

# Platform for Macrophage Metabolic Modulation

Next-Generation Drug Enhancement for Anti-Inflammatory & Anti-Infective Drugs

## A New Approach to Immune Modulation



#### **Diversified Platform**

- First-in-class self-regulating small molecule modulators of immune metabolism oral administration
  - -> Reversing the pathologically changed redox balance (oxidative stress) of macrophages & other immune cells
- Broad anti-inflammatory and host-directed anti-viral & anti-bacterial efficacy
- Outstanding safety profile especially no immune-suppression



### **Pipeline and Development Strategy**

- 3 completed phase II PoC studies (COVID-19, Psoriasis) plus preclinical in vivo studies in further indications
- Focused in-house development on orphan indications (Duchenne Muscular Dystrophy and other orphan diseases) as fastest way to conditional market authorization (EMA) & accelerated approval (FDA)
- Pipeline of large indications (COVID-19, Psoriasis, MS, RA, IBD) to be financed by grants or partners



### **Intellectual Property**

- Strong intellectual portfolio with 21 patent families including 98 granted patents
- Additional medical use patents pending valid until 2042/2043



## MP1032 Pipeline

		Program		Pre-clinical	Phase I	Phase II	Phase III
Equity	Orphan	Duchenne Muscular Dystrophy <sup>1</sup> Juvenile Idiopathic Arthritis <sup>2</sup>	oral oral				
Grants / Partnering	Infectious	COVID-19 <sup>3</sup> Other Infectious Diseases <sup>4</sup>	oral oral/i.v.				
Partnering	Inflammatory	Psoriasis Multiple Sclerosis Rheumatoid Arthritis Inflammatory Bowel Disease	oral oral oral oral				



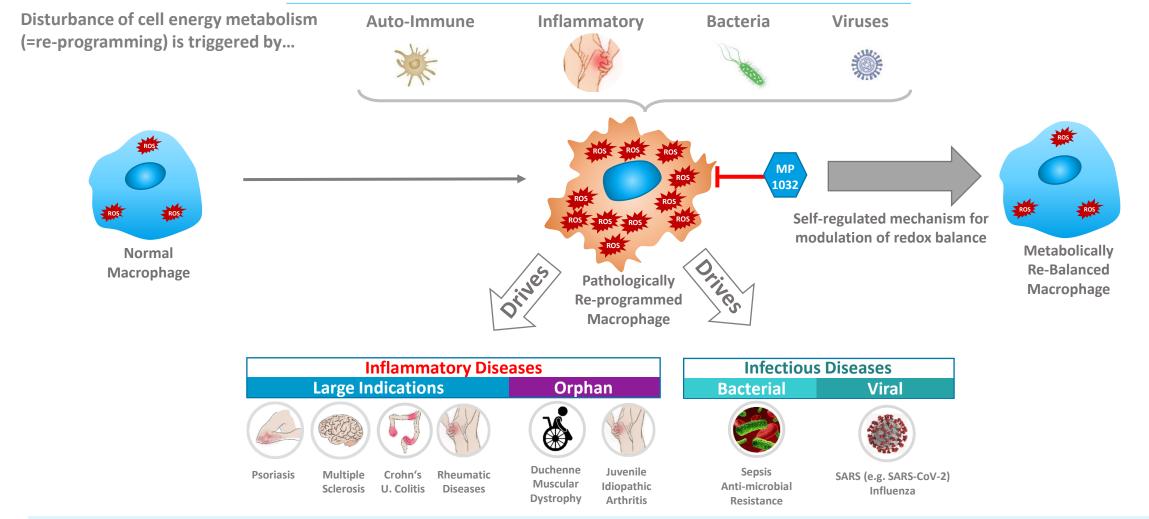
<sup>&</sup>lt;sup>1</sup>Plus further orphan muscular dystrophy indications such as e.g. Becker's Muscular Dystrophy with similar standard therapy

<sup>&</sup>lt;sup>2</sup>On the basis of preclinical in vivo studies for Rheumatoid Arthritis

<sup>&</sup>lt;sup>3</sup> Trial in 7 EU countries plus USA (IND), topline data received in December 2022

<sup>&</sup>lt;sup>4</sup> E.g. Multi Drug Resistant Infections, *Clostridioides difficile*, Sepsis, Acute Respiratory Distress Syndrome (ARDS)

## Macrophage Metabolic Modulation with MP1032 A First-in-Class Self-regulating Drug Mechanism

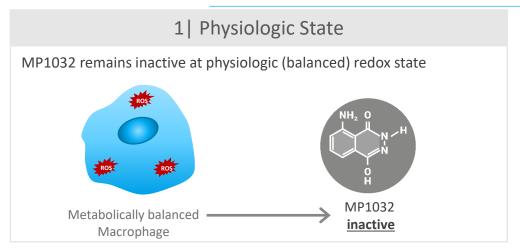


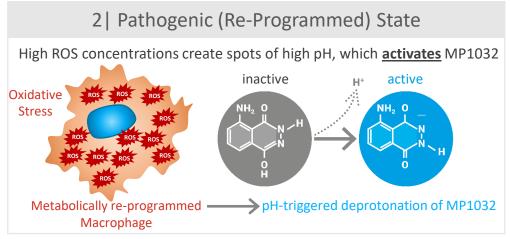
The redox balance of (immune) cells is a key signaling pathway which affects energy metabolism, inflammatory pathways (NFkB, Nrf2), pathogen defense mechanisms and tumor microenvironment. Redox balance is disturbed by metabolic re-programming, which in turn drives disease pathology. MP1032 is a small-molecule metabolic modulator which re-balances cellular redox state.

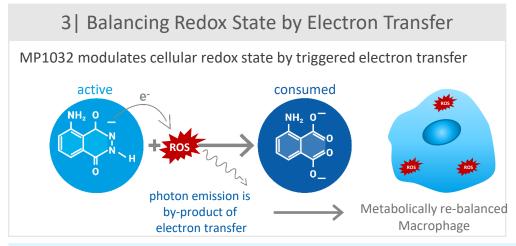


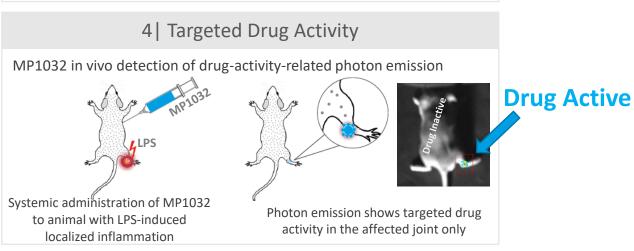
## First-In-Class Self-Regulated Molecular Mechanism of Action

MP1032 is only Activated by Elevated ROS Concentrations in Immune Cells





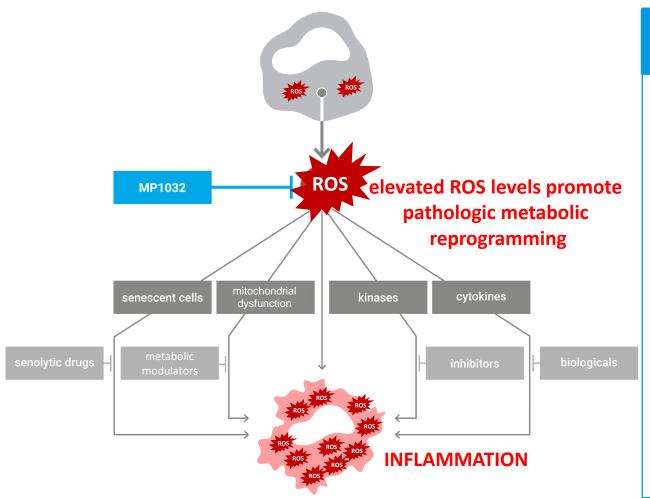


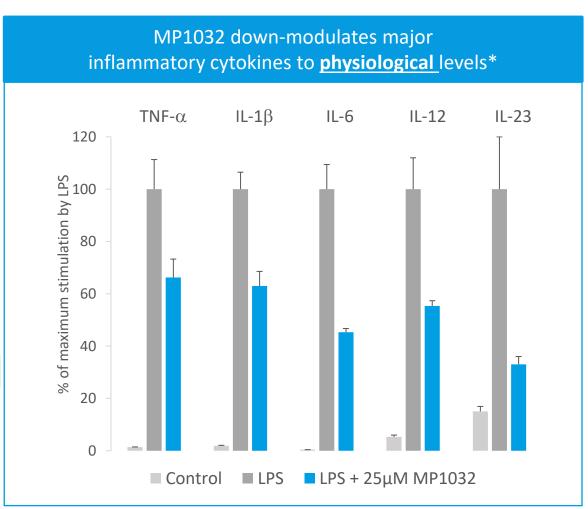


Due to its molecular structure, MP1032 is <u>only activated by elevated ROS concentrations</u> (=oxidative stress) in cells which are <u>pathologically metabolically re-programmed</u>. MP1032 has <u>no</u> influence on the <u>normal</u> redox balance which is essential for physiologic cell signaling and cell metabolism. This auto-regulated activation mechanism restricts the redox modulatory effect of MP1032 exclusively to (immune) cells with oxidative stress. Once cellular redox balance is restored, activation of further drug molecules stops and drug activity ceases. This auto-regulatory activation mechanism ensures that drug <u>modulatory activity stops</u> when physiologic redox balance has been reached, without overshoot into reductive stress.



# MP1032 Acts <u>Upstream</u> of Multiple Inflammatory Pathways Thereby Enhancing the Efficacy of Other Anti-Inflammatory Therapeutics







<sup>\*</sup> in primary mouse macrophages LPS: lipopolysaccharides

## Proven Efficacy and Safety

### Efficacy and safety studies conducted with MP1032 as stand-alone drug (monotherapy)





- Outstanding safety demonstrated in over 250 patients in 4 double-blind placebo-controlled clinical trials.
- Anti-inflammatory and disease-modifying effect demonstrated in two Phase II trials in psoriasis.
- Anti-inflammatory and anti-infective effect shown in a recent Phase II study in COVID-19 patients





Rheumatic Diseases



Crohn's U. Colitis



Multiple Sclerosis



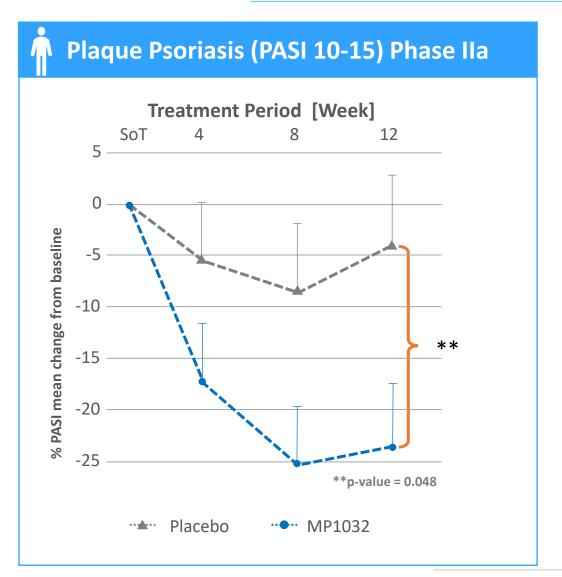
Duchenne Muscular Dystrophy

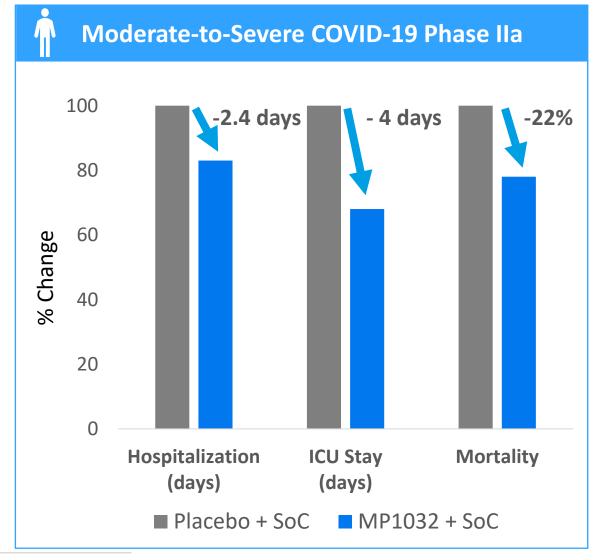
demonstrated in pre-clinical (animal) models of common chronic inflammatory diseases and in animal model of the orphan childhood disease Duchenne Muscular Dystrophy.



## Clinical Data

3 Completed Phase II PoC Studies Demonstrated Disease-Modifying Efficacy and Outstanding Safety





## MP1032 Safety

## Outstanding Safety Profile Pre-Clinically and in Humans

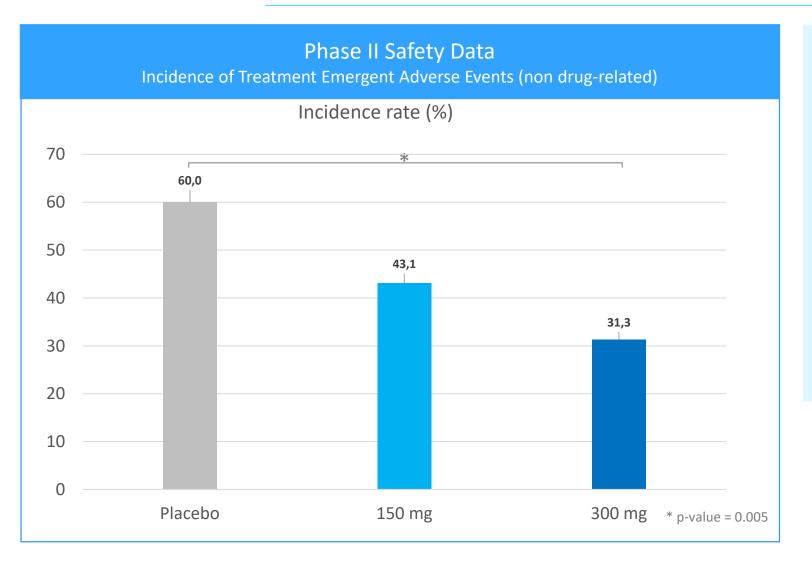
Pre-clinical	Clinical			
Max. oral dosing 6 months – 120x human dose	Phase 1 Max. oral repeat dose  600 mg  No safety issues detected			
No dose-limiting toxicity could be reached  Max. oral dosing	Phase 2a Psoriasis  Max. oral repeat dose  200 mg  No safety issues detected			
12 months  √ 30 x human dose  No observed adverse effect	Phase 2 Psoriasis  Max. oral repeat dose MP1032  No safety issues detected			
	Phase 2a COVID-19  Max. oral repeat dose 600 mg  No safety issues detected			

MP1032 demonstrated excellent safety based on data from preclinical studies and four clinical trials with 366 patients (= 234 verum + 132 placebo).



## MP1032: Less TEAEs in Treatment Groups than in Placebo Group

Potential to Reduce Non-Drug-Related Adverse-Events in Fixed-Dose Combinations (FDCs)



Safety data from Phase II clinical trial MP1032-CT04 Plaque Psoriasis

#### 155 patients; 3 months daily oral

- 55 placebo b.i.d.
- 52 150 mg b.i.d.
- 48 300 mg b.i.d.

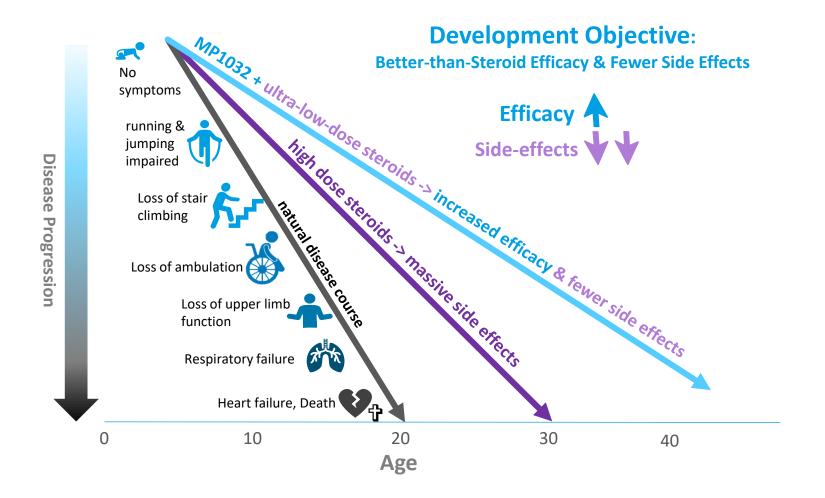
No SAE in MP1032 Groups

300 mg dose reduces TEAEs

SAE = Serious Adverse Event

TEAE = Treatment Emergent Adverse Events

## Duchenne Muscular Dystrophy (DMD)



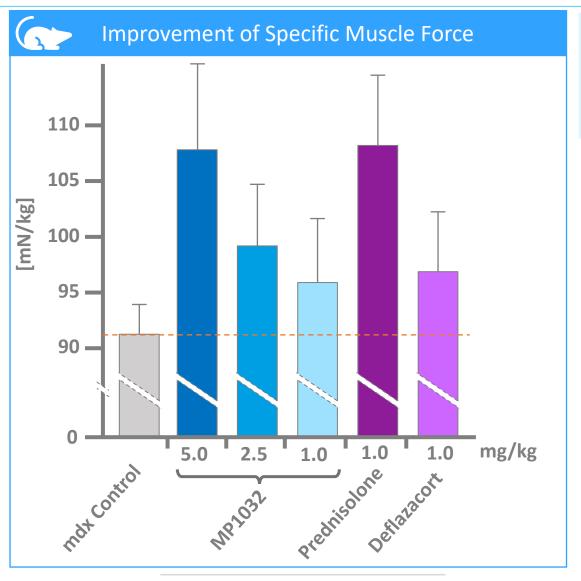


#### **Steroid side effects**

- Growth retardation
- Cushing syndrome
- Osteoporosis
- Hypertension
- Behavioral changes

# MP1032 Muscle Force Preservation Equal to Corticosteroids

in DMD Animal Model (mdx)

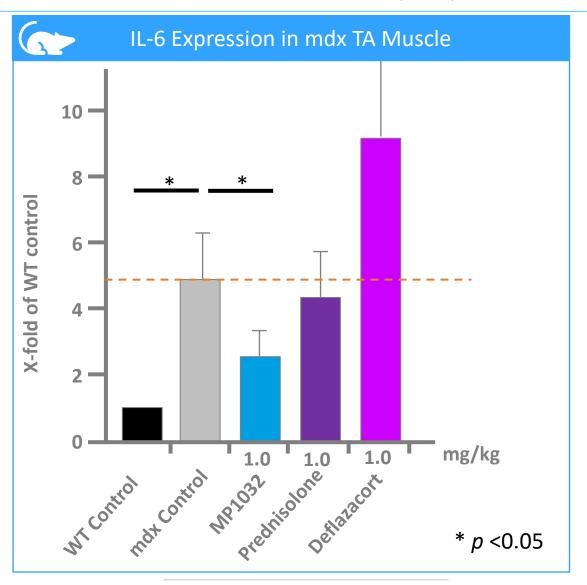


MP1032 improves muscle force in DMD mdx mice with same potency as corticosteroids... ...without any steroid side-effects

Study performed by Agada Research Ltd. Halifax, Canada

# MP1032 – IL-6 Inhibition in Muscle

in DMD Animal Model (mdx)



### **Anti-inflammatory effect**

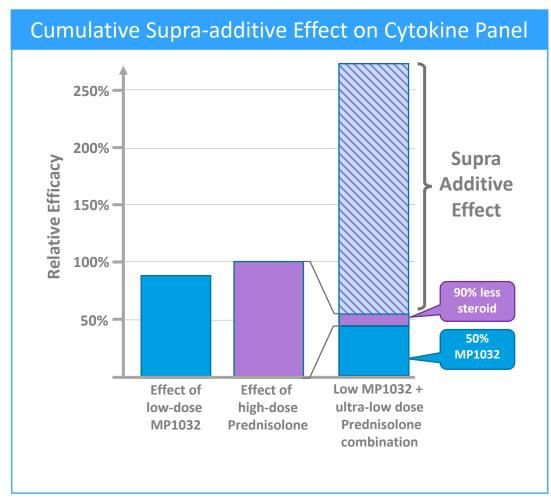
MP1032 elicits meaningful inhibition of IL-6 in *mdx* muscle.

Study performed by Agada Research Ltd. Halifax, Canada



## MP1032 Boosts Corticosteroid Anti-Inflammatory Potency

#### **Efficacy** ↑↑ Side-effects ↓↓



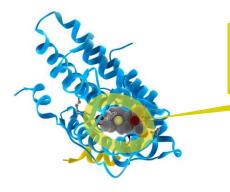
BioMap Assay performed by Eurofins

#### Oncology

Oncology 2000;59(suppl 1):13-18

# Redox Regulation of the Nuclear Receptor

Hirotoshi Tanaka<sup>a</sup> Yuichi Makino<sup>b</sup> Kensaku Okamoto<sup>b</sup> Takahisa Iida<sup>b</sup> Noritada Yoshikawa<sup>b</sup> Takanori Miura<sup>b</sup>



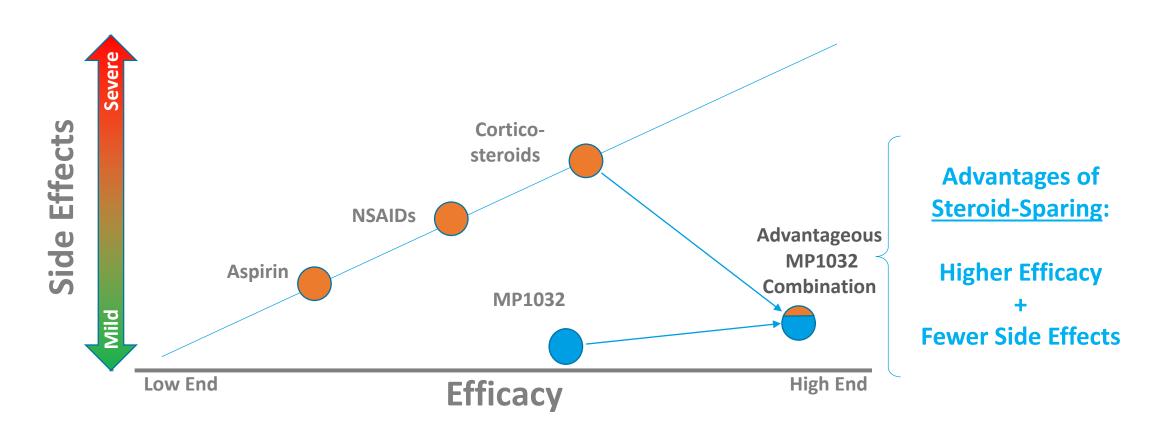
Redox-sensitive region (Cys 481) in vicinity of GCR Ligand Binding Domain

The supra-additive synergistic effect is due to the glucocorticoid receptor's cysteine-rich ligand binding domain, which is sensitive to changes caused by redox changes/oxidative stress/ROS. This weakens steroid binding in cells under oxidative stress, necessitating higher steroid doses for the same effect.

MP1032 can reverse these changes and restores optimal steroid binding. Thus, MP1032 enables lower doses of glucocorticoids.



# Combinatorial Drug Repositioning Strategy <u>in DMD</u>, Rheumatoid Arthritis & further Indications with Corticosteroid Standard Therapies



Immune Metabolic Modulation (MP1032) **boosts the efficacy** of existing anti-inflammatory drugs like corticosteroids in a **highly supra-additive way**. This allows for the creation of a **new class** of next-generation fixed-dose-combination drugs with **improved efficacies and fewer side effects from corticosteroids in a large range of indications** 



## MP1032 – Orphan Indications Development Timelines

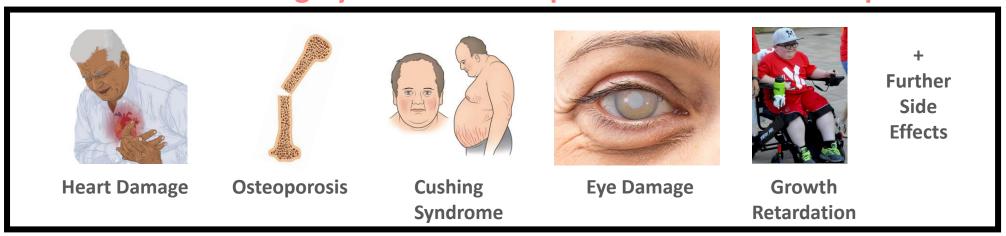
Indication	Development Step	2023	2024	2025	2026	2027
	Orphan Designation EU & USA + Paediatric Voucher					
	MP1032 + steroids validation (mdx)					
	Phase II trial preparation & regulatory					
DMD	Production of trial medication					
Duchenne	Phase IIa					
Muscular Dystrophy	Phase IIb (roll-over from IIa)					
Бузсторпу	Phase III confirmatory trial					
	Early access program – ATU in F					
	Conditional marketing authorization (EU) Accelerated Approval (FDA)					
	2 <sup>nd</sup> Ind. – Preclinical validation					
2 <sup>nd</sup> Orphan	2 <sup>nd</sup> Ind. – Orphan designation USA & EU					
Indication	2 <sup>nd</sup> Ind. – Production of trial medication					
	2 <sup>nd</sup> Ind. – Phase IIa trial					

## Corticosteroid Sparing – A Significant Market Opportunity

## Corticosteroids: still the most widely used therapy for e.g.

#### **Orphan Opportunities Large Non-orphan Indications** • Syst. Lupus erythematosus Asthma Psoriasis Duchenne Musc. Dystrophy Rheumatoid Arthritis Sarcoidosis • COPD • Juvenile Idiopathic Arthritis Polymyalgia Rheumatica Inflammatory Bowel Disease Interstitial Lung Disease Becker Muscular Dystrophy Multiple Sclerosis Polymyositis Rhinitis Other Muscular Dystrophys COVID-19 (hospitalized) • Urticaria Contact Dermatitis Autoimmune Hepatitis

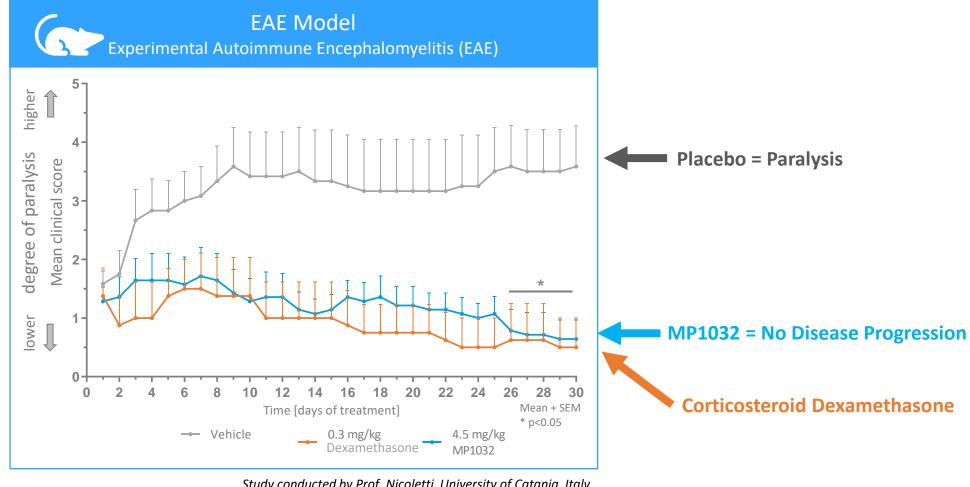
## Corticosteroids: highly effective - but problematic side-effect profile





#### Multiple **Sclerosis**

## Pre-Clinical: Multiple Sclerosis Model



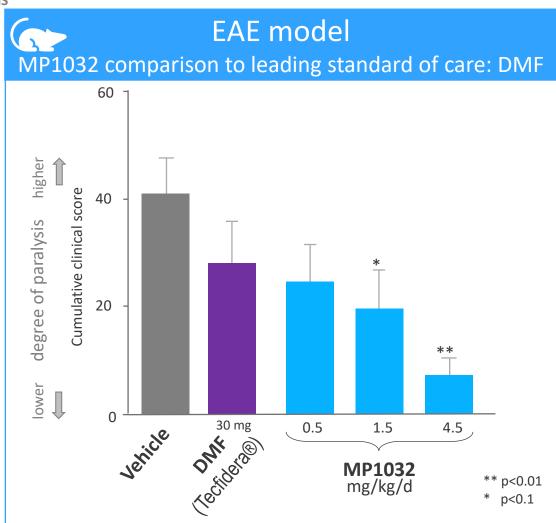






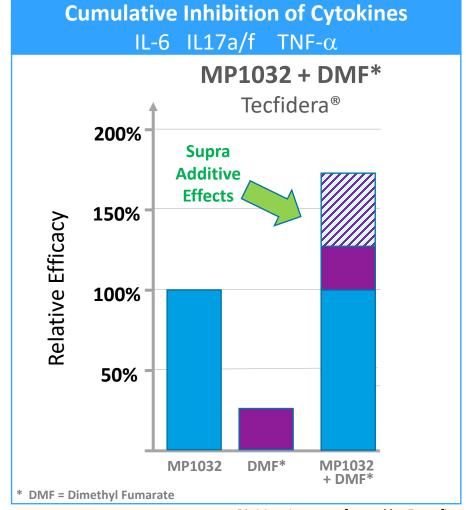
# MP1032 works better than leading oral MS drug





#### Study conducted by Prof. Nicoletti, University of Catania, Italy

### **Synergism with Best-in-Class Potential for MS**



BioMap Assay performed by Erurofins

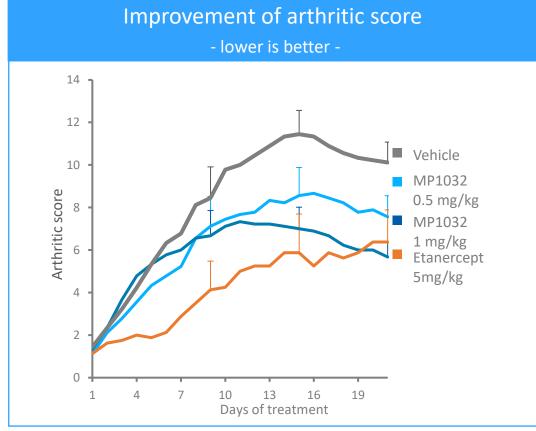




# Pre-Clinical POC: Rheumatoid Arthritis (1) MP1032 improves Arthritic Disease Score and Joint Preservation in CIA Model

Collagen-induced Arthritis (CIA) mouse model

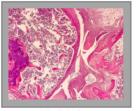
Rheumatoid Arthritis



In Collagen-induced arthritis (CIA) mouse model, MP1032 treatment resulted in significantly improved arthritic disease score, on par with TNF-inhibitor Etanercept (Enbrel®).

### Knee Joint Histology Cross-sections (day 20)

Placebo



Cross section of hind-leg knee joint, showing massive infiltration and destruction of jont morphology

Vehicle

MP1032



 $0.5 \, \text{mg/kg}$ 

Low-dose MP1032 results in less infiltration and partial joint preservation.



1.0 mg/kg

High-dose MP1032 results in minor infiltration and complete joint preservation.

Histological assessment showed dose-dependent disease modifying effect in form of joint preservation.

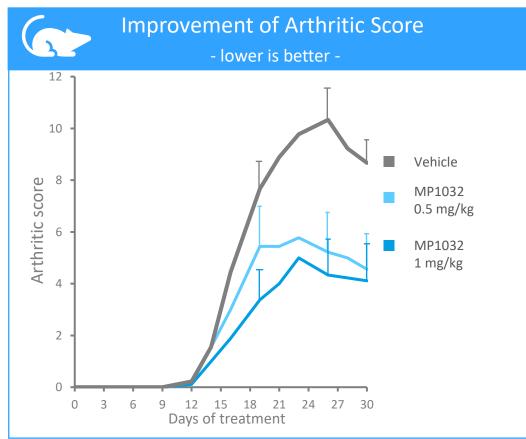
Studies performed by Prof. Nicoletti, University of Catania, Italy



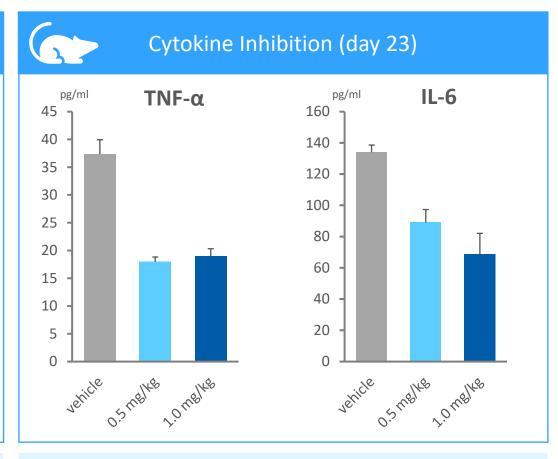


## Pre-Clinical: Rheumatoid Arthritis Model (2)

Antigen-induced Arthritis (AIA) mouse model



In this antigen-induced arthritis (AIA) mouse model, MP1032-mediated immune metabolic modulation improved arthritic disease score compared to vehicle.



MP1032 induced a significant inhibition of two key pro-inflammatory cytokines involved in auto-immune arthritis in mouse AIA model.

Studies performed by Prof. Nicoletti, University of Catania, Italy

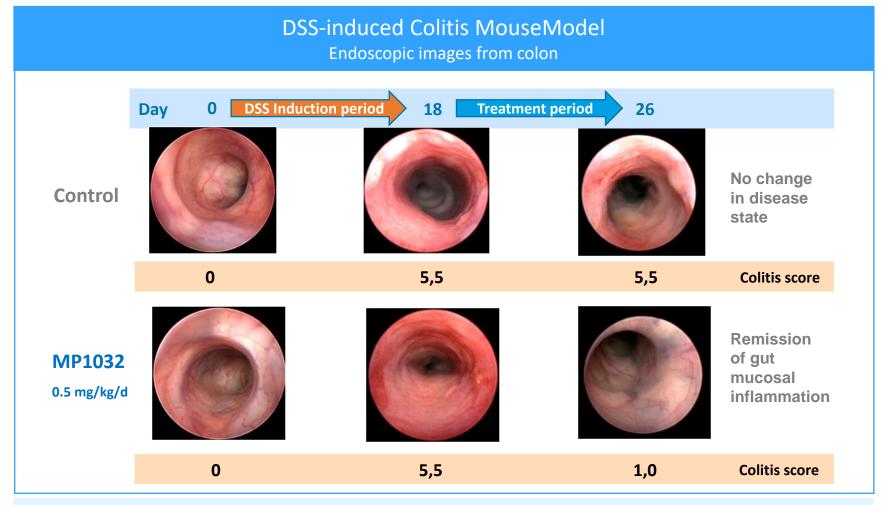




## Pre-clinical POC: Inflammatory Bowel Disease

MP1032-mediated metabolic modulation improves gut inflammation in DSS-induced Colitis Mouse Model

Crohn's U. Colitis

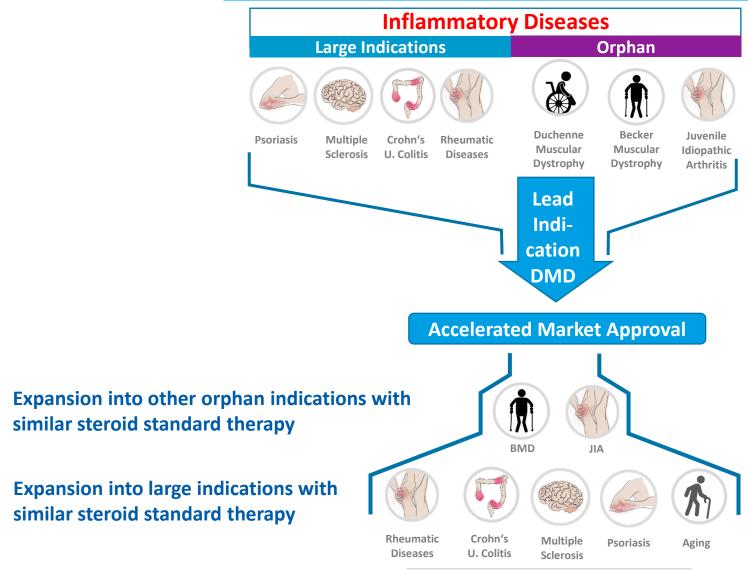


In DSS-induced colitis mouse model. Systemic once-daily treatment with MP1032 metabolic modulator after full induction (therapeutic treatment) resulted in a near-complete remission of gut mucosa within 8 days. Endoscopic images of colon.

Study perfomed by Dr. Grötzinger, Charité, Berlin



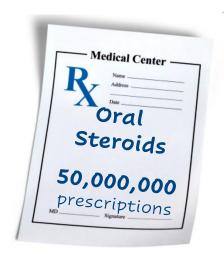
# Development Strategy: Initial Focus on Orphan Diseases

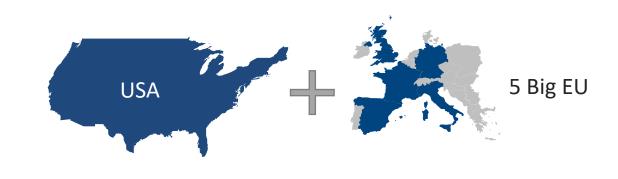


#### **Duchenne Muscular Dystrophy**

- High medical need
- Orphan disease
- Regulatory fast track
- Strong support from patient organizations

## Glucocorticoid<sup>1</sup> Market Opportunity

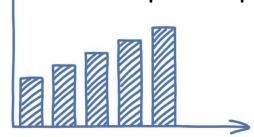




Total Addressable Market: Worldwide Estimated >>200 Million Prescriptions per Year

## **Projected Market Growth**

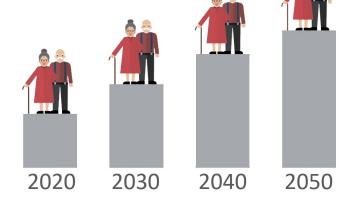
4% compound per year



<sup>&</sup>lt;sup>1</sup> Glucocorticoids are one of the two types of corticosteroids

### **Growth Drivers:**

- Aging
- Demographic Change
- Rise in Chronic Diseases



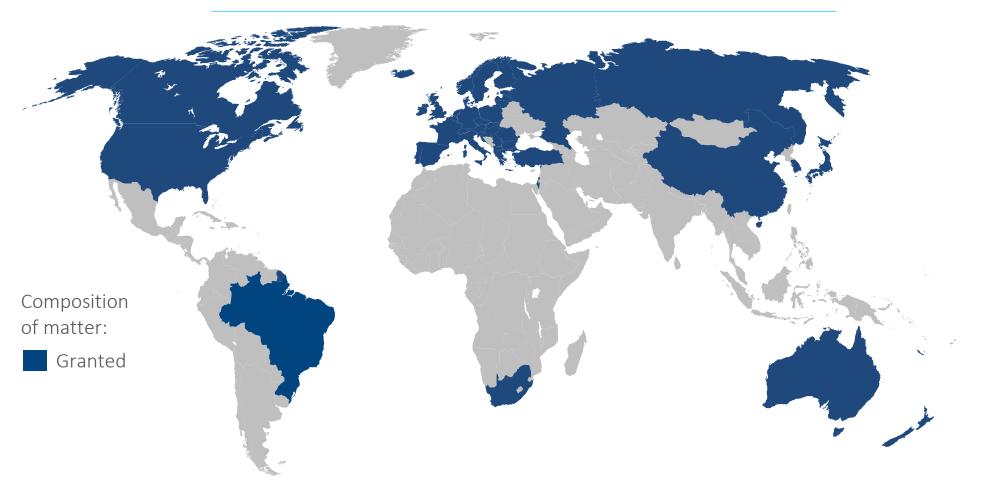


## Total Market Potential for MetrioPharm Pipeline

Indication	Medical Need & Market Opportunity	Total Market	
Duchenne Muscular Dystrophy	Steroid-sparing therapies with improved disease-slowing properties and outstanding safety profile (PoC for other inflammatory diseases)	\$ 4 Billion	
Juvenile Idiopathic Arthritis	Steroid-sparing therapies with improved disease-slowing properties and outstanding safety profile (PoC for other inflammatory diseases, see below)	\$ 2 Billion	
Psoriasis	A safer and more effective oral drug, especially for the large, underserved segment of mild-to-moderate psoriasis (e.g. by steroid-sparing)	\$ 26 Billion	
Multiple Sclerosis	A more effective oral therapy with better tolerability compared to currently leading drugs (e.g. by steroid-sparing or other fixed-dose combinations)	\$ 24 Billion	
Inflammatory Bowel Disease	Oral maintenance therapies with higher response rates than salicylates and better long-term safety than corticosteroids (by steroid-sparing)	\$ 20 Billion	
Rheumatoid Arthritis	An effective, oral early-intervention treatment for safe long-term use (e.g. by steroid-sparing)	\$ 28 Billion	
COVID-19 and other potentially pandemic infectious diseases	<ol> <li>Virus-variant-independent oral drug for safe prophylactic &amp; early intervention use in immune-compromised patients &amp; Long/Post COVID</li> <li>PoC for host-directed therapies for other (potentially pandemic) infectious diseases such as Influenza Virus, Respiratory Syncytial Virus &amp; others (see below)</li> </ol>	\$ ?? Billion	
Other Infectious Diseases	Host-directed therapy for Multi Drug Resistant Infections, Clostridioides difficile, Sepsis, Acute Respiratory Distress Syndrome (ARDS) etc.	\$ 10+ Billion	



## Strong Intellectual Property Portfolio



- Strong intellectual property portfolio with 21 patent families including 98 granted patents to-date
- Composition of matter patents: valid until 2031 (plus PTE/SPC options)
- Medical use patent applications in various fixed-dose combinations: valid until 2042/2043



## Corporate Strategy 2023-2027

#### I. Focus on <u>orphan</u> indication(s):

Duchenne Muscular Dystrophy (-> replace anti-inflammatory standard therapy of high-dose corticosteroids with severe side effects)

- > Accelerate regulatory path by Orphan Drug Designation, PRIME and Break-Through Designations in the EU & US
- > Increase support from international KOLs & international patient advocacy groups
- Execute **phase IIa & IIb and <u>start</u> phase III** (to be supported by public and charity grants)
- Achieve ATU (Autorisation Temporaire d'Utilisation) early access program in France
- > Reach most important value inflection point: **Conditional Marketing Authorization** (EMA) / **Accelerated Approval** (US-FDA)
- > Fulfill conditions for **Pediatric Voucher for any other indication** (high value for large pharma companies)

#### II. Raise up to CHF 40M (at least CHF 20 M) equity financing

Thereof so far CHF 18 M raised in May 2023

#### III. Further financing by grants (public & from charities) and/or by pharma partnering for

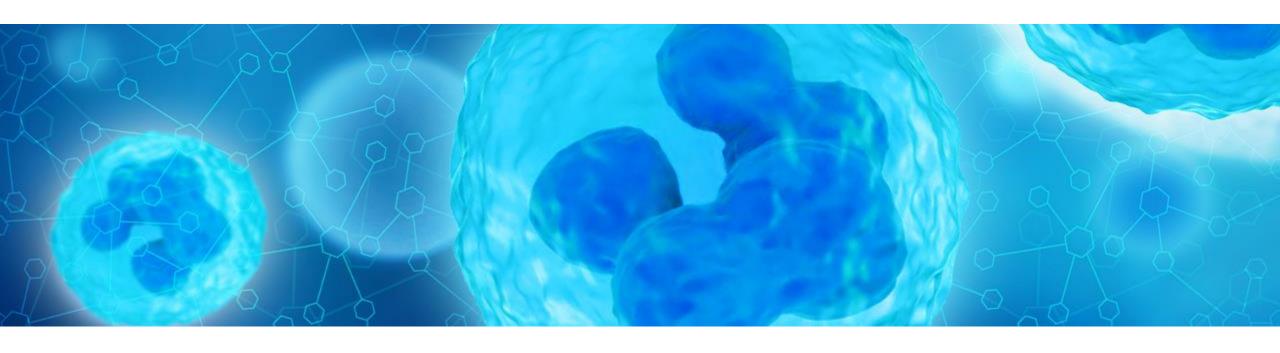
- Clinical trials for **Duchenne Muscular Dystrophy** (DMD) and **other orphan indications** in US & Europe
- COVID-19 as proof of concept for host-directed therapy (HDT) for (potentially pandemic) infectious diseases

### IV. Partnering (preferably in China or Japan)

- Find partner for DMD, Psoriasis, Multiple Sclerosis, Rheumatoid Arthritis, Inflammatory Bowel Disease, Sepsis and HDT indications
- > Conduct a phase IIa study to be financed by partner and/or grants







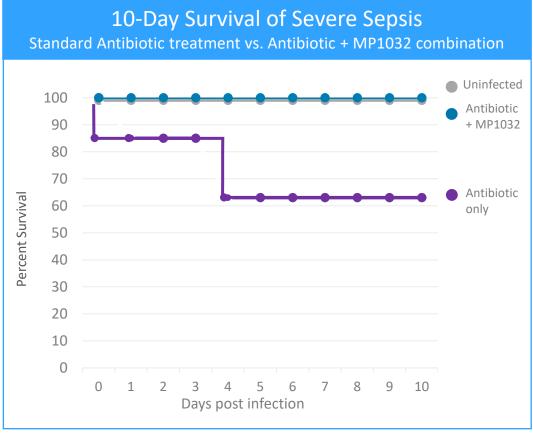
# APPENDIX



# Preclinical POC: Sepsis (1)

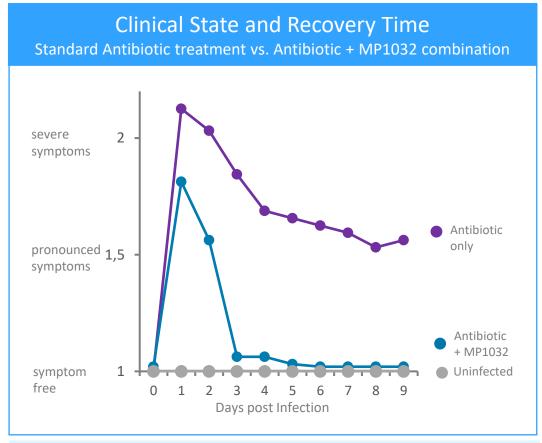
Feces-Injection Peritonitis Model (Mouse)

Bacterial Infection Sepsis



100% animals treated with antibiotic Meropenem plus MP1032 combination therapy survived and fully recovered.

62% of animals in the Meropenem-only group survived, albeit in a clinically poor condition.



The Gonnert score evaluates clinical and behavioral signs of disease and health in animals: movement vs. apathy; food intake, fur, stool. Ranges from 1.0 (normal/healthy) to 3.0 (terminally ill).

Animals treated with antibiotic + MP1032 combination fully recovered within 3 days. Surviving animals treated with antibiotic monotherapy recovered only partially.

Double-blinded study performed by Dr. Ignazio Rubio, Center for Sepsis Control and Care, Jena, Germany

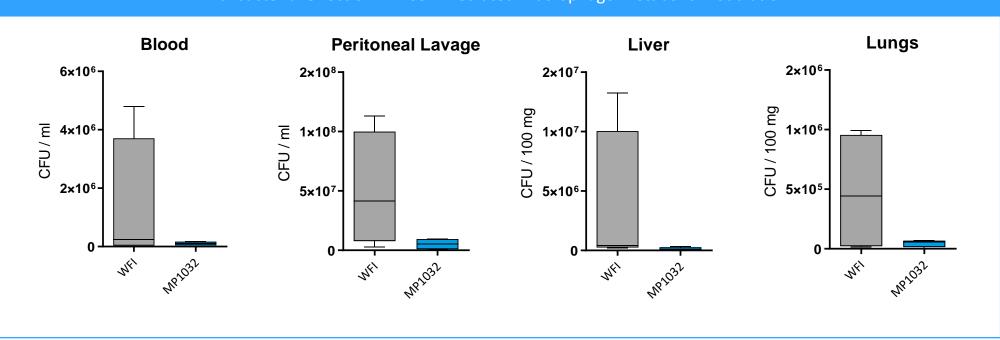




## Preclinical POC: Sepsis (2)

### Host-Mediated Anti-Bacterial Effect of MP1032 Metabolic Modulation

# Colon Ascendens Stent Peritonitis (CASP) Sepsis Model Anti-bacterial effect of MP1032-mediated Macrophage Metabolic Modulation



Number of bacteria (CFU = colony forming units) in different tissues 12 hours after CASP peritonitis induction. Animals were treated with two systemic doses of MP1032, 1h and 7h post sepsis induction as sole treatment. Water for injection (WFI) was used as control.

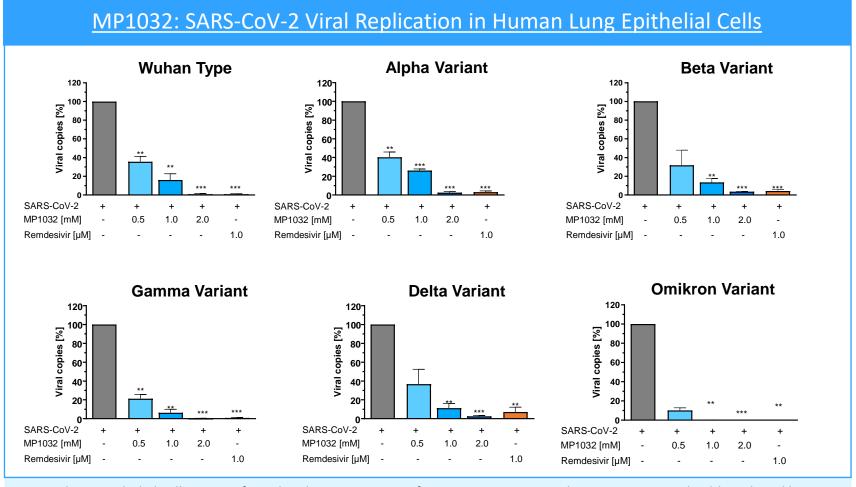
This marked **anti-bacterial effect was mediated solely by MP1032 Macrophage Metabolic Modulation**, since direct treatment of bacterial cultures with MP1032 had no influence on bacterial growth (data not shown). Consequently, redox metabolic modulation is a **highly promising approach to treat bacterial infections** that also covers **all antibiotic-resistant strains**.

Study performed by Prof. Traeger, University of Greifswald, Germany





# Anti-Viral Activity of MP1032 Against Various SARS-CoV-2 Variants Host-Mediated & Dose Dependent Efficacy - Independent from Virus Variants



Human lung epithelial cells were infected with virus variants of SARS-CoV-2. Virus replication was reproducibly reduced by MP1032 in dose-dependent manner. Anti-viral effect was consistent, independent of virus variant.

Data from Schumann S et al. Immune-Modulating Drug MP1032 with SARS-CoV-2 Antiviral Activity In Vitro: A potential Multi-Target Approach for Prevention and Early Intervention Treatment of COVID-19. Int J Mol Sci. 2020 Nov 20;21(22):8803. Further data from ImmunoLogik GmbH in collaboration with Prof. Ulrich Schubert of University of Erlangen, Germany.



# COVID-19<sup>1</sup> Phase IIa Study <u>Final</u> Data Analysis <u>PoC</u> for <u>Host-Directed</u> Therapies for <u>Potentially Pandemic</u> Infectious Diseases<sup>1</sup>

# Final data analysis reveals significantly better results than early top-line data suggested Efficacy and safety advantages compared to Standard of Care (SoC)<sup>2</sup>:

- ➤ Hospitalization times reduced by 2.4 days (Better than published data of existing drugs Remdesivir and Molnupiravir at similar endpoints)
- Median Intensive-Care-Unit-stay: 4 days shorter
- ➤ 23% lower relative long-term (60d) mortality
- Favorable biomarker readouts compared to placebo + SoC
  - ➤ Lower C-Reactive Protein (CRP) => lower general inflammation
  - Higher GFR => better kidney function (predictor of better clinical outcomes)



<sup>&</sup>lt;sup>1</sup> Financed by EU Grant of EUR 7.9m -> further developments to be financed by grants and/or partnering with large pharma companies

<sup>&</sup>lt;sup>2</sup> Findings from MP1032 treatment group + SoC compared to placebo group + SoC as calculated by Saarmetrics

## USA: Medical Need and Government COVID Therapeutics Strategy

## **Outpatient**

Administration for Strategic
Preparedness & Response

PrEP

PEP

Therapy

No Illness

**Exposed** 

Per CDC Close Contact Criteria

COVID ++

Mild to Moderate Symptoms



# Pre-Exposure Prophylaxis (PrEP)

- No approved PrEP treatment available
- "Evusheld" not authorized for emergency use anymore (FDA)

## Post-Exposure Prophylaxis (PEP)

- No current PEP treatments
- Studying new and improved treatments a virus variants change

#### **COVID-19 Treatment**

Effective when started within a specific limited timeframe from onset of illness

- Oral antiviral
- IV antiviral
- Monoclonal antibodies (mAbs)

**Paxlovid** 

Lagevrio (molnupiravir)





**MP1032 COVID Market Opportunity** 

Still no approved drug available for these market segments





# MP1032 is Effective Against 4 Cardinal Drivers of Long COVID

MP1032 Immune-Metabolic Modulation: A Multi-modal Therapy Opportunity to Treat Long COVID

COVID-19

	Long Covid Pathology	References	MP1032 Therapeutic Effect
1	Persistent Virus	Couzin-Frankel J. Clues to long COVID. Science. 2022 Jun 17;376(6599):1261-1265  Zollner A, Koch R, et al. Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases. Gastroenterology. 2022 Aug;163(2):495-506	MP1032 inhibits SARS-CoV-2 replication independent of virus variants  MP1032 Effect  SARS-CoV2  MP1032 Effect  Fights persistent virus
2	Immune  Metabolic  Dysregulation  TNF-α  IL-1β  IL-1β  IL-6	Phetsouphanh C, Darley DR, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022 Feb;23(2):210-216. Schultheiß C, Willscher E, et al. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. Cell Rep Med. 2022 Jun 21;3(6):100663	MP1032 inhibits  we observed by principal received and a second and a
3	Micro Embolisms	Buonsenso D, Di Giuda D, et al. Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection. Lancet Child Adolesc Health. 2021 Sep;5(9):677-680.	MP1032 induces the endogenous factor thrombomodulin  MP1032 Effect  Prevention of micro-embolisms
4	Lung Fibrosis Normal COVID	Mohammadi A, Balan I, et al. Post-COVID-19 Pulmonary Fibrosis. Cureus. 2022 Mar 2;14(3)	MP1032 inhibits fibrotic biomarkers  MP1032 Effect  Anti Fibrotic Inhibits pulmonary fibrosis

Long COVID is emerging as a multi-facetted systemic disease which shows the typical hallmarks of pathologic macrophage re-programming. This has detrimental effects on a number of different organ systems. MP1032-mediated macrophage metabolic modulation is a drug mechanism that broadly targets the diverse causes and symptoms of Long Covid. The high unmet medical need and lack of approved therapeutics for Long Covid makes this a highly promising and attractive target indication for MP1032.







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