Clinical trial results:
Efficacy and safety assessment of T4032 (unpreserved bimatoprost 0.01%) versus Lumigan® 0.01% in ocular hypertensive or glaucomatous patients.

Summary

EudraCT number	2017-000846-23
Trial protocol	FR GB DE LT GR BE PL ES SK CZ LV BG IT
Global end of trial date	24 February 2021

Results information

Result version number	v1 (current)
This version publication date	16 March 2022
First version publication date	16 March 2022
Summary attachment (see zip file)	LT4032-301_CSR synopsis (Synopsis v1.0 with signature.pdf)

Trial information

Trial identification

Sponsor protocol code	LT4032-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03825380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Laboratoires Théa
Sponsor organisation address	12 Rue Louis Blériot, Clermont-Ferrand, France, 63017
Public contact	Clinical department, Laboratoires THEA, 0033 473981436, Aude.BARDIOT@theapharma.com
Scientific contact	Clinical department, Laboratoires THEA, 0033 473981436, Aude.BARDIOT@theapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2021
Global end of trial reached?	Yes
Global end of trial date	24 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of T4032 unpreserved Bimatoprost 0.01% eye drops compared to Lumigan® 0.01% in terms of efficacy.

Protection of trial subjects:

Different assessments were done during subject visits in order to ensure subject safety:
- 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, other ocular abnormality) 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 and by the patient.
- Ocular and systemic AE reporting.

All AEs experienced by a patient, irrespective of the suspected causality, was monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the investigator and Medical expert, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Georgia: 12
Country: Number of subjects enrolled	Mauritius: 1
Country: Number of subjects enrolled	Russian Federation: 61
Country: Number of subjects enrolled	Tunisia: 36
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 1

Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 80
Country: Number of subjects enrolled	Czechia: 40
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Latvia: 20
Country: Number of subjects enrolled	Lithuania: 7
Worldwide total number of subjects	485
EEA total number of subjects	337

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	251
From 65 to 84 years	226
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

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.
The recruitment started on 23-NOV-2018 and was completed on 28-AUG-2020 and the last patient completed the study on 24-FEB-2021.

Pre-assignment

Screening details:

Incl/Excl criteria checked at screening visit, then patients discontinued their current treatment to start the run-in period with Azopt, for 5 weeks. The Azopt was stopped 1 or 2 weeks before the randomisation visit (Day 1). Incl/Excl criteria are confirmed at Day 1.
723 screened patients, 485 randomised patients, 238 screen failure patients.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Investigator, Data analyst[2]

Blinding implementation details:

blinded investigator and sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	T4032 arm

Arm description:

The investigator-masked, 3-month T4032 treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Test product: T4032
•Unpreserved bimatoprost 0.01% eye drops presented in unit dose (UD)

Arm type	Experimental
Investigational medicinal product name	T4032
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye gel in single-dose container
Routes of administration	Ocular use

Dosage and administration details:

1 eyedrop in each eye at 20:00 every day

Arm title	Lumigan arm

Arm description:

The investigator-masked, 3-month Lumigan treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Reference product: Lumigan
•Preserved bimatoprost 0.01% eye drops presented in multidose (MD) container

Arm type	Active comparator
Investigational medicinal product name	Lumigan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

1 drop in each eye at 20:00 every day

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Subject is not blinded. The study is not considered as double blinded study. However investigator and data analyst are blinded.

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Subject is not blinded. The study is not considered as double blinded study. However investigator and data analyst are blinded.

Number of subjects in period 1	T4032 arm	Lumigan arm
Started	236	249
Completed	218	227
Not completed	18	22
Consent withdrawn by subject	1	3
Covid crisis	10	14
Adverse event, non-fatal	6	4
Lost to follow-up	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	T4032 arm

Reporting group description:

The investigator-masked, 3-month T4032 treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Test product: T4032
•Unpreserved bimatoprost 0.01% eye drops presented in unit dose (UD)

Reporting group title	Lumigan arm

Reporting group description:

The investigator-masked, 3-month Lumigan treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Reference product: Lumigan
•Preserved bimatoprost 0.01% eye drops presented in multidose (MD) container

Reporting group values	T4032 arm	Lumigan arm	Total
Number of subjects	236	249	485
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	126	125	251
From 65-84 years	104	122	226
85 years and over	6	2	8
Age continuous Units: years			
arithmetic mean	63.03	63.67	
standard deviation	± 11.85	± 10.92	-
Gender categorical Units: Subjects			
Female	141	153	294
Male	95	96	191

Subject analysis sets	
Subject analysis set title	Modified intention-to-treat T4032
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

T4032 arm - All randomised patients having 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-randomised (i.e., according to the treatment unit assigned at Day 1). m-ITT set will be the primary population for efficacy analysis.

Subject analysis set title	Modified intention-to-treat Lumigan
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Lumigan arm - All randomised patients having 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-randomised (i.e., according to the treatment unit assigned at Day 1). m-ITT set will be the primary population for efficacy analysis.

Reporting group values	Modified intention-to-treat T4032	Modified intention-to-treat Lumigan	
Number of subjects	229	240	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	124	121	
From 65-84 years	100	117	
85 years and over	5	2	
Age continuous			
Units: years			
arithmetic mean	62.72	63.75	
standard deviation	± 11.80	± 11.00	
Gender categorical			
Units: Subjects			
Female	137	148	
Male	92	92	

End points

End points reporting groups

Reporting group title	T4032 arm

Reporting group description:

The investigator-masked, 3-month T4032 treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Test product: T4032
•Unpreserved bimatoprost 0.01% eye drops presented in unit dose (UD)

Reporting group title	Lumigan arm

Reporting group description:

The investigator-masked, 3-month Lumigan treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Reference product: Lumigan
•Preserved bimatoprost 0.01% eye drops presented in multidose (MD) container

Subject analysis set title	Modified intention-to-treat T4032
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

T4032 arm - All randomised patients having 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-randomised (i.e., according to the treatment unit assigned at Day 1). m-ITT set will be the primary population for efficacy analysis.

Subject analysis set title	Modified intention-to-treat Lumigan
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Lumigan arm - All randomised patients having 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-randomised (i.e., according to the treatment unit assigned at Day 1). m-ITT set will be the primary population for efficacy analysis.

Primary: Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 8:00 in the worse eye.

End point title	Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 8:00 in the worse eye.

End point description:

The primary endpoint was defined as the change in IOP between Day 1 and Week 12 at 8:00, 10:00 and 16:00 in the worse eye, therefore 3 definitions needed for describing the primary endpoint.

Three independent mixed model with repeated measures (MMRM) were performed, one for each time point (8:00, 10:00 and 16:00).

Least Squares (LS) means were adjusted by baseline IOP, wash-out duration as continuous covariates and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group and visit interaction with baseline IOP group, using the restricted maximum likelihood (REML) and unstructured covariance matrix.

The worse eye was defined as the eligible eye with the highest IOP at Day 1 at 8:00. In case of no IOP difference between both eyes, the right eye was considered as the worse eye.

End point type	Primary

End point timeframe:

Baseline, Week 12 at 8:00.

End point values	Modified intention-to-treat T4032	Modified intention-to-treat Lumigan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	239		
Units: mmHg				
least squares mean (standard error)	-9.67 (± 0.19)	-9.50 (± 0.18)		

Statistical analyses

Statistical analysis title	Analysis of change from BSL in IOP at 8:00 at Wk12

Statistical analysis description:

Primary analysis of the change from baseline in IOP (mmHg) at 8:00 at Week 12 - MMRM analysis – Worse eye - m-ITT set

Comparison groups	Modified intention-to-treat Lumigan v Modified intention-to-treat T4032
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Adjusted mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.23

Notes:

[1] - Noninferiority was demonstrated if the upper bound of the two-sided 95% Confidence Interval (CI) for the difference in mean change in IOP between treatment groups (T4032 - Lumigan) was lower than the margin of +1.5 mmHg for each of the 3 time points 8:00, 10:00 and 16:00.

Primary: Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 10:00 in the worse eye.

End point title	Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 10:00 in the worse eye.

End point description:

The primary endpoint was defined as the change in IOP between Day 1 and Week 12 at 8:00, 10:00 and 16:00 in the worse eye, therefore 3 definitions needed for describing the primary endpoint.

Three independent mixed model with repeated measures (MMRM) were performed, one for each time point (8:00, 10:00 and 16:00).

Least Squares (LS) means were adjusted by baseline IOP, wash-out duration as continuous covariates and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group and visit interaction with baseline IOP group, using the restricted maximum likelihood (REML) and unstructured covariance matrix.

The worse eye was defined as the eligible eye with the highest IOP at Day 1 at 8h00. In case of no IOP difference between both eyes, the right eye was considered as the worse eye

End point type	Primary

End point timeframe:

Baseline, Week 12 at 10:00

End point values	Modified intention-to-treat T4032	Modified intention-to-treat Lumigan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	240		
Units: mmHg				
least squares mean (standard error)	-9.41 (± 0.18)	-9.26 (± 0.17)		

Statistical analyses

Statistical analysis title	Analysis change from BSL in IOP at 10:00 at Wk12

Statistical analysis description:

Primary analysis of the change from baseline in IOP (mmHg) at 10:00 at Week 12 - MMRM analysis – Worse eye - m-ITT set

Comparison groups	Modified intention-to-treat Lumigan v Modified intention-to-treat T4032
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Adjusted mean difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[2] - Noninferiority was demonstrated if the upper bound of the two-sided 95% Confidence Interval (CI) for the difference in mean change in IOP between treatment groups (T4032 - Lumigan) was lower than the margin of +1.5 mmHg for each of the 3 time points 8:00, 10:00 and 16:00.

Primary: Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 16:00 in the worse eye.

End point title	Change in Intraocular Pressure (IOP) between Day 1 and Week 12 at 16:00 in the worse eye.

End point description:

The primary endpoint was defined as the change in IOP between Day 1 and Week 12 at 8:00, 10:00 and 16:00 in the worse eye, therefore 3 definitions needed for describing the primary endpoint.

Three independent mixed model with repeated measures (MMRM) were performed, one for each time point (8:00, 10:00 and 16:00).

Least Squares (LS) means were adjusted by baseline IOP, wash-out duration as continuous covariates and country, visit and treatment group as categorical fixed effects, as well as visit interaction with treatment group and visit interaction with baseline IOP group, using the restricted maximum likelihood (REML) and unstructured covariance matrix.

The worse eye was defined as the eligible eye with the highest IOP at Day 1 at 8h00. In case of no IOP difference between both eyes, the right eye was considered as the worse eye.

End point type	Primary

End point timeframe:

Baseline (Day 1), Week 12 at 16:00

End point values	Modified intention-to-treat T4032	Modified intention-to-treat Lumigan		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	239		
Units: mmHg				
least squares mean (standard error)	-8.97 (± 0.18)	-8.78 (± 0.18)		

Statistical analyses

Statistical analysis title	Analysis change from BSL in IOP at 16:00 at Wk12

Statistical analysis description:

Primary analysis of the change from baseline in IOP (mmHg) at 16:00 at Week 12 - MMRM analysis – Worse eye - m-ITT set

Comparison groups	Modified intention-to-treat T4032 v Modified intention-to-treat Lumigan
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Adjusted mean difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[3] - Noninferiority was demonstrated if the upper bound of the two-sided 95% Confidence Interval (CI) for the difference in mean change in IOP between treatment groups (T4032 - Lumigan) was lower than the margin of +1.5 mmHg for each of the 3 time points 8:00, 10:00 and 16:00.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting extends from start of the treatment until Day 112 follow-up phone call.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	T4032

Reporting group description:

The investigator-masked, 3-month treatment period lasted from the randomisation visit (Day 1; Visit#2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Test product: T4032
•Unpreserved bimatoprost 0.01% eye drops presented in unit dose (UD)

Reporting group title	Lumigan

Reporting group description:

The investigator-masked, 3-month Lumigan treatment period lasted from the randomisation visit (Day 1; Visit #2) to the final Week 12 visit (Day 84±7 days; Visit #4).
Reference product: Lumigan
•Preserved bimatoprost 0.01% eye drops presented in multidose (MD)

Serious adverse events	T4032	Lumigan	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 236 (0.42%)	2 / 249 (0.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 236 (0.42%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 236 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 236 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	T4032	Lumigan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 236 (5.51%)	17 / 249 (6.83%)	
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	13 / 236 (5.51%)	17 / 249 (6.83%)	
occurrences (all)	13	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2019	On 05-JUL-2019 a new protocol version (Version 3.0) was created with the following updates: -Increase the number of countries and sites involved in the study -Extension of the study duration -Increase of the planned number of screened patients: 668 instead of 434 -Prolongation of the run-in/wash-out period: 49 days instead of 42 days, including 2 weeks ofwash-out instead of 1 week -Clarification regarding premature discontinuation visit -Clarification regarding analysis (efficacy analysis – washout duration)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 March 2020	The World Health Organization (WHO) declared on Wednesday, 11 March 2020 that the Covid-19 epidemic is now considered a pandemic. To stop the Covid-19 spread, governmental authorities have implemented restrictive measures (closure of borders and shops, self-isolation of people …). The situation is evolving quickly and measures differ in each country. In this exceptional, unexpected situation that could affect the benefit/risk ratio of the clinical trial, Laboratoires Théa decided to: - Temporary stop recruitment - Temporary stop onsite monitoring visits. Please note that for already included patients, the decision to continue the study according to the protocol requirements or to withdraw the patient will be assessed by the investigator and based on the regulatory situation in the concerned country.	27 May 2020

Notes:

Limitations and caveats

None reported