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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** SAR366234	**Study Identifiers:** U1111-1153-3544, NCT02531152 **Study code:** TDR13459
Title of the study: A randomized, observer-masked study of the safety, tolerability and pharmacodynamics of sequential ascending 28—day repeated topical doses of SAR366234 versus latanoprost in patients with open angle glaucoma or ocular hypertension	
Study center(s): Five centers in the USA	
Study period: Date first patient enrolled: 08/Sep/2015 Date last patient completed: 15/Apr/2016	
Phase of development: I	
Objectives: **Primary:** To assess the local and systemic safety and tolerability of ascending repeated topical doses of SAR366234 monotherapy in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) as compared to those of latanoprost. **Secondary:** To assess the pharmacodynamic (PD) activity of ascending repeated topical doses of SAR366234 in patients with OAG or OHT as compared to that of latanoprost.	
Methodology: Multi-center, randomized, observer-masked, parallel cohorts, sequential ascending 28-day repeated topical doses of SAR366234 as monotherapy in patients with OAG or OHT, with latanoprost as positive control, preceded by a treatment-free run-in/washout period.	
Number of patients: Planned: up to 75 completed patients (up to 5 dose level cohorts of 15 patients each [12 on SAR366234 and 3 on latanoprost]) Randomized: 54 Treated: 54 **Evaluated:** pharmacodynamics: 53 Safety: 54 Pharmacokinetics: not applicable	
Diagnosis and criteria for inclusion: Male and female patients aged ≥ 18 years with OAG or OHT who have an intraocular pressure (IOP) ≥ 22 mmHg and <36 mmHg on the morning of the baseline visit. Eligible patients were planned to be included after an appropriate treatment-free run-in period depending on previous glaucoma medication washout requirements.	

Study treatments

Investigational medicinal product(s): SAR366234

Formulation: 5-mL glass vials each containing 2-mL of a preservative–free aqueous solution of SAR366234 (at 3 different concentrations) and Cremophor EL® 3.6%

Route(s) of administration: Topical ocular administration (eye drops)

Dose regimen: Once daily (QD) drops in the evening or twice daily (BID) drops in the morning and evening, in both eyes

Dose 1: SAR366234 at a low concentration, total of 2 drops per eye per day, BID administration (1 drop in each eye in the morning and 1 drop in each eye in the evening)

Dose 2: SAR366234 at a medium concentration, total of 1 drop per eye per day, QD administration (1 drop in each eye in the evening)

Dose 3: SAR366234 at a medium concentration, total of 2 drops per eye per day, BID administration (1 drop in each eye in the morning and 1 drop in each eye in the evening)

Dose 4: SAR366234 at a high concentration, total of 1 drop per eye per day, QD administration (1 drop in each eye in the evening)

Dose 5: SAR366234 at a high concentration, total of 2 drops per eye per day, BID administration (1 drop in each eye in the morning and 1 drop in each eye in the evening) (planned but not administered)

Noninvestigational medicinal product(s): latanoprost (Xalatan®)

Formulation: 5-mL bottles containing 2.5-mL of a sterile, isotonic, buffered aqueous solution of latanoprost at 0.005% with benzalkonium chloride 0.02% as preservative

Route of administration: Topical ocular administration (eye drops)

Dose regimen: per FDA label, total of 1 drop per eye per day, QD administration (1 drop in each eye in the evening)

Duration of treatment: 28 days

Duration of observation: Total duration up to 11 weeks including screening (up to 6 weeks run-in; depending on washout requirements), an ambulatory treatment period of 4 weeks (from Day 1 to Day 28), an end-of-treatment visit on Day 29, and a follow-up visit approximately 1 week after last administration (end—of—study [EOS] visit).

Criteria for evaluation: proof of concept study

Safety: Patient safety was mainly monitored by adverse event (AE) reporting (throughout the whole study period up to EOS), ophthalmological examinations (at screening [best corrected visual acuity only], baseline, and at selected time points postdose up to EOS), and local ocular tolerance assessments (patient evaluation, on 100 mm visual analogue scales [VAS; from 0 mm “no symptoms” to 100 mm “worst possible symptoms”], of foreign body sensation, burning, stinging, itching, eye pain, sticky feeling, blurred vision, and photophobia, in either eye).

Ophthalmological examinations included:

- Slit lamp biomicroscopy and corneal fluorescein staining with evaluation of eyelid, conjunctiva, cornea, iris/pupil, and lens each on a 5 box grading system (from 0 to 4), as well as assessment of anterior chamber cells and flare with the Standardization of Uveitis Nomenclature scoring.
- Ultrasound pachymetry for evaluation of central corneal thickness (in µm).
- Dilated fundoscopy with evaluation of the vitreous, retina, optic disc, and choroid.
- Best Corrected Visual Acuity testing with Early Treatment Diabetic Retinopathy Study (ETDRS) score.

Safety and tolerability data up to at least Day 15 of each dose cohort were evaluated by a safety review team (SRT) including a sponsor clinical representative, the coordinating investigator, and an independent ophthalmologist. The decision of whether or not to move to the next dose cohort was taken by the SRT.

Pharmacodynamics: IOP measurements at screening, baseline and at selected time points up to EOS.

Statistical methods: The sample size for this study was based upon empirical considerations.

Safety: Individual values were flagged for potentially clinically significant abnormalities, treatment—emergent adverse events (TEAEs) were tabulated (counts and percents), and listings were generated by treatment and time point for ophthalmological data.

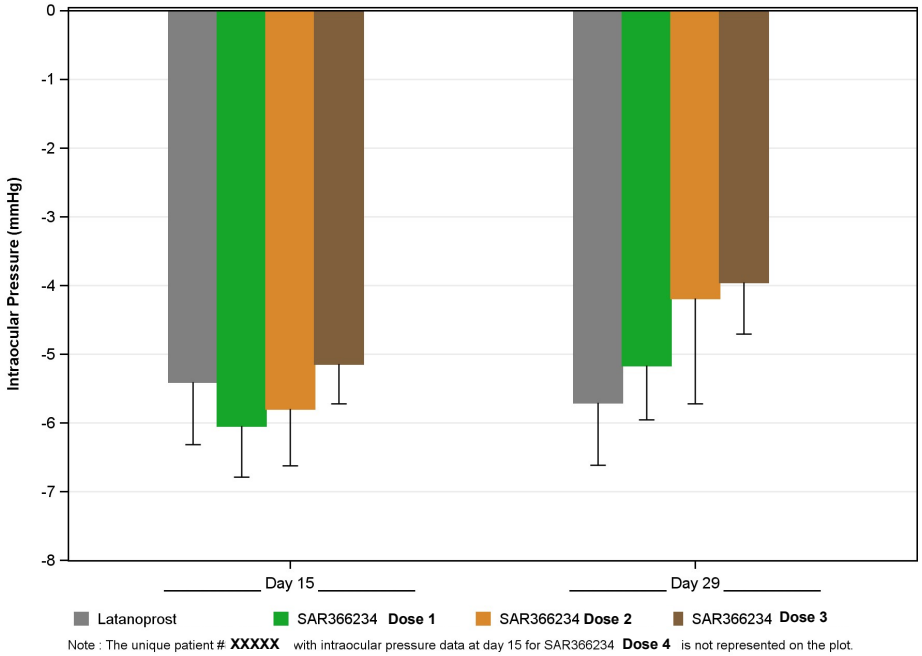
Pharmacodynamics: Descriptive statistics and graphs on IOP raw data and change from baseline (diurnal and time—matched) were provided for both the study eye (ie, the eye with the greater mean diurnal IOP at baseline; if both eyes showed equal mean value, the right eye was chosen as study eye) and the non-study eye. The statistical analysis of the comparison of the effect of SAR366234 on IOP changes versus latanoprost was also provided.

Summary:

Population characteristics: Of the 54 patients randomized in 4 cohorts, 20 patients (37.0%) were males and 34 (63.0%) were females, with a mean age of 65.9 (range from 34 to 97) years. Twenty four patients (44.4%) were Caucasian/White, 29 (53.7%) were African American, and 1 (1.9%) was Asian/Oriental. Demography characteristics were similar in all treatment groups. The mean diurnal baseline IOP for the study eye was 24 mmHg in each treatment group (min-max = 21 to 32 mmHg for all groups), and the mean IOP at each baseline time point ranged from 22 to 26 mmHg for all groups. Forty-five patients completed the study per protocol (9 in the latanoprost group, 12 in each of the Dose 1, Dose 2, and Dose 3 SAR366234 groups, none in the Dose 4 SAR366234 group). Of the 9 patients discontinued, 4 discontinued treatment for adverse event(s) (all on Dose 4 SAR366234). These adverse events (corneal endothelial cell loss and corneal opacity, corneal pigmentation, asthenopia, and photophobia) led to the discontinuation of the Cohort 4 dose level (ie, Dose 4 SAR366234) and ultimately the study. Dose 5 of SAR366234 was not administered.

Pharmacodynamic results:

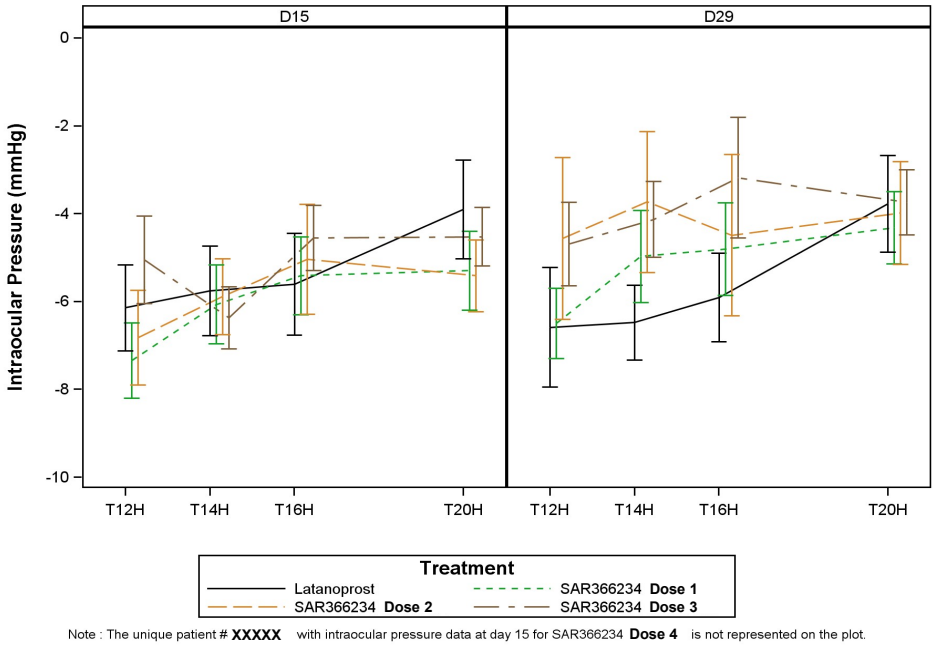
Summary plot of intraocular pressure change from diurnal baseline (mmHg) by treatment group at Day 15 and Day 29 (Mean -SEM) – Study eye – Pharmacodynamic population



Note : The unique patient # **XXXXX** with intraocular pressure data at day 15 for SAR366234 **Dose 4** is not represented on the plot.

The diurnal baseline value is the average of the 4 IOP measurements performed at Day 1 T-12h, T-10h, T-8h and T-4H before first dosing.

Summary plot of intraocular pressure change from time-matched baseline (mmHg) by treatment group at Day 15 and Day 29 (Mean±SEM) – Study eye – Pharmacodynamic population



Note : The unique patient # **XXXXX** with intraocular pressure data at day 15 for SAR366234 **Dose 4** is not represented on the plot.

The time-matched baseline for one time point is the value corresponding to the same theoretical time point on Day 1.

Intraocular pressure baseline and changes (mmHg) by treatment group for the study eye after 28 days of treatment – Mean (±SEM) – Descriptive statistics

Day	Latanoprost (N=11;9)*	SAR366234 Dose 1 (N=13;12)*	SAR366234 Dose 2 (N=12;11)*	SAR366234 Dose 3 (N=12;12)*
With diurnal baseline				
D1 (baseline)	24.35 (0.855)	23.70 (0.569)	23.94 (0.379)	24.22 (0.538)
D29 diurnal mean change from baseline	-5.70 (0.912)	-5.17 (0.791)	-4.19 (1.533)	-3.95 (0.754)
With time-matched baseline				
D1 T-12h (baseline)	25.57 (0.837)	25.70 (0.954)	25.40 (0.717)	25.61 (0.614)
D1 T-10h (baseline)	24.79 (0.904)	23.45 (0.600)	23.92 (0.439)	24.60 (0.636)
D1 T-8h (baseline)	24.24 (1.033)	23.08 (0.381)	23.87 (0.543)	23.60 (0.570)
D1 T-4h (baseline)	22.75 (0.869)	22.51 (0.708)	22.58 (0.527)	23.00 (0.658)
D29 T12h mean change from baseline	-6.59 (1.358)	-6.50 (0.795)	-4.56 (1.843)	-4.69 (0.951)
D29 T14h mean change from baseline	-6.48 (0.852)	-4.98 (1.050)	-3.74 (1.608)	-4.13 (0.865)
D29 T16h mean change from baseline	-5.91 (1.012)	-4.81 (1.050)	-4.49 (1.840)	-3.18 (1.374)
D29 T20h mean change from baseline	-3.78 (1.098)	-4.33 (0.820)	-3.98 (1.170)	-3.74 (0.738)

* Number of patients on Day 1 (baseline);Day 29
The diurnal baseline value is the average of the 4 IOP measurements performed at Day 1 T-12h, T-10h, T-8h and T-4H before first dosing

After 26 to 28 days of SAR366234 dosing, the lowest tested dose (Dose 1) gave the best mean IOP decrease for the study eye, as assessed graphically, while for the non-study eye it was Dose 2. The observed effect on Day 29 was lower than that achieved on Day 15 for all doses. The comparison for Day 29 of the effect of SAR366234 versus latanoprost on IOP changes did not show numerical superiority of SAR366234 at any dose. The statistical analyses confirmed these results; SAR366234 did not show any statistically significant superiority to latanoprost on IOP changes from baseline at any dose.

Safety results: There were no patients with TEAEs related to eye disorders in the latanoprost group, whereas 31% to 33% of patients experienced eye disorders in the Dose 1, Dose 2, and Dose 3 SAR366234 groups with 1 to 2 patients (8% to 15%) presenting AEs of conjunctival hyperaemia (grade 1 or 2 at the slit lamp exam), eye irritation, and punctate keratitis in each of these groups. All 5 patients in the Dose 4 SAR366234 group experienced ocular TEAEs, leading to treatment discontinuation in 4 of them (80%; see below). All 5 patients in the Dose 4 SAR366234 group presented conjunctival hyperaemia at the slit lamp exam (grade 2 or 3), 4 of which were declared as AEs.

No findings for either cells or flare in the anterior chamber or signs of iritis were observed at the slit lamp examination for any of the SAR366234 doses tested.

Changes in visual acuity were observed in some patients and, while not considered as AEs by the investigators, the SRT considered the change of clinical relevance. All ETDRS score decreases >10 letters were only seen in Cohort 3 in patients receiving latanoprost (1 patient) or SAR366234 at Dose 3 (2 patients).

Summary of patients with loss in Early Treatment Diabetic Retinopathy Study score >5 letters in either eye at any time during the study – Number of patients

Category	Latanoprost (N=11)	SAR366234 Dose 1 (N=13)	SAR366234 Dose 2 (N=13)	SAR366234 Dose 3 (N=12)
>5 and ≤10 letters loss	1	1	3	1
>10 and ≤15 letters loss	1	0	0	2
>15 letters loss (SAE per protocol)	0	0	0	0

Patients were counted only once per category with no overlap between categories (worst occurrence)

All patients with a decrease in their ETDRS score of more than 5 letters from baseline at EOS were followed. Three patients were identified (1 patient in the latanoprost group, 1 patient in the Dose 2 SAR366234 group, and 1 patient in the Dose 3 SAR366234 group). Except for the patient in the latanoprost group, values had returned to baseline at the follow-up visit.

There was 1 serious adverse event (SAE) and 1 adverse event of special interest (AESI) reported during the study. A 65-year old male in the Dose 1 SAR366234 group was diagnosed with atrial fibrillation (SAE) on a routine electrocardiogram at the end-of-treatment visit and was hospitalized for observation and evaluation 1 week later. The event, unrelated to the investigational medicinal product (IMP) by the investigator, resolved 9 days after onset under appropriate corrective treatment (amiodarone 200 mg BID for 2 weeks, then 200 mg QD). A 46-year old female in the Dose 4 SAR366234 group experienced photophobia (AESI) on Day 6. The event was considered related to IMP and treatment was discontinued by the investigator; the photophobia resolved 23 days later.

The AEs leading to treatment discontinuation all happened in the Dose 4 SAR366234 group. All AEs (corneal endothelial cell loss and corneal opacity, corneal pigmentation, asthenopia, and photophobia) were noted on Day 6 at the first postdose ophthalmological exam. The 4 patients experiencing these events discontinued the IMP after 5 or 6 days of dosing. In addition, all 4 patients presented grade 3 conjunctival hyperaemia at the Day 6 slit lamp exam.

Number (%) of patients with treatment-emergent adverse events by primary system-organ class and preferred term – Safety population

Primary system organ class Preferred term [n (%)]	Latanoprost (N=11)	SAR366234 Dose 1 (N=13)	SAR366234 Dose 2 (N=13)	SAR366234 Dose 3 (N=12)	SAR366234 Dose 4 (N=5)
Any class	1 (9.1%)	6 (46.2%)	4 (30.8%)	4 (33.3%)	5 (100%)
Infections and infestations	1 (9.1%)	1 (7.7%)	1 (7.7%)	0	0
Bronchitis	0	1 (7.7%)	0	0	0
Sinusitis	0	0	1 (7.7%)	0	0
Tonsillitis	0	0	1 (7.7%)	0	0
Urinary tract infection	1 (9.1%)	0	0	0	0
Endocrine disorders	0	1 (7.7%)	0	0	0
Hypothyroidism	0	1 (7.7%)	0	0	0

Eye disorders	0	4 (30.8%)	4 (30.8%)	4 (33.3%)	5 (100%)
Conjunctival hyperaemia	0	1 (7.7%)	2 (15.4%)	1 (8.3%)	4 (80.0%)
Asthenopia	0	0	0	0	1 (20.0%)
Conjunctival oedema	0	0	0	0	1 (20.0%)
Corneal endothelial cell loss	0	0	0	0	1 (20.0%)
Corneal opacity	0	0	0	0	1 (20.0%)
Corneal pigmentation	0	0	0	0	1 (20.0%)
Eye pain	0	0	0	0	1 (20.0%)
Photophobia	0	0	0	0	1 (20.0%)
Eye irritation	0	2 (15.4%)	1 (7.7%)	1 (8.3%)	0
Foreign body sensation in eyes	0	0	0	1 (8.3%)	0
Halo vision	0	0	0	1 (8.3%)	0
Punctate keratitis	0	1 (7.7%)	1 (7.7%)	2 (16.7%)	0
Visual acuity reduced	0	0	1 (7.7%)	0	0
Cardiac disorders	0	1 (7.7%)	0	0	0
Atrial fibrillation	0	1 (7.7%)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (7.7%)	0	0	0
Asthma	0	1 (7.7%)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (7.7%)	0	0	0
Night sweats	0	1 (7.7%)	0	0	0
Investigations	0	0	0	1 (8.3%)	0
Intraocular pressure increased	0	0	0	1 (8.3%)	0
Injury, poisoning and procedural complications	1 (9.1%)	0	0	0	0
Laceration	1 (9.1%)	0	0	0	0

TEAE: treatment emergent adverse event, SOC: system-organ class, PT: preferred term
MedDRA 19.0
N = Number of patients treated within each group, n (%) = number and % of patients with at least one TEAE in each category
Note: Table sorted by SOC internationally agreed order and decreasing frequency of PT in SAR366234 Dose 4 group.
Note: An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product (IMP) administration up to the end of study visit (included)

Issue date: 21-May-2019