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Leukocyte Interleukin, Injection For Head And Neck Cancer

## **Multikine™ Pre-Surgical Cancer Therapy**

## **Forward Looking Statements**

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. You can generally identify these forward-looking statements by forwardlooking words such as "anticipates," "believes," "future," "could." "expects," "intends," "estimates," "plans," "would." "should." "potential," "continues" and similar words or expressions (as well as other words or expressions referencing future events. conditions or circumstances). These forwardlooking statements involve risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements, including, but not limited to: the progress and timing of, and the amount of expenses associated with, our research, development and commercialization activities for our product candidates, including Multikine; the success of our clinical studies for our product candidates; our ability to obtain U.S. and foreign regulatory approval for our product candidates and the ability of our product candidates to meet existing or future regulatory standards; our

expectations regarding federal, state and foreign regulatory requirements; the therapeutic benefits and effectiveness of our product candidates; the safety profile and related adverse events of our product candidates; our ability to manufacture sufficient amounts of Multikine or our other product candidates for use in our clinical studies or, if approved, for commercialization activities following such regulatory approvals; our plans with respect to collaborations and licenses related to the development, manufacture or sale of our product candidates; our expectations as to future financial performance, expense levels and liquidity sources; our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates; anticipated trends and challenges in our potential markets; and our ability to attract, retain and motivate key personnel.

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Multikine is the trademark that CEL-SCI has registered for this investigational therapy, and this proprietary name is subject to FDA review in connection with CEL-SCI's future anticipated regulatory submission for approval. Multikine has not been licensed or approved for sale, barter or exchange by the FDA or any other regulatory agency. Similarly, its safety or efficacy has not been established for any use. Each page of this presentation must be looked at in the context of the whole presentation, not by itself, and is merely meant to be a summary of the full and detailed information concerning the Company in its public filings and its website.

Our mission	Create the first <b>pre-surgical</b> cancer treatment, initially for head and neck cancer, and then for other cancers. Activate the immune system to fight cancer before it is weakened by surgery, radio and chemotherapy.		
Our flagship drug	Multikine injected locally around the tumor, rather than being given systemically by IV.		
Phase 3 results in the target population	Multikine cut the risk of death in half at five years versus the control in the finalized target population, and there were no systemic toxicities or Multikine-related deaths in 529 Multikine-treated subjects.		
Pathways to approval	Pursuing accelerated/conditional approval pathways in the US, EU, UK, and Canada.		
Manufacturing	facturing We built our own 75,000 sqft manufacturing facility near Baltimore, MD with capacity 1 produce more than 12,000 treatments annually.		



Natural	Multikine is a mixture of immune-boosting cells (cytokines) and other small molecules that naturally occur in our bodies.	
First-line (neoadjuvant)	Multikine is given <u><b>right after diagnosis</b></u> , before surgery, when the immune system is strongest (before radiation, chemotherapy, or disease progression have weakened it).	
Immune System Activation	Multikine's cellular components <i>activate the immune system</i> to recognize and attack the tumor, as well as lowering the tumor's defenses and ability to hide from such attacks.	
Target population	The target population is advanced primary head and neck cancer patients with no lymph node involvement and with low PD-L1 tumor expression (about 145,000 p.a. globally).	
Phase 3 results in the target population	Multikine <u>cut the risk of death in half at five years</u> versus the control, and there were no systemic toxicities or Multikine-related deaths in 529 Multikine-treated subjects.	



Multikine would be added to the current standard of care, delivered locally via injections around the tumor and adjacent lymph nodes for three weeks, 5 days per week before surgery:







- No Multikine-related deaths.
- Multikine-related adverse events before surgery were local and resolved after surgery.
- Adverse event rates in the Multikine and control groups were not significantly different.
- Cytokines in Multikine are not toxic because they are given locally at low dosage.



1. The post-randomization/pre-surgery interval is not adjusted for SOC (median 12 days) vs LI(MK) (median 35 days), thus requiring a 2.92 multiplier to adjust (resulting in a TEAE rate of 35.7%). All other intervals did not have time differences, thus not requiring adjustment.

- Advanced primary head and neck patients who present with:
  - No lymph node involvement (N0) (via PET scan)
  - Low PD-L1 tumor expression (via biopsy)
    - (Note, this differentiates Multikine from high PD-LI checkpoint inhibitors)
- Physicians routinely assess these features at baseline as part of standard practice.
- A clear definition is an essential requirement for regulators to write an approval label.
- This population represents about 145,000 patients globally per year.







- A pre-surgical response is a significant change in disease <u>before surgery</u>.
  - These emerged just a few weeks after treatment onset.
- We saw two kinds of responses in the Phase 3 trial:
  - *"Tumor reductions"* There were "reductions" in the size of the tumor a reduction of 30% or more qualified as a "pre-surgical reduction" or "PSR" for short.
  - "Disease downstages" There were disease "downstages," e.g., the disease improved from Stage IV to Stage III. We call this a "pre-surgical downstaging" or "PSD" for short.
- Pre-surgical responders saw greatly improved 5-year survival.



## Pre-Surgical Reductions (PSR)

>30% reduction in tumor dimensions

## Pre-Surgical Downstages (PSD)

Stage IV to III, Stage III to II

## We Observed Significantly Increased PSRs/PSDs Across The Entire Phase 3 Study



SLIDE 10

### **PSRs/PSDs Led To Significantly Better Survival Across The Entire Phase 3 Study**





## Even Higher PSR/PSD Rates In The Target Population





## **Overall Survival in Multikine Target Population**



Kaplan-Meier Overall Survival for Multikine target population (n=114) in the Phase 3 study

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## Multikine Cut The Risk Of Death At 5-years In Half In The Target Population





## Why We Are Confident That Multikine Will Be Approved.

- ✓ 73% survival for Multikine vs 45% in the control, at 5 years
- ✓ 28% jump in 5-year absolute survival
- $\checkmark$  Statistically significant p = 0.0015
- $\checkmark$  5-year risk of death cut from 55% to 27%
- ✓ Hazard ratio = 0.35 (95% CIs [0.19, 0.66])
- ✓ Tumor reduction rate >13%
- ✓ Tumor downstaging rate >35%
- No safety signals or toxicities vs standard of care





## Multikine Accelerated Approval Pathway with the U.S. FDA



- We plan to submit the proposed protocol for the confirmatory trial to the FDA in Q1 2024.
- Get FDA buy-in for the confirmatory clinical trial (n=212); discussion of potential accelerated approval timing and endpoints needed.
- New law (Food and Drug Omnibus Reform Act) in December 2022 requires enrollment in the confirmatory study to be underway before accelerated approval will be given in the U.S.
- The FDA has acknowledged the longstanding need for improved treatments for head and neck cancer.
- The FDA is open to a close collaboration with CEL-SCI to help demonstrate that Multikine could be such a therapy.



We are hopeful for meetings in H1 2024 to understand if conditional approval can be given with a promise to do a confirmatory study after conditional approval or if it is possible to get a conditional approval with the enrollment of patients in the confirmatory study with:



#### Health Canada - Potential Conditional Approval Pathway

• We will continue towards filing our application for the Notice of Compliance with Conditions (NOC/C) approval, as Health Canada has suggested, which we expect to file as early as H2 2024.



#### European Medicines Agency - Potential Conditional Marketing Authorization (CMA)

- EMA recently granted us a Waiver of Strict Pediatric Requirements, helping to clear the path towards marketing authorization for Multikine.
- We plan to submit the protocol for the confirmatory study to both EMA and also FDA and plan to use that opportunity to discuss future plans.



#### **UK MHRA - Potential Conditional Marketing Authorization (CMA)**

- NICE (National Institute for Health and Care Excellence) has selected Multikine to be evaluated as the potential new standard of care for squamous cell carcinoma of the head and neck in the UK.
- We submitted our final target population data to the MHRA.
- We expect to have a meeting in HI 2024.



## **State-of-the-Art Manufacturing Facility**

#### cGMP and BSL-I facility near Washington, DC, USA

- Built specifically for Multikine
- State-of-the art facility
- Over 73,000 ft<sup>2</sup> of Manufacturing and R&D space available
- About 45,000 ft<sup>2</sup> fully developed
- Proprietary automated cold fill to ensure no loss of biological activity during fill
- Commissioning was achieved in Feb 2024, and validation expected to be completed in Spring/Summer 2024.

Over \$200 million invested in drug manufacturing. Dedicated facility was built before the Phase 3 trial started and the capacity was recently doubled in preparation for commercialization.

#### Inspected several times by European Qualified Person (QP)

• Inspected by the QP for the manufacture and release of Sterile Medicinal Products (per ICH and EU Directives)

#### **Barriers to competition - Process of manufacture**

• In house manufacturing process for complex biologic with initial capacity 12,000+ treatments per year.





## The CEL-SCI Team



#### Geert Kersten, Esq.

- CEO since 1995
- Experience in investment banking and law
- Accounting, MBA and JD degrees



#### Eyal Talor, PhD

- Chief Scientific Officer since 2009
- Inventor / developer of Multikine®
- 30 years at CEL-SCI in R&D, Manufacturing and Clinical development
- Author of over 30 peer-reviewed publications
- Adjunct Faculty at Johns Hopkins University



#### John Cipriano

- Senior VP of Regulatory Affairs since 2004
- Former FDA Deputy Director, Division of Biologics Investigational New Drug
- Former FDA Deputy Director, IND Branch, Division of Biologics Evaluation, Office of Biologics
- Degrees in pharmacy and pharmaceutical chemistry



## **Top-Tier Physician Consultants**



#### Barbara Burtness, MD

- Anthony N. Brady Professor of Medicine (Medical Oncology) at Yale
  School of Medicine
- Chief Translational Research Officer, Yale Cancer Center
- Chief, Head and Neck Cancers/Sarcoma and Co-Leader, Developmental Therapeutics, Yale Cancer Center
- Associate Cancer Center Director for Translational Research, Yale Cancer Center
- Internationally recognized for her work in head & neck cancer and leads national and international head and neck cancer trials, extensively published



#### Marshall Posner, MD

- Consultant for CEL-SCI since 2005
- Principal Investigator and Chair of the IDMC in CEL-SCI's Phase 3 study
- Director, Head and Neck Oncology, Mt. Sinai NY
- Co-Leader, Cancer Clinical Investigation Program, Tisch Cancer Institute
- More than 250 peer-reviewed publications



#### Mehmet Sen, MD, FRCR

- Practicing head and neck oncologist and radiologist for >30 years in UK and Europe
- Consultant Clinical Oncologist & Honorary Senior Lecturer, St. James Institute of Oncology, Leeds, UK
- Council Member of the British Association of Head and Neck Oncologists (BAHNO)
- Member, EORTC Head and Neck Cancer Group and the EORTC Radiotherapy Group (ROG)
- Internationally recognized for his work in head & neck cancer and leads national and international head and neck cancer trials, extensively published



#### J. Edward M. Young, MD

- Clinical Professor of Surgery, McMaster University
- 45+ years managing head and neck cancer
- Former President of Society of Head and Neck Surgeons
- Former head Surgical Oncology, Hamilton Regional Oncology Center
- Principal Investigator in CEL-SCI's Phase 2 and 3 studies



Strong survival data:	We have observed statistically significant survival data in the final target population vs control in a Phase 3 study conducted for Multikine.		
Addressing an unmet medical need:	Multikine focuses on the 70% of patients not well served by the two leading approved drugs, Keytruda and Opdivo which are also not approved as pre-surgical treatments.		
FDA approval pathway:	We plan to submit the proposed study protocol to the FDA in Q1 2024. The goal is to get FDA buy-in for the confirmatory clinical trial (n=212); also, discussion of potential accelerated approval timing and endpoints.		
EMA and UK MHRA approval pathway:	We expect meetings with the EMA and UK MHRA in H1 2024. Europe/UK have more than twice the number of head and neck cancer cases diagnosed each year as compared to the US.		
Health Canada approval pathway:	We plan to file for NOC/C in Canada as early as H2 2024.		
Commissioned manufacturing facility:	The commissioning of our manufacturing facility has been completed, and validation is expected in Spring/Summer 2024, which will position CEL-SCI to supply up to about 12,000+ treatments per year.		



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# Appendix



## **Pipeline**

Candidate	Preclinical	Phase 1	Phase 2	Phase 3	Marketing Approval
MULTIKINE					

Head and Neck Cancer

Neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck

administered right after diagnosis, before the first standard cancer treatment – Global Pivotal Phase 3 Study

HPV Cervical dysplasia in HIV/HPV co-infected patients (Univ.of Maryland)

#### LEAPS

Rheumatoid Arthritis CEL-2000 Phase 1 enabling studies CEL-4000 (NIH Grant)



- Multikine investigational immunotherapy is comprised of a mixture of cytokines; it is not one cell or one protein.
- It is a combination of proteins derived from the stimulation of a normal immune system cell culture.
- Multikine is allogeneic and <u>not</u> made from the patient's own cells, so it is available off-the-shelf and frozen -20 degrees centigrade ready for use,
- CEL-SCI uses a proven biological mechanism (cytokines in the treatment of cancer) to develop a better and less toxic cancer therapy with these key features:
  - Multikine is delivered locally, not systemically, in small doses to avoid the serious toxicity seen with many other cytokine treatments.
  - Multikine is administered while the immune system is still intact, with an intent to cure, while other cytokine treatments are generally used for recurrences.
  - Multikine combines cytokines in a manner similar to how the body naturally does so, as opposed to giving only one or two cytokines.

Major Cytokine(s) and other Cellular Products in Multikine				
IL-1 α	IL-6			
IL-1β	IL-8			
IL-2	ΤΝ <b>F</b> -β			
IL-3	G-CSF			
TNF-α	RANTES			
IFN-γ	ΜΙΡ-1α			
GM-CSF	ΜΙΡ-1β			



- Multikine and Multikine activated immune cells potentially may:
  - Recognize and/or bind to multiple (different) antigens (or receptors) on the cancer cells.
  - Signal the immune system to produce an antitumor immune response.
  - Directly affect/kill cancer cells.
- The various cytokines present in the Multikine investigational therapy, such as TNF, IL-2, IFN, along with other cytokines, could be responsible for this potential activity.
- Clinical data also suggest that Multikine could augment the type of cells that infiltrate and attack the tumor changing the tumor microenvironment ratio of CD4/CD8 cells from CD-8 cells to predominantly CD-4 cells.
- These CD-4 cells have the potential to bring about an anti-tumor immune response





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Thank you.

NYSE American: CVM

