SYNOPSIS

Name of Sponsor: Laboratoires THEA	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: T4030a and T4030c	Volume: Page:	
Name of Active Ingredient: Bimatoprost and timolol		

Number and Title of Study: Study# LT4030-201: 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.

Coordinator Investigator: Professor Ewa MRUKWA-KOMINEK (Medical University of Silesia, Katowice, Poland)

Study Centres: 24 participating centres (at least one patient with signed informed consent) in 4 countries: Austria (1), Belgium (1), Hungary (10) and Poland (12).

Centralised Control Laboratory:

SGS France, 29 Avenue Aristide Briand, 94111 Arcueil Cedex, France

Publication (reference): None | **Phase of Development:** II

Studied Period: First Patient Enrolled: 28 September 2018 Last Patient Completed: 12 February 2020

Primary objective:

To compare each combination of T4030 unpreserved eye drops (fixed combination of bimatoprost 0.01% and timolol 0.1% or 0.5%) with Ganfort® UD (unpreserved fixed combination of bimatoprost 0.03% and timolol 0.5% eye drops) in terms of efficacy.

Secondary objectives:

To evaluate the efficacy, safety and blood concentration of each combination of T4030 unpreserved eye drops *versus* Ganfort® UD.

Methodology:

Phase II, international, multicentre, randomised, 3 parallel groups, investigator-masked, 12-week treatment duration study in ocular hypertensive or glaucomatous patients.

Number of patients:

130 patients signed the informed consent form, 87[1] were randomised in the study.

There were 86 patients in the intent-to-treat (ITT), modified intent-to-treat (mITT) and Safety sets, and 79 patients in the per-protocol (PP) set.

Diagnosis and Main Criteria for Inclusion

[1] One patient withdrew from the study before randomisation but was incorrectly randomised in the Ganfort group.

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Inclusion criteria:

At Screening visit (Day -42±3): Informed consent signed and dated; patient aged ≥18 years old; 500 µm ≤ central corneal thickness ≤600 µm in both eyes; open-angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes either (1) initially treated and controlled for at least 6 months by dual therapy of prostaglandin and timolol (fixed combination or not), with (a) both eyes ≤18 mmHg, (b) history of IOP insufficiently controlled with first-line monotherapy (based on insufficient IOP reduction or significant IOP reduction but progression of glaucoma, *i.e.*, target IOP not reached **OR** (2) initially treated with first-line monotherapy for at least 6 months, insufficiently controlled and requiring a dual therapy (bitherapy).

At Randomisation visit (Day 1): Both eyes with 22 mmHg ≤IOP <36 mmHg with asymmetry between eyes ≤3 mmHg.

Key exclusion criteria:

Fundoscopy and visual field not performed or available within 12 months; Advanced stage of glaucoma defined by at least one of the following criteria: (i) absolute defect in the ten degrees central point of the visual field, (ii) severe visual field loss (MD <-18 dB), (iii) risk of visual field worsening as a consequence of participating in the study according to the investigator's judgement; History of non-response to bimatoprost and/or timolol; Far best-corrected visual acuity (Far BCVA) ≥+0.7 LogMar; 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; Presence of at least one severe objective sign among the following: (i) conjunctival hyperaemia (Grade 5 on McMonnies scale), (ii) superficial punctate keratitis (Grade 4-5 on Oxford scale), (iii) blepharitis (Grade 3 on 0-3 scale); Severe dry eye as assessed by the investigator; Corneal ulceration; Palpebral abnormalities incompatible with a good examination; Any electrocardiogram (ECG) abnormalities considered clinically significant and/or contraindicating the prescription of Timolol (sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, or any relevant abnormalities) according to centralised medical review; Heart rate <50 bpm and/or systolic arterial blodd pressure ≤90 mmHg; History of bronchopulmonary disorders (e.g. asthma, chronic obstructive pulmonary disease; Any other abnormality preventing accurate assessment.

Investigational Medicinal Products (IMPs), Dose and Mode of Administration, Batch Number:

One drop of T4030a (bimatoprost 0.01%/timolol 0.1%) or T4030c (bimatoprost 0.01%/timolol 0.5%) administered in the conjunctival cul-de-sac of each eye, once daily at 20:00 (±1 hour).

Batch numbers:

T4030a: T4030-1609-L05 (exp: 03/2020)

T4030c: T4030-1607-L06 (exp: 04/2020)

Reference Therapy, Dose and Mode of Administration, Batch Number:

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One drop of Ganfort® UD (bimatoprost 0.03%/timolol 0.5%) was administered in the conjunctival cul-de-sac of each eye, once daily at 20:00 (±1 h).

Batch number: E83011 (exp: 03/2020)

Duration of Treatment:

The treatment was administered for 12 weeks (from Day 1 to Day 84±7 days).

Criteria for Evaluation:

Primary efficacy endpoint

The primary efficacy endpoint was the change in IOP between Day 1 and Week 12 at 08:00 in the worse eye.

Secondary efficacy endpoints

- Change in IOP between baseline and Week 12 at 10:00 and 16:00 in the worse eye
- Change in IOP between baseline and Week 12 at 08:00, 10:00 and 16:00 in the contralateral eye
- Change in IOP between baseline and Week 6 at 08:00 in the worse 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 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 on Oxford scale
- Cardiovascular parameters (ECG, heart rate and blood pressure)
- Far 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)

Pharmacokinetic endpoints

Plasma concentrations of bimatoprost and timolol before instillation and 30 min, 1 h, 1 h 30 min, 4 h, 8 h, and 12 h after instillation at Baseline and Week 12 in a subgroup of patients

Statistical Methods:

Statistical analyses were performed using the following analysis sets:

- **Safety Set**: All enrolled patients who received at least one dose of IMP and considered as-treated
- **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, 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
- **PK Set**: All enrolled patients who received at least one dose of IMP, with at least one blood sampling performed and with available concentration and considered as-treated

Quantitative and qualitative variables were summarised for each treatment group (and for the overall population for baseline descriptions), including:

- The number of non-missing observations (n), mean, SD, median, lower quartile (Q1), upper quartile (Q3), minimum and maximum, and 95% Confidence Interval (CI) for the mean/median of the quantitative variables
- The number of non-missing observations (n), count and percentage of each modality, and 95% CI for qualitative variables. The number of missing values were reported in the tables but were not counted for the percentage calculation. 95% CI of a proportion was calculated using the scoring method of Wilson without continuity correction.

Quantitative parameters were compared between treatment groups using Mixed Model for Repeated Measures (MMRM) or Analysis of Covariance (ANCOVA) model. For each model (MMRM or ANCOVA), if there was a strong violation of normality assumption (or violation of homogeneity of variances for ANCOVA), in addition to the initial model, a rank transformation was done, and the model was applied to ranks. For ordered qualitative variables, treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test, with modified ridit scores 'row mean score differ' option.

This was a phase II pilot study and the analyses were considered as exploratory. Thus, the acceptable risk of error for the statistical tests was set at 5%, except for 'treatment-by-country', 'treatment-by-previous treatment' and 'treatment-by-baseline IOP value' interactions, for which the level of significance was set as 7% and no adjustment of the type I error rate was made.

For patients who prematurely discontinued from the study, evaluations performed during the premature withdrawal visit were considered the first unobserved scheduled visit whatever their actual dates.

Primary efficacy endpoint

The primary efficacy endpoint was analysed using a MMRM. The model included as fixed factors: treatment, scheduled visit time point (Week 6 and Week 12), baseline IOP and previous treatment type (monotherapy or dual therapy) as covariates, and treatment by visit interaction, baseline IOP by visit interaction, and patient as random factor. The Restricted Maximum Likelihood (REML) estimation approach was used, and the default covariance was unstructured. Consistent with MMRM model fitting, no explicit imputation of missing assessments for a given time point was performed. 95% CI for treatment effects (T4030a *vs* Ganfort, T4030c *vs* Ganfort and T4030a *vs* T4030c) was estimated at Week 12 in the model.

To support the validity of the conclusions drawn from this analysis, sensitivity analyses were performed using an ANCOVA model considering all observed data or using the last observed carried forward (LOCF) method to explore the dropout pattern and its possible impact on treatment comparisons.

As supporting analyses, separated MMRM were fitted to investigate possible treatment by covariate (baseline IOP, previous treatment type [monotherapy or dual therapy]) interaction, by including the additional interaction term to the primary model as specified above.

A possible country effect was also investigated, and this covariate (country) and covariate by treatment interaction were added to the main model as secondary analysis of the primary efficacy endpoint.

Secondary efficacy endpoints

Statistical analyses were performed using the same MMRM as for the main analysis of the primary efficacy endpoint, with 95% CI estimated for treatment effects (T4030a *vs* Ganfort, T4030c *vs* Ganfort and T4030a *vs* T4030c). Also, the same ANCOVA model was used for sensitivity analysis. Global assessment of efficacy by the investigator was presented by frequency distribution (very satisfactory/satisfactory/not very satisfactory/unsatisfactory) and frequency distribution after regrouping 'very satisfactory' with 'satisfactory', and 'not very satisfactory' with 'unsatisfactory'. After regrouping, comparison of treatment groups (T4030a *vs* Ganfort, T4030c *vs* Ganfort and T4030a *vs* T4030c) was performed using a CMH test.

Complementary analyses were also performed as following:

- IOP by classes at Baseline, Week 6 and Week 12
- IOP variation by classes at Baseline and Week 12
- Mean diurnal IOP and change from baseline at Week 12

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.

Pharmacokinetic endpoints

Plasma concentrations of timolol and bimatoprost were described at Baseline and Last Visit. AUC (0-12h), Cmax, Tmax and T1/2 were calculated and described at Baseline and Last Visit.

SUMMARY

Study population and demographics

One-hundred and thirty patients were screened and 87 were randomised: 29 in the T4030a group, 29 in the T4030c group and 29 in the Ganfort group. However, one patient who performed the screening visit, withdrew from the study before the randomisation visit but was incorrectly randomised in the Ganfort group. This patient was not included in the study or any of the data sets.

Six patients prematurely discontinued the study, 2 patients in each treatment group. Each premature discontinuation was due to an adverse event. Seven (8.1%) patients had at least one major protocol deviation

during the study: 3 (10.3%) in the T4030a group, 2 (6.9%) in the T4030c group and 2 (7.1%) in the Ganfort group. The most common protocol deviation was the mean IOP missing for the worse eye at Week 12: 2 (6.9%) patients in the T4030a group, 1 (3.4%) in the T4030c group and 2 (7.1%) in the Ganfort group.

There were no major differences in demographic data between treatment groups. The mean age was 61.6±10.9 years (range: 27 to 80 years). Most patients were female (68.6%). The main aetiology was primary OAG and was similar between treatment groups (82.8% of patients in the T4030a group, 79.3% in the T4030c group and 82.1% in the Ganfort group) and most patients had previously been treated with a dual therapy (62.1% of patients in the T4030a group, 62.1% in the T4030c group and 64.3% in the Ganfort group). Baseline values for the 3 treatment groups were similar except for time to diagnosis, which was higher in the T4030c group (median of 132.0 months), compared to the T4030a (64.2 months) and Ganfort (70.9 months) groups.

EFFICACY RESULTS

Primary efficacy endpoint

In the mITT Set, the mean IOP change from baseline at Week 12 (08:00) in the worse eye was -9.83±2.08 mmHg in the T4030a group, -10.14±2.54 mmHg in the T4030c group and -9.98±2.64 mmHg in the Ganfort group.

Primary efficacy variable: change in IOP (mmHg) from baseline to Week 12 at 08:00 in the worse eye (mITT Set)

		T4030a (N=29)	**T4030c (N=29)**	**Ganfort (N=28)**
Baseline	**N**	**29**	**29**	**28**
	Mean±SD	24.67±2.26	25.50±2.96	24.57±2.08
	Min; Max	22.0; 30.0	22.0; 34.0	22.5; 30.0
	95% CI	23.81; 25.53	24.37; 26.63	23.76; 25.38
Week 12	**N**	**27**	**28**	**26**
	Mean±SD	14.83±2.39	15.38±2.45	14.65±2.62
	Min; Max	10.5; 20.0	10.5; 20.0	11.5; 21.0
	95% CI	13.89; 15.78	14.43; 16.33	13.59; 15.71
Mean Change (Week 12 – Baseline)	**N**	**27**	**28**	**26**
	Mean±SD	-9.83±2.08	-10.14±2.54	-9.98±2.82
	Min; Max	-14.0; -6.0	-15.5; -4.8	-17.0; -3.0
	95% CI	-10.66; -9.01	-11.12; -9.15	-11.12; -8.84

CI=confidence interval, SD=standard deviation

Using a MMRM, the adjusted mean difference between T4030a *minus* Ganfort was 0.16±0.60 (95% CI: -1.04; 1.36), between T4030c *minus* Ganfort was 0.18±0.60 (95% CI: -1.03; 1.39) and between T4030a *minus* T4030c was -0.02±0.60 (95% CI: -1.21; 1.17).

Between-group comparison for change in IOP (mmHg) from Baseline to Week 12 at 08:00 in the worse eye using a MMRM (mITT Set)

	Number of patients	Adjusted mean difference±SE	95% CI	*p-value*
T4030a *vs* Ganfort	29 28	0.16±0.60	-1.04; 1.36	*0.793*
T4030c *vs* Ganfort	29 28	0.18±0.60	-1.03; 1.39	*0.767*
T4030a *vs* T4030c	29 29	-0.02±0.60	-1.21; 1.17	*0.971*

MMRM including as fixed factors: treatment, scheduled visit time point (Week 6 and Week 12), baseline IOP and previous treatment type (monotherapy or dual therapy) as covariates, treatment by visit interaction, baseline IOP by visit interaction, and patient as random factor.

CI=confidence interval; SE=standard error

Analyses was similar for the PP Set (the ITT Set was identical to the mITT Set).

Using an ANCOVA model for the sensitivity analysis (considering observed data or using an LOCF method), results were similar to the main analysis. For the supporting analysis, there was no statistically significant treatment-by-baseline IOP (*p=0.788*) or treatment-by-previous treatment type (*p=0.129*) interaction. However, a statistically significant treatment-by-previous treatment type interaction was found when observed data was used in the ANCOVA model (*p=0.013*). Additional analyses were performed based on whether patients had previously been treated by monotherapy or dual therapy. The adjusted mean difference for patients previously treated with monotherapy was for T4030a *minus* Ganfort was -1.36±0.89 (95% CI: -3.19; 0.46) and for T4030c *minus* Ganfort, -2.17±0.89 (95% CI: -4.00; -0.34). When patients had previously been treated with dual therapy, the adjusted mean difference of T4030a *minus* Ganfort was 0.84±0.75 (95% CI: -0.66; 2.35) and for T4030c *minus* Ganfort, 1.42±0.75 (95% CI: -0.08; 2.93).

Secondary analyses of the primary efficacy endpoint was similar to the main analysis, including country as additional factor and treatment-by-country interaction (*p=0.778*).

Secondary efficacy endpoints

Secondary efficacy endpoints on the IOP change from baseline at different time points in the worse eye (Week 12, 10:00 and 16:00; Week 6, 08:00) and contralateral eye (Week 12, 08:00, 10:00 and 16:00; Week 6, 08:00) were similar to the main analysis.

At the morning assessment (08:00) at Week 12, the percentage of patients with an IOP <18 mmHg was higher in the T4030a (92.6% of patients) compared to the T4030c (78.6%) and Ganfort (76.9%) groups, but by 16:00, the percentage of patients with an IOP <18 mmHg was similar in the three treatment groups (85.2% of patients in the T4030a group, 82.1% in the T4030c group and 84.6% in the Ganfort group). At Week 12, the percentage of patients with a dirunal IOP variation ≤6 mmHg was similar between treatment groups (100% in the T4030a and Ganfort groups, and 96.4% in the T4030c group). Results were also similar between treatments group for the mean change in diurnal IOP from baseline at Week 12: -9.0±2.0 mmHg in the T4030a group, -9.3±2.8 mmHg in the T4030c group and -9.5±2.8 mmHg in the Ganfort group.

The efficacy assessed by the investigator as 'satisfactory' or 'very satisfactory' was similar in all treatment groups at Week 6 (for 96.4% [Ganfort] to 100% [T4030a] of patients) and at Week 12 (for 92.9% [T4030c] to 100% [Ganfort] of patients).

SAFETY RESULTS

Ocular adverse events

The percentage of patients who experienced an ocular treatment-emergent adverse event (TEAE) was similar in the 3 treatment groups (17.2% in the T4030a group, 20.7% in the T4030c group and 25.0% in the Ganfort group).

This was also observed for the percentage of patients who experienced an ocular TEAE considered as related to the study treatment (13.8%, 17.2% and 21.4%, respectively). The number of patients who had at least one ocular TEAE leading to premature study withdrawal was the same in all treatment groups (2 patients in each group). All AEs causing study withdrawals were assessed by the investigators as related to the study treatment, except for 1 patient in the T4030a group (with conjunctivitis and blepharitis). No patients experienced a serious ocular TEAE during the study.

Systemic adverse events

Systemic TEAEs were reported in 6 (20.7%) patients in the T4030a group, 6 (20.7%) patients in the T4030c group and 7 (25.0%) patients in the Ganfort group. One (3.6%) patient in the Ganfort group experienced a systemic TEAE (headache) which was considered related to the IMP by the investigator. No patient had to prematurely withdraw from the IMP due to a systemic TEAE. One (3.4%) patient experienced a serious systemic TEAE (osteoarthritis) in the T4030a group, which was not considered related to the IMP by the investigator.

Conjunctival hyperaemia

The percentage of patients who experienced a worsening from baseline in their conjunctival hyperaemia score was higher in the T4030c group (27.6%) compared to the T4030a (20.7%) and Ganfort (17.9%) groups at Week 6. The incidence of worsening increased further at Week 12 in the T4030c group (39.3% of patients), whilst it decreased in the T4030a group (10.7%) and remained similar in the Ganfort group (19.2%). An improvement in conjunctival hyperaemia was noted in 25.0% of patients in the T4030a group, 32.1% in the T4030c group and 23.1% in the Ganfort group.

Subjective ocular symptoms throughout the day

The percentage of patients who experienced a worsening from baseline of total score of subjective ocular symptoms at Week 6 was higher in the T4030c (34.5%) and Ganfort (32.1%) groups compared to the T4030a (20.7%) group. However, at Week 12 the percentage of patients with a worsening total score of subjective ocular symptoms reduced in the T4030c (14.3%) and Ganfort (7.7%) groups and remained similar in the T4030a (17.9%) group.An improvement from baseline to Week 12 was similar between treatment groups for irritation/burning (21.4% of patients in the T4030a group, 17.9% in the T4030c group and 19.2% in the Ganfort group), and eye dryness feeling (7.1% in the T4030a group, 7.1% in the T4030c group and 7.7% in the Ganfort group). In T4030a and T4030c groups, a greater improvement was observed compared to the Ganfort group for tearing (14.3% in the T4030a group, 14.3% in the T4030c group compared to 7.7% in the Ganfort group) and foreign bdy sensation (10.7% in the T4030a group, 10.7% in the T4030c group compared to 3.8% in the Ganfort group). For itching, there was a greater percentage of patients with an improvement in the T4030a (17.9%) group, compared to the T4030c (7.1%) and Ganfort (3.8%) groups, whilst for stinging, improvement of this symptom was greater in the T4030a (14.3%) and Ganfort (11.5%) groups compared to the T4030c (3.6%) group.

Subjective ocular symptoms upon instillation

The mean total score of ocular symptoms upon instillation was similar in the T4030a (0.8±1.2), T4030c (1.0±2.2) and Ganfort (1.3±2.5) groups at Week 6, and at Week 12 reduced in all treatment groups (0.5±1.0, 0.6±1.3 and 0.5±1.1, respectively).

Irritation/burning upon instillation was less frequent in the T4030a group (7.1% of patients) compared to the T4030c (17.8%) and Ganfort (15.4%) groups at Week 12. Stinging was experienced by 7.1% and 7.2% of patients in the T4030a and T4030c groups, respectively, whilst in the Ganfort group it was higher (15.3%). The ocular symptoms itching, tearing, eye dryness feeling, and foreign body sensation were experienced by less than 11% of patients in any treatment group at Week 12. Itching which was less prevalent in the T4030c group (96.6% of patients with no symptom) compared to the Ganfort group (78.6%) at Week 6 (*p=0.047*, CMH).

Slit lamp examination

The percentage of patients with blepharitis worsening in the worse eye at Week 12 was similar between treatment groups (3.6% of patients for T4030a, none for T4030c and 3.8% for Ganfort). A similar finding applied to the percentage of patients with eyelid oedema worsening (3.6% of patients for T4030a and T4030c, and none for Ganfort), folliculo-papillary conjunctivitis worsening (3.6% for T4030a and T4030c, and no patient for Ganfort) and iris pigmentation worsening (3.6% for T4030a and T4030c, and no patients for Ganfort) at Week 12.

Worsening of the ocular sign abnormal eyelashes aspect (worse eye) from baseline at Week 12 was noted in a higher percentage of patients in the T4030c (10.7%) and Ganfort (15.4%) groups compared to the T4030a group (3.6%).

Similar results were observed for the contralateral eye. However, a statistically significant between-group difference for abnormal eyelashes aspect was observed at Week 12 in favour of T4030a *vs* Ganfort (*p=0.045*, CMH).

Corneal fluorescein staining

The percentage of patients with a worsening of corneal fluorescein staining from baseline to Week 12 was higher in the T4030a group (25.0%) and T4030c group (21.4%), compared to the Ganfort group (15.4%), and were similar for the contralateral eye. The percentage of patient with an improvement in CFS staining was greater in the Ganfort (23.1%) group compared to the T4030a (7.1%) and T4030c (7.1%) groups.

Far best-corrected visual acuity

No relevant change in far BCVA between Baseline and Week 12 was observed in any treatment group in either eye.

Fundoscopy and automated visual field at last visit

Fundoscopy was performed on 21 patients (9 in the T4030a group, 5 in the T4030c group and 7 in the Ganfort group). Abnormalities were observed in 3 patients at Screening and Final visits: 1 patient in the T4030a group (glaucomatous excavation of the optic nerve head in the contralateral eye), 1 patient in the T4030c group (drusenoidal pigment epithelial detachments in the worse eye) and 1 patient in the Ganfort group (age-related macular degeneration in the contralateral eye).

Automated visual field was performed on 14 patients (7 in the T4030a group, 5 in the T4030c group and 2 in the Ganfort group). All patients had a stable automated visual field compared to the previous visit except for one

patient in the T4030a group. However, this was not considered clinically significant in the investigator's judgement.

Vital signs

No relevant changes in mean resting systolic blood pressure, diastolic blood pressure and heart rate were observed between screening and Week 12.

Ocular tolerance by the investigator and patient

According to the investigator, tolerance of the IMP was 'satisfactory' or 'very satisfactory' for 93.1% of patients in the T4030a group, 89.7% in the T4030c group and 89.3% in the Ganfort group at Week 6. This increased in all the treatment groups at Week 12 (100% for T4030a and Ganfort, and 92.9% for T4030c).

Tolerance was 'satisfactory' or 'very satisfactory' for 96.6% of patients in the T4030a group, 86.2% in the T4030c group and 92.9% in the Ganfort group at Week 6. This increased in the T4030c (89.3%) and Ganfort (100%) groups and remained similar in the T4030a group (96.4%) at Week 12.

PHARMACOKINETIC RESULTS

No quantitative analyses were performed on bimatoprost plasma concentrations as all values were below the evaluable threshold of 0.100 ng/mL, except for one patient in the Ganfort group who had a value of 0.105 ng/mL at Baseline (T0h30).

Following the first IMP administration (at Day 1), the plasma concentration (AUC 0-12 h) of timolol was 25.5±24.3 ng/mL in the T4030a group, significantly lower compared to the T4030c (251.2±121.9 ng/mL) and Ganfort (378.0±253.0 ng/mL) groups. The ratio of (AUC_{IMP}/Dose)/(AUC_{T4030a}/Dose) demonstrated low linear correlation between exposure and dose with 2.0 and 3.0 values for T4030c and Ganfort groups respectively. The plasma concentration increased in all treatment groups at Week 12, while remaining significantly lower in the T4030a group (85.5±45.9 ng/mL) compared to the T4030c (442.9±227.2 ng/mL) and Ganfort (369.2±149.3 ng/mL) groups. Ratio of (AUC_{IMP}/Dose)/(AUC_{T4030a}/Dose) achieved high linear exposure-dose correlation with value of 1.0 and 0.9 for T4030c and Ganfort groups respectively.

CONCLUSIONS

This study indicates a similar efficacy of both T4030a and T4030c formulations in reducing IOP in OAG or OHT patients as compared to Ganfort UD, with a similar change in IOP from baseline at Week 12 (08:00) in the worse eye for all treatment groups. This was confirmed by the sensitivity and supporting analyses, as well as the secondary and other efficacy endpoints analyses also suggesting a comparable conclusion of efficacy

Overall, T4030a and T4030c were well tolerated when instilled once daily for 12 weeks in OAG or OHT patients, with no serious ocular TEAE reported during the study. There were no serious AEs, which were assessed as related to the IMP by the investigator.

The systemic concentration of timolol was significantly lower after 12 weeks in patients treated with T4030a than in patients treated with T4030c or Ganfort, which is to be expected with the lower formula concentration of timolol in T4030a.

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These results have to be supported in a larger Phase III clinical study, to validate the use of a preservative-free ophthalmic formulation of T4030 as a useful tool in the therapeutic management of glaucoma and OHT.		
Date of Report: 01 December 2020		