SYNACT PHARMA

INFLAMMATION RESOLUTION

SynAct Pharma AB

Treating Inflammation through Resolution Therapy

CMD – Stockholm 23 September 2024

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INFLAMMATION RESOLUTION

SynAct Pharma AB

Welcome to Capital Market Day

Stockholm 23 September 2024

Forward Looking Statements

Certain information set forth in this presentation contains “forward-looking information”, including “future-oriented financial information” and “financial outlook”, under applicable securities laws (collectively referred to herein as forward-looking statements). Except for statements of historical fact, the information contained herein constitutes forward-looking statements and may include, but is not limited to, the (i) projected financial performance of the Company; (ii) completion of, and the use of proceeds from, the sale of the shares being offered hereunder; (iii) the expected development of the Company’s business, projects, and joint ventures; (iv) execution of the Company’s vision and growth strategy, including with respect to future M&A activity and global growth; (v) sources and availability of third-party financing for the Company’s projects; (vi) completion of the Company’s projects that are currently underway, in development or otherwise under consideration; (vi) renewal of the Company’s current customer, supplier and other material agreements; and (vii) future liquidity, working capital, and capital requirements. Forward-looking statements are provided to allow potential investors the opportunity to understand management’s beliefs and opinions in respect of the future so that they may use such beliefs and opinions as one factor in evaluating an investment.

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Agenda

10:00	**Introduction and corporate update – Jeppe Øvlesen, CEO**
10:15	**SynAct strategy and direction – Anders Kronborg, Chairman of the Board**
10:25	**Resolution therapy - Novel approach to the clinical management of inflammatory diseases – Prof. Mauro Perretti**
10:45	**Current and Future Treatments of Early Rheumatoid Arthritis and the Medical Need – Asger Reinstrup Bihlet, CSO at Sanos Group**
11:05	**Q&A session**
11:25	***Break***

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Agenda

11:40	Resomelagon program and ADVANCE study – Thomas Jonassen, CSO
12:05	Emerging Clinical profile in newly-diagnosed RA patients - the business case – Jim Knight, CBO
12:30	Sector and market overview – Sten Scheibye, Member of the Board
12:40	Q&A session
12:55	Wrap-up and summary – Jeppe Øvlesen, CEO
13:00	Reception and lunch

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Introduction and corporate update

Jeppe Øvlesen, CEO

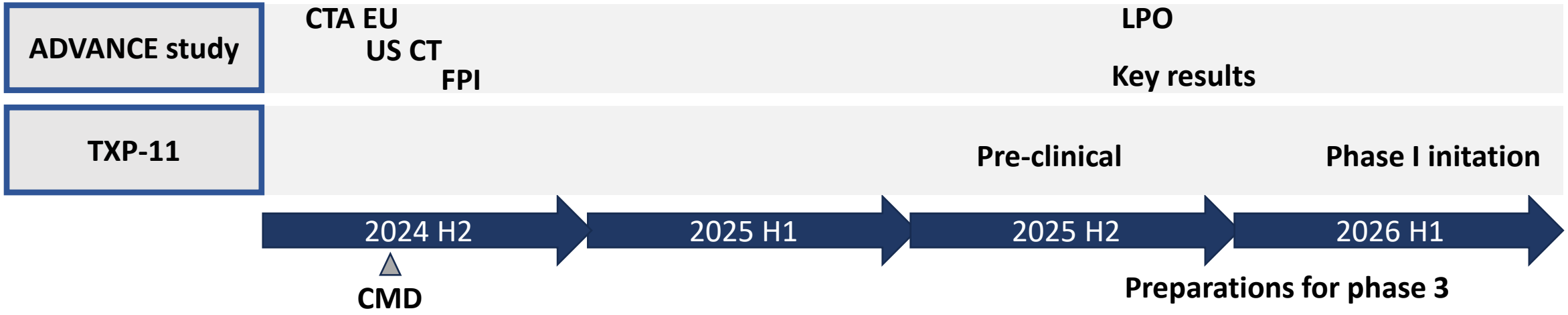
Brief recap of the history of Synact Pharma

2013	Company Founded
2016	Listed at Spotlight Stock Market in Sweden
2019	Completes Phase I – AP 1189
2020	Completes Phase II – AP 1189 – in RA
2021	Completes Phase IIa – AP 1189 – COVID
	Completes Phase IIa – AP 1189 – RA (Begin study)
2022	Uplisted to Nasdaq, Stockholm
2023	Acquisition of TXP Pharma
	Completes Resolve and Expand studies – Phase IIB
2024	New focused strategy implemented

Recent achievements and key milestones

Q1- 2024
- New Board and management
- Raised 50 MSEK. in a directed issue at 30% premium
- Strengthening the investor base
- Strengthening the clinical organization

Q2 – 2024
- Reduced costs to management by 27%
- Reduced costs to board by 46%
- Phase II-b ready – study to start in Q3
- AGM held, all proposals approved



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SynAct strategy and direction

Anders Kronborg, Chairman of the board

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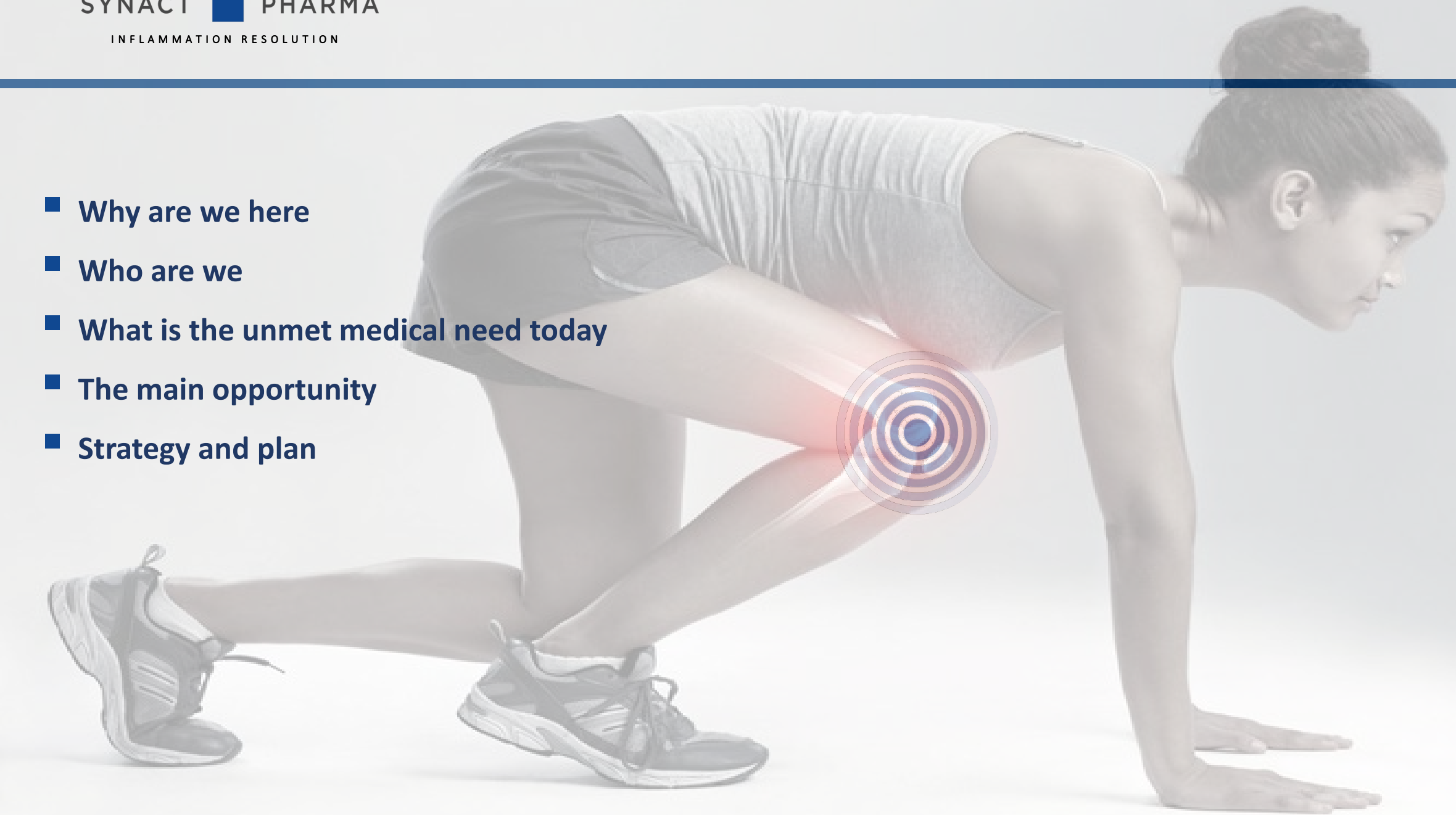
- Why are we here
- Who are we
- What is the unmet medical need today
- The main opportunity
- Strategy and plan



Synact Pharma

SynAct Pharma AB is a clinical stage biotechnology company focused on the resolution of inflammation through the selective activation of the melanocortin system. The company has a broad portfolio of oral and injectable selective melanocortin agonists aimed at inducing anti-inflammatory and inflammation resolution activity in autoimmune and inflammatory diseases to help patients achieve immune balance and overcome their inflammation.

VISION

To lead the development of inflammation resolution therapeutics, a new approach to treating inflammatory diseases that does not suppress the immune system and that enables patients to achieve immune balance and live beyond their inflammation.

MISSION

SynAct seeks to develop resomelagon (AP1189) and its peptide melanocortin agonists through proof-of-concept Phase 2 clinical studies. SynAct will seek to establish partnerships and collaborations with like-minded parties for Phase 3 studies and beyond

SynAct Pharma – highly experienced Management Team

Jeppe Øvli Øvlesen, MBA – CEO

- Over 20 years of experience as CEO of various companies
- Founding Board Member of more than 10 biotech and MedTech companies
- Co-founder of TXP Pharma
- Former CFO and VP of Business Development at Action Pharma

Björn Westberg, MSc – CFO

- Over 25 years of experience within various financial roles in the pharmaceutical industry
- Former CFO of Recipharm, Bonesupport, Enea
- Various finance management roles in AstraZeneca
- Experience in investor relations, financing, acquisitions and other business deals

Thomas Jonassen, MD – CSO, Co-founder

- Associate Professor at Cardiovascular Pharmacology, University of Copenhagen
- Visiting Professor at WHRI, Barts and London School of Medicine
- Co-founder of TXP Pharma and ResoTher Pharma
- Co-founder and former CSO of Action Pharma

Thomas Boesen, PhD – COO

- Over 20 years of experience in the biotech and pharmaceutical industry
- Inventor on 35 granted patents
- Co-founder of MedChem and TXP Pharma
- Former VP of Discovery at Action Pharma

James Knight, MBA – CBO

- Over 25 years of experience in the biotech industry, ranging from R&D to Commercial Strategy and Business Development
- Former VP of Portfolio Strategy at Questcor Pharmaceuticals

Kirsten Harting, MD & Executive MBA - CMO

- Over 30 years of experience from the global pharmaceutical industry and biotech
- Senior Vice president & Chief Medical Officer
- Responsible for development and approval of several new innovative drugs
- Global launch of new medicine
- Integrating medical and commercial understanding

Strengthening the clinical organisation

Mette Arnum Msc. Head of clinical operation

- 15 years of experience with clinical drug development including drug safety, clinical development strategy, clinical trial operation and management
- Various positions within the pharmaceutical and biotech industry including Takeda, Novo Nordisk and several smaller biotech companies.

SynAct Pharma – very experienced Board of Directors

	Shareholder	Company independent	Independent to major shareholders
Anders Kronborg, M.Econ	Yes	Yes	Yes
Sten Scheibye, PhD and B.Com	Yes	Yes	Yes
Sten R Sörensen, BSc	Yes	No	Yes
Jeppe Øvli Øvlesen, MBA	Yes	No	Yes

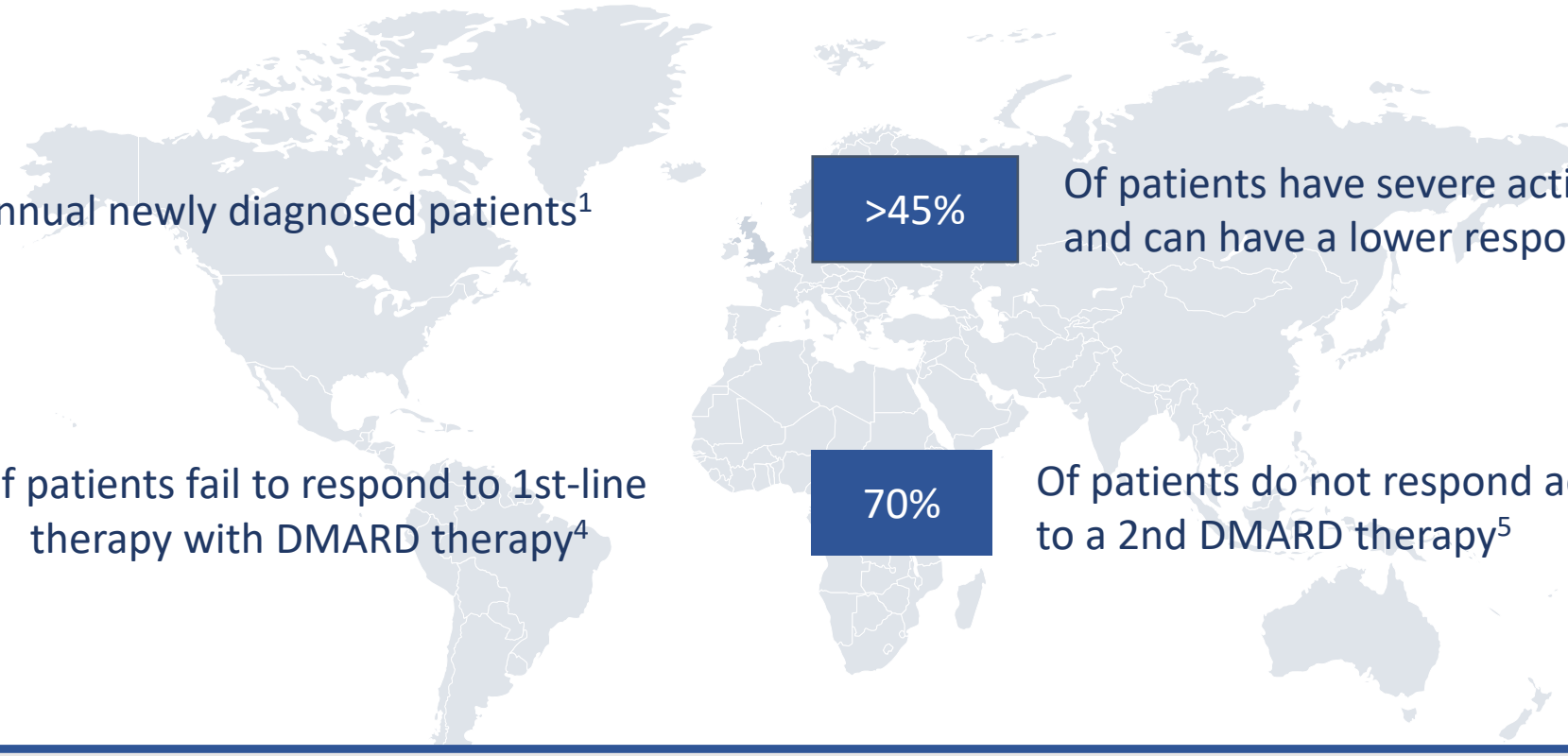
- CEO or CFO, during 1996-2007 in Danish media companies
- Kinnevik, 2007-2015, various positions including COO between 2012-2015
- LEO Pharma, 2015-2022 as CFO and interim CEO supporting growth by several M&A activities
- Resother Pharma, CEO since 2022

- Started as medical sales rep, registration officer before moving into more commercial roles and senior leadership
- Coloplast as CEO. During his tenure, Coloplast 6-doubled turnover and 8-doubled share performance
- Chairman of Novo Nordisk A/S, where he had a board seat for 10 years, then became Chairman of the Novo Nordisk Foundation
- Various board positions

- Over 30 years in the pharmaceutical and biotech industries
- Head of marketing positions in Monsanto and AstraZeneca
- Initiated two groundbreaking preventive survival studies in heart failure
- Cereno Scientific, CEO since 2015

- See previous page

1st-line therapies fail most RA patients especially those with severe disease



400K+ Annual newly diagnosed patients[1]

>45% Of patients have severe activity at diagnosis and can have a lower response rate to MTX[2,3]

>50% Of patients fail to respond to 1st-line therapy with DMARD therapy[4]

70% Of patients do not respond adequately to a 2nd DMARD therapy[5]

Resomelagon could be well suited to a help early-stage patients presenting with severe disease activity

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1. GlobalData_RheumatoidArthritisEpidemiologyForecastto2029_250424; 2) Albrecht and Zink Arthritis Research & Therapy (2017) 19:68; 3. Shpatz et al. IMAJ (2021) vol 23; 4. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982; 4. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982; 5. GlobalData RA custom primary market research studies 2021-2023, on file;

Resomelagon - Adding efficacy to MTX without adding steroids

Emerging AP1189 Clinical profile	
• **Once-Daily Oral Dosing**	• Once daily oral tablet • Oral convenience for early lines of therapy
• **High-degree of efficacy**	• BEGIN 1-mo responses were in-line with JAK inhibitors • Robust EXPAND 3-mo data is newly diagnosed with severe disease activity (with eCRP)
• **Safe and Well Tolerated**	• No emerging safety issues seen thus far in clinical assessment • No signs of increased infection rates or other serious safety concerns
• **Steroid-Free MoA**	• Efficacy in early RA with severe disease without need for steroids
• **Compatible with MTX**	• Shown to be compatible with MTX • No known compatibility concerns with TNF or other biologics

- The combination of efficacy, safety and oral once-daily convenience is very well suited for this opportunity
- Preliminary estimates for resomelagon in newly diagnosed patients with severe disease > $2B annually

Transforming vision into strategic objectives

Lead the development of inflammation resolution therapeutics	**- New approach to treating inflammatory diseases** **- Enabling patients to achieve “immune balance”** **- Safe and well tolerated compound (-s)**
Prioritized development on key indication (-s)	**- Rheumatoid Arthritis (RA) is key priority** **- Significant other inflammation opportunities**
Find partnerships and/or business deals	**- Develop indication opportunities of great potential** **- Maintain and further develop Big Pharma relations**
Effective use of funds	**- Finance attractive indication opportunities** **- Efficient organization and processes**
Highly skilled management	**- Secure highly competent and experienced employees**

Executing strategy

Lead the development of inflammation resolution therapeutics

Prioritized development on key indication (-s)

Find partnerships and/or business deals

Effective use of funds

Highly skilled management

Recently executed

- **Good results in RA specific patient groups**
- **Exciting data-virus induced inflammation**
- **Successful financing 23Q3 and 24Q2**
- **Reduced board and management fees**
- **Strengthened management**

Plan ahead

- **ADVANCE study-RA 1st line treatment**
- **Make TXP-11 phase 1 ready**
- **Business development – Pharma Co's**

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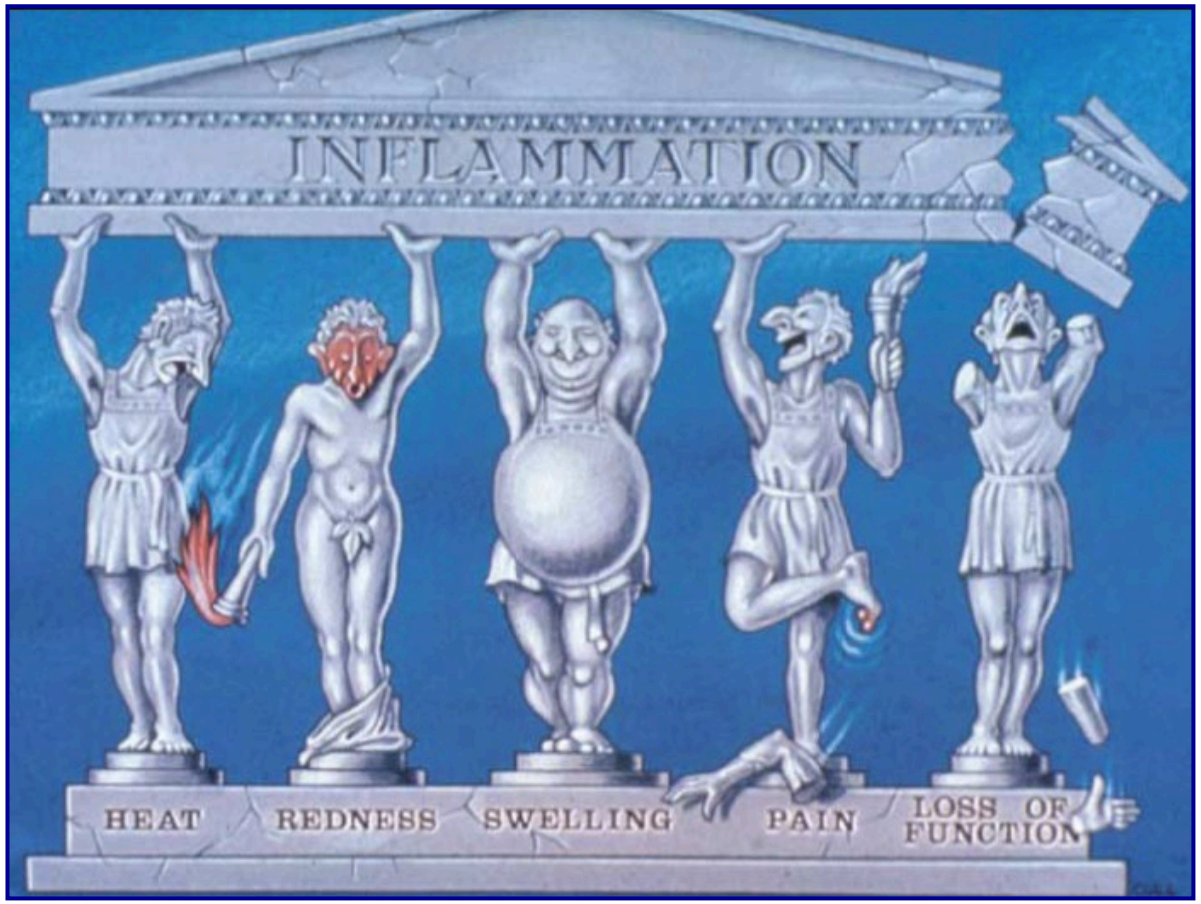
Resolution therapy – Novel approach to the clinical management of inflammatory diseases

Prof. Mauro Perretti

Resolution Pharmacology and AP1189

Mauro Perretti, PhD
Professor of Immunopharmacology
The William Harvey Research Institute
Queen Mary University of London
London, United Kingdom

Inflammation



Cardinal signs of inflammation:

Calor (heat)

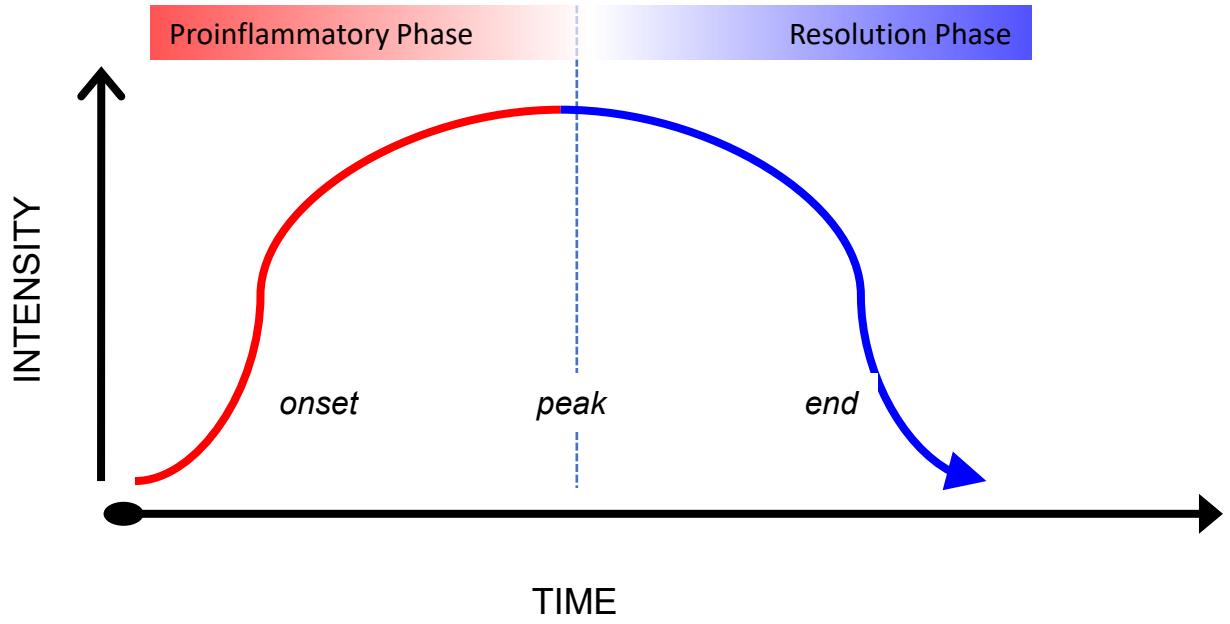
Rubor (redness)

Tumor (swelling)

Dolor (pain)

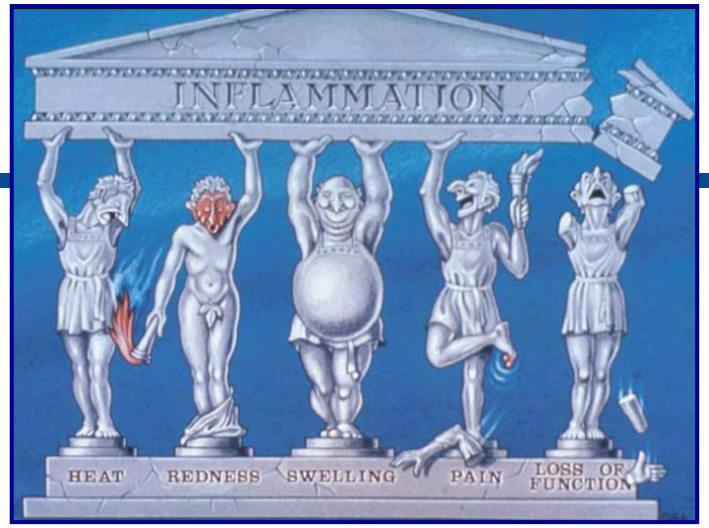
Aulus Cornelius Celsus, De medicina, c. A.D. 25

The dynamics of inflammation



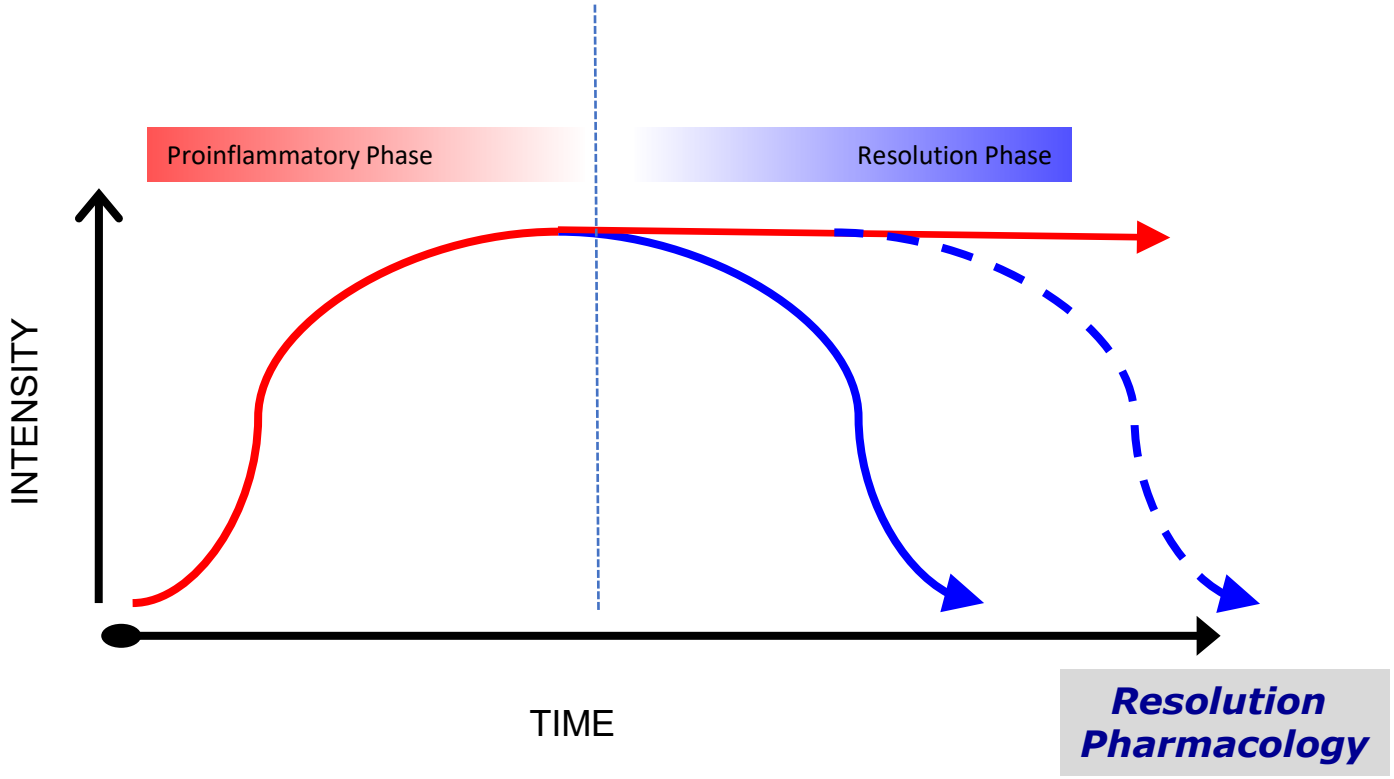
Physiological Inflammation

Perretti, Cooper, Dalli, Norling
Nature Review Rheumatol (2017; PMID: 28053331)


INFLAMMATION
HEAT
REDNESS
SWELLING
PAIN
LOSS OF FUNCTION

nature
REVIEWS
IMMUNOLOGY
FIRE

The dynamics of inflammation



Pathological Inflammation

Perretti, Cooper, Dalli, Norling
Nature Review Rheumatol (2017; PMID: 28053331)

Pro-inflammatory mediators: Targets for anti-inflammatory therapy

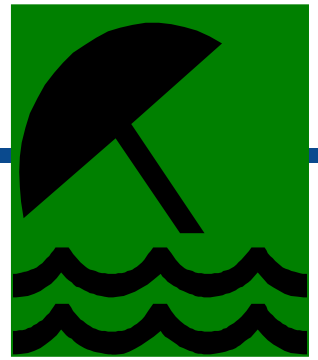
Complement

Autacoids (Histamine; SP; CGRP)

Eicosanoids (PGs, LTs; …)

Cytokines/Chemokines

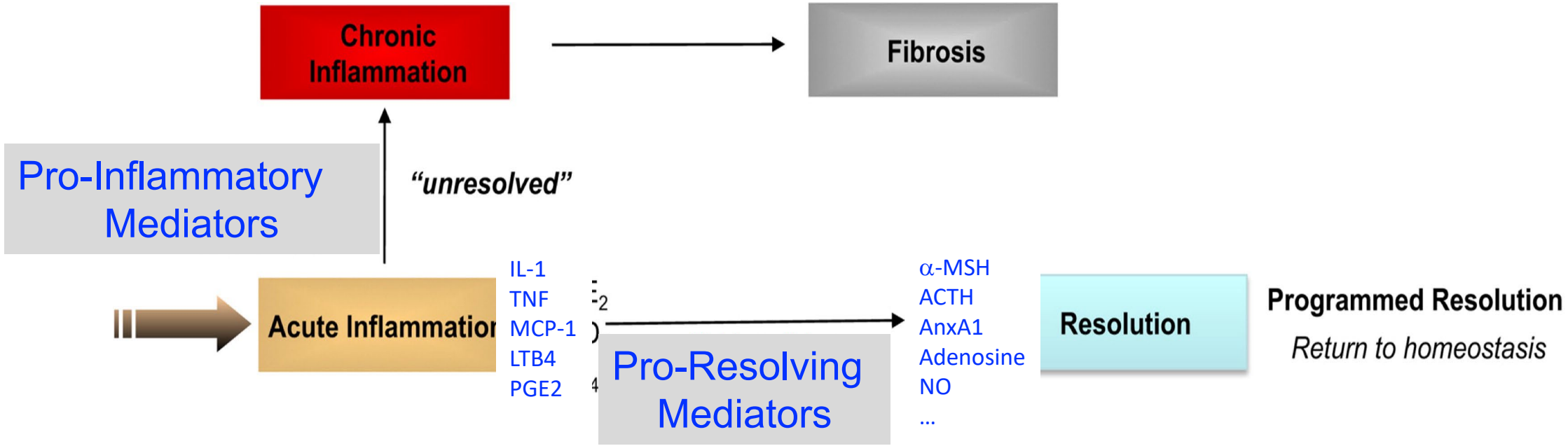
Adhesion Molecules



Pro-Resolving Mediators: Activated for pro-resolving therapy

Adenosine
Cortisol
NO
CO (H_2S)
Heparins
Lipoxins
Resolvins
PGD_2
CycloP-PGs
Agonists at NR
Etc …

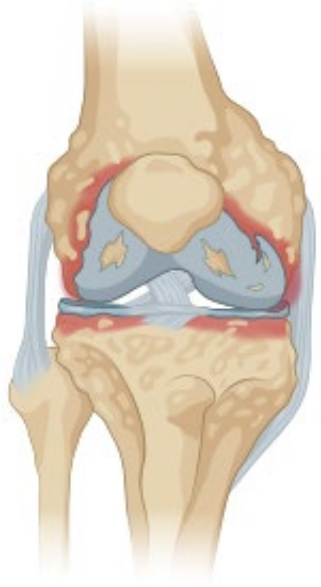
Somatostatin
Annexin A1
Galectin 1 and 9
Melanocortins
ACTH
Axonal Factors
IL-10
IL-1RA
Heat Shock Proteins
Heme Oxygenase 1
Etc …



Adapted from Serhan CN, Am J Pathol 2010

Problems with current anti-RA therapies

- Proportion of patients do not respond to therapy
- Secondary-effects (immunosuppression)
- Anti-drug antibodies (biologics)
- Ineffective on RA cardiovascular complications



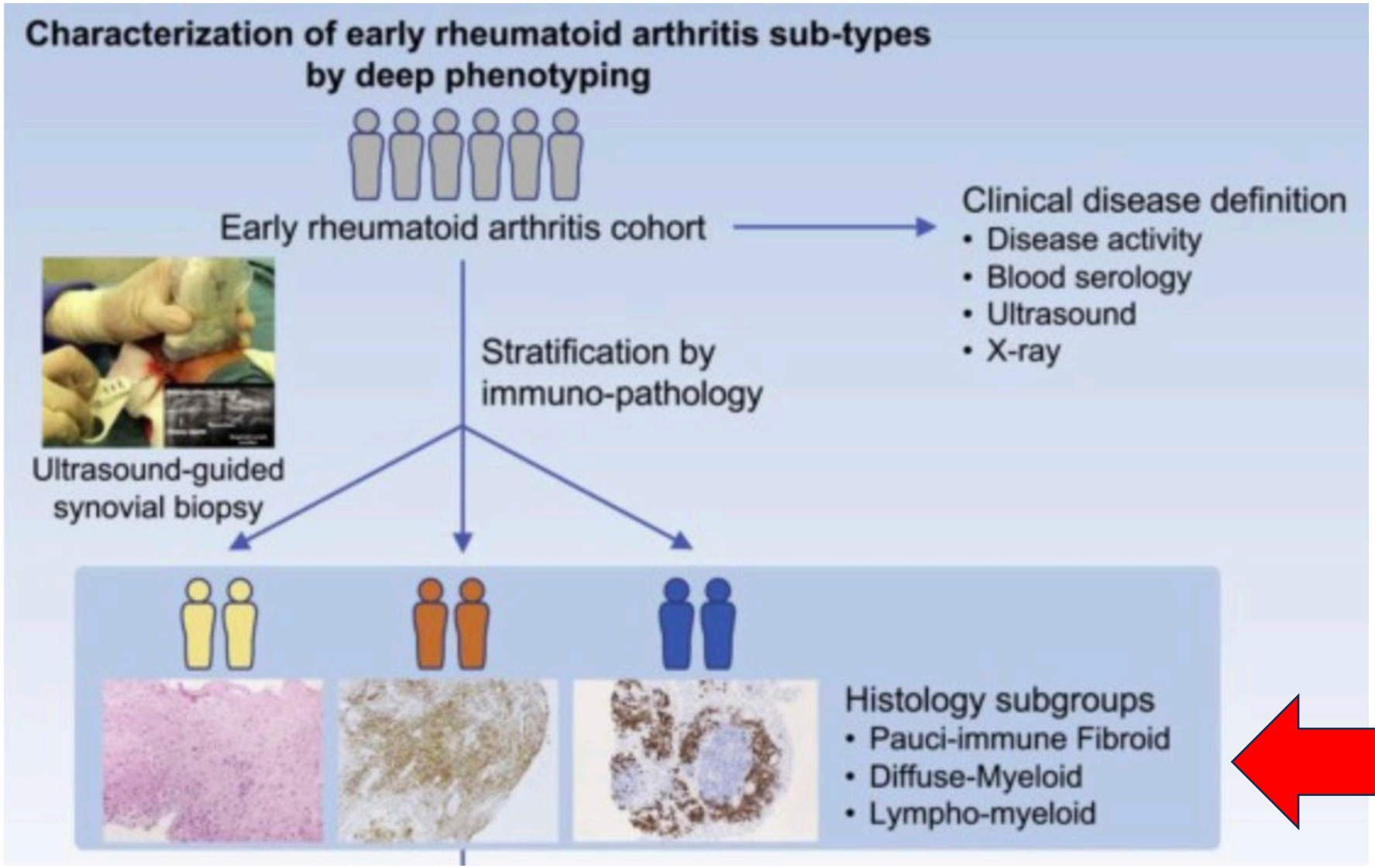
Rheumatoid Arthritis (RA) is a chronic disease of the joints

- The cause remains unknown
- There are cycles of '**active disease**'
- Active phases are called '**flares**'

- Flares are characterized by immune cell invasion, pain and reduced joint function

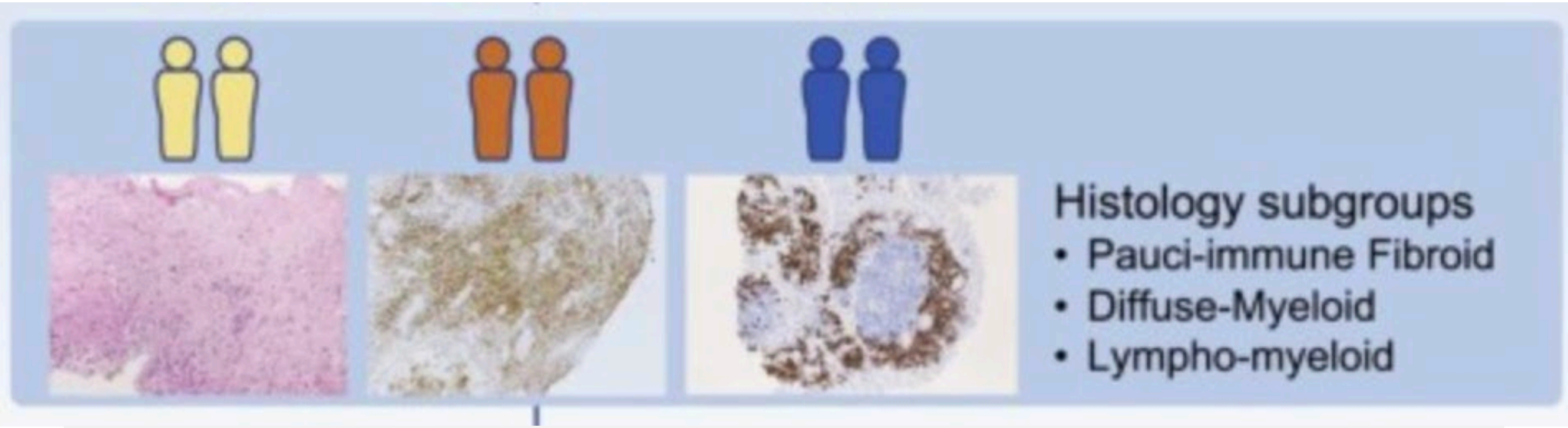
However, with RA we cluster a set of diseases with different pathotypes, that is ***different pathological phenotypes***

RA - different pathotypes = pathological phenotypes



Rivellese, Pitzalis Sem Immunol 2021

RA - different pathological phenotypes



Results from clinical trials indicate that definition of the synovial tissue can inform treatment response in patients with RA.

*Histological and molecular profiles support the notion of **disease endotypes**, i.e. disease subtypes defined by distinct pathological mechanisms.*

Integration of endotypes into clinical algorithms may help optimizing treatment decision.

Rivellese, Pitzalis Sem Immunol 2021

Two Examples

A Pauci-Immune Synovial Pathotype Predicts Inadequate Response to TNFα-Blockade in Rheumatoid Arthritis Patients

Alessandra Nerviani, Maria Di Cicco, Arti Mahto, Gloria Lliso-Ribera, Felice Rivellese, Georgina Thorborn, Rebecca Hands, Mattia Bellan, Daniele Mauro, Marie-Astrid Boutet, Giovanni Giorli, Myles Lewis, Stephen Kelly, Michele Bombardieri, Frances Humby and Costantino Pitzalis**

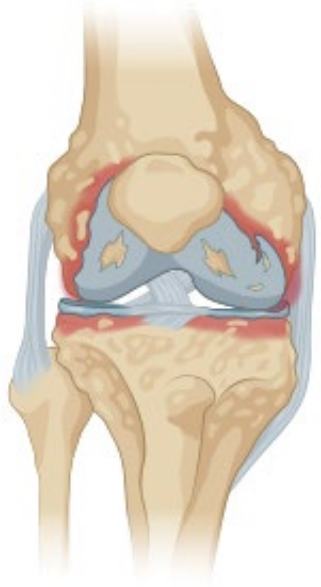
Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

Cell Reports
Resource

OPEN ACCESS
CellPress

Molecular Portraits of Early Rheumatoid Arthritis Identify Clinical and Treatment Response Phenotypes

Myles J. Lewis,[1] Michael R. Barnes,[2,3] Kevin Blighe,[1] Katriona Goldmann,[1] Sharmila Rana,[1,2] Jason A. Hackney,[4] Nandhini Ramamoorthi,[5] Christopher R. John,[1] David S. Watson,[2,3,6] Sarah K. Kummerfeld,[4] Rebecca Hands,[1] Sudeh Riahi,[1] Vidalba Rocher-Ros,[1] Felice Rivellese,[1] Frances Humby,[1] Stephen Kelly,[1] Michele Bombardieri,[1] Nora Ng,[1] Maria DiCicco,[1] Désirée van der Heijde,[7] Robert Landewé,[8] Annette van der Helm-van Mil,[7] Alberto Cauli,[9] Iain B. McInnes,[10] Christopher D. Buckley,[11,12] Ernest Choy,[13] Peter C. Taylor,[12] Michael J. Townsend,[5,*] and Costantino Pitzalis[1,14,*]



The near future is to ‘understand’ the type of RA – hence patient stratification

Effective patient stratification can enable optimal treatment with current as well as novel anti-RA drugs

One way to stratify patients is through their CRP levels

Examples from Different Diseases

Circulation

PERSPECTIVE

The Time to Initiate Anti-Inflammatory Therapy for Patients With Chronic Coronary Atherosclerosis Has Arrived

Paul M Ridker, MD, MPH

have recurrent coronary events and persistent symptoms despite aggressive guideline directed therapy. For now, I am also likely to take a conservative stance and limit low-dose colchicine to those with hsCRP levels >2 mg/L for whom I am concerned that inflammation is a silent driver of disease progression.

Although results from CANTOS, LoDoCo2, and COLCOT are persuasive, much remains uncertain. Will anti-inflammatory therapy be useful for patients with large-vessel peripheral arterial disease where few medical therapies are effective? Might early anti-inflammatory therapy provide a novel intervention to reduce vascular risk among patients with metabolic syndrome and insulin resistance? Might anti-inflammatory therapy provide benefit for those who present with chronic carotid rather than chronic coronary disease? Will the proven role of anti-inflammatory therapy in stable coronary disease extend to individuals with acute coronary ischemia or acute stroke where issues of rapid reperfusion are typically more important than issues of underlying disease progression?

All these questions will be addressed by the clinical research community. However, as of today, barring contraindications, the time to consider initiating anti-inflammatory therapy for patients with chronic coronary atherosclerosis and residual inflammatory risk has already arrived.

Two further concepts

Concept #1 –

A proper inflammatory reaction brings in resolution.

In other words, pro-resolving therapy is more effective if there is a vigorous inflammatory status

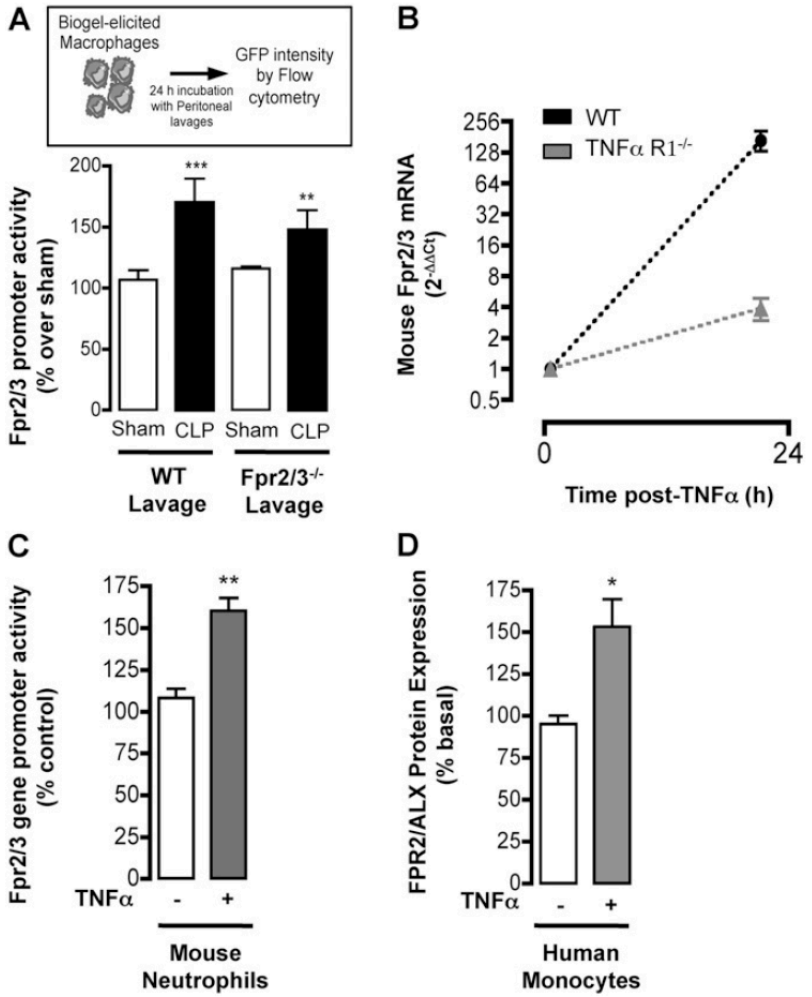
Pro-inflammatory mediators upregulate mediators and targets of resolution

Formyl Peptide Receptors and Annexin A1: Complementary Mechanisms to Infliximab in Murine Experimental Colitis and Crohn's Disease

Marina de Paula-Silva[1,2], Gustavo Henrique Oliveira da Rocha[1], Milena Fronza Broering[1], Maria Luíza Queiroz[3], Silvana Sandri[1], Rodrigo Azevedo Loiola[1], Sonia Maria Oliani[4], Andrea Vieira[3], Mauro Perretti[2] and Sandra Helena Poliselli Farsky[1]*

[1] Department of Clinical and Toxicological Analyses, University of São Paulo (USP), São Paulo, Brazil, [2] Centre for Biochemical Pharmacology, The William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London (QMUL), London, United Kingdom, [3] Gastroenterology Service, Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil, [4] Department of Biology, São Paulo State University (UNESP), São José do Rio Preto, São Paulo, Brazil

Non-responsiveness to anti-TNF-α therapies presents relevant rates in inflammatory bowel disease patients, presenting the need to find biomarkers involved in therapeutic efficacy. Herein, we demonstrate that higher levels of colonic formyl peptide receptor 1 and annexin A1 correlate with histological recovery in Crohn's disease patients under remission. Using the dextran sulfate sodium colitis model in mice, we suggest that infliximab induces annexin A1 expression and secretion in activated intestinal leukocytes. Conversely, this mechanism might stimulate epithelial formyl peptide receptors, inducing wound healing and consequent histological remission. Our data indicate that assessing intestinal expressions of formyl peptide receptors and annexin A1 might provide precious information on the disease activity and responsiveness to infliximab in inflammatory bowel disease patients.



Subtle inflammation or para-inflammation is typical of unhealthy settings yet without overt or aggressive disease

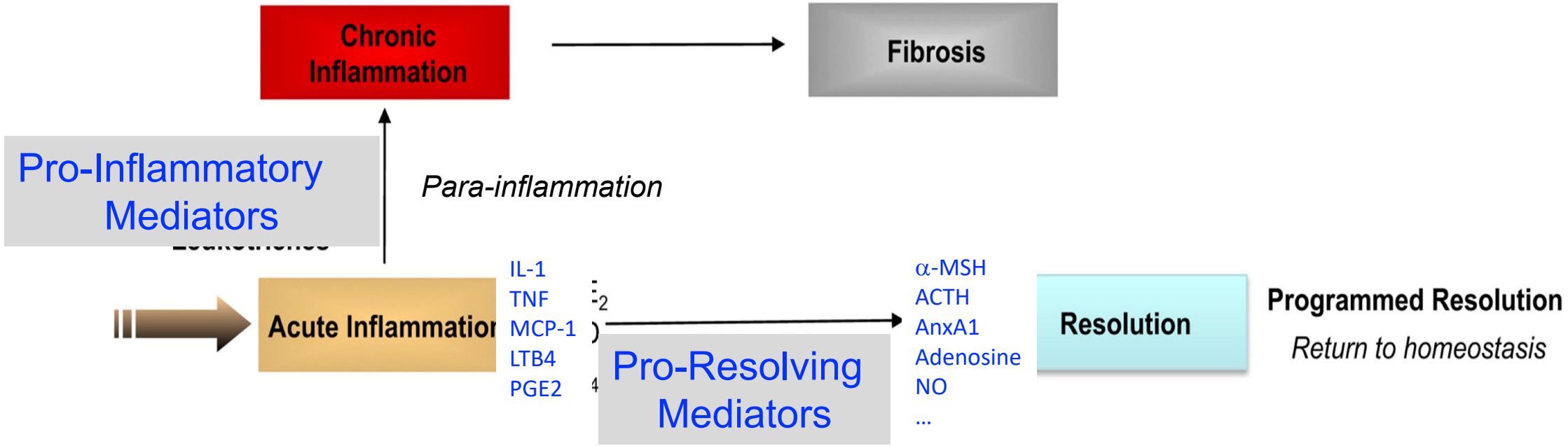
From: Origin and physiological roles of inflammation

Para-inflammatory responses are graded: at one extreme, they are close to the basal state, whereas, at the other, they start to transition into inflammation .

The induction of a para-inflammatory response does not require overt tissue injury or infection; instead, it is switched on by tissue malfunction, in order to restore tissue functionality and homeostasis. If tissue malfunction is present for a sustained period, ***para-inflammation can become chronic.***

Many chronic inflammatory diseases … e.g. obesity, type 2 diabetes, atherosclerosis, asthma and neurodegenerative diseases are all characterized by chronic low-grade inflammation (para-inflammation), which might not have any physiological counterparts.

Furthermore, the chronic para-inflammation that persists in these conditions can, in turn, contribute to further disease progression, in part because of changes in homeostatic set points (such as insulin sensitivity or blood pressure).



Adapted from Serhan CN, Am J Pathol 2010

Concept #2 –

Pro-Resolution therapy
≠
Anti-Inflammatory therapy

The biased agonist AP1189

The Melanocortin System

Historic work:

1. ACTH effective in RA (1949)
2. ACTH effective in Gout (1950)
3. ACTH effective in controlled clinical trials (Gout 1997)
4. ACTH effective in severe gout patients (2016)

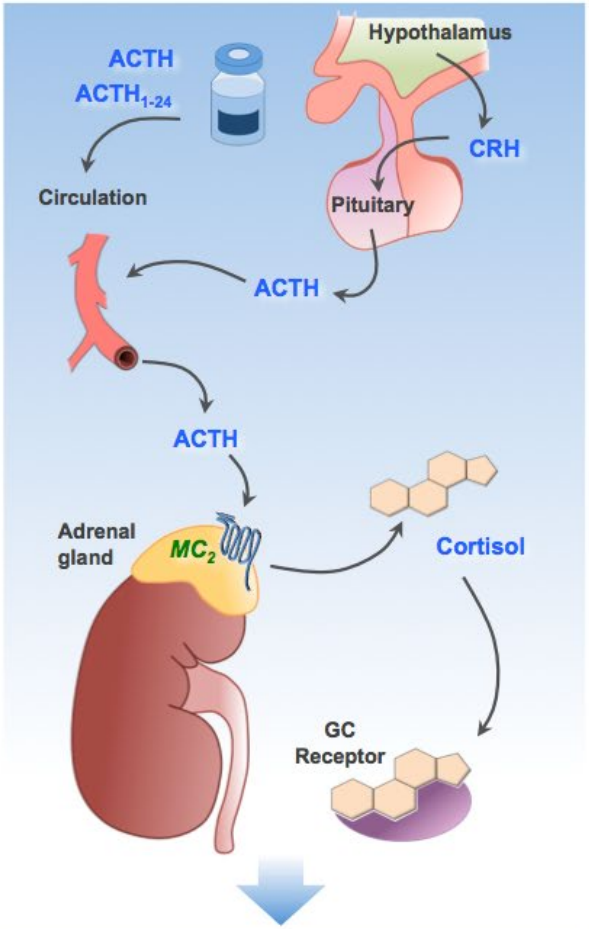
Licenced melanocortin-based drugs:

1. SCENESSE® Afamelanotide (16mg)
2. Bremelanotide ®
3. Acthar® Gel

On Going Trials:

1. AP214 (Phase IIb; AKI in cardiac surgery)
2. AP1189 (Phase I/IIa completed; Phase IIb inRA, Nephrotic Syndrome)
3. PPL8177 (Phase I completed)

GC-dependent mechanism



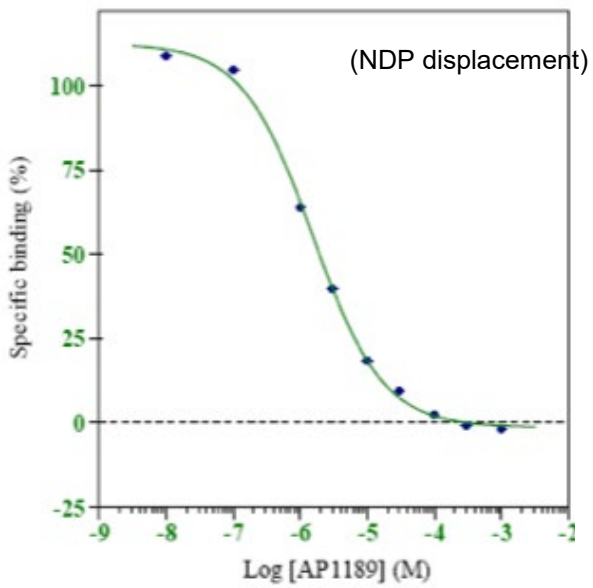
↓ Cytokines, chemokines, iNOS, COX2…
↑ Anti-inflammatory proteins: IL-10, AnxA1, DUSP1
↓ Neutrophil transmigration
↑ Phagocytosis of apoptotic neutrophils

**Montero-Melendez T, Seminars in Immunology 2015;27:216-226*

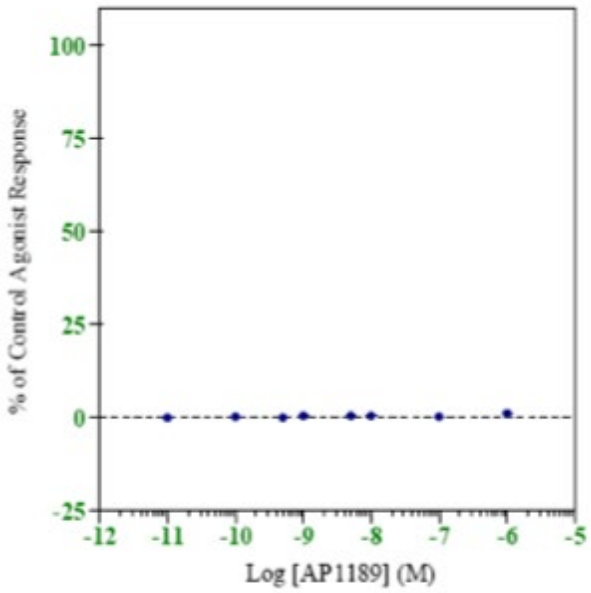
AP1189 – MC small molecule

mMC$_1$

Binding

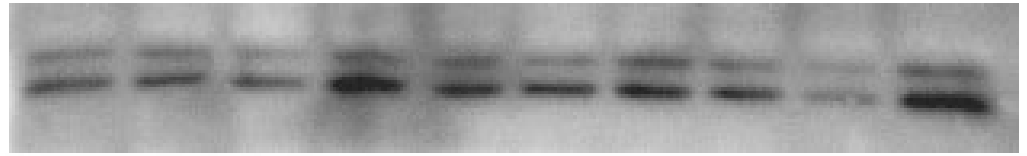


cAMP



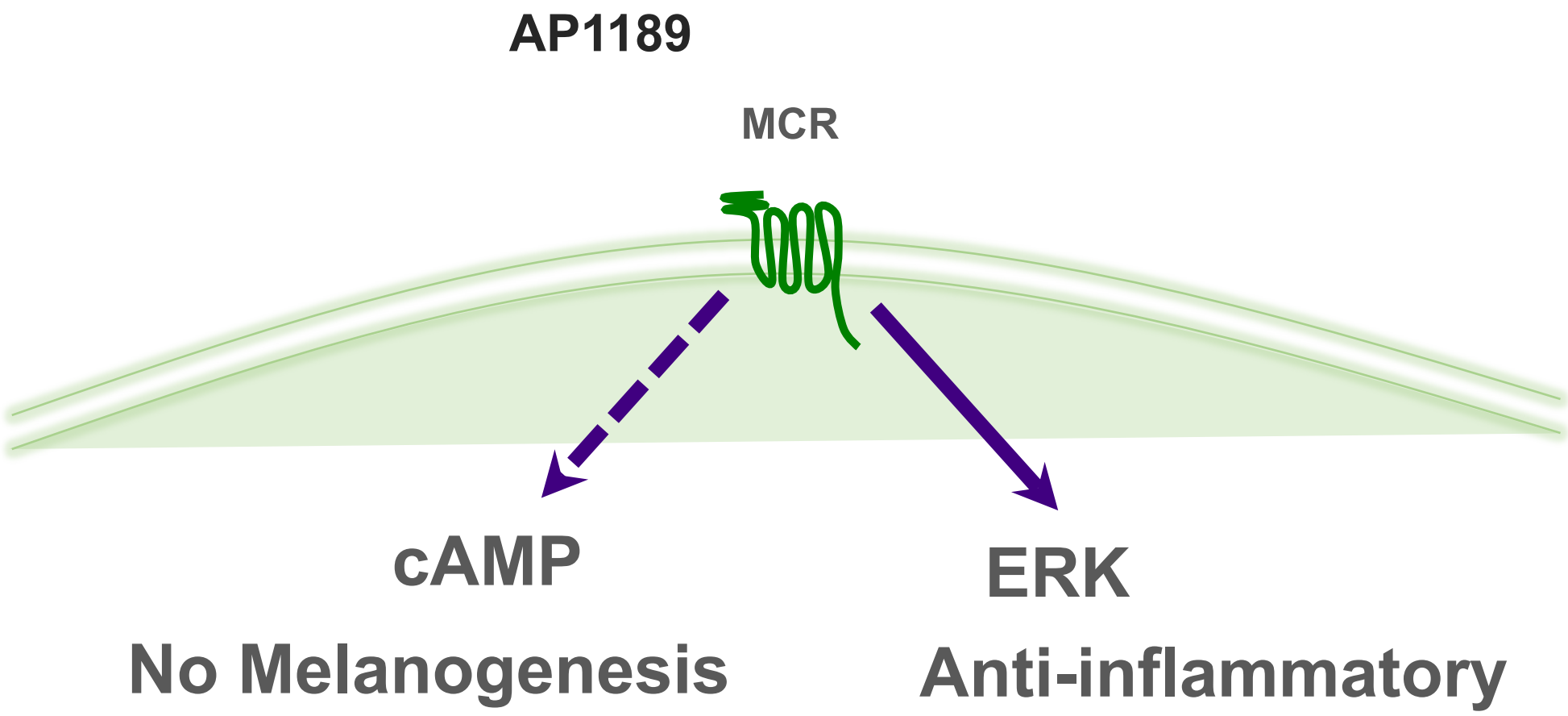
AP1189 (1nM)

ERK1/2 phosphorylation



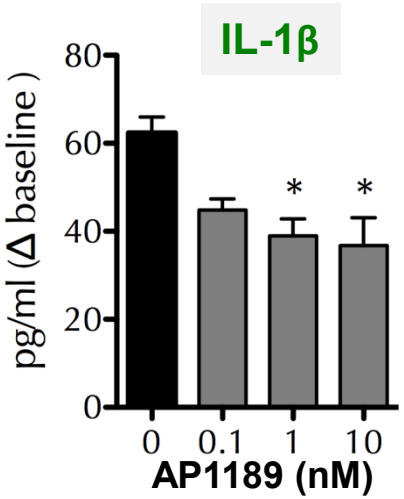
MC1-HEK293 cells

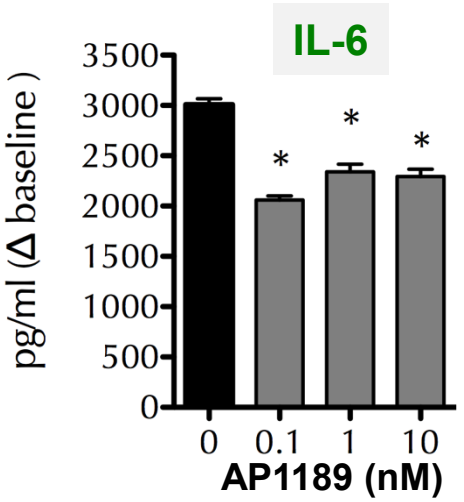
Biased Agonist AP1189 = functional selectivity

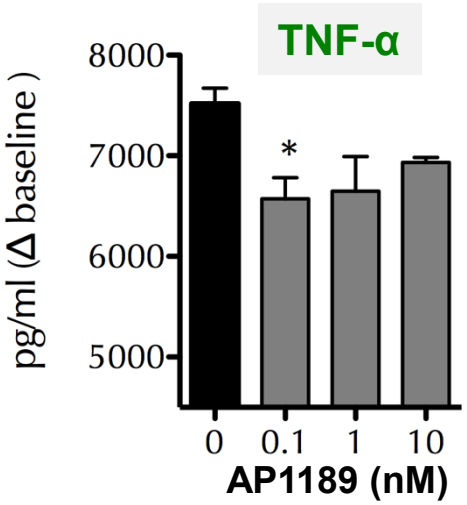


Trini Montero-Melendez, et al, J Immunol 2015

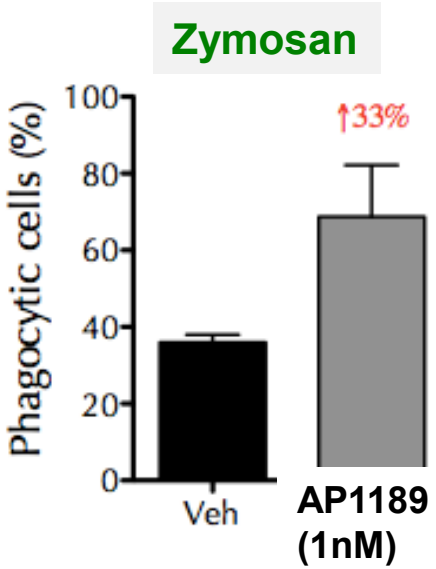
AP1189 – Pharmacological properties

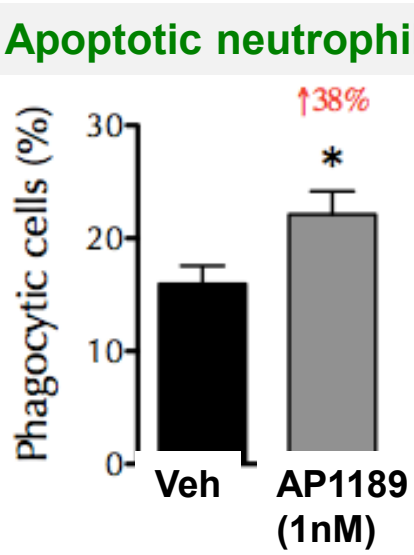






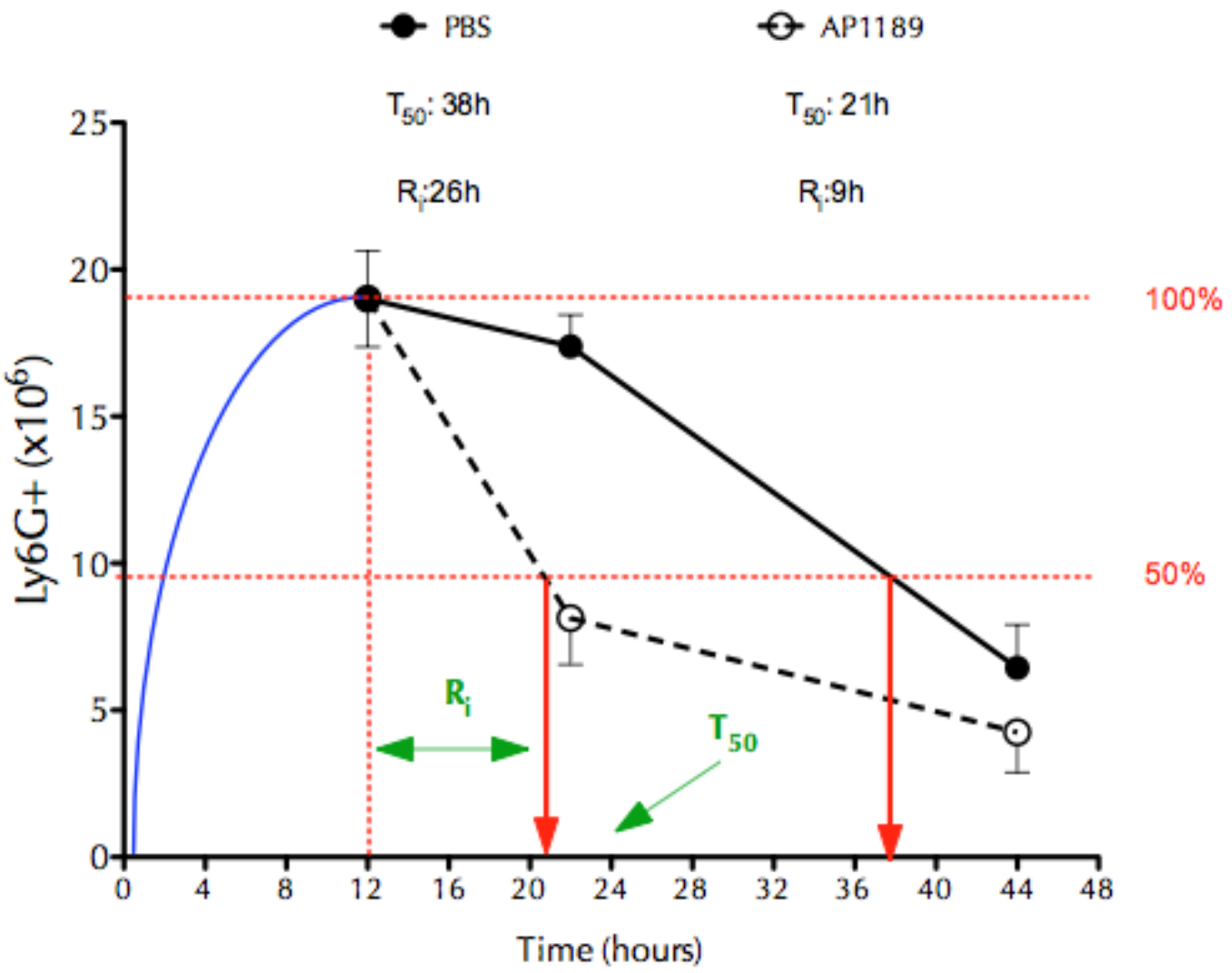
Primary macrophages
Zymosan 25 µg/ml,
(6h, n=3)

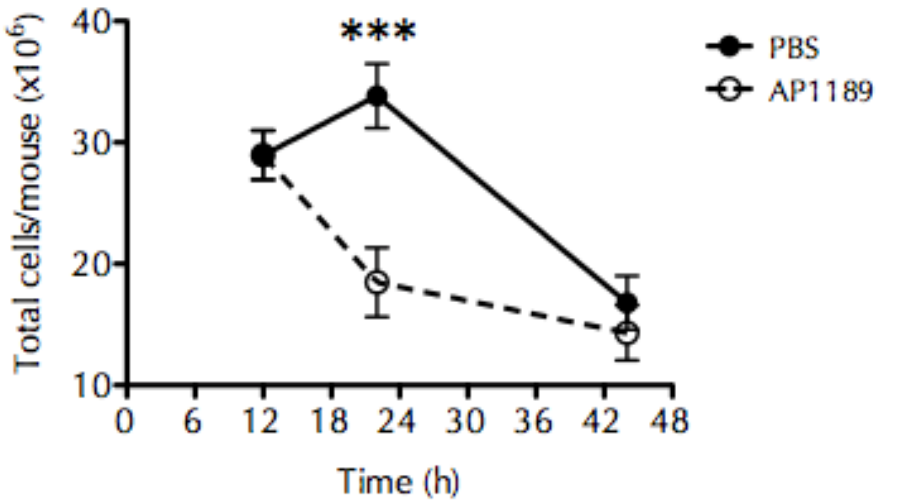


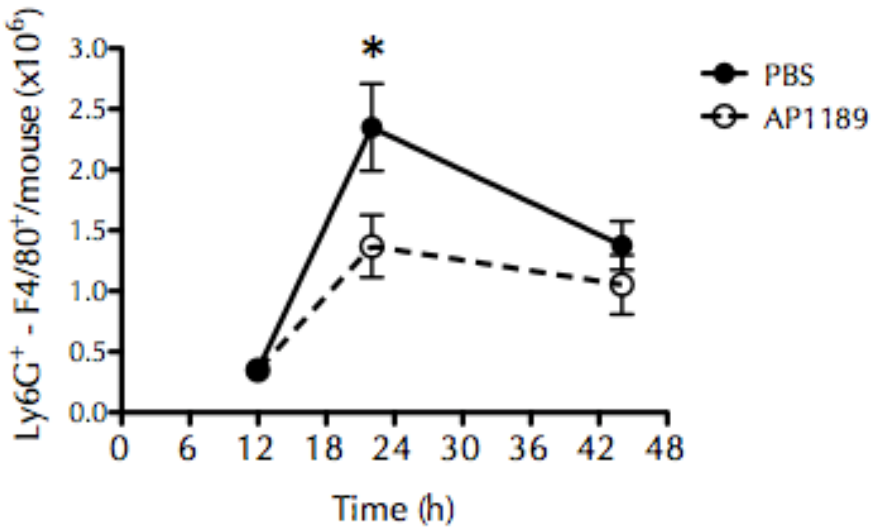


Primary macrophages
PMN 1:5 ratio,
(1h, n=3)

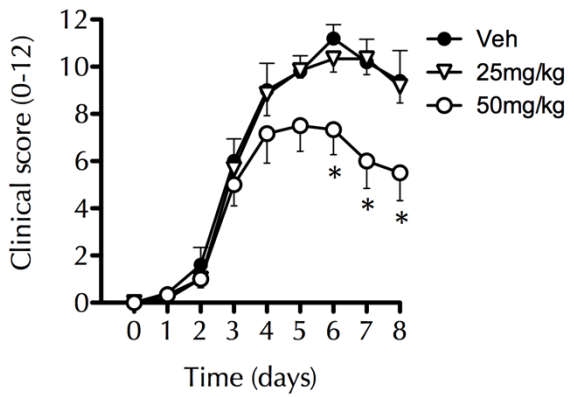
AP1189 pro-resolving activities

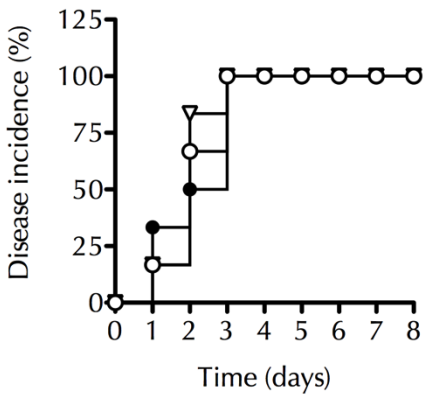


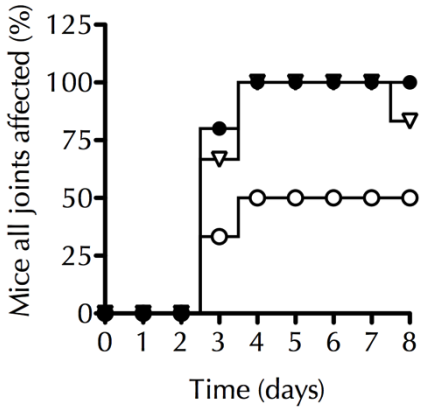


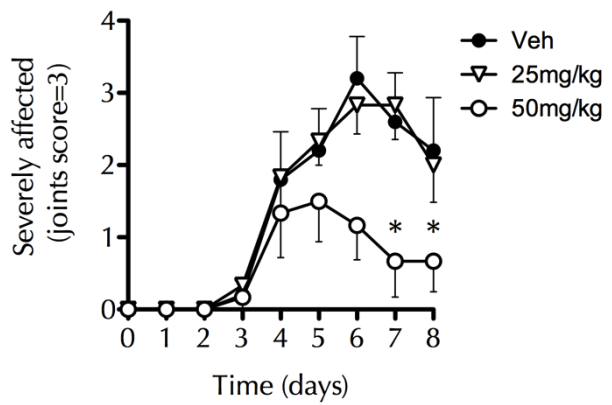


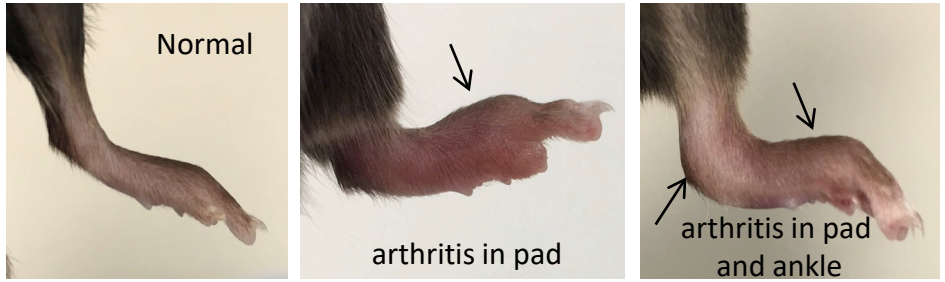
AP1189: anti-arthritic actions



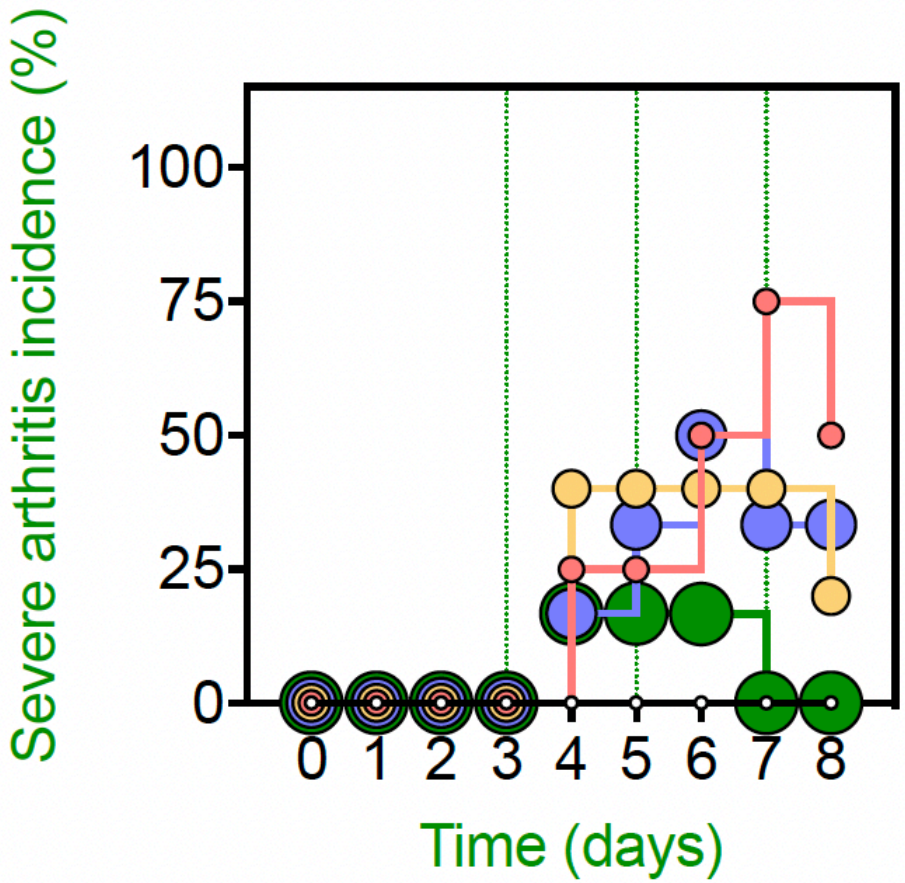








AP1189 and MTX

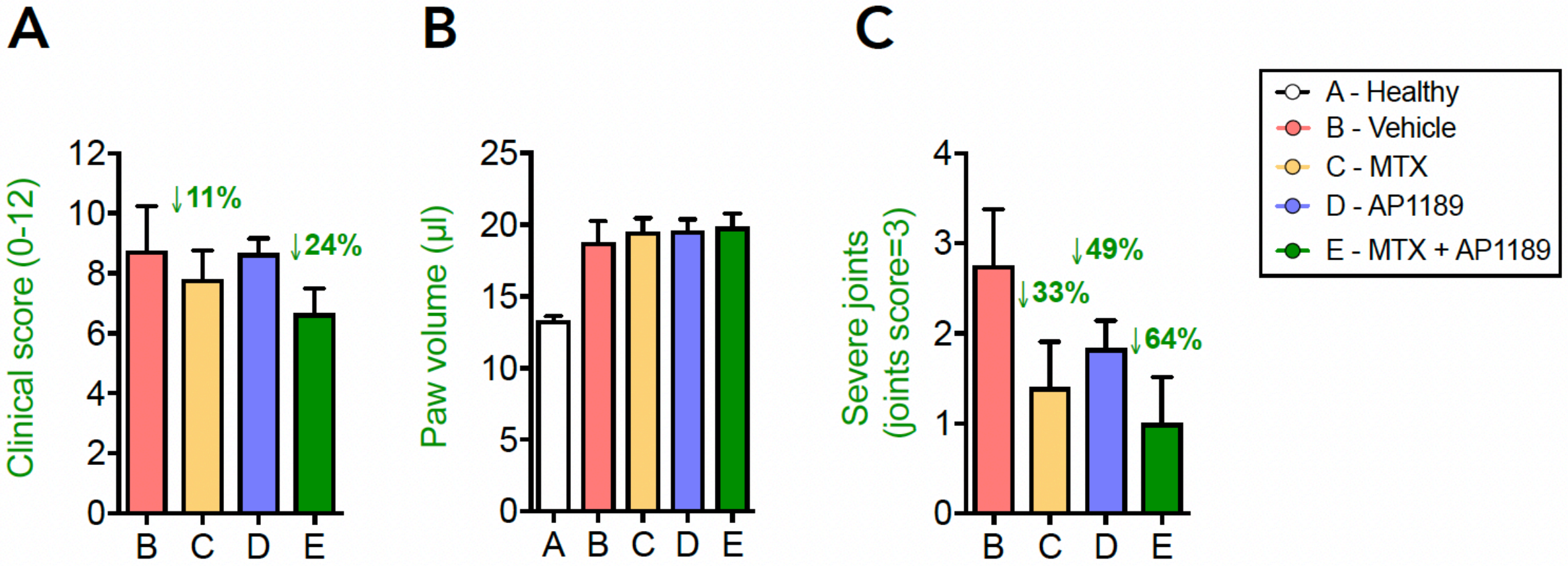


A - Healthy
B - Vehicle
C - MTX
D - AP1189
E - MTX + AP1189

The incidence of severe arthritis was calculated as the % of mice in each group that reached a total score of ≥ 10.

In the vehicle control group, 75% of mice at day 7 presented a score ≥ 10. This was reduced around 50% by AP1189 and MTX (groups C and D). and completely abrogated in the combination therapy (group E).

AP1189 and MTX



Concept #2 –

Pro-Resolution therapy
≠
Anti-Inflammatory therapy

Classical Pharmacology ANTI- INFLAMMATION

Innovation RESOLUTION Pharmacology

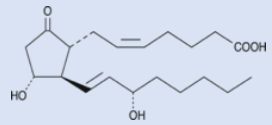
CLASSES

- Glucocortociods
- NSAIDs
- Biologics
- Methotrexate
- Colchicine
- DMARDs
- Cyclosporin
- H1 antagonists
- Chromones
- Lukast drugs

- Annexin A1
- Melanocortins
- Galectins
- Chemerin 15
- Somatostatin
- ω-3 derived: Resolvins, Protectins, Maresins
- Lipoxin A_4
- Adenosine
- Cannabinoids

ACTIONS

Pg synthesis inhibition

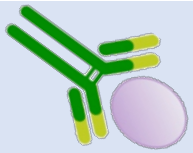


GI Toxicity

e on
tosis
tosis

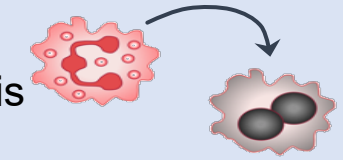
αMSH
AnxA1
RvD1

Cytokine blockade



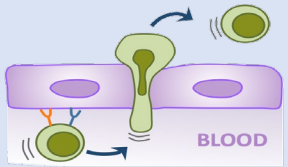
Inflixima
Anakinra
Toci

nduction of neutrophil apoptosis



LXA_4
CDK inhib.
HDACIs

Inhibition leukocyte migration



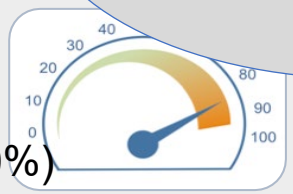
Infection

hage
pe switch

RvD1
AnxA1

MoA

- Based on "*inhibition*""
- Directed actions
- Strong inhibition (80-90%)

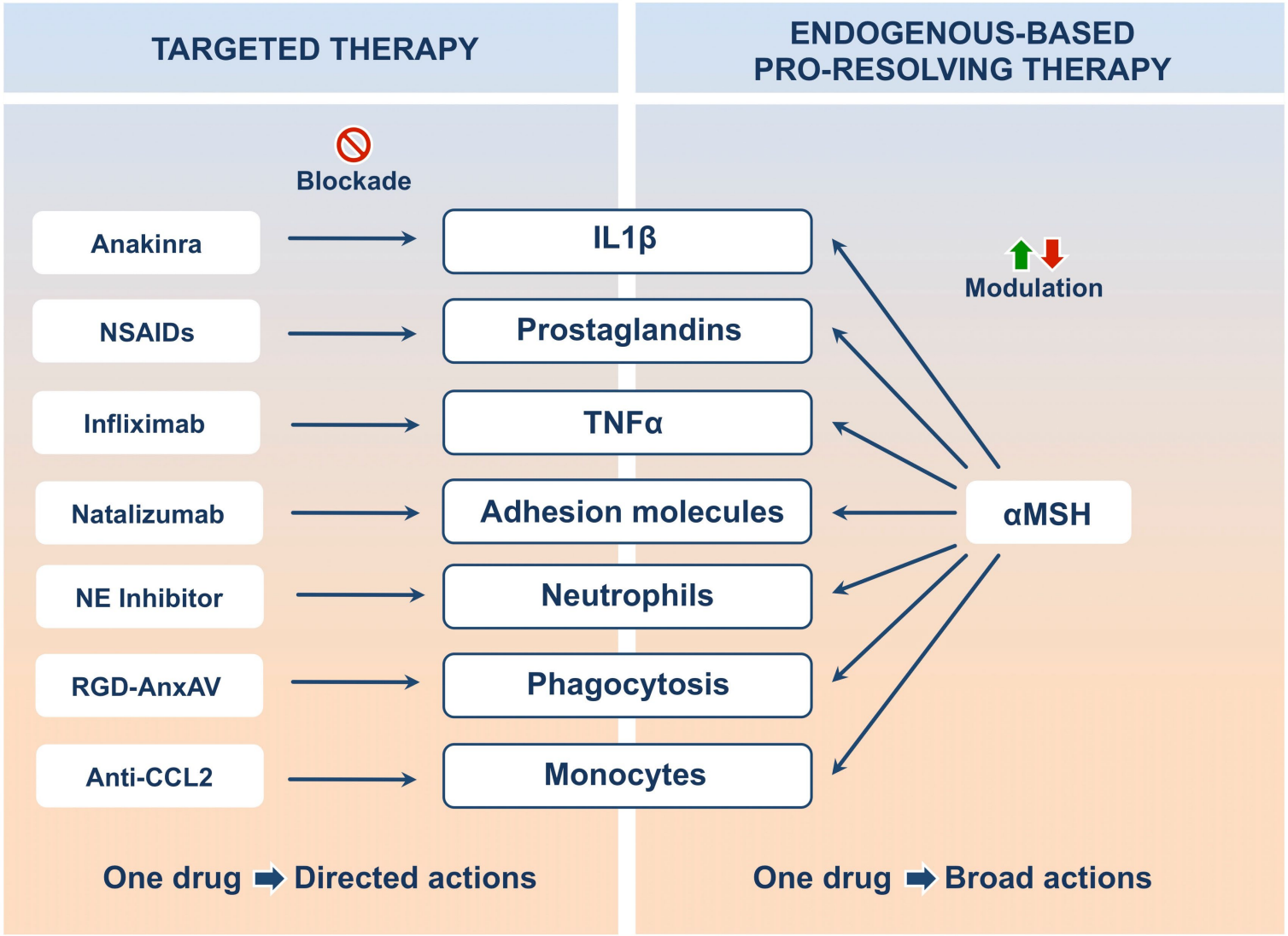


- Based on "*activation*"
- Broad actions
- Modulation (40-50%)

SIDE EFFECTS

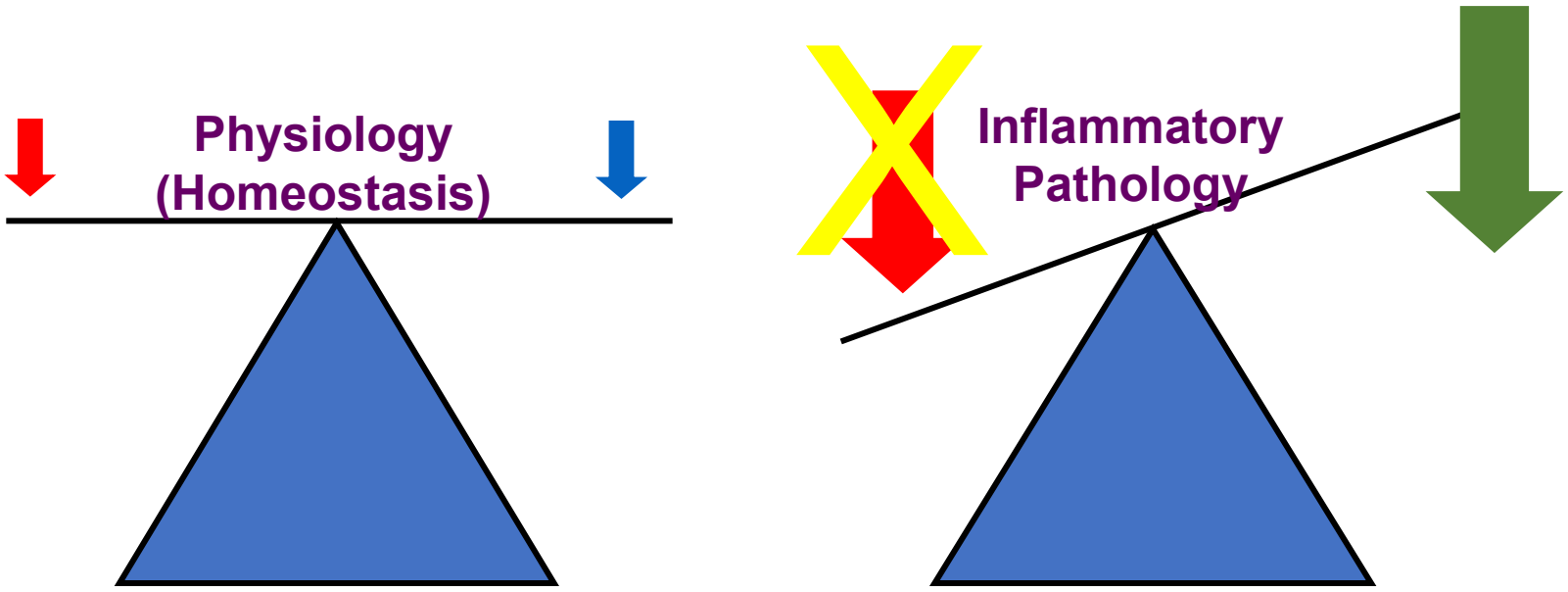
- Immunosuppressive
- Resolution toxic
- Compensation/Tolerance

- Unknown



Montero-Melendez T. ACTH: The Forgotten Therapy. Seminars in Immunology 2015

Resolution Pharmacology
Innovation for anti-inflammatory therapeutics



The next decade: Resolution-based anti-inflammatories:

1) **Better Drugs – mimic the way our body naturally resolves inflammation.**
2) **Lower Burden of Side Effects.**
3) **Multiple actions; not immunosuppressive.**

Resolution Pharmacology

Pro-resolving Molecules in Clinical Trial/Use

AP214 Alpha-MSH analogue (Action Pharma –> Abbvie, Phase III)

TP-317 Resolvin E1 (Thetis Pharmaceuticals LLC; IBD)

H_2S-NSAIDs (Antibethera; ATB-346, OA Phase III)

CINOD, NO-PG (Nicox; Ophthalmology, in clinical use)

Activating Anti-ChemR23 mAb (Ose Immunotherapeutics –> Sanofi)

ORACAL (Tarsa; Bone Resorption Phase III)

Dubloxins (University College Dublin; Sepsis, Fibrosis)

Resolvix (Med'inn'Pharma; preclinical)

Benzo-Lipoxin A_4 (Forsyth; Periodontal disease; Phase I/II)

FPR2 small molecule (Bristol Myers Squibb; Phase I, Heart Failure/MI)

AP1189 biased melanocortin agonist (SynAct Pharma; Phase IIa/b)

RTP-026 Annexin peptide (ResoTher Pharma, Phase I, AMI)

Adenosine Agonists (several molecules)

Take-home message(s)

- Resolution of inflammation is a natural process (typical of acute inflammation)
- A proper inflammatory response can bring about resolution
- Pro-resolving therapy works better in presence of a good degree of inflammation

- Resolution Pharmacology represents a new frontier to afford control of chronic inflammatory diseases

- Rheumatoid Arthritis identify a ‘cluster’ of joint diseases
- Selecting the right group of patients can increase response to therapy (and patient benefit!)

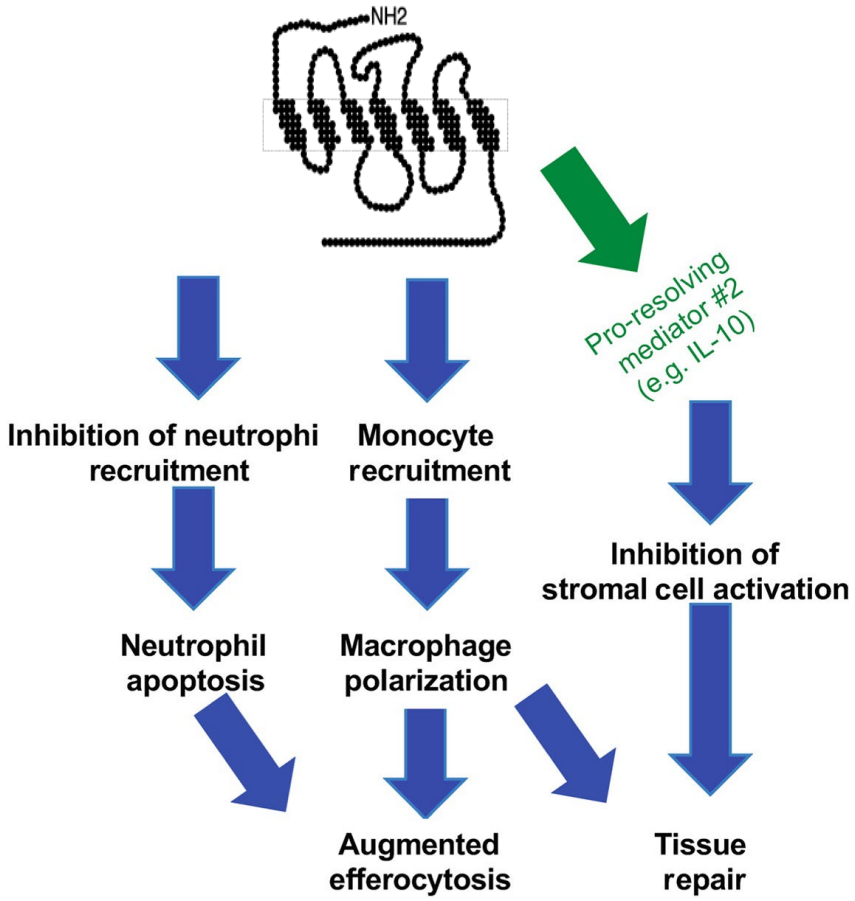
Thank you.

Targeting Resolution Pathways provides a therapeutic opportunity for chronic ('complex') diseases

INNOVATION:

1. Integrated actions of resolution
2. Amplification through pro-resolving receptors

Pro-Resolving Mediator #1

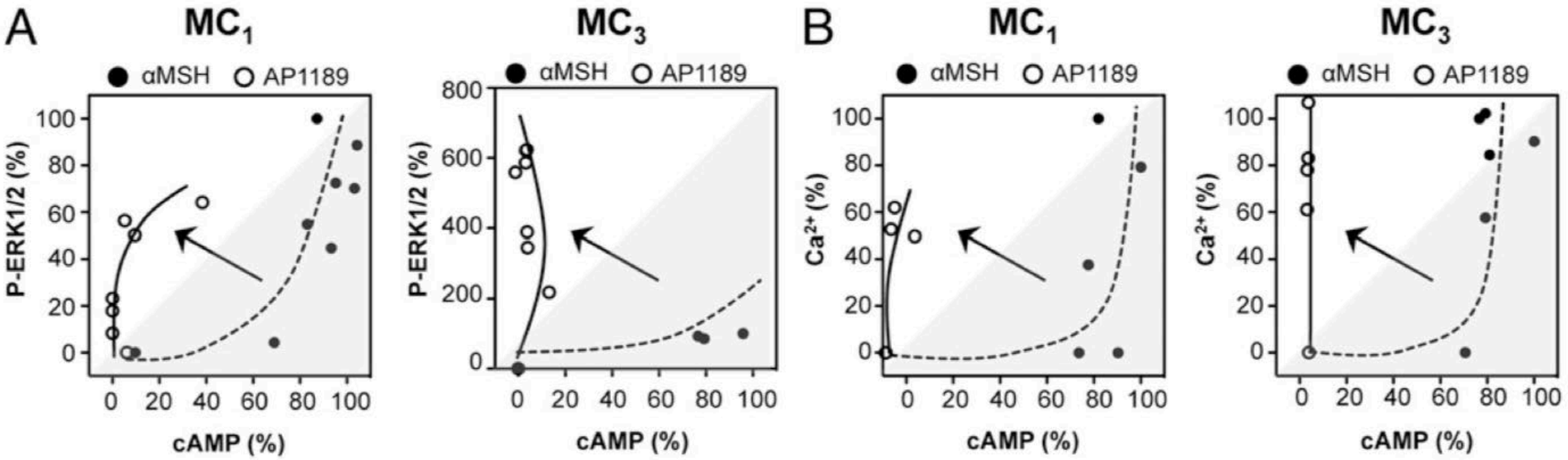


AGONIST!

- Cell gene reprogramming
- Cell phenotype switch
- Long-lasting effects
- Resolution of tissue inflammation

Resolution Pharmacology

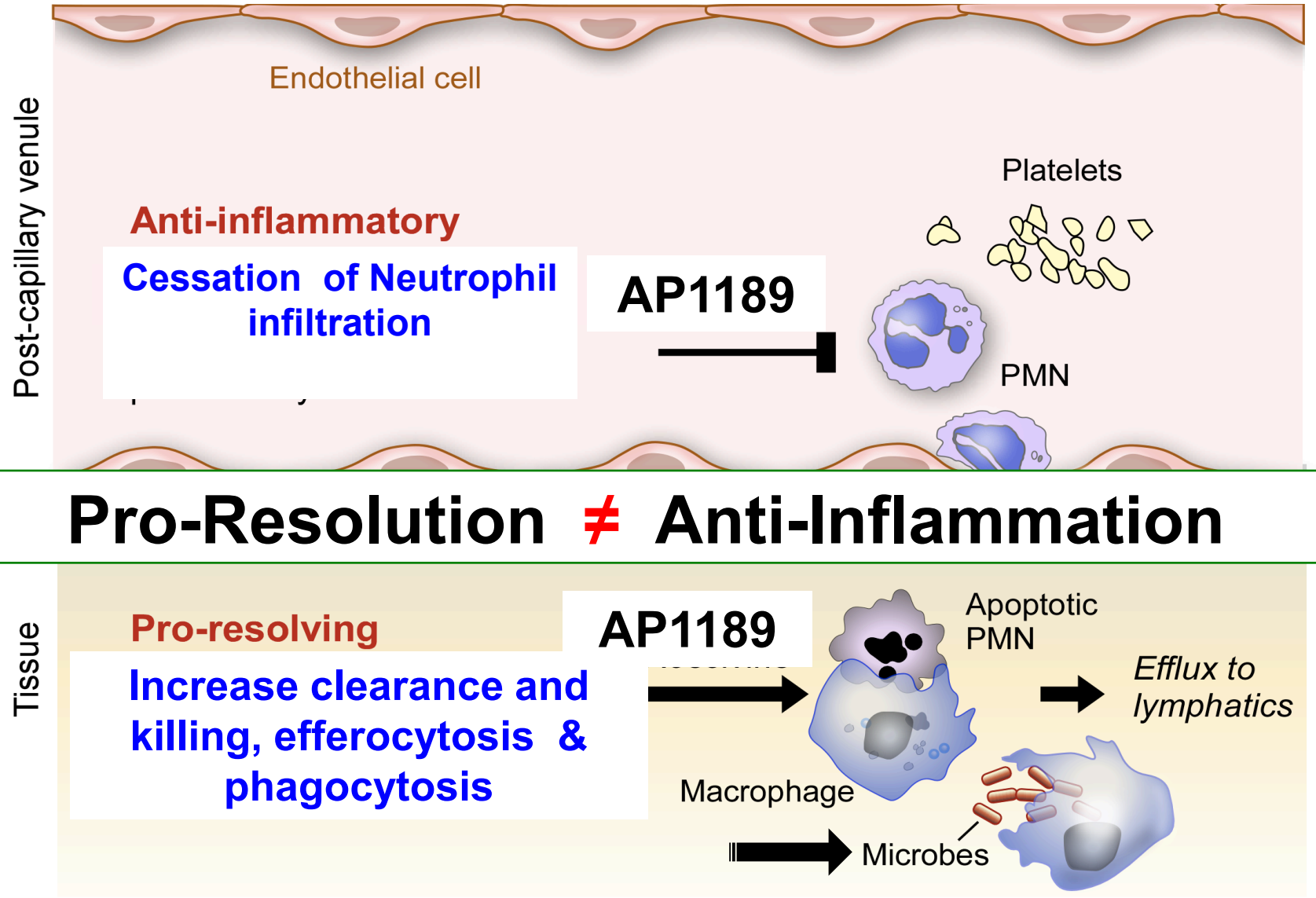
AP1189 – Pan-Receptor Biased Agonist



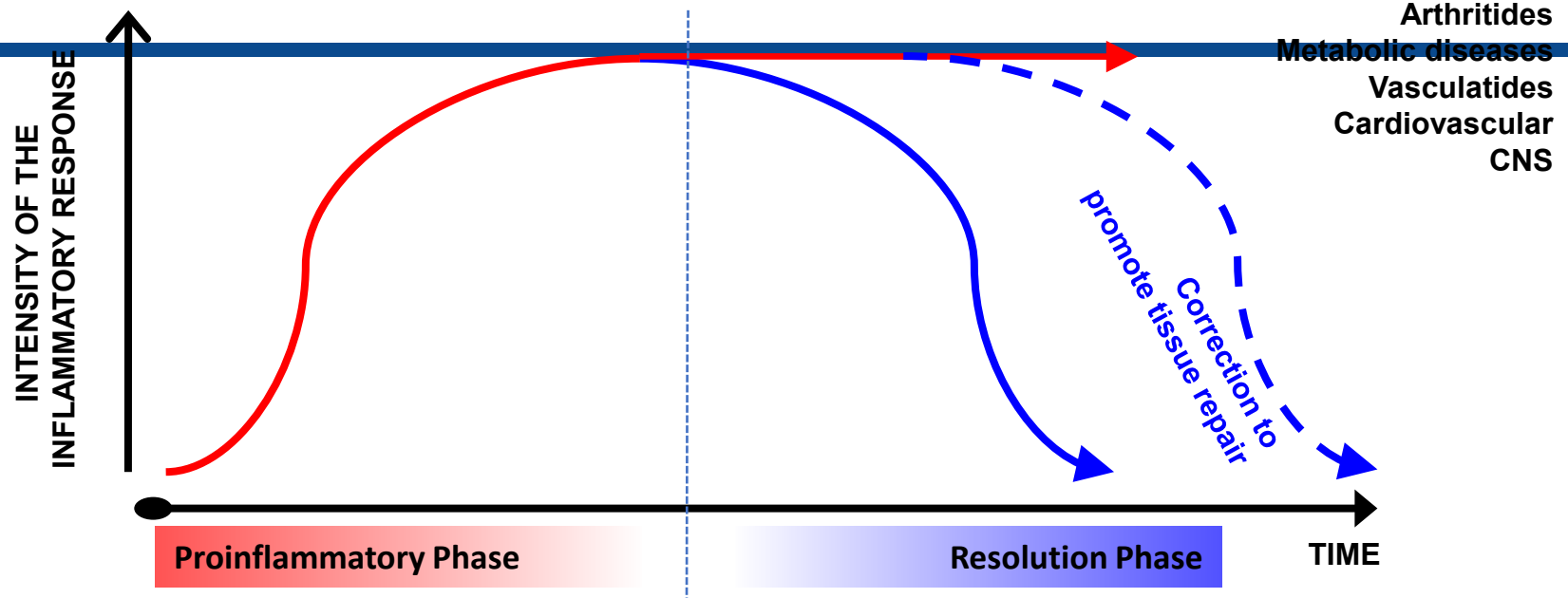
Erk/cAMP

Ca^{2+}/cAMP

AP1189 pro-resolving activities



adapted from C.N. Serhan et al., Semin Immunol. 2015; 27:200-15

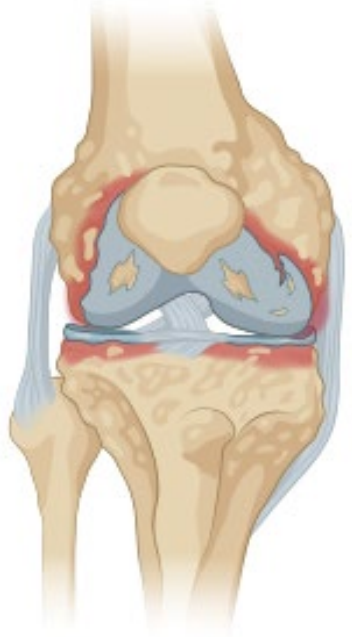


Current therapeutics often inadequate:

a) ~50% of patients do not respond
b) Lack of tissue recovery/repair
c) Major systemic toxicity
d) Elicit an immune response

Resolution-based therapeutics

a) Exploit patient's own tissue protective and reparative processes
b) Modulatory action
c) Lower burden of side effects



Rheumatoid Arthritis (RA) is one of the most common chronic inflammatory disorders affecting ~1 % of adults worldwide.

RA is characterized by symmetrical, erosive polyarthritis, resulting from chronic synovitis, i.e. inflammation of the synovial membrane, driven by the infiltration of immune cells, including both cells of innate and adaptive immunity.

In turn, ongoing inflammation leads to the proliferation of the synovial resident stromal cells (synoviocytes), leading to the thickening of the intimal layer, accompanied by the growth of new blood vessels facilitating the perpetuation of the inflammatory response through the incoming of more inflammatory cells from the systemic circulation.

SYNACT PHARMA

INFLAMMATION RESOLUTION

SynAct Pharma AB

Capital Market Day

Current and Future Treatments of Early Rheumatoid Arthritis and the Medical Need

Asger Reinstrup Bihlet, CSO at Sanos Group

Current and Future Treatments of Early Rheumatoid Arthritis and the Medical Need

Asger R. Bihlet MSc, PhD
Chief Scientific Officer
Sanos Group

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Brief Bio

Asger Reinstrup Bihlet, MSc., PhD

Chief Scientific Officer of NBCD A/S and Sanos Group A/S.

Expert clinical trial methodologist in rheumatic diseases, broad, 20+ years experience in the pharmaceutical industry, past roles in Sanofi and Ferring Pharmaceuticals.

Lead scientist on multiple successful, major clinical development programs, in collaboraton with multiple leading pharma and biotech.

Highly cited scientist with frequent oral presentations and invited speaker assignments at major international rheumatology meetings and 40+ peer reviewed publications in high-impact journals such as JAMA, Nature Medicine, and The Lancet Rheumatology.

Overview

- Introduction and Recap of the Current Early RA-Treatment Guidelines
- Overview of the Evidence behind Current Treatments in Early RA
- The Global Drug Development Pipeline
- Conclusions

69

Intro and Recap of Current RA Treatment Guidelines

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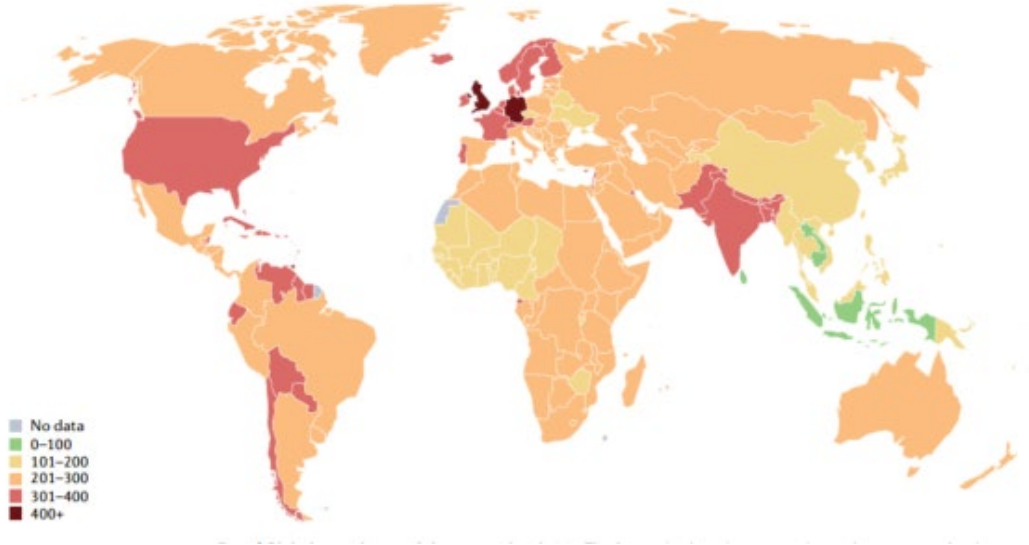
Rheumatoid Arthritis now and in the future

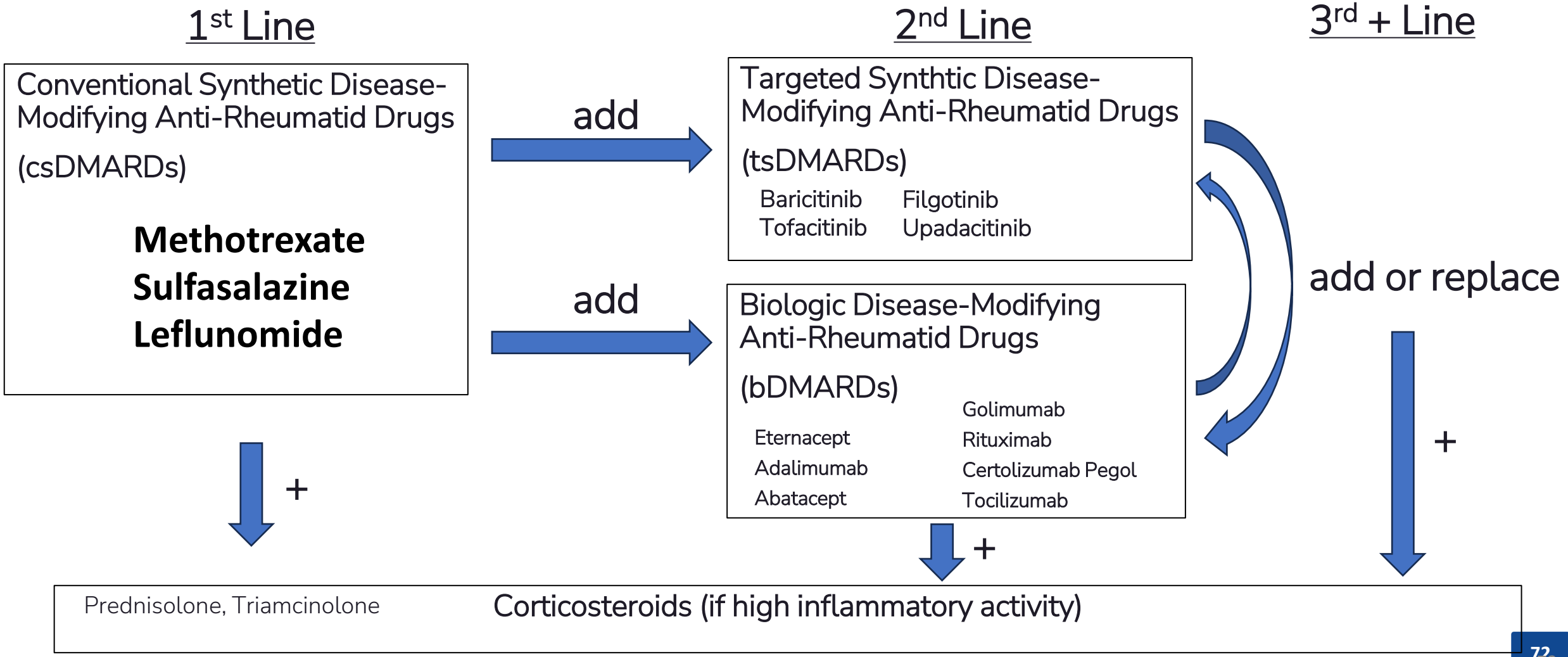
- Currently approximately 18 million people worldwide with RA
- Prevalence is between 0.2-1.0%, larger in industrialized countries
- Prevalence, age expectancy is rising - > larger RA global burden



Rheumatoid Arthritis prevalence per 100,000 of the population
From Finckh et al. 2022

Global Burden of Disease Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2023
Finckh A et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol 2022

Current RA Treatment Landscape



Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease- modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020

Considerations from EULAR and the Medical Need

- Target is maximising response rate as fast as possible as safely as possible
- Use of corticosteroids should minimized in dose and duration
- Current treatments, including MTX, are all immunosuppressant and associated with safety risks
- New, immune-modulatory treatments are needed

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Josef S Smolen [1], Robert B M Landewé [2], Sytske Anne Bergstra [3], Andreas Kerschbaumer [1], Alexandre Sepriano [4], Daniel Aletaha [1], Roberto Caporali,[5] Christopher John Edwards,[6] Kimme L Hyrich [7], Janet E Pope [8], Savia de Souza [9], Tanja A Stamm [10], Tsutomu Takeuchi [11], Patrick Verschueren [12], Kevin L Winthrop [13], Alejandro Balsa [14], Joan M Bathon,[15] Maya H Buch [16], Gerd R Burmester [17], Frank Buttgereit [17], Mario Humberto Cardiel,[18] Katerina Chatzidionysiou [19], Catalin Codreanu,[20] Maurizio Cutolo [21], Alfons A den Broeder,[22] Khadija El Aoufy,[23] Axel Finckh [24], João Eurico Fonseca [25], Jacques-Eric Gottenberg [26], Espen A Haavardsholm,[27] Annamaria Iagnocco [28], Kim Lauper [24], Zhanguo Li,[29] Iain B McInnes,[30] Eduardo F Mysler,[31] Peter Nash [32], Gyula Poor,[33] Gorica G Ristic,[34] Felice Rivellese [35], Andrea Rubbert-Roth [36], Hendrik Schulze-Koops [37], Nikolay Stoilov,[38] Anja Strangfeld [19,39], Annette van der Helm-van Mil,[3] Elsa van Duuren,[40] Theodora P M Vliet Vlieland [41], René Westhovens [12], Désirée van der Heijde [3]

Overview of the Evidence Behind Current Treatments for Early RA

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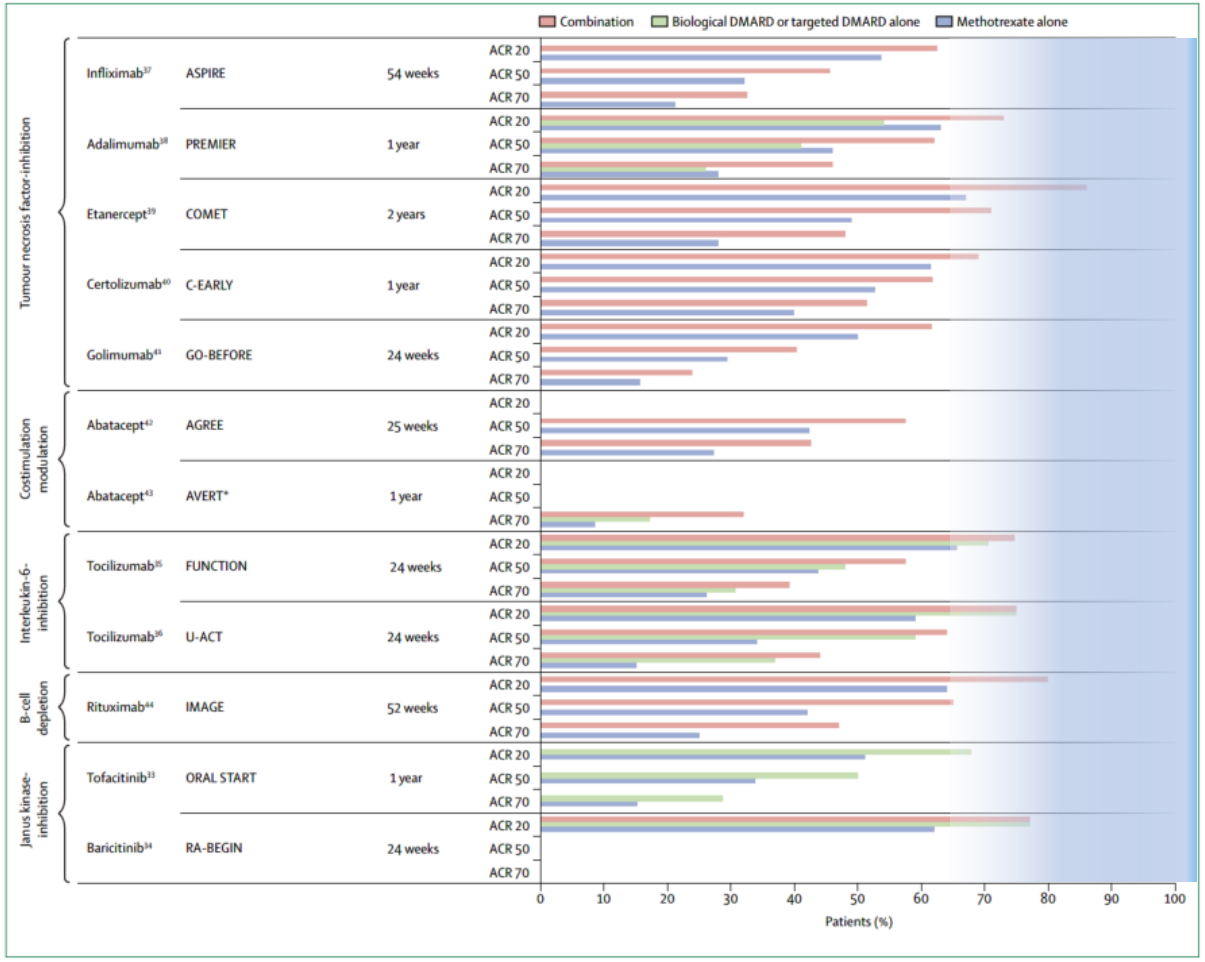
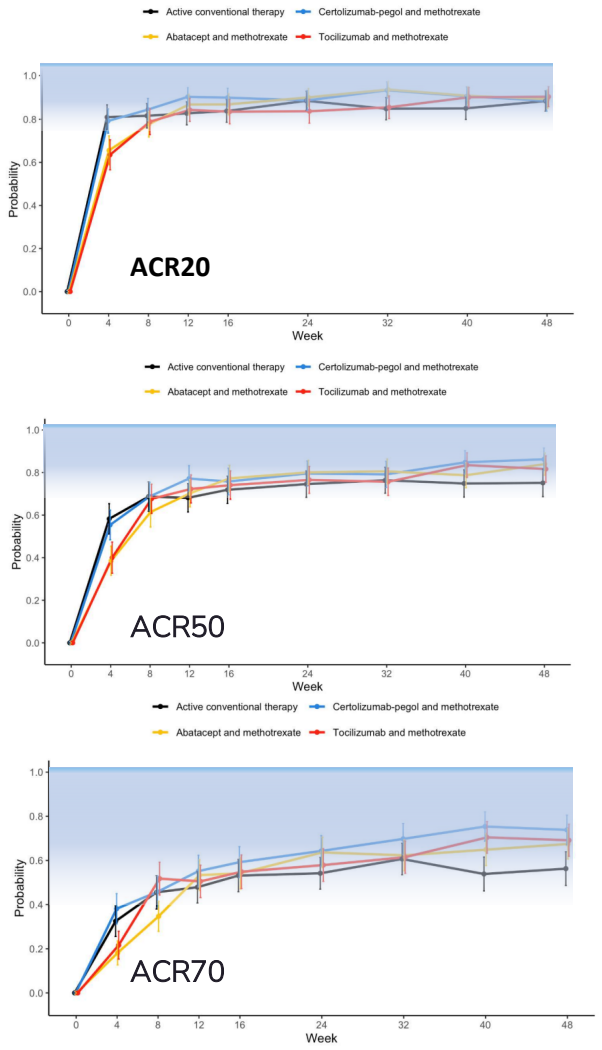
Room for improvement in the treatment of Rheumatoid Arthritis – Efficacy

Response gap:20-40%





To the most aggressive treatment strategy:

- > 20 % do not respond to MTX + steroids or biologics

- > 35-50 % have modest or no response to MTX + steroids or biologics

Burmester GR, Pope JE. Targeted treatments for rheumatoid arthritis 2 Novel treatment strategies in rheumatoid arthritis. Lancet 2017

Ostergaard M et al. Certolizumab pegol, abatacept, tocilizumab or active conventional treatment in early rheumatoid arthritis: 48- week clinical and radiographic results of the investigatorinitiated randomised controlled NORD-STAR trial. Ann Rheum Dis 2023

Room for improvement in the treatment of Rheumatoid Arthritis – Safety

Infections

ARTICLES · Volume 386, Issue 9990, P258-265, July 18, 2015

Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

Prof Jasvinder A Singh, MBBS, MPH [a,b,c,†] · Chris Cameron, MSc [d,e,†] · Shahrzad Noorbaloochi, BA [f] · Tyler Cullis, MA [b] · Matthew Tucker, BSc [b] · Robin Christensen, PhD [g] · et al. Show more

Affiliations & Notes · Article Info · Linked Articles (1)

Interpretation—Standard-dose and high-dose biologics (with/without traditional DMARDs) are associated with an increase in serious infections compared to traditional DMARDs in RA, while low-dose biologics are not.Clinicians should discuss the balance between benefit and harm with the individual RA patient before initiating biologic therapy.

Original article

A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis

Katie Bechman [1], Sujith Subesinghe[1], Sam Norton [2], Fabiola Atzeni[3], Massimo Galli[4,5], Andrew P. Cope [1], Kevin L. Winthrop[6] and James B. Galloway [1]

Conclusion. The absolute SI rates were low. However across the JAK inhibitors, the incidence of HZ is higher than expected for the population (3.23 per 100 patient-years). While the risk was numerically greatest with baricitinib, indirect comparisons between the drugs did not demonstrate any significant difference in risk.

CONCLUSION:

Serious safety risks apply with all available treatments

Cardiovascular, Cancer risk

Comparative Risk of Cardiovascular Events with Biologic and Synthetic Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis

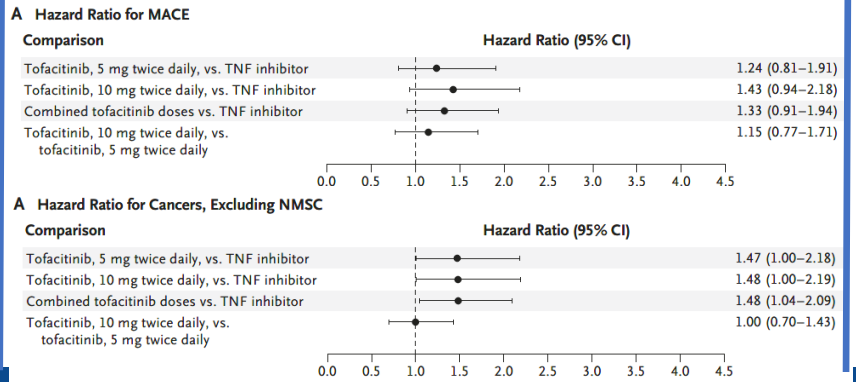
Siddharth Singh, MD MS[1,2,*], Mathurin Fumery, MD[3,*], Abha G. Singh, MD[4], Namrata Singh, MD MS[5], Larry J. Prokop, MLS[6], Parambir S. Dulai, MD[1], William J. Sandborn, MD[1], Jeffrey R. Curtis, MD MS MPH[7]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*



MTX general safety

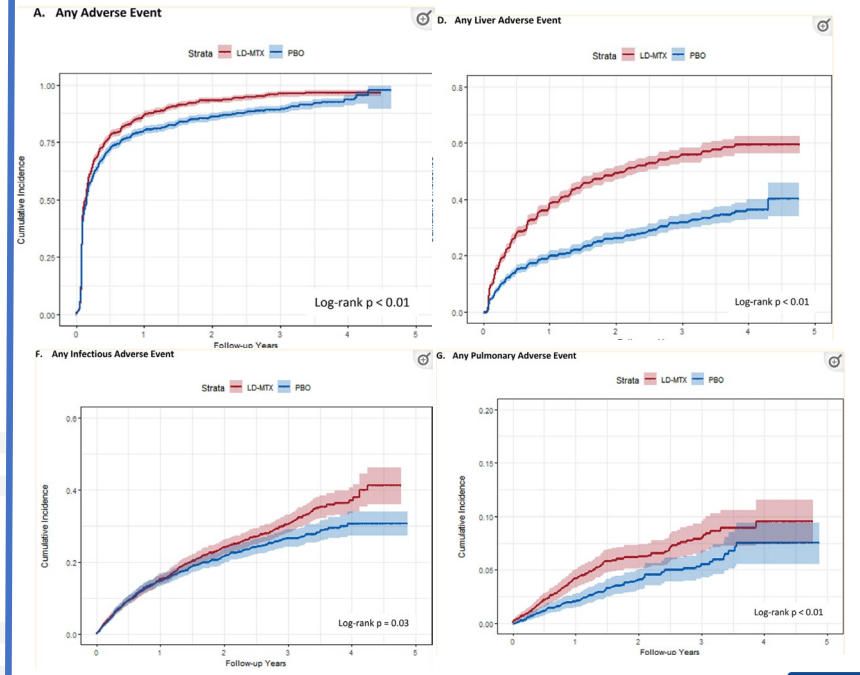
Annals of Internal Medicine®

Original Research | 18 February 2020

Adverse Effects of Low-Dose Methotrexate: A Randomized Trial

Authors: Daniel H. Solomon, MD, Robert J. Glynn, PhD, Elizabeth W. Karlson, MD, Fengxin Lu, MD, Cassandra Corrigan, BA, Josh Colls, BA, Chang Xu, MS, ... SHOW ALL ..., and Paul M Ridker, MD | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 172, Number 6



The Global RA Drug Development Landscape

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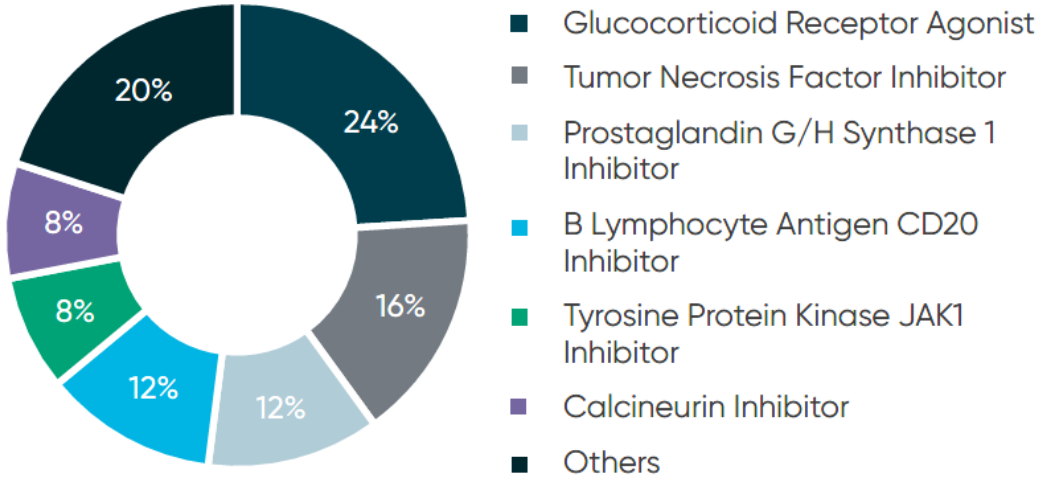
Global Drug Development Landscape in RA

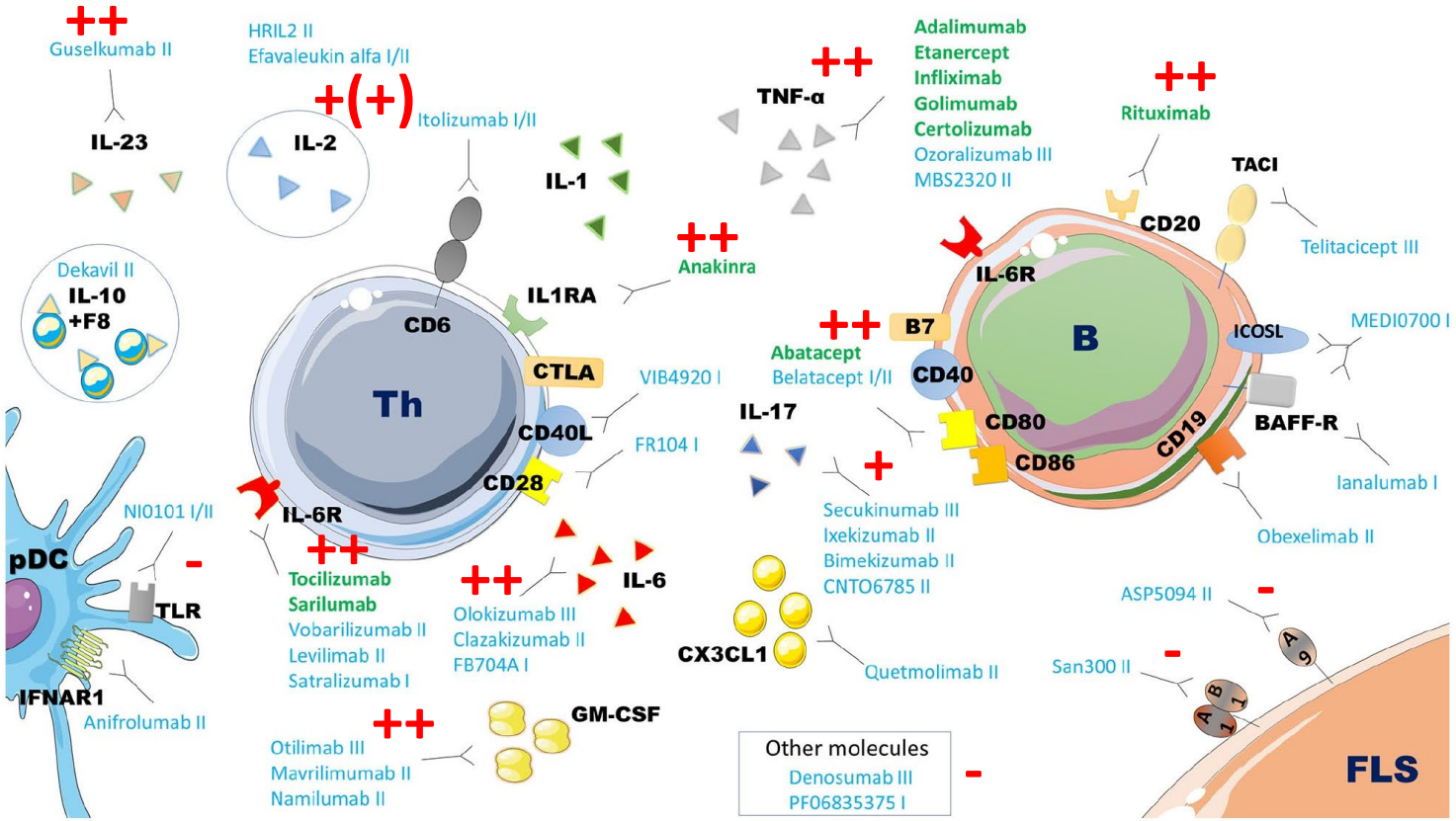
Number of product by phase of development

Source: Biocentury, Novotech January 2024

Share of phase 3 trials by mechanism of action



Source: GlobalData, Novotech January 2024



CONCLUSION:

Global Pipeline is active, most candidates are immunosuppressant

Figure from Blaess J et al. Immunosuppressive agents for rheumatoid arthritis: a systematic review of clinical trials and their current development stage. Ther Adv Musculoskel Dis. 2020, Vol. 12: 1–12

Final Conclusions

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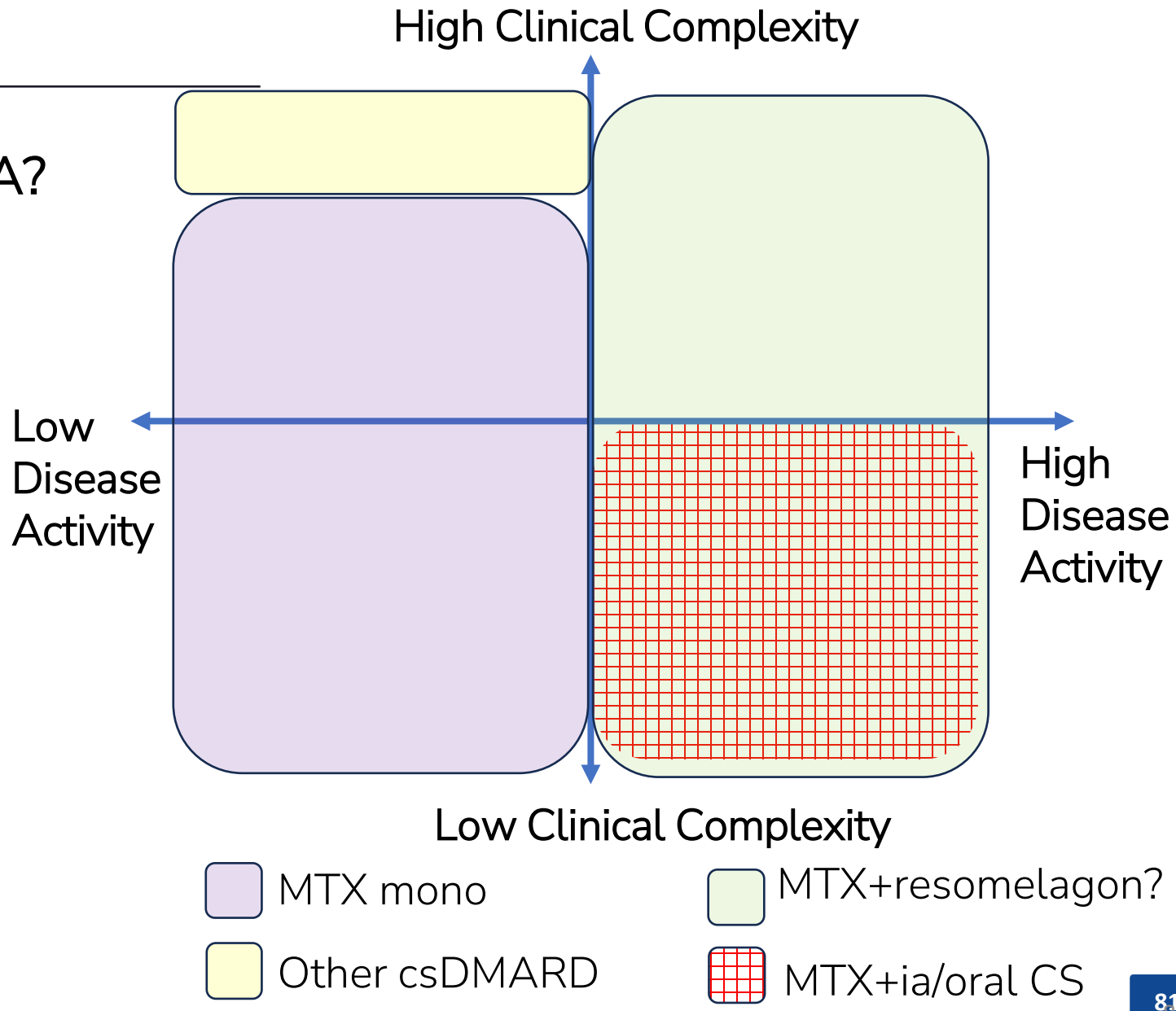
Conclusion

What is the medical need in Early RA?

- **A substantial proportion of RA-patients do not respond to even the most aggressive treatments for early RA**
- **Current treatments are associated with risks of serious safety issues**
- **<u>Addressing these issues should ideally be safe, immunopreserving, simple to use, and offer at least comparable or additional efficacy</u>**



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SYNACT PHARMA

INFLAMMATION RESOLUTION

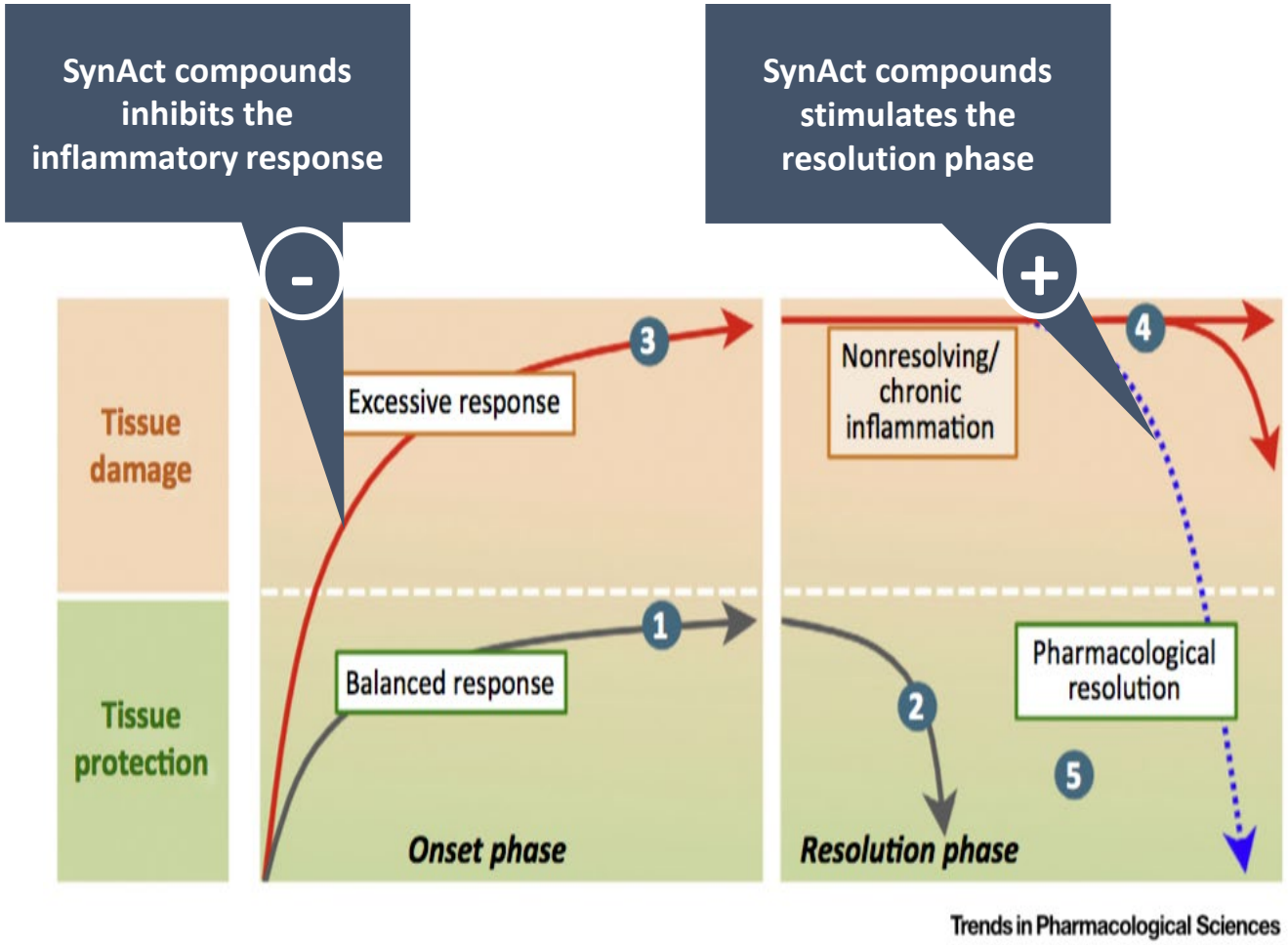
SynAct Pharma AB

Capital Market Day

Resomelagon program and ADVANCE study

Thomas Jonassen, CSO and Founder

SynAct compounds promotes resolution of inflammation



The inflammatory response

1. Inflammatory response effectively controlled in extent and time – protects tissues and limits damage
2. Pathways activated to safely terminate the inflammatory response and promote healing
3. Exaggerated response to inflammatory stimuli can have detrimental consequences and harm tissues
4. Failure to achieve resolution of inflammation can result in chronic inflammation
5. Activation of endogenous resolution pathways has the potential to restore tissues and function

Cartoon adapted from Perretti *et al. Trends Pharmacol Sci* 2015;36:737–55

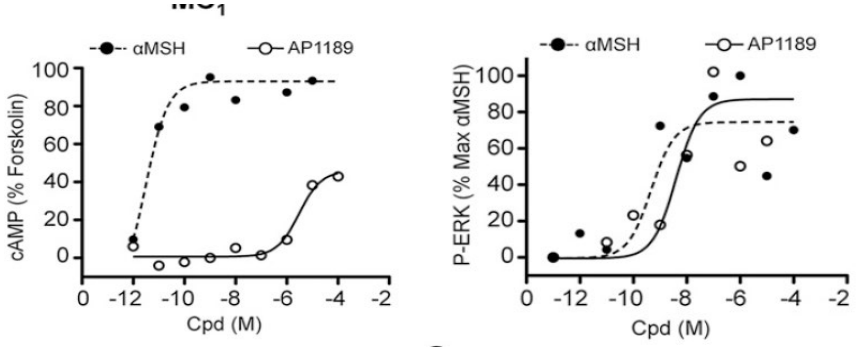
AP1189 – First-in-class biased MCR agonist – novel mode of action

SYNACT PHARMA

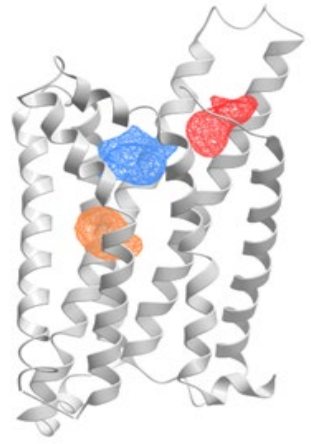
AP1189

- First-in-class biased melanocortin receptor type 1 and 3 agonist- potent inducer of ERG phosphorylation- weak inducer of cAMP stimulation[1]
- Homology modelling from recently published MCR crystal structure[2] identified allosteric binding pocket (red) in addition to othosteric binding pocket (blue)
- AP1189 fits very well into allosteric binding pocket

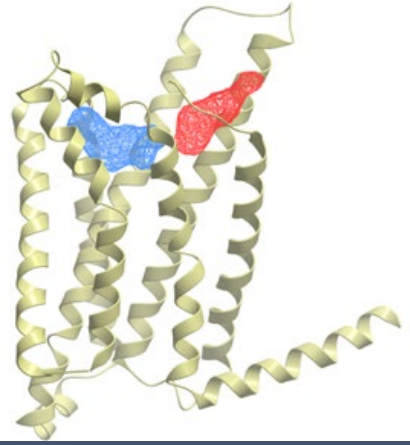
MC1 receptor activation in transfected cells[1]



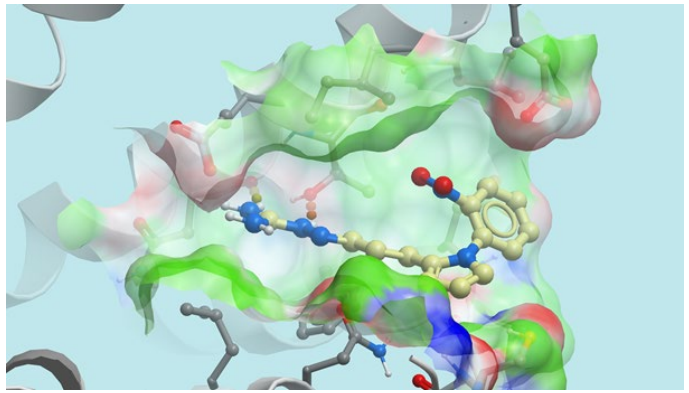
AP1189 selectively engages MC1R



MC1r Model



MC3r Model



Proposed binding mode of AP1189

1. Montero-Melendez et al. J Immunol. 194:3381-8, 2015; 2. Data from Completed Phase 1 study in healthy volunteers; 2. Yu, J. *et al.* Determination of the melanocortin-4 receptor structure identifies Ca as a cofactor for ligand binding. *Science* **368** , 428–433 (2020).

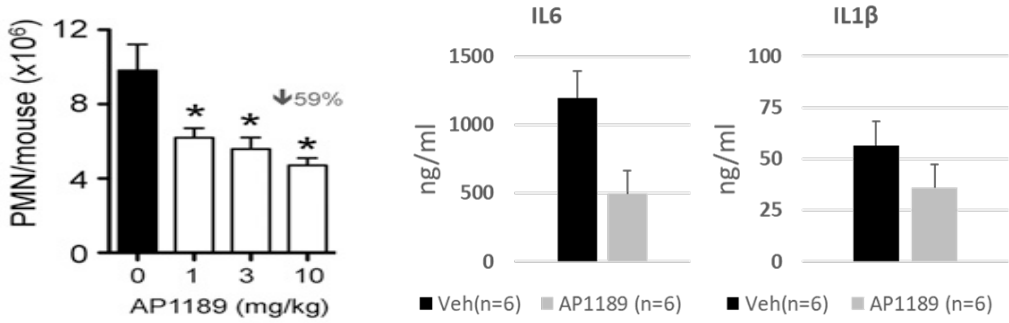
AP1189 Pharmacology – in model of acute inflammation

?

AP1189

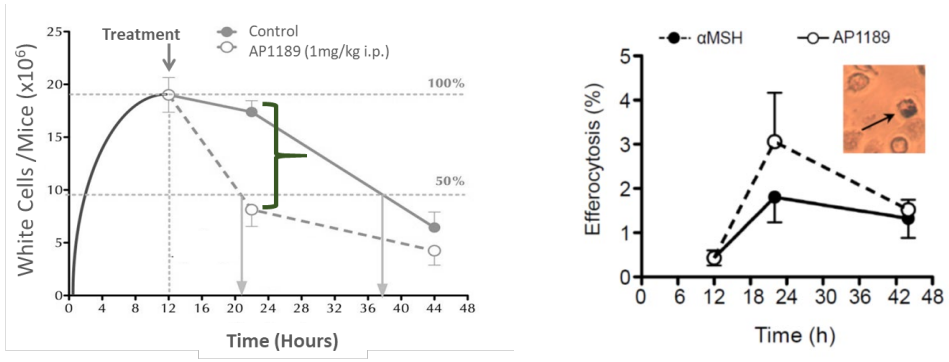
- AP1189 induces anti-inflammation as shown by reduced accumulation of neutrophils and reduced concentration of pro-inflammatory cytokines following systemic administration in murine peritonitis model –
- Therapeutic administration of AP1189 in murine peritonitis- ie treatment during ongoing inflammatory- induces fast clearance of Neutrophils
- AP1189 given therapeutic induces efferocytosis by macrophages
- AP1189 induces its treatment effects by a combination of anti-inflammation and promotion of inflammatory resolution

Administration at disease induction in peritonitis[1]



AP1189 – inhibition of inflammatory responses

Therapeutic treatment in peritonitis [1]



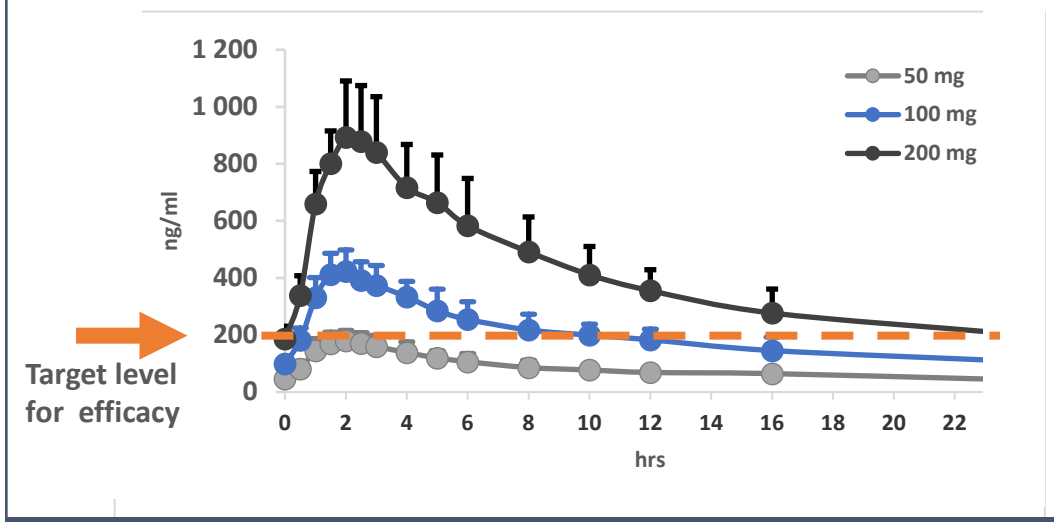
AP1189 – Promote inflammatory resolution

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

CONFIDENTIAL

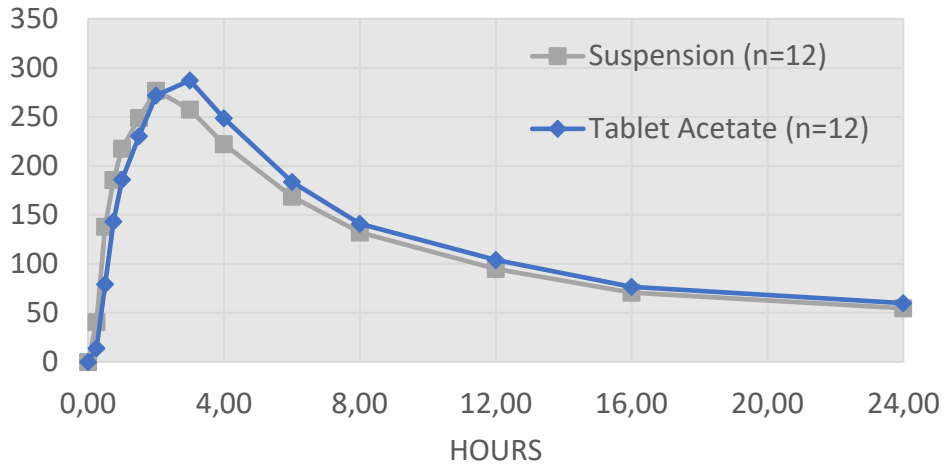
Resomelagon (AP1189) – PK profile support once daily oral dosing

PK profile following repeat dosing in man-



Data from clinical trial CS001- Phase 1 FIM- suspension

PK profiles from Bioequivalence study testing new tablet formulation- single dose

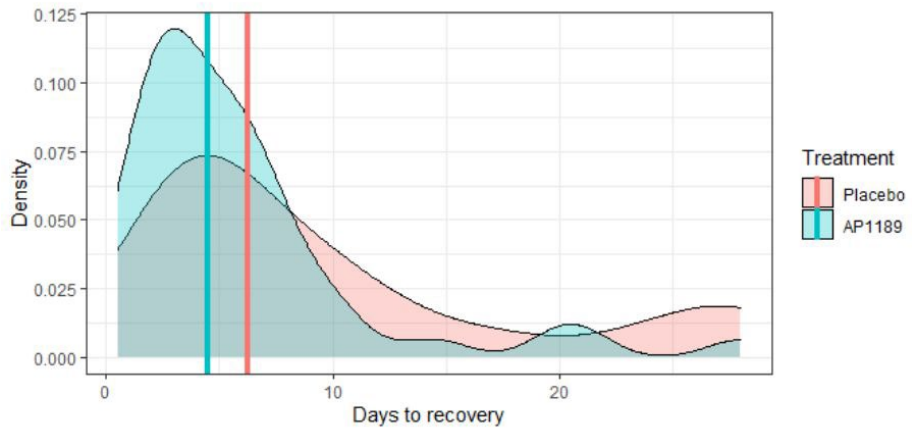


Data from clinical trial CS004- Phase 1 Bioequivalence

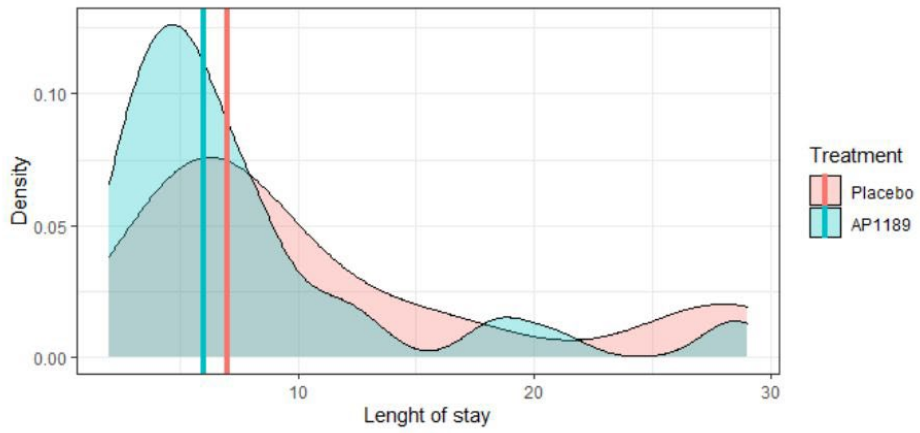
Once daily dosing in relevant doses reach a peak concentration higher than 200 ng/ml with trough concentration below this threshold – thereby reducing the risk for development of receptor desensibilization and tachyphylaxis

RESOVIR-1 study (n=60) – Resomelagon treatment facilitate early recovery in severe COVID-19 infection-

Respiratory Recovery



Hospitalization



Resomelagon-treated patients experienced significantly faster respiratory recovery ((P<0.0001) and had shorter hospital stay than patients given placebo (P<0.0001)

The RESOVIR-1 study
Resomelagon as Add-On Therapy in COVID-19 Infected Patients-

Key inclusion criteria:
- Positive COVID-19 infection
- Age 18-85 years
- Disease history less than 15 days
- Need for supportive respiratory assist[1]
- Signed informed consent

Primary efficacy endpoint:
Time to respiratory recovery defined as the time from initiation of treatment to the time when the patient's SpO2 is ≥93% determined by pulse oximetry in the patient on ambient air for a minimum of 30 minutes

Selected Secondary endpoints:
- Days of hospitalisation
- Oxygen free days till day 28
- Need for mechanical ventilation
- Circulating inflammatory markers (work in progress)

Study conducted as part of the RESOVIR collaboration at sites in Belo horizonte, Brasil with Professor Mauro Teixeira, MD , PhD as principal investigator

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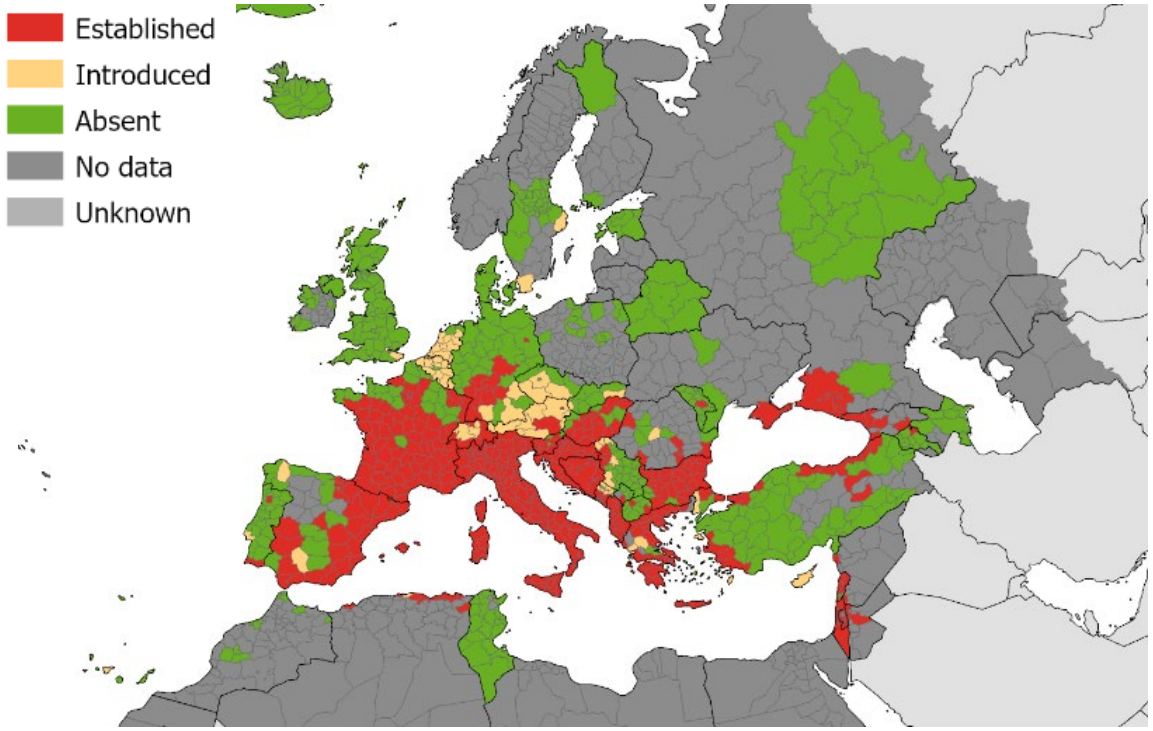
1. Defined as either SpO2 < 93% without supportive oxygen treatment or PaO2/ FiO2 <300 mmHg despite supportive oxygen treatment

B J Pharnacol – Published August 19, 2024

Asian Tiger mosquito (aedes albopictus) now endemic in part of Europe

Presence of the Mosquito as of May 2024



Source: European Centre for Disease Prevention and Control (ECDC)

Dengue Virus, Chikungunya virus, Zika virus

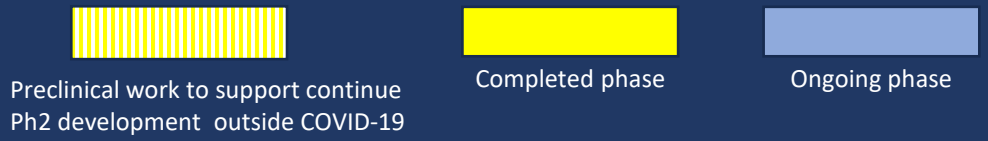
Even though still rare, autochthonous cases (ie infected in Europe) of Dengue fever are increasing as reported by health Authorities in France, Spain and Italy.

Most cases are reported in Urban areas including large tourist destinations as the Balearic Islands, Madrid, Cote dAzur, Paris, Milan and Rome.

With higher temperatures and increased rainfall, it is likely that the mosquitoes spread further North

Pipeline - overview

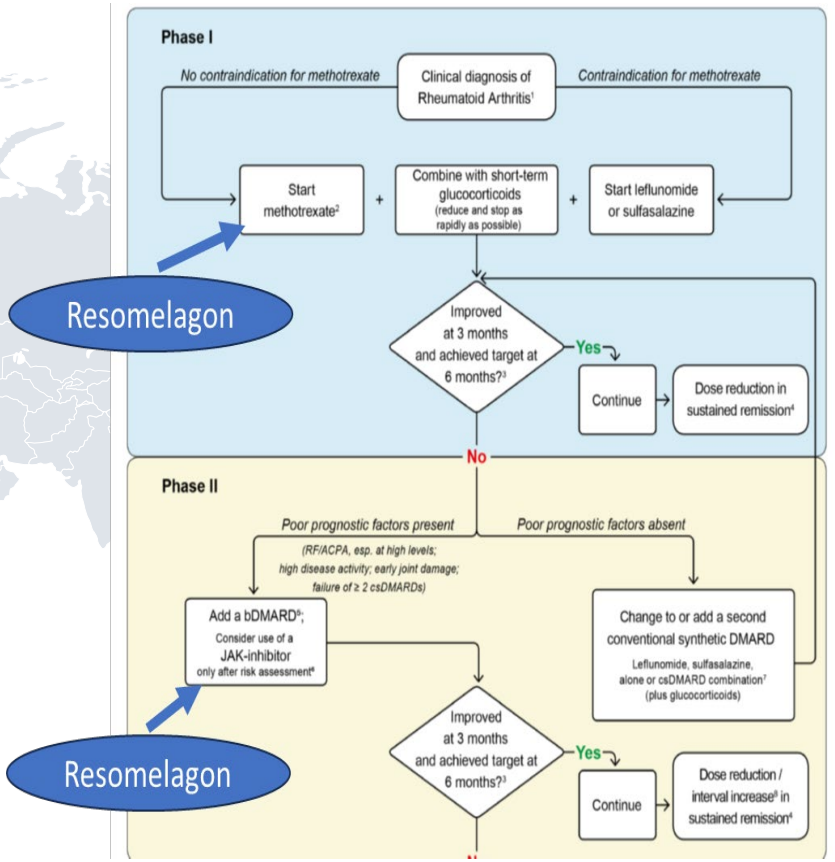
ASSET	INDICATION	PRE-CLINICAL	PHASE 1	PHASE 2A	PHASE 2B	STATUS & NEXT MILESTONE
RESOMELAGON (AP1189)	Rheumatoid Arthritis					• ADVANCE Ph2b study initiated
	Idiopathic membranous Nephropathy (iMN)					• Ph-2A study – low recruitment rate due to lack of pt
	Virus-induced hyper-inflammation					• Pharmacology program to support • Ph-2 in target population ongoing
TXP-11	Prevent organ failure in surgery					• Preclinical pharmacology to support Ph1 CTA ongoing – aim to be Ph1 ready in 2025
Next generation	Discovery phase					• Discovery



Resomelagon (AP1189) in the current treatment roadmap

- Therapy with cDMARDs, ie MTX should be started as soon as the diagnosis of RA is made
- Treatment should aim at reaching a target of sustained remission or low disease activity in every patient
- GCs should be considered when initiating MTX treatment but should be tapered and discontinued within 3 months (EULAR 2022).
- TNF–blockers are not recommended for first line treatment because of the additional risks of toxicity (ACR 2021)

EULAR treatment roadmap for moderate and severe RA



Early intervention with resomelagon (AP1189) could be a novel treatment approach to increase the likelihood of disease control

SYNACT PHARMA

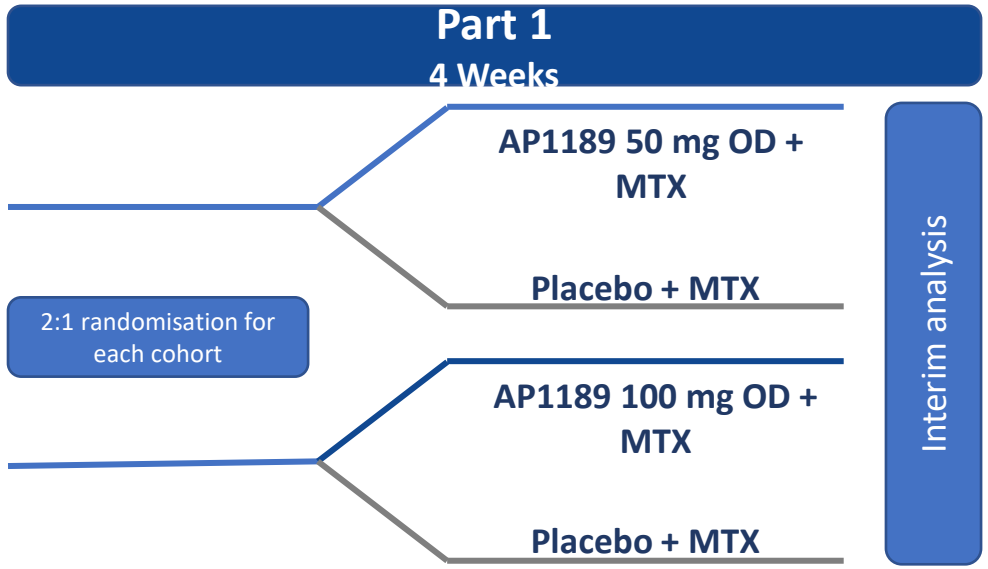
EULAR 2019: Ann Rheum Dis 2020;79:685–699; ACR 2021: Arthritis Care & Research 2021: 73, 7:924–939; EULAR 2022: Ann Rheum Dis 2023;82:3–18.

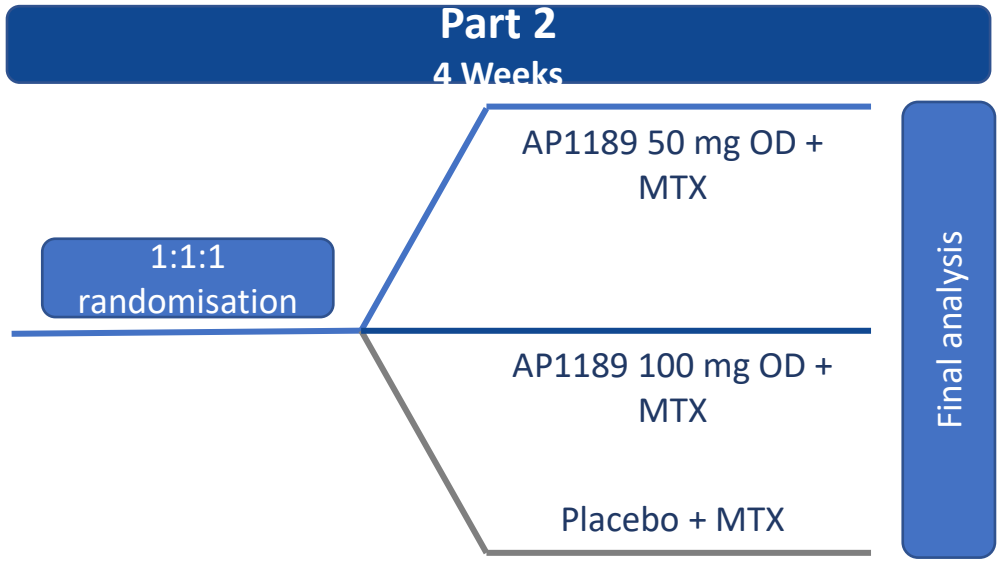
The BEGIN Study-

the first pt study in the target population of early RA patients with high disease activity

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

Study Population	Primary safety endpoint	Primary efficacy endpoint
MTX treatment naïve RA patients with high disease activity CDAI >22, who are about to begin up-titration with MTX	Safety of AP1189 vs placebo (AEs and SAEs)	changes in CDAI score

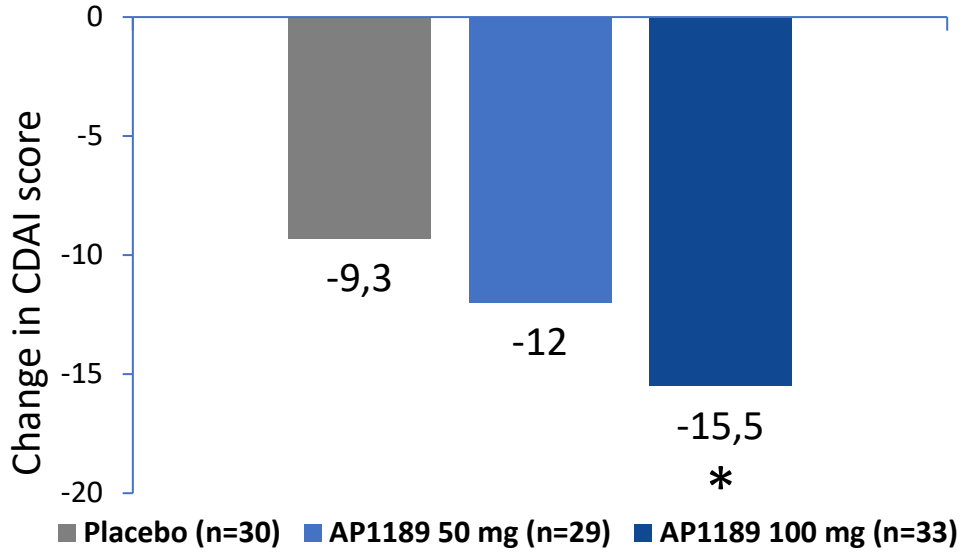




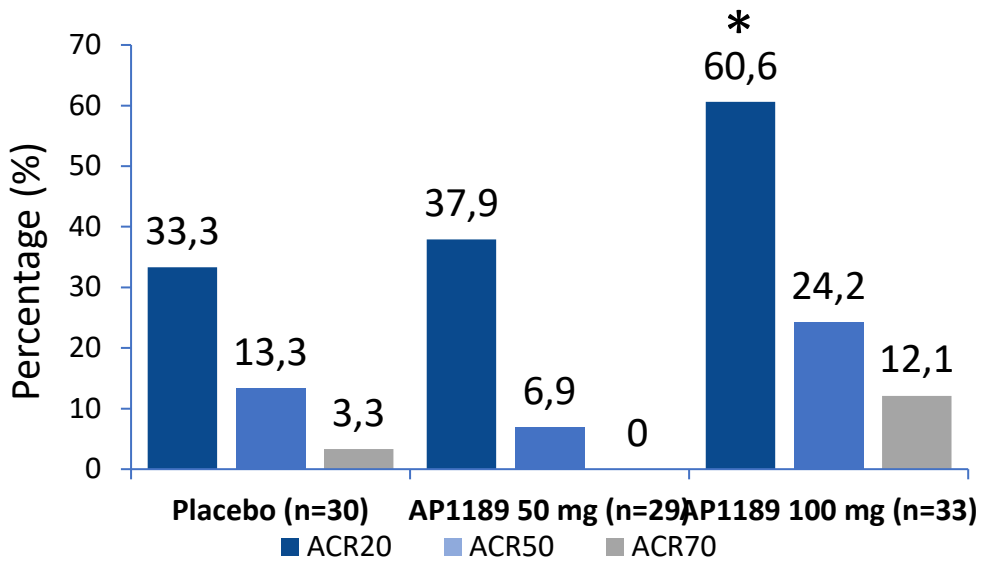
Resomelagon (AP1189) demonstrated significant treatment effects in treatment naive RA patients - the 4 week BEGIN P2a clinical trial

Phase 2a double- blind placebo-controlled study in treatment naive RA patients with high disease activity (CDAI >22 at randomization) in combination with MTX with 4 weeks treatment

Mean change in CDAI from baseline



ACR 20/50/70 Response Rates



80% of had CRP higher than normal range and the majority of the patients were treated within weeks of RA diagnose- None of the subjects were treated with GCs – Treatment: once daily oral dosing using suspension

SYNACT PHARMA

∗ = p<0.05 vs placebo

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

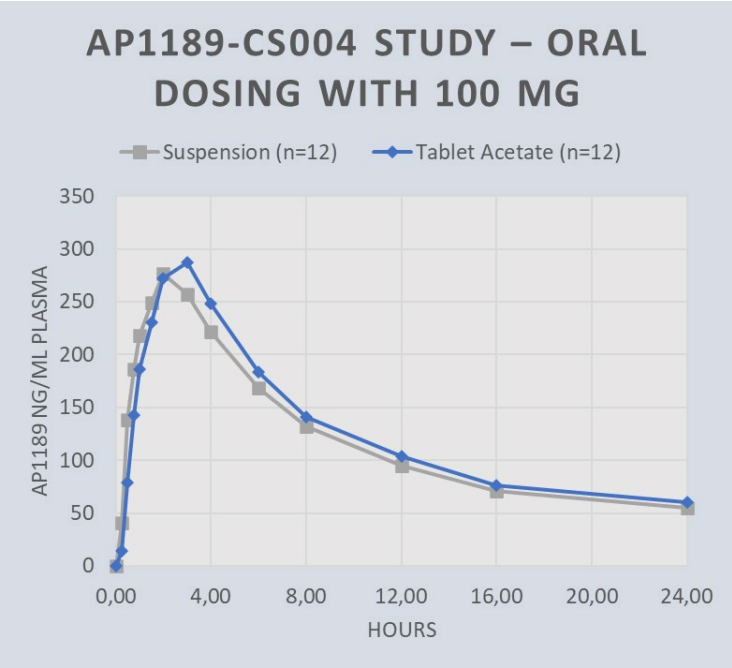
Summary from BEGIN study – and parallel conducted Bioequivalence study on new tablet formulation

Resomelagon (AP1189) in the given dose was safe

Statistically significant treatment effects in treatment naïve RA patients when given in combination with MTX
- Significant reduction in CDAI relative to placebo treatment
- Significant higher fraction of pt reaching ACR20 when compared to placebo treatment

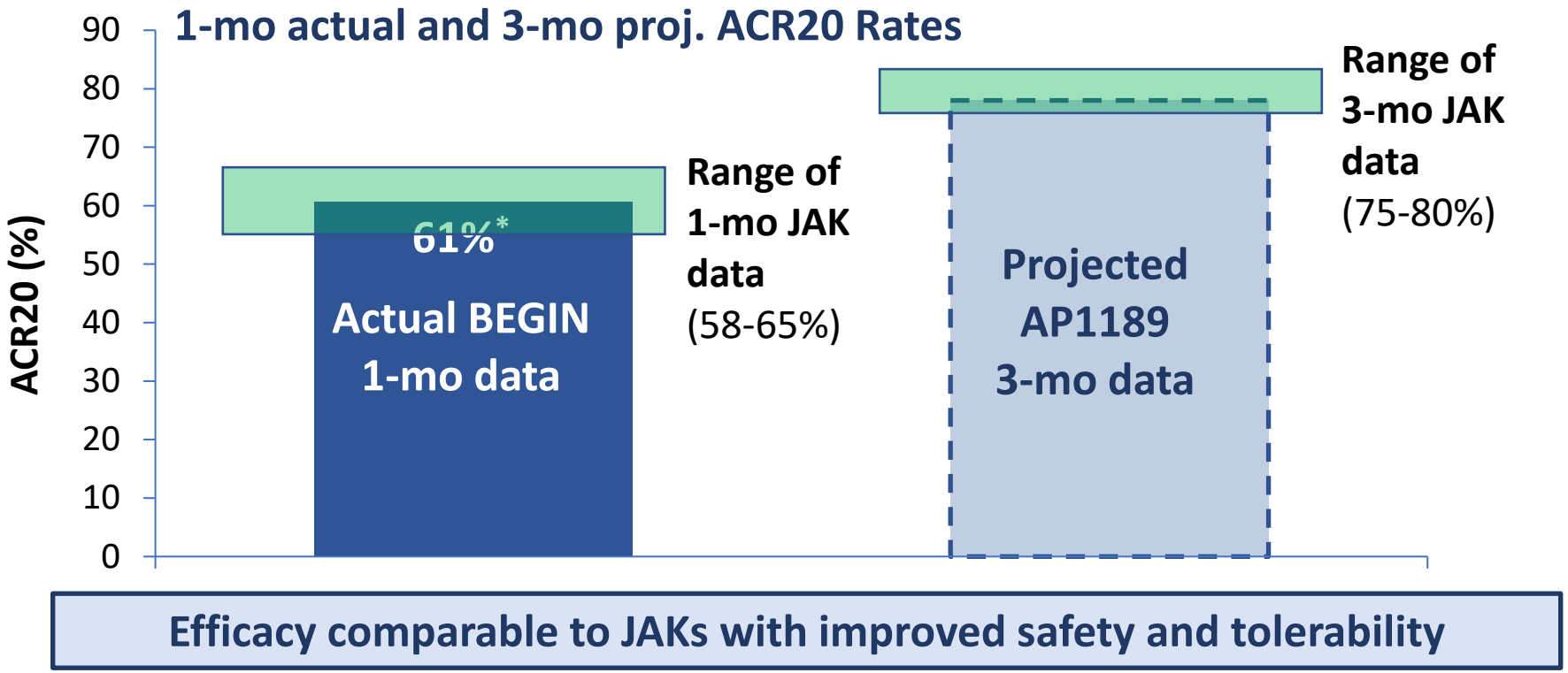
Together this strongly supported continued development in RA with new tablet formulation developed and tested in bioequivalence study in parallel with the BEGIN study-

Bioequivalence study (AP1189-CS004) documented that the fast release tablet had a very attractive PK profile when compared to the suspension successfully used in the BEGIN study



Resomelagon (AP1189) 100 mg 4 weeks ACR20 scores are comparable to JAKs ACR20 in MTX-Naïve P3 trials

Following the BEGIN study it was projected that AP1189 could induce a treatment response comparable to JAK inh- in treatment naïve patients-



* = p<0.05 vs placebo

1) Lee et. Al., N Engl J Med 2014;370:2377-86.
2) Fleishman et. Al., Arthritis & Rheumatology, Vol. 69, No. 3, March 2017, pp 506–517
3) van Vollenhoven et. Al., Arthritis & Rheumatology, Vol. 72, No. 10, October 2020, pp 1607–1620
4) Westhovens et al. Ann Rheum Dis 2021;80:727–738.

2022 development strategy- Parallel development path evaluation the compound as a new treatment approach in first line as well as second line treatment in RA

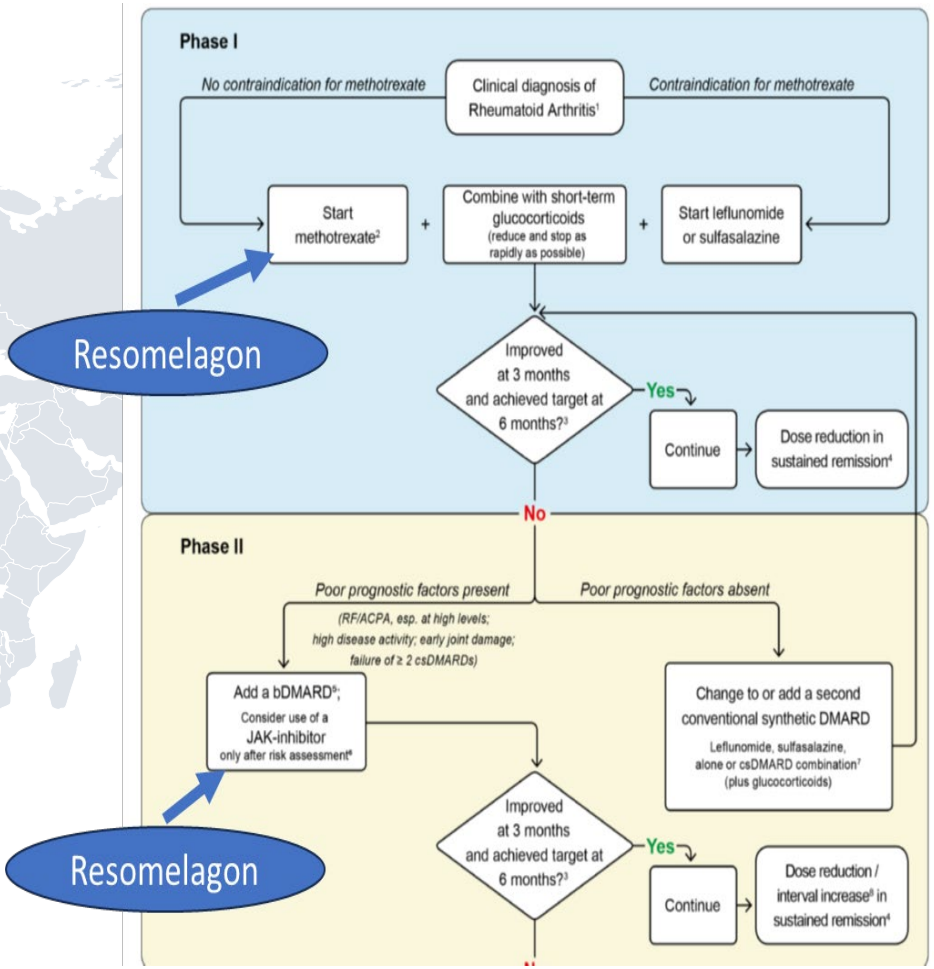
First line treatment:

- The EXPAND study – 12 weeks dosing in treatment naïve RA pts with CDAI >22-
- 100 mg AP1189 vs placebo in combination with MTX.
- It was not specified that the pt should be newly diagnosed and not specified that CRP should be increased
- Post hoc analyses showed that the intentional pt population of newly diagnosed pt with high disease activity including signs of systemic did responded very well to the treatment

Second line treatment:

- The RESOLVE study- two-part study where part A was a 4 weeks dose range study in DMARD-IR pts-
- Part B a 12 weeks Ph2b was approved by FDA, but has been set on hold until further as part A was inconclusive
- Only a fraction <10% of the patients would qualify as RA pt who 3-6 months MTX treatment showed lack of effect –
- Large fraction of patients to be considered chronic RA pts-

EULAR treatment roadmap for moderate and severe RA

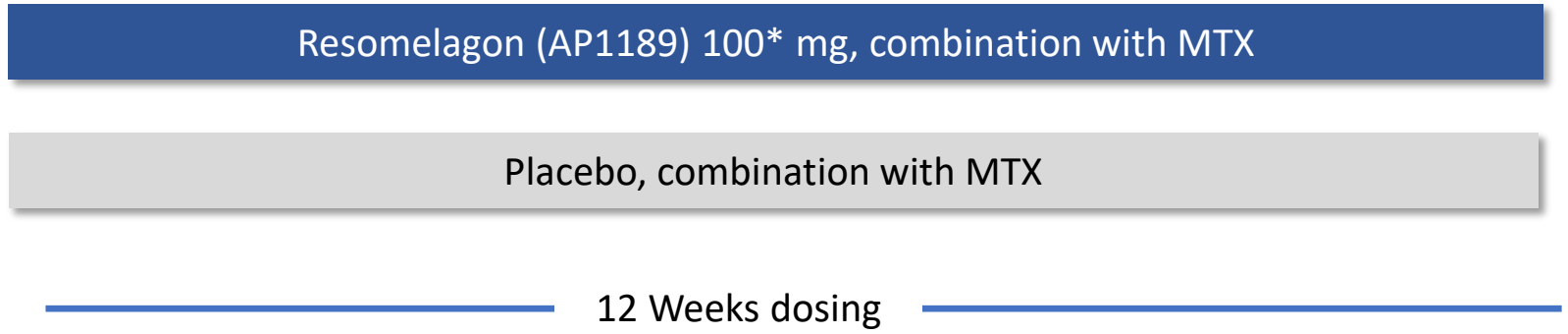


EULAR 2019: Ann Rheum Dis 2020;79:685–699; ACR 2021: Arthritis Care & Research 2021: 73, 7:924–939; EULAR 2022: Ann Rheum Dis 2023;82:3–18.

EXPAND STUDY P2b study in treatment naive RA patient- Completed 2023

Patient Population:

- Treatment naïve, eligible for initiation of cDMARD 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- Active recruitment in 2022-23
Study Size and Sites	▪ Designed to recruit 60 patients per group – actual number randomized 127
Primary Endpoints	▪ ACR20 response rate at 12 weeks as compared to placebo
Secondary Endpoints	▪ CDAI score; DAS28 score; HAQ- DI score
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

The EXPAND study – Safety profile

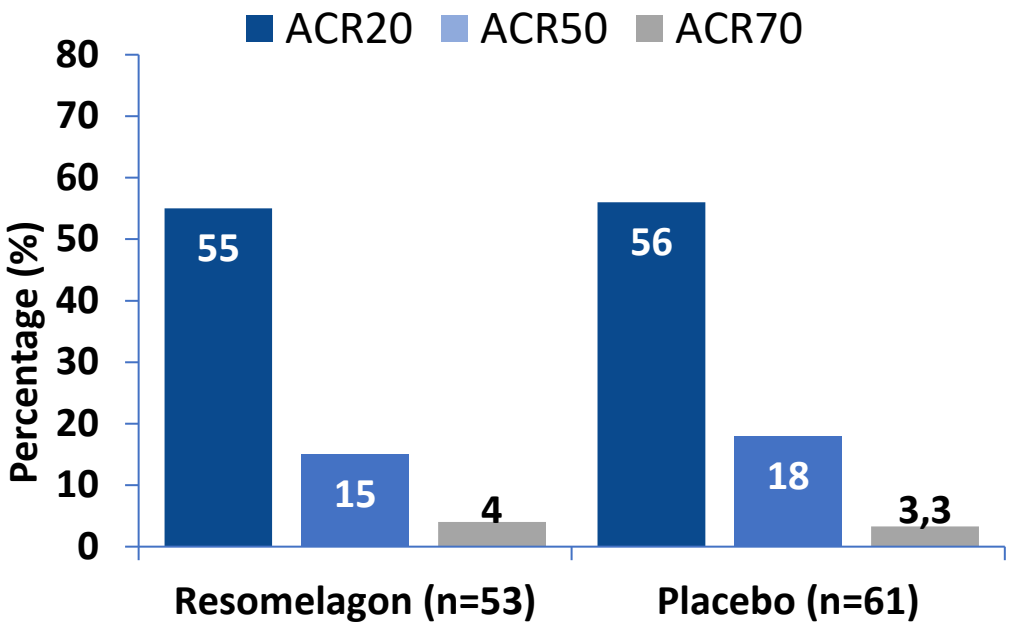
Treatment Emergent Adverse Events (TEAE)

Group (n)	Placebo+ MTX (64)	AP1189 100mg + MTX (63)	Overall (127)
Serious Treatment Emergent AEs			
Patients with ≥ 1 Serious AE n (%)	1 (1.6)	1 (1.6)	2 (1.6)
Non-Serious Treatment Emergent AEs			
TEAEs n (%)	43	45	88
Mild/Mod/Severe	24/19/0	25/20/0	49/39/0
Patients with ≥ 1 TEAE	28 (44.4)	27 (42.2)	55 (43.3)
Patients with ≥ 1 TEAE leading to study discontinuation	1 (1.6)	5 (7.9)	6 (4.7)
Patients with 1 or more TEAE leading to death	0	0	0
TEAEs in ≥ 5% of patients n (%)			
Overall infections	10 (15.6)	7 (11.1)	17 (13.4)
Elevated liver enzymes	6 (9.4)	3 (4.8)	9 (7.1)
Headache	6 (9.4)	0	6 (9.4)
Abdominal pain	2 (3.1)	4 (6.3)	6 (4.7)
Nausea	2 (3.1)	4 (6.3)	6 (4.7)
Vomiting	2 (3.1)	4 (6.3)	6 (4.7)

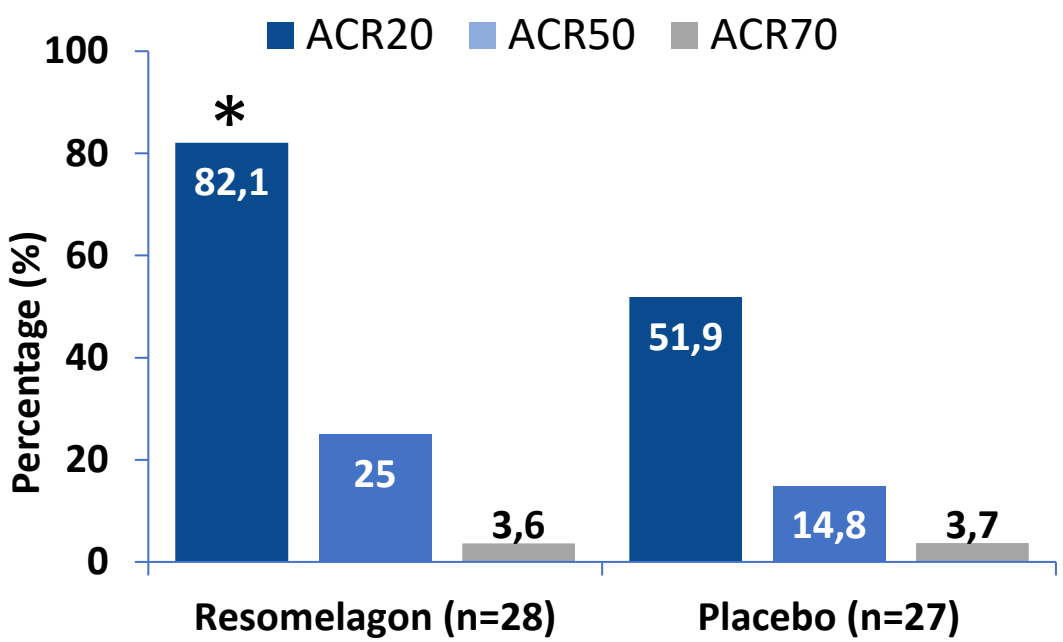
The EXPAND study - ACR Scores following 12 weeks treatment in combination with MTX in treatment naïve patients with high disease activity (CDAI>22)

once daily oral dosing with tablet – no GC bridge treatment – Double blind placebo controlled multicenter study

All pts



Only newly diagnosed pts with signs of systemic inflammation

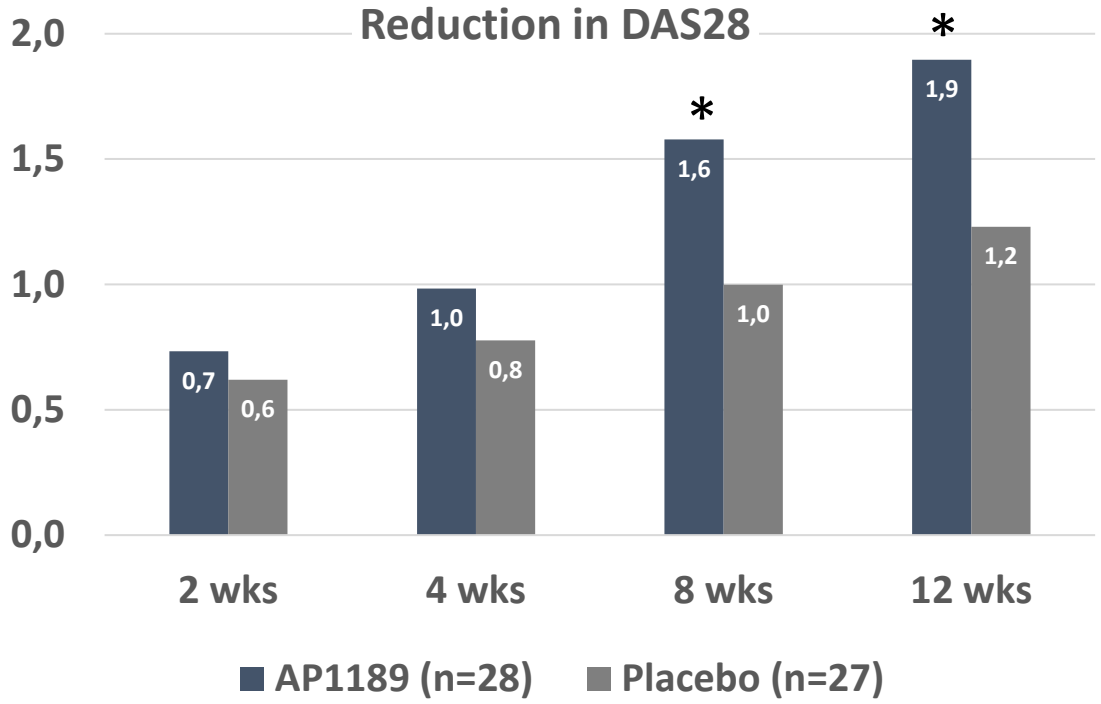


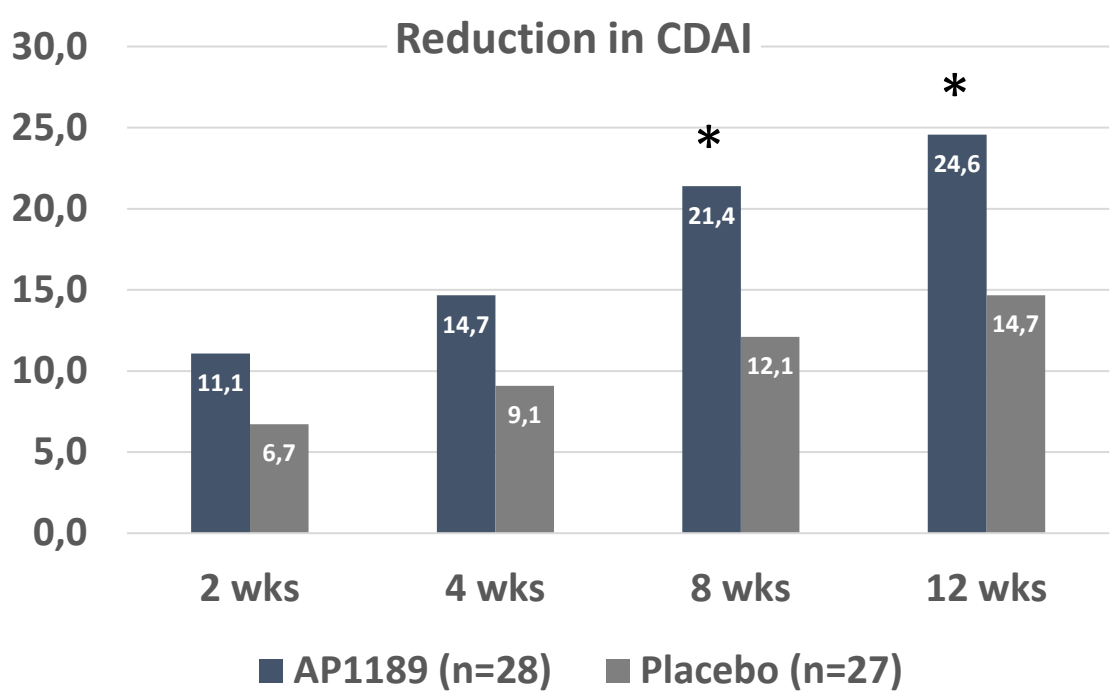
Baseline hsCRP > 3, RA diagnosis within 6 months from BL

Post hoc analyses: ∗: p<0.023 vs placebo (Fischer exact test)

The EXPAND study – Post hoc analyses shows significant treatment effect in newly diagnosed patients with sign of systemic inflammation

BL CRP>3_ RA diagnose within 6 months from BL

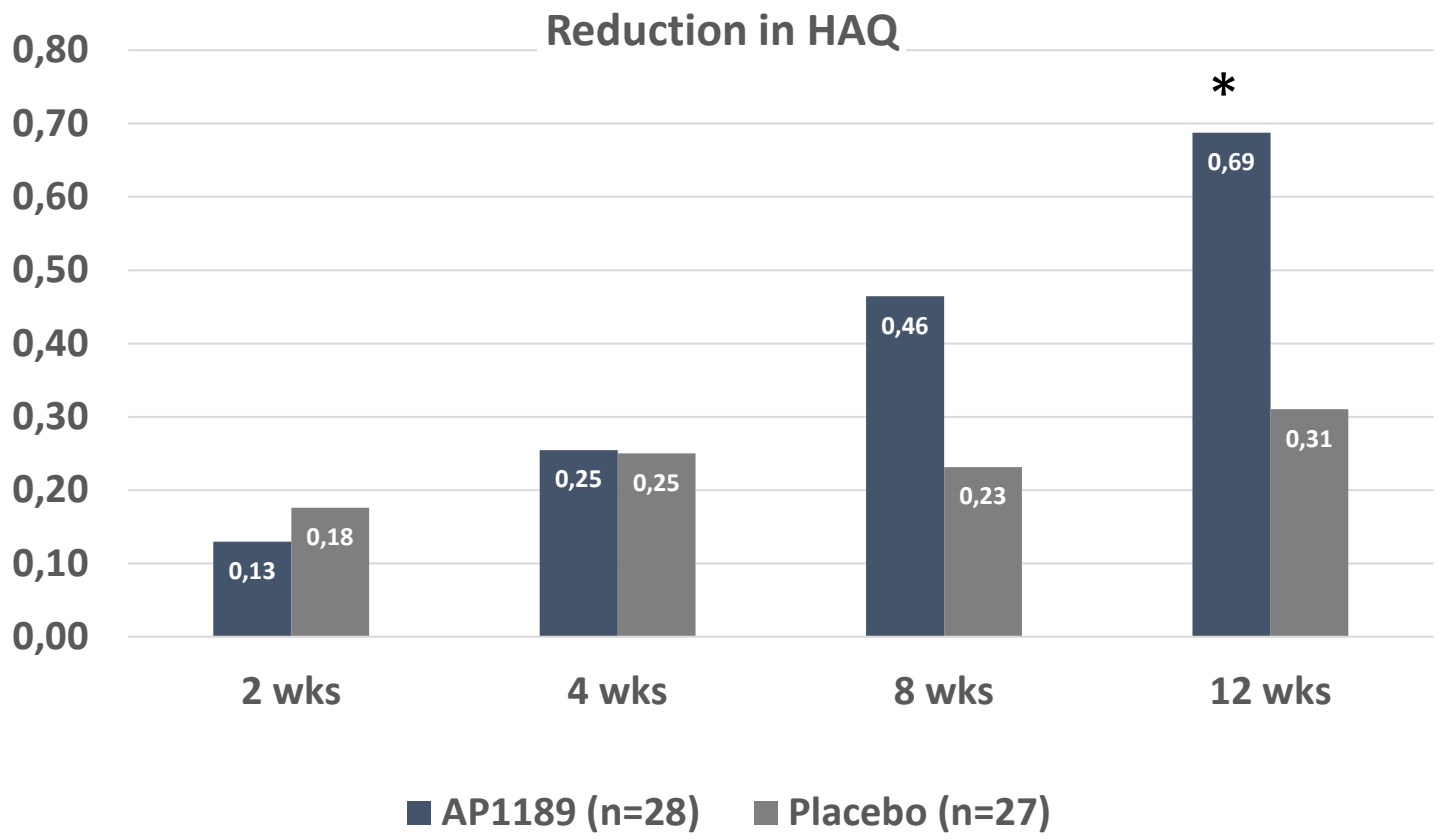




Post hoc analysis on PP dataset; Mean per group ∗:p<0.01 vs placebo

The EXPAND study – Reduction in HAQ – Post hoc analyses shows significant treatment effect in newly diagnosed patients with sign of systemic inflammation

pts with baseline hsCRP>3 and RA diagnose within 6 months from BL



Post hoc analysis on the PP dataset; Mean per group ∗:p<0.05 vs placebo

EXPAND Study – focusing on the “right” patient population strongly support consistent activity of the compound

- **Newly diagnose resomelagon (AP1189) treated patients with elevated CRP at baseline (> 3mg/L) exhibited consistent responsiveness over placebo at 12 weeks across all outcome measures**

  - At statistically significant higher proportion of resomelagon (AP1189) treated patients (n=28), 82%, reached ACR20 response compared to 52% of the placebo treated (n=27)

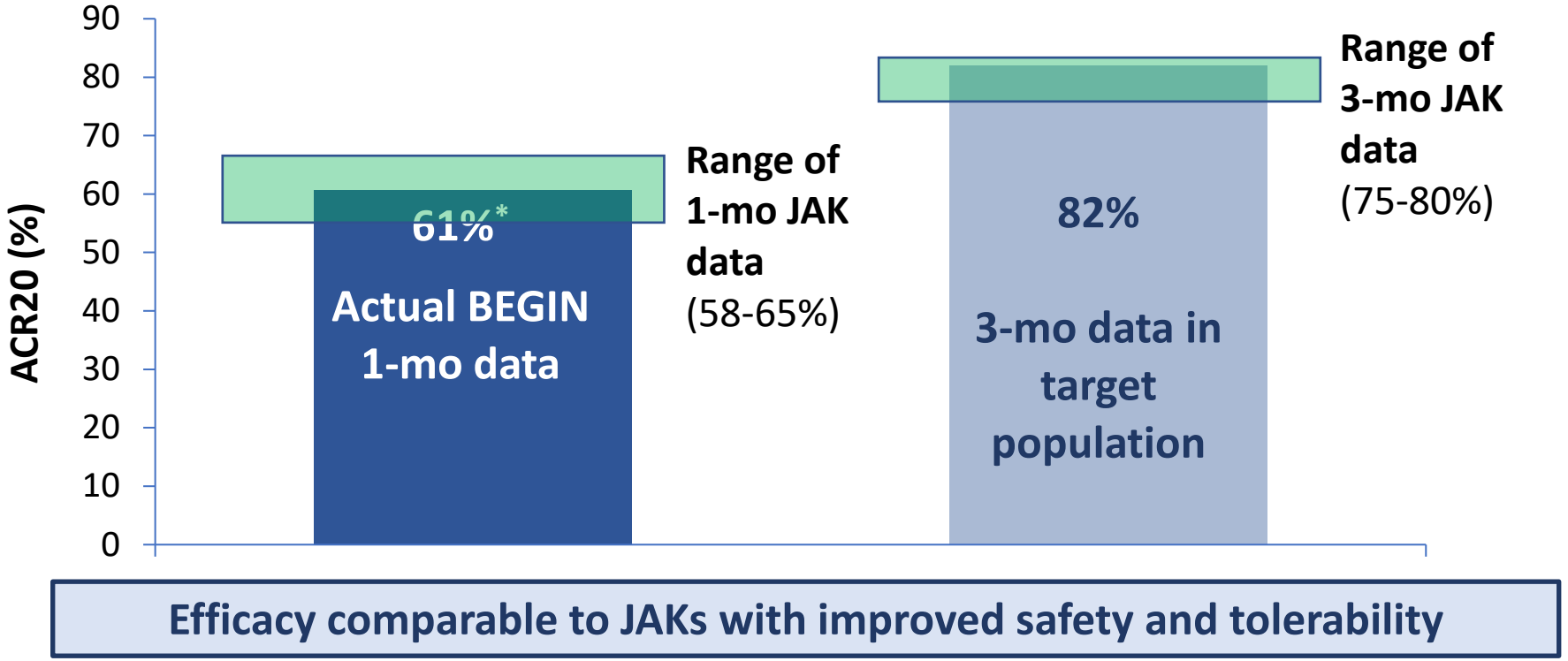
  - Resomelagon treated pts had a statistically significantly larger reduction in CDAI and DAS28 scores when compared to placebo treated patients

  - Resomelagon treated pts had a statistically significantly higher improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI), HAQ-DI score when compared to placebo treated patients

Consequently, in newly diagnosed RA patients with high disease activity including activated systemic inflammation, the compound shows significant treatment effect compared to placebo treatment – indicating early interaction with the compound to promote pharmacological resolution.

Resomelagon (AP1189) – Post hoc analyses focusing on the target population of newly diagnosed RA pt with signs of systemic inflammation shows response rates on ACR20 comparable to what has been reported on JAKs in MTX-Naïve P3 trials

Following the BEGIN study it was projected that AP1189 could induce a treatment response comparable to JAK inh- in treatment naïve patients-



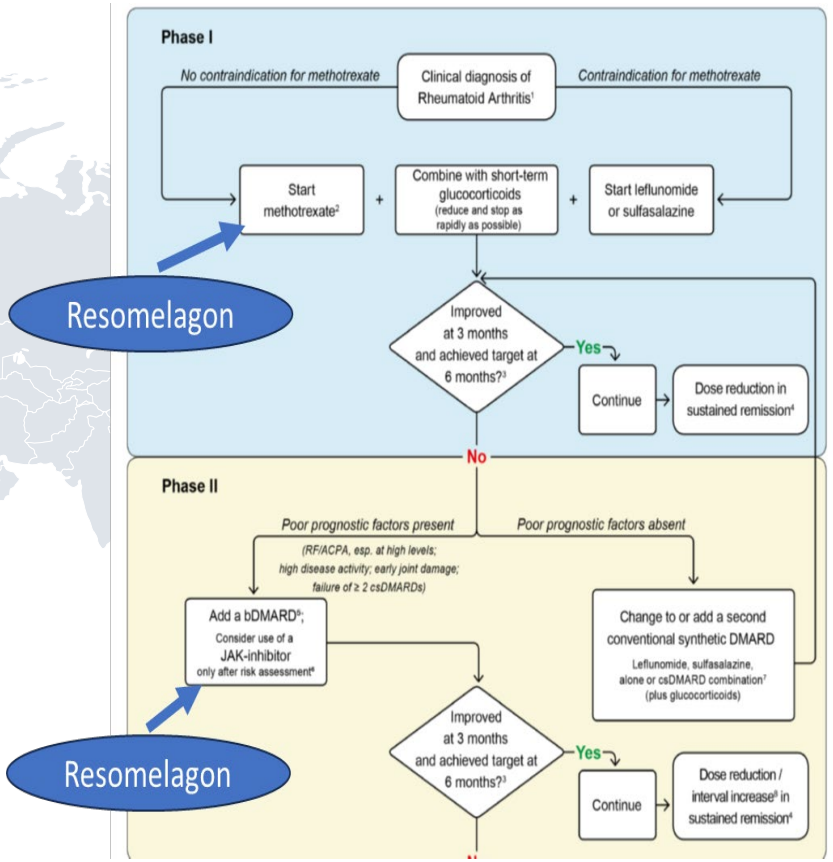
* = p<0.05 vs placebo

1) Lee et. Al., N Engl J Med 2014;370:2377-86.
2) Fleishman et. Al., Arthritis & Rheumatology, Vol. 69, No. 3, March 2017, pp 506–517
3) van Vollenhoven et. Al., Arthritis & Rheumatology, Vol. 72, No. 10, October 2020, pp 1607–1620
4) Westhovens et al. Ann Rheum Dis 2021;80:727–738.

Resomelagon (AP1189) – continued development in RA

- First line treatment with potential to reduce need of GCs and post pone use of TNF-blockers
  - Could be a novel pt friendly treatment option who is best case could reduce use of less well tolerated drugs
- Second line treatment in pts who following initial MTX treatment still have high disease activity
  - As a patient friendly alternative to TNF-blockers –
- Treatment of flairs – ie treatment of pt with established RA experiencing exacerbations
  - As a patient friendly alternative to GCs

EULAR treatment roadmap for moderate and severe RA



Phase 2b development in early RA with high disease activity –defined as newly diagnosed RA with high disease activity including signs of systemic inflammation- would support further development in all three patients segments

SYNACT PHARMA

EULAR 2019: Ann Rheum Dis 2020;79:685–699; ACR 2021: Arthritis Care & Research 2021: 73, 7:924–939; EULAR 2022: Ann Rheum Dis 2023;82:3–18.

Resomelagon (AP1189) – Phase 2b development in newly diagnosed pts with high disease activity including signs of systemic inflammation

- **Focus on newly diagnosed pts with high disease activity and signs of systemic inflammation**
- **The patients are in need of new treatment options as MTX monotherapy often is insufficient – that GC-cotreatment should be reduced as much as possible – and the none of current second line treatment options due to unwanted side effect profiles are recommended for first line treatment**
- **Clinical studies are feasible as there is a large flow of newly diagnosed pt available at sites in US and Europe**
- **New treatment option as first line could be continued beyond Ph2b with development to market- with a partner**
- **Phase 2b development in the pt could support parallel development in segment of pt in need for second line treatment and in pts presenting with flairs- pt population that from a development perspective are much more difficult to find- and where the competition from existing treatment possibility are much higher**

EULAR 2019: Ann Rheum Dis 2020;79:685–699; ACR 2021: Arthritis Care & Research 2021: 73, 7:924–939; EULAR 2022: Ann Rheum Dis 2023;82:3–18.

Resomelagon – development fits into current treatment recommendations - EULAR Guidelines says[1*]

- Treatment should aim at **best care** based on a shared decision between patient and rheumatologist
- Treatment decisions based on **disease activity**, **safety** and other **patient factors**, such as comorbidities and progression of structural damage
- Patients require access to **multiple drugs** with **different modes of action** to address the heterogeneity of RA - patients may require multiple successive treatments throughout life
- RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist

Resomelagon fulfill the need for a novel treatment

*US Guidelines in line with above[2]

1. Smolen JS, et al. Ann Rheum Dis 2023;82:3–18. doi:10.1136/ard-2022-223356. 2. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & Rheumatology Vol. 73, No. 7, July 2021, pp 1108–1123 DOI 10.1002/art.41752

Resomelagon (AP1189) + Methotraxate (MTX) in newly diagnosed RA patients with high disease activity incl signs of systemic inflammation

400K+ **Annual newly diagnosed RA-patients[1]**

>50% **RA-patients with high disease activity[2,3]**

Potential indication

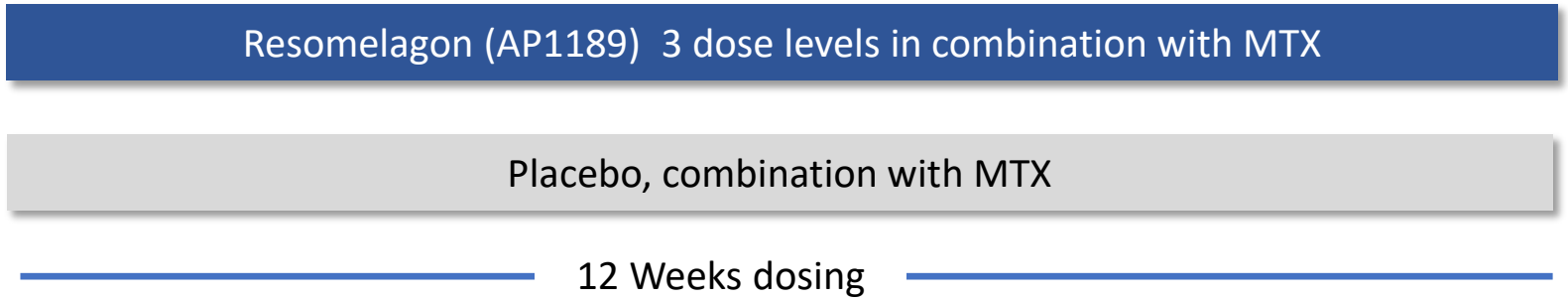
Resomelagon + Methotraxate indicated for newly diagnosed RA-patients with high disease activity and active inflammation

1. GlobalData_RheumatoidArthritisEpidemiologyForecastto2029_250424; 2) Albrecht and Zink Arthritis Research & Therapy (2017) 19:68;
3. Shpatz et al. IMAJ (2021) vol 23

ADVANCE STUDY P2b dose-range study in treatment naive RA patients with high disease activity incl signs of systemic inflammation .

Patient Population:

- Newly diagnosed treatment naïve RA pts, eligible for initiation of MTX treatment
- CRP at baseline >3 mg/L
- CDAI >22 at baseline DAS28-CRP >5.1 – 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 resomelagon (AP1189) tablet or placebo- conducted at sites in US and Europe
Study Size and Sites	▪ Designed to recruit 60 patients per group – dose levels: 40, 70 and 100 mg once daily - ▪ Study initiated at sites in US- Expected to initiate the study in Europe in Q4, 2024. – plan for 12 months recruitment period -
Primary Endpoints	▪ Safety and Tolerability ▪ Change in **DAS28 –CRP** during the 12 weeks treatment period
Secondary Endpoints	▪ ACR20/ACR50/ACR70; CDAI score; HAQ/RAQol

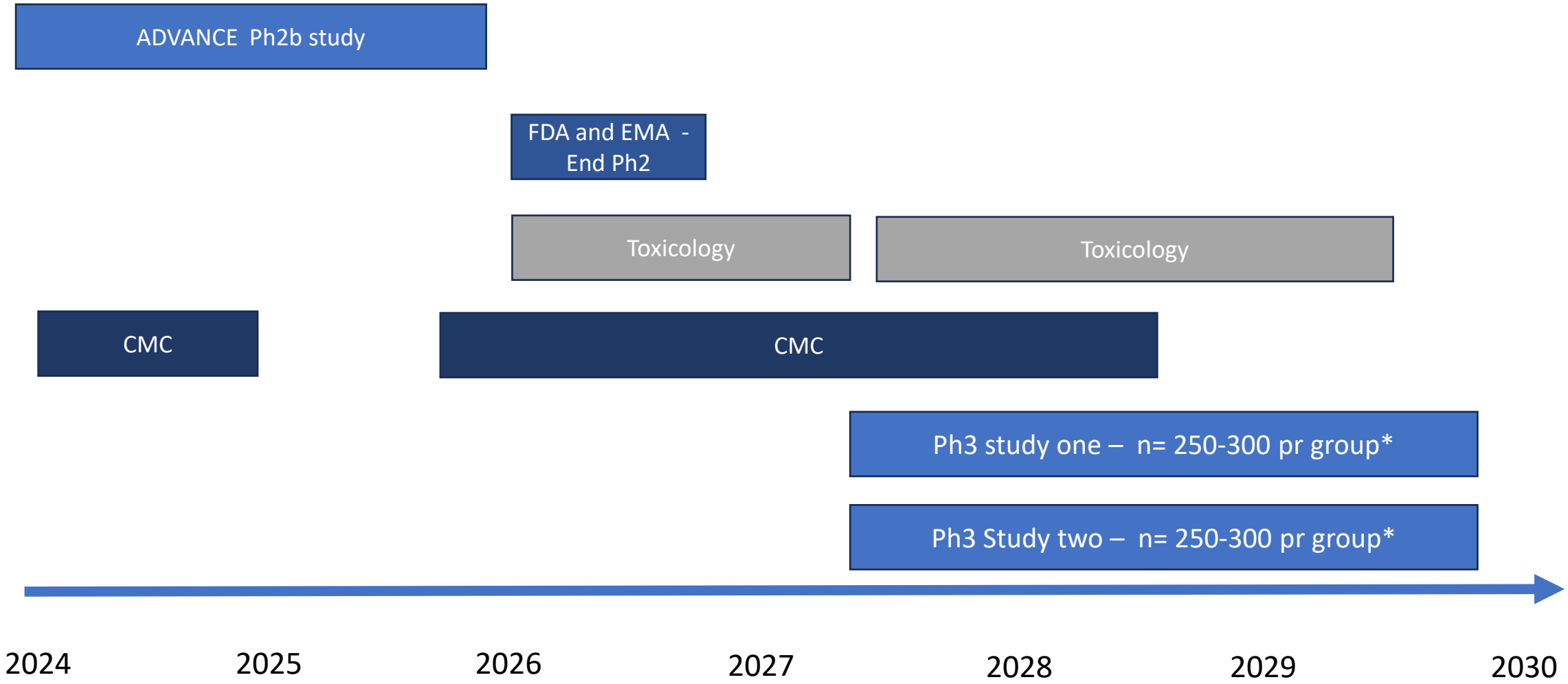
The ADVANCE study- Primary read out-

Primary efficacy read out will be **DAS-28-CRP** ,which is in accordance with **FDA recommendations** for selection of end points in **dose range studies in RA**:

"Using endpoints sensitive to change to provide better discriminatory power for dose response assessment. **A clinical endpoint such as the ACR20 response criteria may not be optimal for this purpose, because it is a dichotomous endpoint, and using the proportion of responders in a small group of patients could be unreliable**. **Endpoints such as DAS28**, hybrid ACR response, and other continuous variables **may be more sensitive to change and provide a more suitable alternative to ACR responder index**. (FDA: Guidance for industry- Rheumatoid Arthritis……)."

With this is mind the **ADVANCE study** is set up with **change from baseline in DAS28-CRPD as primary efficacy readout** assuming a dose response relationship with increasing dose doses of AP1189 (40, 70 and 100 mg) in addition to MTX and compared to placebo and MTX and powered to be able to identify a relevant treatment effect between active and placebo- 80% statistical power with a one-sided test and significance level of a=5% - based on 13% dropout rate.

Resomelagon (AP1189) – Development in RA beyond Phase 2b



∗:Most likely 2 doses of active vs placebo. Sample size to set based on ADVANCE study

SYNACT PHARMA

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Thank You

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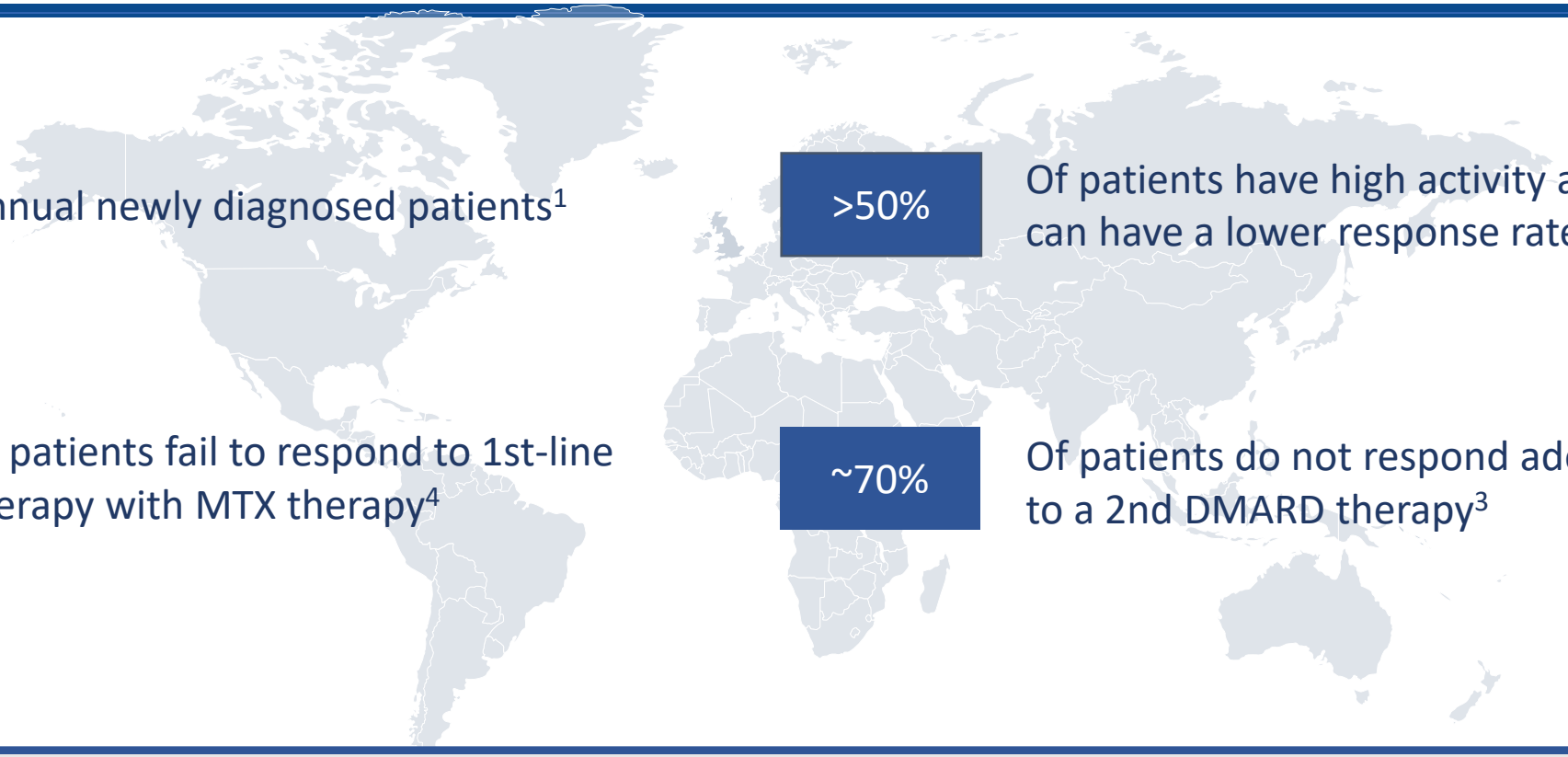
Capital Market Day

Resomelagon positioning and opportunities

Jim Knight, CBO

Methotrexate (MTX) is insufficient for most RA patients especially those with high activity



400K+ Annual newly diagnosed patients[1]

>50% Of patients have high activity at diagnosis and can have a lower response rate to MTX[2,3]

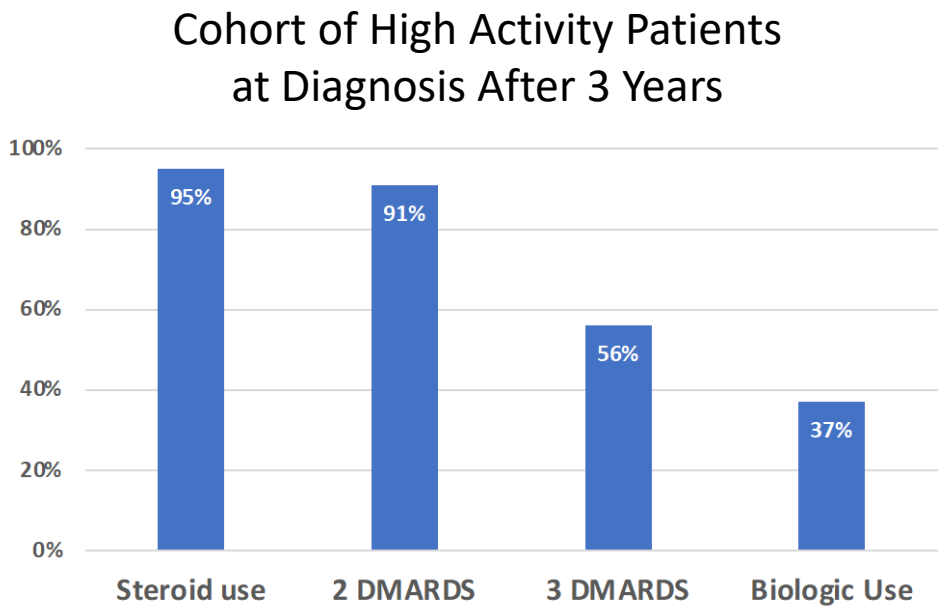
>50% Of patients fail to respond to 1st-line therapy with MTX therapy[4]

~70% Of patients do not respond adequately to a 2nd DMARD therapy[3]

Resomelagon could be well suited as a complementary combination therapy to MTX when MTX alone is insufficient

1. GlobalData_RheumatoidArthritisEpidemiologyForecastto2029_250424; 2. Shpatz et al. IMAJ (2021) vol 23; 3. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982; 4. GlobalData RA custom primary market research studies 2021-2023, on file;

Patients presenting with high disease activity have a poorer disease prognosis and are can be less responsive to MTX



- **Highly active disease is the key poor prognostic indicator in ACR and EULAR recommendations[1]**

  "Damage to joints occurs in the first 2–3 years. There is a narrow window to preserve the joints and the patient's quality of life."[2]

- **Highly active patients tend to have lower responses to MTX with 6mo response rates ranging from 33% to 52%[3]**

- **In newly diagnosed RA patients followed for 3 years:[2]**
  - 95% of patients required steroids (avg 15mg/day)
  - 56% had added/cycled with 3 DMARD agents
  - 37% had initiated use of at least 1 biologic

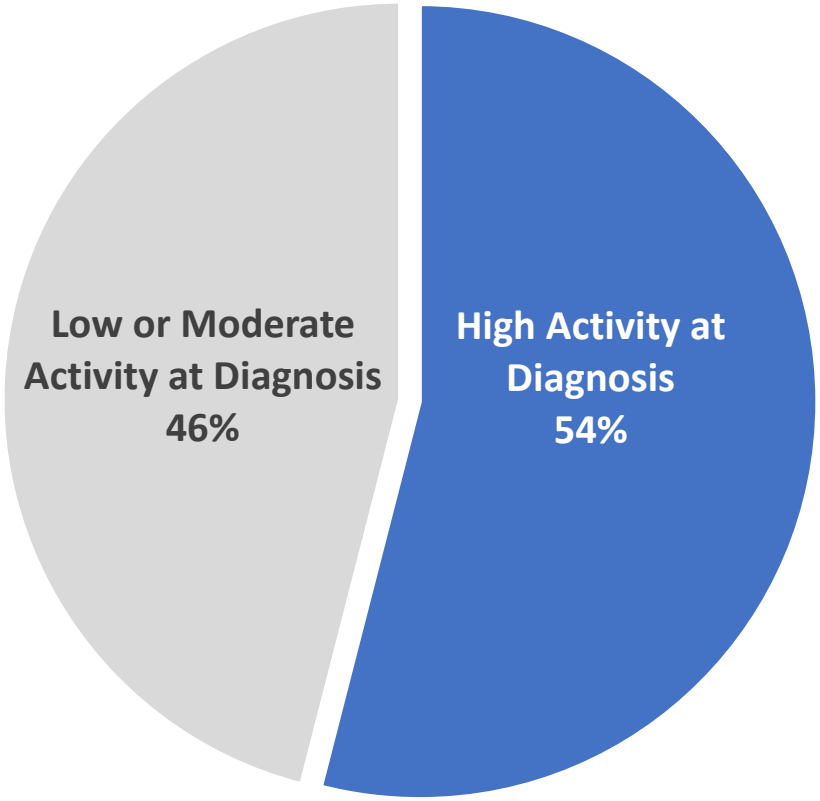
Resomelagon could be well suited to address the needs of patients with high disease activity not fully addressed by MTX therapy alone

1. Albrecht and Zink Arthritis Research & Therapy (2017) 19:68; 2. Shpatz et al. IMAJ (2021) vol 23;
3. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982

Resomelagon with MTX could become the treatment of choice for patients with high activity at diagnosis

Requirements for MTX Complementary Therapy	AP1189 Clinical Profile In Early High Activity Patients
Complimentary MoA	• Resomelagon has been shown to provide benefit over MTX alone • Inflammation resolution appears complementary with MTX
High-Degree of Efficacy	• **BEGIN**: 61% of AP1189/MTX patients achieved an ACR20 response at 1mo compared to 33% of patients treated with Placebo/MTX (pts w eCRP) • **EXPAND**: 82% of AP1189/MTX vs 52% of MTX/Placebo patients achieved an ACR20 response at 3mo (pts w eCRP)
Safe and Well Tolerated	• Resomelagon has been shown to be safe and well tolerated in >75 volunteers and >200 patients • No emerging safety issues seen over MTX alone when used in combination
No or Low Need for Steroids	• Steroids only allowed as rescue therapy in resomelagon early high activity trials
Convenient for Patients	• Resomelagon has a convenient and well tolerated once-daily tablet formulation

Patients with high activity at diagnosis are a significant underserved global population



- **Up to 54% of RA patients can present with highly active disease at diagnosis[1,2]**
  - ~400K annual newly diagnosed Us and EU patients[3]
  - @54% high activity equates to **>200K annual newly diagnosed patients with highly active disease**
- **The RA populations in India and China are estimated to be ~10M people with between ~600-700K annual newly diagnosed patients**

Activity in highly active patients is a PoC for resomelagon potential as a complementary RA Tx

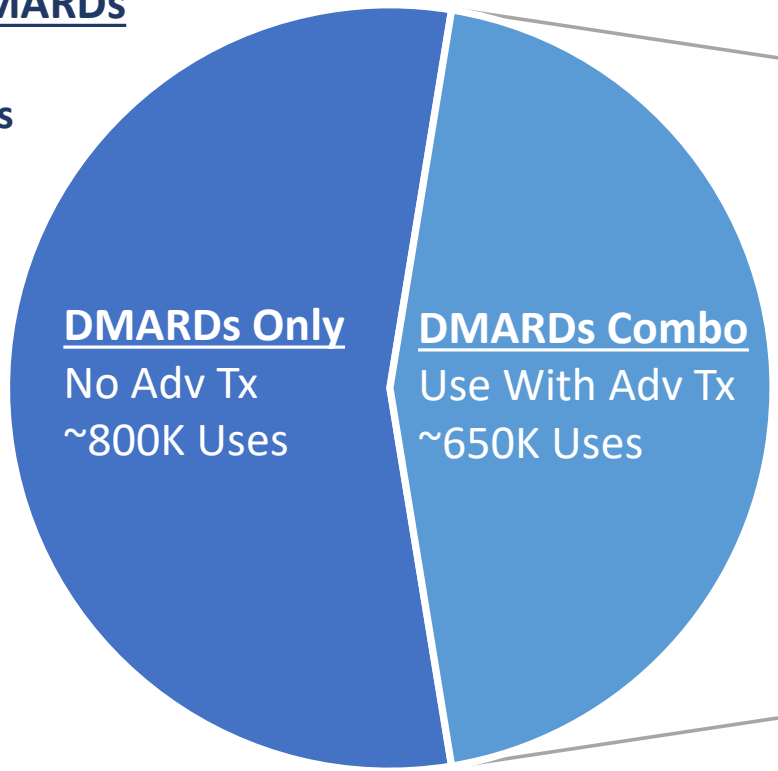
1. Shpatz et al. IMAJ (2021) vol 23; 2. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982; 3. GlobalData Rheumatoid Arthritis Epidemiology forecast

Combination use of DMARDs in the US - The need for improved complementary therapies

Complementary to DMARDs

High Activity at Diagnosis
- ~ 200K/year
- ADVANCE population

Primary DMARD-IR
- ~ 200K/year
- Patients IR 3-6mo after initial DMARD Tx



Complementary to Advanced Therapies

Anti-TNF
~350K Uses

- Up to 40% initial incomplete response
- Causes cycling between agents and switching between MoAs

Other Bios
~175K Uses

- Most initial uses are for TNF-IR

JAK Inhib
~125K Uses

- Oral but safety discourages combo with bios

Resomelagon has the profile to become the complementary RA therapy of choice

Data adapted from GlobalData Rheumatoid Arthritis Market Forecast Model (to 2029)

Business Development:
Build broad momentum with ADVANCE and complimentary Tx opportunity

Big Pharma

- Rebuild momentum with ADVANCE and complementarity RA therapy approach
- Investigate any opportunities to collaborate on additional complementary opportunities

Specialty Pharma

- Identify partners who may be interested in targeting broad first-line use
- Could be regional players or focused on certain market segments

Regional

- Seek geographic partners well suited to co-development and commercialization
- Could be a regional need addressed by resomelagon (i.e. avoidance of immunosuppression in Japan) or a large population-based need like high activity RA at diagnosis in China

Drive Partnering Momentum to Earlier Engagement

- **Align on shared objectives and goals**
- **Look for 'sponsorship' of aligned activities**
- **Identify any opportunities to accelerate partner interest and involvement in RA and beyond**

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SynAct Pharma AB

Capital Market Day

Sector and market overview

Sten Scheibye, Member of the board

Sector and Market overview

I would rather talk about:

Is Resomelagon administered together with Methotrexate as first line treatment in RA without GlucoCorticoids …

UTOPIA ?

Personal UTOPIA's

In MedTech business (CEO, Coloplast, 1995-2008):

1. In the Ostomy Division we sold millions of adhesive plastic bags to collect faeces for people with this rather personal need

➢ One UTOPIA was to develop a bag-free solution for intimate needs. An adhesive "plug" to be used for shorter periods like swimming, sexual activity etc. Not a huge seller but extremely important to show committment to end-users and their nurse advisors

2. Another UTOPIA was the product COMPEED used to remove pain and heal blisters fast

➢ Coloplast had no experience in consumer marketing as we sold to specialized nurses and physicians. Johnson & Johnson eventually acquired the rights to the brand (sub-brand to BandAid) and Colplast got a handsome profit – and continued the production for many years

Personal UTOPIA's

Based on Novo Nordisk (Board member and Chairman 2003-2013)

Insulin administered orally is impossible

GLP-1's can not be administered orally

GLP-1's for obesity – there is no market

Novo Nordisk currently have sales of ~ 68 bn SEK in obesity

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SynAct Pharma AB

Capital Market Day

Wrap-up and summary

Jeppe Øvlesen, CEO

Capital Market Day – Wrap up

Chairman Anders Kronborg	Focused strategy with good news flow towards data end of 2025
Prof. Mauro Perretti	Strong Scientific evidence supporting resolution therapy with resomelagon (AP1189) as a new way forward in RA and other autoimmune and inflammatory diseases
CSO Sanos Asger Bihlet	A very clear need for new patient friendly treatment options in RA where resomelagon (AP1189) could fit as a new patient friendly first line treatment option
CSO Synact Thomas Jonassen	Data from the BEGIN study and in the "right" patients in the EXPAND study strongly support continued development in the Ph2b ADVANCE study that is now ongoing in the US
CBO Jim knight	Large market for first line treatment and beyond – keep potential partners ready for deal making
Board member Sten Scheibye	Learnings from two great companies- emphasizing that if you have a product that addresses a significant medical need it is possible to build an attractive business case

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Thank You