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 treprostinil treprostil (C16TR) prodrug formulated in a lipophilic 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 (Cmax) and area under the concentration time curve at 0 to 24 hours (AUC0-24) compared with inhaled TRE.1,2
- A dry powder formulation of INS1009 (DPI-INS1009) has been developed that maintains the integrity of the C16TR lipophilic nanoparticle 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 vivo to determine which would be best suited to deliver an experimental dry powder formulation of INS1009.

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 (20% Lactohale® 30). The lactose Lactohale® 30 was mixed with INS1009 (INS1009 Lactohale® 30 (INS1009)/Lactohale® 30 (INS1009) ratio, followed by two rounds of micronisation in a 350 µm 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® 30 (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 pin), Device 2 (high resistance, 2 pin), and Devices 3 and 4 (low resistance, 4 pin, 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 DPI-INS1009.
  - The MMAD values were then compared with that of the dry powder aerosol obtained from the nose-only inhalation chamber study. The dry powder aerosol was generated from a dry powder dispenser (Vilnius Aerosol Generator (VAG), CH Technologies, Westwood, NJ, USA) and was measured at the ports of the Next Generation Impactor (NGI) (Figure 4).

RESULTS
DPI Device
- MMAD results of micronized lactose after being aerosolized with 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 distribution was measured by high-performance liquid chromatography (HPLC) (Figure 2).
  - There was no significant difference in MMAD values when DP-INS1009 was aerosolized with a nose-only inhalation chamber using the DPI Device 4, as shown in Table 3.

Aerosolized Micronized Lactose
- The aerosol particle size distribution of micronized lactose from Device 4 is shown in Figure 4.
  - The aerosol particle size distribution of micronized lactose from DPI Device 4 is summarized in Table 3. Values are the mean ± standard deviation (SD).

No-Only Inhalation
- A small amount of powder (50-200 mg) can be aerosolized with the Vilnius Aerosol Generator.
  - There is a correlation between the voltage setup and the resulting peak dry powder concentration, as summarized in Table 2.
  - 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 Table 2 (Figure 7).

CONCLUSIONS
- A dry powder aerosol delivery system was set up successfully with only small amount of formulation powder required (in milligrams range).
- Aerosol particle size from DPI Device 4 was less than 4 µm by NGI measurement and comparable to that using the ne-nose-only inhalation tower. MMAD, mean mass median aerodynamic diameter.

REFERENCES
- Data on file. Insmed Incorporated, Bridgewater, NJ, USA.

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DISCLOSURES
Manjari Bhamidipati is a graduate student at Rutgers University, Piscataway, New Jersey.