Sponsor

Novartis Pharma GmbH

Generic Drug Name

Tobramycin

Therapeutic Area of Trial

Cystic Fibrosis

Approved Indication

Cystic fibrosis patients with chronic P. aeruginosa infection

Study Number

CTBM100DDE01

Title

A multicenter, open label, 2 period cross-over study to evaluate the Pharmacokinetics of an 8 week continuous treatment with 1x300mg/d and 2x300mg/d Tobramycin nebulized solution (TNS) inhaled with the PARI eFlow™ rapid in Cystic Fibrosis (CF) Subjects.

Phase of Development

III

Study Start/End Dates

27-FEB-2008 to 18-AUG-2009

Study Design/Methodology

This was a randomized, open-label, 2 period cross-over, multi-center study to evaluate the PK of two doses of TNS in an 8 week continuous treatment. The selected doses were 1x300mg/d and 2x300mg/d TNS inhaled with the PARI eFlow™ rapid in CF Subjects.
Patients entered into this study were diagnosed Cystic Fibrosis patients of 6 years old or older with a chronic infection of P. aeruginosa and who had experienced no exacerbations in the 2 weeks preceding Visit 1.

Centres

The study was conducted at 8 centers in Germany

Publication

none

Objectives

Primary objective(s)

To evaluate the serum pharmacokinetics (PK) of inhaled Tobramycin nebulised solution (=TNS) ($AUC_{0-90'}$) of continuous daily dosing regimens with 2x300mg/d TNS inhaled with the PARI eFlow™ rapid in Cystic Fibrosis (CF) subjects.

Secondary objective(s)

- To evaluate the serum pharmacokinetics (PK) of inhaled TNS ($AUC_{0-90'}$) of continuous daily dosing regimens with 1x300mg/d TNS inhaled with the PARI eFlow™ rapid in Cystic Fibrosis (CF) subjects.
- To compare the serum PK of inhaled TNS (trough-/peak-level) of both dosing regimens in Cystic Fibrosis (CF) Subjects with a $FEV_1 \geq 80\%$ vs. CF-Subjects with a $FEV_1 < 80\%$.
- To evaluate the change of MIC of P. aeruginosa during a continuous treatment with 1x300mg/d and 2x300mg/d TNS.
- To assess the safety of a continuous daily dosing regimen with 1x300mg/d and 2x300mg/d TNS over 8 weeks, compared to historic safety data of the 4 week on/off dosing regimen with 2x300mg/d.

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

Patients were treated with Tobramycin nebulised solution (=TNS) 300mg/5ml.

TNS is a sterile, non-pyrogenic, preservative-free antibiotic prepared for aerosolization. TNS is approved for twice daily (b.i.d.) inhalation in a 4 week on/off dosing scheme using the PARI LC PLUS™ jet nebulizer and a suitable compressor.

In this study TNS was inhaled with the PARI eFlow™ rapid nebulizer continuously for 8 weeks. In one period TNS was used once daily (o.d.) in the other period twice daily (b.i.d.).

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

not applicable

Criteria for Evaluation

Primary variables

Serum tobramycin PK parameters (AUC, C_{max})

Secondary variables

Spirometry (FEV_1, FVC), CFQ

Safety and tolerability

(S)AEs, safety lab, vital signs

Statistical Methods

The primary variable was the serum tobramycin $AUC_{0-90'}$ computed by the trapezoidal rule. For all comparisons the AUC was log-transformed.
The primary comparison was AUC measured after 4 weeks of treatment with tobramycin high

dose (300 mg b.i.d.) vs AUC measured after 8 weeks. The comparison was computed by an ANOVA model for the log-transformed AUCs with factors patient and time (4 wks vs. 8 wks) for the AUCs under the high dose only. The LS-mean-difference and its 90% confidence interval were then retransformed to obtain estimates for the ratio of the AUCs.
The same methodology was applied to all other PK analyses, all other endpoints were analyzed descriptively.

Study Population: Inclusion/Exclusion Criteria and Demographics

Indication and main criteria for inclusion:
Subjects ≥6 years at the time of screening, with a confirmed diagnosis of CF and with P. aeruginosa present in sputum or deep throat swab at screening and within 6 months prior.

Main exclusion criteria were:

- History of sputum (or BAL) culture yielding Burkholderia cepacia (B. cepacia) within 2 years prior to screening and/or sputum culture yielding B cepacia at screening.
- FEV_1<25% of normal predicted values for age, sex, and height based on Knudson criteria at screening [Knudson 1983; criteria programmed into the spirometers].
- Hemoptysis of more than 60 cc at any time within 30 days prior to study drug administration.
- Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics.
- GFR<60ml/min/1.73m^2 calculated with the Formula by Schwartz, BUN 40 mg/dl or more, or an abnormal urinalysis defined as 2+ or greater proteinuria.
- History of tinnitus or pathologic audiometry
- diagnosis of Allergic bronchopulmonary aspergillosis (ABPA) at screening
- Initiation of treatment with macrolide antibiotics within 28 days prior to study drug administration (subjects may be taking macrolide antibiotics at the time of enrollment, but they must have initiated treatment at least 28 days prior to study drug administration).
- Use of loop diuretics within 7 days prior to study drug administration.
- Initiation of treatment with dornase alpha within 28 days prior to study drug administration (subjects may be taking dornase alpha at the time of enrollment, but they must have initiated treatment at least 28 days prior to study drug administration).
- Initiation of treatment with inhaled steroids or modification of dose within 28 days prior to study drug administration (subjects may be taking inhaled steroids at the time of enrollment, but they must have initiated treatment at least 28 days prior to study drug administration).

Number of Subjects

	(N=29) n (%)
Patient disposition	
treated	29 (100)
discontinued	5 (17.2)
completed	24 (82.8)
Reason for discontinuation	
Adverse event(s)	3 (10.3)
Administrative problems	2 (6.9)

Demographic and Background Characteristics

	Statistic	(N = 29)
Age [yrs]		
	Mean (SD)	19.8 (6.31)
	Median	19.0
	Range	8 - 35
< 18 years	n (%)	9 (31.0)
>= 18 years	n (%)	20 (69.0)
Sex		
Male	n (%)	17 (58.6)
Female	n (%)	12 (41.4)
Race		
Caucasian	n (%)	29 (100)

Primary Objective Result(s)

For b.i.d. treatment a 40% decrease in serum levels was assessed after 8 weeks compared to 4 weeks (AUC_{0-90}, ratio: 0.608, 90% CI: 0.461 - 0.802).

Tobramyzin AUC 0-90: b.i.d. 8 wks vs. b.i.d. 4 wks
Population: PP population

Variable: Tobramycin AUC0-90

			Unadjusted	Results from ANOVA model *)		
		n	Mean (SD)	LS-Mean	90% CL	p|Diff=0
log-scale	b.i.d. Week 4	23	4.296 (1.03)	4.296		
	b.i.d. Week 8	23	3.799 (1.22)	3.799		
	Diff b.i.d. Week 8 - b.i.d. Week 4		-0.498	-0.498	[-0.775 , -0.220]	0.0055
original scale (exp.)	b.i.d. Week 4	23	73.439	73.439		
	b.i.d. Week 8	23	44.651	44.651		
	Ratio b.i.d. Week 8 / b.i.d. Week 4		0.608	0.608	[0.461 , 0.802]	0.0055

*)ANOVA model: log(variable) = patient, Treatment*time; Retransformed means (original scale) are geometric means

Secondary Objective Result(s)

For o.d. treatment, serum levels were 20% higher after 8 weeks compared with 4 weeks (AUC_{0-90}, ratio: 1.203, 90% CI: 0.860 - 1.396).
AUC_{0-90}, of o.d. and b.i.d. after 8 weeks did not differ significantly (AUC_{0-90}, ratio: 0.721, 90% CI: 0.514 – 1.092).

Tobramyzin AUC 0-90: o.d. 8 wks vs. o.d. 4 wks
Population: PP population

Variable: Tobramycin AUC0-90

			Unadjusted	Results from ANOVA model *)		
		n	Mean (SD)	LS-Mean	90% CL	p|Diff=0
log-scale	o.d. Week 4	23	3.941 (1.18)	3.941		
	o.d. Week 8	22	4.126 (0.93)	4.033		
	Diff o.d. Week 8 - o.d. Week 4		0.185	0.091	[-0.151 , 0.334]	0.5237
original scale (exp.)	o.d. Week 4	23	51.482	51.482		
	o.d. Week 8	22	61.924	56.404		
	Ratio o.d. Week 8 / o.d. Week 4		1.203	1.096	[0.860 , 1.396]	0.5237

*)ANOVA model: log(variable) = patient, Treatment*time; Retransformed means (original scale) are geometric means

Safety Results

Number (%) of patients with AEs overall and by system organ class

MedDRA SOC term	TOTAL (N=29) n (%)	o.d. (N=26) n (%)	b.i.d. (N=28) n (%)
All System Organ Classes	**26 (89.7)**	**20 (76.9)**	**21 (75.0)**
INFECTIONS AND INFESTATIONS	19 (65.5)	14 (53.8)	11 (39.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	19 (65.5)	10 (38.5)	14 (50.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 (44.8)	7 (26.9)	10 (35.7)
GASTROINTESTINAL DISORDERS	9 (31.0)	5 (19.2)	6 (21.4)
NERVOUS SYSTEM DISORDERS	7 (24.1)	5 (19.2)	5 (17.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (10.3)	1 (3.8)	2 (7.1)
EAR AND LABYRINTH DISORDERS	2 (6.9)	0 (0.0)	2 (7.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (6.9)	2 (7.7)	0 (0.0)
INVESTIGATIONS	2 (6.9)	1 (3.8)	1 (3.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (3.4)	1 (3.8)	1 (3.6)
EYE DISORDERS	1 (3.4)	0 (0.0)	1 (3.6)
IMMUNE SYSTEM DISORDERS	1 (3.4)	0 (0.0)	1 (3.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (3.4)	0 (0.0)	1 (3.6)

Treatment refers to the last treatment received before AE start. Percentages based on the no. of patients exposed to that treatment ('N=x').

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Number (%) of patients with most frequent AEs

MedDRA preferred term	TOTAL (N=29) n (%)	o.d. (N=26) n (%)	b.i.d. (N=28) n (%)
NASOPHARYNGITIS	10 (34.5)	10 (38.5)	3 (10.7)
HEADACHE	7 (24.1)	5 (19.2)	5 (17.9)
COUGH	7 (24.1)	2 (7.7)	6 (21.4)
CONDITION AGGRAVATED	6 (20.7)	4 (15.4)	4 (14.3)
PYREXIA	5 (17.2)	3 (11.5)	4 (14.3)
LUNG DISORDER	5 (17.2)	3 (11.5)	3 (10.7)
LUNG INFECTION	4 (13.8)	2 (7.7)	3 (10.7)
UPPER RESPIRATORY TRACT INFECTION	4 (13.8)	2 (7.7)	2 (7.1)
DYSPNOEA	4 (13.8)	1 (3.8)	3 (10.7)
HAEMOPTYSIS	4 (13.8)	3 (11.5)	2 (7.1)
ENTERITIS	3 (10.3)	3 (11.5)	1 (3.6)
OROPHARYNGEAL PAIN	3 (10.3)	0 (0.0)	3 (10.7)
ABDOMINAL PAIN UPPER	2 (6.9)	1 (3.8)	1 (3.6)
GASTROENTERITIS	2 (6.9)	1 (3.8)	1 (3.6)
BRONCHIAL OBSTRUCTION	2 (6.9)	0 (0.0)	2 (7.1)

Only AEs occuring in more than one patient are shown in this table. Treatment refers to the last treatment received before AE start. Percentages based on the no. of patients exposed to that treatment ('N=x').

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	TOTAL (N=29) n (%)	o.d. (N=26) n (%)	b.i.d. (N=28) n (%)
All AEs	26 (89.7)	20 (76.9)	21 (75.0)
with suspected drug relation	5 (17.2)	0 (0.0)	5 (17.9)
leading to dose adjustment or temp. interruption	1 (3.4)	0 (0.0)	1 (3.6)
leading to permanent discontinuation	3 (10.3)	0 (0.0)	3 (10.7)
requiring concomitant medication/non-drug therapy	17 (58.6)	13 (50.0)	13 (46.4)
Serious AEs	3 (10.3)	3 (11.5)	2 (7.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
SAEs with suspected drug relation	0 (0.0)	0 (0.0)	0 (0.0)
SAEs leading to permanent discontinuation	0 (0.0)	0 (0.0)	0 (0.0)

Treatment refers to the last treatment received before AE start. Percentages based on the no. of patients exposed to that treatment ('N=x').

Date of Clinical Trial Report not yet finalized
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