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Meaningfully Improving the Lives of Patients with Rare Cardiopulmonary Disease

Targeting the Hyperproliferative Cause of Pulmonary Arterial Hypertension

April 2024

Nasdaq: AVTE

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Experienced Management Team

Timothy Noyes
Chief Executive Officer

- 30 years' commercial experience in pharma and biotech, including Merck, Genzyme, Proteon
- Extensive launch planning and commercial launch experience

Ben Dake, PhD
President & Founder

- Entrepreneur, Cancer Biologist and Investor
- Conceptualized AV-101 and secured up to $79M in financing for Aerovate

Hunter Gillies, MB ChB
Chief Medical Officer

- Led AMBITION trial for Gilead that established current first-line PAH combination therapy
- Led successful Phase 2 and 3 trials for PAH product candidates at Pfizer and Gilead

Donna Dea
Head of Regulatory

- 35 years of pharmaceutical experience at AstraZeneca
- 20 years of global regulatory experience designing/ implementing strategies resulting in approval of treatments for asthma, COPD, rhinitis and others

Susan Fischer
EVP, Clinical Ops.

- 20 years' experience in clinical operations in both academic and the pharmaceutical industry.
- Previously built/led clinical ops teams at Syndax, EMD Serono, Acetylon

George Eldridge
Chief Financial Officer

- 25 years' experience in biotech, with both public and private companies, including Curis, Targanta, Proteon
- Extensive background raising capital in private, IPO and follow-on settings, investment banking and M&A

Ralph Niven, PhD
Chief Development Officer

- 25 years' broad expertise in translational medicine and inhalation dosage forms
- Managed experimental and clinical development at public and private companies, including Amgen, AIR and Novartis

Timothy Pigot
Chief Commercial Officer

- 25 years' experience in biotech and pharma working to launch and commercialize a range of products
- 10 years' experience in PAH overseeing the US launches of Revatio and Leairis while at Pfizer and Gilead Sciences, respectively

Marco Verwijs
Chief Technical Officer

- 15 years' experience developing drugs from clinical product development thru commercial launch
- Proven leader in drug product scale-up and validation.

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Aerovate: An Inventive Way Forward in PAH

Demonstrated Clinical Benefit

The molecule in AV-101, imatinib, already has shown clinical benefit in a Phase 3 clinical trial conducted by Novartis of oral imatinib mesylate in PAH patients on top of two or more standard of care therapies.

Unfortunately, AEs with oral imatinib were common and development was discontinued

Inventive Solution

Anti-proliferative targeted inhaled dry powder PAH product candidate AV-101 designed to provide robust clinical benefit of imatinib without systemic AEs observed with oral imatinib

Significant Unmet Need

Despite three drug classes approved, 5-year survival for newly diagnosed PAH patients is 61%

Efficient Execution

FDA and EMA orphan designation for AV-101 for the treatment of PAH

Phase 1 SAD/MAD in healthy volunteers complete

Phase 2b portion fully enrolled of seamless Ph2b/3 IMPAHCT trial and already enrolling in Phase 3 portion

Ph2b data expected in June 2024

Established Market

$6B+ market, yet outcomes are poor

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Relentless Disease Progression Impairs Daily Life

No limitation

Activity limited

Comfortable at rest, but ordinary physical activity causes shortness of breath, fatigue, chest pain, fainting

Marked limitation

Comfortable at rest, but less than ordinary physical activity causes shortness of breath, fatigue, chest pain, fainting

Severe limitation

Symptoms at rest. Overt heart failure

Despite standard of care (SOC) most patients progress to overt heart failure

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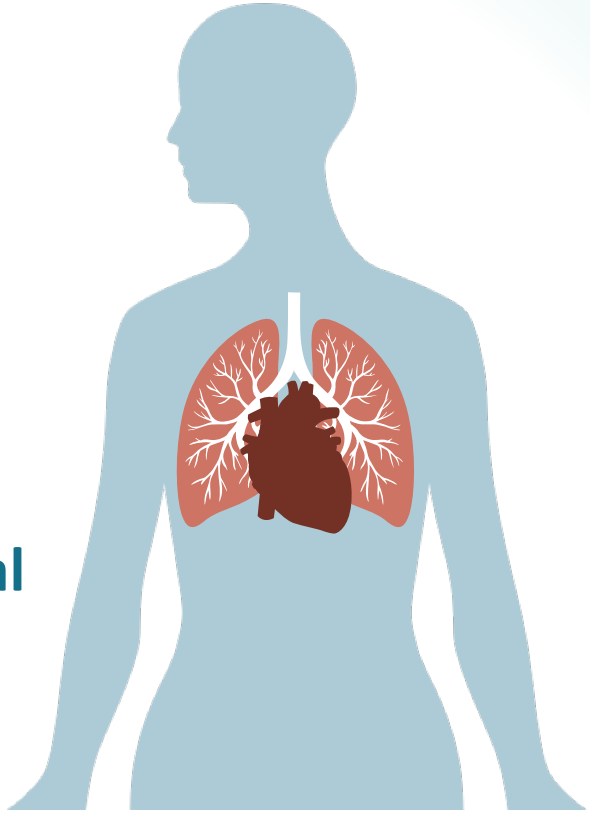
Pulmonary Arterial Hypertension

~ 70,000 People with PAH in the US/EU	**~ 35,000** People with PAH in the US	**$6B+** Global annual drug spending
65-80% Female	**53 years** Average age at diagnosis	**61-65%** **5-year survival** Newly diagnosed and prevalent patients



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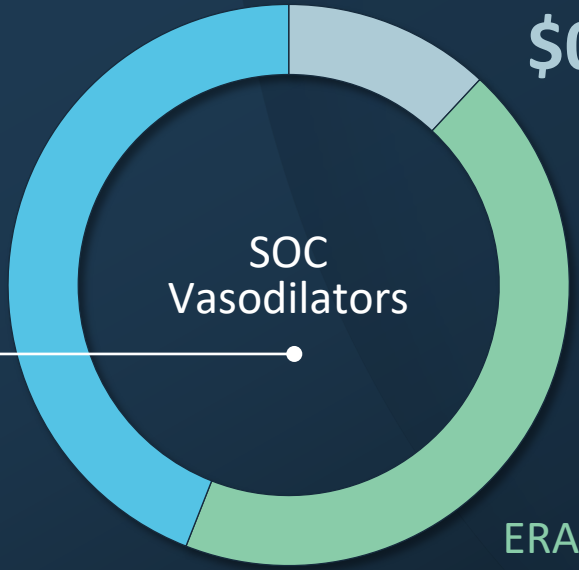
Patient Outcomes Are Poor Despite $6B+ PAH Vasodilator Market

~65% patients take
2-3 drugs

5-year survival
61-65%
for newly diagnosed and prevalent patients



No approved PAH therapy primarily addresses abnormal cellular proliferation

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Reinventing Imatinib From a Cancer Drug to a Potential PAH Therapy

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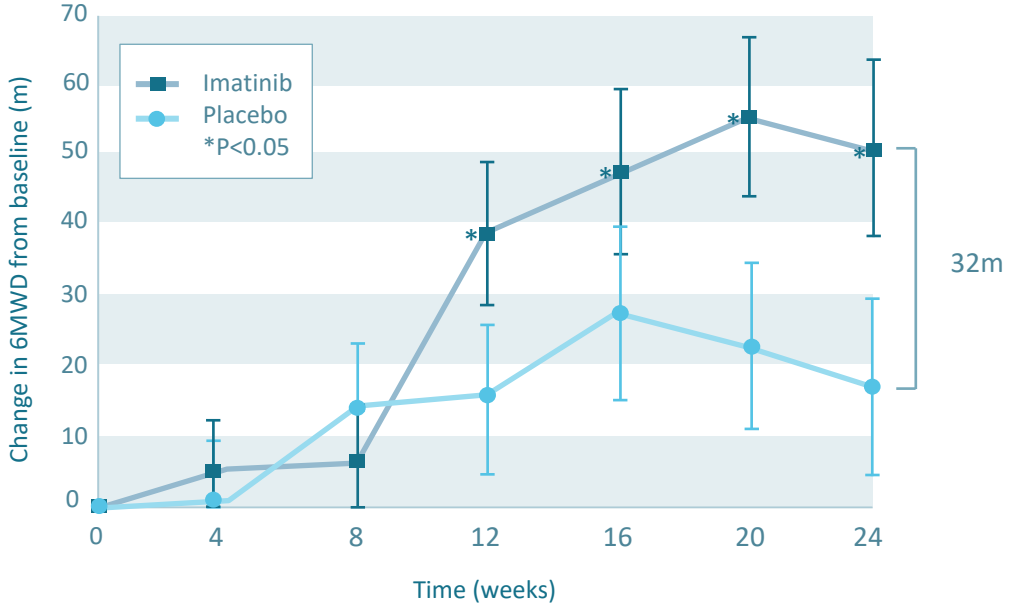
Phase 3 IMPRES Trial: Oral Imatinib Demonstrated Improvement on Top of Maximal Background

- Novartis global Phase 3 trial (n=202) of oral imatinib
- Required to be on at least 2 SOC PAH drugs
- WHO functional class II- IV
- Statistically significant and clinically meaningful benefit on primary endpoint 6MWD after 24 weeks
- 6MWD is an accepted endpoint for approval in PAH



(Adapted from Circulation. 2013;127:1128-1138.)

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Phase 3 IMPRES Trial: Benefit Consistent Across Secondary Endpoints

Secondary Endpoints (24wk)

Demonstrated robust hemodynamic effect

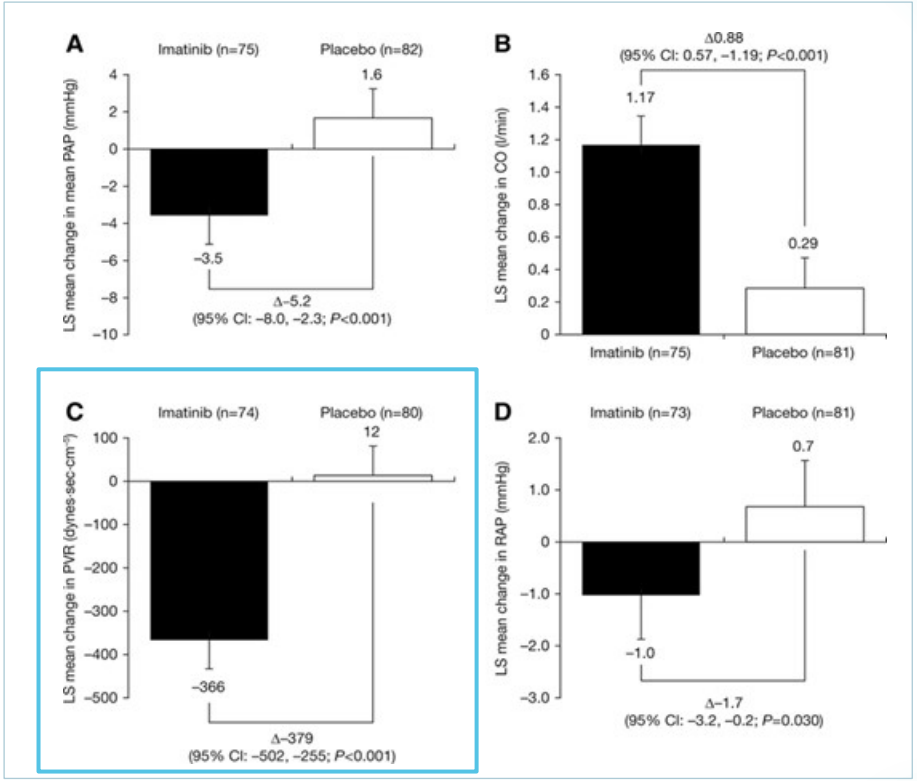
(A) Decreased mean pulmonary artery pressure

(B) Increased cardiac output

(C) Pulmonary vascular resistance (PVR) dropped 32% (P < 0.001), a validated efficacy endpoint typically used for dose-finding

(D) Right atrial pressure lowered

PVR is the primary endpoint for Aerovate's Phase 2b



(Circulation. 2013;127:1128-1138.)

Oral Imatinib Caused Systemic Adverse Events

	Imatinib n=103 (%)	Placebo n=98 (%)
Adverse Event +	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Peripheral edema	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)

	Imatinib n=103 (%)	Placebo n=98 (%)
Serious Adverse Event +	45 (44)	29 (30)
Worsening of pulmonary hypertension	6 (6)	8 (8)
Anemia	7 (7)	1 (1)
Dyspnea	6 (6)	2 (2)
Peripheral edema	6 (6)	0
Presyncope	5 (5)	0
Diarrhea	3 (3)	2 (2)
Device-related infection	3 (3)	0
Syncope	1 (1)	5 (5)
Subdural hematoma *	2 (2)	0

* In long-term extension portion of the trial, 6 additional patients experienced a subdural hematoma.

+ Individual adverse events are shown if they occurred in >10% in the imatinib group. Individual serious adverse events are shown if they occurred in ≥3 patients in either group.

(Circulation. 2013;127:1128-1138.)

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AV-101

Potential Targeted Treatment for PAH

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AV-101

AV-101 is a combination product comprised of a proprietary dry powder imatinib formulation in a capsule delivered by a dry powder inhaler designed to:

- Deliver drug to the lungs
- Limit systemic exposure
- Be easily administered

Imatinib molecular structure unmodified

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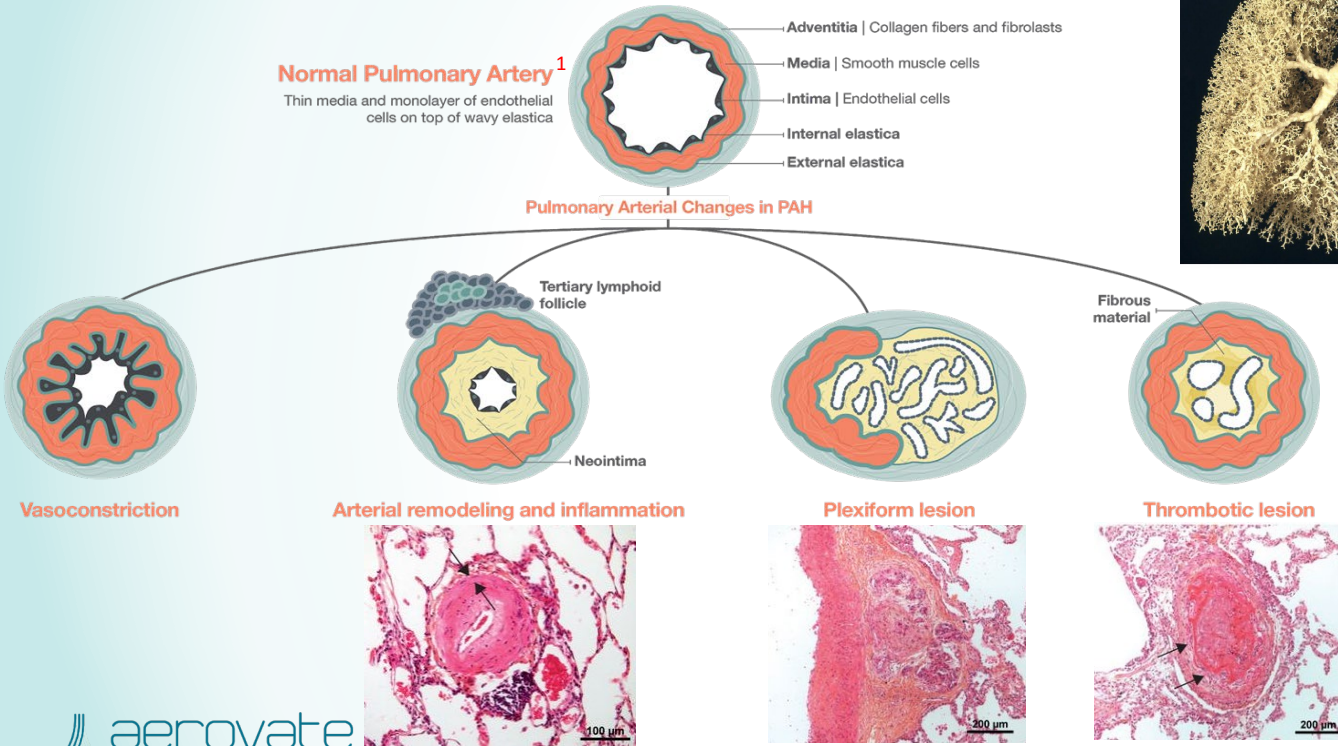
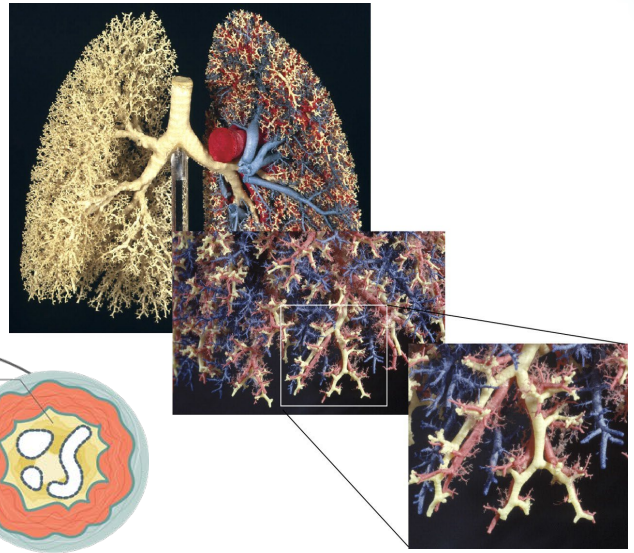
PAH is a Disease of All Layers of the Pulmonary Arteries





Latex cast of human airway (white), arterial tree (red), and venous tree (blue)[3]

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1. Adapted from J Am Coll Cardiol. 2015 May 12;65(18):1976-97. 2. Eur Respir J. 2019 Jan 24;53(1):1801887. 3. J Appl Physiol (1985). 2011 Apr;110(4):1119-29.)

AV-101 Phase 1 Trial

A single and multiple ascending dose Phase 1 study (n=82) in healthy volunteers to determine safety and tolerability

SAD	MAD	STUDY ASSESSMENTS
Five AV-101 cohorts from 1 mg to 90 mg **n=6 Active / 2 Placebo**	Seven days of BID dosing	Vital Signs
	Low dose 10 mg	Pulmonary Function Testing (FEV1 and FVC)
400 mg imatinib tablet for systemic exposure comparison **n=8**	Med dose 30 mg	Oxygen Saturations
	High dose 90 mg	QTc
		Adverse Events
n=8 per cohort	**n=12 per cohort; 9 Active / 3 Placebo**	

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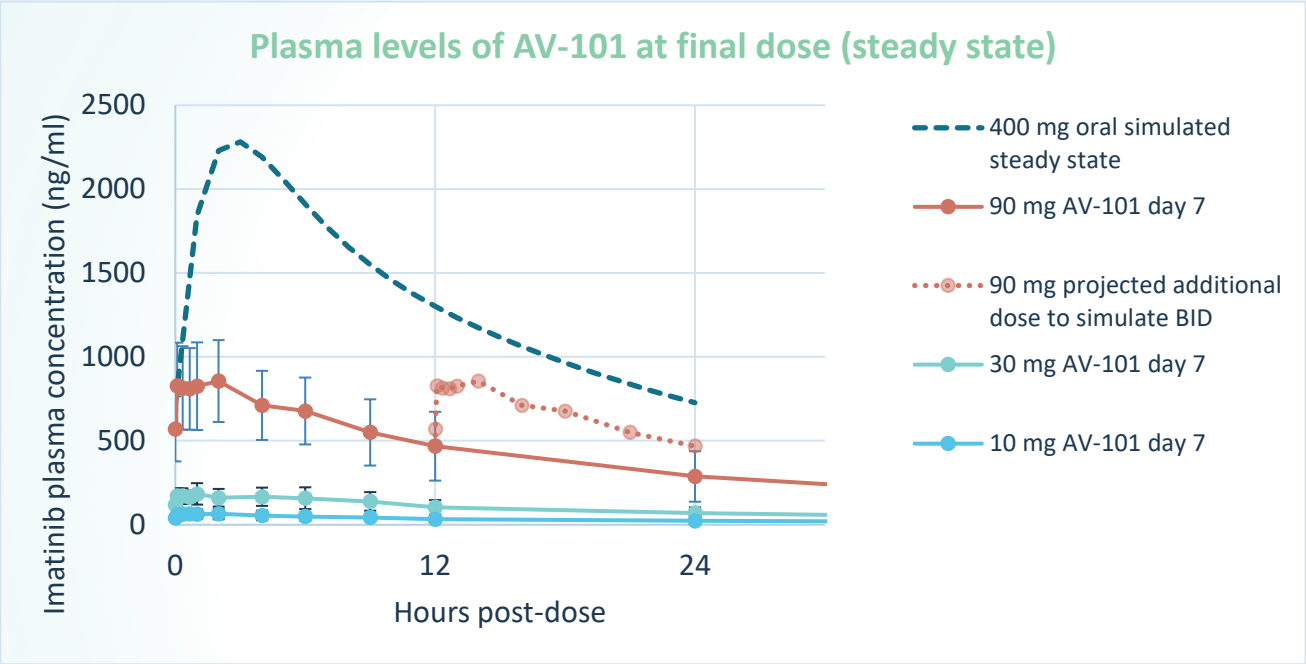
AV-101 Phase 1 Trial: Lower Systemic Exposures Observed



Systemic exposures for all doses of AV-101 observed to be lower than simulated steady-state exposure of 400 mg of oral imatinib

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AV-101 Phase 1 Tolerability Profile

AV-101 was generally well tolerated

- No serious adverse events were reported
- No change in pulmonary function, oxygen saturation, and QTc interval
- Most AEs mild to moderate
- One discontinuation due to vomiting on Day 1 in the MAD 90 mg Cohort
- Most common AE, cough, was at max dose and limited to within 30 minutes of dosing

Adverse Event n(%)	10 mg (n=8)	30 mg (n=9)	90 mg* (n=9)
Cough	1 (13)	1 (11)	5 (56)
Persistent cough	-	-	-
Headache	-	-	4 (44)
Nausea	-	-	2 (22)
Chest discomfort	-	-	2 (22)
Throat irritation	-	1 (11)	1 (11)
Musculoskeletal pain	-	-	2 (22)

Single incidence AEs: Vomiting (discontinued), Dysgeusia, Musculoskeletal chest pain, Nasal congestion, Oropharyngeal pain, Back pain, Abdominal pain, Covid-19, Presyncope, Alanine aminotransferase increased

*90mg dose was administered as 9 x 10mg capsules

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Phase 2b Dose-Ranging Trial

- Placebo controlled dose-ranging study
  - 10 mg, 35 mg and 70 mg AV-101 BID for 24 weeks
  - Targeting 200 patients across 4 dose groups
- Multicenter international trial
- Two or more background PAH therapies
- Functional class II - IV
- Primary endpoint: change in pulmonary vascular resistance (PVR) at 24 weeks
  - Statistically significant improvement on PVR already demonstrated with oral imatinib in multiple third-party clinical trials
  - Validated endpoint
  - Powered to detect statistically significant change
- Key secondary endpoints: Change in 6MWD, NTproBNP, QoL

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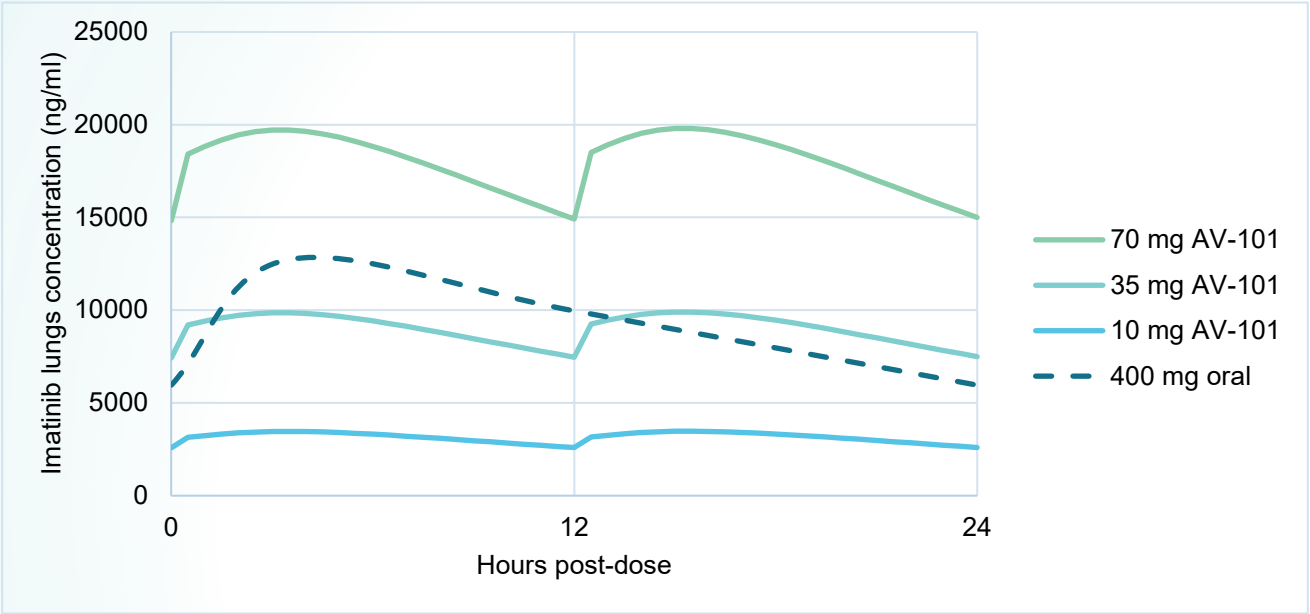
Expected AV-101 Lung Exposures of IMPAHCT Doses, Extrapolated based on Phase 1 Results



Predicted lung concentrations of Phase 2b doses of AV-101 in IMPAHCT trial overlap or surpass 400 mg oral imatinib dose

Predicted lung concentrations extrapolation based on a published PK model using plasma levels observed in Phase 1 trial

CPT Pharmacometrics Syst Pharmacol. 2018 Mar;7(3):147-157. doi: 10.1002/psp4.12270.
ERJ Open Res. 2023 Mar 13;9(2):00433-2022. doi: 10.1183/23120541.00433-2022.

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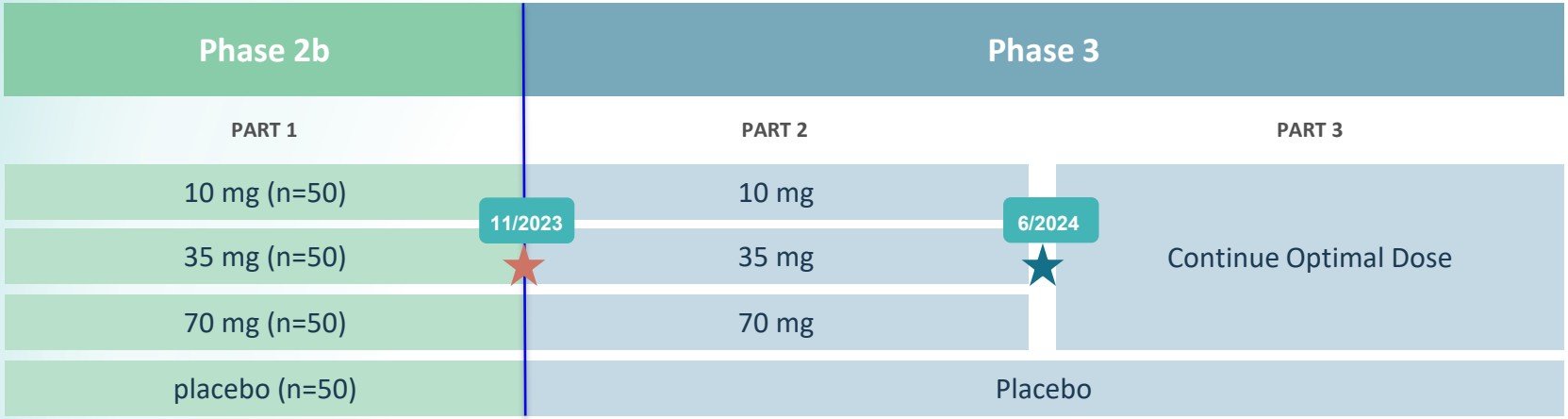
IMPAHCT Phase 2b/3 Seamless Trial of AV-101



- All patients are treated for 24 weeks
- 6MWD is primary endpoint in Phase 3

★ Phase 3 enrollment began immediately upon completion of Phase 2b enrollment

★ Phase 3 dose selected based on Phase 2b data after 24 weeks of follow up

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https://clinicaltrials.gov/study/NCT05036135

Key Baseline Characteristics Among Recent PAH Clinical Trials

Baseline characteristics with first 147 patients from IMPAHCT Ph2b compared with select PAH trials

Measure	IMPAHCT N=147	PULSAR N=106	STELLAR N=323	TORREY N=86
PVR, dynes.sec.cm^{-5}, mean	790	779	764	669
6MWD, m, mean	394	397	401	408
WHO FC II/III	49%; 51%	53%; 47%	49%; 51%	68%; 32%
NTproBNP, pg/mL, mean	754	908	1121	628
Age, years, mean	47	48	48	49
Gender	F82% ; M18%	F87%; M13%	F 79%; M21%	F91%; M9%
IPAH or HPAH	71%	74%	77%	66%
Non-IPAH or HPAH	29%	26%	23%	34%
Mono/Double/triple background	0%; 40%; 59%	9%; 35%; 56%	4%; 35%; 61%	3%; 40%; 57%
Mean PA pressure, mmHg	50.9	52.4	52.6	Not reported
Cardiac index, L/min/m^2	2.7	2.6	2.7	Not reported

The data in the chart above are based on a cross-trial comparison and not a head-to-head clinical trial. Such data may not be directly comparable due to differences in trial design, study protocols, conditions and patient populations.

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Phase 2 Trials for Non-Vasodilator Therapies

	Oral Imatinib	Merck/Acceleron Sotatercept (activin trap)		Gossamer Seralutinib (TKI)
	Phase 2	PULSAR (Ph2)		TORREY (Ph2)
		Low dose	High dose	
PVR	-26.0%	-18.5%	-31.8%	-14.3%
6MWD	+21.7 m P=0.21	+29.4 m P=0.02	+21.4 m P=0.08	+6.5m P=0.597

The data in the chart above are based on a cross-trial comparison and not a head-to-head clinical trial. Such data may not be directly comparable due to differences in trial design, study protocols, conditions and patient populations. The percent reduction in PVR for the Oral Imatinib Phase 2 study is calculated using the placebo corrected arithmetic means. The STELLAR and TORREY study percent reduction in PVR are calculated using least square means (LSM) corrected for placebo.

AV-101: Potential to Be An Ideal Add-On Agent

- Al Launch, AV-101 has the potential to be an ideal add on agent*
  - Compelling clinical profile in combination with current therapies
  - Simplicity and ease-of-use
  - Potential to be part of the future standard of care
- Potential positioning within target populations*
  - In front of inhaled and oral prostacyclin therapy
  - In front of sotatercept for patients who prefer inhalation vs injection and for sotatercept ineligible patients
  - Patients who remain at moderate to high risk of poor outcomes despite sotatercept and prostacyclin therapy
  - Patients who do not tolerate sotatercept and prostacyclin therapy

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*Assumes data and FDA discussions support FDA approval with supportive labeling

AVTE's Perspective on Current And Future PAH Landscape Informed by Extensive Experience, Stakeholder Engagement, and Market Research

- Global Advisory Boards with PAH Experts and PAH Patients
- Interactions with Investigators, KOL's, PAH Treaters, Nurses, Patients, Advocacy Associations*
- Robust Market Research
  - 100+ U.S. Physician Market Landscape Research (Oct 2021)
  - 100+ European Physician Market Landscape Research (June 2022)
  - 150+ U.S. Physician Conjoint Demand Study post Sotatercept Data (Aug 2023)

Prof. Vizza MD investigator discussion

*Individual interactions focus solely on treatment landscape unless seeking bona-fide advice with an appropriate consulting agreement

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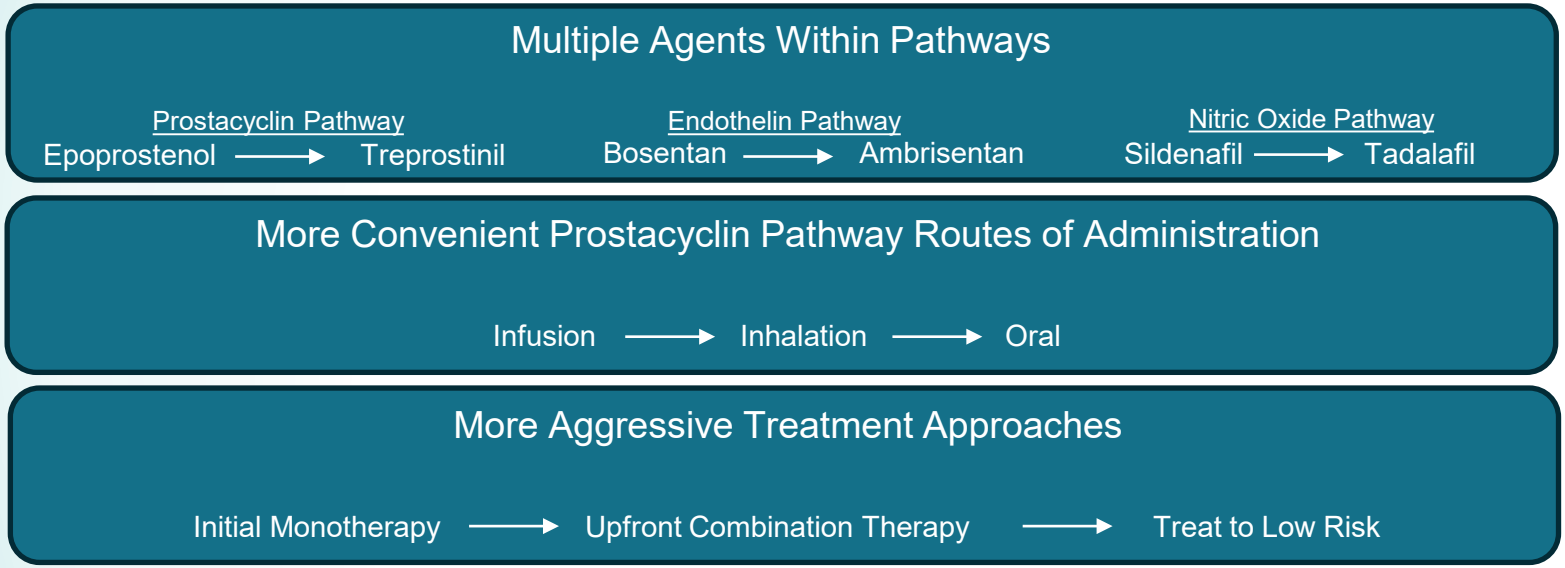
PAH Treatment Pathways Have Not Changed Since 2005 and Outcomes Remain Poor

Significant Efforts to Optimize Traditional Pathways



61%-65% 5 Year Survival among Newly Diagnosed and Prevalent Patients

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Unmet Need Beyond Sotatercept

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Continued Progres
Arteria

Darren B. Taichman, M.D., Ph.D.

Pulmonary arterial hypertension is a devast
disorder characterized by precapillary pu
nary hypertension not caused by respir
disease, obstruction of the pulmonary art
or certain less-common conditions. Idiop
pulmonary arterial hypertension, heritable
monary arterial hypertension, and pulmo
arterial hypertension associated with a co
tive-tissue disease or exposure to drugs su
methamphetamine account for most cases
developed world. For years, pulmonary ar
hypertension was considered to be an un
able, progressive, and rapidly fatal conditio

A new era of treatment for patients with
monary arterial hypertension began three de
ago. Investigations that were focused on i
anced vasoconstriction and vasodilation pro
groundbreaking demonstrations that sus
might be improved with high-dose calc
channel blockers in the small subgroup o
tients with acute vasoreactivity on hemodyn
testing or with continuously infused pros
clin regardless of acute vasoreactivity.[1,2] S
quent trials of agents targeting the prostac
endothelin, or nitric oxide signaling path
led to our current armamentarium of 10
and Drug Administration–approved drugs
alone or in combination to improve exerci
pacity and quality of life and delay disease
gression.[3] Yet despite this era of remar
progress, pulmonary arterial hypertensio
mains deadly for many patients, and ava
treatments provide insufficient functional
quality-of-life gains for many more.

The discovery of disrupted transfor
growth factor β (TGF-β) signaling involvi

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

M.M. Hoeper, D.B. Badesch, H.A. Ghofrani, J.S.R. Gibbs, M. Gomberg-Maitland, V.V. McLaughlin, I.R. Preston, R. Souza, A.B. Waxman, E. Grünig, G. Kopeć, G. Meyer, K.M. Olsson, S. Rosenkranz, Y. Xu, B. Miller, M. Fowler, J. Butler, J. Koglin, J. de Oliveira Pena, and M. Humbert, for the STELLAR Trial Investigators*

ABSTRACT

BACKGROUND

Pulmonary arterial hypertension is a progressive disease involving proliferative remodeling of the pulmonary vessels. Despite therapeutic advances, the diseases-associated morbidity and mortality remain high. Sotatercept is a fusion protein that traps activins and growth differentiation factors involved in pulmonary arterial hypertension.

METHODS

We conducted a multicenter, double-blind, phase 3 trial in which adults with pulmonary arterial hypertension (World Health Organization [WHO] functional class II or III) who were receiving stable background therapy were randomly assigned in a 1:1 ratio to receive subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was the change from baseline at week 24 in the 6-minute walk distance. Nine secondary end points, tested hierarchically in the following order, were multicomponent improvement, change in pulmonary vascular resistance, change in N-terminal pro–B-type natriuretic peptide level, improvement in WHO functional class, time to death or clinical worsening, French risk score, and changes in the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) Physical Impacts, Cardiopulmonary Symptoms, and Cognitive–Emotional Impacts domain scores; all were assessed at week 24 except time to death or clinical worsening, which was assessed when the last patient completed the week 24 visit.

RESULTS

A total of 163 patients were assigned to receive sotatercept and 160 to receive placebo. The median change from baseline at week 24 in the 6-minute walk distance was 34.4 m (95% confidence interval [CI], 33.0 to 35.5) in the sotatercept group and 1.0 m (95% CI, −0.3 to 3.5) in the placebo group. The Hodges–Lehmann estimate of the difference between the sotatercept and placebo groups in the change from baseline at week 24 in the 6-minute walk distance was 40.8 m (95% CI, 27.5 to 54.1; P<0.001). The first eight secondary end points were significantly improved with sotatercept as compared with placebo, whereas the PAH-SYMPACT Cognitive–Emotional Impacts domain score was not. Adverse events that occurred more frequently with sotatercept than with placebo included epistaxis, dizziness, telangiectasia, increased hemoglobin levels, thrombocytopenia, and increased blood pressure.

CONCLUSIONS

In patients with pulmonary arterial hypertension who were receiving stable background therapy, sotatercept resulted in a greater improvement in exercise capacity (as assessed by the 6-minute walk test) than placebo. (Funded by Acceleron Pharma, a subsidiary of MSD; STELLAR ClinicalTrials.gov number, NCT04576988.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hoeper can be contacted at hoeper.marius@mh-hannover.de or at the Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, Carl-Neuberg-Strasse 1, Hannover 30625, Germany.

*The complete list of the STELLAR Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 6, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2211558

N ENGL J MED NEJM.ORG 1

The STELLAR trial represents significant progress in therapy for PAH however…

- 60% of patients did not meet multi-component improvement measure
- 60% of patients did not achieve low risk on the simplified French risk model
- 70% of patients did not improve functional class
- Long term effects not fully established

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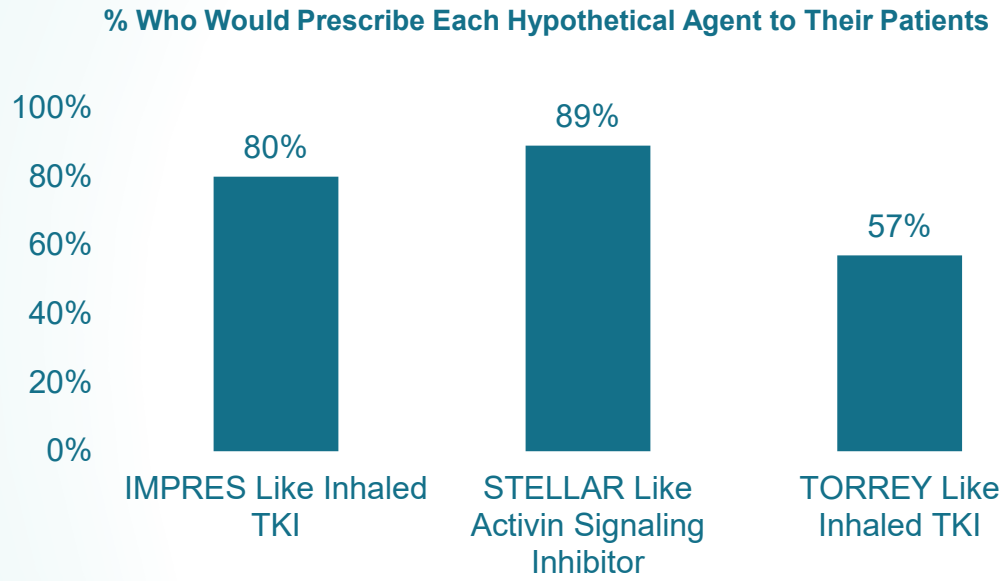
80% of Physicians Would Prescribe an “IMPRES” Like Inhaled TKI if it Were Available Alongside Sotatercept

Market Research with >150 U.S. PAH Treating Physicians Conducted Post STELLAR Data*



*Proprietary Market Research with U.S. PAH Treating Physicians; Aug 2023. Data based on product allocation exercise assuming all hypothetical agents were available

AV-101: Unmet Need, Blockbuster Potential

Positioning

Added to two agents before prostacyclin

Added to three agents before parenteral prostacyclin

~65% (~22,750)

We estimate to be taking 2-3 drugs

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Positive Regulatory Interactions and Feedback

Regulatory Interactions Completed

- FDA Pre-IND meeting in January 2020
- FDA and EMA Orphan Designation granted for AV-101 for the treatment of PAH
- Received EMA Scientific Advice in March 2021
- End-of-Phase-1 Meeting with FDA in April 2021

Feedback from FDA and EMA on Clinical Development

- A single Phase 2b/3 trial could support NDA
- Aligned on Phase 2b/3 endpoints for potential NDA/MAA submission

Intellectual Property Protection for AV-101 to 2040+

Multiple issued US patents covering AV-101 drug product and methods of use

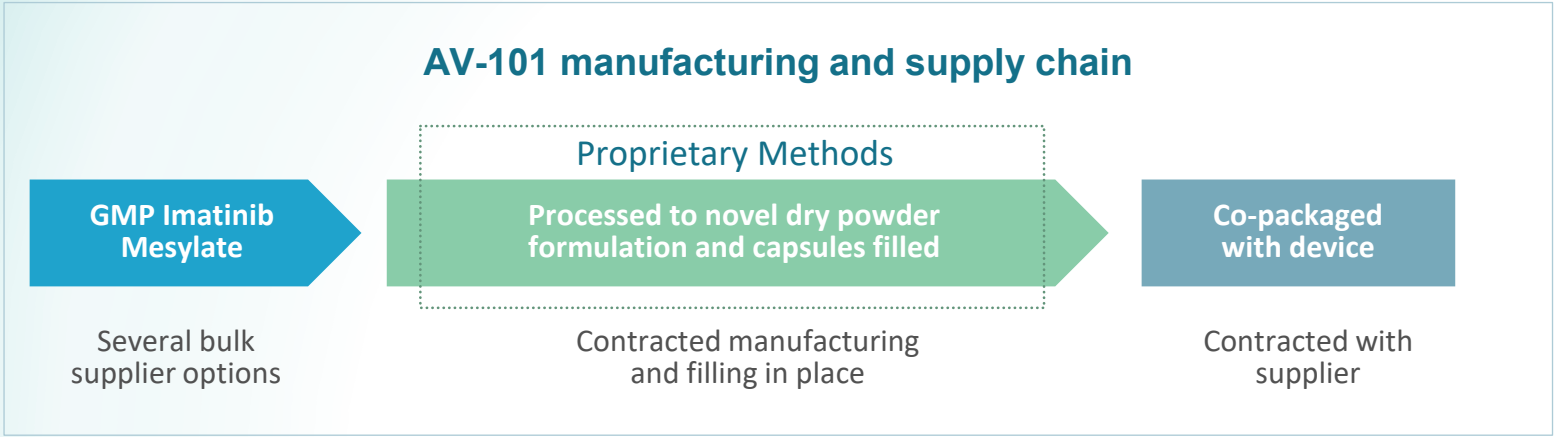
- Patent coverage extends at least until 2040
- Current US patents being extended worldwide

Multiple additional pending applications pursuing

- Methods of manufacture
- Filing on other aerosol compositions
- Filing on mechanism of action (composition agnostic)

Regular reviews enacted to extend or file new IP based on discoveries in research, clinical trials and CMC

Chemistry, Manufacturing and Controls



Stability of AV-101

- Release and stability testing supports
  - API stability of at least 36 months
  - Drug product stability of at least 30 months
- Filled product stability testing ongoing

AV-101 Device and Delivery Performance

AV-101 Device

- Off-the-shelf commercial scale dry powder inhaler
  - No batteries, compressors or cords
  - No sterile vials containing solutions or suspensions
  - CE mark in EU and Device Master File registered with FDA
- Designed for ease of use and convenience
- Intended dosing of 2 capsules twice a day
- Device replaced weekly

AV-101 Delivery Performance

- Consistently high delivered and fine particle dose
- Ideal size and size distribution for lung penetration

NOTE: Device in IMPAHCT was not used in Phase 1 trial, but delivery performance was assessed.

Aerovate: An Inventive Way Forward in PAH

Demonstrated Clinical Benefit

The molecule in AV-101, imatinib, already has shown clinical benefit in a Phase 3 clinical trial conducted by Novartis of oral imatinib mesylate in PAH patients on top of two or more standard of care therapies.

Unfortunately, AEs with oral imatinib were common and development was discontinued

Inventive Solution

Anti-proliferative targeted inhaled dry powder PAH product candidate AV-101 designed to provide robust clinical benefit of imatinib without systemic AEs observed with oral imatinib

Significant Unmet Need

Despite three drug classes approved, 5-year survival for newly diagnosed PAH patients is 61%

Efficient Execution

FDA and EMA orphan designation for AV-101 for the treatment of PAH

Phase 1 SAD/MAD in healthy volunteers complete

Phase 2b portion fully enrolled of seamless Ph2b/3 IMPAHCT trial and already enrolling in Phase 3 portion

Ph2b data expected in June 2024

Established Market

$6B+ market, yet outcomes are poor

aerovate therapeutics

Thank you!