CBO Jim Knight

AP1189 and MC Peptides: Opportunities in RA and Beyond

SYNACT PHARMA

INFLAMMATION RESOLUTION

The emerging AP1189 clinical profile supports continued RA development for potential broad utility

Emerging AP1189 Clinical profile	
• **Once-Daily Oral Dosing**	• New oral tablet being used in both EXPOAND and RESOLVE • Oral convenience for early lines of therapy
• **Quick Onset of Action**	• Efficacy seen at 2-week time point in BEGIN • Efficacy seen in 1st day in hospitalized COVID study
• **High-degree of efficacy**	• BEGIN 1-mo responses were in-line with JAK inhibitors
• **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**	• Melanocortin efficacy with no steroid-associated side-effects (no MC2R)
• **Compatible with MTX**	• Shown to be compatible with MTX • No known compatibility concerns with TNF or other biologics

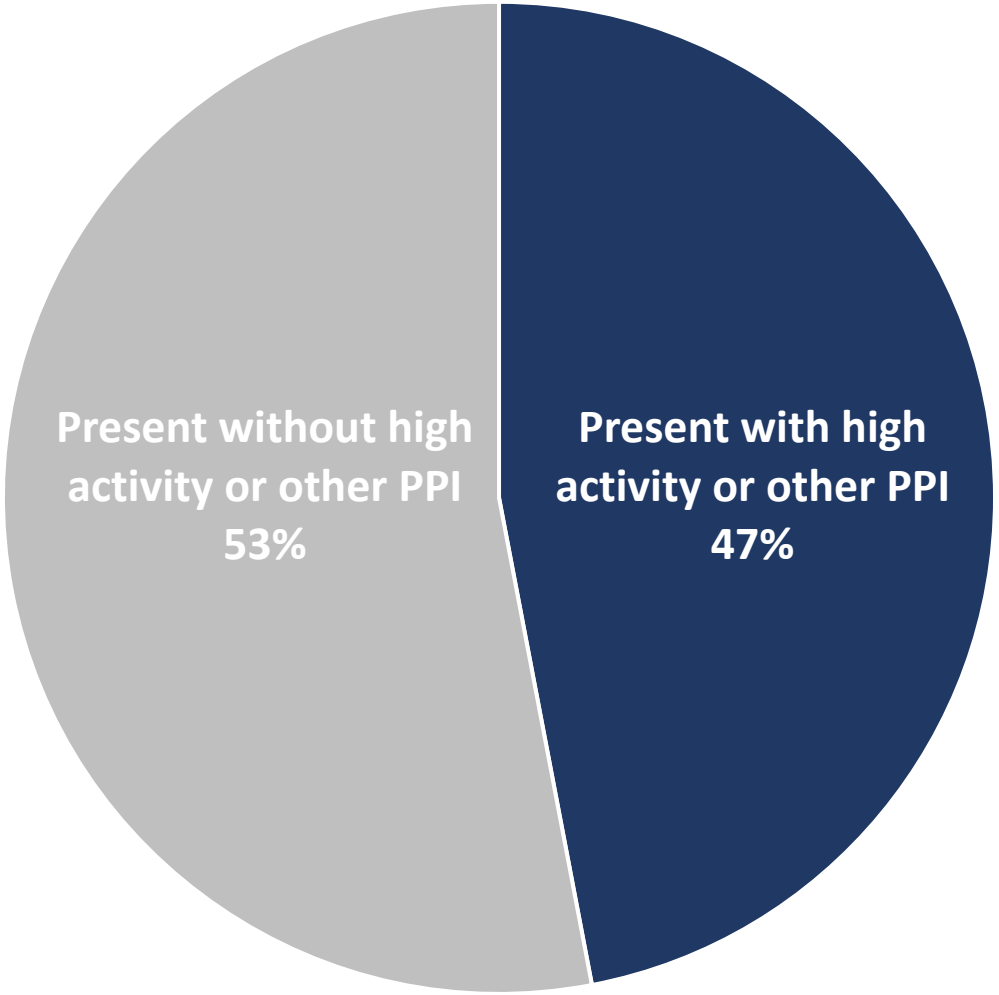
- Initial development has been focused on first-line use with MTX in patients presenting with high disease activity (HAN) and in patients with incomplete responses to MTX (MTX-IR)

AP1189 can resolve Inflammation without causing immunosuppression which may make it potentially suitable for broad use in RA

- **Most approved RA therapies are immunosuppressive and have black boxed warnings of potentially serious and possibly fatal serious adverse event reactions**
- **AP1189 in contrast resolves inflammation without immunosuppression in a convenient oral form making it potentially suitable for broad foundational use in RA**

	1st-Line - DMARDS	2nd-Line -	3rd-Line	4th-Line
Key Approved Therapies	MTX, sulfasalazine, hydroxychloroquine, azathioprine, leflunomide	Humira, Enbrel, Cimzia, Remicade, Actemra, Rinvoq, Olumiant, Xeljanz, biosimilars	Actemra, Orencia, Rituxan, Rinvoq, Olumiant, Xeljanz, biosimilars	Actemra, Orencia, Rituxan, Rinvoq, Olumiant, Xeljanz, Acthar (US), biosimilars

Treatment naïve RA patients present with high activity and other poor prognostic indicators almost 50% of the time

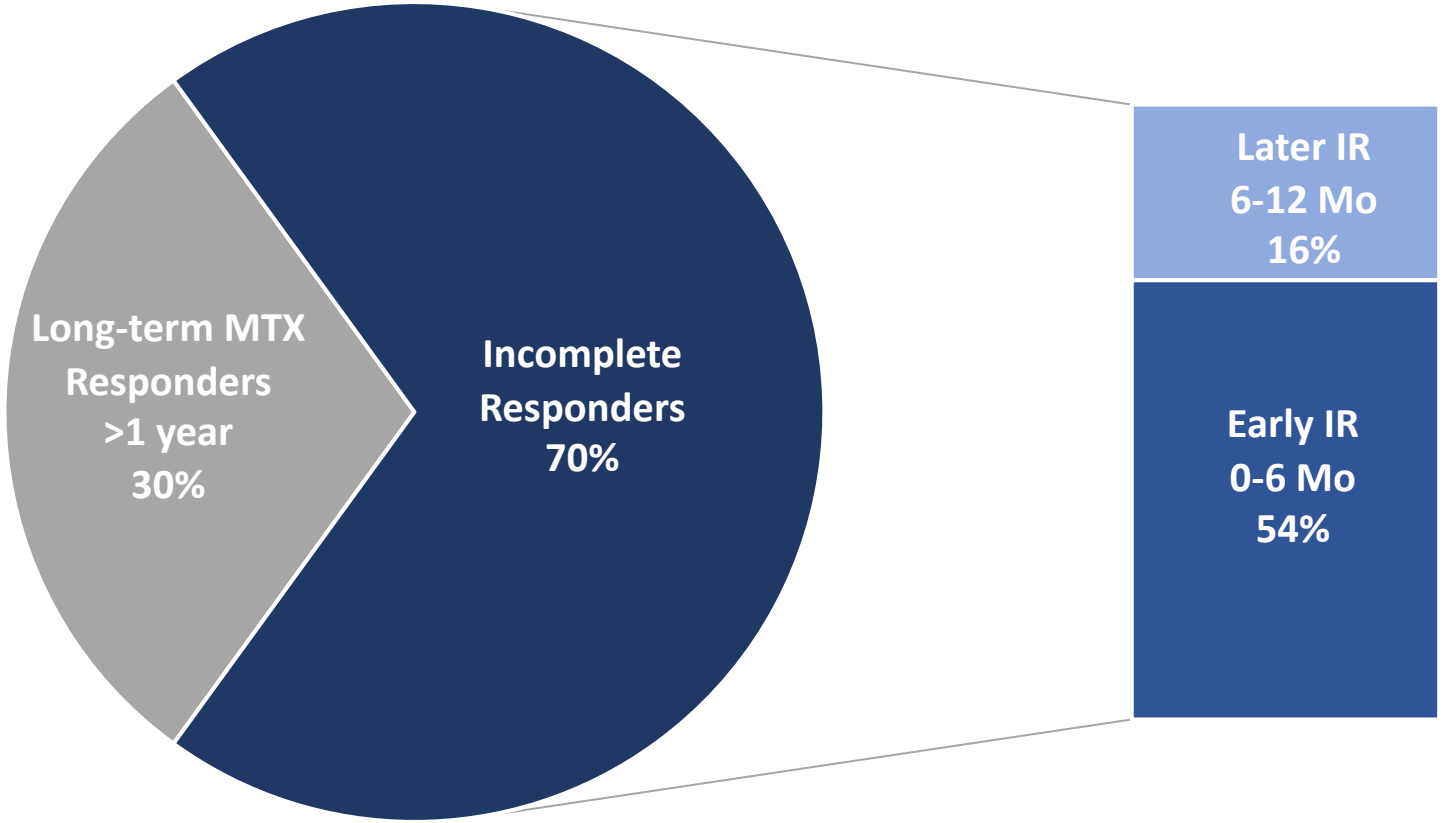


Highly-Active Naïve:

- Studied in BEGIN and EXPAND studies
- Highly active disease is the dominating poor prognostic indicator (PPI) in ACR and EULAR recommendations[1]
- Up to 47% of treatment-naïve RA patients can present with highly active disease and these patients tend to have a lower response to DMARDs including MTX[2,3]

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

DMARDs are time-tested 1st-line RA therapies but the majority of treated patients will not achieve a durable response on DMARD monotherapy



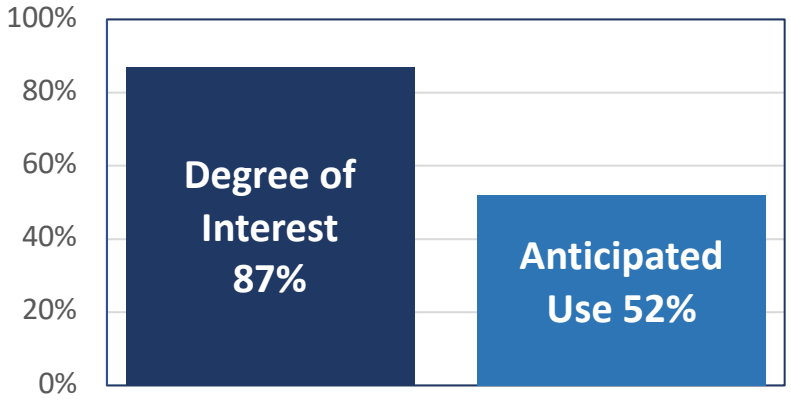
DMARD-IR:

- This is the patient population being studied in RESOLVE
- Up to 50% of 1st DMARD Tx will not achieve low disease activity and 70% will fail a 2nd DMARD Tx[1]
- Up to 54% of MTX-Tx patients will be DMARD-IR at 3mo[2]
- ~20% of patients who initially respond to MTX will loose responsiveness[2]
- Up to 22% of patients experience intolerance even with long-term MTX usage[3]

1. Baganz et al. Seminars in Arthritis and Rheumatism 48 (2019) 976!982; 2. GlobalData RA custom primary market research studies 2021-2023, on file; 3. Amaral et al. Advances in Rheumatology (2020) 60:4

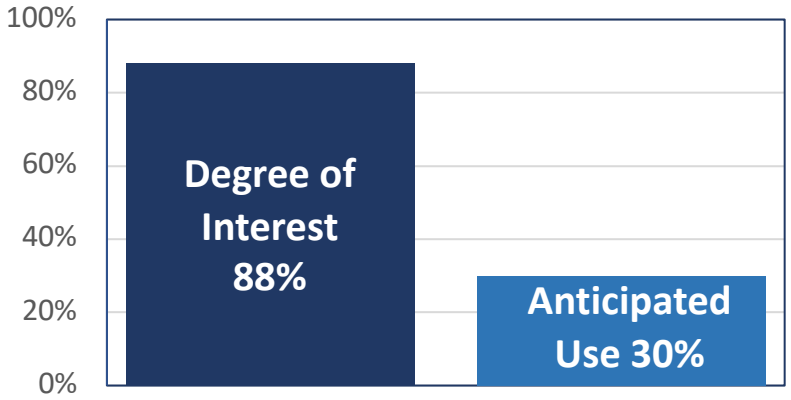
US high-volume rheumatologists stated a strong interest and high intent to use in both DMARD-IR and anti-TNF-IR RA patients

Rheum Interest in AP1189 for DMARD-IR



"Oh man. I'd love to use this up front. I'd love to use it right after methotrexate. I'd love to use it before. I'd love to see this upfront. I mean the non immunosuppressive working kind of endogenously and not doing all the steroid evils, but almost kind of kicking butt like a steroid, uh, yeah, count me in for that one. . ."

Rheum Interest in AP1189 for ant-TNF-IR



"There will be patients that present in such bad shape that I take them to a TNF with MTX right off the bat simply because of my comfort level with TNFs. If those patients don't respond to the TNF, then this would certainly be an option. .."

GlobalData RA custom primary market research studies 2021-2023, on file

External innovation has been key in the development of the leading RA therapies which have multiple indications despite serious safety warnings

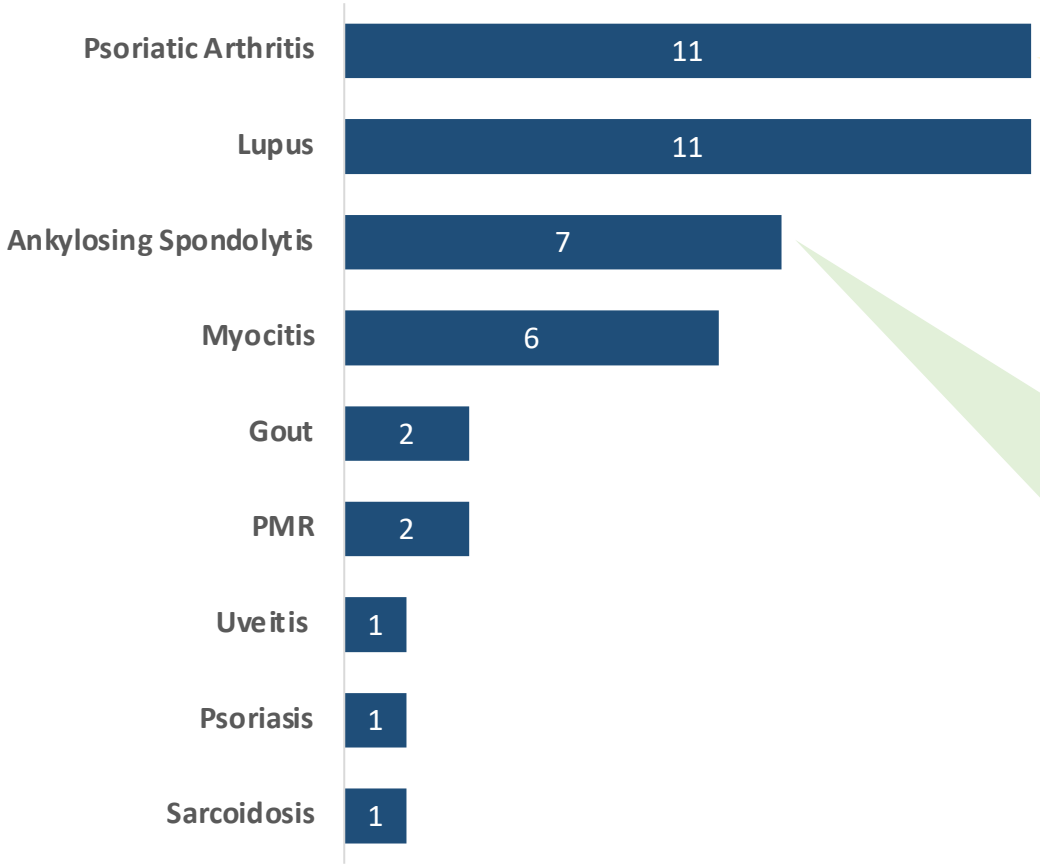
Product	~2021 RA Sales	Marketer	Innovator	Boxed Warnings	Indications
Humira	$8.3B	AbbVie	CAT	• Serious Infections • Malignancy	9
Enbrel	$4.5	Amgen	Immunex	• Serious Infections • Malignancy	5
Orencia	$2.9B	***BMS***	***BMS***	• None	4
Actemra	$1.6B	Roche	Chugai	• Serious Infections	6
Simponi	$1.5B	J&J	Centocor	• Serious Infections • Malignancy	4
Rinvoq	$1.4B	***Abbvie***	***AbbVie***	• Serious Infections • Malignancy • MACE • Thrombosis	6
Xeljanz	$1.4B	Pfizer	NIH	• Serious Infections • Malignancy • MACE • Thrombosis	5
Remicade	$1.3B	J&J	Centocor	• Serious Infections • Malignancy	8
Cimzia	$1.0B	***UCB***	***UCB***	• Serious Infections • Malignancy	6
Olumiant	$600M	Lilly	Incyte	• Serious Infections • Malignancy • MACE • Thrombosis	3

- **Autoimmune or inflammation directed (AI/I) therapies tend to have broad applicability**
- **Total product revenue is driven by use similar use positioning across multiple indications**
- **Many of these additional indications fall within rheumatology**
- **In order to showcase the full potential and value of AP1189 it will be crucial to present additional opportunities both inside and outside of rheumatology**
- **Importantly, 7/10 of the top RA brands were sourced externally underscoring the importance of external innovation**

GlobalData RA custom primary market research studies 2021-2023, on file

AP1189 - Beyond RA – Rheumatologists express significant Interest for development in additional rheumatology diseases

Additional rheumatology diseases-of-interest for AP1189



Psoriatic arthritis

Use may depend on if Product X improves both dermal symptoms and joint symptoms

Interest in AP1189: **7.9/10** [5-10]

Potential patient eligibility for AP1189: **58%** [15-85%]

Treatment paradigm: Similar to RA

"I would definitely expect [Product X] to work because ACTH, that is Acthar, and corticotropin, are both approved for PSA, PSO, lupus, and gout…[but it doesn't address dermal presentation] very well" –US11

Lupus

Interest in AP1189: **7.9/10** [7-9]

Potential patient eligibility for AP1189: **44%** [20-75%]

Treatment paradigm: Similar to RA

"We're always looking for stuff for lupus, which is, by nature, very refractory and we have few options"–US04

Ankylosing spondylitis

Interest in AP1189: **7.5/10** [5-10]

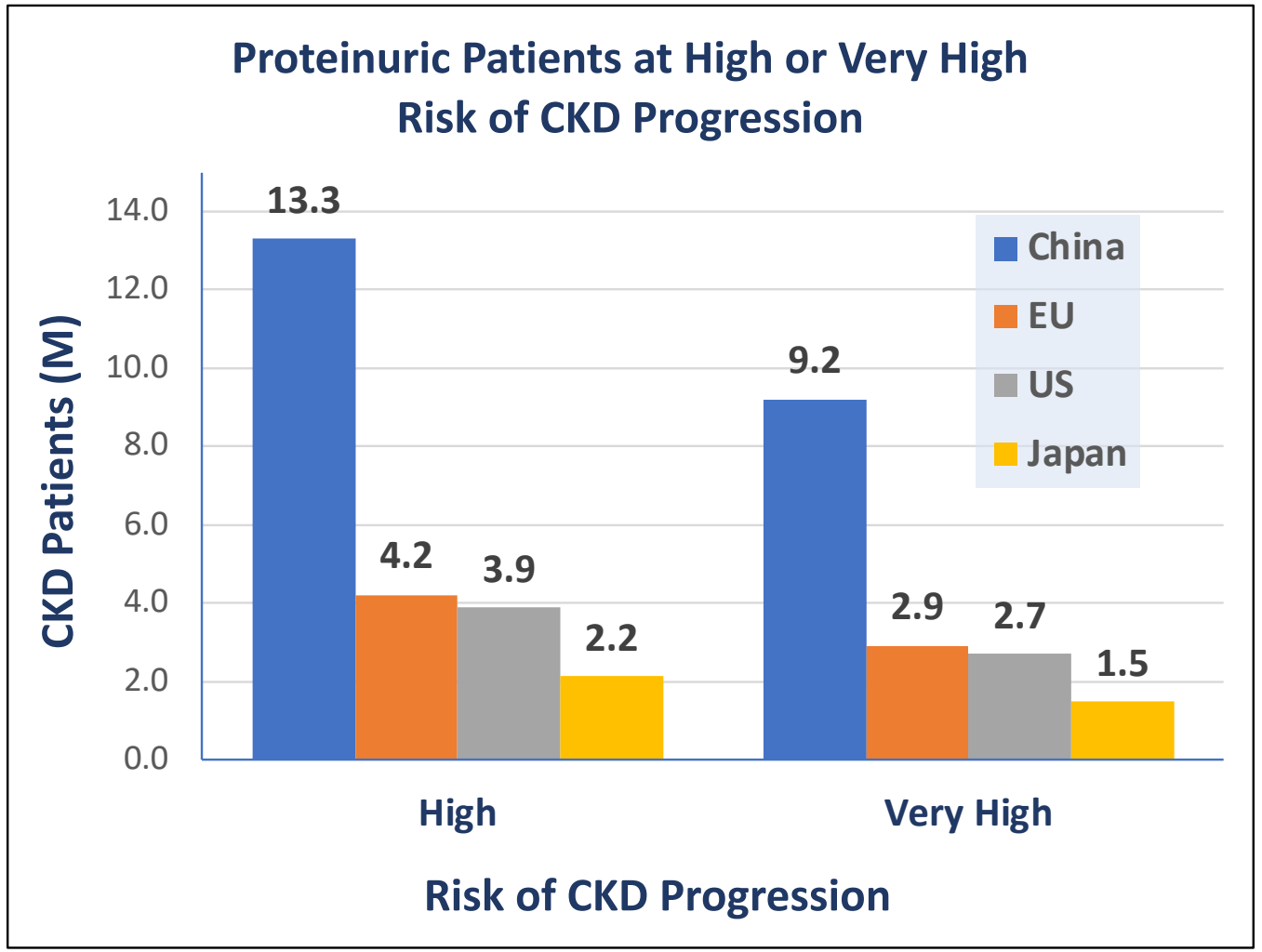
Potential patient eligibility for AP1189: **50%** [25-75%]

Treatment paradigm: Similar to RA

"Theoretically whatever can be used in any inflammatory disease can be used across the board. They're not all the same but they share some common pathways." -US16

GlobalData RA custom primary market research studies 2021-2023, on file

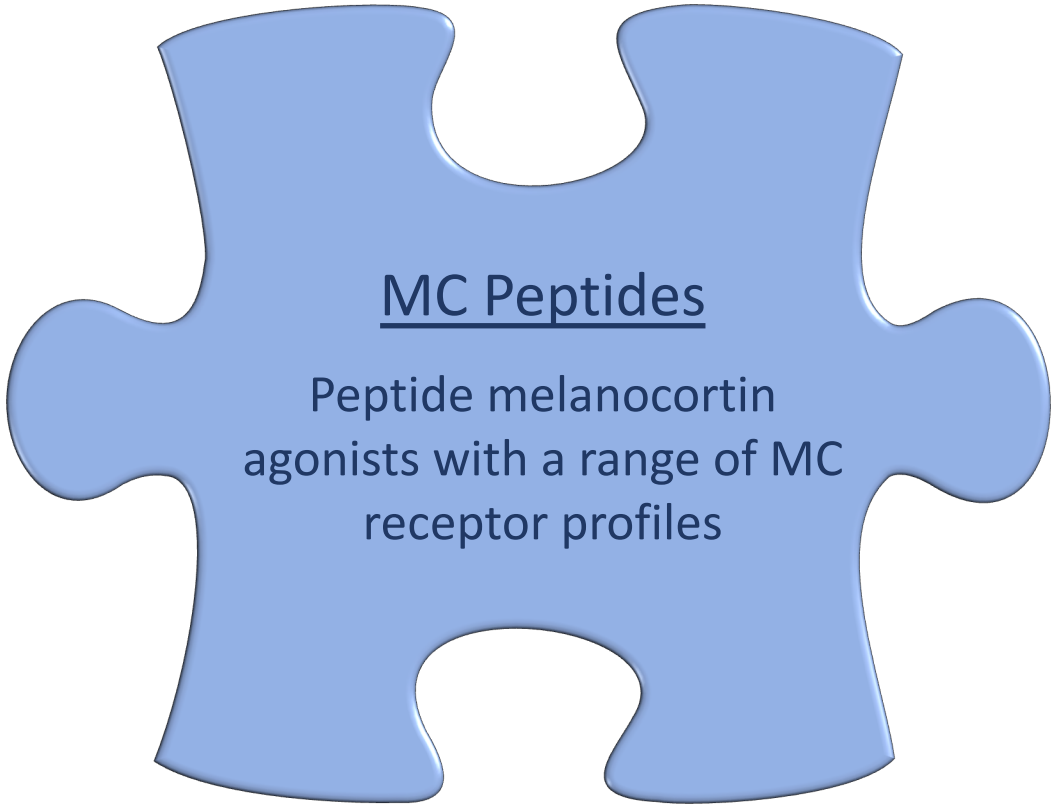
Proteinuria is a significant driver of chronic kidney disease progression and other nephrology conditions like iMN



- There are an estimated 40M CKD patients with moderate or severe proteinuria who are at a high or very high risk of disease progression across the US, Western EU, Japan and China
- ~24M of these are at a high risk of progression and 16M are at a very high risk of progression
- AP1189 is currently being evaluated in idiopathic membranous nephropathy (IMN) in patients with high levels of proteinuria
- While IMN is an orphan disease, oral convenience and good safety position AP1189 well for larger nephrology conditions like chronic kidney disease (CKD) and diabetic nephropathy

United States Renal Data System. *2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. https://adr.usrds.org/2020
GBD CKDC Lancet 2020; 395: 709–33

MC Peptides Provide the Opportunity to Develop Unique Assets Tailored to the Target Disease and Patient Population



Broad family of >70 unique peptide agonists
Differing receptor profiles allow for tailoring peptide agonist for the target disease and patient population

Favorable Properties over Natural Ligands
Increased stability, binding affinity and potency over naturally occurring melanocortin peptides

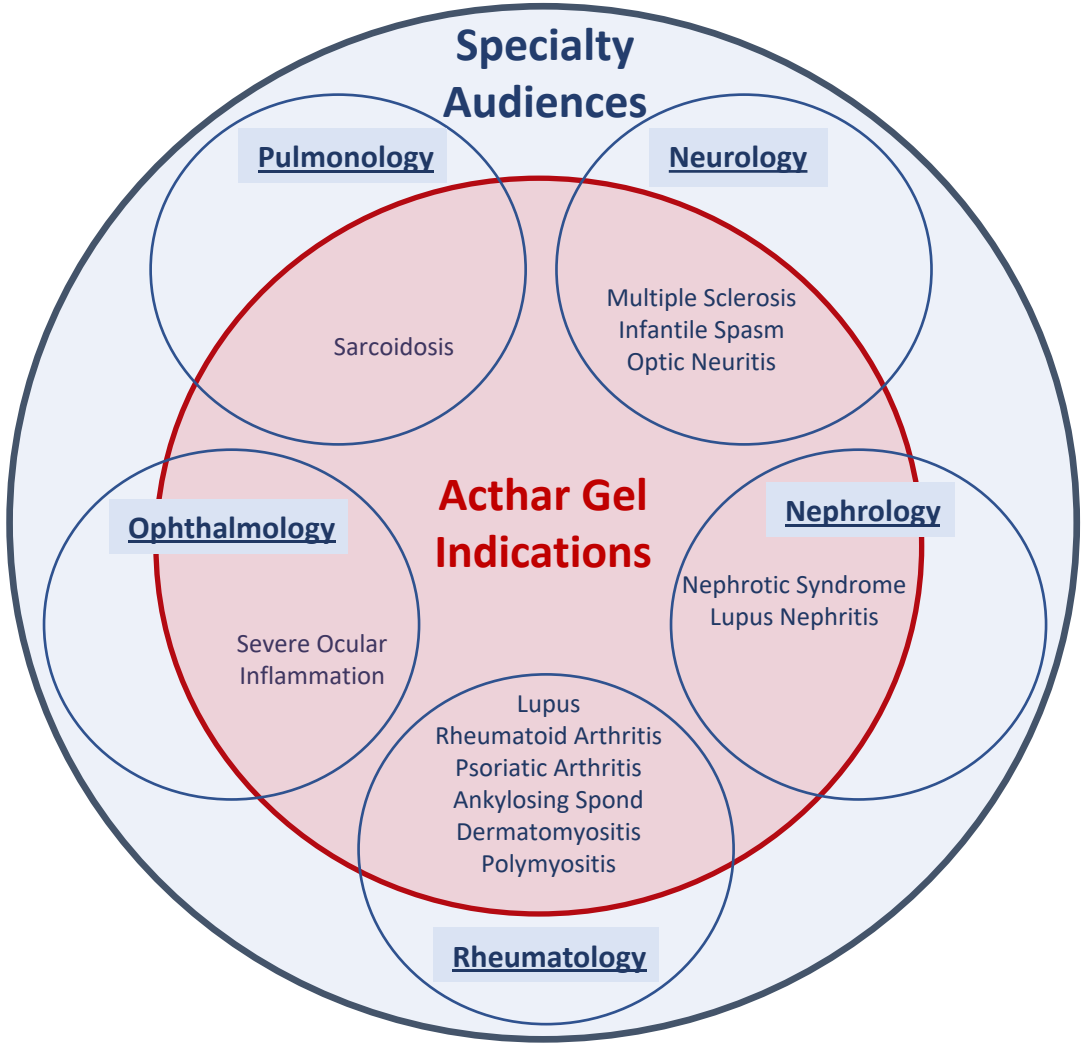
Formulation Flexibility
Including IV and sustained release SC, with possibility of additional routes of administration

Strong Composition of Matter IP
Strong patent position in 3 families, two of which have been granted in main jurisdictions

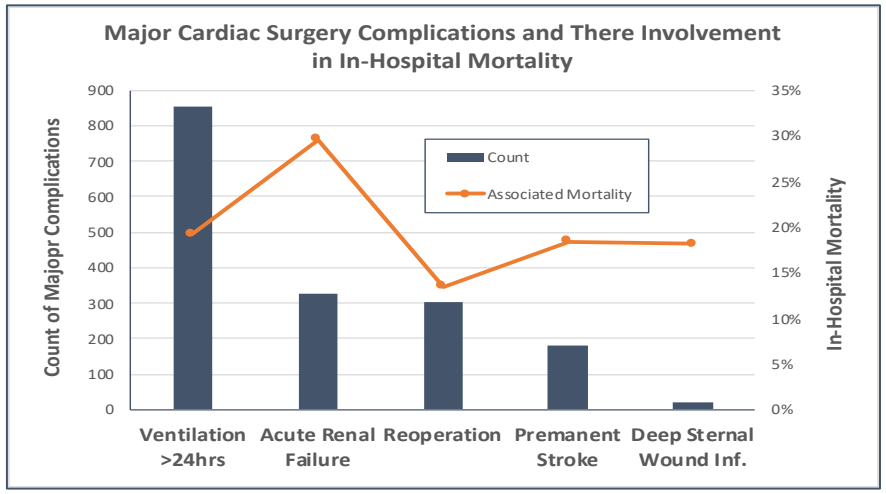
Peptide MC Agonists are Validated as Drugs
Acthar Gel, bremelanotide, setmelanotide, and afamelanotide are approved peptide melanocortin agonists

MC Peptides - Acthar Gel is a proof of concept of the broad peptide potential

- **Acthar is an ACTH-based injectable treatment that is FDA approved for a wide-range of inflammatory and autoimmune diseases**
  - Typically administered as a SC injection 2x/week
- **Acthar sales grew from ~$100M to over $1B in under 5 years as Acthar was re-positioning for refractory patients who had exhausted other treatment options**
  - A position where Acthar had demonstrated meaningful efficacy across several indications
- **The benefits seen with Acthar across a wide-range of inflammatory conditions across 5 medical specialist audiences highlights the broad potential of the injectable MC peptides**



Cardiac surgery in particular is associated with major postoperative complications and high rates of organ failure



Postoperative Organ Failure After Cardiac Surgery[2,3,4,5]

Organ Complication		Postoperative Rate
	AKI	Up to 50%
	AF	20-80%
	ARDS	Up to 20%
	Stroke	Up to 5%

Major Surgical Complications Associated With Cardiac Surgery[1]

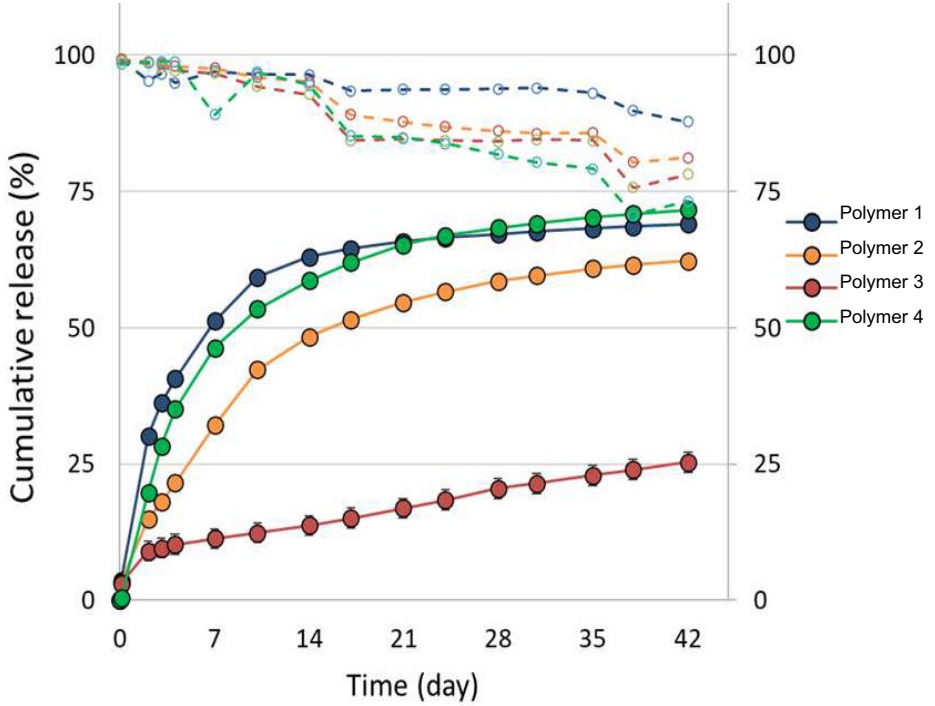
- Cardiac surgery is associated with 5 major surgical complications as described by the Society of Thoracic Surgeons
- In a recent review published in 2020 the rate of major complications was seen to be 17% at a major US surgical center
- In-hospital mortality highly associated with multiple complications and ranged from 8% for a single complication to 52% for 3+ complications
- Any incidence of renal failure in combination with any other complication was associated with the highest level of associated mortality of 30%

[1] Seese, et al., Ann Thorac Surg 2020;110:128-35; [2] Hobson et al., Crit Care Clin 31 (2015) 705–723; [3] Bessissow et al., J Thromb Haemost 2015; 13 (Suppl. 1): S304–S12; [4] Su et al., Medicine (2019) 98:29; [5] Sultan et al., Ann Thorac Surg 2020;110:448-56

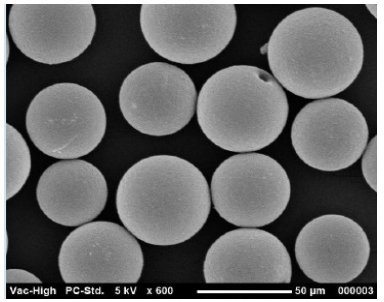
Sustained-release of MC peptides would allow for the broad targeting of autoimmune and inflammatory conditions with an infrequent SC injection

- **Acthar has demonstrated efficacy in the joints, CNS, kidneys, lungs, eyes, muscles and skin via a 2x/week SC injection**
- **Working with a formulation partner with proprietary polymer technology, prototype SR formulations of peptide-35 with release profiles ranging from days to over 1 month**
  - Further formulation optimization to conducted in 2023
  - Good potential flexibility on release profile w/wo immediate burst
  - Polymer technology should be applicable to other peptides
  - Exclusive MC option to technology secured for broad filed of inflammation and inflammatory and autoimmune diseases”
- **The proprietary polymer technology will also create significant additional IP runway**
  - The combination of final polymer and peptide would have an estimated ~**LoE in 2044** not including PTE

Peptide 35 SR in vitro release kinetics



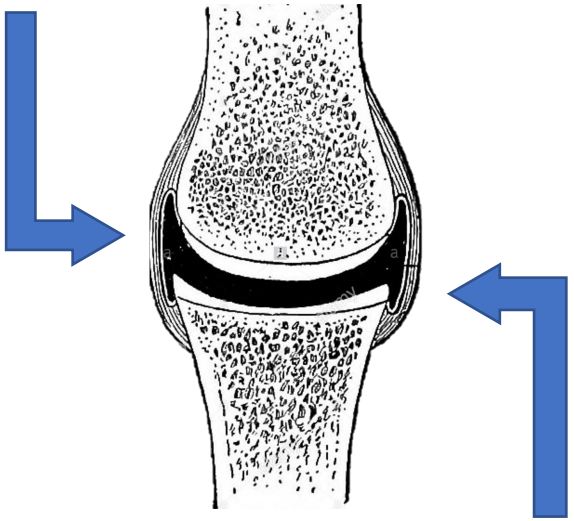
D50 (COV)	TXP-35 target loading	Actual loading (%)	EE (%)
58 µm (32%)	8.7	8.7	99.9
58 µm (38%)	8.7	7.9	90.2
68 µm (65%)	8.7	8.2	94.6
55 µm (28%)	8.7	9.7	111.1



Systemic rheumatologic and/or orphan diseases are prime targets for the MC peptides especially in a sustained-release formulation

Systemic Lupus (SLE)

- >500K SLE patients in US/EU/Japan
- High unmet needs in extra-articular disease
- High dependency on high dose steroids



Inflammatory Myopathies

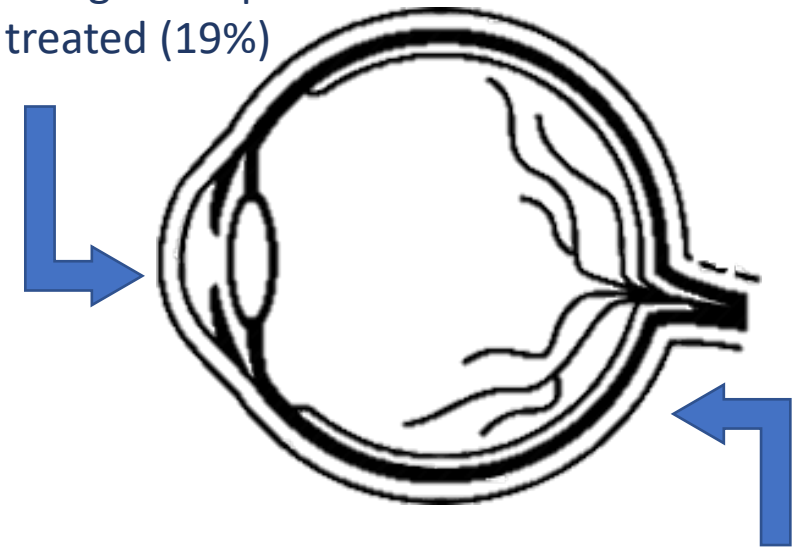
- Orphan diseases with ~150K prevalent patients in US and EU
- Acthar and IVIG are only FDA approved products

- **Acthar demonstrated good efficacy in inflammatory indications with multiple system involvement like systemic lupus and inflammatory myositis**
- **Systemic lupus is an attractive target indication**
  - There are limited treatment options available for lupus and there is a reliance upon steroids at high doses, often used chronically
- **Myositis is an attractive orphan target indication for TXP-35**
  - Inflammatory myopathies (myositis) cause muscle wasting and and non-muscular complications involving skin, lung and heart
  - These are orphan conditions that can result in significant disability and a shortened life expectancy
  - There are numerous additional orphan conditions outside of rheumatology including infantile spasm, sarcoidosis, optic neuritis and non-infectious uveitis

Ophthalmologic diseases are also prime targets for MC peptides especially in a sustained-release formulation

- **The MC system plays a central role in ocular immunity and immune privilege**[1,2]
- **Despite billion-dollar therapies in diseases like wAMD, there remains a high-degree of unmet need in ophthalmology**
- **DED is an attractive target for MC agonism**
  - Only 19% of diagnosed patients are actively treated[3]
  - Acthar and PL9643 (Palatin) are human PoC for SC and topical
- **AMD is an attractive target for MC agonism**
  - α-MSH and analogs have been shown to protect RPE cells and rescue photoreceptors in models of retinal degeneration[4,5]
  - Only 4% of diagnosed patients are actively treated[3]
- **Ophthalmology is a very active partnering space with active deal making across all development stages**

Dry-Eye Disease[5]
~$4.5B sales in 2021
145M diagnosed pts
27M treated (19%)

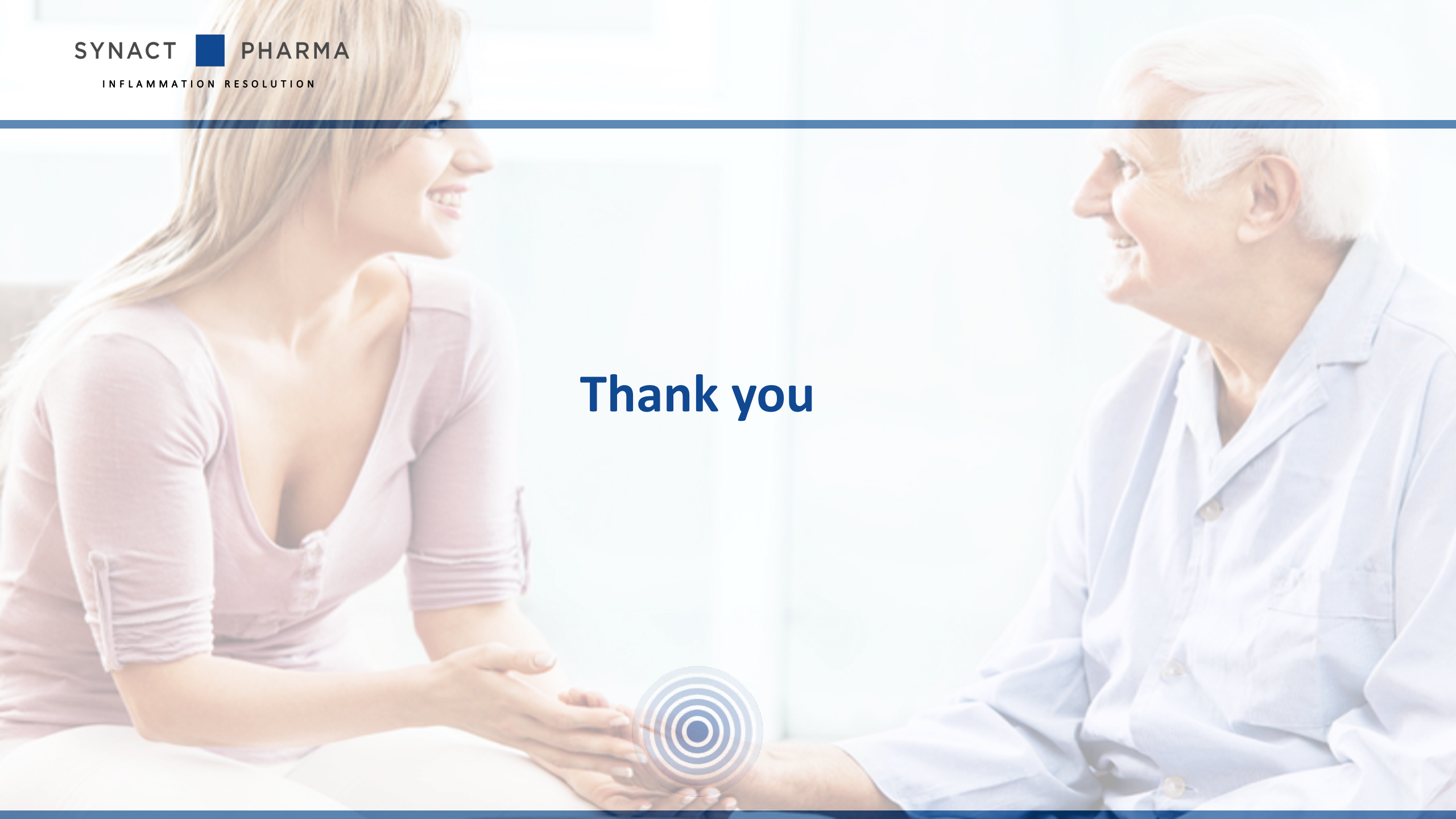


Age-Related MD[5]
~$7.5B sales in 2021
50M diagnosed pts
2M treated (4%)

1. Taylor et al. Adv Exp Med Biol., 2010, 681:143–149; 2. Edling et al., J. of Neuroimmunology 236 (2011) 1–9; 3. GlobalData
4. Rossi et al., Mediators of Inflammation Volume 2016; 5. Naveh et al., Arch Clin Exp Ophthalmol (2003)241:1044–1050 ;

SYNACT PHARMA

INFLAMMATION RESOLUTION



Thank you

SYNACT PHARMA

INFLAMMATION RESOLUTION

Q&A