Sponsor

Novartis

Generic Drug Name

None

Therapeutic Area of Trial

Primary open-angle glaucoma or ocular hypertension

Approved Indication

Investigational

Study Number

CRKI983A2201

Title

A 4-week multi-center, single-masked, randomized, latanoprost-controlled, parallel group study to assess the efficacy, tolerability and safety of RKI983 (0.05% and 0.10%) ophthalmic solution given twice a day versus once daily latanoprost 0.005%, in patients with primary open-angle glaucoma or ocular hypertension

Phase of Development

I/II

Study Start/End Dates

15-Jan-2009 to 23-Apr-2009

Study Design/Methodology

This was a multi-center, single-masked, randomized, active-controlled, parallel-group study of patients with primary open-angle glaucoma or ocular hypertension treated twice daily with an ophthalmic solution of RKI983 0.05% or 0.10% or once daily latanoprost 0.005%, for 29 days after a screening/wash-out period of up to 28 days.

Centres

30 centers in US

Publication

Ongoing

Objectives

Primary objective(s)

The primary objective of the study was to evaluate whether RKI983 0.05% or 0.10% bid is superior to latanoprost 0.005% qd as measured by the mean reduction of the daily average IOP (average of measurements at 0800, 1000, 1200, 1600 and 1800 hrs) between baseline and day 29.

Secondary objective(s)

- To evaluate whether RKI983 is superior to latanoprost in terms of mean IOP reduction from each assessment time point at baseline to the corresponding assessment time point at each visit up to day 29.
- To evaluate whether RKI983 is superior to latanoprost in terms of mean reduction of the daily average IOP (average of measurements at 0800, 1000, and 1200 hrs), from baseline to days 8, 15 and 22.
- To compare the ocular and systemic tolerability and safety between the three treatment arms.

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

RKI983 0.05% & RKI983 0.10% sterile ophthalmic solution, given twice daily in the morning and the evening.

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

Latanoprost 0.005% ophthalmic sterile solution given once daily in the evening.

Criteria for Evaluation

Primary variables

The mean reduction in daily average IOP from baseline to day 29.

Secondary variables

1. The mean IOP reduction from each assessment time point at baseline to the corresponding assessment time point at each visit up to day 29.
2. The mean reduction in daily average IOP (average of 0800, 1000 and 1200 hrs measurements), from baseline to days 8, 15 and 22.

Safety and tolerability

Safety was assessed by recording the frequency and severity of all adverse events (AEs), with their severity and relationship to study drug, including pregnancies, clinically significant findings during the physical examination, clinically significant changes in vital signs, laboratory values and ECGs, and by performing ophthalmic examinations.

Pharmacology

NA

Other

NA

Statistical Methods

The statistical hypothesis to be tested is that there was no difference between any of the RKI983 doses and the latanoprost mean reduction of the daily average IOP evaluations obtained at 0800, 1000, 1200, 1600 and 1800 hrs from Baseline to Day 29; the alternative hypothesis being that there was a difference in the mean reduction of the daily average IOP between at least one of the dose groups of RKI983 treated patients and the latanoprost treated patients.

Changes from baseline of the mean daily average intraocular pressure would be compared between groups using ANOVA/ANCOVA models (baseline mean of the daily average intraocular pressure as covariate, further details will be given in the Statistical Analysis Plan). Comparisons of the adjusted mean for each of the RKI983 doses compared to latanoprost together with 95% confidence intervals would be presented.

All efficacy evaluations would be carried out on the Full Analysis Set. A supportive analysis of efficacy would be carried out on the Per Protocol Analysis Set for the primary and secondary efficacy variables only. All safety evaluations would be carried out on the Safety Analysis Set.

Approximately 213 patients were expected to be randomized for the study in a 1:1:1 ratio to receive: 1) RKI983 0.05%, 2) RKI983 0.10%, 3) latanoprost. Seventy-one patients will be random-

ized in each of the treatment arms.

With a difference in the reduction from baseline in IOP of 1.5 mmHg between any of the RKI983 groups and the latanoprost group, based on a standard deviation of 3.0 mmHg, then with 71 patients in any of the treatment groups, there was approximately 84% power to detect a difference in the change from baseline at the two-sided alpha-level of 5.0%.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria for patients

Patients who met the following criteria were randomized :

1. Written informed consent must have been given before any study related procedure was performed
2. Males or females =18 years of age
3. Females were eligible only if they were post-menopausal or surgically sterile or, if they were of childbearing potential, concomitantly using two acceptable forms of effective contraception. Further details are provided in the protocol
4. Clinical diagnosis of POAG or OH

Inclusion criteria for study eye

5. Cornea that was clear and without pathology or signs of previous trauma seen by slit lamp examination
6. a) For study eyes **not previously treated with anti-glaucoma medications** (treatment naïve study eyes):
   - IOP had to be =22 mmHg at =2 assessment time points at screening, **and**
   - IOP had to be =22 mmHg at =2 assessment time points at baseline, **and**
   - IOP had to be =20 mmHg and =36 mmHg at all screening and baseline assessment time points

   OR

   b) For study eyes **previously treated with anti-glaucoma medications** :
   - IOP had to be =14 mmHg and =24 mmHg at =2 assessment time points at screening, **and**
   - IOP had to be =22 mmHg at =2 assessment time points at baseline (after wash-out), **and**
   - IOP had to be =20 mmHg and =36 mmHg at all baseline assessment time points

Exclusion criteria concerning patient's conditions/diseases

1. Closed or narrow anterior chamber angles or a history of acute angle closure in either eye
2. Patients with advanced glaucoma who, in the investigator's opinion, could be at risk by participating in the study
3. History of or current clinically significant ocular conditions in either eye that would contraindicate the use of an investigational drug or latanoprost (e.g. active intraocular inflammation), or that might affect interpretation of the results of the study
4. History or presence of clinically significant medical problems that contraindicate the use of

an investigational drug or latanoprost, including but not limited to:

- Uncontrolled hypertension with systolic blood pressure =160 mmHg and/or diastolic blood pressure =100 mmHg measured at more than one blood pressure reading at screening or baseline
- myocardial infarction within the 3 month period prior to randomization
- active, severe viral infections such as active encephalitis, meningitis, hepatitis, herpes simplex, or herpes zoster (minor viral upper respiratory infections such as colds did not require exclusion)

5. A clinically significant laboratory finding that indicates a reasonable suspicion of a disease or a condition that contraindicates the use of an investigational drug or latanoprost or that may render the subject at risk for a treatment complication
6. Drug allergy or known hypersensitivity to drugs chemically related to RKI983, latanoprost, benzalkonium chloride, or other ingredients in the study medication

Exclusion criteria concerning patient's prior treatments/interventions

1. Exposure during the four weeks preceding the baseline visit to any topical, inhaled or systemic corticosteroids
2. Any alteration in dose or regimen of existing chronic, systemic therapy or the initiation of new therapy with agents which could have had a substantial effect on IOP, including but not limited to, beta-adrenergic blocking agents (i.e. propranolol, timolol, atenolol), alpha-adrenergic agonists and antagonists, and diuretics within the 30 days prior to visit 1

Enrollment or participation within 30 days preceding the screening visit in any investigational drug or device trial, or previous enrollment or screening for this trial

Disposition of Patients

	RKI983 0.10% N=74 n (%)	RKI983 0.05% N=71 n (%)	LATAN 0.005% N=73 n (%)	Total N=218 n (%)
Completed	72 (97.3)	71 (100)	73 (100)	216 (99.1)
Discontinued	2 (2.7)	0	0	2 (0.9)
Reason for discontinuation:				
Adverse event	2 (2.7)	0	0	2 (0.9)

Demographic and Background Characteristics

	RKI983 0.10% N=74	RKI983 0.05% N=71	LATAN 0.005% N=73	Total N=218
Age (years)				
n	74	71	73	218
Mean (SD)	66.3 (9.98)	64.9 (12.86)	62.5 (10.83)	64.6 (11.33)
Median	66.0	67.0	64.0	66.0
Range	38 to 90	27 to 86	31 to 86	27 to 90
Sex - n (%)				
Male	29 (39.2)	37 (52.1)	31 (42.5)	97 (44.5)
Female	45 (60.8)	34 (47.9)	42 (57.5)	121 (55.5)
Race - n (%)				
Caucasian	45 (60.8)	43 (60.6)	51 (69.9)	139 (63.8)
Black	26 (35.1)	27 (38.0)	21 (28.8)	74 (33.9)
Asian	2 (2.7)	0	1 (1.4)	3 (1.4)
Native American	1 (1.4)	0	0	1 (0.5)
Pacific islander	0	1 (1.4)	0	1 (0.5)
Other	0	0	0	0
Weight (kg)				
n	74	71	73	218
Mean (SD)	83.29 (16.808)	85.74 (19.777)	82.68 (19.184)	83.88 (18.576)
Median	81.42	82.56	81.65	81.65
Range	44.9 to 122.5	56.7 to 152.0	53.5 to 138.3	44.9 to 152.0
Height (cm)				
n	74	71	73	218
Mean (SD)	165.70 (9.991)	169.06 (10.456)	166.52 (9.381)	167.07 (10.005)
Median	165.10	170.18	165.10	165.10
Range	144.8 to 188.0	147.0 to 193.0	149.0 to 190.5	144.8 to 193.0

Primary Objective Result(s)

Mean change from baseline in daily average IOP for study eye by visit (Full analysis set, LOCF)

Visit Treatment	n	Baseline mean (SD)	Mean at visit (SD)	LS Mean change (SE)	Treatment group vs Latanoprost Difference in LS mean change Mean (SE)	95% CI	p-value*
Day 2							
RKI983 0.10% (N=74)	73	24.299 (2.4474)	19.646 (3.0659)	-4.650 (0.2472)	1.099 (0.3497)	(0.41, 1.79)	0.002*
RKI983 0.05% (N=71)	71	24.131 (2.2323)	20.412 (2.9776)	-3.731 (0.2508)	2.018 (0.3524)	(1.32, 2.71)	<0.001*
LATAN 0.005% (N=73)	73	24.360 (2.2277)	18.603 (2.8839)	-5.749 (0.2473)			
Day 8							
RKI983 0.10% (N=74)	73	24.299 (2.4474)	19.756 (3.3874)	-4.536 (0.3048)	1.828 (0.4311)	(0.98, 2.68)	<0.001*
RKI983 0.05% (N=71)	71	24.131 (2.2323)	20.521 (3.0563)	-3.637 (0.3093)	2.727 (0.4345)	(1.87, 3.58)	<0.001*
LATAN 0.005% (N=73)	73	24.360 (2.2277)	17.977 (3.1151)	-6.364 (0.3049)			
Day 15							
RKI983 0.10% (N=74)	73	24.299 (2.4474)	19.885 (3.5731)	-4.407 (0.3139)	2.145 (0.4439)	(1.27, 3.02)	<0.001*
RKI983 0.05% (N=71)	71	24.131 (2.2323)	20.044 (3.3329)	-4.114 (0.3185)	2.438 (0.4474)	(1.56, 3.32)	<0.001*
LATAN 0.005% (N=73)	73	24.360 (2.2277)	17.790 (2.8198)	-6.552 (0.3140)			
Day 22							
RKI983 0.10% (N=74)	73	24.299 (2.4474)	19.828 (3.4612)	-4.465 (0.3256)	2.180 (0.4605)	(1.27, 3.09)	<0.001*
RKI983 0.05% (N=71)	71	24.131 (2.2323)	20.288 (3.5059)	-3.868 (0.3303)	2.776 (0.4641)	(1.86, 3.69)	<0.001*
LATAN 0.005% (N=73)	73	24.360 (2.2277)	17.699 (3.0872)	-6.644 (0.3257)			
Day 29/EOS Primary endpoint							
RKI983 0.10% (N=74)	74	24.262 (2.4507)	19.493 (3.3658)	-4.767 (0.2987)	1.887 (0.4239)	(1.05, 2.72)	<0.001*
RKI983 0.05% (N=71)	71	24.131 (2.2323)	19.756 (3.0640)	-4.409 (0.3050)	2.245 (0.4286)	(1.40, 3.09)	<0.001*
LATAN 0.005% (N=73)	73	24.360 (2.2277)	17.676 (2.6984)	-6.654 (0.3008)			

EOS = End of Study. n = number of patients with measurements at both baseline and the specified visit.
LS mean = least squares mean change from baseline to the specified visit.
* indicates statistical significance (two-sided) at 0.05 level.
Daily average IOP = mean of all available time point assessments (i.e. at 0800, 1000, 1200, 1600 and 1800 hrs for Baseline, Day 2 and Day 29/EOS, and 0800, 1000 and 1200 for Days 8, 15 and 22). If <2 time point assessments were available at Baseline, the Screening value was carried forward, where available (for treatment naïve patients only). If <2 time point assessments were available at Day 29/EOS, or no time point assessments were available at Days 8, 15 or 22, then the previous non-missing post-baseline daily average IOP value was carried forward, where

available.
Change from baseline = post-baseline – baseline value.
ANCOVA: treatment as factor and baseline daily average IOP as a covariate

Secondary Objective Result(s)

Mean change in IOP from baseline to day 29/end of study for study eye by time point (Full analysis set, LOCF)

Time point Treatment	n	Baseline mean (SD)	Mean at day 29 / EOS (SD)	LS Mean Change (SE)	Treatment group vs Latanoprost Difference in LS mean change Mean (SE)	95% CI	p-value*
08:00							
RKI983 0.10% (N=74)	73	25.26 (2.709)	21.01 (3.870)	-4.16 (0.377)	2.63 (0.533)	(1.58, 3.68)	<0.001*
RKI983 0.05% (N=71)	70	24.84 (2.968)	21.15 (3.458)	-3.80 (0.385)	2.99 (0.539)	(1.92, 4.05)	<0.001*
LATAN 0.005% (N=73)	73	25.09 (2.596)	18.29 (3.231)	-6.78 (0.377)			
10:00							
RKI983 0.10% (N=74)	74	24.39 (3.016)	19.30 (3.669)	-5.11 (0.347)	2.18 (0.493)	(1.21, 3.15)	<0.001*
RKI983 0.05% (N=71)	71	24.28 (2.808)	19.63 (3.871)	-4.70 (0.355)	2.59 (0.498)	(1.60, 3.57)	<0.001*
LATAN 0.005% (N=73)	73	24.60 (2.669)	17.25 (2.864)	-7.29 (0.350)			
12:00							
RKI983 0.10% (N=74)	73	23.96 (2.965)	18.90 (3.828)	-5.23 (0.361)	1.66 (0.510)	(0.66, 2.67)	0.001*
RKI983 0.05% (N=71)	71	24.47 (2.818)	19.32 (3.176)	-5.05 (0.365)	1.85 (0.512)	(0.84, 2.86)	<0.001*
LATAN 0.005% (N=73)	73	24.45 (3.114)	17.47 (3.005)	-6.90 (0.360)			
16:00							
RKI983 0.10% (N=74)	74	23.86 (2.496)	18.97 (3.623)	-4.83 (0.352)	1.39 (0.499)	(0.41, 2.37)	0.006*
RKI983 0.05% (N=71)	71	23.46 (2.337)	19.20 (3.451)	-4.37 (0.360)	1.85 (0.505)	(0.86, 2.85)	<0.001*
LATAN 0.005% (N=73)	73	23.79 (2.431)	17.54 (2.914)	-6.22 (0.354)			
18:00							
RKI983 0.10% (N=74)	74	23.83 (2.807)	19.20 (3.880)	-4.59 (0.370)	1.42 (0.526)	(0.38, 2.46)	0.008*
RKI983 0.05% (N=71)	70	23.54 (2.634)	19.41 (3.567)	-4.21 (0.380)	1.80 (0.534)	(0.75, 2.86)	<0.001*
LATAN 0.005% (N=73)	72	23.83 (2.569)	17.78 (3.033)	-6.01 (0.375)			

EOS = End of Study. n = number of patients with both baseline and Day 29/EOS measurements at the specified time

point.
LS mean = least squares mean change from baseline to Day 29/EOS.
* indicates statistical significance (two-sided) at 0.05 level.
If IOP was missing for any time point at the baseline visit, a non-missing value from the same time point at the screening visit was carried forward, where available (for treatment naïve patients only). If IOP was missing for any time point at the Day 29/EOS visit, the previous non-missing value from the same time point at an earlier post-baseline visit was carried forward, where available.
Change from baseline = post-baseline – baseline value.
ANCOVA: treatment as factor and baseline IOP (at the specified time point) as a covariate.

Safety Results

Overall, more AEs occurred in the RKI983 0.10% and 0.05% groups (40% and 44%) compared to latanoprost 0.005% group (32%). As expected, the most common AEs were eye disorders and among these eye conjunctival hyperemia was reported most frequently.

Eye disorders occurred more frequently in the RKI983 0.10% and 0.05% groups (29,3% and 29.2%) than in the latanoprost group (15%).

Vascular disorders were the next most frequent class of AEs occurring at a similar frequency across the 3 treatment groups: 8% to 11% of patients. Infections and infestations occurred most frequently in the lower dose RKI983 0.05% group: 8.3% vs 2.7% on RKI983 0.10% and 1.4% on latanoprost.

AEs by most frequently affected primary system organ classes (>=2% of patients in any group) and treatment (Safety set)

	RKI983 0.10% N=75 n (%)	RKI983 0.05% N=72 n (%)	LATAN 0.005% N=72 n (%)
Total number (%) of patients with any AE	30 (40.0)	32 (44.4)	23 (31.9)
Primary system organ class affected			
Eye disorders	22 (29.3)	21 (29.2)	11 (15.3)
Vascular disorders	8 (10.7)	6 (8.3)	7 (9.7)
Infections and infestations	2 (2.7)	6 (8.3)	1 (1.4)
Cardiac disorders	2 (2.7)	2 (2.8)	2 (2.8)
Musculoskeletal and connective tissue disorders	2 (2.7)	0	0
Respiratory, thoracic and mediastinal disorders	1 (1.3)	3 (4.2)	2 (2.8)
Metabolism and nutrition disorders	0	0	2 (2.8)

Primary system organ classes are sorted in descending order of frequency (n (%) of patients) in the RKI983 0.10% treatment group.

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

Number (%) of patients with most frequent (>=2% of patients in any group) ocular AEs in any eye by preferred term and treatment (Safety set)

	RKI983 0.10% N=75 n (%)	RKI983 0.05% N=72 n (%)	LATAN 0.005% N=72 n (%)
Total number (%) of patients with any ocular* AE	22 (29.3)	21 (29.2)	11 (15.3)
Preferred term			
Conjunctival hyperemia	14 (18.7)	15 (20.8)	6 (8.3)
Punctate keratitis	3 (4.0)	3 (4.2)	1 (1.4)
Eye pruritus	3 (4.0)	2 (2.8)	0
Vision blurred	2 (2.7)	4 (5.6)	1 (1.4)
Lacrimation increased	2 (2.7)	1 (1.4)	0
Conjunctivitis	0	2 (2.8)	0

* selection is made based on “site” as captured in eCRF.
Preferred terms are sorted in descending order of frequency (n (%) of patients) in the RKI983 0.10% treatment group.

Number (%) of patients with most frequent (>=2% of patients in any group) non-ocular AEs by preferred term and treatment (Safety set)

	RKI983 0.10% N=75 n (%)	RKI983 0.05% N=72 n (%)	LATAN 0.005% N=72 n (%)
Total number (%) of patients with any non-ocular* AE	14 (18.7)	18 (25.0)	12 (16.7)
Preferred term			
Hypertension	5 (6.7)	5 (6.9)	5 (6.9)
Hypotension	3 (4.0)	1 (1.4)	2 (2.8)
Cardiac disorder	2 (2.7)	1 (1.4)	0
Sinus congestion	1 (1.3)	3 (4.2)	0
Upper respiratory tract infection	0	4 (5.6)	0
Tachycardia	0	1 (1.4)	2 (2.8)

* selection is made based on “site” as captured in eCRF.
Preferred terms are sorted in descending order of frequency (n (%) of patients) in the RKI983 0.10% treatment group.

Serious Adverse Events and Deaths

No patients died or had SAEs during the study.

Other Relevant Findings

Number (%) of patients with conjunctival hyperemia (pre-IOP) in the study eye, at baseline and post-baseline, irrespective of time point or visit, by treatment group (Safety set)

Period	Conjunctival hyperemia	RKI983 0.10% N=75 n (%)	RKI983 0.05% N=72 n (%)	LATAN 0.005% N=72 n (%)
Best baseline [1]	None	55 (73.3)	50 (69.4)	57 (79.2)
	Present	20 (26.7)	22 (30.6)	15 (20.8)
	Mild	20 (26.7)	22 (30.6)	15 (20.8)
	Moderate	0	0	0
	Severe	0	0	0
Worst baseline [2]	None	47 (62.7)	35 (48.6)	42 (58.3)
	Present	28 (37.3)	37 (51.4)	30 (41.7)
	Mild	28 (37.3)	37 (51.4)	29 (40.3)
	Moderate	0	0	1 (1.4)
	Severe	0	0	0
Post-baseline [3]	None	1 (1.3)	0	10 (13.9)
	Present	74 (98.7)	71 (98.6)	62 (86.1)
	Mild	15 (20.0)	17 (23.6)	41 (56.9)
	Moderate	29 (38.7)	32 (44.4)	17 (23.6)
	Severe	30 (40.0)	22 (30.6)	4 (5.6)
	Missing	0	1 (1.4)	0
Change from best baseline [4]	Present	54 (72.0)	49 (68.1)	47 (65.3)
Change from worst baseline [4]	Present	46 (61.3)	34 (47.2)	32 (44.4)

If the hyperemia rating was missing at 0800 hrs at the baseline visit, a non-missing value from the 0800 hrs time point at the screening visit was carried forward, where available (for treatment naïve patients only). If the screening value was also missing, then the baseline value was imputed with zero (no hyperemia) rating.
[1] Best baseline for each patient is the least severe baseline (visit 2) rating from time points of 0800, 1000, 1200, 1600 and 1800 hrs.
[2] Worst baseline for each patient is the most severe baseline (visit 2) rating from time points of 0800, 1000, 1200, 1600 and 1800 hrs.
[3] Post-baseline value for each patient is the most severe hyperemia rating across all post-baseline visits and time points.
[4] Change from Best (Worst) baseline = number of patients without hyperemia at Best (Worst) baseline and with hyperemia post-baseline.

Date of Clinical Trial Report

01 Apr 2010

Date of Inclusion on Novartis Clinical Trial Results Database

20 Apr 2010

Date of Latest Update