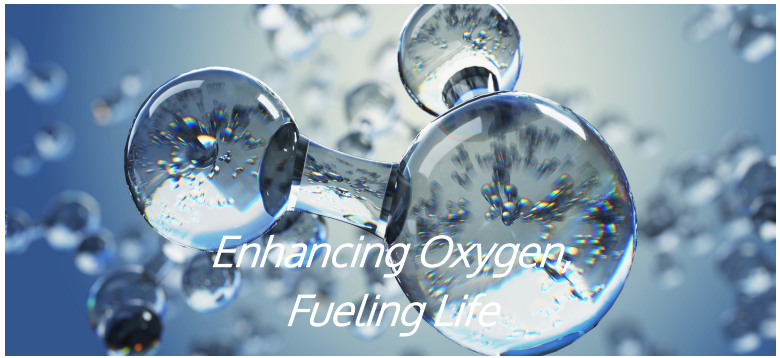
H.C. Wainwright BioConnect Conference 2022

Diffusio$_2$n Pharmaceuticals Inc.

Nasdaq: DFFN



January 10-13, 2022

Virtual Presentation

Note Regarding Forward-Looking Statements

This presentation (including, for purposes of this Note Regarding Forward-Looking Statements, any accompanying or supplemental oral presentation) includes express and implied forward-looking statements relating to: our product candidates and pipeline; our corporate strategy and product development plans; the prospects and potential of our business and our product candidates, including their safety, effectiveness, and commercial prospects; our anticipated clinical trials, other studies, and the timing and substance of data readouts therefrom; certain regulatory matters; business development activities, including potential collaborations; certain matters regarding our financial results and securities; milestones, timing, and other expectations regarding any of the foregoing; and any other matter that is not a statement of historical fact, including statements regarding our intentions, beliefs, projections, outlook, analyses, or expectations. We may, in some cases, use terms such as "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately," or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements.

By their nature, forward-looking statements relate to events, competitive dynamics, and industry change, and depend on economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated, and therefore inherently involve risks and uncertainties, including those discussed under the heading "Risk Factors" in our most recent Annual Report on Form 10-K and our subsequent Quarterly Reports on Form 10-Q and other filings with the U.S. Securities and Exchange Commission. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, as a result of these and other factors, known and unknown, actual results could differ materially from our intentions, beliefs, projections, outlook, analyses, or expectations expressed in any forward-looking statements in this presentation. Accordingly, we cannot assure you that the forward-looking statements contained in this presentation will prove to be accurate or that any such inaccuracy will not be material, and you should not place undue reliance on such statements.

Unless the context requires otherwise, all forward-looking statements that we make in this presentation are based on our beliefs and expectations as of, and speak only as of, the first date set forth on the cover page hereof and, except as required by applicable law or by the rules and regulations of the SEC, we undertake no obligation to update such statements to reflect events or circumstances after such date.

Certain information contained in this presentation relates to or is based on studies, publications, surveys, and other data derived from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involve a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, although we believe our own internal research is reliable, such research has not been verified by any independent source.

Diffusio$_2$n
Pharmaceuticals Inc.

Diffusion Pharmaceuticals Inc. (NASDAQ:DFFN) is a biopharmaceutical company developing novel therapies that enhance the body's ability to deliver oxygen to the areas where it is needed most.

Founded in 2001 based on research by Dr. John Gainer at the University of Virginia.

The lead drug candidate, trans sodium crocetinate (TSC), has broad potential to treat the many conditions complicated by hypoxia.

2021 – A Year of Transformation

Enhanced Financial Capacity

$35 Million
Gross Proceeds from Offering in February

$2.2 Million
Gross Proceeds from Exercises of Common Stock Warrants

$40.3 Million
Cash on hand as of Sep 30th

Enhanced Operating Capabilities

2
New Independent Directors

8
New Operating Team Members

1
New Scientific Advisory Board

Numerous
New Operational Systems and Processes

Advanced Product Development

3
Clinical Studies Initiated

2
Clinical Studies Completed

1
Patent Granted and others filed

No
Interruption of clinical supply

Frequent, High-Quality Communication

25
Press Releases + Shareholder Letter

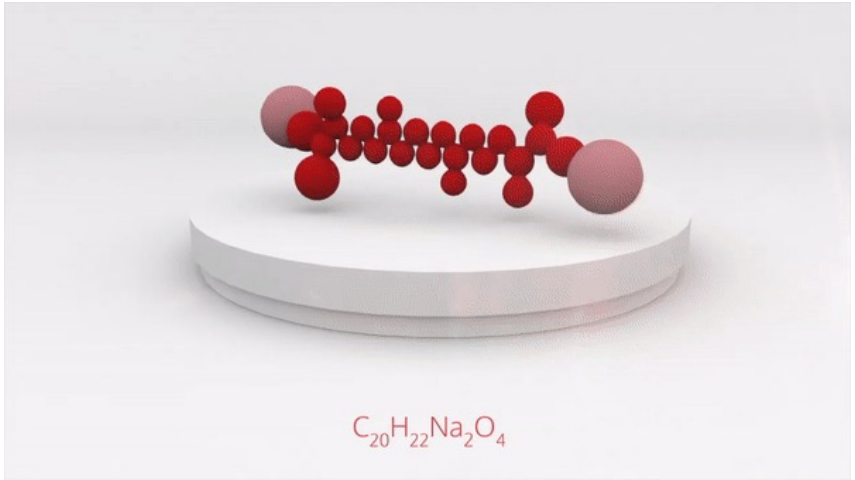
8
Podcasts (available at www.diffusionpharma.com)

5
Print Media Articles

6
Conference Presentations

Diffusion Pharmaceuticals Inc.

Trans Sodium Crocetinate (TSC)



A novel, bipolar synthetic carotenoid designed to enhance the oxygenation of hypoxic tissues.

Sodium salt of the trans isomer of crocetin, which is derived from saffron.

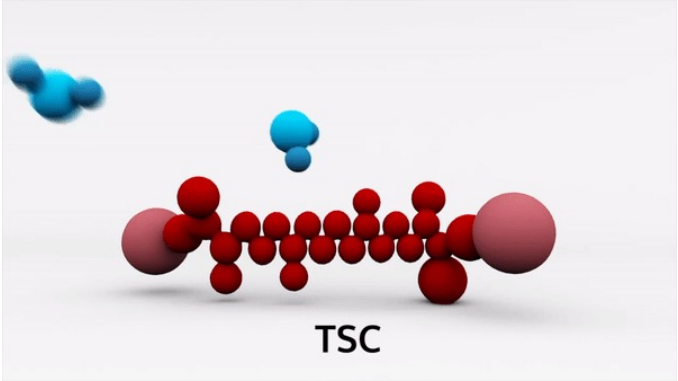
Only the trans isomer is effective in modifying oxygen diffusivity.

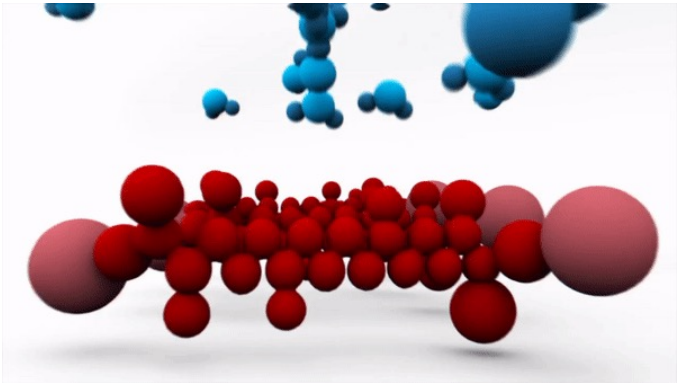
TSC Mechanism of Action

Blood plasma is 90% water. Water molecules constantly move in a loosely organized matrix, bound by hydrogen bonds.

Oxygen diffuses passively through plasma from areas of high to low oxygen concentrations, such as from oxygenated red blood cells into tissues where oxygen powers the cells.

TSC enhances diffusion by increasing the amount of hydrogen bonding, creating a less dense matrix of water molecules, opening more direct pathways for movement down the gradient.

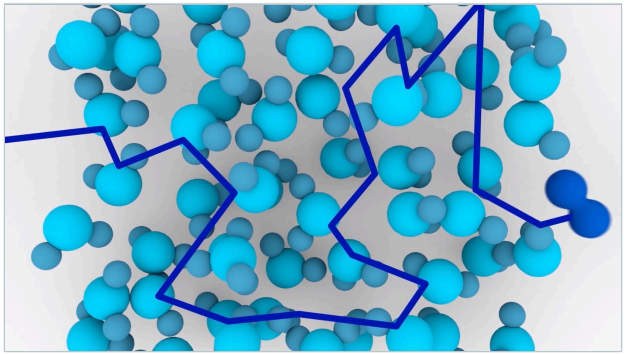


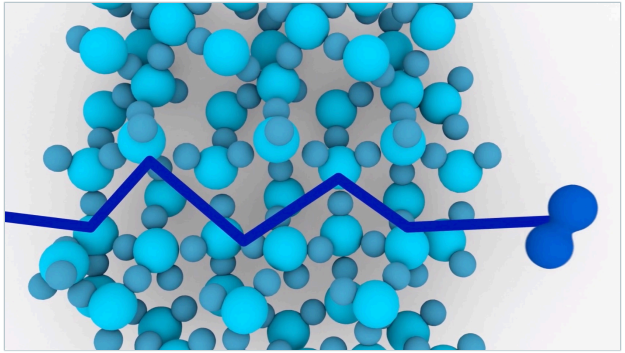


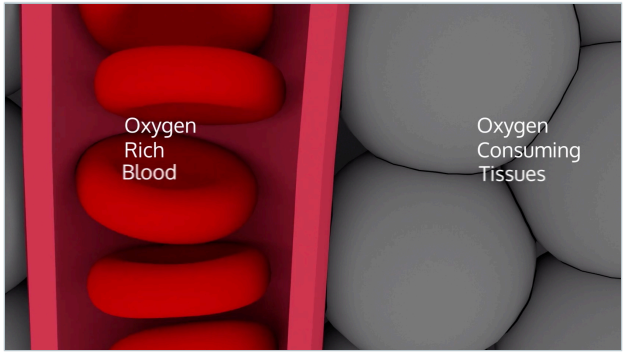
TSC enhances oxygen movement through the blood, facilitating oxygen diffusion into tissues

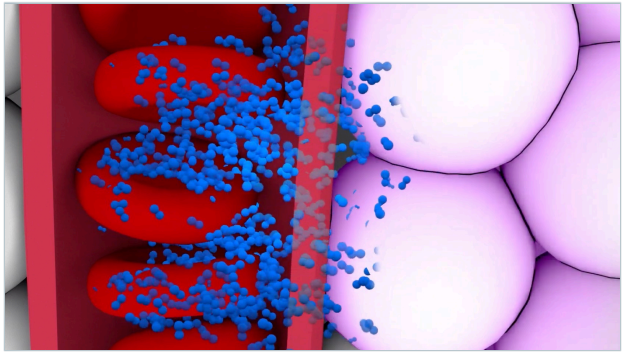
Without TSC

With TSC



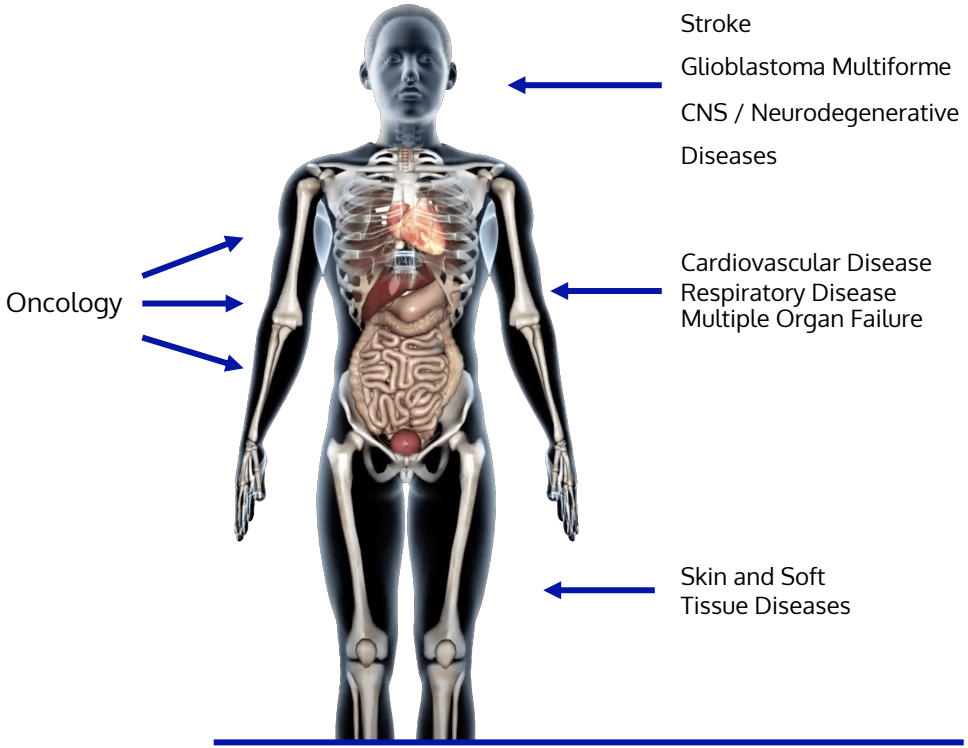






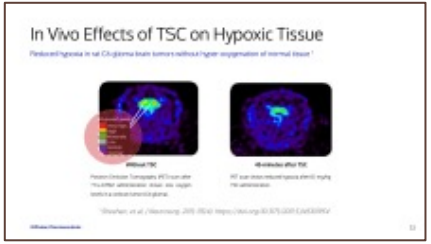
TSC: Potential to Treat Hypoxia-Related Conditions

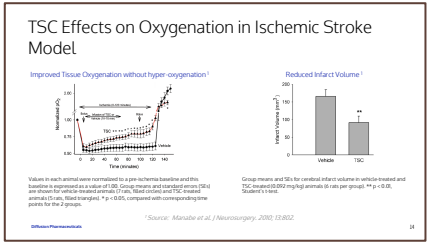
- Hypoxia is associated with the pathophysiology of many acute and chronic conditions
- TSC's novel mechanism of action enhances oxygenation
- In vivo oxygenation and functional effects observed in preclinical models
- Safe and well-tolerated in more than 200 subjects treated in clinical studies

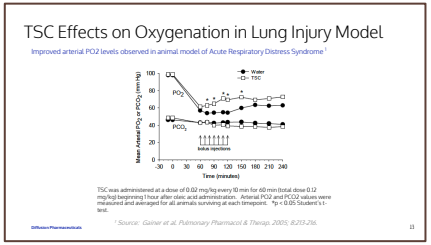


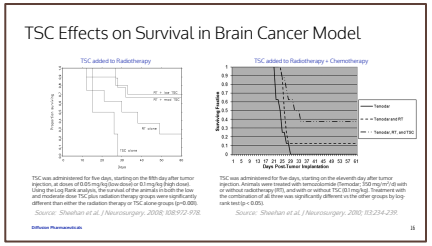
Preclinical Effects of TSC on Oxygenation

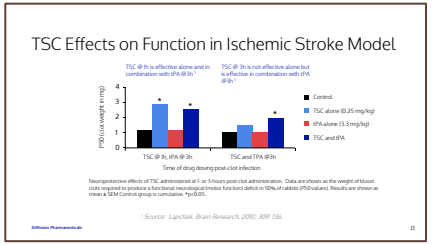
- ✓ Reduced hypoxia in rat C6 glioma brain tumors without hyper-oxygenation of normal tissue
- ✓ Improved survival in rat C6 glioma model when added to radiotherapy with or without chemotherapy
- ✓ Improved tissue oxygenation without hyper-oxygenation and reduce infarct size in rat ischemic stroke model
- ✓ Functional benefit in rabbit ischemic stroke model (with or without tPA at 1 hr; with tPA at 3 hrs)
- ✓ Improved arterial PO2 levels in rat model of Acute Respiratory Distress Syndrome (ARDS)











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Clinical Effects of TSC: *Completed Studies*

Study 100-001 Healthy Volunteers

- N=30 normal healthy volunteers (NHV)
- Single, ascending, intravenous (iv) dose (0.1 to 5 mg/kg) safety and pharmacokinetics
- Maximum tolerated dose (MTD) and pharmacokinetics (PK) characterized for single iv dose

Study 100-301 PAD

- N=48 pts with peripheral artery disease (PAD) and claudication
- Double-blind, placebo-controlled, single, ascending dose (0.25 to 2 mg/kg iv) safety, PK and efficacy
- No dose-related adverse events (AEs), PK characterized and preliminary physical improvement signal

Mohler et al. Vasc Med. 2011; 16:346.

Study 100-202 GBM

- N=59 pts with newly diagnosed glioblastoma multiform (GBM)
- Open-label, add-on of TSC (0.25 mg/kg) to standard of care (SOC) radiation + chemotherapy
- No dose-related AEs
- Survival of biopsy-only subset comparable to complete resection

Gainer et al. J Neurosurg. 2017; 26 (2):460.

Study 100-206 GBM

- N=19-pts with newly diagnosed, biopsy-only GBM
- Lead-in of Phase 3 randomized controlled trial (RCT) to evaluate four escalating dose cohorts (0.25, 0.5, 1.0, and 1.5 mg/kg) administered 3x weekly with SOC
- No dose-related AEs

Study 100-303 COVID-19

- N=24 hospitalized patients with COVID-19
- Open-label dosing every 6 hours for up to 15 days in 6 patient dose cohorts with doses from 0.25 mg/kg to 1.5 mg/kg iv
- No dose-related AEs
- SMC indicated data from patients receiving 1.5 mg/kg dose suggested improved outcomes, including time to improvement in WHO ordinal scale, time on O2 supplementation, and hospital length-of-stay

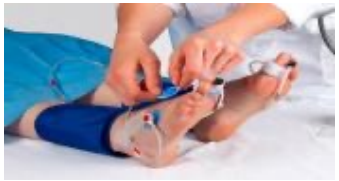
Streinu-Cercel et al. medRxiv. 2021; doi: https://doi.org/10.1101/2021.10.08.21264719

TSC Oxygenation Trial: *'TCOM' (200-301)*

Completed Trial

Background

- Transcutaneous Oxygen Monitoring (TCOM) is a non-invasive test that measures the partial pressure of oxygen (TcpO2) diffusing through the skin and provides insight into local tissue oxygenation
- TCOM sensors are commonly used to evaluate severity of peripheral artery disease (PAD), map amputation, assess wound healing, predict hyperbaric O2 therapy benefit (HBOT)

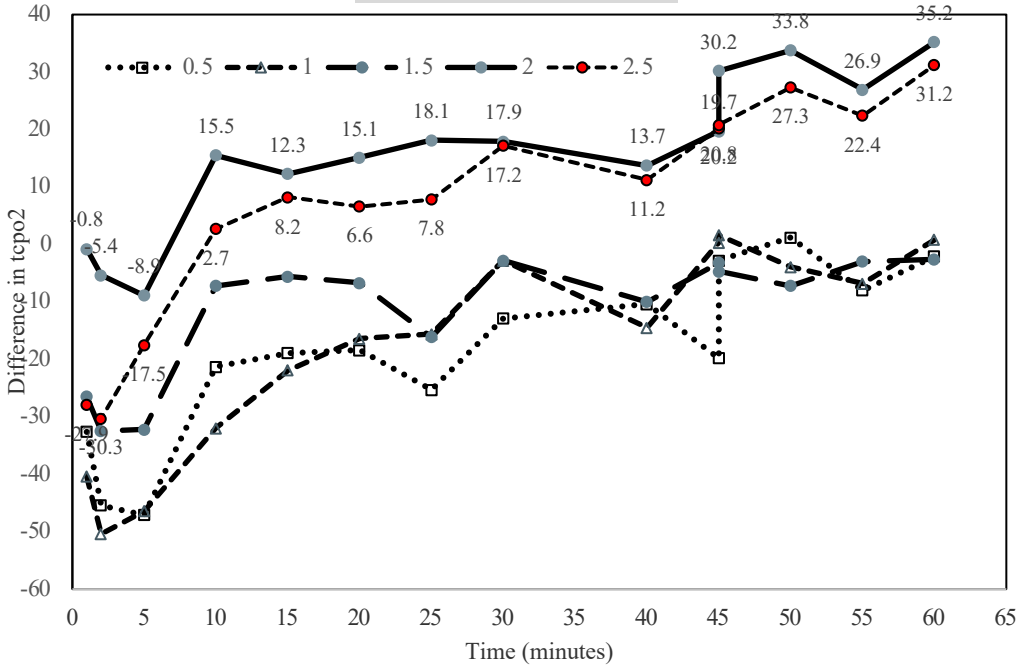


Design

- Randomized, double blind, placebo controlled, pharmacokinetic and pharmacodynamic study to evaluate the dose-response effects of TSC on tissue oxygenation
- N = 30 healthy non-smoking volunteers randomized to receive a single iv dose of placebo or one of five TSC doses (0.5-2.5 mg/kg)
- All participants received supplemental oxygen while supine and continuously monitored with TCOM sensors applied to the lower extremity

TSC Oxygenation Trials: *'TCOM' (200-301) Results*

Completed Trial



Effects of TSC on transcutaneous oxygen pressure (tcpO2). The graph was created by subtracting the median placebo response from the dose and time matched median TSC response.

Observations

- TSC was safe and well-tolerated
- Positive dose-response trend in TCOM readings observed with TSC as compared to placebo that persisted through the measurement period at the highest doses (2.0 and 2.5 mg/kg)
- No evidence of hyperoxygenation
- Results inform dose selection for future trials

TSC Oxygenation Trials: *'Altitude' (200-302)*

Ongoing Trial

Rationale

- Measure effects of TSC under altitude-induced hypoxic conditions that decrease performance
- Partial pressure of O2 (PaO2) decreases with altitude from 21% at sea level to <12% at 15K feet
- Enhanced oxygen delivery may delay or mitigate onset of hypoxia-induced symptoms at any altitude

Design

- Phase 1, single center, randomized, placebo-controlled, cross-over treatment trial in normal healthy volunteers
- Two simulated "altitude" (15K ft) sessions per subject in single day during which subjects perform aerobic after receiving either TSC or control treatment
- Clinical endpoints: vital signs, ECG telemetry, serum lactate, PaO2, SaO2, VO2, safety
- DFFN announced first patient dosed on November 22, 2021

TSC Clinical Development: *'ILD-DLCO' (100-601)*

Ongoing Trial

Rationale

- DLCO is a pulmonary function test that measures gas (carbon monoxide, CO) diffusion from lungs to the bloodstream where CO binds hemoglobin (Hgb)
- Single breath, non-invasive, repeatable, in-office test
- Standard screening tool as part of work-up for Interstitial Lung Disease (ILD), COPD, Heart Failure, Pulmonary Hypertension

Design

- Phase 1b, multi-center, placebo-controlled, single dose (2.5 mg/kg) study in patients with ILD
- Clinical Endpoints: Changes in DLCO and six-minute walk test compared to baseline
- DFFN announced first patient dosed on December 16, 2021

TSC Development: *Summary*

Value Proposition

- Broad potential use for treatment of conditions complicated by hypoxia
- Formulated for intravenous administration
- Safe and well-tolerated in over 200 subjects in clinical studies with single or multiple daily doses
- No evidence of drug or disease interactions, supporting use in conditions that require polytherapy for disease management
- Positive Clinical and Pharmacodynamic (oxygenation) effects observed in clinical studies

Next Steps

- Complete Altitude Trial – 1Q2022
- Complete ILD-DLCO Trial – 1Q2022
- Complete design of clinical program to support the use of repeated dosing of intravenously administered TSC as adjunctive treatment to SOC for hypoxic solid tumors – 1Q2022
    - Submit briefing document to FDA – 1Q2022
    - Start clinical trial – 3Q2022, depending on FDA feedback and drug supply availability

Investment Highlights

- TSC's novel mechanism of action targets hypoxic conditions, an area of high unmet medical need
- Safe and well-tolerated in over 200 subjects included in clinical trials; dose-dependent clinical and pharmacodynamic (oxygenation) effects
- Altitude and ILD-DLCO Trials initiated in 4Q 2021; planned completion in 1Q 2022
- Next step: Design and execute clinical program to support the use of TSC as an adjunctive treatment for hypoxic solid tumors
- Sufficient cash to fund operations and capital expenditures well into 2023
- Continued investment in strong global IP portfolio

Thank You

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