A PHASE 1 PHARMACOSCINTIGRAPHIC STUDY IN HEALTHY VOLUNTEERS COMPARING THE DELIVERY OF TOBRAMYCIN USING THE TOBRAIR® COMPARED TO THE DELIVERY OF TOBRAMYCIN NEBULIZER SOLUTION (TOBI®) BY PARI LC® PLUS

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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. Pharmaero has developed TobrAir® – a fixed drug-device combination product, providing a liquid tobramycin formulation for inhalation. TobrAir® is formulated as a 15% solution, administered as 75 mg b.i.d., resulting in a total daily dose of 150 mg. Compared to the administration of 300 mg TOBI® delivered by PARI LC® PLUS jet nebulizer which needs to be administered over 20 minutes continuous nebulization and cleaned afterwards, TobrAir® significantly reduces the time and burden for the patient.

Objectives

The objective of this Phase 1 healthy volunteer study conducted by Pharmaero was to investigate 1) safety and tolerability, 2) lung deposition, and 3) pharmacokinetics of tobramycin from TobrAir® compared to TOBI® / PARI LC® PLUS and TOBI® Podhaler™ .

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 determined as well. 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 á 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 metered dose of 150 mg tobramycin.

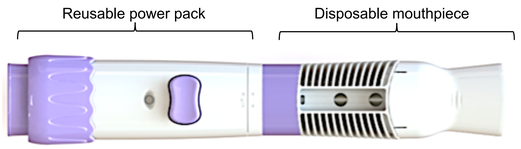

Figure 1: TobrAir® device

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 dose 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.

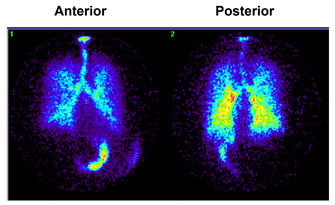

Figure 2: Lung Scintigraphic Analysis after using TobrAIr®

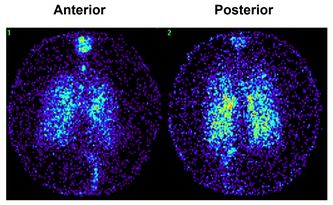

Figure 3: Lung Scintigraphic Analysis after using TOBI® / PARI LC® PLUS

Deposition Pattern (Percentage Delivered Dose):
For TOBI® / PARI LC® PLUS, 58% of the tobramycin solution was retained in the device. The whole lung- and oropharyngeal deposition of the delivered dose was higher for TobrAir®, whereas the amount of tobramycin exhaled was higher for TOBI® / PARI LC® PLUS.

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)

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:
The lungs were divided into 6 concentric lung-shaped regions. 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).

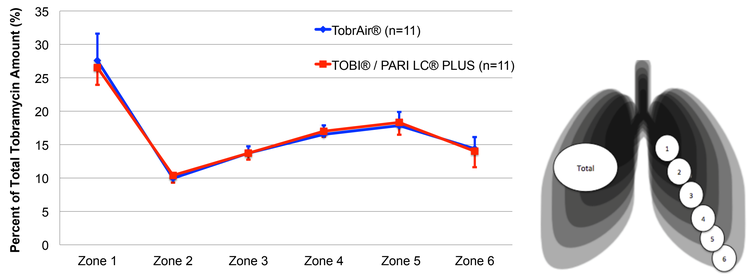

Figure 4: Distribution of tobramycin throughout the different lung zones from use of TobrAir® (blue) and TOBI® / PARI LC® PLUS (red)

Pharmacokinetic (PK) Analysis

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

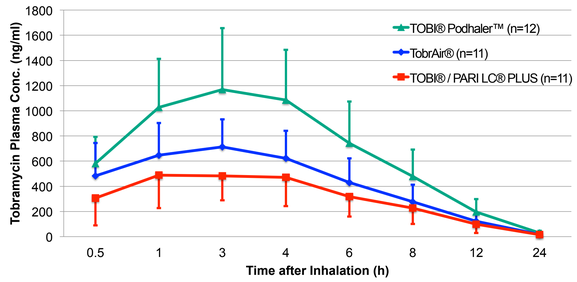

Figure 5: Tobramycin plasma concentrations by use of TOBI® Podhaler™ (green), TobrAir® (blue) and TOBI® / PARI LC® PLUS (red)

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.

Parameter	TobrAir®	TOBI® / PARI LC® Plus	TOBI® Podhaler™
Cmax (ng/mL)	807 (± 267)	573 (± 271)	1210 (± 463)
AUC(0–last) (ng*h/mL)	6040 (± 2170)	4530 (± 2200)	9620 (± 3790)
Tmax (h)	3.00 (1.00–3.08)	3.00 (1.00–4.00)	3.00 (1.00–4.00)
t½ (h)	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™. TobrAir® therefore may become an efficacious and convenient treatment for CF patients infected with *P. aeruginosa.*

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