Clinical trial results:
Efficacy and safety assessment of T4030 eye drops (unpreserved fixed combination of bimatoprost 0.01% and timolol 0.1% or 0.5%) versus Ganfort® UD (Unit Dose) in ocular hypertensive or glaucomatous patients.

Summary

EudraCT number	2017-002823-46
Trial protocol	AT PL HU BE
Global end of trial date	12 February 2020

Results information

Result version number	v1 (current)
This version publication date	24 February 2021
First version publication date	24 February 2021
Summary attachment (see zip file)	LT4030-201 study result summary (LT4030-201_synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	LT4030-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratoires Thea
Sponsor organisation address	12 rue Blériot, Z.I. du Brézet, Clermont-Ferrand, France, 63100
Public contact	Research and Development Department, Laboratoires THÉA, 33 473981436, lydia.bresson@theapharma.com
Scientific contact	Research and Development Department, Laboratoires THÉA, 33 473981436, lydia.bresson@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	19 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2020
Global end of trial reached?	Yes
Global end of trial date	12 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare each combination of T4030 eye drops (unpreserved fixed combination of bimatoprost 0.01% and timolol 0.1% or 0.5%) with Ganfort® UD in terms of efficacy.

Protection of trial subjects:

Different assessments were done during subject visits in order to ensure subject safety:
- Score of each ocular symptom throughout the day (irritation/burning, stinging, itching, tearing, eye dryness feeling, foreign body sensation),
- Score of each ocular symptom upon instillation (irritation/burning, stinging, itching,tearing, eye dryness feeling, foreign body sensation),
- Score of each ocular sign (blepharitis, eyelid oedema, iris hyperpigmentation, abnormal eyelashes aspect, folliculo-papillary conjunctivitis) in each eye,
- Corneal fluorescein staining according to Oxford grading scheme in each eye,
- Far Best Corrected Visual Acuity in each eye,
- ECG,
- Clinical systemic examination (heart rate, blood pressure),
- Ocular tolerance assessed by the investigator,
- Ocular tolerance assessed by the patient,
- Ocular and systemic AE reporting.

All AEs experienced by a patient, irrespective of the suspected causality, 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:

Patients must follow a run-in period with only brinzolamide eye drops 1% (Azopt®), one drop in each eye twice a day (morning and evening) for 5 weeks. The Azopt® treatment must be stopped 7 days before the Randomisation Visit (Day 1).

Evidence for comparator:

This study compare the efficacy, safety and pharmacokinetics of the two different formulations of unpreserved fixed combination of bimatoprost 0.01%/timolol 0.1% or 0.5% (T4030a or T4030c) to the reference product Ganfort® UD (Allergan), in OAG or OHT patients initially treated either by a combination therapy of prostaglandin and timolol (fixed or not) and controlled for at least 6 months or by a first line monotherapy for at least 6 months and insufficiently controlled.

Like for most glaucoma medications (including PGAs and -blockers eye drops),the BAK contained in the BTFC formulation has been proved to cause dose- and timedependent toxic effects to the eye structures of the anterior segment including the tear film,cornea, conjunctiva, and even trabecular meshwork cells (Baudouin et al. 2010). Thus, the
European Medicines Agency (EMA) recommended to avoid the use of preservatives “forthose patients who do not tolerate eye drops with preservatives” and “for long-term
treatment”, or to use, when preservatives are required, “concentration at the minimum levelconsistent with satisfactory antimicrobial function in each individual preparation” (EMEA 2009).
Consequently, a preservative-free BTFC was developed and shown to be non-inferior in terms of efficacy compared to the preserved formulation (Goldberg et al. 2014). This
preservative-free BTFC formulation is marketed since 2013 in unit dose (Ganfort® UD, Allergan)

Actual start date of recruitment	28 September 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	Poland: 43
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Hungary: 36
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	44
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

130 patients signed informed consent. 86 subjects were randomised (+ 1 randomised by mistake)in the study in one period of 1 year.
24 participating centres in 4 countries: Austria (1), Belgium (1), Hungary (10) and Poland (12).
Recruitment started on 28SEP2018 and over on 03OCT2019.

Pre-assignment

Screening details:

Incl/excl criteria are checked at screening visit (Day -42 ±3).Then there is period a run-in period (D-42 to D-7) where patient instilled Azopt wash-out period of 7 days. This period is followed by a wash-out period of 7 days. Incl/Excl criteria are confirmed at randomization visit (D1) there is a treatment period of 12 weeks.

Pre-assignment period milestones

Number of subjects started	130[1]
Number of subjects completed	86

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen failure: 44

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The reported worldwide number enrolled in the trial correspond to the the number of subjects randomized.
However, 130 subjects were screened and start pre-assignement period.

Period 1

Period 1 title	treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Investigator, Data analyst, Assessor[3]

Blinding implementation details:

Subject is not blind. It is not consider as double blind study. However assesor and data analyst are blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	T4030a

Arm description: -

Arm type	Experimental
Investigational medicinal product name	T4030a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye gel in single-dose container
Routes of administration	Ocular use, Ophthalmic use

Dosage and administration details:

 patient administer the assigned treatment T4030a once daily at 20h00 (± 1 hour) in the conjunctival cul-de-sac of each eye.

Arm title	T4030c

Arm description: -

Arm type	Experimental

Investigational medicinal product name	T4030c
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye gel in single-dose container
Routes of administration	Ocular use, Ophthalmic use

Dosage and administration details:

Patient administer the assigned treatment T4030c once daily at 20h00 (± 1 hour) in the conjunctival cul-de-sac of each eye.

Arm title	Ganfort

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ganfort®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ocular use, Ophthalmic use

Dosage and administration details:

patient administer the assigned treatment Ganfort® UD once daily at 20h00 (± 1 hour) in the conjunctival cul-de-sac of each eye.

Notes:

[2] - 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: During treatement period data analyst and assessor were also blinded in this study.

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

Justification: Subject is not blind. It is not consider as double blind study. However assesor and data analyst are blinded.

Number of subjects in period 1	T4030a	T4030c	Ganfort
Started	29	29	28
Completed	27	27	26
Not completed	2	2	2
Adverse event, non-fatal	2	2	2

Baseline characteristics

Reporting groups	
Reporting group title	T4030a
Reporting group description: -	
Reporting group title	T4030c
Reporting group description: -	
Reporting group title	Ganfort
Reporting group description: -	

Reporting group values	T4030a	T4030c	Ganfort
Number of subjects	29	29	28
Age categorical			
The mean age is 61.6±10.9 years (range 27 to 80 years)			
Units: Subjects			
Adults (18-64 years)	14	14	16
From 65-84 years	15	15	12
Gender categorical Units: Subjects			
Female	20	22	17
Male	9	7	11

Reporting group values	Total		
Number of subjects	86		
Age categorical			
The mean age is 61.6±10.9 years (range 27 to 80 years)			
Units: Subjects			
Adults (18-64 years)	44		
From 65-84 years	42		
Gender categorical Units: Subjects			
Female	59		
Male	27		

Subject analysis sets	
Subject analysis set title	modified intent-to-treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients who received at least one dose of IMP, 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)

Reporting group values	modified intent-to-treat		
Number of subjects	86		
Age categorical			
The mean age is 61.6±10.9 years (range 27 to 80 years)			
Units: Subjects			
Adults (18-64 years)	44		

From 65-84 years	42		

Gender categorical Units: Subjects			
Female	59		
Male	27		

End points

End points reporting groups

Reporting group title	T4030a
Reporting group description: -	
Reporting group title	T4030c
Reporting group description: -	
Reporting group title	Ganfort
Reporting group description: -	
Subject analysis set title	modified intent-to-treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients who received at least one dose of IMP, 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)

Primary: Change in IOP between Day1 and Week 12 at 8h00 in the worse eye.

End point title	Change in IOP between Day1 and Week 12 at 8h00 in the worse eye.

End point description:

End point type	Primary

End point timeframe:

The Change in IOP between Day1 and Week 12 at 8h00 in the worse eye. The worse eye is 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 will be considered.

End point values	T4030a	T4030c	Ganfort	modified intent-to-treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	29	28	86
Units: mmHg				
arithmetic mean (confidence interval 95%)	-9.83 (-10.66 to -9.01)	-10.14 (-11.12 to -9.15)	-9.98 (-11.12 to -8.84)	-9.98 (-11.12 to -8.84)

Statistical analyses

Statistical analysis title	Primary analysis MMRM
Comparison groups	T4030a v Ganfort
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	adjusted mean difference
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	1.36

Statistical analysis title	Primary analysis MMRM
Comparison groups	T4030c v Ganfort
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	adjusted mean difference
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	1.39

Statistical analysis title	Primary analysis MMRM
Comparison groups	T4030a v T4030c
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	adjusted mean difference
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	1.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting extend from start of th treatment until the final study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	T4030a
Reporting group description: -	
Reporting group title	T4030c
Reporting group description: -	
Reporting group title	Ganfort

Reporting group description: -

Serious adverse events	T4030a	T4030c	Ganfort
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	T4030a	T4030c	Ganfort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 29 (34.48%)	10 / 29 (34.48%)	9 / 28 (32.14%)
Investigations			
Abnormal sensation in eye			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Vital dye staining cornea present			

subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Blood pressure decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Breath sounds			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Documented hypersensitivity to administered product			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Ankle fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Vascular pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Pyrexia			

subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Blepharitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	2	0	1
Eye irritation			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	0 / 28 (0.00%)
occurrences (all)	1	2	0
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	1 / 28 (3.57%)
occurrences (all)	0	2	1
Conjunctival hyperaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Erythema of eyelid			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Eye allergy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Eye symptom			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Eyelids pruritus			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Athralgia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Arthrisis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 28 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2019	- Adjustment of the number of patients to be screened in the study, due to higher screen failure rate than expected - Adjustment of the expected number of sites participating in the study (three additional sites in Poland and one additional site in Belgium) - Clarification of the exclusion criteria - More flexibility given to sites for the collection of the ICF - More flexibility given to sites for organising and performing the ECG - More flexibility given to site personal for management of pregnancy tests, vital signs and blood samplings - Allowing a time-window at the timepoints for blood sampling for pharmacokinetic analysis - Inclusion and specification of the risk-based monitoring approach - Minor clarification and administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported