



R A P H A E L

Raphael Pharmaceutical

Advancing the Research and Development of  
Medicinal Cannabis *for the People*

**Raphael Pharmaceutical**  
Company Presentation  
June 2024  
OTCQB: RAPH

# Forward Looking Statements

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# Snapshot of Company

- We are a pharmaceutical drug research and development company focused on the discovery and clinical development of life-improving drug therapies based on cannabinoids.
- We collaborate with world-class research experts to harness the power of rigorous scientific methods and advanced technologies to develop safe, effective cannabinoid-based formulas.
- Our most advanced development candidates include novel, patentable formulations designed to treat:
  - Rheumatoid arthritis (lead candidate)
  - Chronic lung inflammation
  - Autoimmune disease
- Our proof-of-concept clinical trial for rheumatoid arthritis is underway in the U.S.
- We believe that medical solutions should be accessible to everyone (“for the people”) and anticipate that our products will be affordable, lower-cost options – a small fraction of the price of existing drugs on the market.

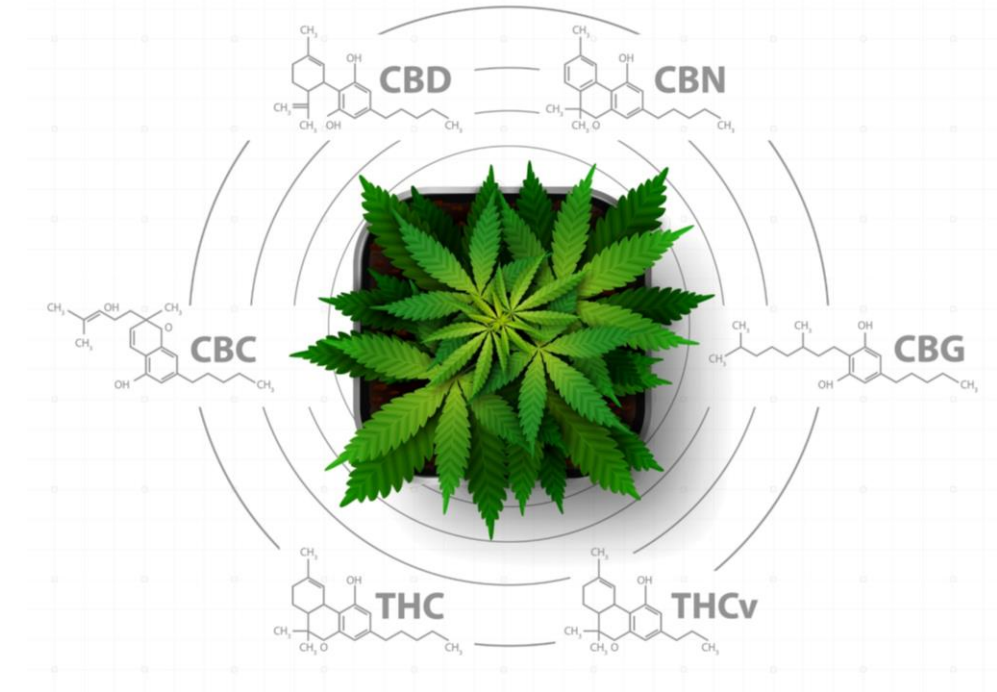
<b>Headquarters</b>	Tel Aviv-Jaffa, Israel
<b>Year Formed</b>	2019
<b>Year Public</b>	2021
<b>Ticker   Exchange</b>	RAPH   OTCQB
<b>Shares Out.</b> (3/28/24)	18.7 mm
<b>Recent Price</b> (6/14/24)	\$1.64
<b>Market Cap.</b> (6/14/24)	\$30.7 mm

## What Makes Us Different?

We are deciphering the mechanism by which cannabis is working. Far from anecdotal evidence, our research is conducted on the molecular and bio-chemical levels. Thus far, studies of cannabis have been based on statistics. We are going deeper, mapping the cannabinoid receptors and scientifically proving the therapeutic effects of cannabinoids on a variety of diseases.

# Cannabinoids Backgrounder

- The cannabis plant has a variety of strains and contains multiple naturally occurring compounds referred to as cannabinoids.
- More than 100 cannabinoids have been identified, including the two main cannabinoids:
  - psychoactive delta-9-tetrahydrocannabinol (“THC”)
  - non-psychoactive cannabidiol (“CBD”)
- Cannabinoids have demonstrated clear health benefits, and the FDA has approved several drugs that contain natural or synthetic cannabinoids, such as Epidiolex®, Marinol®, Syndros®, and Cesamet®.
- The natural, extracted oil formulations in Raphael Pharmaceutical’s product candidates are derived from unique CBD strains with low levels of THC (less than 0.3% THC) and enhanced anti-inflammatory activity.



# Investment Thesis for Raphael Pharmaceutical

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Aligned Management Team and Prominent Scientific Advisory Board



Exclusive Research Agreement with Rambam Health Care Campus



Differentiated Cannabinoid Technology Platform



Promising Lead Product Candidate for Rheumatoid Arthritis



Near-Term Catalysts for Lead Product Candidate



Large and Growing Rheumatoid Arthritis Market Opportunity



Robust Pipeline Based on Platform Technology

# Aligned Management Team



## **Shlomi Pilo, Chief Executive Officer and Chairman of the Board**

- Former Officer, Israeli Army, Intelligence Elite Platoon
- VP Sales & Marketing, Alle Processing (world's largest Glatt Kosher food manufacturer)
- Owner, global food brokering company



## **Dr. Igal Louria-Hayon, Chief Technology Officer**

- Director of Medical Cannabis Research and Innovation Center (MCRIC) at Rambam Health
- Head of Leukemia & Immunotherapy Research Lab in the Clinical Research Institute at Rambam
- Director of SPARK Haifa and Northern Israel



## **Guy Ofir, Chief Financial Officer, General Counsel and Board Member**

- Lawyer, "Guy Ofir Adv" law firm
- Founder, "Easy Energy, Inc." (a green energy company)
- Developer of real estate in Romania



## **Dr. Yehuda Eliya**

- Partner, Ziv Shifer & Co. and Owner, Dr. Yehuda Eliya Attorney & Co.
- Vice President, Chamber of Internal Auditors of Israel
- Director of various volunteer organizations in Israel

**Directors and Officers Own ~43% of RAPH's Total Shares Outstanding as of May 2024**

# Prominent Scientific Advisory Board



**Dr. Igal Louria-Hayon**

- Director of Medical Cannabis Research and Innovation Center (MCRIC) at Rambam Health
- Head of Leukemia & Immunotherapy Research Lab in the Clinical Research Institute at Rambam
- Director of SPARK Haifa and Northern Israel



**Prof. Joseph Press, MD**

- Former general director of Schneider Children's Medical Center of Israel
- Former Director of the Department of Pediatric Emergency Medicine and Chair of the Pediatrics Division at Soroka University Medical Center



**Prof. Alexandra Balbir-Gurman**

- Frontline Director of Clinical Trials and Director of the B. Shine Rheumatology Unit at Rambam
- Member of Executive Committee of Israeli Society of Rheumatology, Scleroderma Research Group (EUSTAR) and EULAR Target US initiative



**Dr. Shachar Eduardo**

- Frontline Director of Clinical Trials at Rambam
- Director of the Clinical Immunology Unit at Rambam Health Care Campus

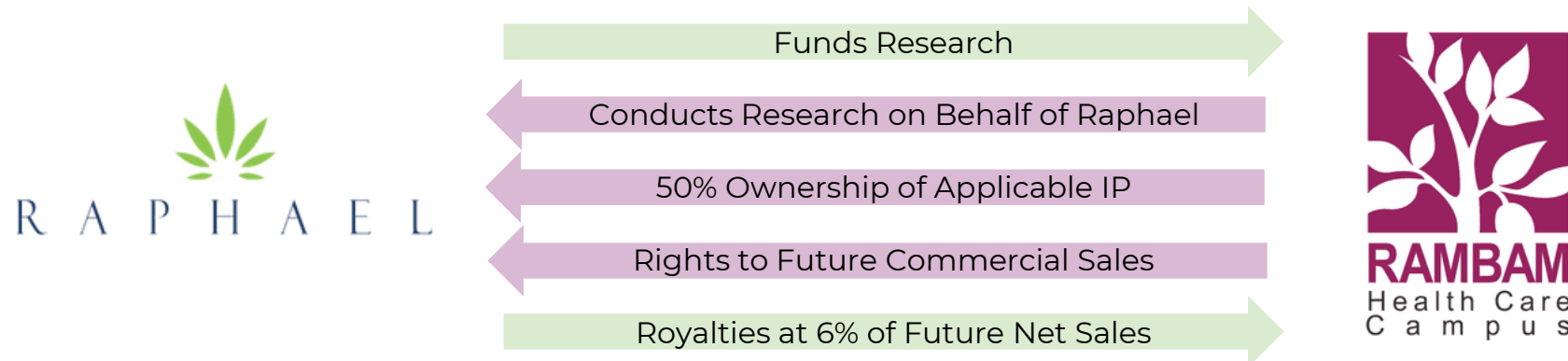
# Exclusive Research Agreement with Rambam Health Care

- **Rambam Health Care Campus**

- A premier teaching hospital and the largest medical center in northern Israel
- Groundbreaking medical innovation, research, and academia
- Home to the Medical Cannabis Research and Innovation Center (MCRIC)
  - Esteemed research team led by cannabinoid expert, Dr. Louria-Hayon, our CTO
  - Cutting-edge medical technologies, equipment, labs, facilities, and data
  - Deep understanding of cannabinoid science



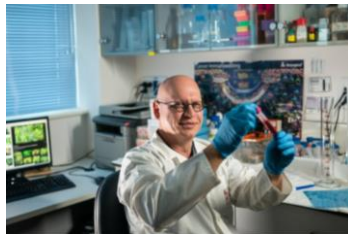
- **Exclusive Research Agreement Provides Raphael with Access to Rambam's World-Class Research Platform and Other Resources**





# Differentiated Cannabinoid Technology Platform

- **Raphael Pharma is Developing a Novel, Patentable Formulation Designed to Treat Inflammation**
  - Cannabinoids are the active pharmaceutical ingredients (“API”)
  - Our formulated oil contains a mix of non-psychoactive, purified, isolated cannabinoids derived from specific strains of low-THC cannabis
- **Uniqueness of Our Technology Platform**
  - Leverages in depth scientifically-based understanding of the mechanisms of cannabinoids activity
  - Ability to decode how cannabinoids impact the network of intercellular communications during inflammation
  - Proprietary real time-polymerase chain reaction method has identified 12 different receptors to cannabinoids in both human and mice models
  - The API in our formulation is designed to interact and communicate with the endocannabinoid system in the human body, activating cannabinoid receptors expressed by immune cells
  - Knowledge of which cannabinoid receptors participate in downregulation of inflammation in cells
  - We believe our platform technology can be applied to various chronic conditions linked to inflammation



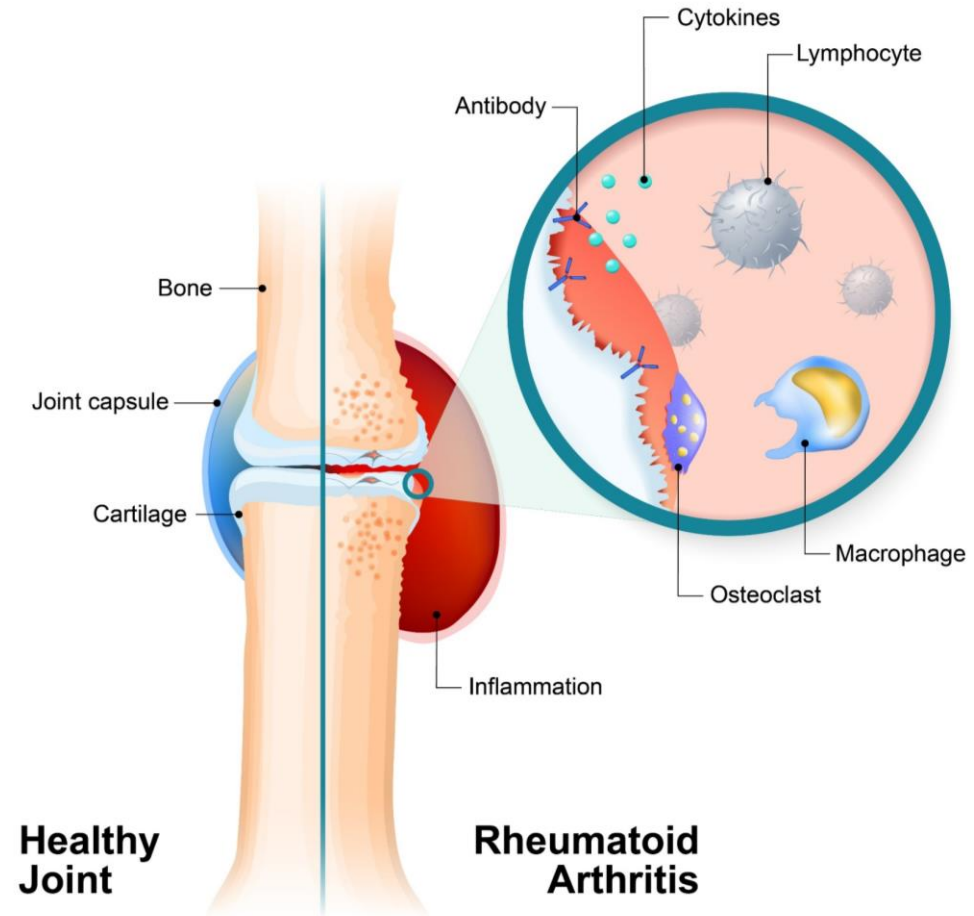
*“Intercellular communication based on cannabis-like substances also exist in the immune system. If we understand how cannabinoid components are used in intercellular communication, we can help influence this communication in the event of a disease, to disrupt it or empower the communication to convey desired messages,”*

**Dr. Igal Louria-Hayon, Chief Technology Officer**

# Promising Lead Product Candidate for Rheumatoid Arthritis

## • Rheumatoid Arthritis (“RA”)

- A chronic autoimmune disease characterized by inflammation in multiple joints
- Individuals with RA may experience:
  - acute and chronic pain
  - fatigue
  - progressive joint damage
  - disability
  - hyperplasia
  - cartilage damage
  - bone erosions
  - sleep disturbances
  - morning stiffness
  - lower quality of life



# Promising Lead Product Candidate for Rheumatoid Arthritis

- **Existing Therapies for RA**

- **DMARDs** – disease modified antirheumatic drugs; the most prevalent conventional DMARDs are methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide
- **Biologic DMARDs** – made using molecular biology and consisting of proteins; target specific molecules, cells and pathways that cause inflammation and damage tissue; examples include tumor necrosis factor (TNF) inhibitors, Interleukin-1 inhibitors, Interleukin-6 inhibitors, T-cell inhibitors, and B-cell inhibitors
- **Corticosteroids** – commonly referred to as steroids, corticosteroids are a type of anti-inflammatory drug

- **Current Treatment Options May Not Be Suitable for Everyone**



### **Efficacy**

- For ~30% of RA patients, conventional/biologic DMARDs may fail or induce only partial responses
- Sohita Dhillon study (2017) suggests that DMARD pain relief plateaus after initial improvement



### **High Costs**

- Can be in the tens of thousands of dollars per year
- List price ('23) for popular drug Humira® ~\$80,000 per year, even with the arrival of biosimilars



### **Side Effects**

- Such as gastrointestinal issues, liver damage, and increased risk of infections and cancer

# Promising Lead Product Candidate for Rheumatoid Arthritis

- **Encouraging Pre-Clinical In-Vitro Study for RA Product Candidate**

- Employed human THP1 cells, which can be induced to differentiate macrophages and to secrete cytokines
- Screened cannabis-derived oil extracts to determine influence on cytokine secretion
- Identified a non-psychoactive cannabis strain, referred to as “CBX”, which demonstrated favorable effects:

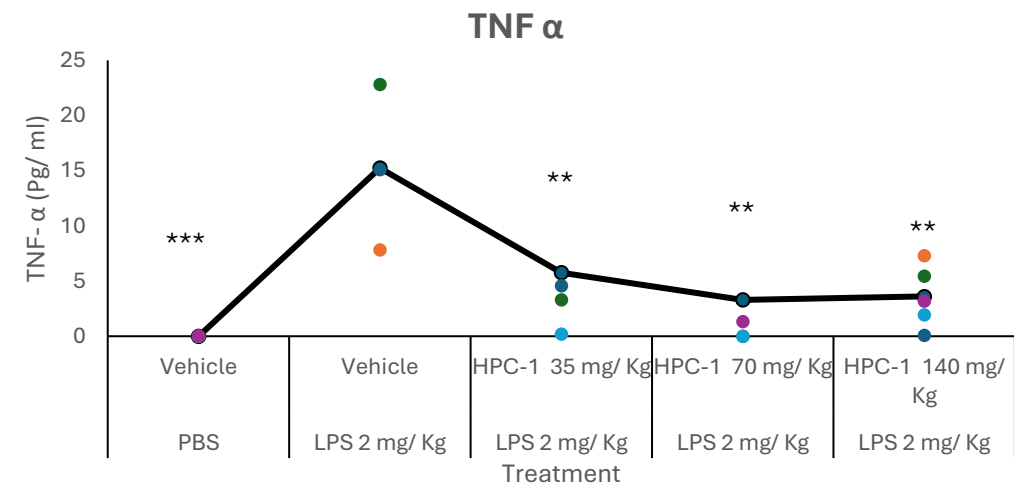
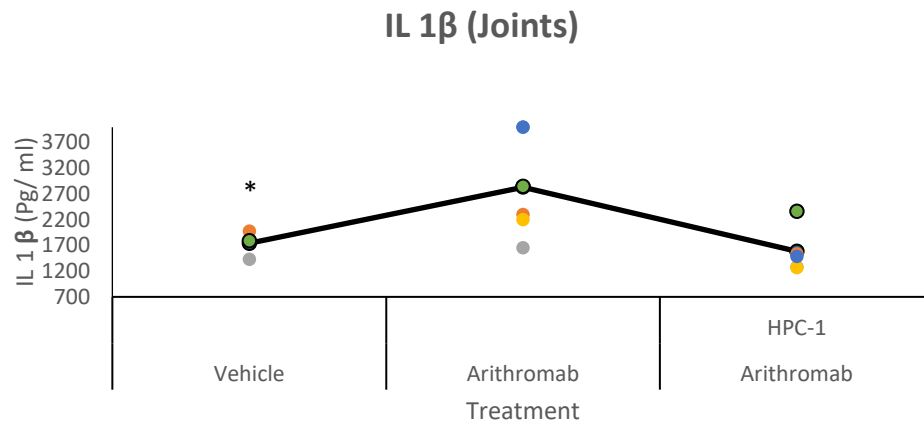
Cytokine	Typical Impact of Cytokine	CBX Influence on Cytokine
TNF Alpha (TNF $\alpha$ )	Pro-Inflammatory	↓
Interleukin 6 (IL-6)	Pro-Inflammatory	↓
Interleukin 8 (IL-8)	Pro-Inflammatory	↓
Interleukin 10 (IL-9)	Anti-Inflammatory	↑

**Based on this pre-clinical study, we believe that the CBX strain may be a potential anti-inflammatory agent with ability to influence activation and migration of cells during inflammation.**

# Promising Lead Product Candidate for Rheumatoid Arthritis

## • Highly Purified Cannabinoid (HPC1) as Treatment Option for Patients with Rheumatoid Arthritis

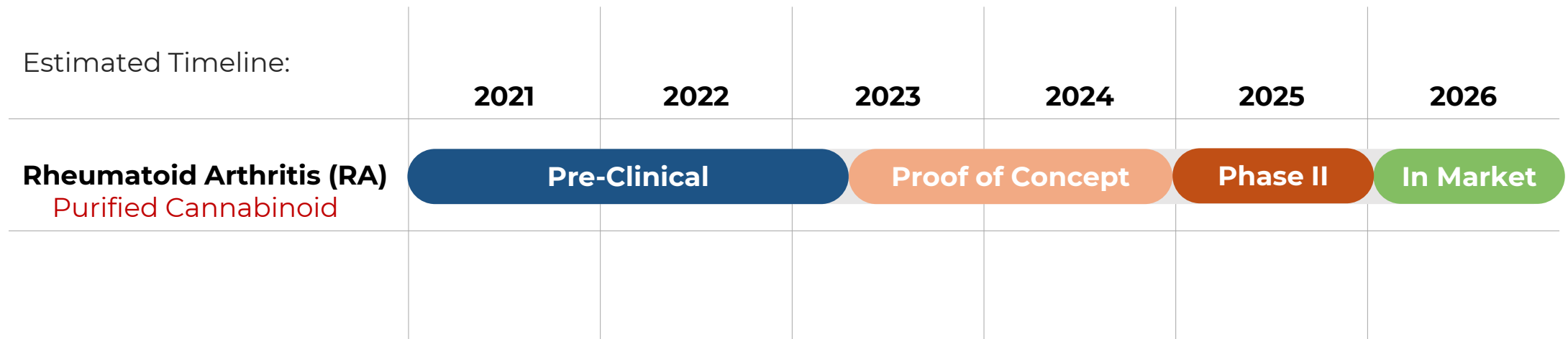
- Our preclinical experiments revealed a highly purified cannabinoid (HPC1) that effectively reduces inflammation in a **mice model** of rheumatoid arthritis
- The cannabinoid **reduced the expression levels of IL1b, TNF alpha and IL6** in the joints and peripheral blood of the sick mice
- This study suggests that HPC1 has the **potential to slow the progression of RA** by acting as an anti-inflammatory agent



# Near-Term Catalysts for Lead Product Candidate

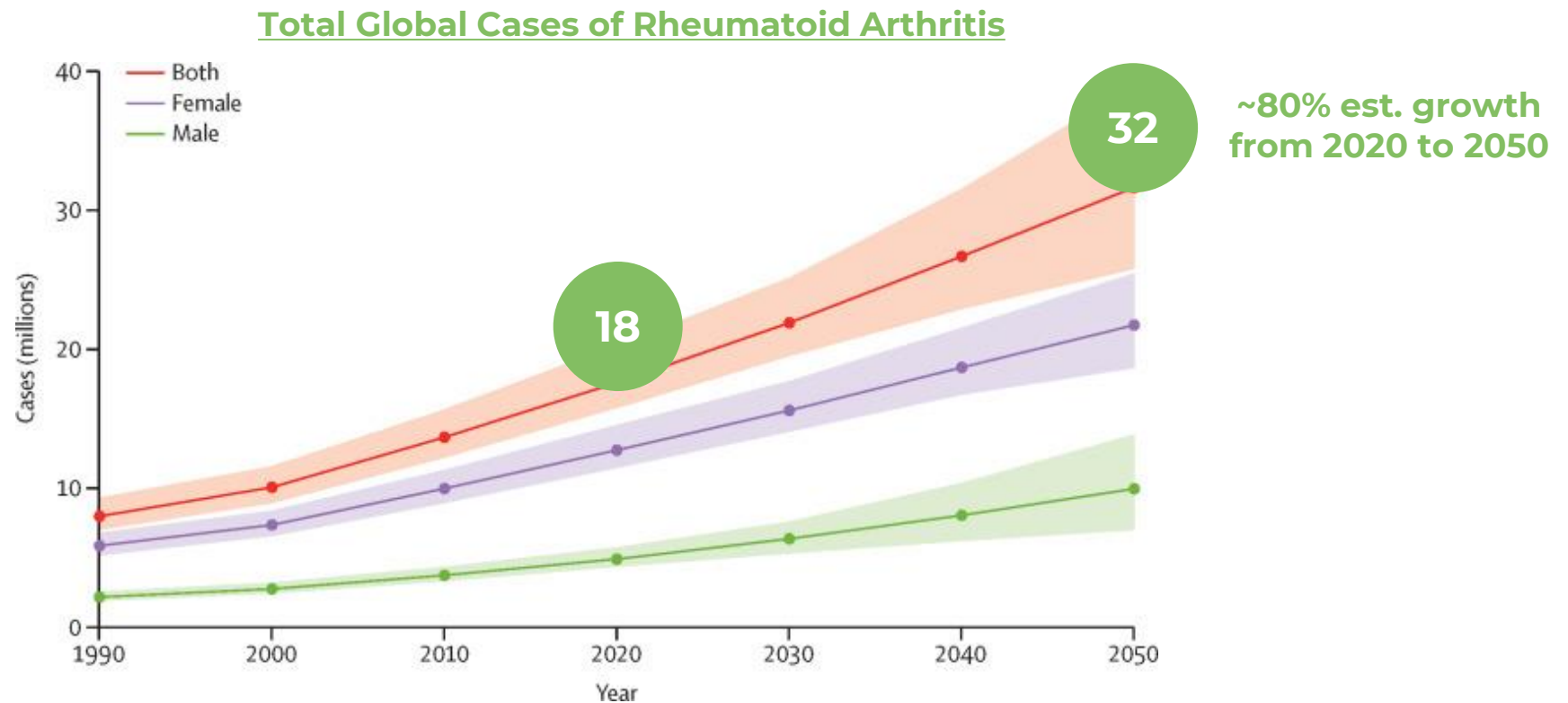
- **Proof of Concept Clinical Study Commenced**

- In March 2024, engaged Citruslabs, a contract research organization (“CRO”)
- In May 2024, commenced proof of concept clinical study in the United States
- This study aims to evaluate the efficacy of purified cannabinoid (HPC1) in patients with active RA
- Enrolled the first of 12 patients in May 2024
- If successful, we anticipate commencing Phase II in 1H 2025 and commercialization as soon as 2026



# Large and Growing Rheumatoid Arthritis Market Opportunity<sup>1</sup>

- In 2020, an estimated 18 million people had rheumatoid arthritis worldwide
- By 2050, an estimated 32 million individuals globally will have the disease

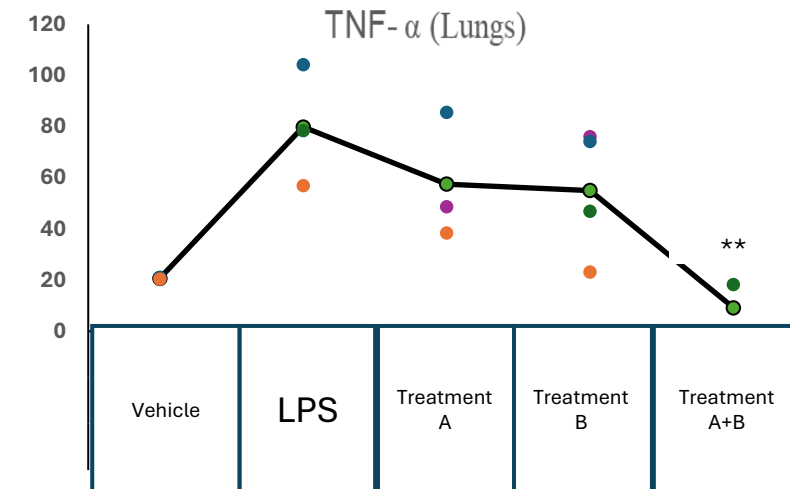
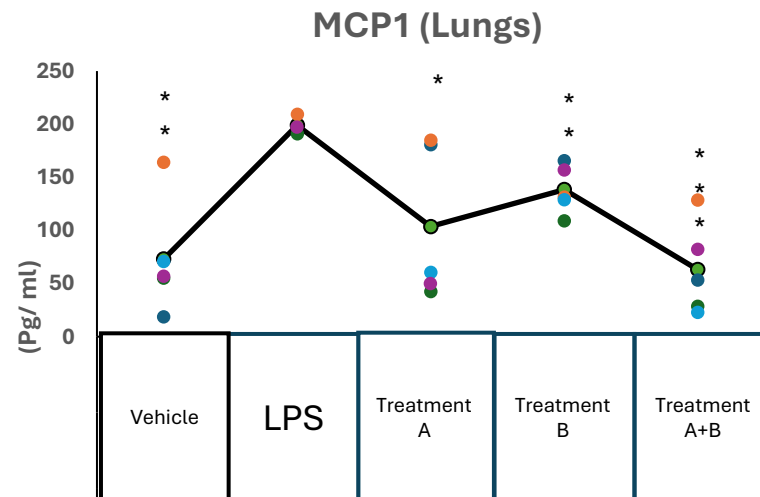
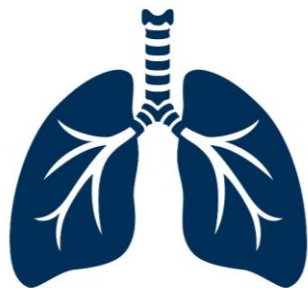


<sup>1</sup>“Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050”  
The Lancet Rheumatology, September 25, 2023

# Robust Pipeline Based on Platform Technology

## Our Research has Demonstrated the Potential of Cannabinoid-Based Treatment for Lung Inflammation

- **Human and Mouse Model Study** - using cells derived from human donors and a mouse model for systemic inflammation and severe lung inflammation, we have found that a specific high-CBD strain (CBX) is effective in preventing cytokine storms (reduces the secretion of IL6 and TNF alpha as well as the inflammation in the mice lungs); also inhibits the migration of immune cells to the lungs
- Our findings were published in [\*Frontiers in Immunology\*<sup>1</sup>](#) in May 2022
- We are developing a novel molecule-based formula as a treatment for patients with autoimmune disease and chronic lung inflammation. The combination of molecules A and B exhibits a **synergistic effect**, leading to a reduction in cytokine secretion in the lungs of a mouse model for lung inflammation:



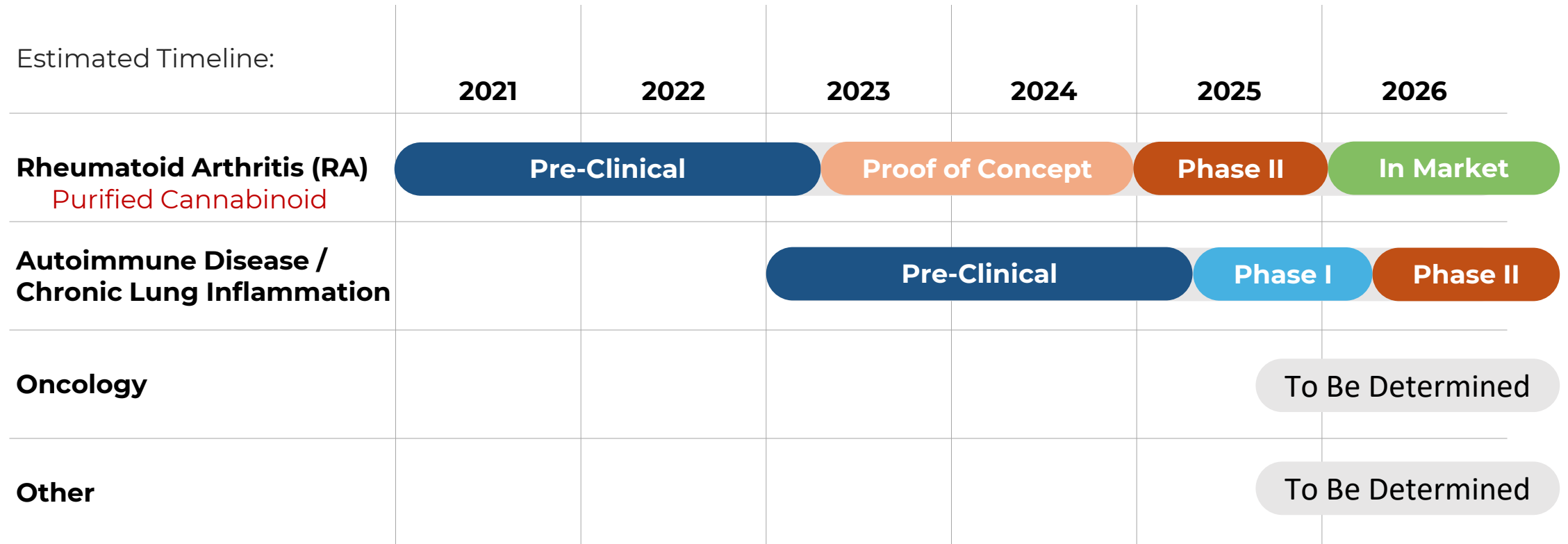
<sup>1</sup>“High-CBD Extract (CBD-X) Downregulates Cytokine Storm Systemically and Locally in Inflamed Lungs,”  
*Frontiers in Immunology*, May 16, 2022



# Robust Pipeline Based on Platform Technology

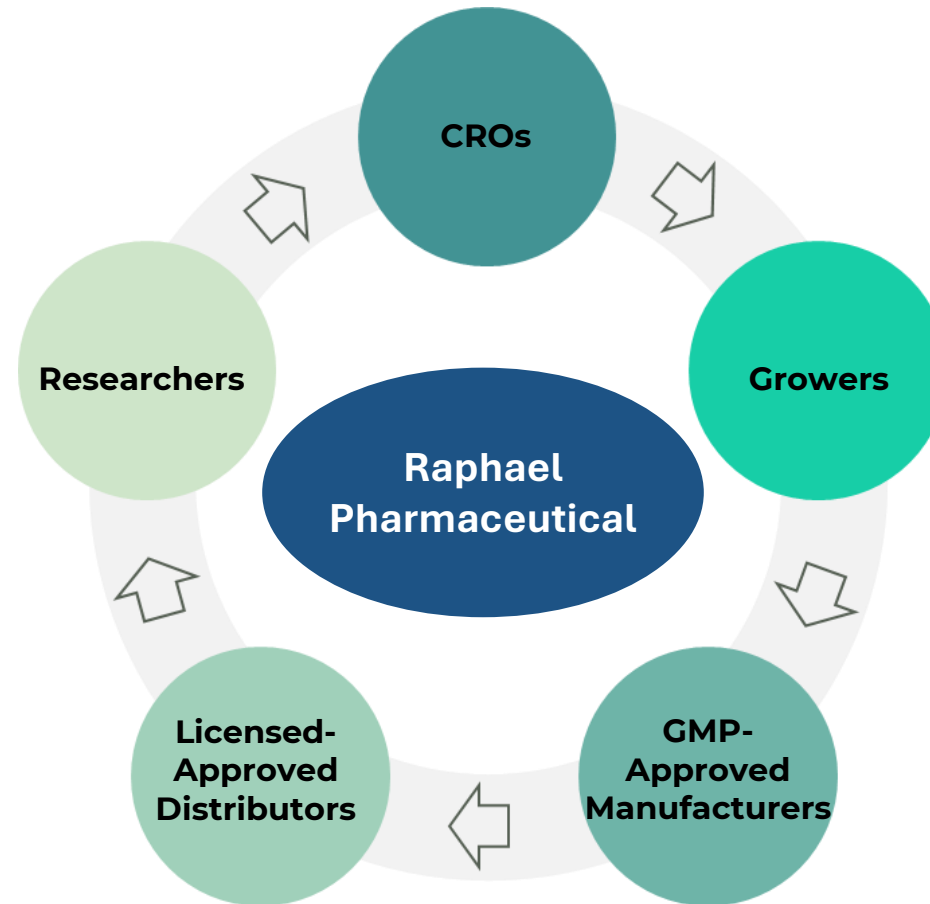
- **Progression of Current R&D pipeline (U.S.)**

- RA – lead product candidate; in-human proof of concept underway
- Autoimmune Diseases / Lung Inflammation – mouse model study complete; pre-clinical commenced
- Oncology – for cancer treatment effects like cachexia, fatigue, anemia, pain and depression (palliative)
- Other – to be determined



# Asset Light, Low-Capex Business Model

Our approach contemplates **royalty-based agreements** and **outsourcing** with the following types of third parties:



# Value-Creation Opportunity

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- Modest investment for potentially ground-breaking technology with vast and growing market
- Significant valuation multiplier in case of successful clinical trials
- Pursuing collaboration with larger companies, which may add to valuation and provide exit points for investors
- Potential to sell medical formulas and patents at Phase 2 to large pharmaceutical, medical cannabis, or other global companies
- Revenue and income based on royalties paid to Raphael Pharma for use of patented, FDA phase 2 approved cannabis-based medical indications
- In addition to initial U.S. regulatory pathway via the FDA, opportunity to pursue Europe via the European Medicines Agency (“EMA”), followed by a roll out to the rest of the world

## Investor Contact:

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