

## Supplementary Online Content

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### eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

## Supplementary Methods.

### Storage:

Trial medication was stored at room temperature 20°C to 25° C (68° F to 77° F) with excursions permitted. A room temperature log was maintained at each study site. The participant or their parent/guardian were instructed not to store or place the study medication where it could be exposed to extreme temperatures (e.g., leaving it in a hot car).

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### Administration and Dispensing:

Site personnel instructed the participant or their parent/guardian on the proper drop instillation technique at the screening/baseline visit using the provided artificial tear ampule. If the participant was deemed old enough to administer the drops, he or she was allowed to administer the drops from the artificial tear ampule under site supervision, at which point the decision was made as to whether the participant could self-administer study medication.

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The key instruction points were as follows:

- Administer the drops in a supine or seated position.
- Twist the top off the ampule (the top can be discarded; the ampule will not be re-used).
- Tilt the head back, gently pull the lower eyelid down, and holding the ampule almost vertically, drop 1 full drop into the conjunctival cul-de-sac without touching the tip of the ampule to the eye.
- To avoid the potential of eye injury and contamination be careful not to touch the ampule tip to the eye or other surfaces.

- If a full drop is not instilled into the eye, the participant or caregiver (parent/guardian or trained individual) should wait approximately 10 to 15 seconds and administer a second drop.
- Keep the eyes gently closed for approximately 30 seconds after the drop is instilled.
- Place the open ampule and remaining contents in the provided receptacle that will be returned to the study center for proper disposal.

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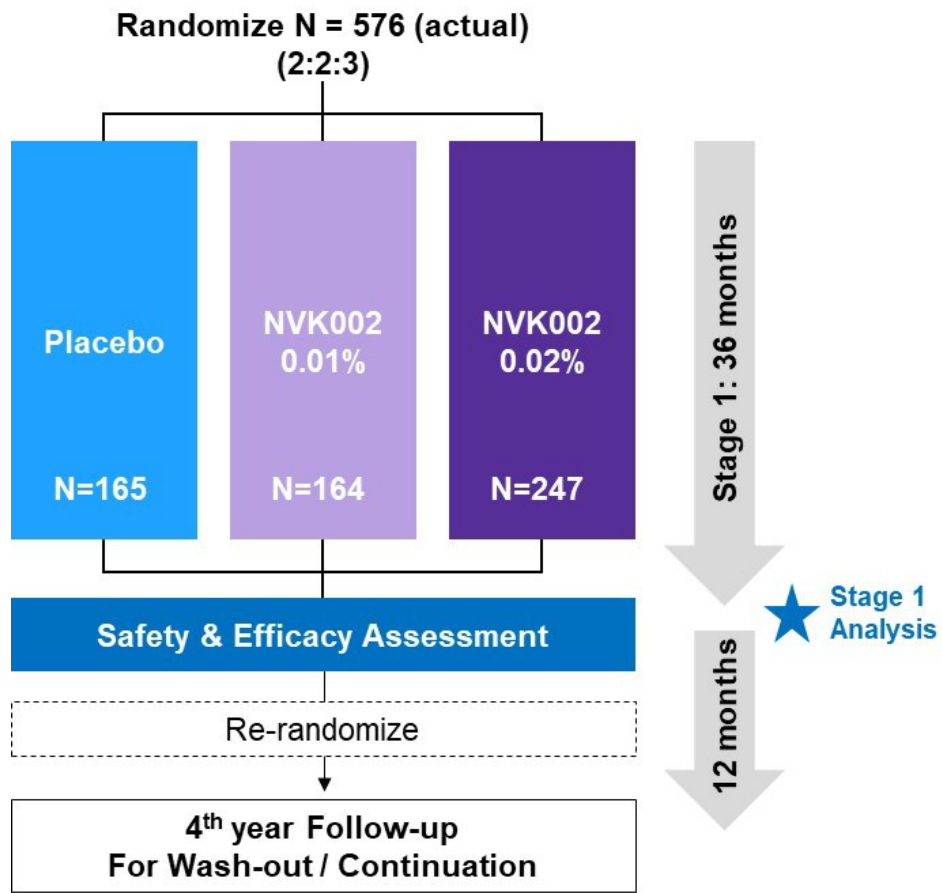
First Dose of Study Medication: The participant (or caregiver, if the participant was not able to self-administer the medication) administered 1 full drop of the study medication into each eye from a single unit dose ampule at bedtime the evening of the randomization visit. Each subsequent evening of dosing, the participant or caregiver administered one full drop into each eye from a single new ampule and the eyes were closed gently for 30 seconds. The used ampule was placed in the provided receptacle for return to the study site.

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Participants received a pair of eyeglasses every 6 months, if needed, as incentives to participate in the trial. Coverage for travel and meals was provided as needed.

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85 **Figure S1. Trial design.**

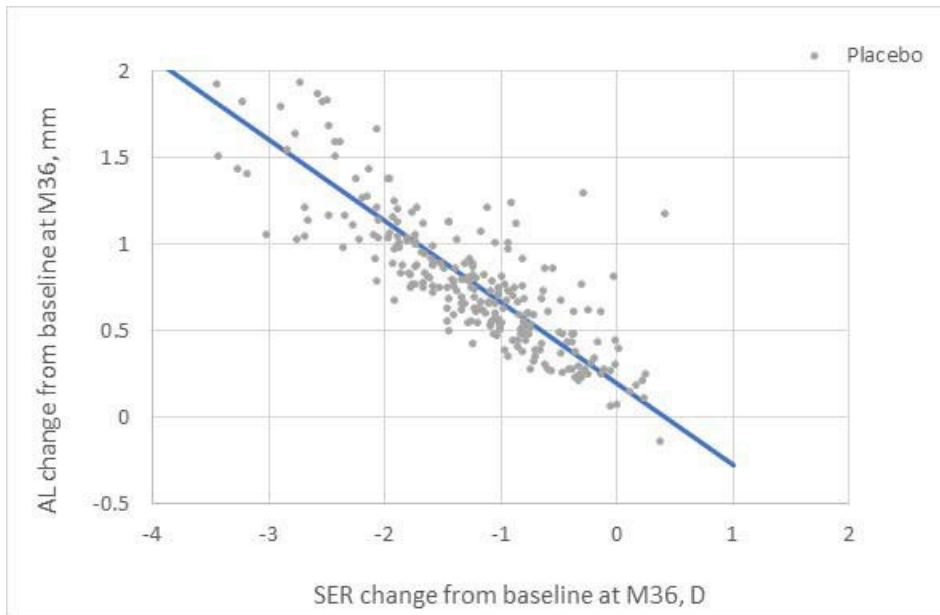


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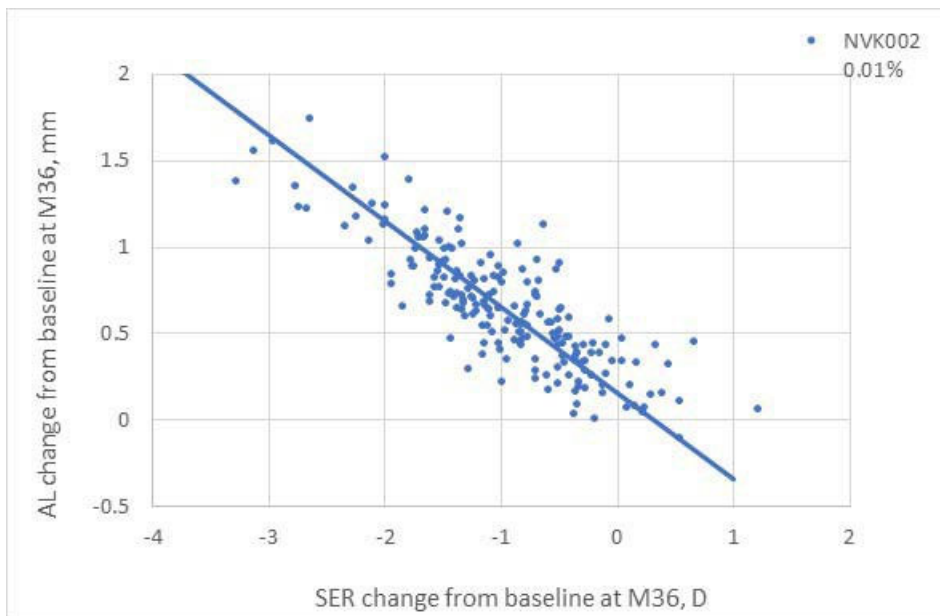
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**Figure S2. Correlation between axial length change from baseline and SER change from baseline at Month 36 for the 3 treatment groups (mITT set).**

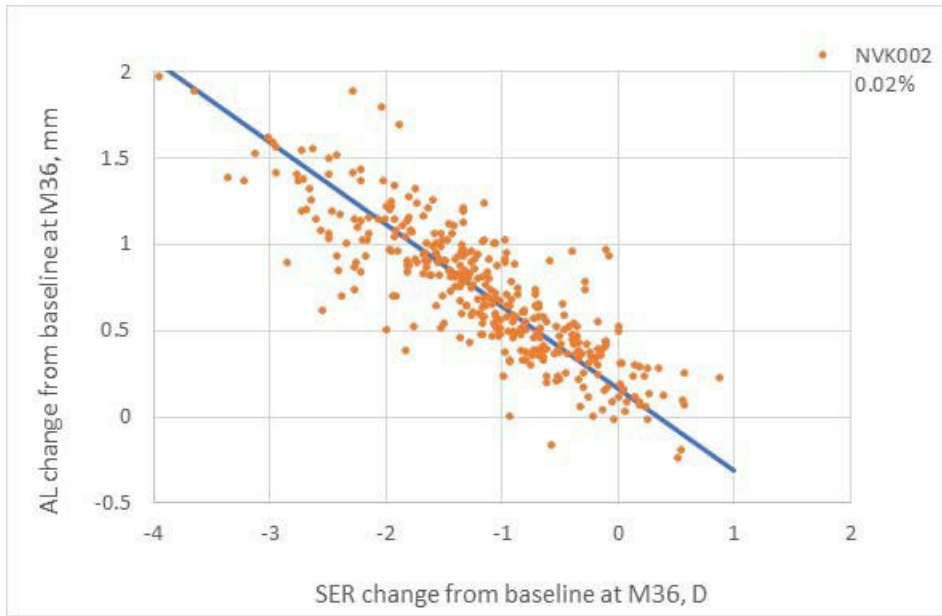
Each point represents 1 eye. For placebo, the Deming regression slope is  $-0.47$  (95% CI,  $-0.52$ ,  $-0.43$ ,  $P < .001$ ), and Pearson product-moment correlation coefficient is  $-0.79$  (95% CI,  $-0.83$ ,  $-0.74$ ,  $P < .001$ ). For NVK002 0.01%, the Deming regression slope is  $-0.50$  (95% CI,  $-0.57$ ,  $-0.44$ ,  $P < .001$ ), and Pearson product-moment correlation coefficient is  $-0.74$  (95% CI,  $-0.80$ ,  $-0.68$ ,  $P < .001$ ). For NVK002 0.02%, the Deming regression slope is  $-0.47$  (95% CI,  $-0.49$ ,  $-0.46$ ,  $P < .001$ ), and Pearson product-moment correlation coefficient is  $-0.85$  (95% CI,  $-0.88$ ,  $-0.82$ ,  $P < .001$ ).



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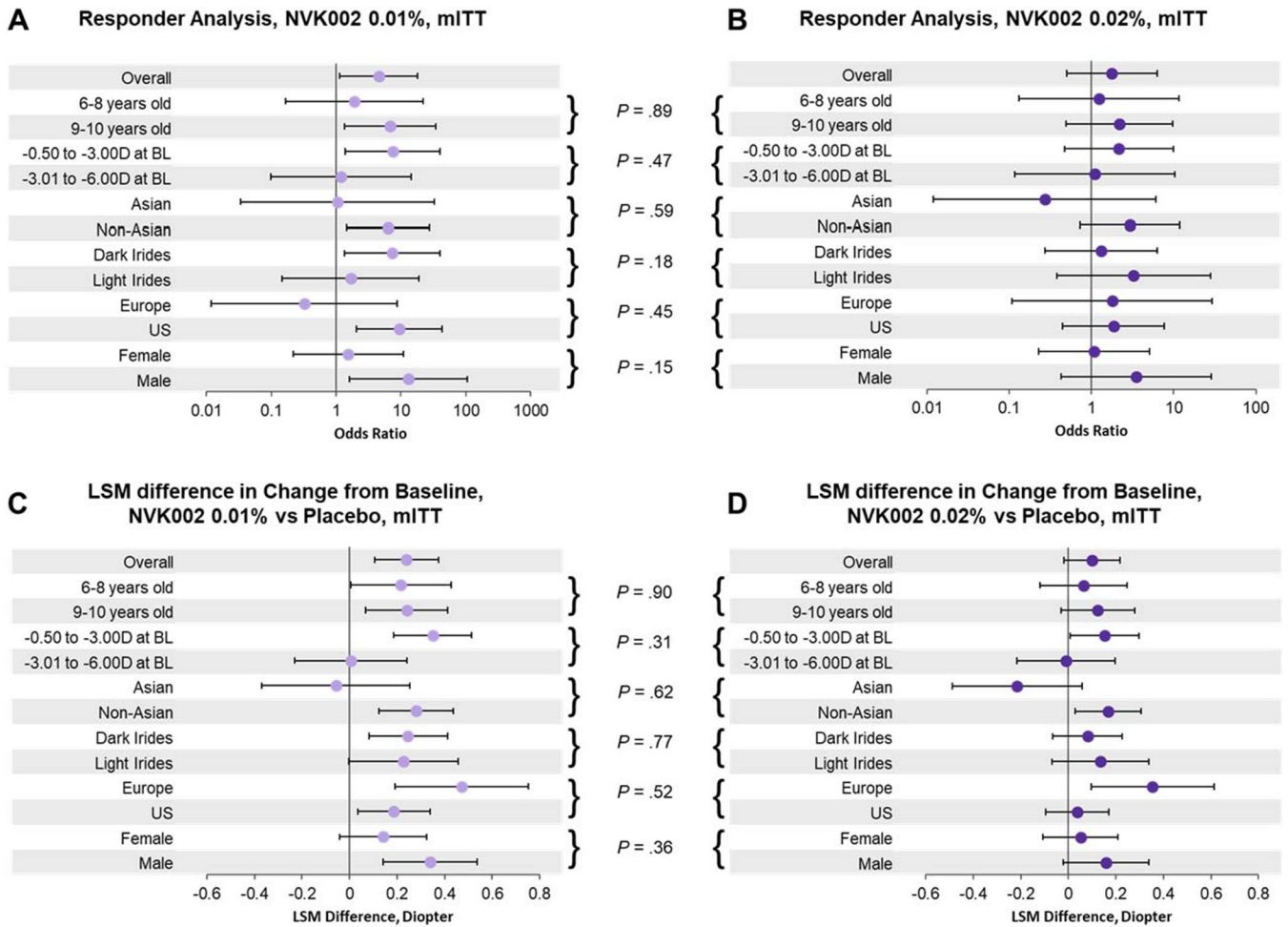
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AL, axial length; CI, confidence interval; D, diopter; mITT, modified intent-to-treat; SER, spherical equivalent refractive error. 102

103 **Figure S3. Subgroup and subgroup-by-treatment interaction analyses (mITT set).**



104 *P* values represent statistics of overall subgroup-by-treatment interaction. Error bars represent 95% CI of for odds ratio (atropine/placebo) or LSM difference (atropine – placebo). BL, baseline; EU, European Union; LSM, least squares mean; mITT, modified intent-to-treat; US, United States.

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**Table S1. Baseline age and Asian/non-Asian distribution (ITT set).**

	<b>Subgroup</b>	<b>Placebo (n = 165)</b>	<b>NVK002 0.01% (n = 164)</b>	<b>NVK002 0.02% (n = 247)</b>	
Age subgroup, n	3-5 years	5	9	7	Chi square test <i>P</i> = .73
	6-8 years	58	55	87	
	9-10 years	86	78	125	
	11-16 years	16	22	28	
Race subgroup, n	Asian	26	29	54	Chi square test <i>P</i> = .27
	Non-Asian	139	135	193	

Abbreviation: ITT, intent-to-treat. 119

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**Table S2. Efficacy Measures by Visit (mITT set).**

	<b>Placebo (n = 144)</b>	<b>NVK002 0.01% (n = 133)</b>	<b>NVK002 0.02% (n = 212)</b>
<b>Responder Analysis: Number (%) of eyes with less than 0.50 D myopia progression</b>			
Month 12	116 (47.5)	131 (60.6)	218 (60.6)
Odds ratio for NVK002/placebo (95% CI)		3.90 (1.35, 11.26)	4.78 (1.75, 13.04)
<i>P</i> value		.01	.002
Month 24	63 (26.5)	71 (36.6)	106 (30.6)
Odds ratio for NVK002/placebo (95% CI)		3.39 (1.00, 11.44)	1.52 (0.49, 4.71)
<i>P</i> value		.05	.46
Month 36	44 (17.5)	57 (28.2)	81 (22.1)
Odds ratio for NVK002/placebo (95% CI)		4.54 (1.15, 17.97)	1.77 (0.50, 6.26)
<i>P</i> value		.03	.37
<b>Refractive Measure: Least squares mean change (95% CI) from baseline in SER, D</b>			
Month 12	-0.57 (-0.66, -0.47)	-0.45 (-0.55, -0.35)	-0.45 (-0.53, -0.37)
Least squares mean difference (95% CI) between NVK002 and placebo		0.12 (-0.01, 0.25)	0.12 (0.00, 0.24)
<i>P</i> value		.08	.05
Month 24	-1.00 (-1.10, -0.91)	-0.79 (-0.89, -0.69)	-0.90 (-0.98, -0.82)
Least squares mean difference (95% CI) between NVK002 and placebo		0.22 (0.08, 0.35)	0.11 (-0.01, 0.23)
<i>P</i> value		.002	.08

Month 36	-1.28 (-1.37, -1.19)	-1.04 (-1.14, -0.94)	-1.18 (-1.26, -1.10)
Least squares mean difference (95% CI) between NVK002 and placebo		0.24 (0.11, 0.37)	0.10 (-0.02, 0.22)
<i>P</i> value		<.001	.10
<b>Biometric Measure: Least squares mean change (95% CI) from baseline in axial length (SD), mm</b>			
Month 12	0.37 (0.32, 0.41)	0.30 (0.25, 0.34)	0.30 (0.27, 0.34)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.07 (-0.13, -0.01)	-0.06 (-0.12, -0.01)
<i>P</i> value		.03	.02
Month 24	0.63 (0.58, 0.67)	0.51 (0.46, 0.56)	0.56 (0.52, 0.59)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.12 (-0.18, -0.06)	-0.07 (-0.12, -0.02)
<i>P</i> value		<.001	.01
Month 36	0.81 (0.76, 0.85)	0.68 (0.63, 0.72)	0.73 (0.69, 0.76)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.13 (-0.19, -0.07)	-0.08 (-0.13, -0.02)
<i>P</i> value		<.001	.005

Abbreviations: CI, confidence interval; D, diopter; mITT, modified intent-to-treat; SD, standard deviation; SER, spherical equivalent refractive error.

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**Table S3. Post-hoc analysis comparing 0.01% vs 0.02% (mITT set).**

	<b>Month 36</b>	<b>95% CI</b>	
0.5 D responder analysis	Odds ratio (0.01%/0.02%) = 2.6	0.77, 8.57	<i>P</i> = .13
SER change from baseline	LSM Difference (0.01% – 0.02%) = 0.14 D	0.02, 0.26	<i>P</i> = .03
AL change from baseline	LSM Difference (0.01% – 0.02%) = –0.05	–0.11, 0.00	<i>P</i> = .07

Abbreviations: AL, axial length; CI, confidence interval; D, diopter; LSM, least squares mean; mITT, modified intent-to-treat; SER, spherical equivalent refractive error. 129

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**Table S4. Post hoc analyses on primary and secondary endpoints (mITT Month 36)  
Excluding post-last dose data from 23 participants who discontinued trial treatment, stayed in trial, and switched to orthokeratology or multifocal contact lens (MFCL) or compounded atropine.**

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Endpoints	Statistics	Pre-specified Analysis	Excluding post-last dose data of Orthokeratology / MFCL / atropine switchers
1. Proportion of participants' eyes with less than 0.5 D myopia progression at M36, <b>0.02%</b> vs vehicle, mITT	Odds ratio (95% CI)	<b>1.8</b> (0.50, 6.26), <i>P</i> = .37	<b>2.5</b> (0.71, 8.7), <i>P</i> = .16
	Absolute risk difference (unmodeled % participants)	<b>4.7%</b>	<b>5.3%</b>
2-1. Mean change from baseline in SER at M36, <b>0.02%</b> vs vehicle, mITT	Least square mean difference (95% CI)	<b>0.099 D</b> (-0.02, 0.22), <i>P</i> = .10	<b>0.15 D</b> (0.03, 0.26), <i>P</i> = .013 *
2-2. Proportion of participants' eyes with less than 0.5 D myopia progression at M36, <b>0.01%</b> vs vehicle, mITT	Odds ratio (95% CI)	<b>4.5</b> (1.15, 18), <i>P</i> = .03 *	<b>7.3</b> (1.9, 28.5), <i>P</i> = .004 *
	Absolute risk difference (unmodeled % participants)	<b>11%</b>	<b>12%</b>
2-3. Mean change from baseline in SER at M36, <b>0.01%</b> vs vehicle, mITT	Least square mean difference (95% CI)	<b>0.24 D</b> (0.11, 0.37), <i>P</i> < .001 *	<b>0.26 D</b> (0.13, 0.39), <i>P</i> < .001 *

\*Of these 23 participants, 9 were in the placebo, 6 in the NVK002 0.01%, and 8 in the 0.02% group. Abbreviations: CI, confidence interval; D, diopter; mITT, modified intent-to-treat; SER, spherical equivalent refractive error. 138

Table S5. Efficacy Measures by Visit (ITT set).

	Placebo (n = 165)	NVK002 0.01% (n = 164)	NVK002 0.02% (n = 247)
<b>Responder Analysis: Number (%) of eyes with less than 0.50 D myopia progression</b>			
Month 12	142 (50.4)	169 (63.1)	262 (62.7)
Odds ratio for NVK002/placebo (95% CI)		4.25 (1.50, 11.98)	4.65 (1.75, 12.39)
<i>P</i> value		.006	.002
Month 24	78 (29.3)	95 (40.6)	130 (34.0)
Odds ratio for NVK002/placebo (95% CI)		3.96 (1.26, 12.49)	1.78 (0.61, 5.25)
<i>P</i> value		.02	.29
Month 36	61 (21.3)	79 (31.6)	106 (25.6)
Odds ratio for NVK002/placebo (95% CI)		3.90 (1.10, 13.87)	1.56 (0.48, 5.10)
<i>P</i> value		.04	.46
<b>Refractive Measure: Least squares mean change (95% CI) from baseline in SER, D</b>			
Month 12	-0.57 (-0.66, -0.49)	-0.43 (-0.52, -0.34)	-0.45 (-0.52, -0.37)
Least squares mean difference (95% CI) between NVK002 and placebo		0.14 (0.02, 0.26)	0.13 (0.02, 0.24)
<i>P</i> value		.03	.03
Month 24	-0.99 (-1.08, -0.90)	-0.74 (-0.84, -0.65)	-0.86 (-0.94, -0.79)
Least squares mean difference (95% CI) between NVK002 and placebo		0.25 (0.12, 0.37)	0.13 (0.02, 0.24)
<i>P</i> value		<.001	.02

Month 36	-1.26 (-1.35, -1.17)	-1.00 (-1.09, -0.91)	-1.12 (-1.20, -1.05)
Least squares mean difference (95% CI) between NVK002 and placebo		0.25 (0.13, 0.38)	0.13 (0.02, 0.24)
<i>P</i> value		<.001	.02
<b>Biometric Measure: Least squares mean change (95% CI) from baseline in axial length (SD), mm</b>			
Month 12	0.37 (0.32, 0.41)	0.27 (0.22, 0.31)	0.30 (0.26, 0.34)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.10 (-0.16, -0.04)	-0.07 (-0.13, -0.01)
<i>P</i> value		.002	.02
Month 24	0.61 (0.57, 0.66)	0.48 (0.43, 0.52)	0.54 (0.50, 0.57)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.14 (-0.20, -0.07)	-0.08 (-0.13, -0.02)
<i>P</i> value		<.001	.01
Month 36	0.78 (0.74, 0.83)	0.65 (0.61, 0.70)	0.70 (0.66, 0.73)
Least squares mean difference (95% CI) between NVK002 and placebo		-0.13 (-0.19, -0.07)	-0.08 (-0.14, -0.03)
<i>P</i> value		<.001	.004

Abbreviations: CI, confidence interval; D, diopter; ITT, intent-to-treat; SD, standard deviation; SER, spherical equivalent refractive error.

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	Placebo (n = 165)	NVK002 0.01% (n = 164)	NVK002 0.02% (n = 247)	Total (N = 576)
<b>Table S6. Compliance to trial medication (ITT set).</b>				
<b>Compliance to study medication, %</b>				

N	143	141	212	496
Mean	87.07	86.42	88.29	87.41
Standard deviation	17.67	19.54	13.18	16.50
Median	93.03	93.32	92.08	92.85
Minimum, Maximum	0.00, 107.71	0.00, 107.43	0.00, 108.67	0.00, 108.67

Study medication accountability was assessed every 3 months upon return of unused ampules and used ampules. Compliance is calculated as (number of ampules used) / [(date of last dose of stage 1 - date of first dose of stage 1) +1] x 100. Abbreviation: ITT, intent-to-treat

147 **Table S7. Complete list of treatment-emergent adverse events (safety set).**

<b>System Organ Class Preferred Term</b>	<b>Placebo (n = 162) n (%)</b>	<b>NVK002 0.01% (n = 164) n (%)</b>	<b>NVK002 0.02% (n = 247) n (%)</b>	<b>Total (n = 573) n (%)</b>
<b>Any treatment-emergent adverse event</b>	<b>116 (71.6)</b>	<b>98 (59.8)</b>	<b>163 (66.0)</b>	<b>377 (65.8)</b>
<b>Infections and infestations</b>	<b>74 (45.7)</b>	<b>50 (30.5)</b>	<b>89 (36.0)</b>	<b>213 (37.2)</b>
Nasopharyngitis	22 (13.6)	17 (10.4)	30 (12.1)	69 (12.0)
COVID-19	18 (11.1)	9 (5.5)	27 (10.9)	54 (9.4)
Influenza	12 (7.4)	6 (3.7)	8 (3.2)	26 (4.5)
Hordeolum	11 (6.8)	3 (1.8)	10 (4.0)	24 (4.2)
Upper respiratory tract infection	7 (4.3)	3 (1.8)	8 (3.2)	18 (3.1)
Pharyngitis streptococcal	8 (4.9)	2 (1.2)	6 (2.4)	16 (2.8)
Gastroenteritis viral	6 (3.7)	2 (1.2)	5 (2.0)	13 (2.3)
Conjunctivitis	5 (3.1)	2 (1.2)	4 (1.6)	11 (1.9)
Ear infection	6 (3.7)	2 (1.2)	3 (1.2)	11 (1.9)
Pneumonia	2 (1.2)	3 (1.8)	5 (2.0)	10 (1.7)
Sinusitis	4 (2.5)	3 (1.8)	2 (0.8)	9 (1.6)
Conjunctivitis bacterial	1 (0.6)	1 (0.6)	3 (1.2)	5 (0.9)
Lower respiratory tract infection	2 (1.2)	1 (0.6)	2 (0.8)	5 (0.9)
Urinary tract infection	1 (0.6)	1 (0.6)	3 (1.2)	5 (0.9)
Appendicitis	2 (1.2)	0	2 (0.8)	4 (0.7)
Conjunctivitis viral	3 (1.9)	0	1 (0.4)	4 (0.7)
Bronchitis	2 (1.2)	1 (0.6)	0	3 (0.5)
Otitis externa	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)
Pharyngitis	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)
Varicella	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)



Hand-foot-and-mouth disease	0	1 (0.6)	1 (0.4)	2 (0.3)
Impetigo	1 (0.6)	0	1 (0.4)	2 (0.3)
Infected bite	1 (0.6)	0	1 (0.4)	2 (0.3)
Localised infection	1 (0.6)	1 (0.6)	0	2 (0.3)
Lyme disease	1 (0.6)	1 (0.6)	0	2 (0.3)
Otitis media	1 (0.6)	0	1 (0.4)	2 (0.3)
Respiratory tract infection viral	0	0	2 (0.8)	2 (0.3)
Acrodermatitis	0	1 (0.6)	0	1 (0.2)
Adenoiditis	1 (0.6)	0	0	1 (0.2)
Atypical pneumonia	0	0	1 (0.4)	1 (0.2)
Candida infection	0	0	1 (0.4)	1 (0.2)
Chronic tonsillitis	1 (0.6)	0	0	1 (0.2)
Coronavirus infection	0	0	1 (0.4)	1 (0.2)
Coxsackie viral infection	1 (0.6)	0	0	1 (0.2)
Croup infectious	0	1 (0.6)	0	1 (0.2)
Ear lobe infection	1 (0.6)	0	0	1 (0.2)
Enterovirus infection	0	0	1 (0.4)	1 (0.2)
Eye infection viral	0	1 (0.6)	0	1 (0.2)
Folliculitis	1 (0.6)	0	0	1 (0.2)
Fungal skin infection	0	1 (0.6)	0	1 (0.2)
Gastroenteritis	1 (0.6)	0	0	1 (0.2)
Gastroenteritis norovirus	0	1 (0.6)	0	1 (0.2)
Gastrointestinal viral infection	0	1 (0.6)	0	1 (0.2)
Herpes virus infection	1 (0.6)	0	0	1 (0.2)
Infectious mononucleosis	1 (0.6)	0	0	1 (0.2)
Keratitis bacterial	0	1 (0.6)	0	1 (0.2)
Kidney infection	1 (0.6)	0	0	1 (0.2)
Parainfluenzae virus infection	0	1 (0.6)	0	1 (0.2)

Paronychia	1 (0.6)	0	0	1 (0.2)
Respiratory syncytial virus infection	0	1 (0.6)	0	1 (0.2)
Rhinitis	0	0	1 (0.4)	1 (0.2)
Staphylococcal infection	1 (0.6)	0	0	1 (0.2)
Suspected COVID-19	0	0	1 (0.4)	1 (0.2)
Tinea capitis	1 (0.6)	0	0	1 (0.2)
Tinea pedis	0	0	1 (0.4)	1 (0.2)
Tonsillitis	1 (0.6)	0	0	1 (0.2)
Viral infection	0	1 (0.6)	0	1 (0.2)
Viral sinusitis	0	0	1 (0.4)	1 (0.2)
Viral tonsillitis	0	1 (0.6)	0	1 (0.2)
Viral upper respiratory tract infection	0	1 (0.6)	0	1 (0.2)
<b>Eye disorders</b>	<b>47 (29.0)</b>	<b>34 (20.7)</b>	<b>54 (21.9)</b>	<b>135 (23.6)</b>
Ocular hyperaemia	10 (6.2)	4 (2.4)	8 (3.2)	22 (3.8)
Photophobia	5 (3.1)	4 (2.4)	11 (4.5)	20 (3.5)
Conjunctivitis allergic	5 (3.1)	3 (1.8)	11 (4.5)	19 (3.3)
Eye pruritus	5 (3.1)	4 (2.4)	5 (2.0)	14 (2.4)
Eye allergy	5 (3.1)	4 (2.4)	4 (1.6)	13 (2.3)
Eye irritation	6 (3.7)	1 (0.6)	2 (0.8)	9 (1.6)
Chalazion	5 (3.1)	3 (1.8)	0	8 (1.4)
Eye pain	4 (2.5)	3 (1.8)	1 (0.4)	8 (1.4)
Punctate keratitis	4 (2.5)	2 (1.2)	2 (0.8)	8 (1.4)
Blepharitis	3 (1.9)	2 (1.2)	1 (0.4)	6 (1.0)
Mydriasis	0	2 (1.2)	4 (1.6)	6 (1.0)
Vision blurred	0	2 (1.2)	4 (1.6)	6 (1.0)
Noninfective conjunctivitis	3 (1.9)	2 (1.2)	0	5 (0.9)

Dry eye	1 (0.6)	1 (0.6)	2 (0.8)	4 (0.7)
Swelling of eyelid	0	3 (1.8)	1 (0.4)	4 (0.7)
Binocular eye movement disorder	2 (1.2)	1 (0.6)	0	3 (0.5)
Eyelid irritation	1 (0.6)	0	2 (0.8)	3 (0.5)
Accommodation disorder	1 (0.6)	1 (0.6)	0	2 (0.3)
Asthenopia	0	1 (0.6)	1 (0.4)	2 (0.3)
Conjunctival haemorrhage	1 (0.6)	1 (0.6)	0	2 (0.3)
Erythema of eyelid	1 (0.6)	1 (0.6)	0	2 (0.3)
Excessive ocular convergence	0	2 (1.2)	0	2 (0.3)
Lacrimation increased	0	1 (0.6)	1 (0.4)	2 (0.3)
Visual impairment	0	0	2 (0.8)	2 (0.3)
Vitreous floaters	1 (0.6)	1 (0.6)	0	2 (0.3)
Abnormal sensation in eye	0	0	1 (0.4)	1 (0.2)
Anisocoria	0	0	1 (0.4)	1 (0.2)
Atopic keratoconjunctivitis	1 (0.6)	0	0	1 (0.2)
Borderline glaucoma	0	0	1 (0.4)	1 (0.2)
Conjunctival hyperaemia	1 (0.6)	0	0	1 (0.2)
Corneal infiltrates	0	0	1 (0.4)	1 (0.2)
Corneal opacity	0	1 (0.6)	0	1 (0.2)
Episcleritis	0	1 (0.6)	0	1 (0.2)
Eye discharge	0	0	1 (0.4)	1 (0.2)
Eye disorder	0	0	1 (0.4)	1 (0.2)
Eye haemorrhage	0	0	1 (0.4)	1 (0.2)
Eye inflammation	1 (0.6)	0	0	1 (0.2)
Eye swelling	0	0	1 (0.4)	1 (0.2)
Eyelid cyst	1 (0.6)	0	0	1 (0.2)
Eyelid pain	0	0	1 (0.4)	1 (0.2)
Eyelid rash	0	0	1 (0.4)	1 (0.2)

Heterophoria	0	0	1 (0.4)	1 (0.2)
Iris disorder	1 (0.6)	0	0	1 (0.2)
Ophthalmoplegia	0	1 (0.6)	0	1 (0.2)
Papilloedema	0	0	1 (0.4)	1 (0.2)
Photokeratitis	0	1 (0.6)	0	1 (0.2)
Pinguecula	1 (0.6)	0	0	1 (0.2)
Retinal degeneration	0	0	1 (0.4)	1 (0.2)
Retinal detachment	0	1 (0.6)	0	1 (0.2)
Strabismus	1 (0.6)	0	0	1 (0.2)
Trichiasis	0	0	1 (0.4)	1 (0.2)
Visual acuity reduced	0	0	1 (0.4)	1 (0.2)
<b>Nervous system disorders</b>	<b>18 (11.1)</b>	<b>20 (12.2)</b>	<b>29 (11.7)</b>	<b>67 (11.7)</b>
Headache	14 (8.6)	14 (8.5)	23 (9.3)	51 (8.9)
Dizziness	3 (1.9)	1 (0.6)	4 (1.6)	8 (1.4)
Migraine	0	3 (1.8)	4 (1.6)	7 (1.2)
Ataxia	0	1 (0.6)	0	1 (0.2)
Epilepsy	1 (0.6)	0	0	1 (0.2)
Idiopathic intracranial hypertension	0	0	1 (0.4)	1 (0.2)
Lethargy	0	1 (0.6)	0	1 (0.2)
Ophthalmic migraine	1 (0.6)	0	0	1 (0.2)
Seizure	1 (0.6)	0	0	1 (0.2)
Sinus headache	0	1 (0.6)	0	1 (0.2)
Somnolence	0	1 (0.6)	0	1 (0.2)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>22 (13.6)</b>	<b>14 (8.5)</b>	<b>26 (10.5)</b>	<b>62 (10.8)</b>
Cough	9 (5.6)	3 (1.8)	7 (2.8)	19 (3.3)
Oropharyngeal pain	7 (4.3)	4 (2.4)	7 (2.8)	18 (3.1)

Nasal congestion	3 (1.9)	2 (1.2)	3 (1.2)	8 (1.4)
Rhinorrhoea	3 (1.9)	1 (0.6)	3 (1.2)	7 (1.2)
Asthma	2 (1.2)	3 (1.8)	1 (0.4)	6 (1.0)
Sinus congestion	0	2 (1.2)	3 (1.2)	5 (0.9)
Epistaxis	1 (0.6)	0	2 (0.8)	3 (0.5)
Allergic sinusitis	0	1 (0.6)	1 (0.4)	2 (0.3)
Asthma exercise induced	0	1 (0.6)	1 (0.4)	2 (0.3)
Rhinitis allergic	2 (1.2)	0	0	2 (0.3)
Allergic bronchitis	0	0	1 (0.4)	1 (0.2)
Dyspnoea	0	1 (0.6)	0	1 (0.2)
Increased viscosity of upper respiratory secretion	1 (0.6)	0	0	1 (0.2)
Nasal dryness	0	0	1 (0.4)	1 (0.2)
Nasal obstruction	1 (0.6)	0	0	1 (0.2)
Sleep apnoea syndrome	1 (0.6)	0	0	1 (0.2)
Snoring	1 (0.6)	0	0	1 (0.2)
Tonsillar hypertrophy	1 (0.6)	0	0	1 (0.2)
Upper-airway cough syndrome	0	1 (0.6)	0	1 (0.2)
Wheezing	0	0	1 (0.4)	1 (0.2)
<b>Injury, poisoning and procedural complications</b>	<b>24 (14.8)</b>	<b>13 (7.9)</b>	<b>22 (8.9)</b>	<b>59 (10.3)</b>
Ligament sprain	4 (2.5)	4 (2.4)	1 (0.4)	9 (1.6)
Hand fracture	3 (1.9)	1 (0.6)	1 (0.4)	5 (0.9)
Fall	0	1 (0.6)	3 (1.2)	4 (0.7)
Foreign body in eye	2 (1.2)	0	2 (0.8)	4 (0.7)
Skin laceration	1 (0.6)	1 (0.6)	2 (0.8)	4 (0.7)
Vaccination complication	2 (1.2)	1 (0.6)	1 (0.4)	4 (0.7)
Arthropod bite	3 (1.9)	0	0	3 (0.5)

Upper limb fracture	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)
Wrist fracture	1 (0.6)	0	2 (0.8)	3 (0.5)
Corneal abrasion	0	1 (0.6)	1 (0.4)	2 (0.3)
Eyelid injury	1 (0.6)	0	1 (0.4)	2 (0.3)
Foot fracture	0	0	2 (0.8)	2 (0.3)
Joint injury	0	1 (0.6)	1 (0.4)	2 (0.3)
Animal bite	0	0	1 (0.4)	1 (0.2)
Arthropod sting	0	1 (0.6)	0	1 (0.2)
Chest injury	0	1 (0.6)	0	1 (0.2)
Clavicle fracture	1 (0.6)	0	0	1 (0.2)
Commotio retinae	0	1 (0.6)	0	1 (0.2)
Concussion	1 (0.6)	0	0	1 (0.2)
Epicondylitis	0	0	1 (0.4)	1 (0.2)
Eye contusion	1 (0.6)	0	0	1 (0.2)
Eye injury	0	0	1 (0.4)	1 (0.2)
Fibula fracture	0	0	1 (0.4)	1 (0.2)
Injury corneal	0	0	1 (0.4)	1 (0.2)
Limb injury	0	1 (0.6)	0	1 (0.2)
Muscle strain	0	1 (0.6)	0	1 (0.2)
Post-traumatic pain	0	0	1 (0.4)	1 (0.2)
Procedural pain	1 (0.6)	0	0	1 (0.2)
Radius fracture	0	0	1 (0.4)	1 (0.2)
Road traffic accident	1 (0.6)	0	0	1 (0.2)
Scratch	1 (0.6)	0	0	1 (0.2)
Skin injury	0	1 (0.6)	0	1 (0.2)
Stress fracture	1 (0.6)	0	0	1 (0.2)
Tendon rupture	0	0	1 (0.4)	1 (0.2)
Tibia fracture	0	0	1 (0.4)	1 (0.2)

Tooth injury	1 (0.6)	0	0	1 (0.2)
Traumatic iritis	0	1 (0.6)	0	1 (0.2)
<b>Immune system disorders</b>	<b>14 (8.6)</b>	<b>19 (11.6)</b>	<b>24 (9.7)</b>	<b>57 (9.9)</b>
Seasonal allergy	9 (5.6)	12 (7.3)	14 (5.7)	35 (6.1)
Hypersensitivity	2 (1.2)	4 (2.4)	6 (2.4)	12 (2.1)
Immunisation reaction	2 (1.2)	3 (1.8)	1 (0.4)	6 (1.0)
Allergy to animal	0	0	2 (0.8)	2 (0.3)
Allergy to arthropod sting	0	2 (1.2)	0	2 (0.3)
Allergy to arthropod bite	0	0	1 (0.4)	1 (0.2)
Drug hypersensitivity	0	0	1 (0.4)	1 (0.2)
Food allergy	0	0	1 (0.4)	1 (0.2)
Milk allergy	0	0	1 (0.4)	1 (0.2)
Perennial allergy	1 (0.6)	0	0	1 (0.2)
<b>General disorders and administration site conditions</b>	<b>15 (9.3)</b>	<b>14 (8.5)</b>	<b>27 (10.9)</b>	<b>56 (9.8)</b>
Pyrexia	6 (3.7)	8 (4.9)	21 (8.5)	35 (6.1)
Instillation site pain	5 (3.1)	2 (1.2)	1 (0.4)	8 (1.4)
Fatigue	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)
Cyst	1 (0.6)	1 (0.6)	0	2 (0.3)
Influenza like illness	1 (0.6)	0	1 (0.4)	2 (0.3)
Pain	0	2 (1.2)	0	2 (0.3)
Administration site pain	0	0	1 (0.4)	1 (0.2)
Application site pain	0	0	1 (0.4)	1 (0.2)
Complication associated with device	0	0	1 (0.4)	1 (0.2)
Face oedema	0	1 (0.6)	0	1 (0.2)
Injury associated with device	0	0	1 (0.4)	1 (0.2)
Instillation site pruritus	1 (0.6)	0	0	1 (0.2)

Malaise	0	0	1 (0.4)	1 (0.2)
Swelling face	1 (0.6)	0	0	1 (0.2)
<b>Gastrointestinal disorders</b>	<b>19 (11.7)</b>	<b>9 (5.5)</b>	<b>20 (8.1)</b>	<b>48 (8.4)</b>
Vomiting	5 (3.1)	4 (2.4)	6 (2.4)	15 (2.6)
Constipation	4 (2.5)	1 (0.6)	2 (0.8)	7 (1.2)
Abdominal pain	2 (1.2)	0	3 (1.2)	5 (0.9)
Nausea	3 (1.9)	1 (0.6)	1 (0.4)	5 (0.9)
Toothache	1 (0.6)	1 (0.6)	3 (1.2)	5 (0.9)
Diarrhoea	2 (1.2)	0	2 (0.8)	4 (0.7)
Abdominal pain upper	1 (0.6)	0	2 (0.8)	3 (0.5)
Gastroesophageal reflux disease	1 (0.6)	0	2 (0.8)	3 (0.5)
Abdominal discomfort	2 (1.2)	0	0	2 (0.3)
Food poisoning	0	1 (0.6)	1 (0.4)	2 (0.3)
Anal fissure	0	0	1 (0.4)	1 (0.2)
Ascites	0	0	1 (0.4)	1 (0.2)
Autoimmune colitis	1 (0.6)	0	0	1 (0.2)
Cheilitis	1 (0.6)	0	0	1 (0.2)
Enterocolitis	0	0	1 (0.4)	1 (0.2)
Functional gastrointestinal disorder	0	0	1 (0.4)	1 (0.2)
Gingival pain	0	1 (0.6)	0	1 (0.2)
Irritable bowel syndrome	0	0	1 (0.4)	1 (0.2)
Lip dry	0	1 (0.6)	0	1 (0.2)
Lip pain	1 (0.6)	0	0	1 (0.2)
Malocclusion	0	0	1 (0.4)	1 (0.2)
Noninfective gingivitis	0	0	1 (0.4)	1 (0.2)
Rectal haemorrhage	0	0	1 (0.4)	1 (0.2)
Tooth impacted	1 (0.6)	0	0	1 (0.2)



<b>Skin and subcutaneous tissue disorders</b>	<b>17 (10.5)</b>	<b>10 (6.1)</b>	<b>17 (6.9)</b>	<b>44 (7.7)</b>
Rash	6 (3.7)	1 (0.6)	2 (0.8)	9 (1.6)
Acne	3 (1.9)	2 (1.2)	2 (0.8)	7 (1.2)
Eczema	1 (0.6)	3 (1.8)	2 (0.8)	6 (1.0)
Urticaria	3 (1.9)	0	2 (0.8)	5 (0.9)
Pruritus	1 (0.6)	0	3 (1.2)	4 (0.7)
Dermatitis contact	2 (1.2)	1 (0.6)	0	3 (0.5)
Dermatitis allergic	1 (0.6)	0	1 (0.4)	2 (0.3)
Dermatitis atopic	0	0	2 (0.8)	2 (0.3)
Ingrowing nail	1 (0.6)	0	1 (0.4)	2 (0.3)
Decubitus ulcer	0	1 (0.6)	0	1 (0.2)
Nail ridging	0	1 (0.6)	0	1 (0.2)
Rash erythematous	1 (0.6)	0	0	1 (0.2)
Rosacea	0	0	1 (0.4)	1 (0.2)
Seborrhoeic dermatitis	0	0	1 (0.4)	1 (0.2)
Skin lesion	0	1 (0.6)	0	1 (0.2)
Skin swelling	0	0	1 (0.4)	1 (0.2)
<b>Psychiatric disorders</b>	<b>4 (2.5)</b>	<b>9 (5.5)</b>	<b>15 (6.1)</b>	<b>28 (4.9)</b>
Depression	0	1 (0.6)	5 (2.0)	6 (1.0)
Anxiety	1 (0.6)	2 (1.2)	1 (0.4)	4 (0.7)
Attention deficit hyperactivity disorder	0	2 (1.2)	2 (0.8)	4 (0.7)
Autism spectrum disorder	1 (0.6)	0	1 (0.4)	2 (0.3)
Insomnia	1 (0.6)	0	1 (0.4)	2 (0.3)
Mood altered	0	1 (0.6)	1 (0.4)	2 (0.3)
Nightmare	0	1 (0.6)	1 (0.4)	2 (0.3)
Panic attack	0	1 (0.6)	1 (0.4)	2 (0.3)

Tic	0	0	2 (0.8)	2 (0.3)
Aggression	0	1 (0.6)	0	1 (0.2)
Body dysmorphic disorder	0	0	1 (0.4)	1 (0.2)
Depressive symptom	0	0	1 (0.4)	1 (0.2)
Neuropsychiatric syndrome	0	1 (0.6)	0	1 (0.2)
Reading disorder	0	0	1 (0.4)	1 (0.2)
Restlessness	1 (0.6)	0	0	1 (0.2)
Sleep disorder	0	0	1 (0.4)	1 (0.2)
Suicidal ideation	0	0	1 (0.4)	1 (0.2)
Suicide attempt	0	0	1 (0.4)	1 (0.2)
<b>Investigations</b>	<b>9 (5.6)</b>	<b>5 (3.0)</b>	<b>8 (3.2)</b>	<b>22 (3.8)</b>
SARS-CoV-2 test positive	2 (1.2)	2 (1.2)	2 (0.8)	6 (1.0)
Heart rate increased	1 (0.6)	0	2 (0.8)	3 (0.5)
Influenza A virus test positive	2 (1.2)	0	0	2 (0.3)
Intraocular pressure increased	1 (0.6)	1 (0.6)	0	2 (0.3)
Vitamin D decreased	0	1 (0.6)	1 (0.4)	2 (0.3)
Blood cholesterol increased	0	1 (0.6)	0	1 (0.2)
Body temperature increased	1 (0.6)	0	0	1 (0.2)
Coronavirus test positive	0	0	1 (0.4)	1 (0.2)
Haemoglobin decreased	0	1 (0.6)	0	1 (0.2)
Heart rate decreased	1 (0.6)	0	0	1 (0.2)
Heart rate irregular	1 (0.6)	0	0	1 (0.2)
Intraocular pressure fluctuation	0	0	1 (0.4)	1 (0.2)
Weight decreased	1 (0.6)	0	0	1 (0.2)
Weight increased	0	0	1 (0.4)	1 (0.2)
<b>Musculoskeletal and connective tissue disorders</b>	<b>8 (4.9)</b>	<b>5 (3.0)</b>	<b>8 (3.2)</b>	<b>21 (3.7)</b>
Arthralgia	2 (1.2)	1 (0.6)	2 (0.8)	5 (0.9)

Neck pain	1 (0.6)	0	2 (0.8)	3 (0.5)
Osteochondrosis	1 (0.6)	2 (1.2)	0	3 (0.5)
Muscle spasms	1 (0.6)	0	1 (0.4)	2 (0.3)
Myalgia	2 (1.2)	0	0	2 (0.3)
Arthritis	0	0	1 (0.4)	1 (0.2)
Back pain	1 (0.6)	0	0	1 (0.2)
Growing pains	0	1 (0.6)	0	1 (0.2)
Joint effusion	0	1 (0.6)	0	1 (0.2)
Limb discomfort	1 (0.6)	0	0	1 (0.2)
Pain in extremity	0	0	1 (0.4)	1 (0.2)
Scoliosis	0	0	1 (0.4)	1 (0.2)
<b>Ear and labyrinth disorders</b>	<b>3 (1.9)</b>	<b>1 (0.6)</b>	<b>4 (1.6)</b>	<b>8 (1.4)</b>
Ear pain	3 (1.9)	1 (0.6)	3 (1.2)	7 (1.2)
Middle ear effusion	0	0	1 (0.4)	1 (0.2)
<b>Metabolism and nutrition disorders</b>	<b>3 (1.9)</b>	<b>1 (0.6)</b>	<b>4 (1.6)</b>	<b>8 (1.4)</b>
Decreased appetite	2 (1.2)	0	0	2 (0.3)
Vitamin D deficiency	0	0	2 (0.8)	2 (0.3)
Dehydration	0	0	1 (0.4)	1 (0.2)
Glucose tolerance impaired	1 (0.6)	0	0	1 (0.2)
Hypercholesterolaemia	0	1 (0.6)	0	1 (0.2)
Lactose intolerance	0	0	1 (0.4)	1 (0.2)
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>2 (1.2)</b>	<b>1 (0.6)</b>	<b>5 (2.0)</b>	<b>8 (1.4)</b>
Skin papilloma	1 (0.6)	1 (0.6)	1 (0.4)	3 (0.5)
Acrochordon	0	0	1 (0.4)	1 (0.2)
Benign neoplasm of conjunctiva	1 (0.6)	0	0	1 (0.2)
Blepharal papilloma	0	0	1 (0.4)	1 (0.2)

Brain neoplasm malignant	0	0	1 (0.4)	1 (0.2)
Pyogenic granuloma	0	0	1 (0.4)	1 (0.2)
<b>Reproductive system and breast disorders</b>	<b>3 (1.9)</b>	<b>3 (1.8)</b>	<b>1 (0.4)</b>	<b>7 (1.2)</b>
Dysmenorrhoea	2 (1.2)	2 (1.2)	1 (0.4)	5 (0.9)
Ovarian cyst	0	1 (0.6)	0	1 (0.2)
Ovarian cyst ruptured	1 (0.6)	0	0	1 (0.2)
<b>Blood and lymphatic system disorders</b>	<b>2 (1.2)</b>	<b>1 (0.6)</b>	<b>2 (0.8)</b>	<b>5 (0.9)</b>
Anaemia	0	0	2 (0.8)	2 (0.3)
Lymphadenitis	2 (1.2)	0	0	2 (0.3)
Lymphadenopathy	0	1 (0.6)	0	1 (0.2)
<b>Cardiac disorders</b>	<b>1 (0.6)</b>	<b>1 (0.6)</b>	<b>2 (0.8)</b>	<b>4 (0.7)</b>
Palpitations	0	0	1 (0.4)	1 (0.2)
Postural orthostatic tachycardia syndrome	0	1 (0.6)	0	1 (0.2)
Sinus arrhythmia	1 (0.6)	0	0	1 (0.2)
Tachycardia	0	0	1 (0.4)	1 (0.2)
<b>Renal and urinary disorders</b>	<b>1 (0.6)</b>	<b>0</b>	<b>2 (0.8)</b>	<b>3 (0.5)</b>
Acute kidney injury	1 (0.6)	0	0	1 (0.2)
Dysuria	0	0	1 (0.4)	1 (0.2)
Haematuria	0	0	1 (0.4)	1 (0.2)
Incontinence	0	0	1 (0.4)	1 (0.2)
Urinary incontinence	0	0	1 (0.4)	1 (0.2)
<b>Congenital, familial and genetic disorders</b>	<b>0</b>	<b>0</b>	<b>2 (0.8)</b>	<b>2 (0.3)</b>
Developmental hip dysplasia	0	0	1 (0.4)	1 (0.2)
Retinal anomaly congenital	0	0	1 (0.4)	1 (0.2)

<b>Endocrine disorders</b>	<b>1 (0.6)</b>	<b>1 (0.6)</b>	<b>0</b>	<b>2 (0.3)</b>
Precocious puberty	1 (0.6)	1 (0.6)	0	2 (0.3)
<b>Hepatobiliary disorders</b>	<b>0</b>	<b>0</b>	<b>1 (0.4)</b>	<b>1 (0.2)</b>
Cholecystitis	0	0	1 (0.4)	1 (0.2)
<b>Surgical and medical procedures</b>	<b>0</b>	<b>1 (0.6)</b>	<b>0</b>	<b>1 (0.2)</b>
Peripheral nerve operation	0	1 (0.6)	0	1 (0.2)
Tenoplasty	0	1 (0.6)	0	1 (0.2)
<b>Vascular disorders</b>	<b>1 (0.6)</b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>
Flushing	1 (0.6)	0	0	1 (0.2)

148 Abbreviations: COVID-19, corona virus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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**Table S8. Myopia progression rate and less than 0.5D responder proportion in placebo arms of randomized pharmacologic trials or single vision lens arms of randomized lens trials in the literature with a trial duration of at least 1 year.**

Reference duration	Regions	Trial	SER change from baseline over the trial duration	Proportion of participants or eyes with less than 0.5D myopia progression at the end of trial duration	Main intervention in the trial
<b>Placebo arms in pharmacologic studies</b>					<b>Intervention arms</b>
Current trial (mITT)	USA, UK,	1 year	-0.57 D	48%	Atropine 0.01%, 0.02%
	Spain,	2 years	-1.00 D	27%	
	Hungary, Ireland, Netherlands	3 years	-1.28 D	18%	
Saxena 2021 <sup>1</sup>	India	1 year	-0.35 D	62%	Atropine 0.01%
Wei 2020 <sup>2</sup>	China	1 year	-0.76 D	30%	Atropine 0.01%
Yam 2019 <sup>3</sup>	China	1 year	-0.81 D	24%	Atropine 0.01%, 0.025%, 0.05%
Yi 2015 <sup>4</sup>	China	1 year	-0.85 D	Not determined	Atropine 1%
Yen 1989 <sup>5</sup>	R.O. China	1 year	-0.91D	37%	Atropine 1% or cyclopentolate 1%
Siatkowski 2004 <sup>6</sup>	USA	1 year	-0.53 D	52%	Pirenzepine 2%
Chua 2006 <sup>7</sup>	Singapore	2 years	-1.2 D	16%	Atropine 1%
Hieda 2021 <sup>8</sup>	Japan	2 years	-1.48 D	Not determined	Atropine 0.01%
Lee 2022 <sup>9</sup>	Australia	2 years	-0.78 D	Not determined	Atropine 0.01%
Zhu 2020 <sup>10</sup>	China	3 years	-2.85 D	Not determined	Atropine 1%
<b>Single vision lens arms in lens studies</b>					<b>Intervention arms</b>

Shih 2001 <sup>11</sup>	R.O. China	1.5 years	-1.4 D	Not determined	Multifocal glasses or atropine 0.5% with multifocal glasses
Gwiazda 2003 <sup>12</sup>	USA	3 years	-1.48 D	Not determined	Progressive addition lens
Chamberlain 2019 <sup>13</sup>	Portugal, UK, Singapore, Canada	3 years	-1.24 D	10%	Dual-focus contact lens

Abbreviations: D, diopter; R.O., Republic Of; UK, United Kingdom.; USA, United States of America.

## Supplementary Appendix References

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