PROTOCOL SYNOPSIS

Title	Efficacy and safety assessment of T4032 (unpreserved bimatoprost 0.01%) *versus* Lumigan® 0.01% in ocular hypertensive or glaucomatous patients.
Sponsor	Laboratoires THÉA
EudraCT-Number	2017-000846-23
Sponsor Study No.	LT4032-301
International Coordinator	
Study Centres	This international study is planned to be carried out at approximately 130 sites spread over 15 to 25 countries.
Planned Schedule	Planned initiation: October 2018 Planned last patient last visit: December 2020
Study Phase	Phase III
Primary Study Objective	To demonstrate the non-inferiority of T4032 unpreserved eye drops compared to Lumigan® 0.01% in terms of efficacy.
Secondary Study Objective(s)	To evaluate the safety and efficacy of T4032 versus Lumigan® 0.01%.
Sample Size	360 evaluable patients Accounting for a 10% drop-out/non evaluable rate, 400 initially treated patients are expected to be randomised. Number of screened patients will depend on the screen failure rate and is estimated at 668 patients.
Study Design	International, multicentre, randomised, 2 parallel groups, investigator-masked, 3-month treatment. 4 visits: • Visit #1: Day -49 ± 3 days (Screening Visit) • Visit #2: Day 1 (Randomisation Visit) • Visit #3: Week 6 (Day 42 ± 3 days) • Visit #4: Week 12 (Day 84 ± 7 days) (Final visit) • Follow-up phone call: Week 16 (Day 112 ± 7 days) **Run-In/Wash-Out:** Patient must be willing to discontinue her/his current treatment for 7 weeks (49 days ± 3 days) prior to the randomisation visit, in order to determine the IOP eligibility. Patient must follow a run-in period with only brinzolamide eye drops (Azopt®), one drop in each eye twice a day (morning and evening) for 5 weeks.

	The Azopt® treatment must be stopped for 2 weeks prior to the randomisation visit.
Study Duration	23 weeks total of study duration: 5 weeks of run-in + 2 weeks of wash-out 12 weeks of treatment duration 4 weeks of follow-up.
Investigational Product(s) (IP)	**Run-in product: Azopt®** Preserved brinzolamide 10mg/mL eye drops presented in multidose container. **Route of administration:** In the conjunctival cul-de-sac of each eye. **Daily dose regimen:** 1 drop in each eye twice a day, morning and evening during 5 weeks. **Test product: T4032** Unpreserved bimatoprost 0.01% eye drops presented in unit dose (UD). **Comparator product: Lumigan® 0.01%** Preserved bimatoprost 0.01% eye drops presented in multidose container. **Route of administration:** In the conjunctival cul-de-sac of each eye. **Daily dose regimen:** 1 drop in each eye once daily at 20:00 (± 1 hour) from Day 1 to Week 12.
Inclusion Criteria	<u>At Screening Visit (D-49)</u>: 1.1 Informed consent signed and dated. 1.2 Patient aged ≥18 years old. 1.3 Both eyes with 500 µm ≤ central corneal thickness ≤ 600 µm. 1.4 Both eyes with diagnosed **open-angle glaucoma** or **ocular hypertension**, initially treated and controlled (including IOP ≤ 18 mmHg) for at least 6 months by any prostaglandin monotherapy. 1.5 Both eyes with IOP ≤ 18 mmHg. <u>At Randomisation Visit (D1) at 8:00</u>: 1.6 Both eyes with 22 mmHg ≤ IOP < 34 mmHg and with asymmetry between eyes ≤ 3 mmHg.
Exclusion Criteria	**<u>Ophthalmic Exclusion Criteria in AT LEAST ONE EYE</u> [2.1]** 2.1.1 Fundus examination not performed or not available within 12 months. 2.1.2 Visual field not performed or not available within 12 months. 2.1.3 Significant worsening according to the two last visual fields (at least 6 months between the two visual fields). 2.1.4 Advance stage of glaucoma, defined by at least one of the following criteria:

	2.1.4.1 Absolute defect in the ten degrees central point of the visual field. 2.1.4.2 Severe visual field loss: MD < -18 dB. 2.1.4.3 Risk of visual field worsening as a consequence of participation in the study according to the investigator's best judgement.
Exclusion Criteria (continued)	2.1.5 History of non-responder to bimatoprost therapy. 2.1.6 Far Best Corrected Visual Acuity ≥ + 0.7 Log Mar (e.g., ≤ 0.2 in decimal value or ≤ 20/100 Snellen equivalent or ≤ 50 ETDRS letters). 2.1.7 History of trauma, infection, clinically significant inflammation within the 3 previous months. 2.1.8 Ongoing or known history of ocular allergy and/or uveitis and/or viral infection. 2.1.9 Clinically significant or progressive retinal disease (e.g. retinal degeneration, diabetic retinopathy, retinal detachment). 2.1.10 Presence of at least one severe objective sign among the following: 2.1.10.1 Conjunctival hyperaemia (Grade 5 / McMonnies scale). 2.1.10.2 Superficial punctate keratitis (Grade 4/5 / Oxford scale). 2.1.10.3 Blepharitis (Grade 3 / 0-3 scale). 2.1.11 Severe dry eye as assessed by the investigator. 2.1.12 Corneal ulceration. 2.1.13 Any palpebral abnormality incompatible with a good examination. 2.1.14 Any other abnormality preventing accurate assessment e.g. reliable tonometry measurement, visual field examination, fundus examination. **<u>Systemic/non Ophthalmic Exclusion Criteria</u> [2.2]** 2.2.1 Uncontrolled diabetic patient. 2.2.2 Known or suspected hypersensitivity to one of the components of the investigational products (T4032, Lumigan®, Azopt®) and sulphonamides, or auxiliary products (fluorescein, oxybuprocaine hydrochloride). 2.2.3 History of or active relevant systemic condition incompatible with the study or likely to interfere with the study results or the patient safety according to the investigator's judgment. 2.2.4 Severe renal impairment 2.2.5 Hyperchloraemic acidosis

	<u>Specific Exclusion Criteria Regarding Childbearing Potential Women</u>[2.3] 2.3.1 Pregnancy or breast feeding. 2.3.2 Childbearing potential woman who is not using a reliable method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant, vaginal ring, patch) and is not surgically sterilised.
Exclusion Criteria (continued)	**<u>Exclusion Criteria Related to General Conditions</u> [2.4]** 2.4.1. Alcohol addiction and heavy smoker, according to the investigator's judgement. 2.4.2. Inability of patient to understand the study procedures or to give informed consent. 2.4.3. Non-compliant patient (e.g., not willing to attend a visit; way of life interfering with compliance). 2.4.4. Participation in this study at the same time as another clinical study. 2.4.5. Participation in this study within the 4 weeks after the end of a previous clinical study (or within 5 half-lives of the previously tested product if longer than 4 weeks). 2.4.6. Patient previously randomised in this study. 2.4.7. Patient being institutionalised because of legal or regulatory order, inmate of psychiatric wards, prison or state institutions, or employee of the study sites or of the sponsor's company. 2.4.8. Patient not covered by the government health care scheme of the country in which he/she is living (if applicable). **<u>Exclusion Criteria Related to Previous and Concomitant Treatments (Medications/Non-Medicinal Therapies/Procedures)</u> [2.5]** 2.5.1 Patient with previous, current or anticipated prohibited listed treatment (or prohibited modification of treatment regimen). *The prohibited treatments (or prohibited modifications of treatment regimen) and their periods of use prohibition are listed in the following* **Table *1: Prohibited treatments (medications/non-medicinal therapies/procedures)***

Table 1: Prohibited treatments (medications/non-medicinal therapies/procedures)

Ocular surgery or topical treatment concerned both eyes

Before the Screening Visit					After the Screening Visit	
At any time	12 months	6 months	1 month	15 days	Run-in/Wash-out Period	Treatment period
Filtration surgery for glaucoma……						
	Laser procedure for glaucoma and cornea……					
		Other ocular surgery ……..……..……				
		Intra ocular injection ……..……..……				
			Systemic anti-glaucoma treatments…….			
			Any change or predictable change in dose regimen for systemic treatments which can have a substantial effect on IOP: • Beta-adrenergic blocking agents • Beta-adrenergic agonist agents • Alpha agonists agents • Alpha blocking agents • Angiotensin converting enzyme inhibitors • Angiotensin II inhibitors • Calcium channel blockers • Diuretics • Corticosteroids			
			Topical ocular steroids and/ or topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs)…			
				Systemic immunosuppressive and systemic nonsteroidal anti-inflammatory drugs……		
				Any topical ocular treatments* (except long-term preservative-free lachrymal substitutes)…….		
					Contact lenses wear……	

* Prostaglandin monotherapy taken for at least 6 months by the patient has to be continued until the Screening Visit.

Patient Withdrawal	The investigator must choose to discontinue a patient for the following reasons: • Adverse event(s) necessitating discontinuation from the study, • Lack of efficacy: if the patient or the investigator does not feel that the IP (T4032 or Lumigan®) has sufficiently controlled the pathology.
Efficacy Parameters	• IOP assessment with Goldmann applanation tonometer in each eye. Three time points in each eye (8:00; 10:00; 16:00) at Day 1, Week 6 and Week 12. • Efficacy assessment by the investigator at week 6 and week 12.

Safety Parameters	• Assessment of the conjunctival hyperaemia on McMonnies photographic scale in each eye. • Score of each ocular symptom throughout the day (irritation/burning, stinging, itching, tearing, eye dryness feeling, foreign body sensation) using 0-3 scale. • Score of each ocular symptom upon instillation (irritation/burning, stinging, itching, tearing, eye dryness feeling, foreign body sensation) using 0-3 scale. • Score of each ocular sign (blepharitis, eyelid oedema, iris pigmentation modification, abnormal eyelashes aspect, folliculo-papillary conjunctivitis) in each eye using 0-3 scale. • Corneal fluorescein staining according to Oxford grading scheme in each eye. • Far Best Corrected Visual Acuity in each eye. • Ocular tolerance assessed by the investigator. • Ocular tolerance assessed by the patient. • Ocular AE reporting. • Systemic AE reporting.
Primary Efficacy Endpoint	The primary efficacy endpoint is the change from baseline (Day 1) to Week 12 in IOP at the three time points (8:00; 10:00; 16:00) in the worse eye. *The worse eye is defined as the eligible eye with the highest IOP at baseline at 8:00. In case of no IOP difference between both eyes, the right eye will be considered.*
Secondary Efficacy Endpoints	• Change from baseline to Week 12 in IOP at the three time points (8:00, 10:00 and 16:00) in the contralateral eye. *Others efficacy endpoints will be analysed:* • Change from baseline to Week 6 in IOP at the three time points (8:00; 10:00; 16:00) in the worse eye and in the contralateral eye. • Efficacy assessed by the investigator.
Safety Endpoints	• Conjunctival hyperaemia on McMonnies scale at 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 the sum of these scores. • Score of each ocular symptom upon instillation and the sum of these scores. • Score of each ocular sign. • Corneal fluorescein staining (Oxford grading scheme). • Far Best Corrected Visual Acuity expressed in Log MAR. • Ocular tolerance assessed by the investigator.

	• Ocular tolerance assessed by the patient. • Ocular and systemic AE by System Organ Class and Preferred Term.
Statistical Method	The sample size determination is based on the primary efficacy endpoint, i.e. the change in IOP at the three time-points (8:00, 10:00, 16:00) after 12 weeks of treatment, in the worse eye. Non-inferiority of T4032 versus Lumigan® 0.01% is tested with a non-inferiority margin of 1.5 mmHg. Non-inferiority will be concluded if it is achieved for each of the three time points 8:00, 10:00 and 16:00. The evaluation is based upon a two-sided 95% CI on the difference on mean change in IOP after 12 weeks of treatment. With data available for 180 patients in each arm, there is more than 90 % power to show that the T4032 unpreserved eye drops is non-inferior to Lumigan® 0.01% preserved eye drops. The hypothesis is based on the 1.5 mmHg margin, assuming no difference between the 2 groups (average difference of 0 mmHg), a standard deviation of 3 mmHg and correlation between time-points of 0.7 on the primary efficacy variable. Accounting for a 10% drop-out/non evaluable rate, 400 initially treated patients are expected to be randomised. The sample size of 400 randomised patients is also justify to collect enough safety data. Number of screened patients will depend on the screen failure rate and is estimated at 668 patients. No Interim analysis is planned.
Schedule of Assessments	Please refer to the **Table 2: Schedule of Visits and Procedures**.

Table 2: Schedule of Visits and Procedures

	Visit# 1 Screening Visit *Day -49 (± 3 days)*	2 weeks before visit#2	Visit# 2 Randomisation Visit *Day 1*		Visit# 3 *Day 42 (± 3 days)* *Week 6*		Visit# 4 Final Visit or premature discontinuation visit *Day 84 (± 7 days)* *Week 12*		Follow-up Phone call Day 112 (± 7 days) *Week 16*
	First ophthalmologist investigator		First ophthalmologist investigator	Second investigator	First ophthalmologist investigator (the same as Day 1)	Second investigator	First ophthalmologist investigator (the same as Day 1)	Second investigator	
Informed consent	X								
Demography	X								
History of glaucoma or ocular hypertension	X								
Ocular medical and surgical history (other than the studied disease)	X								
Systemic medical and surgical history	X								
Previous and concomitant ocular/non ocular treatments	X		X			X		X	X[11]
Ocular symptoms throughout the day [1]	X			X		X		X	
Ocular symptoms upon instillation [1]						X		X	
Far Best Corrected Visual Acuity (BCVA)	X		X				X		
Intra-Ocular Pressure (IOP) assessment [2]	X		X		X		X		
Fundus examination	X[3]						X[4]		
Central corneal thickness measurement	X[3]								
Automated visual field	X[3]						X[4]		
Slit lamp examination [6]	X		X		X		X		
Corneal fluorescein staining (Oxford grading scheme)	X		X		X		X		
Conjunctival hyperaemia (McMonnies scale)	X		X		X		X		
Pregnancy test [7]	X		X			X		X	
Adverse event			X	X	X	X	X	X	X
Verification of inclusion and exclusion criteria / Patient status	X		X						
Run-in treatment (Azopt®) dispensation [8]	X								
Run-in treatment /Wash-out compliance				X					

Wash-out[5]

Randomisation (IWRS)				X					
Investigational Product (IP) dispensation [9]				X		X			
IP (T4032 or Lumigan®) compliance						X		X	
Efficacy assessment by the investigator [10]			X		X		X		
Ocular tolerance assessment by the investigator [10]			X		X		X		
Ocular tolerance assessment by the patient [10]			X			X		X	

In case of premature discontinuation during the run-in/wash-out period or patient non-eligibility at visit#2, the investigator must perform the evaluations described for the randomization visit (visit #2) except to IOP measurements at 10:00 and 16:00, pregnancy test, randomization and IP dispensation.

All the ocular assessments have to be performed in both eyes.

(1) Ocular symptoms (irritation/burning, stinging, itching, tearing, eye dryness feeling, foreign body sensation), scored using 0-3 scale, will be collected by the investigator /delegate.

(2) At Screening Visit, one IOP measurement should be performed at 8:00 (± 30 minutes). At Day 1, Day 42/Week 6 and Day 84/Week 12, IOP should be measured at three time points: 8:00, 10:00 and 16:00 (each ± 30 minutes) with a.m. measurements of IOP at least 2 hours apart. IOP measurements should be done at the same hours (± 30 min) than Day 1, by the same investigator and using the same technique (Goldmann applanation tonometer) for all visits.

(3) To be performed if fundus examination / central corneal thickness measurement / automated visual field not done within the previous 12 months and/or results dating from the last 12 months not available.

(4) To be performed only if the IOP is not stable at the Week 12 visit or if the ophthalmologist judges that it is necessary.

(5) Azopt® must be stopped for 2 weeks before the Randomisation Visit.

(6) Slit lamp examination: Score of each ocular sign (blepharitis, eyelid oedema, iris pigmentation modification, abnormal eyelashes aspect, folliculo-papillary conjunctivitis or other ocular abnormality) will be recorded in each eye using 0-3 scale.

(7) Urinary test to be done for childbearing potential women.

(8) Run-in treatment (Azopt®) will be instilled by the patient one drop in each eye twice a day (morning and evening) for 5 weeks.

(9) One drop of IP (T4032 or Lumigan®) will be instilled by the patient in each eye once daily at 20:00 (± 1 hour) for 12 weeks.

(10) Efficacy and ocular tolerance will be assessed by the investigator and the patient as very satisfactory, satisfactory, not very satisfactory, or unsatisfactory.

(11) In case of AE, all treatments of the follow-up period will be collected.