ARCTURUS® therapeutics


# Next Generation RNA Medicines

August 2024

# Forward Looking Statements

This presentation contains forward-looking statements. These statements relate to future events and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future performances or achievements expressed or implied by the forward-looking statements. Each of these statements is based only on current information, assumptions and expectations that are inherently subject to change and involve a number of risks and uncertainties. Forward-looking statements include, but are not limited to, statements about: our strategy, future operations, collaborations, the likelihood of success (including safety and efficacy) and promise of our pipeline, the timing for selection of lead candidates, the development, manufacture or commercialization of our pipeline and partnered pipeline assets, the likelihood of success of, and achievement of revenues from, our partnered programs, the planned initiation, design or completion of clinical trials the likelihood that we will obtain clearance from regulatory authorities to proceed with planned clinical trials, the ability to enroll subjects in clinical trials, the timing for receipt of data, the likelihood that preclinical or clinical data will be predictive of future clinical results, the likelihood that clinical data will be sufficient for regulatory approval or completed in time to submit an application for regulatory approval within a particular timeframe, the anticipated timing for regulatory submissions, the timing of, and expectations for, any results of any preclinical or clinical studies or regulatory approvals, the potential administration regimen or dosage, or ability to administer multiple doses of, any of our drug candidates, our manufacturing methods and technologies (including purification, lyophilization and stability of our products), the likelihood that a patent will issue from any patent application, our current cash position and adequacy of our capital to support future operations, and any statements other than statements of historical fact.

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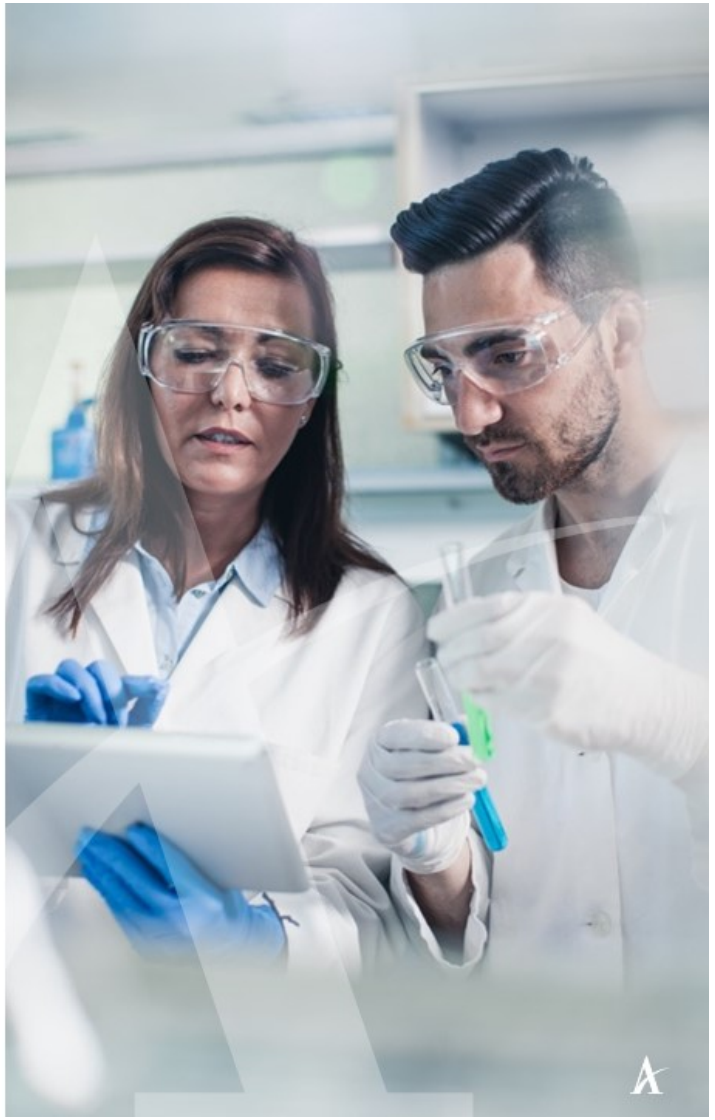
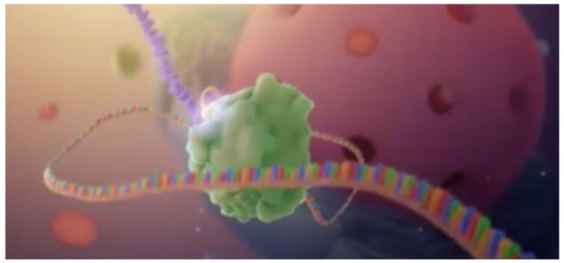


# Arcturus Therapeutics



Global mRNA Medicines Company

Nasdaq: ARCT

**Headquarters:** San Diego, CA

**Founded:** 2013

mRNA Medicine Candidates

**LUNAR-OTC** *Ornithine Transcarbamylase Deficiency*

**LUNAR-CF** *Cystic Fibrosis*

Additional Earlier Stage Programs

## Strategic Partners

CSL

CYSTIC FIBROSIS FOUNDATION

BARDA

# Proprietary mRNA Technologies Driving Therapeutic Programs

## Broad Intellectual Property Portfolio

### mRNA Technology

mRNA for protein replacement

Self-amplifying mRNA (STARR®) low-dose vaccine technology

### LUNAR® Delivery

Hepatocytes – *intravenous*

Myocytes – *intramuscular*

Bronchial Cells – *inhaled*

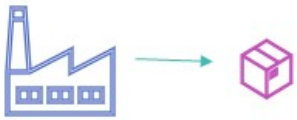
### Manufacturing Know-How

mRNA Drug Substance Production

mRNA Purification

LNP Drug Product Production

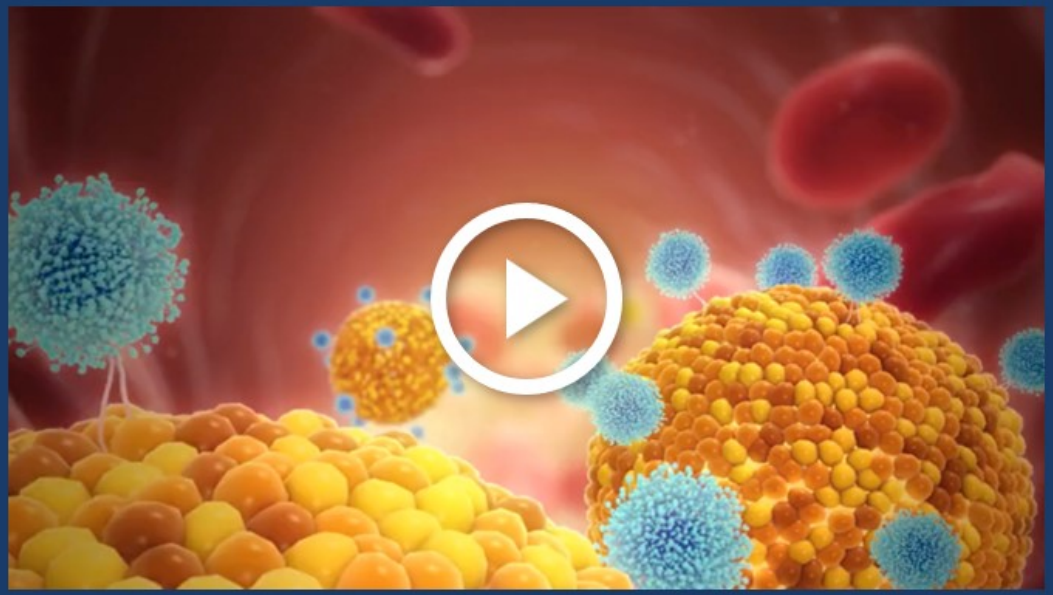
Fill Finish / Lyophilization



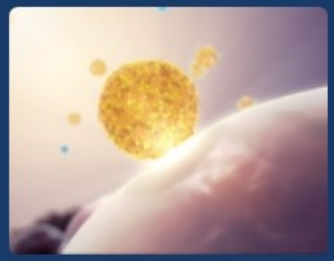
400+ Patents & Patent Applications

# LUNAR® - Lipid Nanoparticle (LNP) Delivery Technology

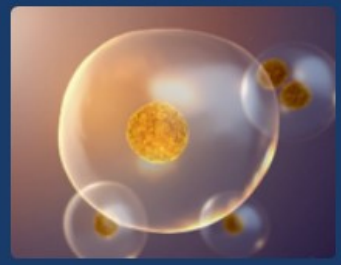
## Proprietary, Biodegradable, Optimized for Each Cell Type



LUNAR® interacts with cell membrane

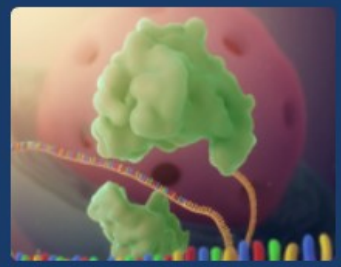


LUNAR® internalized inside endosome



mRNA release

mRNA translated into protein of interest



# Pipeline of Arcturus-Owned mRNA Therapeutic Candidates

| Franchise | Candidate | Funded By | Indication | Global Prevalence | Upcoming Milestone |
|---|---|---|---|---|---|
| **Hepatic** | LUNAR-OTC (ARCT-810) | ARCTURUS therapeutics | Ornithine Transcarbamylase Deficiency (OTC) | > 10,000 | Phase 2 Interim Data Q4 2024 |
| **Respiratory** | LUNAR-CF (ARCT-032) | CYSTIC FIBROSIS FOUNDATION | Cystic Fibrosis | 85,000-100,000 | Phase 2 Initiation H2 2024 |

Each Arcturus-Owned Program Represents a Significant Commercial Opportunity

# Pipeline of Partnered Self-amplifying mRNA Vaccines

| Candidate | Partner | Indication | Stage |
|---|---|---|---|
| **Kostaive®**<br>(ARCT-154)<br>Monovalent: Ancestral | CSL | COVID-19 | Approved (JP)<br>MAA Filed (EU) |
| **Kostaive® Bivalent**<br>(ARCT-2301)<br>Ancestral / Omicron BA.4/5 | CSL | COVID-19 | Phase 3 |
| **Kostaive® XBB.1.5**<br>(ARCT-2303)<br>Monovalent: XBB.1.5 | CSL | COVID-19 | Phase 3 |
| **LUNAR®-FLU**<br>(ARCT-2138)<br>Quadrivalent | CSL | Seasonal Influenza | Phase 1 |
| **LUNAR®-FLU**<br>(ARCT-2304)<br>Pandemic | BARDA | Pandemic Influenza | Pre-clinical |

Greater than $5 Billion in Potential Milestones & Profit Sharing / Royalties

# CSL: Arcturus Therapeutics Global Vaccine Partner

CSL

- $13.3 Billion USD Annual Revenue
- Operating in 40+ Countries Worldwide
- 32,000+ Employees Worldwide
- 13 Phase III programs – including Kostaive®
- Focused on four strategic technology platforms – plasma protein; recombinant technology; cell and gene therapy; and vaccines
- Therapeutic areas of focus of immunology, hematology, respiratory, cardiovascular, transplant, nephrology and vaccines

CSL Seqirus

**A World Leader in Flu Vaccines**

- $2.03 Billion USD Annual Revenue

CSL Seqirus is one of the Three Core Businesses of CSL

CSL Annual Report 2023, CSL Capital Markets Day 16, October 2023

# CSL Vaccine Partnership

## Up to $4.3 billion in Milestone Payments

- Collaboration combines CSL's global vaccine commercial and manufacturing infrastructure with Arcturus' expertise in mRNA design and modification, LUNAR® lipid nanoparticle (LNP) technology and manufacturing know-how.
- Deal terms encompass the development, manufacture, and commercialization of mRNA-based vaccines targeting COVID-19, Influenza and three additional respiratory infectious disease vaccines.

### Partnership Terms

| CSL | ARCTURUS therapeutics |
|---|---|
| **$200** million | Upfront Payment |
| **$1.3** billion | Development Milestones |
| **$3.0** billion | Commercial Milestones |

**40% profit sharing** for COVID-19 vaccines (defined as 40% of gross profits, less 40% of development costs)

Up to **double digit royalties** for influenza and three additional respiratory infectious disease vaccines

# Meiji: Background Information

**The Meiji Group provides food and pharmaceuticals indispensable to their customers**

- $7.9 Billion USD Net Sales (As of March 31, 2023)
- 113 Locations Worldwide with 17,290 Employees

**Meiji Seika Pharma provides antibacterial drugs, vaccines, central nervous system drugs, and generic drugs**

- $1.4 Billion USD Net Sales (As of March 31, 2023)
- Received rights in Q4 2022 to conduct Kostaive® clinical study in Japan
- Granted significant subsidy from Japanese government in Q4 2022
- Entered into agreement with CSL Seqirus in April 2023, responsible for obtaining regulatory approval, distribution, sales and marketing Kostaive® of in Japan

Meiji Seika Pharma, a Subsidiary of Meiji Holdings Co. Ltd., Funded and Conducted the Kostaive® Phase 3 Comparator Booster Study and Obtained Regulatory Approval in Japan

Meiji Holdings Co., Ltd., IR Team, Corporate Communications Dept. Data Book, Fiscal Year 2022, May 11, 2023
Meiji Holdings Co., Ltd., IR Team, Corporate Communications Dept. Data Book, H1 of FYE March 2024, November 9, 2023

# ARCALIS: Arcturus' Joint Venture mRNA Manufacturing Partner

**ARCALIS is a CDMO Specializing in Manufacturing of mRNA Vaccines and Therapeutics**

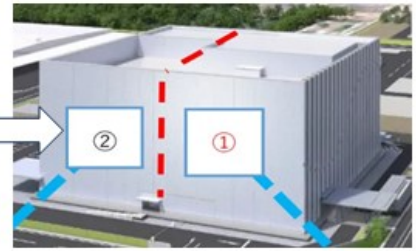
- Joint Venture Founded in 2021
- Major Equity Owners: Axcelead & Arcturus, subject to dilution
- Meiji Seika Pharma is collaborating with ARCALIS for domestic mRNA vaccine production

**ARCALIS' cGMP mRNA Drug Substance Manufacturing Plant**

- Completed July 2023; Located in Minamisoma City, Japan
- Capacity: Up to 5 kg in bulk mRNA drug substance per year
- 78,059 sq ft (7,252 sq m) floor space

**ARCALIS' cGMP mRNA Drug Product Manufacturing Expansion**

- Capacity: 30 L (3 Lines); building to 100 L (2 Lines)




ARCALIS Awarded with $165 Million in Grants from the Japanese Government

# Kostaive® Phase 3 Clinical Studies

**Kostaive® (Monovalent, Kostaive®)**

**Phase 3 Non-inferiority safety and immunogenicity trial**

- Kostaive® administered at an 83.3% lower dose than Comirnaty® (N = 828)
- 50% of participants received Kostaive® (5 mcg); 50% of participants received Comirnaty® (30 mcg)
- Conducted in Japan

**Achieved Primary Endpoint** of non-inferiority of neutralizing antibody response against SARS-CoV-2 Ancestral strain compared to Comirnaty®
**Achieved Secondary Endpoint** of superiority of Kostaive® in neutralizing antibody response against SARS-CoV-2 Omicron BA.4/5 variant; increased immunogenicity associated with Kostaive® versus Comirnaty® at Day 29, with a geometric mean ratio of neutralizing antibodies against the vaccine strain of 1.43
**Generally safe and well tolerated**
**Phase 3 Study published** in *The Lancet Infectious Diseases*[1]

THE LANCET Infectious Diseases

**Kostaive® (Bivalent, ARCT-2301)**

**Bivalent Kostaive®** (ARCT-2301: ancestral D614G and Omicron BA.4-5)

- Results consistent with monovalent Kostaive®
- Phase 3 clinical booster vaccination study was also conducted in Japan

**Bivalent Kostaive®** was assessed in comparison with bivalent conventional mRNA vaccine (Comirnaty®):

- Day 29 superiority of neutralizing antibody response against SARS-CoV-2 Ancestral strain was established
- Day 29 superiority of neutralizing antibody response against SARS-CoV-2 Omicron BA.4/5 subvariant was established
- Day 29 neutralizing immune response against SARS-CoV-2 Omicron XBB.1.5 subvariant was higher compared to Comirnaty

**Kostaive® Received Approval Nov 2023 from Japan's Ministry of Health, Labor and Welfare (MHLW)**

[1]Yoshiaki Oda, Yuji Kumagai, Manabu Kanai, Yasuhiro Iwama, Iori Okura, Takeshi Minamida, Yukihiro Yagi, Toru Kurosawa, Benjamin Greener, Ye Zhang, Judd L Walson. Immunogenicity and safety of a booster dose of a self-amplifying RNA COVID-19 vaccine Kostaive® versus BNT162b2 mRNA COVID-19 vaccine: a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial, *The Lancet Infectious Diseases*, 2023, https://doi.org/10.1016/S1473-3099(23)00650-3.

# Historic Approval of World's First sa-mRNA Product

## CSL-Arcturus Collaboration Results in Groundbreaking Approval of Kostaive®

### First Arcturus Approval

Kostaive® self-amplifying mRNA COVID vaccine was **approved in Japan by the MHLW in November 2023**

The STARR® vaccine was created, optimized, clinically developed and approved in under 4 years

MHLW
Ministry of Health, Labour and Welfare of Japan

### Enduring Vaccine with Strong Clinical Data

**Approval based on positive clinical data from several Kostaive® studies**

- 18,000+ subjects have received sa-mRNA COVID vaccines

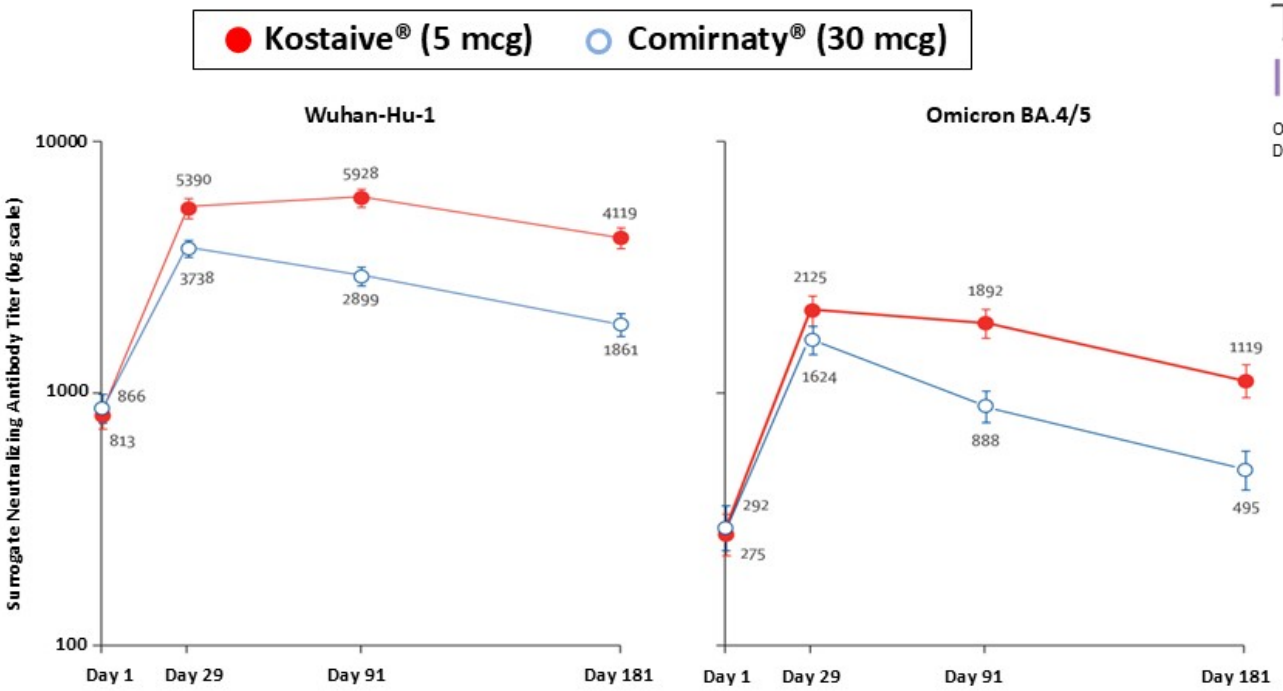
Partner **Meiji Seika Pharma** advanced the MHLW approval and is the exclusive distributor of Kostaive® in Japan

CSL ARCTURUS therapeutics meiji Meiji Seika Pharma

Unprecedented approval paves the way for additional sa-mRNA vaccines

# Kostaive®: More Durable Post-boost Immune Response

## Phase 3 Persistence Data Comparing Kostaive® (5 mcg) to Comirnaty® (30 mcg)




THE LANCET Infectious Diseases

Oda Y et al. Lancet Infect Diseases; February 1, 2024
DOI: (10.1016/S1473-3099 mcg(mcg 24)00060-4)

Comimaty® is the brand name of BNT162b2

Kostaive® sa-mRNA Booster Shows Higher Durability of Immune Response Compared to Approved mRNA Vaccine

# ARCT-032

## Inhaled mRNA Therapeutic Candidate for Cystic Fibrosis

# Cystic Fibrosis

## ARCT-032 Market Opportunity

### Cystic Fibrosis

85,000-100,000 worldwide prevalence

Caused by mutations in the CFTR gene, resulting in poor chloride transport and dehydrated, sticky mucus in the airways

Chronic airway obstruction leads to infection and inflammation, which causes progressive airway damage and ultimately, respiratory failure

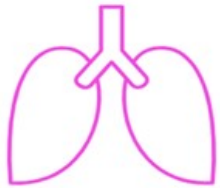
### Unmet Medical Need

Highly effective CFTR modulators are not approved for treatment of all people with CF and may not be tolerated in others

Standard of care therapies do not prevent the chronic, progressive loss of lung function that ultimately requires lung transplantation or leads to early death

8% of CF patients have genotypes making them ineligible for modulators[1]

Additional 10% of CF patients are eligible but not prescribed modulators[1]



### LUNAR-CF Aims to Restore CFTR Function

An mRNA replacement therapy has the potential to produce wild-type CFTR into the lungs of CF patients, independent of genotype

Functional CFTR protein can restore chloride efflux in the airways, reducing mucus accumulation and airway damage and minimizing the progressive respiratory impairment observed in people with CF

[1]Cystic Fibrosis Foundation. (2024). 2023 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS. In https://www.cff.org/medical-professionals/patient-registry.

# ARCT-032 Clinical Update

**Phase 1 Study in Healthy Volunteers (New Zealand)**

- Objectives: Assess safety, tolerability and PK of ARCT-032 in healthy adults
- Status: Completed dosing across 4 ascending single-dose cohorts (8 subject per cohort)
- Total number of subjects N = 32
- Safety and tolerability data supported transition to Phase 1b study

**Phase 1b Study in Adults with Cystic Fibrosis (NZ)**

- Objectives: Assess safety, tolerability and PK of ARCT-032 in adults with CF
- Status: Completed enrollment and dosing of 7 adults with CF
- Safety and tolerability data support transition to Phase 2 study

**Phase 2 Study**

- Submitted IND application for multiple ascending dose study to determine safety, tolerability and efficacy

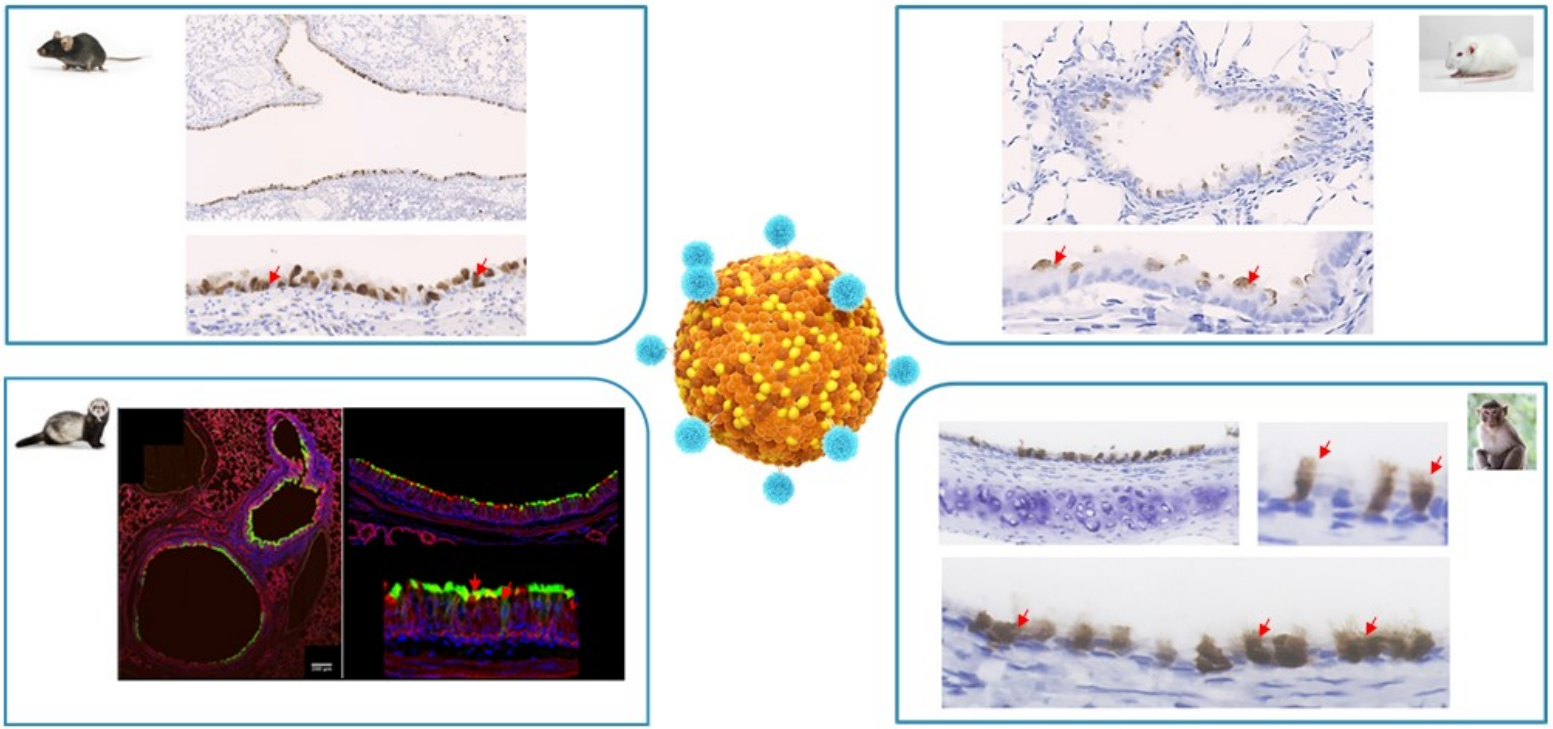
**The Cystic Fibrosis Foundation has committed ~$25 Million to advance ARCT-032**

**ARCT-032 received Rare Pediatric Disease Designation and Orphan Drug Designation from the U.S. FDA and Orphan Medicinal Product Designation from the European Commission (EC)**

IND Application Submitted July 2024; Phase 2 Study Initiation Expected H2 2024

# LUNAR®-mRNA in Healthy Animals (four different species)

## Successful delivery to airway epithelium; transduction demonstrated by Brown and Green staining

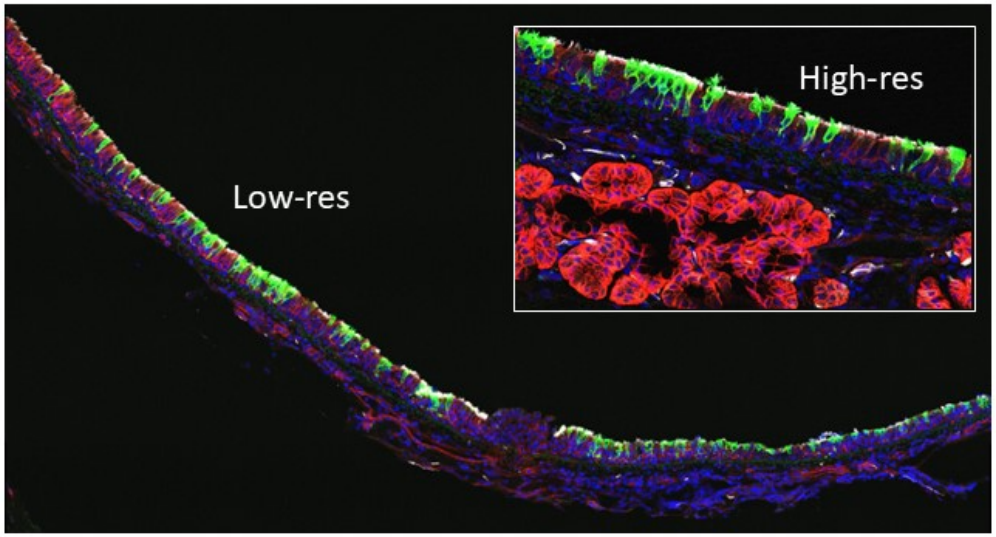


LUNAR® Delivery to Airway Epithelium is Demonstrated in Rodent and Non-Rodent Species

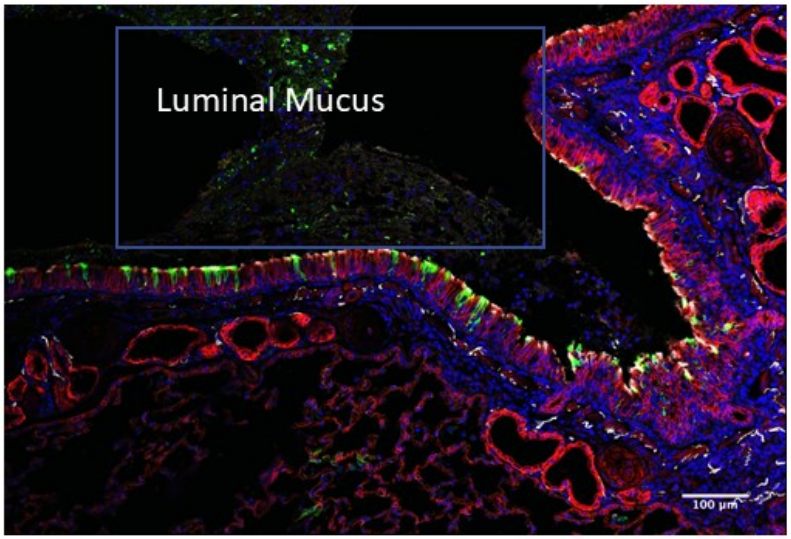
# LUNAR®-mRNA in Cystic Fibrosis Ferret Model

## Successfully Transduces Epithelium in the Presence of CF Mucus

**Trachea**




**Bronchus**



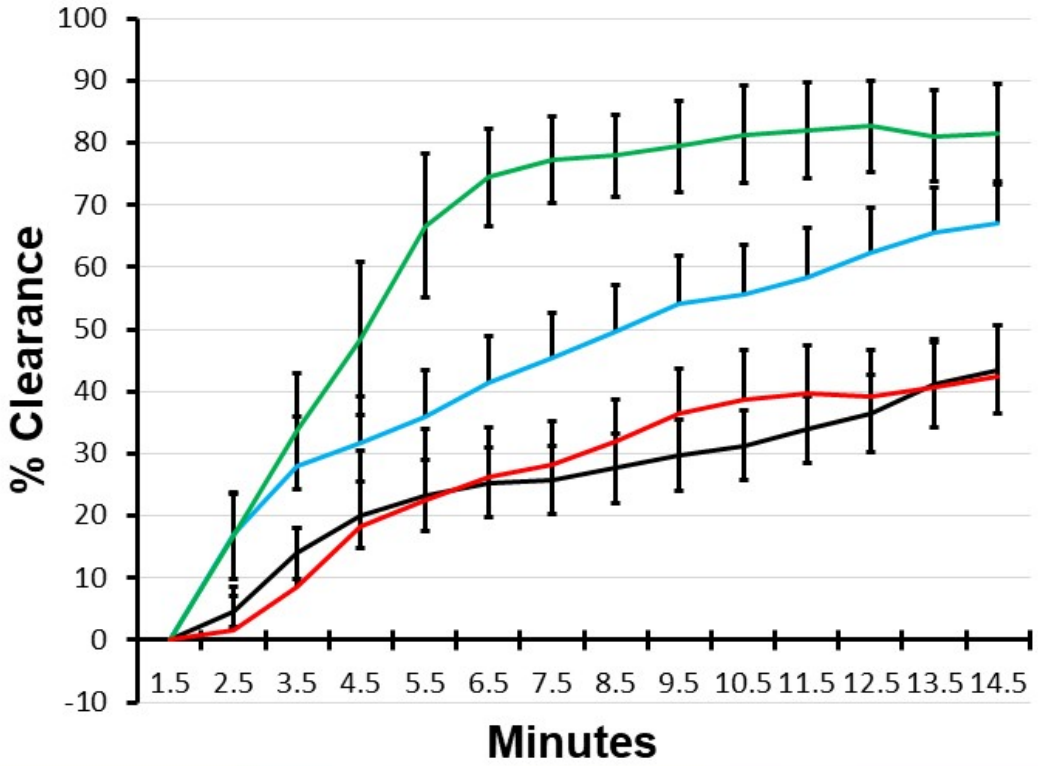

**Green denotes functional expression of protein (Cre)**

In collaboration with Univ. of Iowa; presented at North American CF Conference Nov 2023

LUNAR® Effectively Delivers mRNA Expressing Cre in a Ferret CF Model (G551D)

# ARCT-032 in a Kalydeco®-responsive CF Ferret Model (G551D)

## Proof of Activity: Mucociliary clearance improves after single administration of ARCT-032



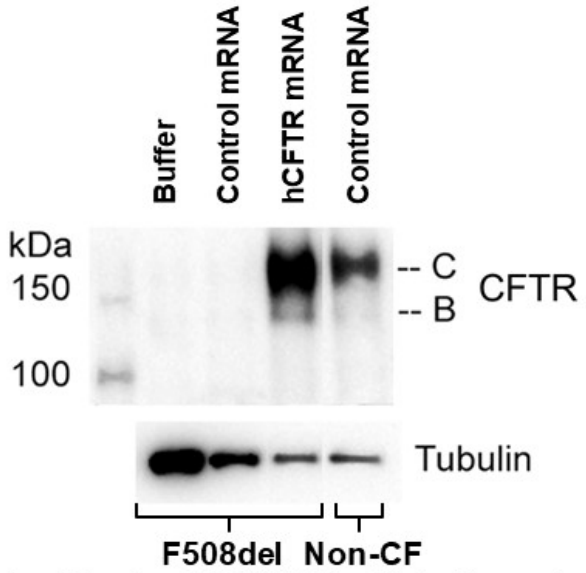

**ARCT-032 (LUNAR®-CF)**
Kalydeco® (Positive Control)
LUNAR-TdTomato (Negative Control)
Off Kalydeco® (Baseline)

In collaboration with Univ. of Iowa; presented at North American CF Conference Nov 2023

ARCT-032 Functionally Restores Mucociliary Clearance to Normal Levels in CF Ferrets

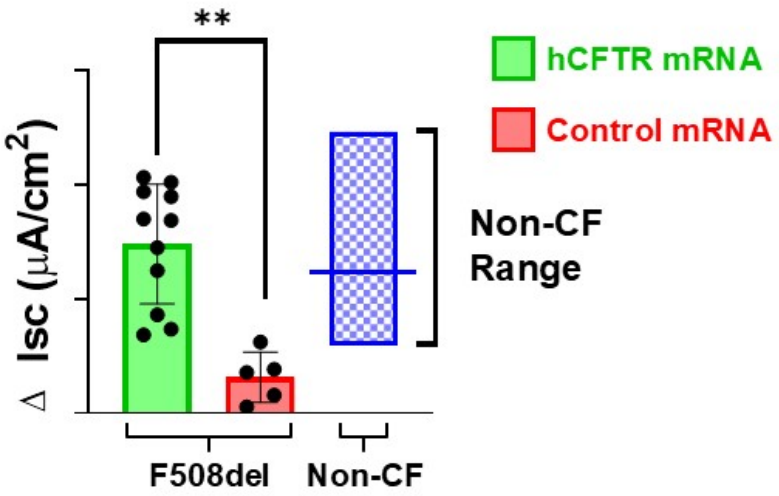
# ARCT-032 Restores CFTR Expression & Function

High Expression Levels of CFTR protein




In collaboration with UAB CFRC and Javier Campos-Gomez

Restored chloride activity (chloride gradient)




**P<0.01; Data from two F508del donors; Using chamber studies performed with chloride secretory gradient

In collaboration with Univ. of Alabama-Birmingham; presented at North American CF Conference Nov 2022

Restoration of CFTR Expression and Function in CF Human Bronchial Epithelial Cells

# ARCT-810

## Systemically Delivered mRNA for Ornithine Transcarbamylase (OTC) Deficiency

# Ornithine Transcarbamylase (OTC) Deficiency

## ARCT-810 Market Opportunity

### The most common urea cycle disorder

The urea cycle converts neurotoxic ammonia to water-soluble urea that can be excreted in urine

Deficiency in OTC causes elevated blood ammonia, which can lead to neurological damage, coma, and death

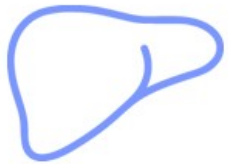
10,000 worldwide prevalence

### Unmet Medical Need

Present standard of care involves a strict diet (low protein, high fluid intake) plus ammonia scavengers (e.g. glycerol phenylbutyrate)

Present standard of care does not effectively prevent life-threatening spikes of ammonia

Severe OTC Deficiency patients are referred for liver transplant, currently the only cure



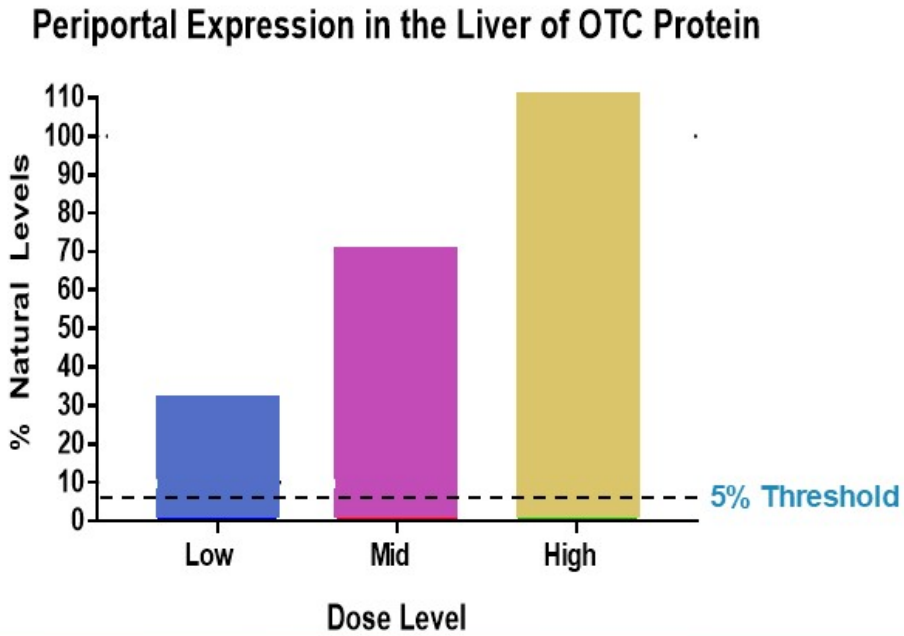
### LUNAR-OTC Aims to Restore Enzyme Function

Establishing expression of OTC enzyme in liver has potential to restore urea cycle activity to detoxify ammonia, preventing neurological damage and potentially removing need for liver transplantation

# LUNAR-OTC

## Exceeds Target of 5% Enzyme Replacement in OTC-Deficient Mouse Model

- OTC deficiency impacts ureagenesis (ammonia detoxification)
- The main site of ureagenesis is the **periportal** region of the liver*
- The critical threshold of **5%** residual enzymatic OTC activity helps avoid severe manifestations of the disease (neonatal coma, mortality)*




LUNAR-OTC Treatment Increases OTC Expression in Mouse Periportal Hepatocytes (Main Site of Ureagenesis)

*Li, L. et al. PGC-1α Promotes Ureagenesis in Mouse Periportal Hepatocytes through SIRT3 and SIRT5 in Response to Glucagon. Scientific Reports. 6:24156 | DOI: 10.1038/srep24156, April 2016
*Lamers, W.H., Hakvoort, T.B.M., and Köhler, E.S. 'Molecular Pathology of Liver Diseases' in Monga S.P.S. (ed.), MOLECULAR PATHOLOGY LIBRARY SERIES, Springer Publishing, NewYork, pp. 125-132 | DOI: 10.1007/978-1-4419-7107-4
*Scharre, Svenja. *"In vitro* enzyme activity predicts phenotypic severity in male individuals with ornithine transcarbamylase deficiency." SSIEM Annual Symposium 2022, Freiburg, Germany. 30 August – 2 September 2022. Poster Presentation.

# ARCT-810 Clinical Update

**Phase 1 (NZ) Study in Healthy Volunteers**

- Completed dosing up to 0.4 mg/kg, total number of subjects N = 24, generally safe and well tolerated

**Phase 1b (U.S.) Single Ascending Dose (SAD) Study in OTCD Adults**

- Completed enrollment and dosing of all cohorts (N=16)
- Dose cohorts were 0.2, 0.3, 0.4 and 0.5 mg/kg; no serious or severe adverse events

**Phase 2 (UK and EU) Single and Multiple Ascending Dose, Placebo-controlled Study in OTCD Adolescents & Adults**

- Completed enrollment of 8 subjects at the 0.3 mg/kg dose level
- Up to 6 bi-weekly doses for each participant with the following endpoints
  - Primary Endpoints: Safety and tolerability
  - Secondary Endpoints: PK and PD (ureagenesis assay, plasma ammonia: 24-hr profile and peak level)
  - Exploratory Endpoints: Plasma amino acids and OTC enzyme activity; urine orotic acid

**Phase 2 Expansion (U.S.)**

- Enrolling patients with more severe disease; screening initiated

**ARCT-810 received Orphan Drug Designation, Fast Track Designation & Rare Pediatric Disease Designation from the U.S. FDA and Orphan Medicinal Product Designation from the European Commission (EC)**

Interim Phase 2 Data Expected Q4 2024

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