

Design of a Capsule-Based Dry
Powder Inhaler for PAH
Patients: the AOS™ DPI

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PERIPHERAL LUNG-TARGETED THERAPEUTICS TO TREAT CARDIOPULMONARY DISEASES

Pulmonary Arterial Hypertension (PAH)

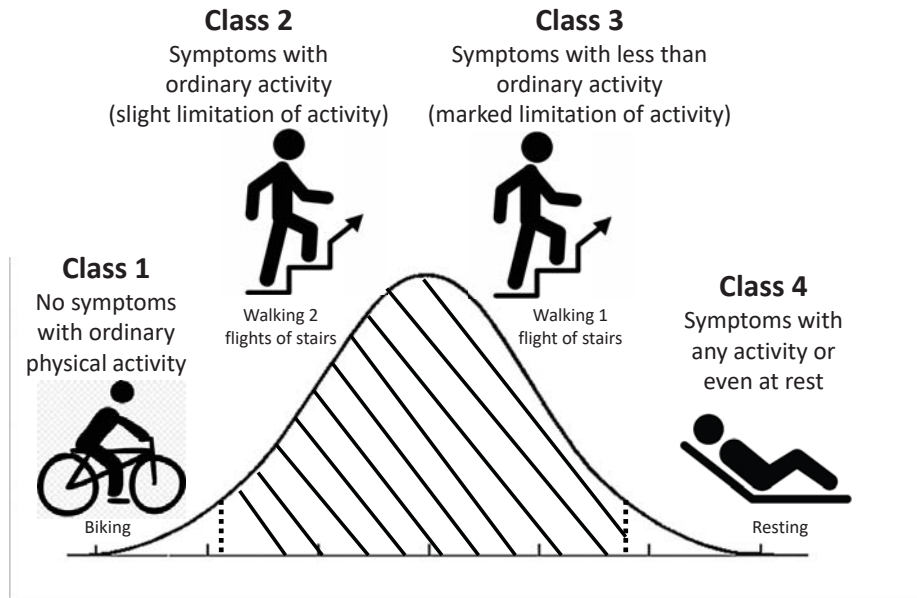


Source: Farber, 2004

- **PAH is a chronic disease characterized by proliferation and remodeling of vascular endotheli and smooth muscle cells in the small pulmonary arteries and arterioles**
 - ~ 50,000 PAH patients in the United States
 - ~ 80% are female
 - Mean age is 53 ± 15 years
- **Most common symptoms are:**
 - Dyspnea (i.e. shortness of breath)
 - Physical fatigue
 - Low exercise capacity

PAH Functional Classes

Patient's Quality of Life (QoL) is affected by the progressive increase in symptoms over time



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PAH symptoms and treatments have a profound impact on a patient's Quality of Life (QoL)

➤ Impact of PAH on daily life

- Inability to perform at work
- Difficulty completing household & family activities
- Impact on relationships
- Fear of being alone during severe bouts of symptoms
- Embarrassment of experiencing symptoms in public
- Loss of independence or of purpose

➤ QoL improves with a patient's ability and capacity to satisfy his or her needs

Improving a patient's QoL is an unmet medical need



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Treatment designed to improve the QoL of PAH patients

Key features:

- **'As-needed' dosage form and convenient (i.e., PRN medication)**
- **Rapid onset of action (within ~15 min)**
- **Acceptable duration of action (~3 h)**
- **No added issues over background therapy (i.e., safety, tolerability)**
- **Noninvasive, portable delivery system that is:**
 - Designed for PAH patients
 - Does not contribute significantly to a patient's daily treatment burden
 - Discreetly administered outside the home
 - Simple to administer with no cleaning requirements



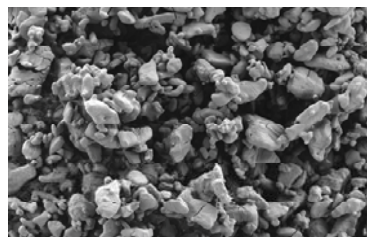
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RT234: Vardenafil Inhalation Powder

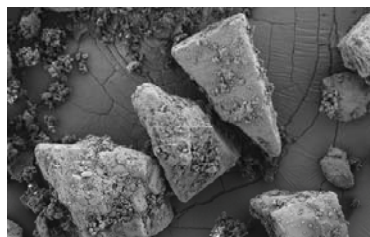
RT234 is a drug-device combination product

RT234 Product: AOS™ DPI delivering Vardenafil Inhalation Powder

It is an **'as-needed'** treatment of PAH symptoms to improve exercise capacity, physical function, and disease-associated symptoms



Drug substance
Vardenafil hydrochloride trihydrate



Drug Product
Adhesive mixture with lactose carrier particles filled into HPMC capsules



Primary Packaging
HDPE bottle / cap

Device
AOS™ DPI



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Dispersing the drug particles is patient driven

- Patients must pierce the capsule to allow the drug to release from the capsule



Insert the capsule into the capsule seat



With the AOS DPI upright, press the piercing buttons all the way in



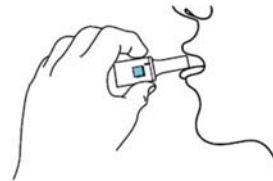
Release the piercing buttons
Close the mouthpiece



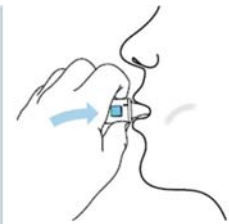
- Upon inhalation, the pierced capsule will rotate allowing the drug and lactose to leave the capsule

- As the particles travel through the inhaler, the drug separates it from the lactose allowing travel to the deep lungs

- Dispersion is patient driven by their inhalation



Place the mouthpiece in the mouth **over the tongue**
Seal lips around the mouthpiece



Inhale with maximal effort until your lungs are full



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Respira's Axial Oscillating Sphere Dry Powder Inhaler (AOS™ DPI)

- Identical in size and shape to Plastiapi's RS01 DPI
- Identical user operation (i.e., Instructions for Use)
- Differentiation can be achieved by changing the artwork, cap, or buttons



AOS™ DPI

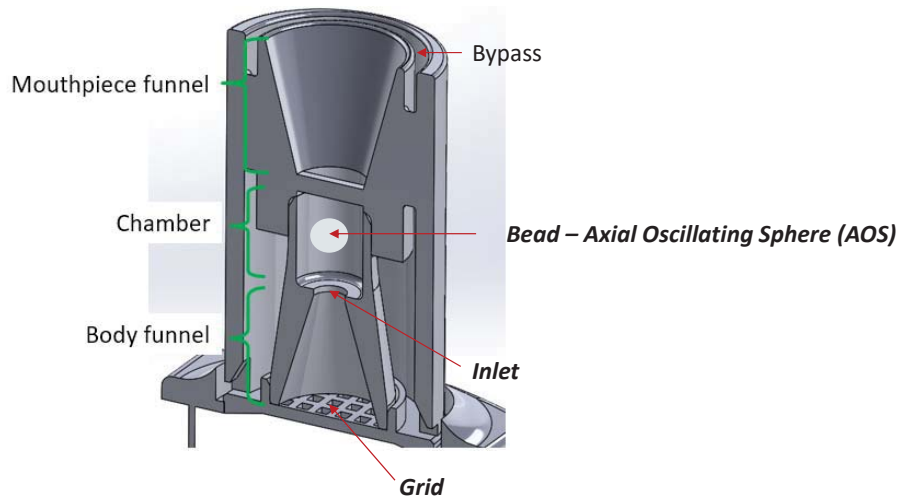
Plastiapi's RS01 DP

So where does the difference lie?
Respira's Aerosol Engine



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AOS™ Aerosol Engine

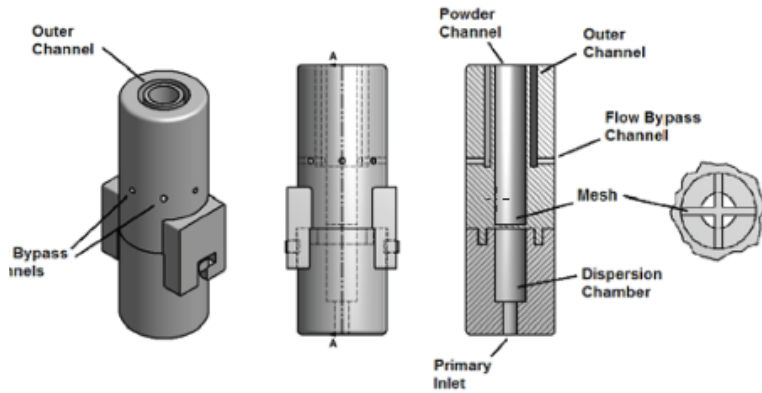


AOS™ Engine

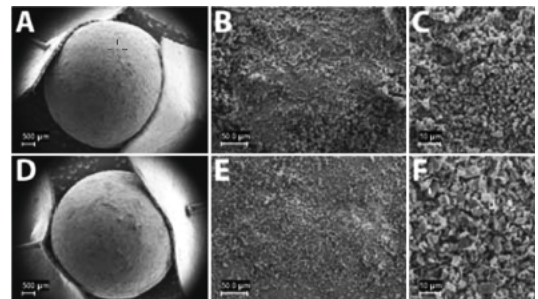


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Evolution of the AOS™ DPI



Drug on Bead Technology



Source: Donovan MJ, Gibbons A, Pappo J, Smyth HDC: Nov resistance DPI for high efficiency delivery in a broad range of classes. Respiratory Drug Delivery 2012.

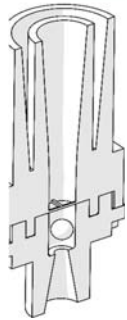
API	Dose (mcg)	FPF (%)
Budesonide	215	83 (2%)
Fluticasone Propionate	112	81 (2%)
Albuterol Sulphate	81	91 (2%)
Salmeterol	36	89 (3%)
Tiotropium Bromide	20	85 (2%)



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Concept evolved into using the bead as part of an aerosol engine to enhance powder dispersion

Add AOS engine onto marketed inhalers



Device	API/Product	Dose (µg)	FPD<3µm ² (µg)	AOS FPD Enhancement
Diskus	Flovent	250	30	2.2X
Diskus+AOS			67	
HH	PDE5i	4000	632	2.6X
HH+AOS			1633	
RS01	Foradil	12	1.8	1.5X
RS01+AOS			2.7	
RS01	PDE5i	4000	1254	1.7X
RS01+AOS			2136	

Source: Hannon J et al: Novel high efficiency inhaler for PDE5i delivery. Respiratory Drug Delivery 2016



Diskus®

FPD_{<3µm}: ↑2.2x



Handihaler®

↑2.6x



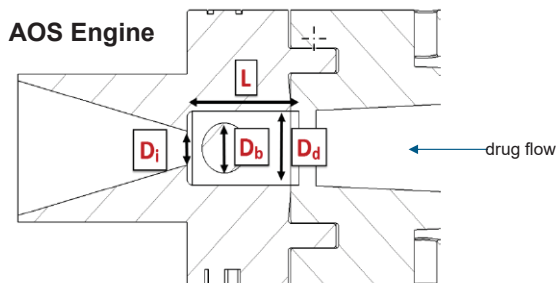
RS

↑1



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Design optimization of the AOS™ DPI



Features studied

- Use of bypass flow to lower resistance
- Dimensions of the AOS chamber
- Size of the inlet orifice
- Size, density, and material used for the bead
- Pitch of inlet and outlet funnels
- Shape of the exit funnel (circular vs. o

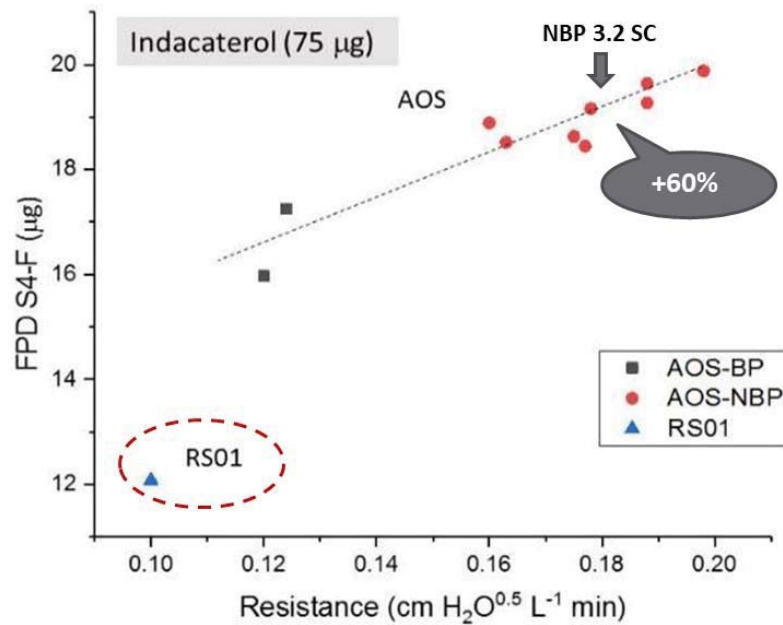
Constraints imposed

- High device resistance
- Optimization of FPDS4-F
- Use RS01 base assembly
- Maintain external dimensions of RS01 mouthpiece



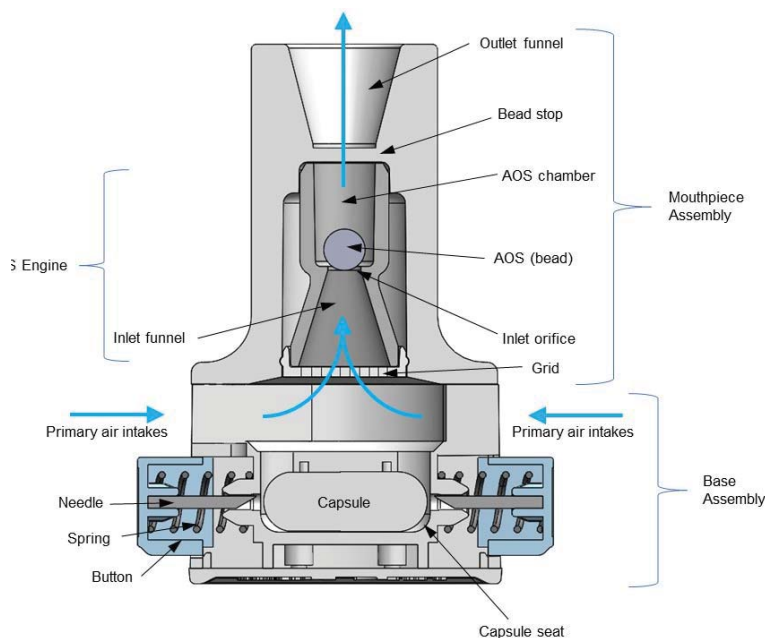
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FPD_{S4-F} improves with device resistance



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Design elements of the AOS™ DPI



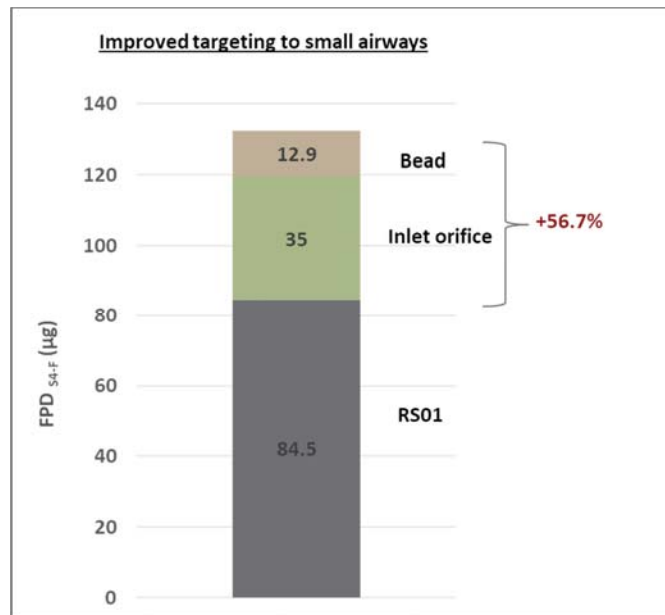
Four distinct dispersion elements lead improved dose delivery to the small airways / pulmonary arterioles

- 4. AOS (or Bead)** Impaction force with AOS and w
- 3. Inlet Orifice** Increased particle velocity thru inlet orifice resulting in increase particle shear (Bernoulli effect)
- 2. Grid** Impaction force with static grid
- 1. Capsule** Collision between particles as they leave the capsules during rotation



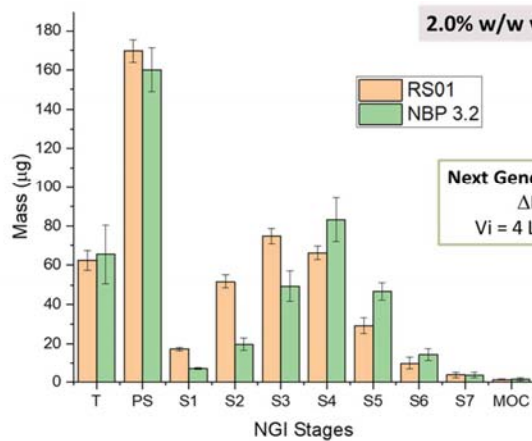
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AOS™ DPI improves $FPD_{S4-F} > 50\%$ over RS01



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Addition of the AOS engine into the RS01 mouthpiece assembly increases peripheral delivery



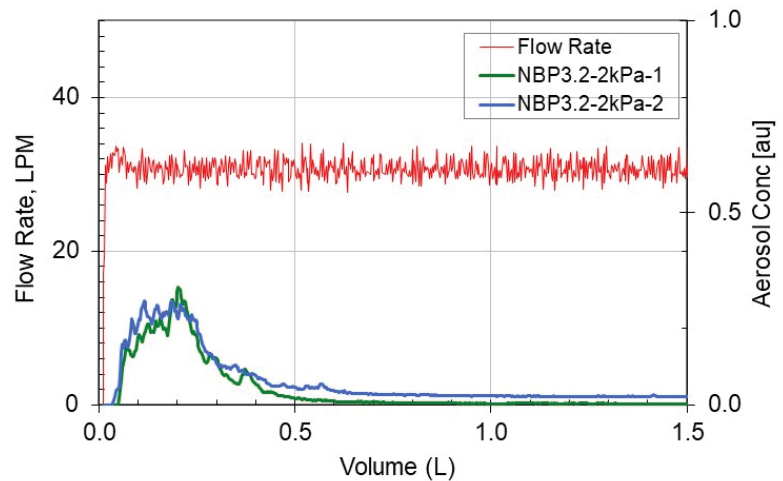
Drug Formulation	FPD _{S4-F} (%ED)		
	RS01	AOS	AOS/RS01
Vardenafil (LB)	17.2	28.6	+ 70%
Indacaterol (LB)	21.7	38.6	+ 80%
Ciprofloxacin (EP)	36.0	60.7	+ 70%
Amphotericin B (EP)	84.0	94.5	+ 10%



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Capsule emptying with the AOS™ DPI

- Laser photometry
- $\Delta P = 2\text{kPa}$
- $V_i \sim 0.5\text{ L}$ empties a 25 mg fill mass capsule

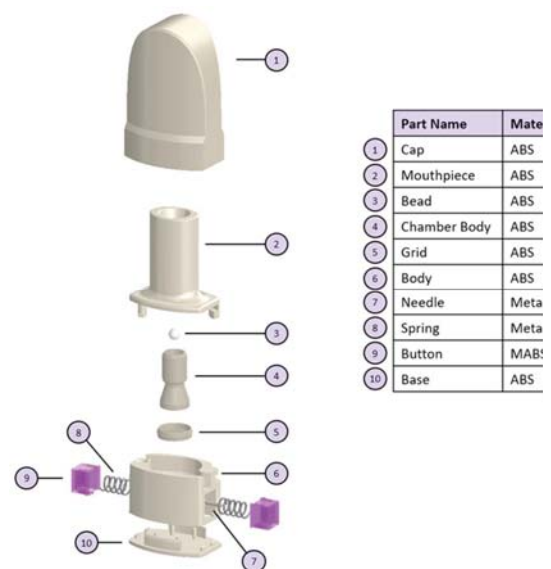


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Manufacturing of the AOS™ DPI

- Manufacturer is Plastiape S.p.A., Osnago, Italy
- Plastiape S.p.A. holds the Declaration of Conformity for the AOS DPI's CE Mark
- Resins are the same as the RS01 DPI
- AOS components are molded using 2 cavity hard steel tools
- AOS (i.e. Bead) is a bought-in component using the same resin
- Assembly process is semi-automated in ISO 7 clean room
 - Hand-assemble the AOS Mouthpiece
 - Existing automation line is used for final assembly



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Can a PAH patient use the AOS™ DPI?

➤ Increased resistance

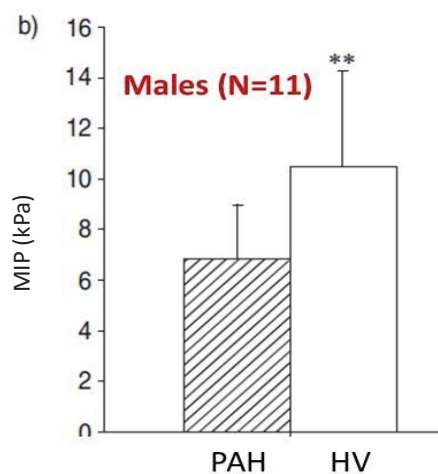
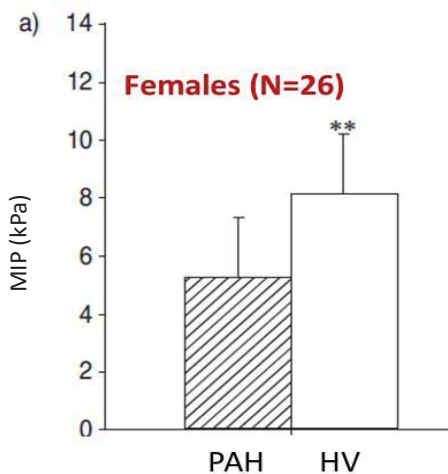
- Hypothesis: Increased device resistance leads patients to provide greater inspiratory effort – without having to instruct them to

➤ Capsule piercing force

- Hypothesis: Current springs used to puncture the capsules are not too difficult for the patients



PAH patients have decreased muscle strength



❖ On average, female PAH patient exhibit the MIP of a seven-year old child (Clark, 2015)

❖ To achieve effective dose delivery a user must provide a PIP > 1 kPa (Clark, 2019)

sources: - Meyer FJ et al: Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J. 2005;25:125-130.
- Clark AR: The role of inspiratory pressures in determining the flow rate through dry powder inhalers: a review. Curr Pharm Design. 2015;21:3973-3983.
- Clark AR et al: The confusing world of dry powder inhalers: It is all about inspiratory pressures, not inspiratory flow rates. J Aerosol Med Pulm Drug Deliv. 2019; doi: 10.1089/jamp.2019.1556.



Human Factors Study in subjects with PAH

aka: "Breathing Study"

➤ Study objectives, to assess:

- Impact of device resistance (high, medium & low) on inspiratory flow profiles
- Impact of inhalation instructions on inspiratory flow profiles (using the AOS DPI)
- Subject's ability to depress the spring-loaded buttons and pierce the capsule
- Suitability of the AOS™ DPI for PAH patients use

➤ Study conducted

- at Houston Methodist, Sandeep Sahay, MD as the Principal Investigator
- where 35 PAH patients were tested (no drug was administered)



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Patient demographics

Characteristic	Value (N=35)
Sex (% Female)	91.7
Age (mean ± SD), years	49.7 ± 12.2
Functional Class (% Class I)	2.8
Functional Class (% Class II)	62.9
Functional Class (% Class III)	31.4
Functional Class (% Class IV)	2.8
FEV ₁ % predicted (mean ± SD)	67.0 ± 18.0
% moderately severe*	25.7
% severe, very severe*	14.3
6MWT (mean ± SD), meters	394.8 ± 57.5

*ATS/ERS Guidelines

Etiology	Subjects (%)
Idiopathic, familial	45.7
Associated with connective tissue disease	40.0
Other	14.3

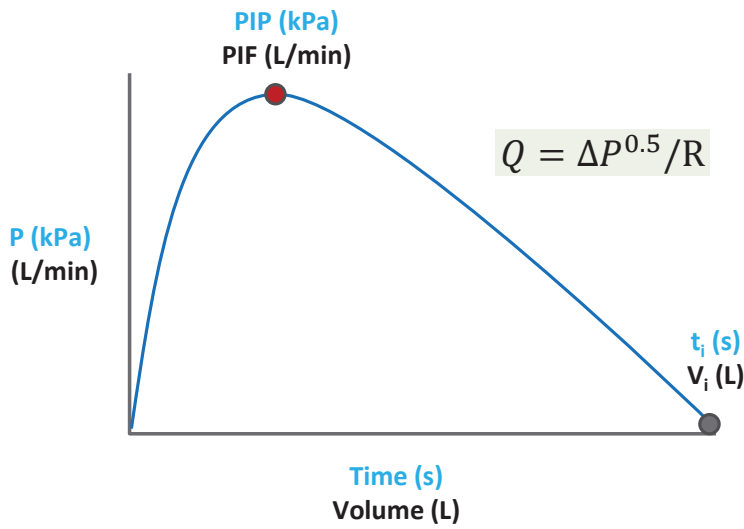
Background Medications	Subjects (%)	
ERA	5.7	} Monotherapy: 5.7
PDE5i / ERA	28.6	
PDE5i / PC	8.6	} Dual therapy: 42.9
ERA / PC	2.9	
sGC/ERA	2.9	
PDE5i / ERA / PC	31.4	} Triple therapy: 51.3
sGC / ERA / PC	20.0	



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Idealized inspiratory flow profile



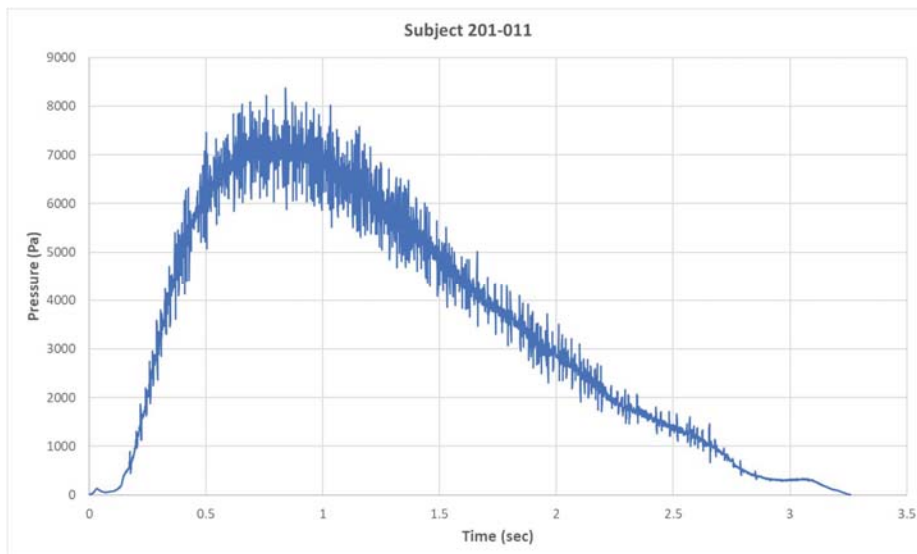
Metric	Parameter
PIP	Maximum pressure drop
PIF	Peak inspiratory flow rate
V_i	Inhalation volume
t_i	Inhalation time
Q	Flowrate
ΔP	Pressure drop
R	Device resistance

R is measured in the lab
 ΔP , PIP and t_i are measured
 Q, V_i and PIF can be calculated



1 subject's inspiratory profile

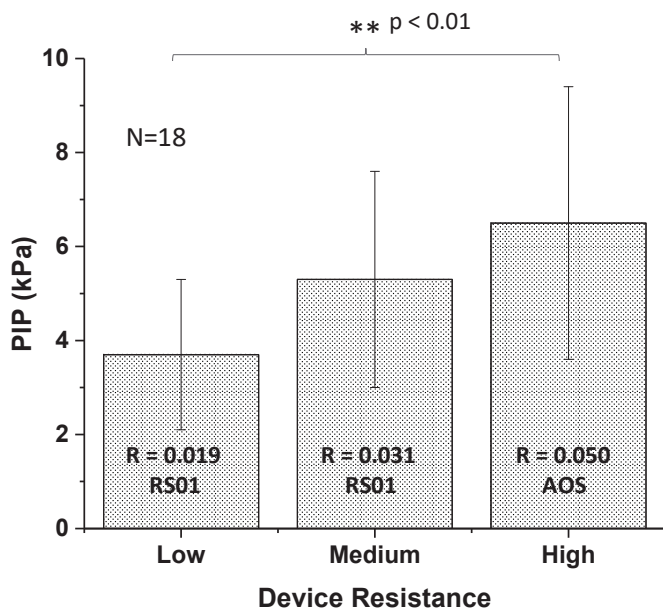
- Signature inhalation profile of the AOS™ DPI
- Fluctuations in the profile is a function of the Bead oscillating



Metric	Parameter
PIP	7.2 kPa
PIF	54 LPM
V_i	1.8 L
t_i	3.3 sec
R	0.16 cmH ₂ O ^{0.5} /LPM



Inhaling against a resistance encourages PAH subjects to provide greater effort

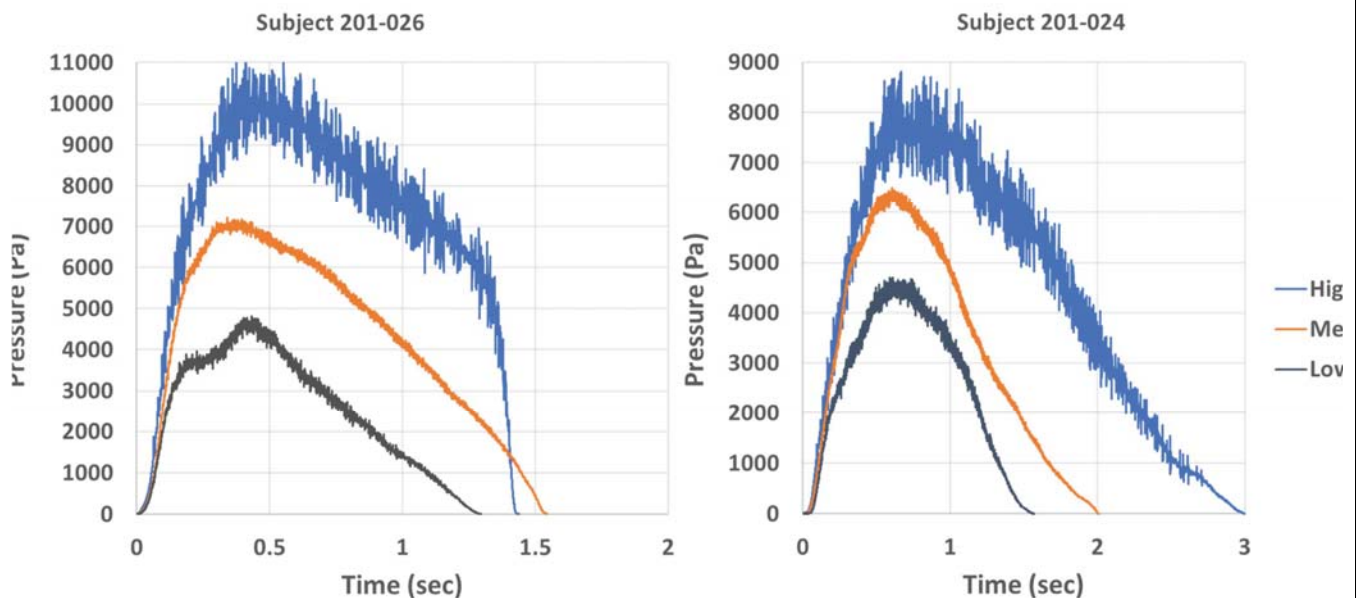


- 3 device resistances were tested (randomized)
 - High-AOS™ DPI = 0.16 cmH₂O^{0.5}/LPM = 0.050
 - Med-RS01 DPI = 0.10 cmH₂O^{0.5}/LPM = 0.031
 - Low-RS01 DPI = 0.06 cmH₂O^{0.5}/LPM = 0.019
- Subjects were instructed to **Exhale fully, Inhale with maximal effort until your lungs are full**
- Mean PIP increased from
 - 3.7 kPa for the low resistance RS01 DPI to
 - 6.5 kPa for the high resistance AOS™ DPI
- Mean inhaled volume was
 - 1.9 L for the RS01 DPI and
 - 1.7 L for the AOS DPI



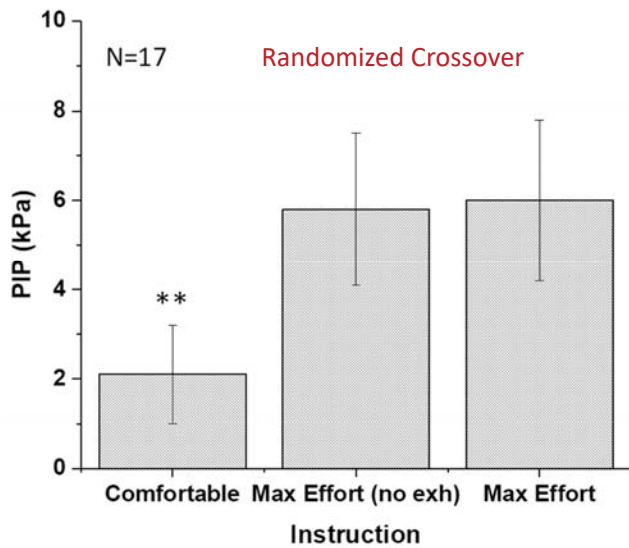
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Inspiratory flow profiles with varying resistance DPIs



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AOS™ DPI inhalation instructions are important

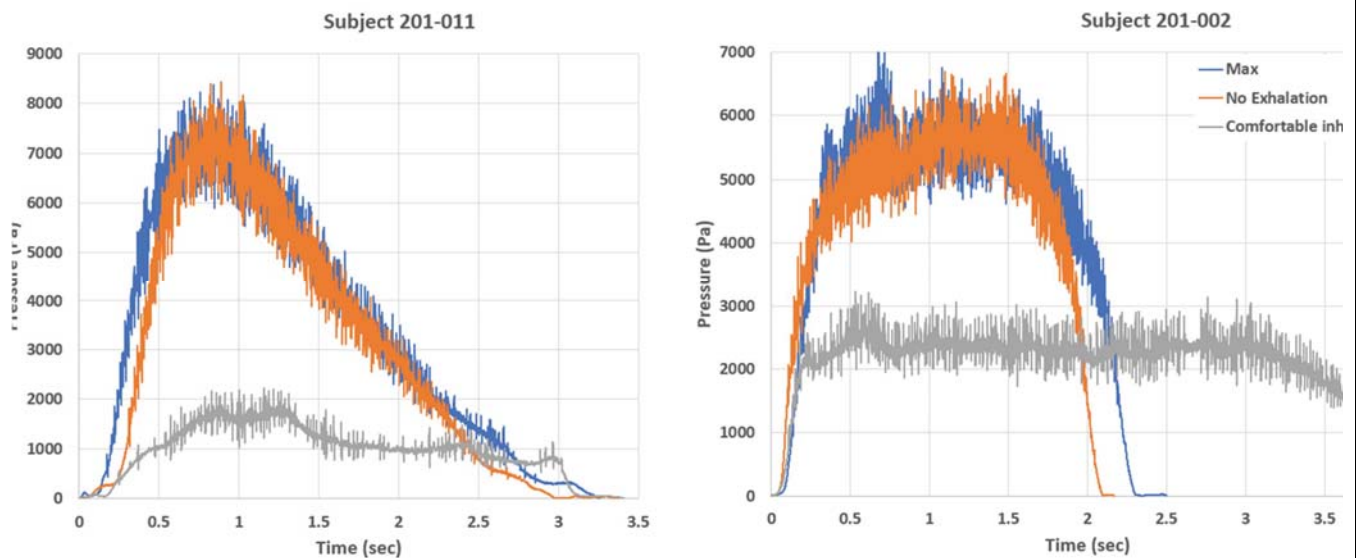


- ❖ AOS™ DPI resistance = 0.16 cmH₂O^{0.5}/LPM
- ❖ 3 instructions were given in a randomized order
 - Exhale fully, Inhale with maximal effort until your lungs are full
 - Inhale with maximal effort until your lungs are full
 - Exhale fully, Inhale with comfortably until your lungs are full
- ❖ Maximal effort instructions leads to a significantly greater PIP
 - 6.0 kPa for maximal effort versus 2.1 kPa for comfortable effort
- ❖ Exhalation before inhalation is not critical to dose delivery



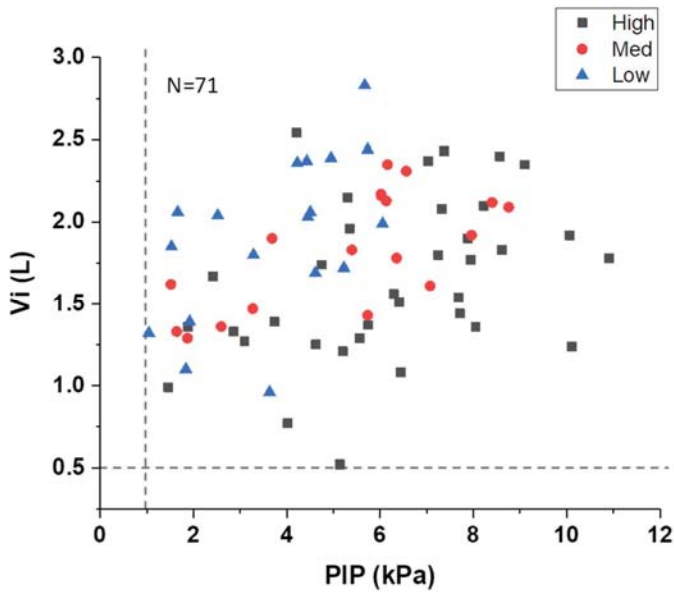
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Inspiratory flow profiles with varying inhalation instructions



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Higher resistance AOS™ DPI leads PAH subjects to achieve higher PIP values



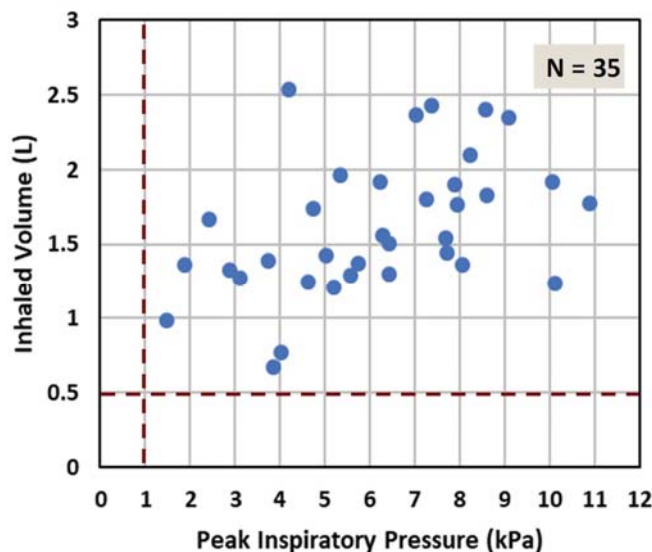
- ❖ 3 device resistances
 - High-AOS DPI = 0.16 $\text{cmH}_2\text{O}^{0.5}/\text{LPM}$
 - Med-RS01 DPI = 0.10 $\text{cmH}_2\text{O}^{0.5}/\text{LPM}$
 - Low-RS01 DPI = 0.06 $\text{cmH}_2\text{O}^{0.5}/\text{LPM}$
- ❖ All subject profiles met the target criteria of $V_i > 0.5$ L
- ❖ A greater proportion of the RS01 (low and medium resistance) PIP values are less than 2 kPa



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All PAH subjects achieved the inspiratory parameters needed for effective dose delivery

Instruction: Exhale fully, Inhale with maximal effort until your lungs are full



Mean PIP ± SD : 6.2 ± 2.4 kPa
 Mean V_i ± SD : 1.6 ± 0.5 L



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PAH patients find it 'easy' to pierce capsules

Very Easy – Easy – Moderate – Difficult – Very Difficult
 5 4 3 2 1

Capsule Piercing Metrics	Spring 1	Spring 2	Spring 3
Mean	4.09	4.40	4.66
SD	0.66	0.60	0.48
% Easy / Very Easy	83	97	100
% Medium	17	3	0
Difficult / Very Difficult	0	0	0

- ❖ Each subject was asked to puncture capsules using 3 different inhalers (n=35 randomized)
- ❖ 3 different springs forces used in a randomized order to puncture capsule
 - Spring 1 requires 12 N – utilized by AOS DPI
 - Spring 2 requires 8.7 N
 - Spring 3 requires 5.3 N
- ❖ Likert Scale: Ease of Piercing capsule
 - Very Easy = 5
 - Easy = 4
 - Moderate = 3
 - Difficult = 2
 - Very Difficult = 1



PAH patients have plenty of strength to puncture a capsule

Mean pinch force: 54.0 ± 16.3 N (N=26)



➤ **54 N exceeds the 12 N required to puncture the capsule using the AOS™ DPI**



Conclusions

- **AOS™ DPI is a noninvasive portable delivery system that is able to**
 - Disperse drug formulations effectively for delivery to the small arteries
 - Be used by PAH patients
- **AOS™ DPI holds a CE Mark and utilizes semi-automated manufacturing**
- **AOS™ DPI inhaling with maximal effort**
 - Helps PAH patients achieve PIP values close to their projected MIP values (MIP ~ 6 kPa)
 - Were able to achieve PIPs needed for effective dose delivery (PIP > 1 kPa)
 - Were able to achieve inhaled volumes to empty the powder from the capsule ($V_i > 0.5$ L)
- **PAH patients**
 - Found piercing capsules with the AOS™ DPI to be easy
 - Mean pinch force was 54.0 N exceeding the 12.0 N force required to pierce the capsules with the AOS™ DPI



Last thoughts

- **AOS™ DPI – Instructions For Use**
 - Patients should be instructed to “Inhale with maximal effort until their lungs are full”
 - Exhaling before inhaling is not a critical step in dose delivery
- **RT234 Product may have a profound impact on a PAH patient’s Quality of Life**



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- **Plastiape S.p.A.**



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3



*" I have seen a medicine that's
able to breathe life into a stone "*

All's Well That Ends Well — William Shakespeare