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ORIGINAL ARTICLE

Myopia outcome study of atropine in children: Two-year result of daily 0.01% atropine in a European population

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Abstract

Purpose: The Myopia Outcome Study of Atropine in Children (MOSAIC) is an investigator-led, double-masked, randomized controlled trial investigating the efficacy and safety of 0.01% atropine eye drops for managing myopia progression in a predominantly White, European population.

Methods: Children aged 6–16 years with myopia were randomly allocated 2:1 to nightly 0.01% atropine or placebo eye drops in both eyes for 2 years. The primary outcome was cycloplegic spherical equivalent (SE) progression at 24 months. Secondary outcomes included axial length (AL) change, safety and acceptability. Linear mixed models with random intercepts were used for statistical analyses.

Results: Of 250 participants enrolled, 204 (81.6%) completed the 24-month visit (136 (81.4%) treatment, 68 (81.9%) placebo). Baseline characteristics, drop-out and adverse event rates were similar between treatment and control groups. At 24 months, SE change was not significantly different between 0.01% atropine and placebo groups (effect = 0.10 D, $p = 0.07$), but AL growth was lower in the 0.01% atropine group, compared to the placebo group (−0.07 mm, $p = 0.007$). Significant treatment effects on SE (0.14 D, $p = 0.049$) and AL (−0.11 mm, $p = 0.002$) were observed in children of White, but not non-White (SE = 0.05 D, $p = 0.89$; AL = 0.008 mm, $p = 0.93$), ethnicity at 24 months. A larger treatment effect was observed in subjects least affected by COVID-19 restrictions (SE difference = 0.37 D, $p = 0.005$; AL difference = −0.17 mm, $p = 0.001$).

Conclusions: Atropine 0.01% was safe, well-tolerated and effective in slowing axial elongation in this European population. Treatment efficacy varied by ethnicity and eye colour, and potentially by degree of COVID-19 public health restriction exposure during trial participation.

KEYWORDS
atropine, children, Europe, myopia, myopia control

1 | INTRODUCTION

Atropine, a non-selective, muscarinic acetylcholine receptor antagonist, is widely considered an efficacious pharmacological agent for the control of myopia progression (Huang et al., 2016; Tsai et al., 2022; Walline et al., 2020). This perspective is largely based on data from clinical trials conducted in parts of South and East Asia (Chia et al., 2012; Chua et al., 2006; Saxena et al., 2021; Wang et al., 2017; Yam et al., 2019, 2020, 2022). These studies have collectively shown that atropine's efficacy is dose-dependent, with higher concentrations (0.5% and 1%) exerting the greatest therapeutic effect (Chia et al., 2012; Huang et al., 2016; Tsai et al., 2022; Yi et al., 2015). Its potency at higher concentrations, however, comes at the cost of significant side effects

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including photophobia, reading difficulty and hypersensitivity reactions (Gong et al., 2017). The principal justification for exploring lower concentrations comes as a serendipitous finding from the Atropine Treatment Of Myopia (ATOM) 2 study, which initially suggested that 0.01% atropine might deliver effective myopia control with a dramatically improved side-effect profile (Chia et al., 2012; Yam et al., 2019). Recent reports from Hong Kong, China, Japan and India have provided additional evidence that low-concentration atropine in the 0.01% to 0.05% concentration range can control the refractive progression and axial elongation characteristic of progressive myopia in these populations with few side effects (Chia et al., 2012; Saxena et al., 2021; Yam et al., 2019, 2020, 2022, 2023).

There is also a need for safe and effective myopia control interventions among European and North American populations, where a significant proportion of children and young adults develop myopia (Harrington et al., 2019; O'Donoghue et al., 2010; Vitale et al., 2009; Williams et al., 2015; Williams, Verhoeven, et al., 2015). Considering the behavioural, environmental, epidemiologic and genetic differences between children in Asian countries and elsewhere, caution is required in extrapolating Asian trial outcomes to other regions such as Europe and North America (Harrington et al., 2019; Rudnicka et al., 2016). The recently published Western Australian (WA)-ATOM study is the first placebo-controlled randomized controlled trial (RCT) of 0.01% atropine conducted in a non-Asian population (Lee et al., 2022). The study cohort was racially diverse, however, and notable differences in 0.01% atropine efficacy were observed across the different ancestries included. With just 75 children of European descent (48% of participants) included in the trial, the WA-ATOM study findings reinforce the need for more data on the safety and efficacy of low-concentration atropine in non-Asian populations (Lee et al., 2022).

The Myopia Outcome Study of Atropine in Children (MOSAIC), an investigator-led, 3-year, double-masked, placebo-controlled randomized clinical trial of 0.01% and 0.05% atropine eye drops, was designed to explore the efficacy, safety, acceptability and mechanisms of action of low-concentration atropine for myopia control in predominantly White, European children. This paper reports trial results for the initial 2 years of the study, evaluating 0.01% atropine versus placebo eye drops.

2 | MATERIALS AND METHODS

The MOSAIC trial (ISRCTN36732601) was approved by the Research Ethics Committees at the Mater Misericordiae University Hospital and Technological University Dublin (TU Dublin), Ireland. Participants and their parents provided written informed assent and consent, respectively, prior to participating in MOSAIC. The study protocol has been published (see Data S1) (McCrann et al., 2019). The initial phase of MOSAIC involves assignment to either 0.01% atropine or placebo eye drops for 24 months.

2.1 | Participants

Myopic children (spherical equivalent refractive error [SE] ≤ −0.50 D in both eyes) aged 6–16 years were recruited from July 2019 to September 2020 and examined at a single research centre in Dublin, Ireland. Recruitment limitations were implemented to ensure the study population was approximately representative of the predominantly White (90%) Irish population (McCrann et al., 2019). Participants were recruited via a combination of referrals from eye care providers, engagement with schools and school organizations, and advertising through traditional and social media. Further details on recruitment methods are published elsewhere (McCrann et al., 2019). Participants were excluded if they had ocular comorbidities, astigmatism >2.50 D, least myopic meridian ≥−0.50 D, anisometropia >1 D, previous history of myopia control, corrected visual acuity 0.2 logMAR (logarithm of the minimum angle of resolution) or worse in either eye, known hypersensitivity to atropine, intraocular pressure ≥21 mmHg, or other significant health problems (McCrann et al., 2019).

2.2 | Intervention

Participants were randomized 2:1 to receive either preservative-free 0.01% atropine or placebo eye drops, respectively, dispensed as single-use disposable ampoules and packaged identically. Labels specified only the identifying kit number, expiration date and batch number (Vyluma, Bridgewater, New Jersey, USA). Pharmacological stability of the preparations was independently confirmed prior to the study. Treatment was administered at home, once nightly, in both eyes for 2 years. Study investigators, participants, and parents were all masked to the study medication and treatment assignment throughout the 2-year period.

2.3 | Examinations

Examinations were scheduled at 6 monthly intervals. COVID-19 lockdowns and social distancing requirements caused the 6-month visit to be abandoned and 12-month visit to be shortened by excluding near and accommodation tests to minimize close contact time with participants. Iris colour was graded using a validated scale (Mackey et al., 2011).

2.3.1 | Efficacy assessments

Cycloplegic autorefraction was conducted at least 30 minutes after instillation of 1% cyclopentolate eye drop in both eyes using the Grand Seiko Open Field autorefractor (WAM-5500 Auto Ref/Keratometer, Grand Seiko, Kagawa, Japan). Additional cyclopentolate eye drops were administered to participants with darker irides (5 min after the first drop and every 10 min thereafter) or incomplete cycloplegia at 30 min assessed by pupil size and responses. Axial length (AL) was measured with

a low-coherence interferometry biometer (TOPCON Aladdin HW3.0, Visia Imaging S.R.L., San Giovanni Valdarno, Italy).

2.3.2 | Treatment acceptability

Treatment adherence was calculated as the number of used ampoules returned divided by the number of days elapsed since the previous visit. Treatment acceptability was assessed using the Amblyopia Treatment Index (ATI, a validated, parent-reported questionnaire of treatment impact) (Holmes et al., 2008), mesopic and photopic pupil size, accommodative amplitude, accommodative facility, accommodative lag, near and distance visual acuity and reporting of adverse events (see Data S1).

2.4 | Sample size

The MOSAIC sample size calculation indicated that 136 children were required to provide sufficient power to address the primary outcome (McCrann et al., 2019). Since we hypothesized that atropine tolerability would be lower among European children, we recruited 250 children to allow for attrition.

2.5 | Statistical analysis

A statistical analysis plan was published prior to unmasking of the investigator performing statistical analysis (Data S1) (Lingham et al., 2022; McCrann et al., 2019). The primary and secondary efficacy outcomes, respectively, change in SE and AL at 24 months and analyses were all intention-to-treat.

Efficacy and tolerability over the study period were analysed using linear mixed models with random intercepts for eye nested within participant, a fixed effect visit by treatment interaction and adjustment for the baseline value of the outcome (see Data S1). The pre-planned mixed-measures analysis of variance (ANOVA) was not conducted because: (i) measurements were not equally spaced due to COVID-19, violating an assumption of mixed-measures ANOVA; (ii) the homogeneity of variances assumption was violated (Armstrong, 2017); and (iii) linear mixed models could better handle missing data (Nash et al., 2014). All analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using the lme4 and emmeans packages.

2.6 | Sub-group analyses

Pre-planned analyses investigating the efficacy of atropine 0.01% within subgroups of ethnicity (White vs. non-White), iris colour (blue, green and brown) (Mackey et al., 2011), baseline age (6–10 vs. 11–16 years) and baseline myopia (<−3.00 D vs. ≥ −3.00 D) were performed. For these analyses, linear mixed models were constructed as described for the primary and secondary efficacy outcomes, but included a three-way interaction term between visit, treatment group and the modifier (e.g. age group; to allow treatment effect to vary by age group and visit). Each subgroup variable was investigated in separate models to avoid potential collinearity between these variables, e.g., between ethnicity and eye colour, myopia category and age. In addition, adjustment for the baseline value of the variable, age and sex was included to minimize confounding, unless already included as an exposure variable (e.g. baseline age and myopia category).

2.6.1 | COVID-19 impact analysis

The potential impact of public health restrictions on treatment efficacy was explored by: (i) examining change in SE and AL across the course of the study; and (ii) conducting sub-group analyses to examine change in SE and AL for participants whose treatment period coincided with the full duration of COVID-19 public health restrictions (high COVID impact), and those recruited later after initial public health restrictions from mid-March to late-July 2020 were relaxed and schools had re-opened (low COVID impact), following the methods described for the sub-group analyses above.

2.7 | Missing data

Missing data were treated as missing at random. As linear mixed models rely on maximum likelihood estimation, which is unbiased by missing data, only observed data were analysed. Multiple imputation of missing data was planned where drop-out rates were unequal between treatment groups or where myopia progression was unequal between drop-outs and remaining participants, but was not required because neither condition was met.

3 | RESULTS

3.1 | Baseline characteristics

An outline of enrolment, treatment allocation and follow-up is shown in Figure 1. Baseline characteristics are shown in Table 1 and were not significantly different between the treatment and placebo groups. Participants were biased toward females (62%) and toward non-White ethnic groups (17%) when compared to 5–19-year-olds (49% female, 10% non-White) at the 2016 Irish census ($p < 0.001$ for both) (Central Statistics Office, 2017).

3.2 | Discontinuation of study treatment

Discontinuation in the 0.01% atropine ($n = 31$ [18.6%]) and placebo ($n = 15$ [18.1%]) groups was not significantly different at the 24 months (Table S1 in Data S1).

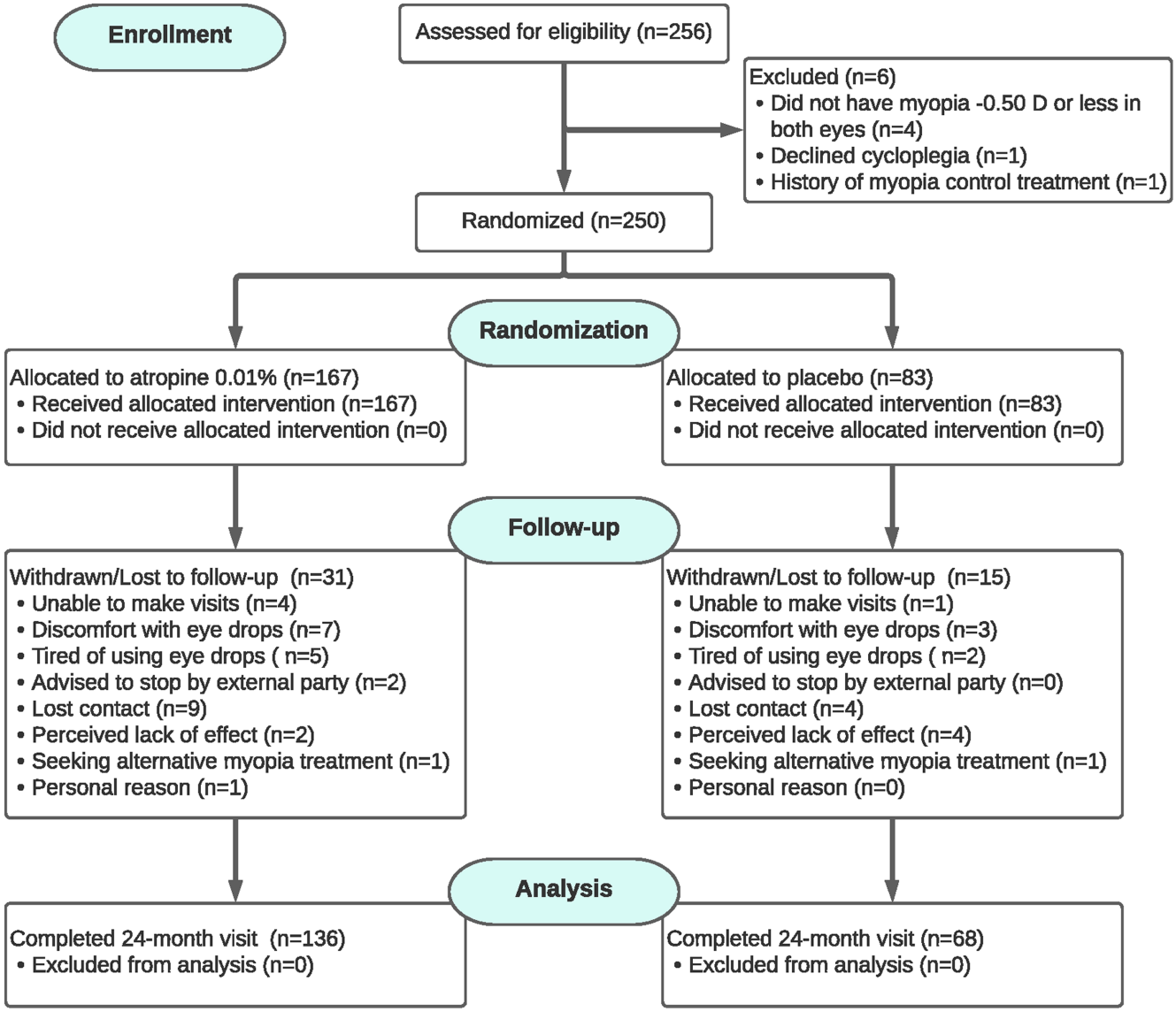

FIGURE 1 CONSORT flow diagram showing enrolment, randomization, follow-up and analysis for the myopia outcome study of atropine in children.

3.3 | Safety and tolerability

3.3.1 | Adverse events

Thirty-two adverse events were reported during the 24-month period, 23/136 (16.9%) in the atropine and 9/68 (13.2%) in the placebo groups ($p=0.38$; Table 2). Adverse event severity, causality and expectedness were not significantly different between the two groups. Seven adverse events were possibly or probably related to the study medication (eye discomfort, $n=3$; temporary blurred vision at near, $n=1$; temporary pupil dilation, $n=1$; rash on the eyelid, $n=2$). One serious adverse event, hospitalization for an abdominal surgical procedure, was judged unrelated to the study medication (Table 2).

3.3.2 | Acceptability profile

Between the 0.01% atropine and placebo groups, there was no significant difference in distance visual acuity, near visual acuity, accommodative amplitude, accommodative lag, accommodative facility (Table 3), parent-reported ATI scores or child-reported outcomes (Table S2 in Data S1). Photopic and mesopic pupil diameters were larger at each follow-up visit in the 0.01% atropine group (Table 3) with small non-significant reductions in accommodative amplitude and facility (Table 3). No participants required varifocal or photochromic lenses.

3.4 | Efficacy outcomes

Changes in the primary (SE) and secondary (AL) efficacy outcomes are shown in Figure 2 and Table 3. Myopia progression was not significantly different between the atropine and placebo groups at the 24-month visit ($p=0.07$) but was significantly lower in the treatment group at the 18-month visit ($p=0.049$). Axial elongation was lower in the atropine group at the 18-month ($p=0.04$) and 24-month visits ($p=0.009$), compared to the placebo group. No significant difference was observed in the proportion of eyes that progressed by >−0.25 D, −0.25

TABLE 1 Comparison of baseline characteristics of participants in the atropine 0.01% and placebo groups of the myopia outcome study of atropine in children.

	Atropine 0.01%	Placebo	*p* value
n	167 (66.8)	83 (33.2)	
Age (years), mean (SD)	11.84 (2.47)	11.78 (2.17)	0.87
Age first prescribed glasses (years), mean (SD)	7.56 (2.18)	7.71 (2.27)	0.61
Daily reading time (hours), median [IQR]	2.00 [1.00, 3.00]	1.50 [1.00, 2.50]	0.34
Daily outdoor time (hours), median [IQR]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.90
Body mass index (kg/m^2), median [IQR]	18.61 [16.75, 20.85]	18.32 [16.90, 20.27]	0.63
Sex			
Male, *n* (%)	65 (38.9)	30 (36.1)	0.77
Female, *n* (%)	102 (61.1)	53 (63.9)	
Number of parents with myopia, *n* (%)			
Zero	32 (19.2)	18 (21.7)	0.64
One	97 (58.1)	43 (51.8)	
Two	38 (22.8)	22 (26.5)	
Race, *n* (%)			
White	135 (80.8)	72 (86.7)	0.62
Asian	15 (9.0)	7 (8.4)	
Black	3 (1.8)	1 (1.2)	
Mixed	12 (7.2)	2 (2.4)	
Other	2 (1.2)	1 (1.2)	
Iris colour, *n* (%)			
Blue	78 (46.7)	42 (50.6)	0.60
Green	45 (26.9)	24 (28.9)	
Brown	44 (26.3)	17 (20.5)	
Final visit attended, *n* (%)			
Baseline	18 (10.8)	4 (4.8)	0.07
12-month	7 (4.2)	9 (10.8)	
18-month	6 (3.6)	2 (2.4)	
24-month	136 (81.4)	68 (81.9)	
SE (D), median [IQR]	−3.21 [−4.51, −2.12]	−3.38 [−4.34, −1.95]	0.75
Axial length (mm), mean (SD)	24.85 (1.02)	24.93 (1.09)	0.57
Distance visual acuity (logMAR), mean (SD)	−0.03 (0.09)	−0.02 (0.08)	0.58
Near visual acuity (logMAR), mean (SD)	0.05 (0.08)	0.06 (0.07)	0.71
Amplitude of accommodation (D), median [IQR]	20.00 [18.00, 22.00]	20.00 [20.00, 22.00]	0.36
Accommodative facility (cyc/min), median [IQR]	4.00 [2.00, 6.25]	5.00 [2.00, 6.00]	0.94
Accommodative lag (D), median [IQR]	1.03 [0.68, 1.44]	1.02 [0.59, 1.43]	0.68
Photopic pupil size (mm), mean (SD)	4.21 (0.69)	4.18 (0.65)	0.73
Mesopic pupil size (mm), mean (SD)	5.06 (0.77)	5.07 (0.84)	0.98

Note: Ocular data presented are the mean of both eyes. Approximately normally distributed variables are described with mean (standard deviation [SD]) and skewed data are described with median (interquartile range [IQR]). Outdoor and reading time are the reported daily average over the preceding 2 weeks. Tests used to compare the two groups are Chi-square test for categorical variables, independent samples *t*-test for approximately normally distributed variables and the Mann–Whitney test for skewed variables.

Abbreviations: cyc/min, cycles per minute; D, diopters; logMAR, log Minimum Angular Resolution; mm, millimetres; *n*, number; SE, spherical equivalent refractive error.

to −0.75 D and <−0.75 D at 24 months, between placebo and 0.01% atropine groups ($p=0.28$; Figure S1 in the Data S1).

3.4.1 | Modifiers of efficacy

There were statistically significant treatment effects for SE at 18 months and AL at 18 and 24 months among White, but not non-White, participants (Figure 3 and Table S3 in the Data S1). Significant treatment effects were observed among blue-eyed participants at 18 months (SE difference = 0.17 D, $p=0.04$; AL difference = −0.10 mm, $p=0.008$) and 24 months (SE difference = 0.18 D, $p=0.03$; AL difference = −0.12 mm, $p=0.001$), but not among participants with green or brown eyes (Table S3 in Data S1). Treatment efficacy was similar among participants with low (≥−3.00 D) vs high (<−3.00 D) myopia at baseline (Table S3 in Data S1). Axial elongation was lower in older (≥11 years) participants assigned to atropine, compared

TABLE 2 Number and characteristics of adverse events in the treatment and placebo groups.

	Atropine	Placebo	Total	*p*
n	23/136 (16.9%)	9/68 (13.2%)	32	
Causality				
Not related	11 (47.83%)	5 (55.56%)	16	0.26
Unlikely	5 (21.74%)	4 (44.44%)	9	
Possibly	3 (13.04%)	0 (0%)	3	
Probably	4 (17.39%)	0 (0%)	4	
Definitely	0 (0%)	0 (0%)	0	
Severity				
Mild	17 (73.91%)	7 (77.78%)	24	0.2
Moderate	6 (26.09%)	1 (11.11%)	7	
Severe	0 (0%)	1 (11.11%)	1	
Life-threatening	0 (0%)	0 (0%)	0	
Death	0 (0%)	0 (0%)	0	
Expectedness				
Expected	6 (26.09%)	2 (22.22%)	8	0.31
Unexpected	8 (34.78%)	1 (11.11%)	9	
N/A	9 (39.13%)	6 (66.67%)	15	

Note: *p* value from Chi-square test. *p* values are approximations for all characteristics due to low count numbers (<5) in some cells.

to placebo, at 18 (difference = −0.08 mm, $p = 0.02$) and 24 months (difference = −0.09 mm, $p = 0.006$), but no significant differences were observed among younger (<11 years) participants (Table S3 in Data S1).

3.4.2 | COVID-19 impact

At baseline, low COVID impact participants were younger than high COVID impact participants [mean age 11.37 (2.42) vs. 12.04 (2.32) years, respectively, $p = 0.04$] and had shorter mean AL [24.68 (1.06) vs. 24.97 (1.03) mm, respectively, $p = 0.04$]. Significant treatment effects were observed in the low COVID impact group (Figure 4) at the 18-(SE difference = 0.28 D, $p = 0.006$; AL difference = −0.13 mm, $p = 0.004$) and 24-month visits (SE difference = 0.31 D, $p = 0.003$; AL difference = −0.16 mm, $p < 0.001$), after adjusting for age, sex and baseline SE or AL, respectively, but not in the high COVID impact group at any time point (SE difference at 24 months = 0.01 D, $p = 0.80$; AL difference = −0.04, $p = 0.24$).

4 | DISCUSSION

MOSAIC is the first placebo-controlled RCT to investigate the safety, tolerability and efficacy of 0.01% atropine treatment for myopia management in a predominantly White, European population. As observed in other trials (Chia et al., 2016; Hieda et al., 2021; Lee et al., 2022; Repka et al., 2023; Saxena et al., 2021; Yam et al., 2019, 2020, 2022; Zadnik et al., 2023), 0.01% atropine exhibited an excellent safety profile. Treatment was very well tolerated by study participants and only a small number of participants experienced mild eye drop-related discomfort. Biologic activity was confirmed via pupillary and accommodative changes observed in treated participants, but the ocular effects were small and not associated with complaints of photophobia or blurring of near vision (Lee et al., 2022; Loughman & Flitcroft, 2016).

In our relatively slow progressing population, this level of reduction delivered a modest myopia control impact from a clinical standpoint with 24-month absolute effect sizes of +0.10 D and −0.07 mm for myopia progression and axial elongation, respectively. The MOSAIC effect sizes compared well with other studies at both the 12- and 24-month points, with the exception of ATOM-J (Figure S2 in the Data S1), which reported faster placebo group progression and greater effect sizes. Other than the recently published Pediatric Eye Disease Investigator Group (PEDIG) study in USA, which reported no treatment effect of 0.01% atropine eye drops and represents an outlier in relation to other studies, the absolute and relative treatment effects of 0.01% atropine eye drops in this study were similar to other studies as shown in Figure S3 in Data S1 (Chia et al., 2012; Hieda et al., 2021; Lee et al., 2022; Repka et al., 2023; Saxena et al., 2021; Wei et al., 2020; Yam et al., 2019, 2020, 2022; Zadnik et al., 2023). Myopia progression and axial eye growth in the MOSAIC cohort were reduced by 15.9% and 17.5%, respectively, among treated participants at the 24-month visit, similar to the relative reduction observed in other two-year placebo-controlled RCTs from Australia (18.0% and 10.5%, respectively), Japan (14.9% and 18.2%, respectively) and the multinational Childhood Atropine for Myopia Progression (CHAMP) study (21% and 19%, respectively) (Hieda et al., 2021; Lee et al., 2022; Zadnik et al., 2023). The similar relative effect sizes, as opposed to absolute effect sizes, seen in Figure S3 in Data S1 are suggestive of a proportional treatment effect of atropine 0.01%, perhaps related to receptor binding.

To allow readers to compare MOSAIC results to the recently completed CHAMP trial (Study of NVK-002

TABLE 3 Change in ocular outcomes in the atropine 0.01% and placebo groups at the 12-, 18- and 24-month visits.

		12 months				18 months				24 months				Treatment by visit interaction
		Atropine 0.01%	Placebo	Group difference[a]	p[b] value	Atropine 0.01%	Placebo	Group difference[a]	p[b] value	Atropine 0.01%	Placebo	Group difference[a]	p[b] value	p[c] value
SE (D)	*n* (eyes)	298	154			280	138			272	134			
	mean (SD)	−0.24 (0.41)	−0.27 (0.47)	0.02 [0.07]	0.76	−0.41 (0.49)	−0.53 (0.56)	0.13 [0.07]	0.049	−0.53 (0.56)	−0.63 (0.65)	0.12 [0.07]	0.07	<0.001
Axial length (mm)	*n* (eyes)	298	154			280	138			272	136			
	mean (SD)	0.20 (0.19)	0.24 (0.20)	−0.04 [0.03]	0.25	0.29 (0.23)	0.35 (0.26)	−0.06 [0.03]	0.04	0.33 (0.27)	0.40 (0.31)	−0.07 [0.03]	0.009	<0.001
Distance visual acuity (logMAR)	*n* (eyes)	298	154			280	138			272	136			
	mean (SD)	0.03 (0.11)	0.02 (0.11)	0.004 [0.01]	0.72	0.02 (0.11)	0.00 (0.11)	0.02 [0.01]	0.17	0.00 (0.11)	−0.02 (0.11)	0.008 [0.01]	0.51	0.57
Near visual acuity (logMAR)	*n* (eyes)					278	138			272	136			
	mean (SD)	NA	NA			−0.02 (0.07)	−0.02 (0.07)	−0.002 [0.006]	0.78	−0.03 (0.07)	−0.03 (0.07)	0.0005 [0.006]	0.93	0.65
Accommodative amplitude (D)	*n* (eyes)					276	138			268	136			
	mean (SD)	NA	NA			−0.57 (4.42)	−0.76 (4.66)	0.51 [0.52]	0.33	−1.88 (4.85)	−0.84 (5.21)	−0.56 [0.29]	0.29	0.008
Accommodative lag (D)	*n* (eyes)					267	138			257	136			
	mean (SD)	NA	NA			0.04 (0.64)	−0.02 (0.87)	0.04 [0.07]	0.57	−0.06 (0.65)	−0.16 (0.71)	0.10 [0.07]	0.10	0.36
Accommodative facility (cyc/min)	*n* (eyes)					276	138			268	136			
	mean (SD)	NA	NA			0.57 (2.90)	1.03 (2.80)	−0.40 [0.37]	0.57	1.18 (3.05)	1.88 (3.15)	−0.63 [0.37]	0.15	0.48
Photopic pupil diameter (mm)	*n* (eyes)	285	142			265	130			255	124			
	mean (SD)	0.32 (0.79)	−0.17 (0.47)	0.54 [0.08]	<0.001	0.33 (0.92)	−0.10 (0.63)	0.47 [0.08]	<0.001	0.12 (0.83)	−0.22 (0.59)	0.38 [0.08]	<0.001	0.17
Mesopic pupil diameter (mm)	*n* (eyes)	286	143			264	130			256	126			
	mean (SD)	0.30 (0.74)	−0.11 (0.69)	0.44 [0.08]	<0.001	0.40 (0.78)	−0.03 (0.73)	0.46 [0.08]	<0.001	0.19 (0.85)	−0.14 (0.72)	0.36 [0.08]	<0.001	0.38

Note: Near visual acuity, accommodative amplitude, accommodative lag and accommodative facility were not assessed at the 12-month visit.

Abbreviations: cyc/min, cycles per minute; D, diopters; logMAR, log Minimum Angular Resolution; mm, millimetres; *n*, number; NA, not applicable (test was not conducted on this visit to keep contact time to a minimum due to COVID public health policies); SD, standard deviation; SE, spherical equivalent refractive error.

[a]Group differences are the difference [standard error] in the estimated marginal means derived from the linear mixed model and are adjusted for the baseline value of the outcome.

[b]p values are testing for a significant difference in mean change in outcome between the treatment and placebo groups at the 12-, 18- and 24-month visits, separately. p values and estimated marginal means are derived from a linear mixed model including random intercepts for eye nested with participant ID, a treatment group by visit interaction and adjusting for the outcome value at the baseline visit.

[c]p value testing whether removing the treatment group by visit interaction term significantly worsens the model. A non-significant result does not indicate a lack of a main treatment group effect.

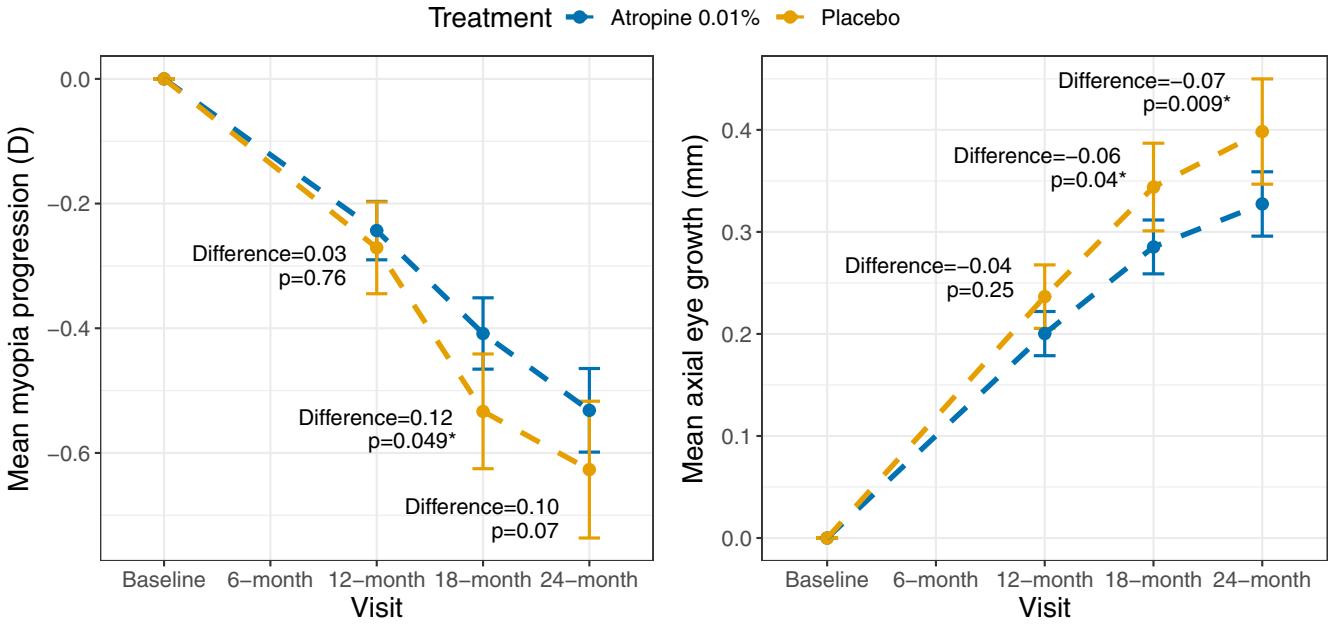

FIGURE 2 Change in spherical equivalent refraction and axial length in the 0.01% atropine and placebo groups. Differences shown are from raw data (i.e., not model estimated), whereas *p* values are derived from a linear mixed model including random intercepts for eye nested by participant, treatment group by visit interaction and adjusting for the baseline value of the dependent variable.

in Children With Myopia, NCT03350620) (Zadnik et al., 2023), which used the same investigational product and enrolled children in Europe and the USA, we performed an intention-to-treat analysis with linear mixed models following the CHAMP statistical analysis plan, which included adjusting for baseline age <9 years ($n=34$, 13.6% of participants compared to 38.4% in CHAMP) and ≥9 years as a dichotomous variable. There were significant differences between MOSAIC 0.01% atropine and control groups at 24 months in both SE (difference = 0.13 D, $p=0.035$) and AL (difference = 0.09 mm, $p<0.001$). However, it should be noted that the MOSAIC trial had a much smaller proportion of participants under 9 years of age than the CHAMP study.

Similar to the Australian WA-ATOM study (Lee et al., 2022), 0.01% atropine eye drops were more effective in slowing myopia progression and axial elongation in White, compared to non-White, participants. Furthermore, efficacy was influenced by iris colour, with significant treatment effects noted in lighter colour eyes, particularly blue, but not in brown eyes. Although the number of non-White participants recruited to MOSAIC was low ($n=43$; 51% Asian), this racial disparity is in apparent conflict with previous studies that have noted significant myopia control effects of atropine among Asian children living in Asia (Chia et al., 2012; Hieda et al., 2021; Saxena et al., 2021; Wei et al., 2020; Yam et al., 2019, 2020, 2022).

0.01% atropine treatment efficacy in MOSAIC was greater during the second year, compared to the first. Previous analyses have generally concluded that myopia control efficacy is greatest in the first year of treatment, particularly for optical treatment studies (Brennan et al., 2021; Huang et al., 2016; Kaphle et al., 2020). However, some studies of 0.01% atropine (Chia et al., 2012; Hieda et al., 2021; Yam et al., 2020) have found that this temporal trend may be reversed for atropine treatment (Figure S3 in Data S1). An exception is the WA-ATOM study in Australia (Lee et al., 2022) which noted a decrease in efficacy in the second year, perhaps driven by a higher drop-out rate of fast myopia progressors in the placebo group (Lee et al., 2022).

The COVID-19 pandemic has been linked to increased myopia incidence and progression in children (Wang et al., 2021). More importantly, however, recent reports suggest that home confinement and the associated behavioural changes that impacted children during the pandemic may have compromised the efficacy of low-concentration atropine treatment. In Israel and South Korea, for example, refractive progression and axial elongation rates of children receiving low-concentration atropine accelerated during the pandemic, compared to pre-COVID rates (Erdinest et al., 2022; Yum et al., 2021). These findings are relevant for clinical trials where study participant behaviours and outcomes were affected by public health response measures initiated to limit the spread of COVID-19 infection.

Almost two-thirds of MOSAIC trial participants were recruited prior to the initial COVID lockdown in Ireland and their participation in MOSAIC coincided with the full duration of school closures and most severe behavioural restrictions. No treatment benefit was observed in this sizeable cohort of high COVID impact participants. Conversely, children recruited after the most severe restrictions had been lifted demonstrated the greatest treatment effect of any participant subgroup in the trial, with 40% less refractive progression and 32% less axial elongation in treated compared to untreated low COVID impact participants. Progression overall was faster, however, in low COVID impact participants compared to high COVID impact participants. Given that age is the dominant influence on myopia progression and axial elongation rate in children (Hyman et al., 2005; Jones-Jordan et al., 2021), this difference likely relates

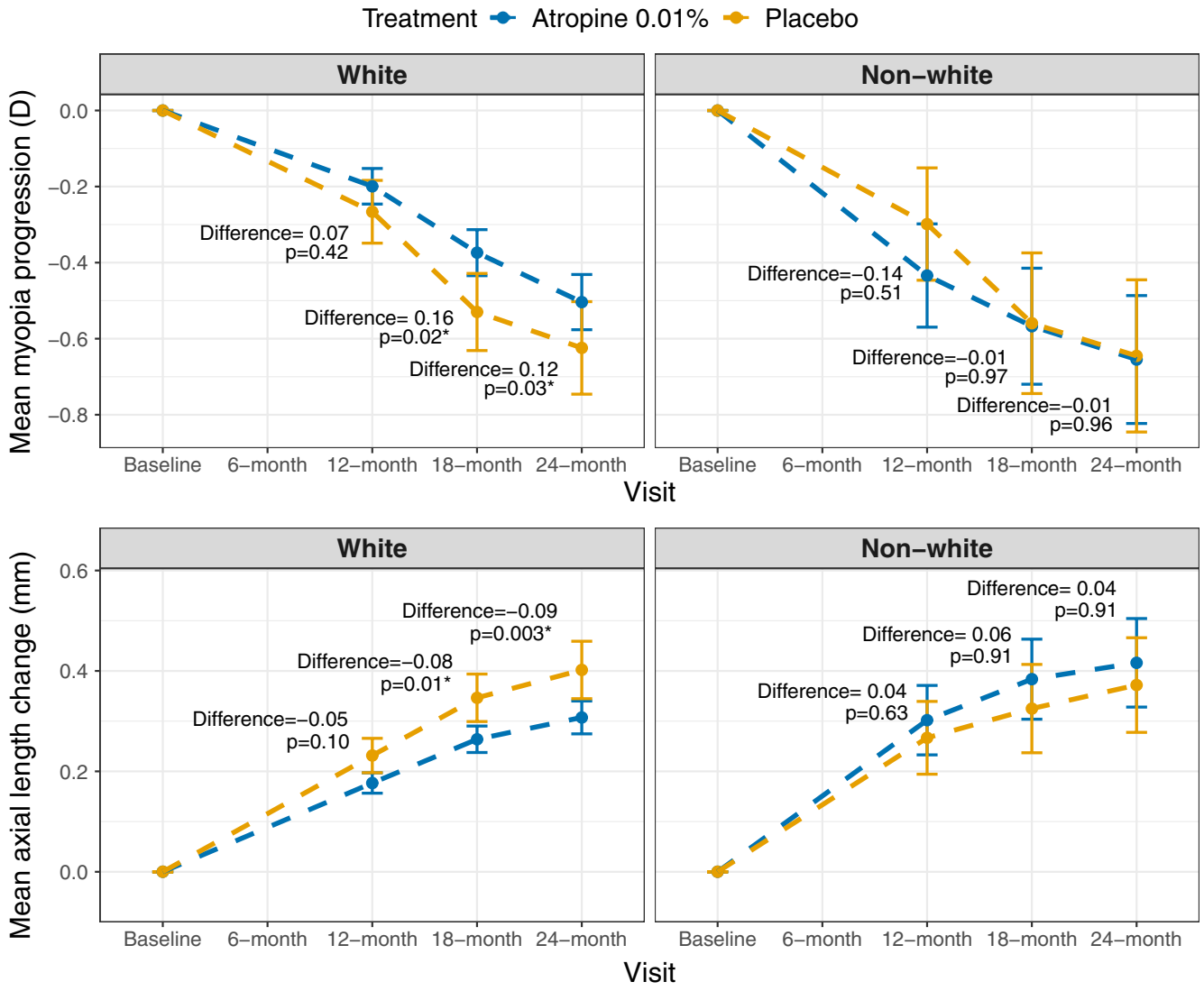

FIGURE 3 Change in spherical equivalent refraction and axial length in the 0.01% atropine and placebo groups stratified by a dichotomous self-reported ethnicity variable. Sample sizes at baseline and 24 months in each subgroup were: 0.01% atropine, White ethnicity [$n=121$] and [$n=111$] (92% retention), respectively; 0.01% atropine, non-White ethnicity [$n=28$] and [$n=25$] (89% retention), respectively; placebo, White ethnicity [$n=66$] and [$n=60$] (91% retention), respectively; placebo, non-White ethnicity [$n=11$] and [$n=8$] (73% retention), respectively.

to the younger age of the low COVID group (0.67 years younger on average) and shorter AL (0.29 mm shorter on average) at baseline. These findings suggest that effective myopia management may require both an effective therapeutic intervention and optimal behavioural modification.

4.1 | Strengths and limitations

The high proportion (83%) of White, European children is a key strength of MOSAIC, as previous studies of low-concentration atropine have almost exclusively involved Asian children (Chia et al., 2012; Hieda et al., 2021; Saxena et al., 2021; Wei et al., 2020; Yam et al., 2019, 2020, 2022). MOSAIC further establishes that 0.01% atropine is well tolerated and safe in European children of various ages, including those with very light-coloured irides.

The broad age range of children recruited to MOSAIC may be viewed as both a strength and limitation. Myopia onset is typically later in European, relative to Asian, children, so this age range is likely more representative of myopia development and progression in Europe (Grzybowski et al., 2020). However, approximately two-thirds of children recruited fell into the older age category (11–16 years). As myopia progression decreases with age (Jones-Jordan et al., 2021; McCullough et al., 2020), this may have contributed to the generally low progression rate observed in the placebo group. Classification of ethnicity is often imperfect and the scheme we used may have grouped disparate ethnicities together.

The MOSAIC study results will be pooled with data from aligned studies in a planned, prospective, patient-level meta-analysis (Azuara-Blanco et al., 2020; Lee et al., 2022). This will provide additional statistical power for subgroup analyses and allow a more definitive exploration of atropine's efficacy and safety in children outside Asia. Evidence published after the MOSAIC was designed suggests 0.05% atropine provides superior treatment efficacy to 0.01% atropine, while maintaining an acceptable safety profile (Yam et al., 2019). In the second phase of MOSAIC, participants originally allocated to placebo cross over to 0.05% atropine for a 12-month

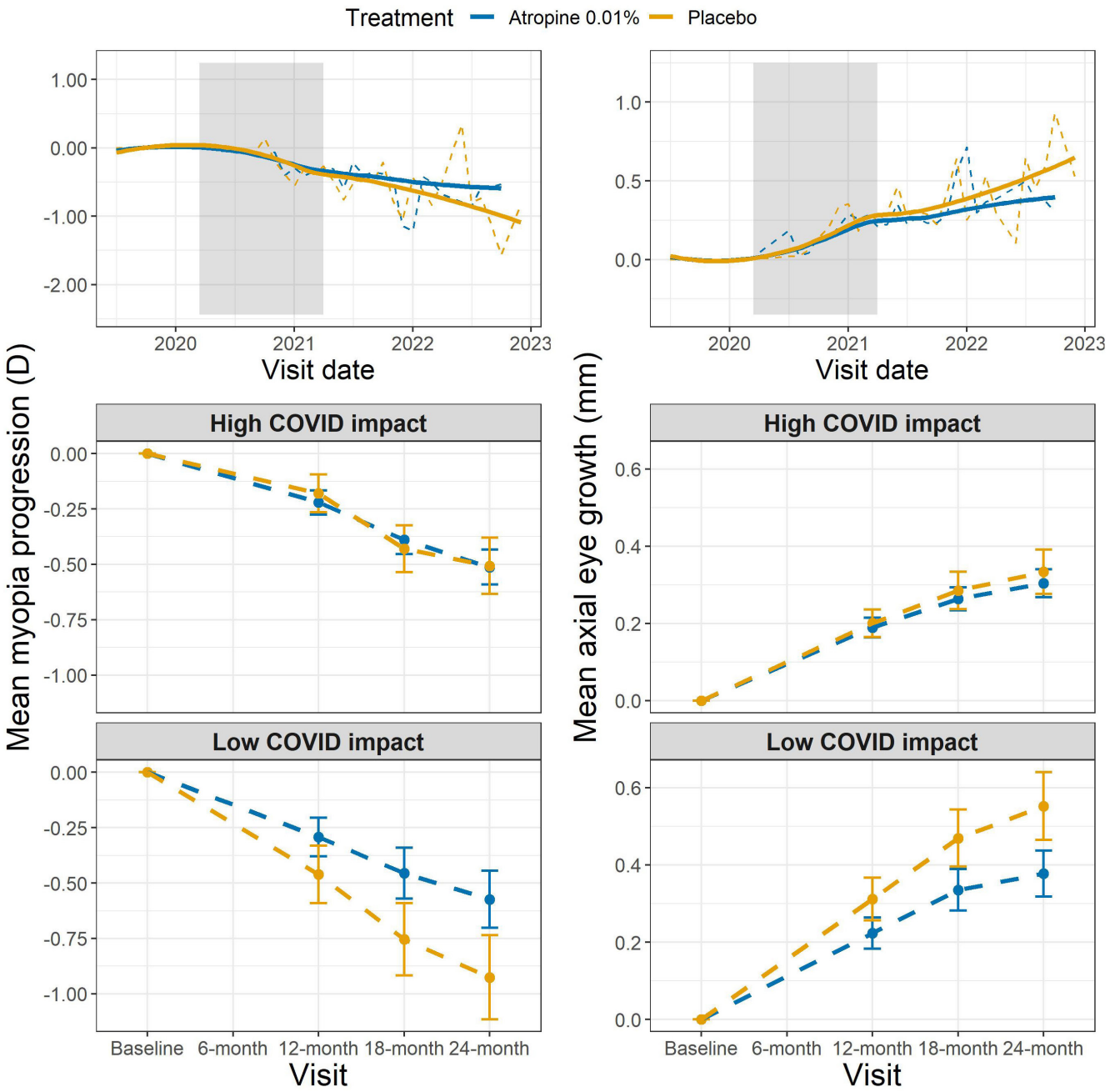

FIGURE 4 Spherical equivalent refraction and axial length change in 0.01% atropine and placebo groups for high and low COVID-19 impact groups. *Top Panel*—Spherical equivalent refraction and axial length change in 0.01% atropine and placebo groups by visit data. The grey shaded area shows the time during which school closures due to the COVID-19 pandemic occurred (March 2020–Sep 2020 and Jan 2021–March 2021). The dashed and solid lines show the raw and Loess smoothed mean change from baseline in each month, respectively. *Middle and Bottom Panel*—Change in spherical equivalent refraction and axial length in the treatment and placebo groups for participants enrolled in the study prior to the first COVID lockdown (High COVID Impact) and for participants enrolled after the end of the first COVID lockdown (Low COVID Impact). Differences shown are from raw data (i.e., not model estimated), but p values are derived from a linear mixed model including random intercepts for eye nested with participant ID, a treatment group by visit interaction and adjusting for the outcome value at the baseline visit. D, diopters; mm, millimetres.

treatment period in the first investigation of this higher concentration in European children.

5 | CONCLUSION

The MOSAIC trial results extend previous observations that 0.01% atropine slows myopia progression and axial elongation in children. While the effects were clinically modest, the potential influence of COVID-19 restrictions needs to be considered. Treatment efficacy varied by ethnicity and eye colour, reinforcing the importance of extending the evidence-base for low-concentration atropine to include more ethnically diverse populations.

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CONFLICT OF INTEREST STATEMENT

JL—Ocumetra, Topcon, Vyluma, Coopervision, Dopavision; EKA—None; GL—None; JB—None; EL—None; SSYL—None; DM—None; IF—Ocumetra, Topcon, Vyluma, Sightglass, Coopervision, Johnson & Johnson, Essilor, Thea.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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