SYNOPSIS LT4032-301

Name of Sponsor:

Laboratoires THEA

Name of finished product:

T4032

Name of active ingredient(s):

Bimatoprost

Number and title of study: Study# LT4032-301: Efficacy and Safety Assessment of T4032 (Unpreserved Bimatoprost 0.01%) versus Lumigan® 0.01% in Ocular Hypertensive or Glaucomatous Patients.

Coordinating investigator(s):

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Study centre(s): 90 participating centres (at least one patient included and randomised in the study) in 21 countries: Belgium (2 centres), Bulgaria (5 centres), Canada (2 centres), Czech Republic (8 centres), Germany (3 centres), Spain (7 centres), Estonia (3 centres), France (6 centres), Georgia (2 centres), Greece (5 centres), Hungary (1 centre), Italy (7 centres), Lithuania (2 centres), Latvia (3 centres), Mauritius (1 centre), Poland (11 centres), Russia (7 centres), Slovakia (6 centres), Tunisia (4 centres), Ukraine (4 centres) and United Kingdom (1 centre)

Publication (reference): None	**Phase of development**: III

Objectives:
This phase III clinical study aimed to assess the efficacy and safety of T4032 eye drops (unpreserved bimatoprost 0.01%) compared with Lumigan® (hereafter referred to as Lumigan) eye drops (preserved bimatoprost 0.01%) in patients with glaucoma or ocular hypertension.

Primary objective
To demonstrate the non-inferiority of T4032 unpreserved eye drops compared to Lumigan in terms of efficacy.

Secondary objectives
The secondary objectives were to evaluate the safety and efficacy of T4032 *versus* Lumigan (based on the criteria for evaluation, described below).

Methodology:
Phase III, international, multicentre, randomised, 2 parallel group, investigator-masked, 3-month treatment duration study

Number of patients (planned and analysed):
It was planned to randomise 400 patients. The number of screened patients depended on the screen failure rate and was estimated at 668 patients.

485 patients (from 723 screened patients) were included and randomised in the study: 485 patients in the intent-to-treat (ITT) set and Safety set, 469 in the modified ITT (mITT) set and 422 in the per-protocol (PP) set.

Diagnosis and main criteria for inclusion and exclusion:
Inclusion criteria: Informed consent signed and dated; male or female aged ≥18 years old; both eyes with diagnosed open angle glaucoma (OAG) or ocular hypertension (OHT), initially treated and controlled (including

intraocular pressure [IOP] ≤18 mmHg) for at least 6 months by any prostaglandin monotherapy; IOP ≤18 mmHg in both eyes; both eyes with 500 µm ≤ central corneal thickness ≤600 µm; at randomisation, both eyes with 22 mmHg ≤IOP <34 mmHg with asymmetry between eyes ≤3 mmHg.

Key non-inclusion criteria: Fundoscopy and visual field not performed or not available within the 12 months before inclusion; significant worsening according to the two last visual fields (at least 6 months between the two visual fields); advance stages of glaucoma; far best-corrected far visual acuity (BCVA) of ≤20/100 in both eyes; history of trauma, infection, clinically significant inflammation within the previous 3 months; ongoing or known history of ocular allergy and/or uveitis and/or viral infection; clinically significant or progressive retinal disease (*e.g.,* retinal degeneration, diabetic retinopathy, retinal detachment); presence of at least one severe objective sign (Grade 5 hyperaemia, Grade 4 superficial punctate keratitis, Grade 3 blepharitis); severe dry eye; corneal ulceration; palpebral abnormalities incompatible with a good evaluation; any abnormality preventing accurate assessments (*e.g.*, reliable tonometry measurement, visual field examination); use of concomitant medications not allowed before and during the study.

Run-in period product, dose, and mode of administration:
One drop of Azopt® (preserved brinzolamide 1%) was administered in the conjunctival cul-de-sac of each eye twice daily in the morning and evening for 5 weeks.

Batch number(s): 18F06IC, 18I30GB, 18K04BA, 9HFK1B, OFRT1B

Test product, dose, and mode of administration:
One drop of T4032 (unpreserved bimatoprost 0.01%) was administered in the conjunctival cul-de-sac of each eye once daily at 20:00 (±1 hour).

Batch number(s): T4032-1608-L05

Reference product, dose, and mode of administration:
One drop of Lumigan (preserved bimatoprost 0.01%) was administered in the conjunctival cul-de-sac of each eye once daily at 20:00 (±1 hour).

Batch number(s): E87007, E86117, E86106, E83279, E82815, E85350, E84896

Duration of investigational medicinal product (T4032 or Lumigan) treatment:
The treatment was administered for 12 weeks (from Day 1 to Day 84±7 days).

Criteria for evaluation:
Primary efficacy endpoint
The primary endpoint variable was the change from baseline in IOP at Week 12 at three time points (08:00, 10:00 and 16:00) in the worse eye (defined as the eye with the highest IOP at Baseline (D1) at 08:00, or as the right eye in case of no IOP difference between both eyes).

Secondary efficacy endpoints
- Change in IOP from baseline to Week 12 at three time points (08:00, 10:00 and 16:00) in the contralateral eye
- Change in IOP from baseline to Week 6 at three time points (08:00, 10:00 and 16:00) in the worse eye and contralateral eye
- Efficacy assessed by the investigator at Week 6 and Week 12

Safety and tolerability endpoints
- Conjunctival hyperaemia on McMonnies scale in each eye at screening, baseline, Week 6, and Week 12
- Change from baseline of the conjunctival hyperaemia on McMonnies scale in 3 classes (improvement, no change, worsening) at Week 6 and Week 12
- Score of each ocular symptom throughout the day and sum of these scores
- Score of each ocular symptom upon instillation and sum of these scores
- Score of each ocular sign

- Corneal fluorescein staining (Oxford grading scale)
- Far best-corrected visual acuity (BCVA) expressed in LogMAR
- Ocular tolerance assessed by the investigator
- Ocular tolerance assessed by the patient

Ocular and systemic adverse events (AE) by system organ class (SOC) and preferred term (PT)

Statistical methods:
Statistical analyses were performed using the following analysis sets:

- **Safety set**: All enrolled patients who received at least one dose of IMP (T4032 or Lumigan) and considered as treated
- **Azopt safety set:** All enrolled patients having received at least one dose of Azopt
- **Intent-to-treat (ITT) set**: All randomised patients and considered as-randomised (*i.e.*, according to the treatment unit assigned at Day 1)
- **Modified ITT (mITT) set**: All randomised patients who received at least one dose of IMP (T4032 or Lumigan), with at least one baseline and one post-randomisation efficacy assessment on treatment and considered as-treated (*i.e.*, according to the treatment unit assigned at Day 1)
- **Per-protocol (PP) set**: All mITT patients without any major protocol violation

Demographic and baseline characteristics of the patients were described overall and by treatment group for the mITT set, Safety set, ITT set (if it differs from the Safety set) and PP set. The mITT set was defined as the primary population for the efficacy analysis. The ITT and PP sets were considered as secondary populations. The safety analyses were performed on the Safety set. Analysis during the run-in period was performed on the Azopt safety set.

Continuous data (quantitative variables) were summarised for each treatment group (and for the overall population for baseline descriptions), including the number of non-missing observations, mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% confidence interval (CI) of the mean/median.

Categorical data (qualitative variables) were summarised for each treatment group (and for the overall population for baseline descriptions), including the number of non-missing observations, count, percentage modality, and 95% CI.

95% CI of a proportion was calculated using the scoring method of Wilson without continuity correction.

Primary efficacy endpoint
The non-inferiority of T4032 to Lumigan was primarily evaluated using a Mixed Model for Repeated Measures (MMRM) approach. Three independent models were performed, one for each time point (*i.e.,* 08:00, 10:00 and 16:00). The model included as fixed factors, treatment, scheduled visit time point (Week 6 and Week 12), baseline IOP, wash-out duration, country as covariates, treatment by visit interaction, baseline IOP by visit interaction, and patient as random factor. The 95% CI for treatment effect (difference T4032 *minus* Lumigan) was estimated at Week 12 in this model. Non-inferiority was achieved if the upper bound of the 95% CI for the difference between treatment groups (T4032 - Lumigan) was lower than the margin of +1.5 mmHg for each of the three time points 08:00, 10:00 and 16:00.

Supporting analyses to check the validity of the main analysis were performed using separated MMRM to investigate the treatment by covariate (baseline IOP, wash-out and country) interactions. Sensitivity analyses were performed using (i) a last observation carried forward (LOCF) approach and (ii) observed IOP values at Day 84 with an Analysis of Covariance (ANCOVA) model including treatment, baseline IOP, wash-out duration and country. Exploratory analysis on possible covariate effect (possible impact of COVID-19 pandemic [based on their screening visit date; respectively, up to and including 18-MARS-2020 or after the 18-MARS-2020]) was investigated in the MMRM and impact of circadian rhythm was also assessed by using time factor within a MMRM, as patient nested in time.

Secondary efficacy endpoints

Other quantitative parameters were compared between groups using a MMRM or ANCOVA model. For ordered qualitative variables, treatment groups were compared using Cochran-Mantel-Haenszel (CMH) test stratified by country with modified ridit scores.

Safety endpoints

Ocular/systemic AEs and other safety endpoints were analysed using descriptive statistics. Between-group comparisons for conjunctival hyperaemia, ocular symptoms throughout the day and upon instillation, ocular signs, corneal staining, and ocular tolerance by the investigator and patient were performed using a CMH test with modified ridit scores stratified by country. Total score of ocular symptoms throughout the day and upon instillation were analysed using MMRM model.

SUMMARY

Study population and demographics

Seven-hundred and twenty-three patients were screened and 485 were included and randomised: 236 in the T4032 group and 249 in the Lumigan group. Of note, 1 patient was planned in the Lumigan group but was treated with T4032 and 1 patient was planned in the T4032 group but was treated with Lumigan.

Forty patients prematurely discontinued the study, 18 in the T4032 group and 22 in the Lumigan group. The most common reason for a premature discontinuation was due to the COVID-19 crisis: 10 (55.6%) patients in the T4032 group and 14 (63.6%) patients in the Lumigan group. Forty-seven (10.0%) patients had at least one major protocol deviation during the study: 21 (9.2%) in the T4032 group and 26 (10.8%) in the Lumigan group. The most common major protocol deviation was the mean IOP missing for the worse eye at Week 12: 11 (4.8%) patients in the T4032 group and 13 (5.4%) in the Lumigan group.

There were no major differences in demographic data between treatment groups in the Safety set. The mean age was 63.4±11.4 years (range: 30 to 91 years). Most patients were female (60.6%). The main aetiology was primary OAG (70.3% of patients in the T4032 group and 75.5% in the Lumigan group), and most patients had previously been treated with latanoprost (58.1% of patients in the T4032 group and 60.6% in the Lumigan group).

Mean IOP at screening and change from screening to randomisation were similar between the T4032 and Lumigan groups in the mITT set.

EFFICACY RESULTS:

Compliance

In the mITT set, the mean T4032/Lumigan treatment duration for the study was 83.3±8.1 days (range: 15 to 119 days) and was similar between treatment groups: 83.0±8.4 days in the T4032 group and 83.5±7.7 days in the Lumigan group. Mean treatment compliance (%) in the mITT set was similar between treatment groups in the worse eye from Day 1 to Week 12, with 99.7±1.5% in the T4032 group and 99.3±5.0% in the Lumigan group.

Primary efficacy endpoint

In the mITT set, the mean change in IOP from baseline at Week 12 in the worse eye in the T4032 group was -9.72±2.97 mmHg at 08:00, -9.41±3.03 mmHg at 10:00 and -8.99±3.36 mmHg at 16:00, and in the Lumigan group it was -9.47±3.06 mmHg at 08:00, -9.19±3.12 mmHg at 10:00 and -8.54±3.44 mmHg at 16:00. Based on the primary analysis (MMRM described below), the adjusted mean difference at Week 12 between the IOP change from baseline in the T4032 group *minus* the IOP change from baseline in the Lumigan group was -0.17±0.23 [95% CI: -0.62; 0.28] mmHg at 08:00, -0.15±0.22 [95% CI: -0.58; 0.27] mmHg at 10:00, and -0.19±0.22 [-0.61; 0.23] mmHg at 16:00. The non-inferiority of T4032 to Lumigan was demonstrated since the upper limit of the 95% CI (0.28, 0.27 and 0.23 mmHg) did not exceed 1.5 mmHg.

Primary efficacy variable: T4032 *versus* Lumigan for change in IOP (mmHg) from baseline to Week 12 in the worse eye using a MMRM[a] (mITT set)

Time Point	Adjusted mean difference±SE	Lower 95% CI	Upper 95% CI
Week 12			
08:00	-0.17±0.23	-0.62	0.28
10:00	-0.15±0.22	-0.58	0.27
16:00	-0.19±0.22	-0.61	0.23
	NON-INFERIORITY ACCEPTED		

IOP=intraocular pressure; CI=confidence interval; SE=standard error

[a] Mixed effect model for repeated measures including as fixed factors, treatment, scheduled visit time point (Week 6 and Week 12), baseline IOP, wash-out duration, country as covariates, treatment by visit interaction, baseline IOP by visit interaction, and patient as random factor

Number of patients in model: 229 in T4032 group at all time points; 239 at 08:00 and 16:00 and 240 at 10:00 in Lumigan group

Adjusted mean difference±standard error (T4032 *minus* Lumigan)

Sensitivity analyses using an ANCOVA model based on LOCF approach or observed IOP data confirmed the results of the primary efficacy endpoint in the mITT set.

For the supporting analysis, there was no statistically significant treatment by covariate interaction for treatment-by-baseline IOP, treatment-by-washout duration or treatment-by-country.

Exploratory analysis on the possible covariate effect (possible impact of COVID-19) using separated MMRM demonstrated no statistically significant treatment-by-possible impact of COVID-19 pandemic interaction at 08:00 (*p=0.568*), 10:00 (*p=0.904*) or 16:00 (*p=0.631*) at Week 12. Impact of circadian rhythm at Week 6 and Week 12 was also consistent with the main analysis.

Consistent results were shown in the ITT and PP sets.

Secondary efficacy endpoints

Change from baseline in IOP at Week 12 in the contralateral eye

Results for the contralateral eye in the mITT set were consistent with the main analysis and sensitivity analyses in the worse eye.

Change from baseline in IOP at Week 6

In the mITT set, the adjusted mean difference at Week 6 between the IOP change from baseline (±SE) in the T4032 group *minus* the IOP change from baseline in the Lumigan group was -0.14±0.23 mmHg [95% CI: -0.58; 0.31] at 08:00, -0.25±0.21 mmHg [95% CI: -0.65; 0.16] at 10:00, and -0.13±0.22 mmHg [95% CI: -0.56; 0.30] at 16:00 for the worse eye.

Similar results were observed for the contralateral eye.

Percentage of patients with IOP < 18 mmHg

In the mITT set, the proportion of patients with IOP <18 mmHg in the worse eye and contralateral eye was consistent over time and above 80% at Week 6 and Week 12 in both treatment groups.

Change from baseline of IOP depending on history of glaucoma or OHT

At Week 6 and Week 12, the mean IOP change from baseline was greater in patients with a history of glaucoma compared to patients with a history of OHT in both treatment groups at all time points. However, it must be noted that the mean baseline IOP value was higher in patients with glaucoma compared to OHT (which may explain the greater change from baseline). Results were similar between treatment groups.

Similar results for the contralateral eye.

Mean diurnal IOP and change from baseline at Week 6 and Week 12
In the mITT set, mean change in diurnal IOP from baseline was similar between the T4032 and Lumigan at Week 6 (-9.08±3.01 mmHg and -8.81±3.14 mmHg, respectively) and Week 12 (-9.38±2.94 mmHg and -9.06±3.02 mmHg, respectively)

Global efficacy assessment by the investigator of IMP (T4032 or Lumigan)
In the mITT set, the global assessment of efficacy by the investigator was similar between the T4032 and Lumigan groups and was considered as "satisfactory" or "very satisfactory" for most patients at Week 6 (96.1% on T4032 *versus* 97.1% on Lumigan; *p=0.489*) and Week 12 (97.3% *versus* 98.2%, respectively; *p=0.500*).

SAFETY RESULTS:
Exposure

In the Azopt Safety set, the mean treatment exposure during the run-in period was 34.9±4.2 days (range: 2 to 65 days).

In the Safety set, the mean treatment exposure during the study was 81.8±11.6 days (range: 2 to 119 days) and was similar in the T4032 (81.8±11.0 days) and Lumigan (81.8±12.2 days) groups.

Ocular adverse events
Azopt® – Ocular TEAEs were reported in 45 (6.7%) patients in the Azopt Safety set, of which the most common were instillation site reaction (7 [1.0%] patients), drug intolerance (5 [0.7%] patients), instillation site burn (5 [0.7%] patients] and dry eye (5 [0.7%] patients). Six (0.9%) patients had at least 1 ocular TEAE leading to premature IMP (Azopt®) withdrawal. No patient experienced a serious TEAE.

IMP (T4032 or Lumigan) – Ocular TEAEs were reported in 54 (22.9%) patients in the T4032 group *versus* 62 (24.9%) in the Lumigan group. The most frequent ocular TEAEs regardless of treatment group was conjunctival hyperaemia which was reported in 13 (5.5%) patients in the T4032 group *versus* 17 (6.8%) patients in the Lumigan group. Most ocular AEs were of mild or moderate intensity. Severe ocular TEAEs were reported for 1 patient in the T4032 group (eczema) and 2 patients in the Lumigan group (dry eye and instillation site burn). Of note, the severe TEAEs were all considered as treatment related. The IMP was withdrawn due to an ocular TEAE in 6 patients in the T4032 group who experienced 6 TEAEs (1 patient with conjunctival irritation, 1 patient with eye irritation, 1 patient with instillation site erythema, 1 patient with instillation site reaction, 1 patient with eczema and 1 patient with madarosis) and in 4 patients in the Lumigan group experiencing 8 TEAEs (1 patient with eye irritation, 1 patient with ocular hyperaemia and instillation site pain, 1 patient with conjunctival hyperaemia and instillation site pruritus, and 1 patient with eye pruritus, ocular hyperaemia and vision blurred). All ocular TEAEs leading to treatment withdrawal were assessed by the investigator as related to the study treatment, except for one case of conjunctival hyperaemia in the Lumigan group. No serious ocular TEAEs were reported in this study.

Systemic adverse events
Azopt® – Systemic TEAEs were reported in 57 (8.5%) patients in the Azopt Safety set, of which the most common were dysgeusia (10 [1.5%] patients) and headache (7 [1.0%] patients). Five (0.7%) patients had at least 1 systemic TEAE leading to premature IMP (Azopt®) withdrawal. Two patients had a serious TEAE (1 patient with COVID-19 and 1 patient with rectal adenocarcinoma) leading to premature IMP withdrawal.

IMP (T4032 or Lumigan) - Systemic AEs were reported in 22 (9.3%) patients in the T4032 group *versus* 27 (10.8%) in the Lumigan group. Three patients experienced a serious TEAE, 1 patient in the T4032 group (asthma) and 2 patients in the Lumigan group (1 patient with cholecystitis acute and 1 patient with pneumonia). Most systemic AEs were of mild or moderate intensity. Severe systemic TEAEs were reported for 3 patients in the T4032 group (1 patient with tooth abscess, 1 patient with asthma, and 1 patient with hypertension) and 3 patients in the Lumigan group (1 patient with cholecystitis acute, 1 patient with pneumonia and 1 patient with sciatica). Treatment-related systemic TEAEs were reported in 1 (0.4%) patient in the T4032 group (dizziness)

and 4 (1.6%) in the Lumigan group (1 patient with dysgeusia, 1 patient with dysgeusia and increased upper airway secretion, 1 patient with abdominal discomfort and blood pressure fluctuation, and 1 patient with headache and nausea). Treatment-related TEAEs headache and nausea experienced by a patient in the Lumigan group resulted in the premature withdrawal of the IMP.

Conjunctival hyperaemia

At baseline, the percentage of patients with a presence of conjunctival hyperaemia (McMonnies score >0) was similar between the T4032 (44.4% of patients) and Lumigan (43.3%) groups. The percentage of patients with a conjunctival hyperaemia score >2 was similar between treatment groups at all visits. At Week 6, the percentage of patients with a presence of conjunctival hyperaemia was lower in the T4032 group compared to the Lumigan group (47.6% *versus* 58.1%, respectively) and remained similar at Week 12 (42.8% *versus* 56.4%, respectively). A lower percentage of patients in the T4032 group compared to the Lumigan group had a conjunctival hyperaemia score of 1 (31.2% *versus* 40.1%) or 2 (8.3% *versus* 13.2%) at Week 12. The between-group difference in conjunctival hyperaemia was statistically significant in favour of T4032 at both Week 6 (*p=0.007*) and Week 12 (*p=0.004*).

The percentage of patients who experienced a worsening from baseline in their conjunctival hyperaemia score was lower in the T4032 group (20.1%) compared to the Lumigan group (29.3%) at Week 6. At Week 12, the incidence of worsening remained similar to Week 6 in the T4032 group (18.3%) and Lumigan group (30.4%). Between-group difference of change from baseline was statistically significant in favour of T4032 at Week 6 (*p=0.016*) and Week 12 (*p=0.007*) (see table below).

Change from baseline in conjunctival hyperaemia score (in classes) in the worse eye at Week 6 and Week 12 (Safety set)

		T4032 (N=236)	Lumigan (N=249)	p-value (CMH test)
Change from baseline to Week 6	**n**	**229**	**239**	
Improvement		28 (12.2)	19 (7.9)	*0.016*
No Change		155 (67.7)	150 (62.8)	
Worsening		46 (20.1)	70 (29.3)	
Change from baseline to Week 12	**n**	**218**	**227**	
Improvement		33 (15.1)	29 (12.8)	*0.007*
No Change		145 (66.5)	129 (56.8)	
Worsening		40 (18.3)	69 (30.4)	

Data are number (%) of patients

n=number of patients with evaluable data; CMH=Cochran Mantel Haenszel test with modified ridit scores stratified by country

Ocular symptoms throughout the day

The mean total symptom score was 1.1±1.8 at baseline, 1.0±1.9 at Week 6 (mean change of -0.0±1.9) and 0.8±1.7 at Week 12 (mean change of -0.2±1.8) in the T4032 group. In the Lumigan group, the mean total symptom score was 1.1±1.8 at baseline, 1.4±2.2 at Week 6 (mean change of 0.3±2.1) and 1.2±2.1 at Week 12 (mean change of 0.1±2.1).

Irritation/burning throughout the day was less frequent in the T4032 group compared to the Lumigan group at Week 6 (18.7% *versus* 23.1%) and Week 12 (12.3% *versus* 19.5%). At Week 12, there was a statistically significant between-group difference in favour of T4032 (*p=0.036*). A similar pattern was also observed for eye dryness feeling between the T4032 and Lumigan groups at Week 6 (17.3% *versus* 27.3%) and Week 12 (16.4% *versus* 25.6%). A statistically significant between-group difference for eye dryness feeling in favour of T4032 was observed at Week 6 (*p=0.015*) and Week 12 (*p=0.013*).

Although the differences in other subjective ocular symptoms throughout the day were not statistically significant, there was a numerical trend in favour of T4032 for itching and foreign body sensation.

Ocular symptoms upon instillation

The mean total score of ocular symptoms upon instillation was lower in the T4032 group compared to the Lumigan group at Week 6 (0.8±1.9 *versus* 1.0±1.9) and at Week 12 (0.6±1.5 *versus* 1.1±2.1).

Irritation/burning upon instillation was less frequent in the T4032 group compared to the Lumigan group at Week 12 (12.8% *versus* 21.2%). There was a statistically significant between-group difference in favour of T4032 for irritation/burning (*p=0.018*). This was also observed at Week 12 for itching (*p=0.048*) and eye dryness feeling (*p=0.012*).

Although the differences in other ocular symptoms upon instillation were not statistically significant, there was a numerical trend in favour of T4032 for stinging, tearing and foreign body sensation.

Slit lamp examination

There were no statistically significant between-group difference in ocular signs (blepharitis, eyelid oedema, abnormal eyelash aspect, folliculo-papillary conjunctivitis, and iris pigmentation) for the worse eye at Week 6 or at Week 12.

Similar results were observed for the contralateral eye.

Corneal fluorescein staining

Most patients presented with no corneal staining (Grade 0) at baseline in the T4032 and Lumigan groups (66.1% and 64.7%, respectively). The percentage of patients with a presence of corneal staining (CFS grade >0) was higher in the Lumigan group compared to the T4032 group at Week 6 (42.3% *versus* 33.2%, respectively) and Week 12 (41.9% *versus* 31.6%, respectively). A statistically significant between-group difference in favour of T4032 was shown at Week 12 (*p=0.037*).

Similar results were observed for the contralateral eye.

Far BCVA

There was no relevant change in Far BCVA between baseline and Week 12 in both treatment groups in both eyes.

Global tolerance assessment by the investigator and patient

Most investigators rated the ocular tolerance of Azopt® as satisfactory or very satisfactory (88.1% of patients) in the Azopt Safety set. Similar results were observed when the patients were asked to assess the ocular tolerance of Azopt® (85.0%).

Assessment of IMP (T4032 or Lumigan) tolerance by the investigator as very satisfactory/satisfactory was higher in the T4032 group *versus* the Lumigan group at Week 6 (93.0% *versus* 88.7%) and Week 12 (95.0% *versus* 89.9%) in the Safety set. At Week 12, there was a statistically significant between-group difference favouring T4032 (*p=0.045*).

At Week 6 and Week 12, more than 90% of patients in both treatment groups assessed the treatment tolerance as satisfactory or very satisfactory. Based on group assessments, no statistically significant between-group difference was observed at Week 6 (*p=0.307*, CMH) and Week 12 (*p=0.216*).

CONCLUSIONS

In conclusion, this study demonstrated that T4032 was non-inferior to Lumigan in ocular hypertensive or glaucomatous patients with respect to change in IOP (mmHg) from baseline at Week 12 in the worse eye with a predefined non-inferiority margin of 1.5 mmHg.

Furthermore, local tolerability appeared to be better for T4032 than for Lumigan.

Version and date of the report: Version 1.0 (28 September 2021)
Dr Beatriz Romero RUBIOLS – Medical Operations Director Date: 7/10/21 Signature: