Sponsor

Novartis

Generic Drug Name

tobramycin

Therapeutic Area of Trial

cystic fibrosis

Approved Indication

cystic fibrosis patients with P. aeruginosa

Study Number

CTBM100B2202

Title

A phase 1, single dose, open label, two-way crossover, pharmacoscintigraphy study of aerosol delivery characteristics (measured by in vivo lung deposition, nebulization time, serum tobramycin concentrations, and pharmacokinetic parameters) and safety of TOBI administered for inhalation by PARI eFLOW® *rapid* electronic nebulizer (no compressor) vs. PARI LC PLUS jet nebulizer (with compressor) in healthy subjects and in subjects with cystic fibrosis.

Phase of Development

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Study Start/End Dates

11-May-2006 to 14-Apr-2007

Study Design/Methodology

This was a randomized, single dose, open label, two-way crossover trial looking at lung deposition of tobramycin using gamma scintigraphy following inhalation of 300 mg/5 mL tobramycin (TOBI) with either LC PLUS or eFLOW *rapid* nebulizer.

Centres

Pharmaceutical Profiles Ltd, Nottingham, UK, and referring centers.

Publication

None

Objectives

Primary objective(s)

The primary objective was to assess the in vivo lung deposition of 300mg tobramycin (TOBI) when inhaled using the eFLOW *rapid* electronic nebulizer, compared with the deposition of 300 mg tobramycin (TOBI) inhaled using the LC PLUS nebulizer.

Secondary objective(s)

The secondary objectives were to evaluate the correlation between deposition of tobramycin in the lung and concentrations and pharmacokinetics of tobramycin in serum; to assess and compare the nebulization time and safety of TOBI delivered by the eFLOW *rapid* electronic nebulizer with that delivered by the LC PLUS jet nebulizer.

Test Product (s), Dose(s), and Mode(s) of Administration

TOBI (300 mg/5 mL; excipient 5 mL of ¼ normal saline pH 6.0 ±0.5) administered as a single dose by inhalation once on the morning of day one of treatment period 1 or 2 using the eFLOW *rapid* nebulizer.

Reference Product(s), Dose(s), and Mode(s) of Administration

The control treatment was
TOBI (300 mg/5 mL; excipient 5 mL of ¼ normal saline pH 6.0 ±0.5) administered as a single dose by inhalation once on the morning of day one of treatment period 1 or 2 using the LC PLUS nebulizer.

Criteria for Evaluation

Primary variables

The primary variables were the percentage of the metered dose and milligrams of drug deposited in the whole lung measured using gamma scintigraphy methodology. Regional lung deposition, deposition in the oropharynx, on nebulizers and on filters were also determined.

Secondary variables

Serum tobramycin concentrations were assessed and pharmacokinetic parameters (area under the curve, AUC; maximum serum concentration, $C_{max;}$ time to maximum concentration, t_{max} and terminal phase half life, $t_{1/2}$) were also calculated.

The nebulization time was measured from start of first tidal breath until the nebulizer automatically stopped (PARI eFLOW *rapid*), or was manually stopped, (PARI LC PLUS).

Safety and tolerability

Safety was assessed by:

• relative change in FEV_1 % predicted, as a measure of bronchospasm.

• changes in other spirometry measurements including forced vital capacity (FVC) and peak expiratory flow rate (PEFR).

• incidence of adverse events.

• potential for increased risk of development of systemic toxicity, determined by serum drug concentrations.

• clinically significant alterations in vital signs or laboratory results.

Statistical Methods

Whole lung deposition was the primary endpoint and was summarized and evaluated descriptively for differences between LC plus and eFLOW *rapid*. The analysis was based on the deposition evaluable population (comprising all subjects who received both doses of study treatment and provided valid deposition information). Additional analysis parameters included nebulization time, serum tobramycin concentrations, pharmacokinetic parameters, spirometry measures (e.g. FEV_1 % predicted), and safety, including bronchospasm (airway reactivity). All analyses of efficacy and safety were preplanned as descriptive statistics, contingency tables, or graphic correlation displays via linear regression plots, as appropriate (ie, no statistical testing was performed). No interim analysis was performed for the study.

This study was not powered to demonstrate non-inferiority/equivalence of devices.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Healthy male and female volunteers aged between 18 and 65, within ± 25% of their ideal weight and with a screening forced expiratory volume at 1 second (FEV_1) % predicted ≥ 80% based on standard calculations were recruited. Male and female cystic fibrosis patients were enrolled who were aged between 18 and 65, were chronically colonized with *Pseudomonas aeruginosa* and had a screening FEV_1 % predicted ≥ 25%. A one week washout period was required of all subjects receiving TOBI or 2-day washout for colistin prior to enrolment. All subjects were required to complete a minimum 3-day washout period between treatments.

Exclusion criteria:

Subjects with a known hypersensitivity to aminoglycosides or salbutamol, impaired renal function, or administration of a loop diuretic in the preceding 7 days were excluded from the trial.

Number of Subjects

Patient disposition – n (%) of patients (Randomized population)

	Healthy volunteers			CF patients		
	eFLOW/LC	LC/eFLOW	All	eFLOW/LC	LC/eFLOW	All
Randomized patients	**3**	**3**	**6**	**4**	**3**	**7**
Completed	3 (100)	3 (100)	6 (100)	3 (75)	3 (100)	6 (86)
Discontinued	0	0	0	1	0	1 (14)
Main cause of discontinuation						
Withdrew consent	0	0	0	1 (25)	0	1 (14)

Demographic and Background Characteristics

Demographic summary by treatment group (ITT population)

		Healthy volunteers N=6			CF patients N=7		
		eFLOW/LC	LC/eFLOW	All	eFLOW/LC	LC/eFLOW	All
Age (yr)	Mean	33.3	44.3	38.8	21.8	21.3	21.6
	SD	9.5	11.2	11.0	4.3	3.1	3.5
	Median	30.0	40.0	38.0	20.0	22.0	21.0
	Range	36-44	36-57	26-57	19-28	18-24	18-28
Gender n(%)	Male	3 (100)	3 (100)	6 (100)	2 (50)	2 (67)	4 (57)
	Female	0	0	0	2 (50)	1 (33)	3 (43)
Weight (Kg)	Mean	76.20	84.23	80.2	62.4	53.7	58.7
	SD	15.2	5.8	11.2	14.3	14.85	14.1
	Median	73.30	86.80	82.2	61.5	53.8	53.8
	Range	62.7-92.6	77.6-88.3	62.7-92.6	47.8-78.9	38.8-68.5	38.8-78.9
Height (cm)	Mean	175.3	175.7	175.5	174.1	160.6	168.3
	SD	8.6	3.1	5.8	12.3	9.7	12.7
	Median	177.0	175.0	176.0	173.8	164.1	168.0
	Range	166.0-183.0	173.0-179.0	166.0-183.0	160.0-189.0	149.6-168.0	149.6-189.0

Primary Objective Result(s)

Distribution of tobramycin (Deposition evaluable patients)

		Whole lung		Oropharyngeal*		Device		Exhaled air**	
		Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6
% metered dose									
LC PLUS	Mean	14.50	14.98	8.15	9.37	53.01	46.65	24.34	28.98
	SD	1.84	6.03	1.84	5.83	13.46	25.49	12.15	15.75
	Median	14.77	15.05	8.45	7.45	58.60	57.5	20.48	20.5
eFLOW *rapid*	Mean	14.19	8.83	5.86	5.35	53.09	63.98	26.87	24.17
	SD	6.49	0.82	3.49	3.36	10.05	11.11	11.25	8.68
	Median	13.32	8.85	4.37	5.05	52.18	65.20	24.95	24.50
Drug deposited (mg)									
LC PLUS	Mean	43.49	44.95	24.46	28.10	159.01	139.95	73.02	92.40
	SD	5.52	18.09	5.53	17.50	40.39	76.46	36.46	43.26
	Median	44.31	45.15	25.36	22.35	175.79	172.50	61.43	70.05
eFLOW *rapid*	Mean	42.57	26.50	17.57	16.05	159.26	191.95	80.61	72.50
	SD	19.46	2.46	10.46	10.08	30.15	33.33	33.76	26.03
	Median	39.94	26.55	13.11	15.15	156.53	195.60	74.84	73.50

* Sum of oesophagus, oropharynx and stomach.

**Sum of exhalation filter, mouthpiece, T-piece, scavenger filter and tissues.

Distribution of tobramycin within the lungs (Deposition evaluable population)

		Lung zone											
		1		2		3		4		5		6	
		Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6
% metered dose													
LC PLUS	Mean	3.74	3.68	1.56	1.48	2.10	2.08	2.66	2.75	2.72	3.00	1.72	2.00
	SD	0.53	1.32	0.23	0.55	0.30	0.69	0.37	1.04	0.43	1.48	0.46	1.09
	Median	3.75	3.85	1.62	1.55	2.11	2.10	2.68	2.80	2.65	2.95	1.48	1.80
eFLOW *rapid*	Mean	3.26	2.60	1.38	0.93	1.89	1.23	2.51	1.55	2.69	1.48	2.33	1.02
	SD	1.51	0.48	0.69	0.08	0.82	0.18	1.18	0.33	1.19	0.35	1.12	0.31
	Median	2.93	2.55	1.23	0.95	1.79	1.30	2.33	1.55	2.83	1.55	2.28	1.10
Drug deposited (mg)													
LC PLUS	Mean	11.21	11.05	4.70	4.45	6.31	6.25	7.98	8.25	8.15	9.00	5.15	6.00
	SD	1.59	3.96	0.68	1.65	0.91	2.06	1.11	3.11	1.30	4.43	1.38	3.28
	Median	11.26	11.55	4.87	4.65	6.34	6.30	8.04	8.40	7.94	8.85	4.45	5.40
eFLOW *rapid*	Mean	9.76	7.80	4.14	2.80	5.67	3.70	7.52	4.65	8.49	4.45	7.00	3.05
	SD	4.52	1.43	2.08	0.25	2.47	0.53	3.54	0.98	3.58	1.05	3.36	0.92
	Median	8.79	7.65	3.69	2.85	5.37	3.90	6.99	4.65	8.07	4.65	6.85	3.30

Distribution of tobramycin in the lungs, airway penetration factors (Deposition evaluable population)

		Lung zone											
		1		2		3		4		5		6	
		Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6	Healthy N=6	CF N=6
APF													
LC PLUS	Mean	1.28	1.27	1.29	1.23	1.22	1.22	1.09	1.12	0.78	0.80	0.35	0.38
	SD	0.09	0.14	0.07	0.04	0.05	0.07	0.05	0.02	0.09	0.11	0.08	0.07
	Median	1.27	1.22	1.26	1.23	1.22	1.21	1.08	1.12	0.82	0.79	0.34	0.36
eFLOW *rapid*	Mean	1.19	1.49	1.21	1.25	1.17	1.19	1.08	1.04	0.88	0.70	0.49	0.33
	SD	0.06	0.40	0.05	0.03	0.03	0.07	0.05	0.13	0.03	0.13	0.05	0.08
	Median	1.19	1.38	1.20	1.25	1.17	1.21	1.08	1.08	0.88	0.74	0.48	0.34

Secondary Objective Result(s)

Summary of dosing and nebulization times (ITT population)

		LC PLUS		eFLOW	
		Healthy	CF	Healthy	CF
		N=6	N=6	N=6	N=7
Dosing time (min)	Mean (SD)	15.7 (2.4)	20.8 (8.0)	9.0 (2.6)	8.3 (3.1)
	Median	16.0	20.0	8.5	8.0
	Range	11-18	13-30	7-14	5-15
Nebulization time (min)	Mean (SD)	15.7 (2.4)	20.7 (8.2)	8.0 (1.5)	7.4 (1.9)
	Median	16.0	20.0	7.5	7.0
	Range	11-18	12-30	7-11	5-11

Total dosing time includes interrupted time.

Tobramycin pharmacokinetics (PK evaluable population)

Parameter	Healthy subjects		Cystic fibrosis patients	
	PARI LC PLUS	PARI eFLOW rapid	PARI LC PLUS	PARI eFLOW rapid
t_{max} (h)	1 (1-2)	1 (1-2)	1 (0.5-2)	1 (0.5-1)
C_{max} (µg/ml)	0.58 ± 0.16	0.72 ± 0.40	1.15 ± 0.63	0.48 ± 0.16
AUC_{0-8} (µg.h/ml)	3.25 ± 0.69	3.62 ± 1.88	5.03 ± 2.96	1.87 ± 0.75
$t_{1/2}$ (h)	5.82 ± 1.97	4.60 ± 1.15	2.66 ± 1.14	2.66 ± 0.67

Values are arithmetic mean ± SD except for t_{max} which is median (range).

Safety Results

Adverse Events by System Organ Class and Preferred Term

Adverse events overall and frequently affected system organ classes - n (%) of patients (ITT population)

	eFLOW all		LC all	
Subject group	Healthy N=6 n (%)	CF N=6 n (%)	Healthy N=6 n (%)	CF N=6 n (%)
Patients with AE(s)	**4 (67)**	**4 (57)**	**1 (17)**	**3 (50)**
Infections and infestations	1 (17)	0	0	0
Upper respiratory tract infection	1 (17)	0	0	0
Investigations	0	0	0	2 (33)
Blood glucose fluctuation	0	0	0	1 (17)
Pulmonary function test decreased	0	0	0	1(17)
Weight decreased	0	0	0	1 (17)
Metabolism and nutrition disorders	0	1 (14)	0	0
Anorexia	0	1 (14)	0	0
Nervous system disorders	0	1 (14)	0	2 (33)
Dizziness	0	0	0	1 (17)
Headache	0	1 (14)	0	2 (33)
Respiratory, thoracic and mediastinal disorders	2 (33)	3 (43)	1 (17)	2 (33)
Cough	0	3 (43)	0	1 (17)
Nasal congestion	1 (17)	0	1 (17)	0
Pharyngolaryngeal pain	1 (17)	0	1 (17)	0
Reproductive cough	0	0	0	1 (17)
Throat irritation	1 (17)	0	0	0
Skin and subcutaneous tissue disorders	1 (17)	0	0	0
Rash papular	1 (17)	0	0	0

arranged in alphabetical order

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations – n (%) of patients (ITT population)

Serious or other significant events	eFLOW/LC		LC/eFLOW		All	
	Healthy N=3	CF N=4	Healthy N=3	CF N=3	Healthy N=6	CF N=7
Death	0	0	0	0	0	0
SAEs	0	1 (25%)	0	0	0	1 (25%)
Other clinically significant AEs						
Discontinued due to AEs	0	0	0	0	0	0
Discontinued for other safety reasons	0	0	0	0	0	0

Other Relevant Findings

Relative changes in % predicted spirometry values, predose to 30 minutes postdose (ITT population)

		eFLOW prd 1 n/N (%)	eFLOW prd 2 n/N (%)	eFLOW all n/N (%)	LC PLUS prd 1 n/N (%)	LC PLUS prd 2 n/N (%)	LC PLUS all n/N (%)
FEV_1 % predicted							
Healthy volunteers	≥ 10% reduction*	0	0	0	0	0	0
CF patients	≥ 10% reduction*	0	1/3 (33%)	1/7 (14%)	1/3 (33%)	0	1/6 (17%)
FVC % predicted							
Healthy volunteers	≥ 10% reduction*	0	0	0	0	0	0
CF patients	≥ 10% reduction	0	2/3 (67%)	2/7 (29%)	1/3 (33%)	0	1/6 (17%)
CF patients	≥ 20% reduction	0	0	0	1/3 (33%)	0	1/6 (17%)
PEFR% predicted							
Healthy volunteers	≥ 10% reduction*	0	0	0	1/3 (33%)	0	1/6 (17%)
CF patients	≥ 10% reduction	0	0	0	1/3 (33%)	0	1/6 (17%)
CF patients	≥ 20% reduction	0	0	0	1/3 (33%)	0	1/6 (17%)

% predicted values are based on standard values calculated from the ECSC formulae using patient sex, age and height
* But < 20%

Date of Clinical Trial Report April 2008
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