Sponsor

Novartis

Generic drug name

Tobramycin

Trial indication(s)

Cystic Fibrosis

Protocol number

CTBM100B2201

Protocol title

Crossover pharmacokinetic study of TOBI Administered for Inhalation by PARI eFlow rapid Electronic Nebulizer (no Compressor) vs. PARI LC PLUS Jet Nebulizer (with compressor) in Cystic Fibrosis Subjects

Clinical trial phase

Phase I

Study Start/End Dates

14-Apr-2006 to 8-Nov-2006

Study Design/Methodology

This was an open-label, randomized, multiple dose, multi-centre, two-period crossover trial. Subjects were randomly assigned to one of two treatment sequences, both of which received Tobramycin solution for inhalation (TOBI) 300 mg/5 mL. Period 1 eFlow rapid nebulizer followed by period 2 LC PLUS nebulizer, or period 1 LC PLUS nebulizer followed by eFlow rapid nebulizer. There was a one week washout interval separating the two crossover periods.

Centers

France (8).

Objectives:

Primary objective

To determine whether systemic exposure to tobramycin using the eFlow rapid nebulizer was comparable to that of the reference LC PLUS nebulizer.

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

Tobramycin solution for inhalation 60 mg/mL; 300 mg in 5 mL delivered by inhalation twice daily for 14 days and once on the morning of the 15th day of each treatment period using either the LC PLUS nebulizer (control) or eFlow rapid nebulizer (treatment).

Reference therapy, dose and mode of administration, batch number:

TOBI 300 mg/5 mL, administered by inhalation twice daily for 14 days and once on the morning of the 15th day of each treatment period using the LC PLUS nebulizer.

Statistical Methods

Pharmacokinetic parameters were descriptively summarized by treatment group and period, with 95% confidence intervals,.
Differences between the day 15 and day 1 log-transformed AUC_{0-8} and C_{max} were descriptively summarized.
The safety data (trough, C_{max} and all specimen concentrations, and incidence of bronchospasm) was descriptively summarized.
Adverse events were compared descriptively between treatment groups.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female subjects aged 6 years or over at the time of screening,

- Chronically colonized with Pseudomonas aeruginosa.
- Diagnosis of cystic fibrosis (CF)
- Ability to expectorate sputum samples on command.
- Ability to tolerate a 1-week washout interval with no inhaled tobramycin or other aminoglycoside treatment.
- Clinically stable in the opinion of the investigator.

Exclusion Criteria:

- Inhaled or intravenous aminoglycosides within 7 days before study drug administration.
- Any investigational drug within 2 weeks before screening.
- Loop diuretics within 7 days before study drug administration.
- Current use of inhaled tobramycin delivered by the PARI LC PLUS jet nebulizer without washout period of at least 1 week before entering the study.
- Women who are, or plan to become, pregnant during the course of the study.
- Serum creatinine or blood urea (BU) above the upper limit of normal for sex and age, or an abnormal urine analysis
- Known local or systemic hypersensitivity to aminoglycosides.

Other protocol defined inclusion/exclusion criteria may apply

Patient Flow Table:

Patient disposition – n (%) of patients

	eFlow/LC	LC/eFlow	All
Patients			
Enrolled	13	13	26
Completed	13 (100)	12 (92)	25 (96)
Discontinued	0 (0)	1 (8)	1 (4)
Main cause of discontinuation			
Adverse event(s)	0 (0)	1 (8)	1 (4)

Baseline Characteristics

Demographic summary by treatment group (ITT population)

		All randomized N = 26		ITT N = 25		PK evaluable N = 22	
		eFlow/LC	LC/eFlow	eFlow/LC	LC/eFlow	eFlow/LC	LC/eFlow
		13	13	13	12	11	11
Age (years)	Mean	27.6	24.2	27.6	24.6	28.2	25.0
	SD	6.3	3.9	6.3	3.9	6.7	3.8
	Median	25.0	24.0	25.0	25.0	25.0	26.0
	Range	22-44	19-32	22-44	19-32	22-44	19-32
Gender – n (%)	Male	7 (54)	9 (69)	7 (54)	8 (67)	6 (55)	7 (64)
	Female	6 (46)	4 (31)	6 (46)	4 (33)	5 (45)	4 (36)
Weight (kg)	Mean	54.0	52.4	54.0	51.9	54.3	52.0
	SD	5.8	8.1	5.8	8.3	6.3	8.7
	Median	54.2	52.8	54.2	51.9	55.0	52.8
	Range	46-62	39-65	46-62	39-65	45-62	39-65
Height (cm)	Mean	164.4	167.1	164.4	166.3	163.6	166.5
	SD	7.0	12.0	7.0	12.2	7.0	12.8
	Median	165.0	172.0	165.0	168.5	165.0	172.0
	Range	155-180	146-187	155-180	146-187	155-180	146-187

Summary of Efficacy

Not Applicable

Primary Outcome Result(s):

Pharmacokinetic results of Tobramycin

Tobramycin pharmacokinetics in serum (PK Evaluable population)

Parameter	LC Plus	PARI eFlow *rapid*
Day 1 (first dose):		
Nebulization time (min)	17.6 ± 4.0	7.4 ± 1.7
C_{max} (µg/ml)	0.9 ± 0.5	0.7 ± 0.6
t_{max} (h)	1 (0.5 – 2)	0.75 (0.5 - 2)
AUC_{0-8} (µg.h/ml)	3.6 ± 1.3	2.6 ± 2.5
$t_{1/2}$ (h)	2.6 ± 0.6	2.9 ± 1.0
Day 15 (steady state):		
Nebulization time (min)	16.0 ± 2.8	9.2 ± 5.0
C_0 (µg/ml)	0.1 ± 0.1	0.1 ± 0.2
C_{max} (µg/ml)	1.3 ± 0.7	1.2 ± 1.0
t_{max} (h)	0.5 (0.5 – 1)	0.5 (0.5 – 1.5)
AUC_{0-8} (µg.h/ml)	5.1 ± 2.6	4.8 ± 3.5
Accumulation ratio	1.4 ± 0.5	2.9 ± 3.4
$t_{1/2}$ (h)	3.1 ± 1.1	3.0 ± 0.7

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

Summary of Safety

Safety Results

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

	eFlow prd 1 N=13 (%)	eFlow prd 2 N=12 (%)	eFlow all N=25 (%)	LC Plus prd 1 N=12 (%)	LC PLUS prd 2 N=13 (%)	LC PLUS all N=25 (%)
Patients with AEs	13 (100)	6 (50)	19 (76)	7 (58)	9 (69)	16 (64)
System organ class						
Nervous system disorders	7 (54)	2 (17)	9 (36)	5 (42)	3 (23)	8 (32)
Respiratory, thoracic and mediastinal disorders	8 (62)	4 (33)	12 (48)	2 (17)	2 (15)	4 (16)
Gastroinstinal disorders	4 (31)	0 (0)	4 (16)	2 (17)	3 (23)	5 (20)
General disorders and administration site conditions	3 (23)	2 (17)	5 (20)	1 (8)	3 (23)	4 (16)
Musculoskeletal, connective tissue and bone disorders	1 (8)	1 (8)	2 (8)	1 (8)	1 (8)	2 (8)
Infections and infestations	1 (8)	0 (0)	1 (4)	2 (17)	2 (15)	4 (16)
Injury and poisoning	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)

Arranged in descending order of frequency

Adverse events overall and by preferred term (ITT population)

	eFlow prd 1 N=13 (%)	eFlow prd 2 N=12 (%)	eFlow all N=25 (%)	LC Plus prd 1 N=12 (%)	LC PLUS prd 2 N=13 (%)	LC PLUS all N=25 (%)
Patients with AEs	**13 (100)**	**6 (50)**	**19 (76)**	**7 (58)**	**9 (69)**	**16 (64)**
Gastrointestinal disorders	**4 (31)**	**0 (0)**	**4 (16)**	**2 (17)**	**3 (23)**	**5 (20)**
Abdominal pain	1 (8)	0 (0)	1 (4)	0 (0)	3 (23)	3 (12)
Abdominal pain upper	1 (8)	0 (0)	1 (4)	1 (8)	0 (0)	1 (4)
Constipation	1 (8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Dyspepsia	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	1 (4)
Haemorrhoids	1 (8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Vomiting	1 (8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
General disorders and administration site conditions	**3 (23)**	**2 (17)**	**5 (20)**	**1 (8)**	**3 (23)**	**4 (16)**
Asthenia	1 (8)	0 (0)	1 (4)	0 (0)	1 (8)	1 (4)
Chest Pain	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)
Fatigue	2 (15)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)
Feeling hot	1 (8)	0 (0)	1 (4)	0 (0)	1 (8)	1 (4)
Pyrexia	0 (0)	1 (8)	1 (4)	1 (8)	1 (8)	2 (8)
Infections and infestations	**1 (8)**	**0 (0)**	**1 (4)**	**2 (17)**	**2 (15)**	**4 (16)**
Bronchitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (4)
Rhinitis	1 (0)	0 (0)	1 (4)	2 (17)	0 (0)	2 (8)
Sinusitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (4)
Injury and poisoning	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)
Arthropod sting	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)
Musculoskeletal, connective tissue and bone disorders	**1 (8)**	**1 (8)**	**2 (8)**	**1 (8)**	**1 (8)**	**2 (8)**
Arthralgia	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)
Back pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	1 (4)
Myalgia	1 (8)	0 (0)	1 (4)	1 (8)	0 (0)	1 (4)
Nervous system disorders	**7 (54)**	**2 (17)**	**9 (36)**	**5 (42)**	**3 (23)**	**8 (32)**
Aphonia	1 (8)	0 (0)	1 (4)	1 (8)	0 (0)	1 (4)

	eFlow prd 1 N=13 (%)	eFlow prd 2 N=12 (%)	eFlow all N=25 (%)	LC Plus prd 1 N=12 (%)	LC PLUS prd 2 N=13 (%)	LC PLUS all N=25 (%)
Patients with AEs	**13 (100)**	**6 (50)**	**19 (76)**	**7 (58)**	**9 (69)**	**16 (64)**
Headache	6 (46)	2 (17)	8 (32)	4 (33)	3 (23)	7 (28)
Respiratory, thoracic and mediastinal disorders	**8 (62)**	**4 (33)**	**12 (48)**	**2 (17)**	**2 (15)**	**4 (16)**
Bronchospasm	1 (8)	0 (0)	1 (4)	0 (0)	1 (8)	1 (4)
Cough	3 (23)	0 (0)	3 (12)	2 (17)	0 (0)	2 (8)
Dyphonia	2 (15)	0 (0)	2 (8)	1 (8)	0 (0)	1 (4)
Dyspnoea	1 (8)	2 (17)	3 (12)	0 (0)	0 (0)	0 (0)
Haemoptysis	1 (8)	1 (8)	2 (8)	1 (8)	0 (0)	1 (4)
Increased bronchial secretion	0 (0)	1 (8)	1 (4)	0 (0)	0 (0)	0 (0)
Nasal congestion	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)
Pharyngolaryngeal pain	1 (8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Rhonchi	0 (0)	2 (17)	2 (8)	0 (0)	0 (0)	0 (0)
Throat irritation	2 (15)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)

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

	eFlow/LC N = 13 n	LC/eFlow N = 12 n	All N = 25 n
Patients with AE(s)			
Serious or other significant events			
Death	0	0	0
SAE(s)	0	2	2
Discontinued due to SAE(s)	0	0	0
Discontinued due to AE(s)	0	1	0

Other Relevant Findings

None

Date of Clinical Trial Report

30-Mar-2007