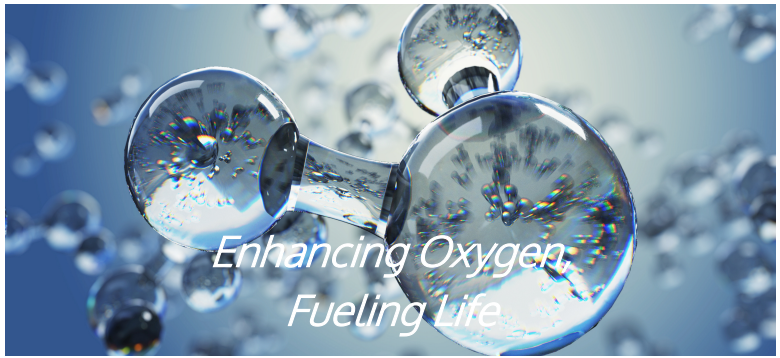
HC Wainwright Annual Global Investor Conference

DiffusiO_2n Pharmaceuticals Inc.

Nasdaq: DFFN



September 13-15, 2021

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. is an innovative 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) is being developed to enhance the diffusion of oxygen to hypoxic tissues.

Recent Company Highlights

2Q21 Financials

- R&D expenses: $2.0 M vs $2.2 M prior year period
- G&A expenses: $1.8 M vs $1.5 M prior year period (increased headcount and separation of former executives)
- Cash and cash equivalents of $43.3 M as of 30 June vs. $18.5M as of Dec 31, 2020, no debt, and a clean balance sheet
- Anticipated cash runway through 2023 as of 30 June, including funding of Phase 2b for TSC

TSC Development

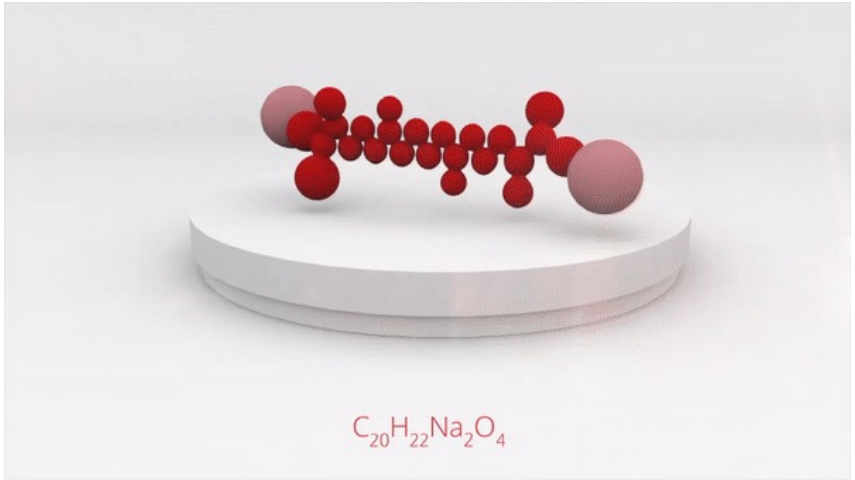
- TCOM: "Positive trend" reported in normal healthy volunteers with no evidence of hyperoxia
- COVID-19: Secondary endpoint analyses suggested improved outcomes at highest doses
- Altitude (hypoxia – 4Q start*)
- ILD-DLCO (lung diffusion – 4Q start*) - new IND to support study cleared by FDA (Aug); 4th open IND for TSC, incl Onc, Neuro, and Cardio/Nephrol

Other

- Appointed New Board Chair, Jane Hollingsworth; elected two new Board members: Diana Lanchoney, MD (CSL Behring) and Eric Francois (Scynexis)
- Enhanced operating team, adding accomplished people in administration, clinical, finance, quality and CMC
- Continued expanding communication avenues with recent Shareholder Letter and debut of podcast series (avail. at www.diffusionpharma.com)

* Anticipated

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.

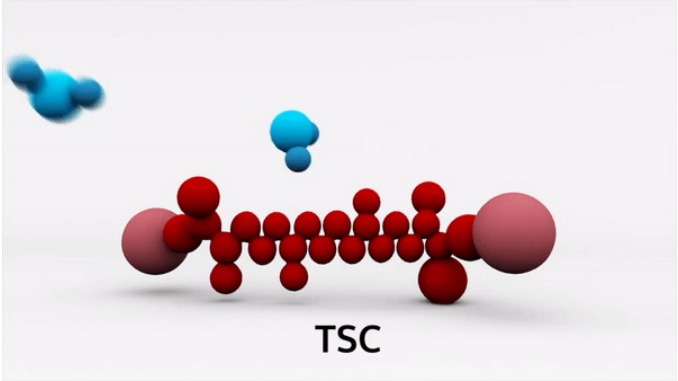
Only the trans isomer is effective in modifying oxygen diffusivity.

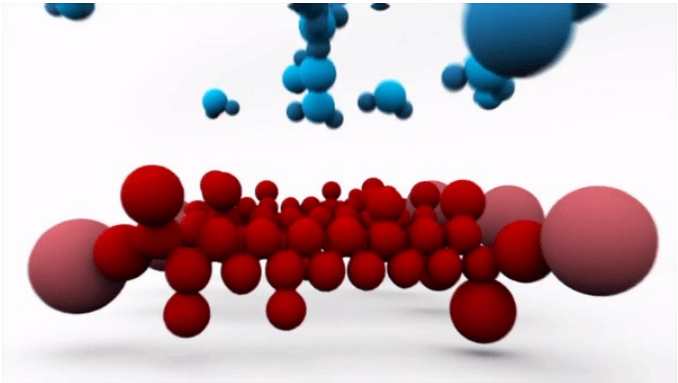
TSC Mechanism of Action

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.

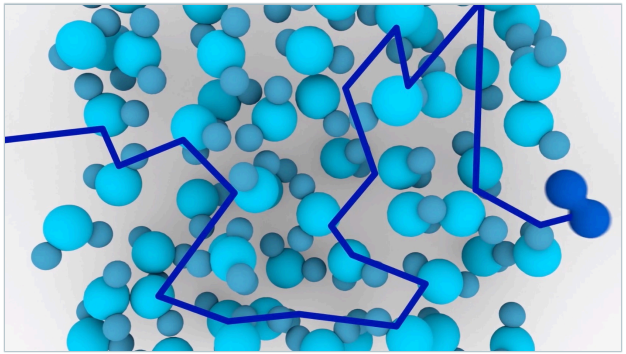


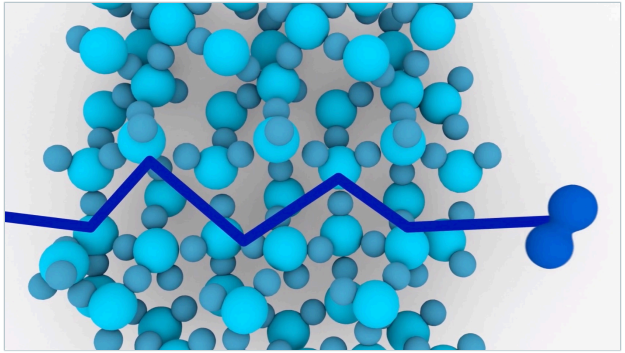


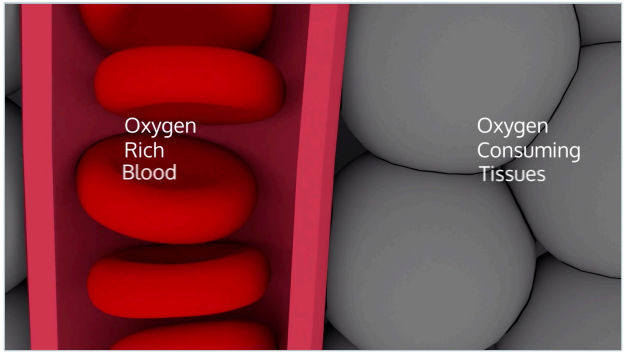
TSC enhances oxygen movement through the blood, facilitating oxygen diffusion into tissues

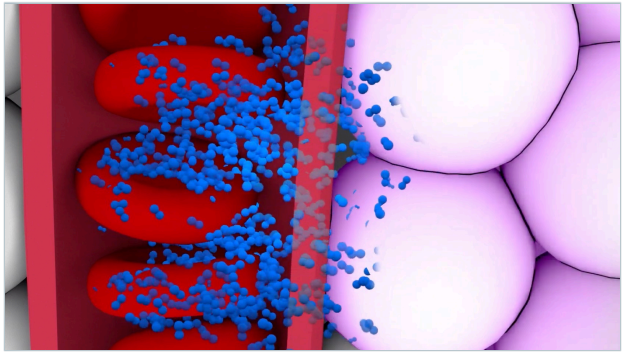
Without TSC

With TSC



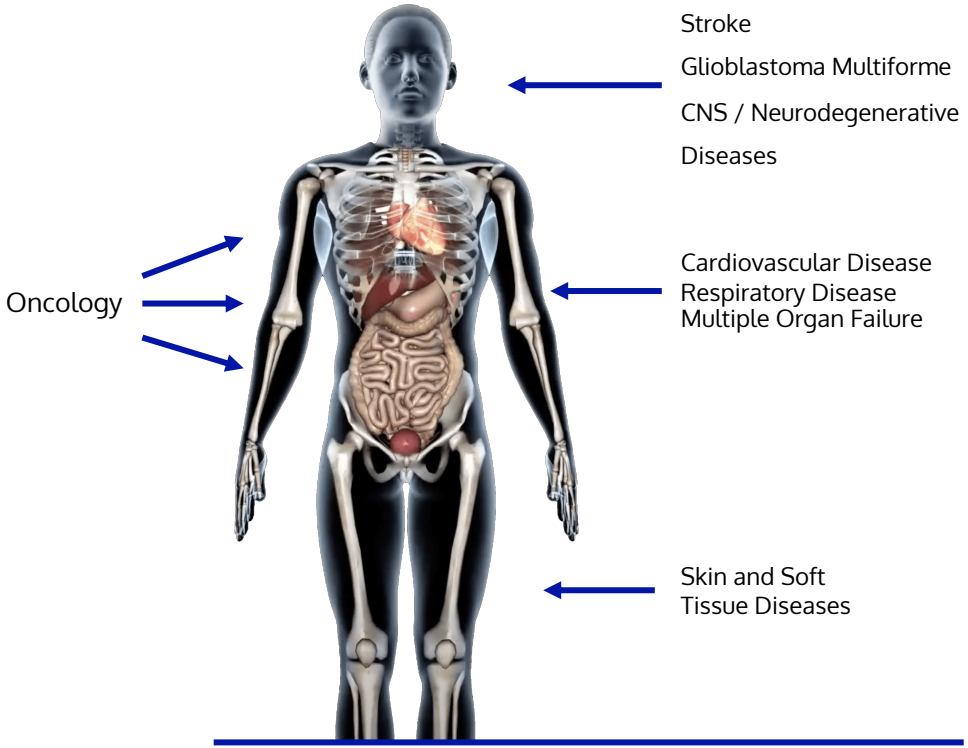






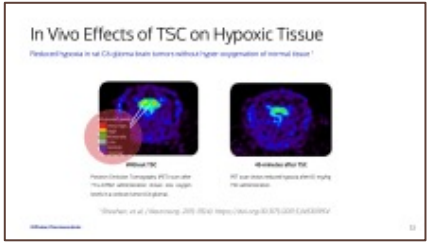
TSC: Potential to Treat Hypoxia-Related Conditions

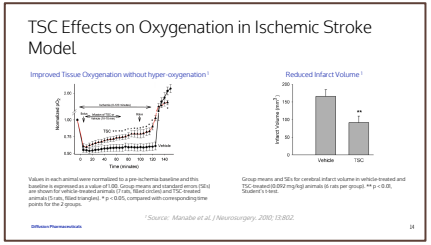
- Hypoxia is associated with the pathophysiology of many acute and chronic conditions
- TSC's novel mechanism of action enhances oxygenation
- In vivo oxygenation and functional effects observed in preclinical models
- Safe and well-tolerated in more than 200 subjects treated in clinical studies

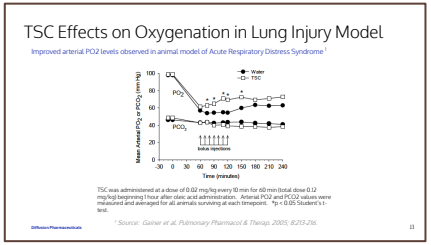


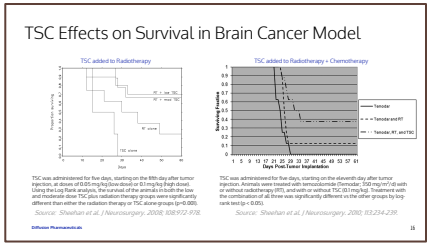
Preclinical Effects of TSC on Oxygenation

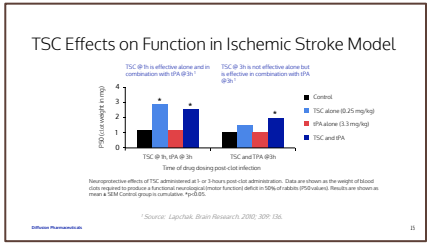
- ✓ Reduced hypoxia in rat C6 glioma brain tumors without hyper-oxygenation of normal tissue
- ✓ Improved survival in rat C6 glioma model when added to radiotherapy with or without chemotherapy
- ✓ Improved tissue oxygenation without hyper-oxygenation and reduce infarct size in rat ischemic stroke model
- ✓ 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











Diffusio$_2$n Pharmaceuticals Inc.

TSC Clinical Development: *Previous 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

TSC Clinical Development: *COVID-19 (100-303)*

Design

- Open-label, ascending dose study of intravenous TSC in hospitalized COVID-19 patients (Romania)
- Patients dosed 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

Results

- **Primary endpoint data:**
  TSC was safe and well-tolerated
- **Secondary and exploratory endpoint data:**
  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
- **SMC recommended additional preliminary work:**
  Test higher TSC doses and a continuous intravenous infusion

TSC Clinical Development: *Near-term Strategy*

Pre-2021 Data

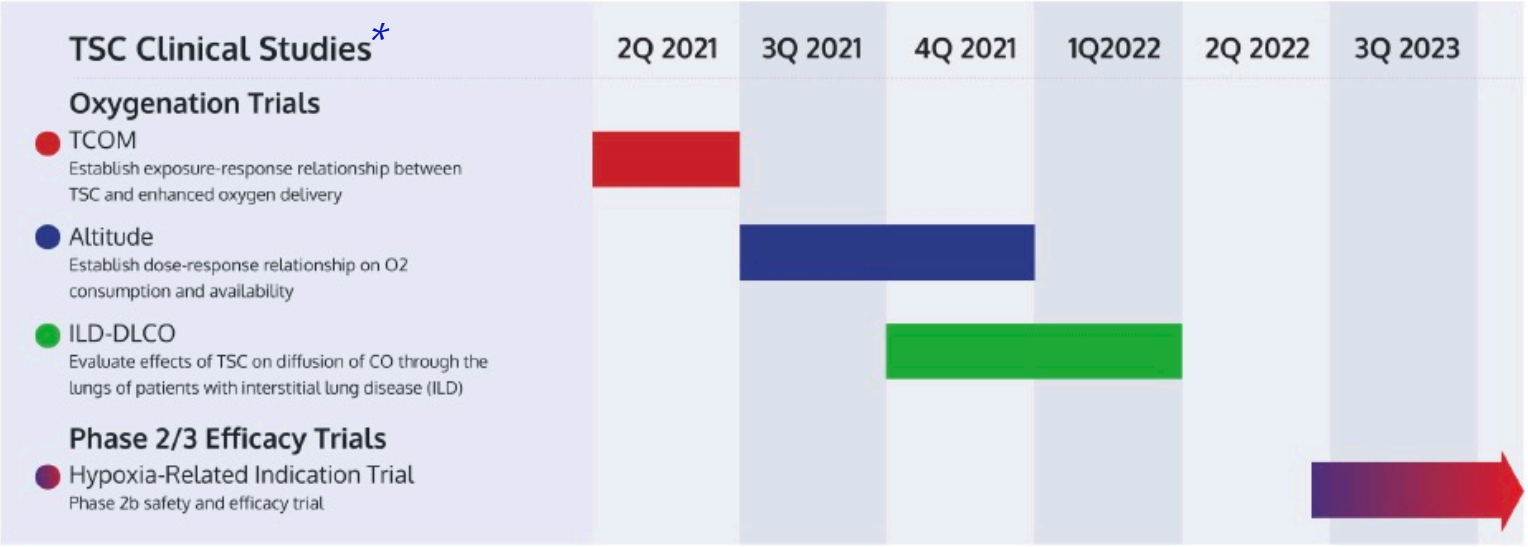
- CMC process and stability
- Preclinical safety and efficacy in wide array of experimental models
- Single dose safety, tolerability, and pharmacokinetics in healthy volunteers
- Clinical safety and efficacy as an adjuvant therapy in peripheral artery disease (PAD), glioblastoma multiforme (GBM) and COVID-19
- Phase 2/3 GBM study initiated – terminated (financial)
- Phase 2 acute stroke study initiated – terminated (COVID-19 pandemic)

Analysis and Conclusions

- Existing data support TSC's potential to enhance standard-of-care in hypoxia-related conditions
- Additional Needs:
  - Multiple-ascending dose pharmacokinetic (PK) data
  - Direct evidence of TSC effects on oxygenation in humans
  - Identify safe and efficacious dose(s) that enhance oxygenation

Oxygenation Trials – short-term studies to determine safe and efficacious TSC dose(s) to directly enhance oxygenation

TSC Clinical Development: *Oxygenation Trials*



** Anticipated timelines*

Clinical Relevance

TCOM Trial = Wounds; Peripheral Vascular Disease; Ischemia and Reperfusion Injury; Tumor Sensitization

Altitude Trial = Anemia; Major Surgeries; Physical Performance

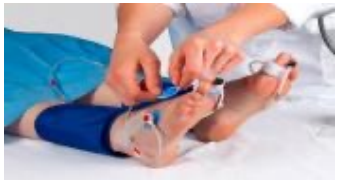
ILD-DLCO Trial = Interstitial Lung Disease; Acute Respiratory Distress Syndrome and Pneumonias; Pulmonary Embolus; COPD and Emphysema

Not an exhaustive list of indications

TSC Clinical Development: *'TCOM' (200-301)*

Design

- Used to evaluate severity of PAD, map amputation, assess wound healing, predict hyperbaric O2 therapy benefit (HBOT)
- Randomized, double blind, placebo controlled, pharmacokinetic and pharmacodynamic study
- N= 30 volunteers randomized to single iv dose of placebo or one of five TSC doses (0.5-2.5 mg/kg)
- All participants received supplemental oxygen while being continuously monitored with TCOM sensors applied to the lower extremity



Results

- Safety:

  TSC was safe and well-tolerated

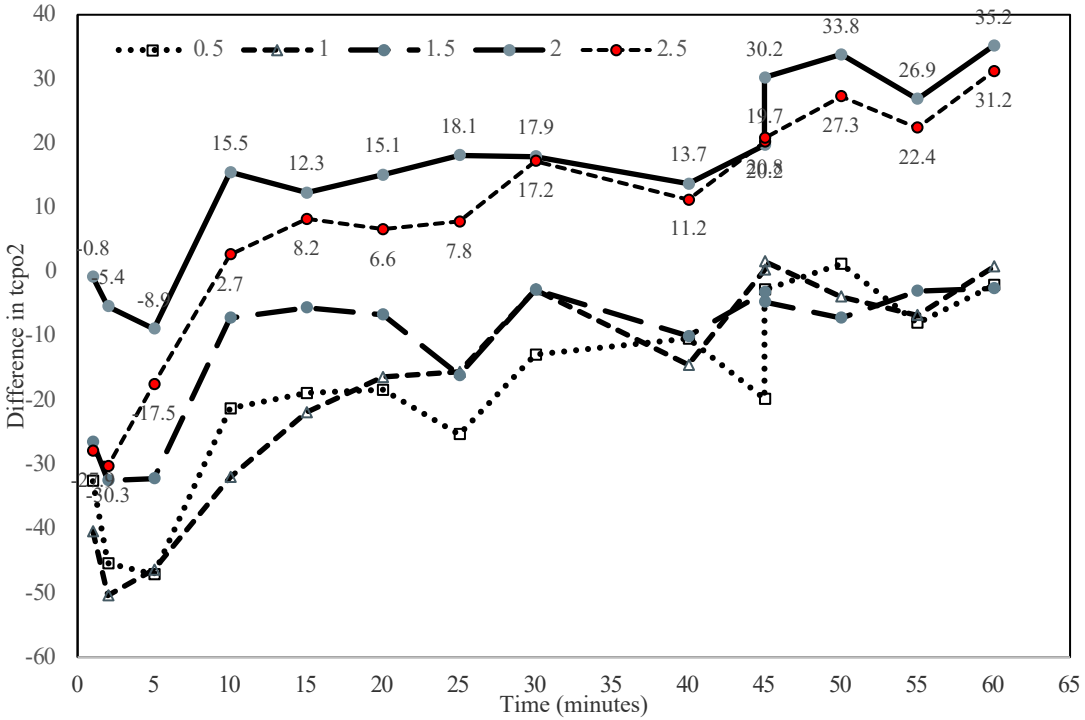
- Primary endpoint data:

  Positive dose-response trend in TCOM readings with TSC as compared to placebo that persisted through the measurement period at highest doses (2.0 and 2.5 mg/kg) – not statistically significant

  No evidence of hyperoxygenation

  Results inform dose selection for future trials

TSC Clinical Development: *'TCOM' (200-301) Cont.*



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

- Evidence that TSC potentially facilitates passive diffusion of O2 without causing hyperoxygenation
- Normal healthy volunteers lying supine with supplemental O2 for 2 hours, but definition of a "statistically significant" response derived from clinical experience from patients with hypoxic tissue
- Innovative design with tcPO2 measured over an extended time-period
- Small sample size

TSC Clinical Development: *'Altitude' (200-302)*

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; aerobic exercise during each session
- Subjects receive TSC or control before each session
- **Clinical endpoints:** vital signs, ECG telemetry, serum lactate, PaO2, SaO2, VO2, safety

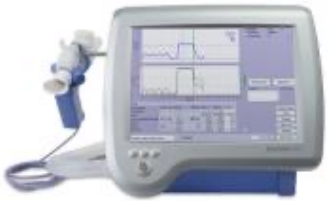
TSC Clinical Development: *'ILD-DLCO' (100-601)*

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, single 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



TSC Development: *Summary*

Value Proposition

- Preclinical data suggest broad potential as a treatment for hypoxia-related conditions
- 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: drug or drug: disease interactions, supporting use in conditions that require polytherapy for disease management
- Preliminary indications of effect on oxygenation in clinical studies

Next Steps

- Complete clinical studies in experimental models of oxygenation
- Data from TCOM study show positive trend in oxygenation at highest doses tested (2.0 and 2.5 mg/kg), although not statistically significant
- Altitude study anticipated to start in 4Q2021
- ILD-DLCO study anticipated to start in late 4Q2021
- Data to guide decision on initial indication on pathway for regulatory approval – expect to announce in 4Q21

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
- TSC safe and well-tolerated in TCOM Trial with positive dose-response trend vs placebo at 2.0 and 2.5 mg/kg (ns) with no evidence of hyperoxygenation
- Altitude and ILD-DLCO Trials initiations, as well as announcement of lead indication and regulatory strategy, expected in 4Q 2021
- Anticipated cash runway through 2023 as of June 30, including projected completion of an anticipated Phase 2/2b study
- Continued investment in strong global IP portfolio

Thank You

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Pharmaceuticals Inc.