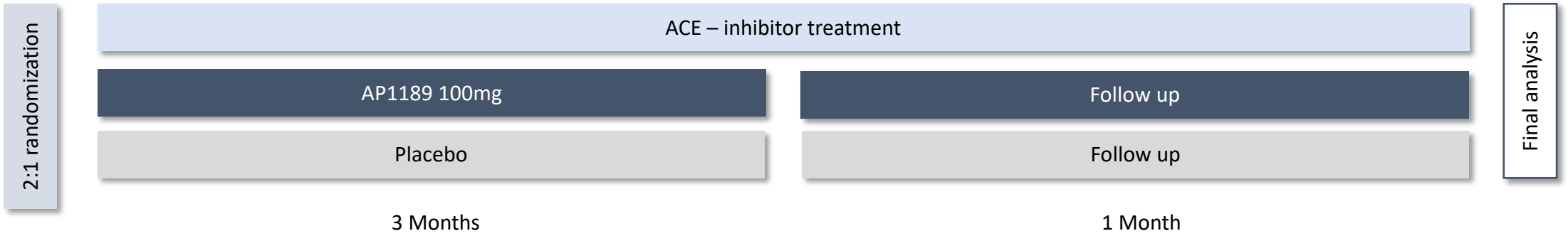
Fractional Albumin Excretion



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**

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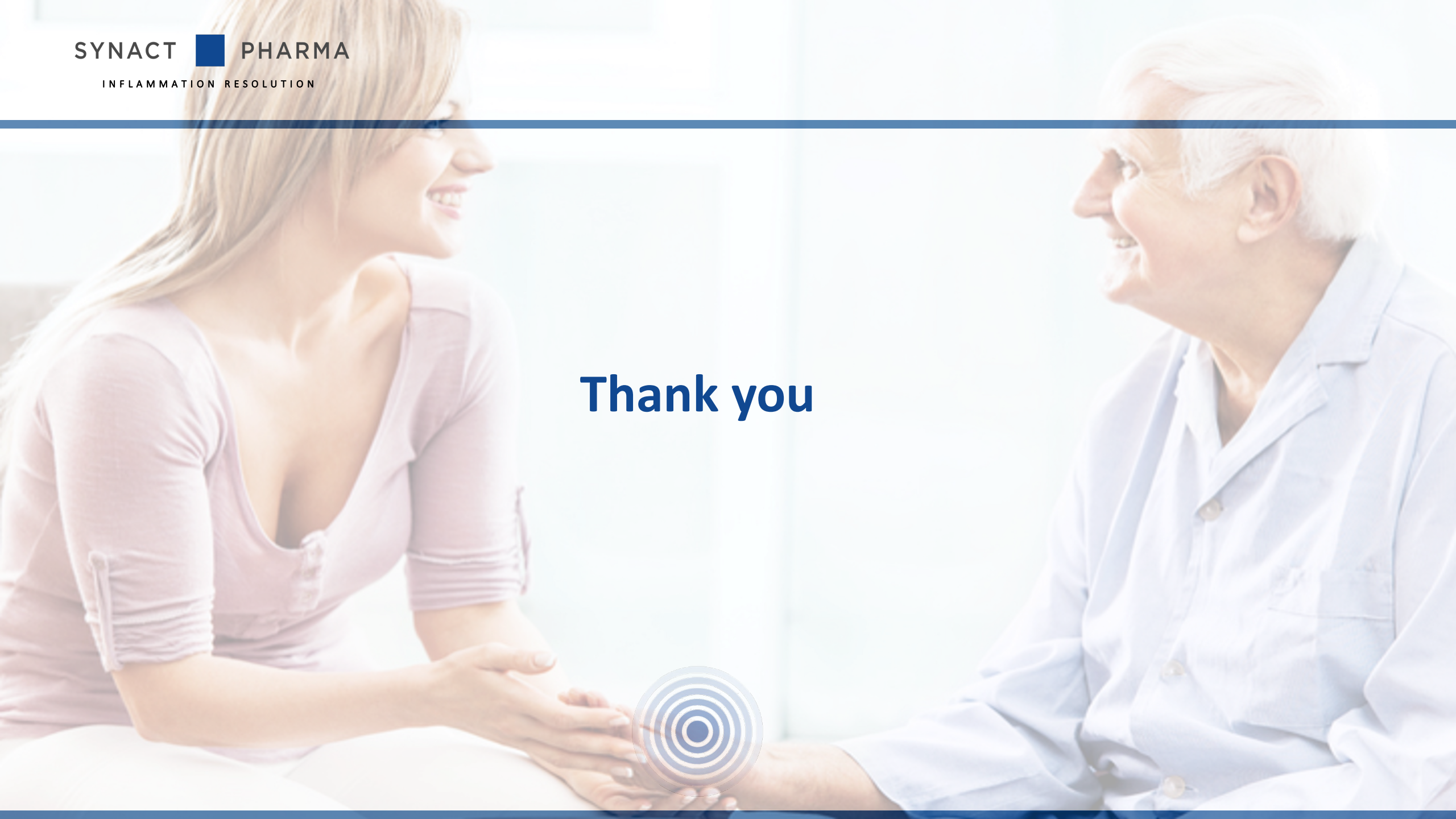
INFLAMMATION RESOLUTION



Thank you