A Phase 1 Study Investigating the Delivery of Tobramycin using the TobrAir® Device Compared with TOBI® / PARI LC® PLUS and TOBI® Podhaler™ using Pharmacokinetic and Pharmacoscintigraphic Methods

Tomas Norling[1], Michael Beckert[2], Wilbur de Kruijf[3]

[1]Pharmaero ApS, Copenhagen, Denmark, [2]CaRACS, Berlin, Germany, [3]Medspray BV, Enschede, Netherlands

Background

Inhaled tobramycin is a well-known, effective antibiotic for the management of Pseudomonas aeruginosa (P. aeruginosa) infections in patients with cystic fibrosis (CF) and is recommended as antibiotic of choice in current treatment guidelines (1). Dry powder inhalers are user friendly and quick in application, but they require sufficient (peak) inspiratory flow and the appropriate breathing technique. Thus, they may not be suitable for every patient, for example young children. Furthermore, not all patients tolerate the inhalation of dry powder, which can cause cough, dysphonia and other airway irritation (2).

Pharmaero has developed a soft mist inhaler TobrAir® – a fixed drug-device combination product, providing a liquid tobramycin formulation for inhalation. Tobramycin as TobrAir® is formulated as a 15% solution, administered as 75 mg b.i.d. with 10 inhalations per dosing and resulting in a total daily dose of 150 mg.

Objectives

In this Phase 1 study, we investigated the 1) safety and tolerability, 2) lung deposition, and 3) pharmacokinetics of tobramycin of the new drug-device TobrAir®, compared to TOBI® / PARI LC® PLUS (as an example for a nebulizer) and TOBI® Podhaler™ (as an example for a dry powder inhaler).

Design & Methods

This randomized cross-over study assessed the aerosol delivery and lung deposition of tobramycin by pharmacoscintigraphy using TobrAir® compared to TOBI® / PARI LC® PLUS. Tobramycin plasma levels after using these two devices and after using the TOBI® Podhaler™ were also determined.

During this study, 12 healthy male and female volunteers received the three different treatment regimens in a randomized order: A single dose of 75 mg tobramycin radiolabelled with ^{99m}Tc delivered to the lungs via TobrAir® (10 inhalations), 300 mg TOBI® radiolabelled with ^{99m}Tc delivered by PARI LC® PLUS and 112 mg tobramycin as a powder via TOBI® Podhaler™, not radiolabelled (4 capsules at 28 mg each).

TobrAir® (tobramycin inhalation spray), is a sterile solution of tobramycin sulfate in Water for Injection (WFI). The drug-device combination includes a syringe containing 1 mL of a 15% tobramycin solution and utilizes a novel inhalation device designed to emit 20 inhalations which is equivalent to 2 administrations per day (10 actuations per administration) of 75 mg tobramycin (b.i.d.), resulting in a daily dose of 150 mg tobramycin.

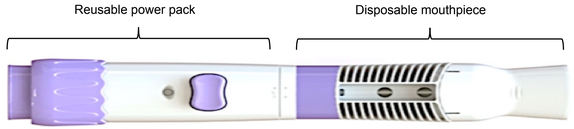

Figure 1: TobrAir® device

Safety & Tolerability

All three devices were comparable with regards to safety and tolerability. Four subjects reported 4 AEs after using TobrAir®, 1 subject reported 4 AEs after using TOBI® / PARI LC® PLUS and 4 subjects reported 4 AEs after using the TOBI® Podhaler™. However, just the 4 AEs vomiting, nausea, headache and viral upper respiratory tract infection were considered being possibly related to the study drug. All AEs were mild in severity and no SAEs occurred. Finally, no clinically significant changes in laboratory parameters, vital signs, lung function or ECGs were detected for any of the subjects.

Lung Deposition

Representative Images: Images were taken after a single administration of 75 mg tobramycin radiolabelled with ^{99m}Tc delivered to the lungs via TobrAir® and 300 mg TOBI® radiolabelled with ^{99m}Tc via the PARI LC® PLUS jet nebulizer and were analyzed through a Bartec MIcasX camera operating system. Before study start, in-vitro experiments were performed to develop and validate the radiolabelling techniques.

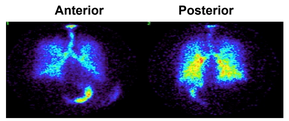

Figure 2: Lung Scintigraphic Analysis after using TobrAir®

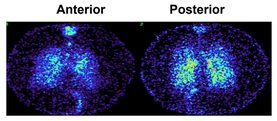

Figure 3: Lung Scintigraphic Analysis after using TOBI® / PARI LC® PLUS

Deposition Pattern (Percentage Delivered Dose): Pharmacokinetic data demonstrated that tobramycin lung deposition of 75 mg tobramycin with 10 inhalations via the TobrAir® device is higher than that attained with 300 mg tobramycin delivered via the TOBI®/PARI LC® PLUS with continuous nebulization over approximately 20 minutes. These favorable delivery properties of the TobrAir® device are also reflected in the deposition pattern, as shown by the table below.

n = 11* each	Whole Lung (%)	Oropharyngeal (%)	Exhaled (%)
TobrAir® Mean (± SD)	57.4 (± 12.9)	42.5 (± 12.9)	0.17 (± 0.16)
TOBI® / PARI LC® PLUS Mean (± SD)	24.7 (± 3.5)	13.4 (± 3.5)	61.7 (± 3.8)

* For one of the 12 subjects, lung distribution and PK data for TobrAir® could not be determined due to inhalation issues during dosing. For another subject, lung distribution and PK data for TOBI® / PARI LC® PLUS could not be determined due to camera issues.

Absolute Delivered Dose to the Lungs: The absolute amount of tobramycin delivered to the lungs was greater for TobrAir® compared to TOBI® / PARI LC® PLUS.

n = 11 each	TobrAir®	TOBI® / PARI LC® PLUS
Mean (± SD)	36.9 mg (± 8.7)	29.5 mg (± 6.6)

Regional Lung Deposition Pattern: In this study, we used a new analysis method for quantifying regional lung deposition, in which each lung was divided into 6 concentric lung-shaped regions (3). Region 1 was defined as the inner most region and region 6 as the outer most region. The amount of radiolabelled tobramycin in each region was expressed as a percentage of the counts in the lung and showed a similar distribution profile for TobrAir® and TOBI® / PARI LC® PLUS (shown are mean and SD).

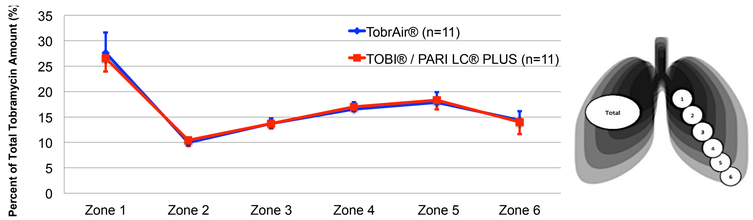

Figure 4: Distribution of tobramycin throughout the different lung zones from use of TobrAir® (blue) and TOBI® / PARI LC® PLUS (red), Mean (± SD).

Pharmacokinetic (PK) Analysis

PK Data: Plasma tobramycin concentrations were determined after a single dose of 75 mg tobramycin solution delivered as TobrAir®, 300 mg TOBI® delivered via PARI LC® PLUS and 112 mg tobramycin as dry powder delivered via TOBI® Podhaler™.

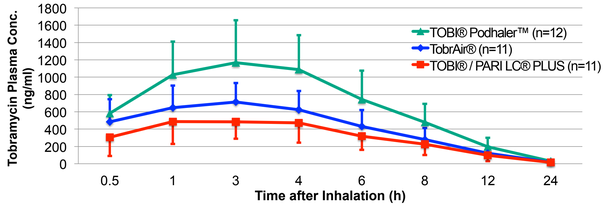

Figure 5: Tobramycin plasma concentrations by use of TOBI® Podhaler™ (green), TobrAir® (blue) and TOBI® / PARI LC® PLUS (red), Mean (± SD).

PK Parameters: Cmax and AUC(0-last) were higher in subjects dosed with TobrAir® compared to TOBI® / PARI LC® PLUS and lower in subjects dosed with TobrAir® and TOBI® / PARI LC® PLUS compared to TOBI® Podhaler™. Tmax and t½ were similar for all three devices with a Tmax of 3h for each device and a t½ ranging from 3.82h to 3.94h.

Parameter	TobrAir®	TOBI® / PARI LC® Plus	TOBI® Podhaler™
Cmax (ng/mL) Mean (± SD)	807 (± 267)	573 (± 271)	1210 (± 463)
AUC(0–last) (ng*h/mL) Mean (± SD)	6040 (± 2170)	4530 (± 2200)	9620 (± 3790)
Tmax (h) Median (± SD)	3.00 (1.00 - 3.08)	3.00 (1.00 - 4.00)	3.00 (1.00 - 4.00)
t½ (h) Mean (± SD)	3.86 (± 0.62)	3.94 (± 0.52)	3.82 (± 0.43)

Relative Bioavailability: The relative bioavailability (F_{rel}) shows that TobrAir® is the most effective device with a mean (± SD) value of 271.0% (± 88.4%) compared to TOBI® / PARI LC® PLUS and 111.1% (± 42.0%) compared to TOBI® Podhaler™ (based on actual dose for TobrAir® and TOBI® / PARI LC® PLUS and nominal dose for TOBI® Podhaler™).

Conclusion

In this Phase 1 study, delivery of tobramycin via Pharmaero's new drug-device combination product was safe and well-tolerated. TobrAir® demonstrated a higher lung deposition and plasma levels with significantly reduced treatment time and burden compared to the delivery via TOBI® / PARI LC® PLUS, as well as a superior relative bioavailability compared to both TOBI® PARI LC® PLUS and TOBI® Podhaler™. Additional studies are planned to measure if TobrAir® may become an efficacious and convenient treatment for CF patients chronically colonized with P. aeruginosa.

References

(1) Mogayzel et al., 2014: Cystic Fibrosis Foundation pulmonary guideline. pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection, Ann Am Thorac Soc 2014, 11(10): 1640-50.
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Acknowledgement

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