Efficacy and tolerability of netarsudil 0.02%/latanoprost 0.005% vs bimatoprost 0.03%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: the MERCURY 3 study

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INTRODUCTION

- Despite the availability of a range of interventions that lower intraocular pressure (IOP), a significant proportion of patients still experience glaucoma progression under clinical care[1]
- The Rho kinase inhibitor (ROCK) netarsudil represents the first pharmacological innovation for glaucoma treatment for 25 years[2]
  - Netarsudil 0.02% has been formulated in a fixed-dose combination (FDC) with the prostaglandin analogue latanoprost 0.005% (NET/LAT)
- Dysfunction of the trabecular meshwork (TM) leads to IOP elevation, which is one of the main risk factors for glaucoma[3, 4]
  - Netarsudil acts on actin stress fibres and modifies the shape of the TM, expanding the juxtacanalicular tissue and improving trabecular outflow[5]
- The previous MERCURY 1 and 2 studies, and a subsequent pooled analysis, have demonstrated that once-daily NET/LAT provided significant reductions in mean IOP that were statistically superior to reductions with either agent alone, in a United States population[6–8]

PURPOSE

- The MERCURY 3 study assessed the efficacy, safety and tolerability of NET/LAT compared with a bimatoprost 0.03%/timolol 0.5% FDC (BIM/TIM) in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT)

METHODS

- MERCURY 3 was a prospective, randomised, double-masked, active-controlled study across 11 European countries
- Adults with POAG or OHT with a medicated IOP of ≥17–<28 mmHg were included
- The primary efficacy outcome was clinical non-inferiority in mean IOP reduction between treatments (95% confidence interval [CI] ≤1.5 mmHg at all time points and ≤1.0 mmHg at ≥5 of 9 time points) through Month 3
  - IOP measurements were taken using Goldmann applanation tonometry at 08:00, 10:00 and 16:00 at Week 2, Week 6 and Month 3
- Secondary efficacy outcomes included:
  - Mean change from diurnally adjusted baseline IOP at each post-treatment time point
  - Percentages of participants achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels
- In the safety assessment, IOP was measured at 10:00 at Months 4, 5 and 6. Ocular adverse events (AEs) and systemic safety assessments were made over 6 months

RESULTS

- Overall, 430 patients were randomised 1:1 to treatment with NET/LAT or BIM/TIM; 95.3% were Caucasian and the mean (range) age was 67.2 (22–91) years (**Table 1**)

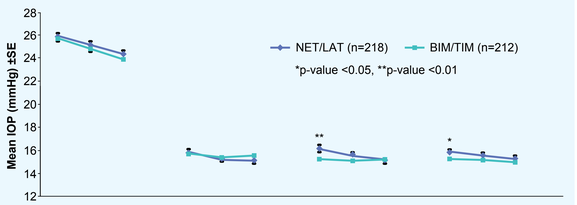
Table 1. Baseline characteristics

Characteristic	All patients (n=430)	NET/LAT (n=218)	BIM/TIM (n=212)	p-value
Age				0.7983
Mean, years (SD)	67.2 (11.65)	67.3 (12.03)	67.0 (11.27)	
Median (range)	69.0 (22–91)	69.0 (25–91)	68.5 (22–91)	
≥65 years	280 (65.1)	147 (67.4)	133 (62.7)	0.3136
Sex, n (%)				
Female	223 (51.9)	131 (60.1)	92 (43.4)	0.0007***
Race, n (%)				
White	410 (95.3)	210 (96.3)	200 (94.3)	
Black/African American	9 (2.1)	4 (1.8)	5 (2.4)	0.2425
Asian	3 (0.7)	0	3 (1.4)	
Other/NA	8 (1.9)	4 (1.8)	4 (1.9)	
Prior PGA hypotensive therapy, n (%)	318 (74.0)	171 (78.4)	147 (69.3)	0.0368*
Mean diurnal IOP mmHg at Day 1 in study eye, mean (SD)	24.936 (3.33)	25.054 (3.41)	24.814 (3.26)	0.4560
Study eye diagnosis, n (%)				
POAG	236 (54.9)	124 (56.9)	112 (52.8)	0.4383
OHT	194 (45.1)	94 (43.1)	100 (47.2)	

*p<0.05, *** p<0.001. Percentages are based on the number of patients (n) in a given treatment group for the intention-to-treat (ITT) population. BIM/TIM, bimatoprost 0.03%/timolol 0.5%; IOP, intraocular pressure; ITT, intention-to-treat; OHT, ocular hypertension; NA, not applicable; NET/LAT, netarsudil 0.02%/latanoprost 0.005%; PGA, prostaglandin analogue; POAG; primary open angle glaucoma; SD, standard deviation.

- For the primary efficacy endpoint, clinical non-inferiority of NET/LAT to BIM/TIM was demonstrated in the intention-to-treat (ITT) population
  - The upper limit of the 95% CIs around the difference (NET/LAT-BIM/TIM) was ≤1.5 mmHg at all 9 time points and ≤1.0 mmHg at ≥5 of 9 time points at Week 2, Week 6, and Month 3 (**Figure 1**)

Figure 1. NET/LAT versus BIM/TIM for mean IOP at specified time points at Week 2, Week 6 and Month 3

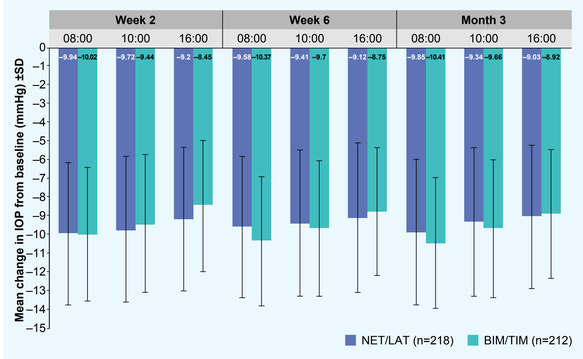


	Baseline			Week 2			Week 6			Month 3		
Time point (hour)	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00
Δ mmHG from BIM/TIM	-	-	-	0.17	−0.17	−0.48	0.88	0.40	−0.08	0.66	0.42	0.19
SE of Δ	-	-	-	0.29	0.27	0.28	0.29	0.28	0.28	0.28	0.31	0.29
95% 2-sided CI	-	-	-	(0.40, 0.74)	(−0.70, 0.35)	(−1.03, 0.08)	(−0.32, 1.44)	(−0.15, 0.94)	(−0.63, 0.46)	(0.12, 1.20)	(−0.18, 1.03)	(−0.38, 0.76)
p-value	-	-	-	0.5581	0.5193	0.0904	0.0023**	0.1510	0.7613	0.0163*	0.1706	0.5126

Least square mean of baseline adjusted ANCOVA IOP: ITT population with Markov Chain Monte Carlo. Chart shows actual mean IOP baseline values for comparison. *p<0.05, **p<0.01. ANCOVA, analysis of covariance; BIM/TIM, bimatoprost 0.03%/timolol 0.5%; CI confidence interval; IOP, intraocular pressure; ITT, intention-to-treat; NET/LAT, netarsudil 0.02%/latanoprost 0.005%; SE, standard error.

- Reduction of IOP, diurnally adjusted from baseline, throughout the day ranged from –9.94 to –9.03 mmHg for NET/LAT and –10.41 to –8.45 mmHg for BIM/TIM (**Figure 2**)
  - NET/LAT provided a reduction of approximately 9.5 mmHg in diurnally adjusted IOP (the baseline mean diurnal IOP was 25.05 mmHg)

Figure 2. NET/LAT compared to BIM/TIM for diurnally adjusted change from baseline IOP



ITT population with Markov Chain Monte Carlo. BIM/TIM, bimatoprost 0.03%/timolol 0.5%; IOP, intraocular pressure; ITT, intention-to-treat; NET/LAT, netarsudil 0.02%/latanoprost 0.005%; SD, standard deviation.

- There was no significant difference in the proportions of patients achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels
- In the overall safety analysis, NET/LAT was associated with more reports of treatment-emergent AEs (TEAEs) than BIM/TIM (**Table 2**)

Table 2. Overall TEAEs

	NET/LAT (n=218)	BIM/TIM (n=212)
TEAE, n	483	290
Ocular AE, n	352	131
Patients with >1 ocular AE, n (%)	131 (60.1)	64 (30.2)
Non-ocular AE, n	131	159
Patients with >1 non-ocular AE, n (%)	69 (31.7)	75 (35.4)
SAE, n	8	10
Patients with >1 SAE, n (%)	7 (3.2)	7 (3.3)
Treatment-related SAE, n (%)	0	0
Treatment-related AE, n	291	91
Patients with >1 TEAE, n (%)	120 (55.0)	53 (25.0)
Patients with AE by maximum severity, n (%)		
Mild	64 (29.4)	65 (30.7)
Moderate	74 (33.9)	35 (16.5)
Severe	15 (6.9)	10 (4.7)

All AEs occurring during the study (i.e., once the subject had received one dose of study drug) were defined as TEAEs. Percentages are based on the number of patients (n) in a given treatment group for the ITT population. AE, adverse event; BIM/TIM, bimatoprost 0.03%/timolol 0.5%; ITT, intention-to-treat; NET/LAT, netarsudil 0.02%/latanoprost 0.005%; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- The most common ocular TEAEs with NET/LAT were conjunctival hyperaemia, cornea verticillata, eye pruritus, punctate keratitis and conjunctivitis allergic (**Table 3**)
  - Most TEAEs were mild or moderate in severity; however, more patients discontinued treatment due to ocular TEAEs in the NET/LAT cohort (20.2%) compared with the BIM/TIM cohort (1.9%)
  - No serious treatment-related TEAEs were reported in either arm
  - Systemic TEAEs were reported among approximately 1% of patients in each group

Table 3. Treatment-related ocular AEs reported in ≥5% of patients

Treatment-related ocular AE n (%)	NET/LAT (n=218)	BIM/TIM (n=212)	p-value
Eye disorders			
Conjunctival hyperaemia	67 (30.7)	19 (9.0)	<0.0001
Cornea verticillata	24 (11.0)	0	<0.0001
Eye pruritus	17 (7.8)	2 (0.9)	0.0006
Punctate keratitis	12 (5.5)	4 (1.9)	0.0718
Conjunctivitis allergic	11 (5.0)	1 (0.5)	0.0057

Percentages are based on the number of patients (n) in a given treatment group for the ITT population. AE, adverse event; BIM/TIM, bimatoprost 0.03%/timolol 0.5%; ITT, intention-to-treat; NET/LAT, netarsudil 0.02%/latanoprost 0.005%.

DISCUSSION

- NET/LAT demonstrated consistent mean IOP reductions throughout the day
- No TEAEs were reported that have not been previously observed in other studies investigating the individual components
  - Conjunctival hyperaemia observed in the NET/LAT treated patients may have been caused by the vasodilatory effects of ROCK inhibition[6]
  - Cornea verticillata forms through phospholipidosis, is typically asymptomatic, and generally resolves after treatment discontinuation[6]
- MERCURY 3 adds to the evidence supporting NET/LAT as a novel and valuable addition to POAG/OHT medical management, updating an armamentarium that has typically relied on the same classes of intervention for more than two decades

CONCLUSIONS

- NET/LAT was non-inferior to BIM/TIM in patients with POAG and OHT, and provided efficacious, sustained reductions of IOP over 3 months
- NET/LAT was associated with more TEAEs than BIM/TIM but was generally well tolerated

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