Poster: 04271

Comparison of Dry Powder Inhaler (DPI) Devices for Use With a Long-Acting Pulmonary Vasodilator, DP-INS1009

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INTRODUCTION

- INS1009 is a long-acting pulmonary vasodilator that contains hexadecyl treprostinil (C16TR) prodrug formulated in a lipid nanoparticle suspension (**Figure 1**) for inhaled delivery by nebulization.[1]
- INS1009 demonstrates long-acting pulmonary vasodilation in rats and dogs with lower plasma treprostinil (TRE) maximum concentration (C_{max}) and area under the concentration time curve at 0 to 24 hours (AUC_{0-24}) compared with inhaled TRE.[2,3]
- In a Phase 1 study in healthy volunteers, nebulized INS1009 had a substantially lower C_{max} than inhaled TRE and provided sustained levels of TRE in plasma over 12 h.[4,5]
- A dry powder formulation of INS1009 (DP-INS1009) has been developed that maintains the integrity of the C16TR lipid nanoparticles and has similar characteristics to nebulized INS1009 in terms of aerosol particle size (*i.e.*, mass median aerodynamic diameter [MMAD] < 4 μm) and plasma and lung pharmacokinetics following inhalation in rats.[3]
- Four different DPI devices were evaluated *in vitro* to determine which would be best suited to deliver an experimental dry powder formulation of INS1009.

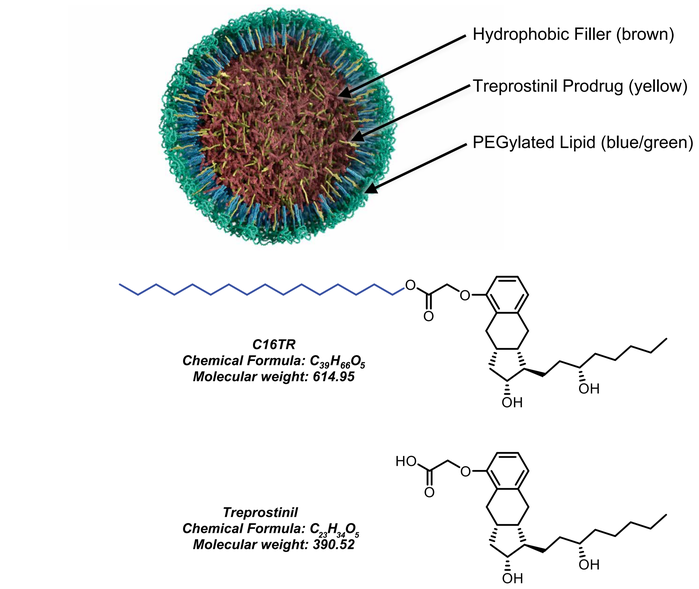


Figure 1. INS1009 (lipid nanoparticle C16TR), and chemical formula and molecular weight for C16TR and treprostinil.

AIMS

- To evaluate different DPI devices to select the best for delivery of DP-INS1009 based upon MMAD.

METHODS

DP-INS1009

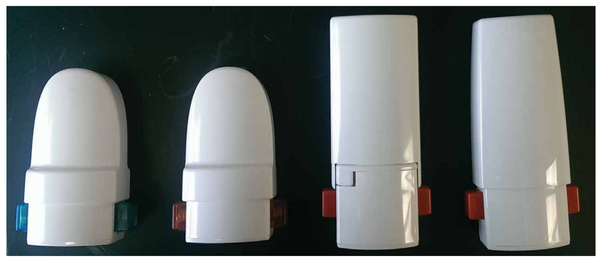
- DP-INS1009 was formulated via a two-stage process involving spray drying of INS1009 mixed with lactose solution (100:1 Lactose/C16TR ratio), followed by two rounds of micronization in a jet mill to reduce particle size (pass 1 and pass 2).

DPI Device

- Four different DPI devices (Plastiape, Italy) were first tested with micronized lactose Lactohale® 300 (d50 < 5 μm, DFE Pharma, Paramus, NJ, USA) for their MMAD values using Next Generation Impactor (NGI) at 60 L/min. The four devices are: Device 1 (low resistance, 2 pins), Device 2 (high resistance, 2 pins), and Devices 3 and 4 (low resistance, 4 pins, different external configuration) (**Figure 2**). Approximately 50 mg of micronized lactose was loaded to a Size # 2 capsule. This capsule was loaded to the DPI device and tested. Using lactose as the test article, the device that resulted in the smallest MMAD value was further tested with pass 1 and pass 2 DP-INS1009. The MMAD values were then compared with that of the dry powder aerosols obtained from a nose-only inhalation chamber study. The drug amount deposited on each stage of impactor and filter were analyzed by high-performance liquid chromatography.

Nose-Only Inhalation

- DP-INS1009 was delivered through a 12-port nose-only inhalation chamber using a dry powder dispenser (Vilnius Aerosol Generator (VAG), CH Technologies, Westwood, NJ, USA). Aerosol MMAD (μm) was measured at the ports of chamber using a Marple Impactor at a flow rate of 2 L/min (**Figure 3**).



Device	1	2	3	4
Resistance	Low	High	Low	Low
Number of pins	2	2	4	4

Figure 2. Four types of dry powder inhalers.

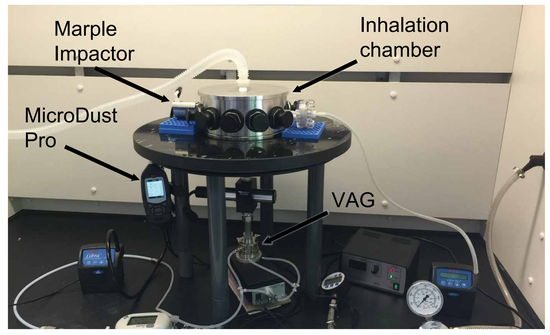


Figure 3. Dry powder delivery system to rats: A 12-port nose-only inhalation chamber with a dry powder dispenser Vilnius Aerosol Generator (VAG).

RESULTS

DPI Device

- MMAD results of micronized lactose after being aerosolized with four different DPI devices are summarized in **Table 1**.
- Device 4 resulted in the smallest MMAD value: 3.8 ± 0.1 μm (n = 3).
- The aerosol particle size distribution of micronized lactose from Device 4 is shown in **Figure 4**. Values are the mean ± standard deviation (SD).
- The particle size and distribution with DP-INS1009 (pass 1 and pass 2, 3.3-3.8 μm) in Device 4 produced similar results to those obtained with micronized lactose using the NGI **(Figure 5)**.

Table 1. Summary of MMAD and Geometric Standard Deviation (GSD) Values of Four DPI Devices With Aerosolized Micronized Lactose

	Device 1	Device 2	Device 3	Device 4
MMAD (μm) ± SD	5.4 (± 0.9)	4.8 (± 0.1)	4.2 (± 0.1)	3.8 (± 0.1)
GSD ± SD	2.1 (± 0.0)	2.1 (± 0.0)	2.0 (± 0.1)	1.9 (± 0.0)

MMAD, mass median aerodynamic diameter; SD, standard deviation.

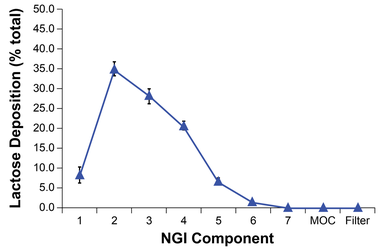


Figure 4. Aerosol particle size distribution of micronized lactose measured in Device 4 from the NGI.
MOC, Micro-Orifice Collector; NGI, Next Generation Impactor.

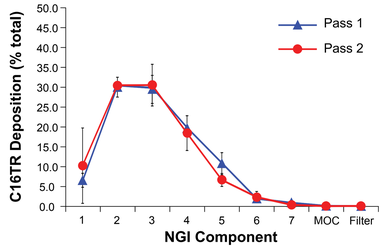


Figure 5. Aerosol particle size distribution of DP-INS1009 (MMAD 3.3 μm and 3.8 μm for pass 1 and pass 2, respectively) measured in Device 4 from the NGI.
MMAD, mass median aerodynamic diameter; MOC, Micro-Orifice Collector; NGI, Next Generation Impactor.

Nose-Only Inhalation

- A small amount of powder (50-200 mg) can be aerosolized with the Vilnius Aerosol Generator.
- The peak DP-INS1009 dry powder concentration measured by MicroDust Pro can be well controlled by the voltage setup of the Vilnius Aerosol Generator, as summarized in **Figure 6**.
- There is a correlation between the voltage setup and the resulting peak dry powder concentration, as summarized in **Table 2** and **Figure 7**.
- The aerosol particle size distribution of aerosolized DP-INS1009 generated with a Vilnius Aerosol Generator and delivered through a nose-only inhalation tower is shown in **Figure 8**.
- There was no significant difference in MMAD values when DP-INS1009 was aerosolized through the nose-only chamber using a Vilnius Aerosol Generator and using the DPI Device 4, as shown in **Table 3**.

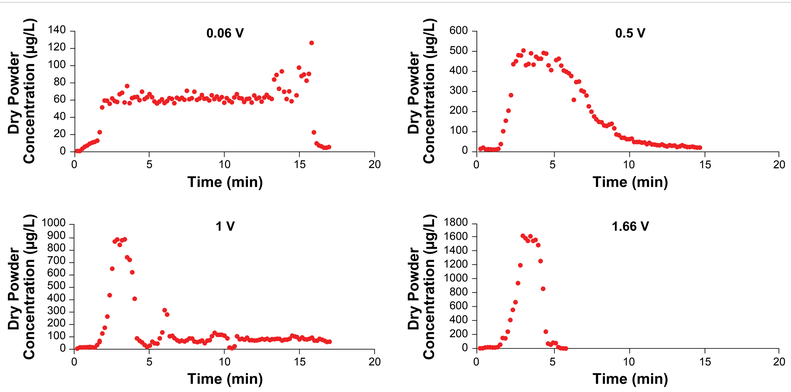


Figure 6. Dry powder aerosol concentration (μg/L, recorded by MicroDust Pro) with time at different setup voltage: 0.06 V, 0.5 V, 1 V, and 1.66 V.

Table 2. Correlation of Setup Voltage vs. Resulting Peak Dry Powder Concentration When DP-INS1009 Was Aerosolized

Vilnius Aerosol Generator Setup Voltage (V)	Average Peak Dry Powder Concentration (μg/L)	Standard Deviation
0.06	62.7	3.9
0.5	460.3	26.9
1	872.3	18.7
1.66	1553.9	46.1

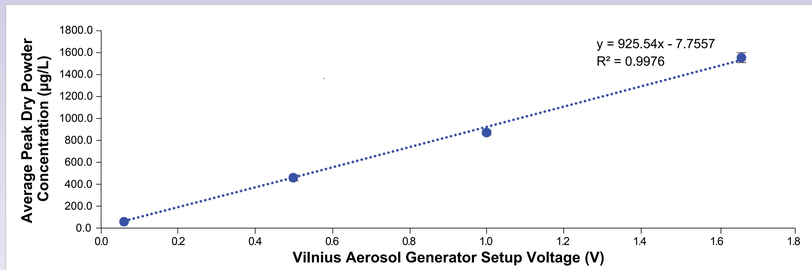


Figure 7. Correlation of setup voltage vs. resulting peak dry powder concentration when DP-INS1009 was aerosolized.

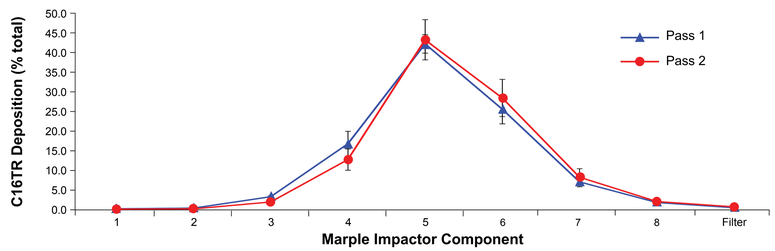


Figure 8. Aerosol particle size distribution of DP-INS1009 (MMAD 3.4 μm and 3.2 μm for pass 1 and pass 2) generated in the nose-only inhalation tower.
MMAD, mass median aerodynamic diameter.

Table 3. Comparison of MMAD (±SD) Values of Aerosols Generated From Dry Powder Dispenser and From DPI

	MMAD		*P*-value[a]
	From Dry Powder Dispenser (NGI)	From DPI (Marple Impactor)	
Pass 1	3.3 μm (± 0.1)	3.4 μm (± 0.1)	0.27
Pass 2	3.8 μm (± 0.8)	3.2 μm (± 0.1)	0.24

DPI, dry powder inhaler; MMAD, mass median aerodynamic diameter; NGI, Next Generation Impactor; SD, standard deviation.
[a]Comparison of NGI and Marple Impactor using a t-test.

CONCLUSIONS

- A dry powder aerosol delivery system was set up successfully with only small amount of formulation powder required (in milligram range).
- Aerosol particle size from DPI Device 4 was less than 4 μm by NGI measurement and comparable to that using a nose-only inhalation system, with the MMAD value by Marple Impactor ranging from 3.2 to 3.4 μm.
- Based upon similarities in the emitted dose characteristics of INS1009 between DPI Device 4 and the device used in prior animal studies, we believe that DPI Device 4 may be suitable for use with DP-INS1009 in future clinical studies.

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ACKNOWLEDGMENTS

The authors acknowledge Connexion Healthcare (Newtown, PA) for providing editorial, layout, and design support. Insmed Incorporated (Bridgewater, NJ) provided funding to Connexion Healthcare for these services. This research was funded by Insmed Incorporated.

DISCLOSURES

Zhili Li, Helena Gauani, Pallavi Venugopal, Adam J. Plaunt, Richard W. Chapman, Vladimir Malinin, Michel R. Corboz, Walter R. Perkins are employees of Insmed Incorporated.
Manjari Bhamidipati is a graduate student at Rutgers University, Piscataway.

Poster presented at Respiratory Drug Delivery (RDD) Europe 2017, 25-28 April, 2017, Antibes, France.