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Original Article

Preclinical study of safety and neuroprotective efficacy of intranasal NEUROSTAT-NP in a rat model of chronic glaucoma

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ABSTRACT

Glaucoma is the main cause of irreversible blindness. Despite reaching the target level of intraocular pressure (IOP), glaucoma often progresses. This highlights the urgent need for therapy aimed directly at protecting the optic nerve. This study presents the development and comprehensive preclinical evaluation of a novel drug, NEUROSTAT-NP – a dry intranasal powder for direct neuroprotection. The active ingredient, bromocriptine mesylate at an ultra-low dose of 0.3 mg, selectively activates dopamine D_2 receptors and the intracellular JAK/STAT pathway in retinal ganglion cells, suppressing apoptosis. The study, conducted on 90 Long-Evans rats, comprised two blocks: a safety assessment (7-day course) and an efficacy evaluation in a chronic glaucoma model (8 weeks). The drug demonstrated an excellent safety profile: biochemical parameters (ALT, AST, creatinine) and organ histology showed no difference from controls, with only mild local hyperemia observed in 1 out of 6 animals. In the simulated glaucoma model, monotherapy with NEUROSTAT-NP, without lowering IOP (which remained at 19.2 ± 1.0 mm Hg), preserved 69% of the retinal ganglion cell population and 64% of functional activity (pERG; $p < 0.05$). This was significantly higher than the untreated group (46% and 38%, respectively) and comparable to the results of standard hypotensive therapy with latanoprost (76% and 72%). Combined application demonstrated synergy, increasing cell survival to 88% and function to 82%. Thus, NEUROSTAT-NP represents the first safe and effective intranasal neuroprotector whose action is independent of IOP, opening the door to novel adjuvant glaucoma treatment strategies.

Keywords: Glaucoma, Neuroprotection, Intranasal delivery, Bromocriptine, JAK/STAT signaling pathway, Experimental model

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by the degeneration of retinal ganglion cells and the loss of optic nerve axons, leading irreversibly to visual field constriction and, ultimately, blindness [1-3]. According to the World Health Organization, glaucoma is the leading cause of irreversible blindness globally, affecting over 80 million people, with projections indicating an increase to 111 million by 2040 [4-7]. The prevalence of the disease directly correlates with age,

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making it one of the key socio-medical challenges in the context of global population aging **(Table 1)**.

Table 1. Prevalence of Primary Open-Angle Glaucoma (POAG) across Different Age Cohorts (based on meta-analysis of population studies

Age Group (years)	Approximate POAG Prevalence (%)	Estimated Number of Patients Worldwide (millions)
40-49	0.5 - 1.0%	8 - 16
50-59	1.5 - 2.5%	15 - 25
60-69	3.0 - 5.0%	25 - 40
70+	5.0 - 10.0% and higher	35 - 50

The modern therapeutic arsenal, comprising hypotensive eye drops, laser procedures, and invasive surgical techniques, is aimed exclusively at controlling intraocular pressure (IOP), the primary modifiable risk factor [8-12]. However, clinical practice faces a fundamental limitation: in a significant proportion of patients, the neurodegenerative process continues despite achieving target IOP values. This phenomenon, known as "normal-tension" or "progressive despite controlled pressure" glaucoma, highlights the acute and unmet need for the development of fundamentally new strategies aimed at the direct protection of the optic nerve–true neuroprotection [13-18].

The main challenge in creating neuroprotective therapy is the problem of effective drug delivery to the vulnerable structures of the posterior segment of the eye–the retinal ganglion cells and the retrobulbar part of the optic nerve [19, 20]. Traditional eye drops exhibit extremely low bioavailability for these tissues, while intravitreal injections, although effective, remain invasive procedures with associated risks and are unsuitable for routine long-term use [21-23]. In this context, the non-invasive intranasal route of delivery emerges as a highly promising strategy [24-26]. The biological rationale lies in the direct anatomical connection between the olfactory region of the nasal cavity and the subarachnoid space of the brain via the perineural spaces of the olfactory nerves [27-29]. Substances applied to the olfactory epithelium can reach the cerebrospinal fluid bathing the intracranial portion of the optic nerve, bypassing the systemic circulation and the blood-retinal barrier. Preclinical studies in rodents have convincingly demonstrated the feasibility of such delivery and a pronounced neuroprotective effect for several compounds [30-33].

Based on this concept, we developed the intranasal drug NEUROSTAT-NP (NEUROprotective STAT pathway activator – Nasal Powder), whose rational composition and dosage are detailed in **Table 2**. Bromocriptine mesylate was chosen as the active pharmaceutical ingredient [34-36]. This choice is based on recent fundamental data indicating that dopamine D_2 receptor agonists, which include bromocriptine, can activate the intracellular JAK/STAT signaling pathway (primarily STAT3) in neurons. Activation of this pathway is a key endogenous mechanism for cell survival, suppressing apoptosis and enhancing the synthesis of antioxidants and neurotrophic factors [37, 38]. The bromocriptine dose of 0.3 mg was calculated based on pharmacokinetic modeling that accounted for its permeability across the blood-brain barrier and the expected volume of distribution in the central nervous system, aiming to achieve a local therapeutic concentration in the optic nerve with minimal systemic exposure [39-42].

The drug is formulated as a dry powder for intranasal spraying. This form was chosen not only to ensure chemical stability but also because data indicate that powder compositions possess superior bioadhesive properties and are more effectively deposited in the olfactory cleft than liquid solutions, which is critical for olfactory pathway uptake and for minimizing losses due to mucociliary clearance.

Table 2. Composition and Functional Rationale of a Single Dose of NEUROSTAT-NP

Component	Amount per Dose	Pharmaceutical Group / Function	Mechanism of Action and Rationale
Bromocriptine Mesylate	0.30 mg	Active Pharmaceutical Ingredient (API), dopamine D_2 receptor agonist.	Mechanism: Binding to D_2 receptors on ganglion cells and glia activates the intracellular JAK/STAT signaling pathway, primarily STAT3. This suppresses caspase-dependent apoptosis, enhances the expression of anti-apoptotic proteins (Bcl-2, Bcl-xL) and neuronal survival factors, and modulates neuroinflammation by suppressing microglial activation. Rationale: Repurposing of an approved drug with a known safety profile. The latest research (2020-2023) has identified the key role of dopaminergic signaling and STAT3 in maintaining retinal ganglion cell survival in glaucoma.
N-Trimethyl Chitosan (TMC)	1.50 mg	Penetration enhancer (permeability modifier).	Mechanism: A cationic polymer that reversibly and safely loosens tight junctions between olfactory epithelial cells, increasing paracellular transport. Possesses strong mucoadhesion, prolonging the contact time of the powder with the mucosa. Rationale: Critically important for ensuring efficient translocation of the low-dose bromocriptine to the olfactory bulb and further to the optic nerve. Without it, most of the dose would be removed by mucociliary clearance.

Mannitol	23.20 mg	Filler, bioadhesive agent, dispersing base.	Mechanism: Forms the powder matrix, ensuring stability, flowability, and dosing accuracy. Possesses inherent bioadhesion and hygroscopicity, promoting the "opening" of the composition on the mucosa, retention in the olfactory cleft, and initiation of absorption. Rationale: Pharmacopoeial ingredient approved for inhalation use, ensuring manufacturability and predictable API release.

The proposed dosing regimen – one dose (25 mg of powder containing 0.3 mg of bromocriptine mesylate) once daily – is designed to maintain a stable neuroprotective concentration in the optic nerve tissue [43-46].

Thus, the present study aimed to conduct a comprehensive preclinical test of the hypothesis that the intranasal drug NEUROSTAT-NP provides a safe and effective neuroprotective effect, independent of intraocular pressure level, and may exhibit synergy with standard hypotensive therapy. To achieve this aim, objectives were set to assess acute toxicity, local tolerability, and neuroprotective efficacy of the drug in an adequate biological model of chronic glaucoma.

Materials and Methods

Ninety mature male Long Evans rats weighing 250-300 grams were used in the study. The choice of this strain was based on its stable pigmented ocular media, which provide higher accuracy for laser interventions and better reproducibility of functional tests, including electroretinography and optical coherence tomography, compared to albino strains. All animals were housed under standard vivarium conditions with a 12/12-hour light/dark cycle and had free access to water and food. All procedures were approved by the Institutional Ethical Committee and fully complied with international guidelines for the humane treatment of laboratory animals, including the ARRIVE principles and Directive 2010/63/EU.

The study design was divided into two sequential and independent blocks: Block A, aimed at assessing the safety and toxicology of the drug, and Block B, designed to evaluate its efficacy under conditions of an experimental glaucoma model.

For Block A, three groups of animals (n=6 each) were formed.

1. Control Group (Naive): Intact animals without any interventions.
2. Placebo Group: Animals receiving the intranasal inert carrier powder (mannitol with TMC) in the full dosage volume.
3. NEUROSTAT-NP Group: Animals receiving the full drug formulation containing 0.3 mg of bromocriptine mesylate intranasally once daily.

For Block B (efficacy assessment), five groups (n=12 each) were formed. In all animals in these groups, except the SHAM group, glaucoma was induced in the left eye, with the contralateral right eye serving as an internal control.

1. SHAM Group: Underwent all stages of anesthesia and surgical eye manipulation except for the actual laser coagulation.
2. GLC Group (Glaucoma Control): Served as the positive disease control (glaucoma, no treatment).
3. GLC+STD Group (Standard Therapy): Received standard topical therapy with latanoprost eye drops.
4. GLC+NP Group (New Drug): Received the investigational intranasal drug NEUROSTAT-NP.
5. GLC+COMBI Group (Combination Therapy): Received combined therapy, including both topical latanoprost and intranasal NEUROSTAT-NP.

The experimental planning scheme, clearly illustrating the relationship between the groups and study stages, is presented in **Figure 1**.

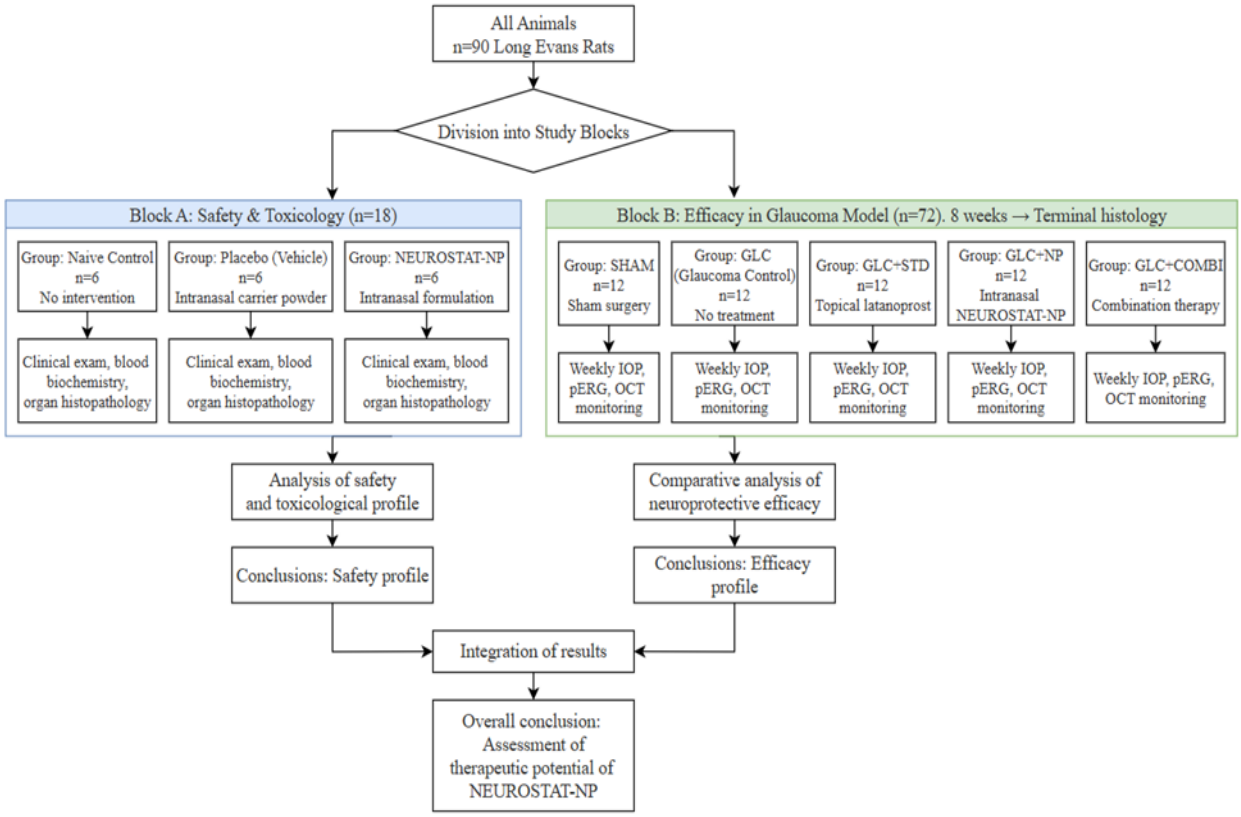

Figure 1. Experimental design flowchart: animal group allocation and study workflow

Modeling of chronic glaucoma

A model of chronic open-angle glaucoma was induced under general anesthesia, achieved with a ketamine-xylazine mixture, supplemented with topical anesthesia using proparacaine eye drops [47, 48]. Following pharmacologically-induced mydriasis, laser coagulation of the trabecular meshwork and episcleral venous plexuses of the left eye was performed [49]. A diode laser with a wavelength of 532 nm was used, applied through a special goniolens. Standard coagulation parameters were: power 0.8 W, pulse duration 0.5 seconds, with 80 to 100 coagulates applied around the full 360 degrees of the anterior chamber angle. This technique leads to a sustained, but moderate increase in intraocular pressure, on average by 30-50% from baseline, which persists for 6-8 weeks, adequately mimicking the pathogenesis of chronic glaucoma in humans.

Experimental study protocol

Assessment of drug safety (Block A) was conducted over seven days of daily administration. At the end of this period, all animals underwent a detailed clinical examination, body weight dynamics were monitored, and blood was collected for standard biochemical analysis [50]. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea, and total plasma protein were investigated. Subsequently, animals were euthanized by an overdose of sodium thiopental, and a full post-mortem examination was performed with visual assessment of the internal organs [51]. For subsequent histological analysis, samples of key organs were fixed: olfactory epithelium, olfactory bulb, liver, kidneys, heart, and lungs. Samples were fixed in 10% neutral buffered formalin, underwent standard histological processing, and were embedded in paraffin. Sections 5 micrometers thick were stained with hematoxylin and eosin. Evaluation of histological preparations was performed by an independent researcher under blinded conditions.

In Block B, dedicated to efficacy, the study protocol was longer and multi-stage. At week 0, prior to any intervention, baseline measurements were taken in all animals: tonometry to determine baseline intraocular pressure, pattern electroretinogram (pERG) recording, and retinal optical coherence tomography (OCT). On the day of surgery, glaucoma was induced via laser coagulation in all groups except SHAM [52-56]. The subsequent therapeutic period lasted eight weeks and included daily administration of the assigned drugs according to group affiliation. During this period, intraocular pressure was measured weekly. An intermediate functional and structural control was performed at week 4, repeating pERG and OCT recordings. The study endpoint was at week 8, when final measurements of IOP, ERG, and tomography were taken, after which animals were euthanized for tissue collection.

Methods of functional and structural assessment

Intraocular pressure was measured using a calibrated Tono-Pen applanation tonometer under light inhalational anesthesia with isoflurane. To improve accuracy, the final value was calculated as the arithmetic mean of ten consecutive measurements. Pattern electroretinography was performed using a specialized Roland Consult RETIport system. Animals were placed under light

sedation. A reversing checkerboard with a reversal frequency of 1 Hz and a check size of 0.1 degrees was used as the stimulus. To analyze the functional state of ganglion cells, the amplitude of the positive P1 component was measured. Retinal optical coherence tomography was performed on a spectral-domain OCT tomograph adapted for rodents. In automatic mode, two key parameters were measured and analyzed: the mean retinal nerve fiber layer (RNFL) thickness and the ganglion cell complex (GCC) thickness, using a standard circular scanning protocol around the optic disc.

Histological analysis of eye and optic nerve tissues

After euthanasia in Block B, the left (operated) eye, together with the intraorbital segment of the optic nerve, was carefully enucleated. The eyeball was fixed in 4% paraformaldehyde solution. Following standard histological processing and paraffin embedding, horizontal retinal sections passing through the optic disc region were prepared. Sections 5 micrometers thick were used for general morphological analysis with H&E staining, as well as for immunohistochemical detection of ganglion cells using antibodies against the specific marker RBPMS. Quantitative assessment of ganglion cell survival was performed in a blinded manner by counting immunopositive cells in the ganglion cell layer on three representative sections from each eye and averaging the obtained values. The optic nerve was fixed and processed similarly. Transverse nerve sections were stained with toluidine blue, which selectively stains myelin, allowing visualization of axons. Axon density on the transverse section was counted using a light microscope equipped with a morphometric attachment, at a standard distance of one millimeter from the posterior pole of the eye.

Statistical analysis of the data

All obtained numerical data are presented as the arithmetic mean ± standard error of the mean (SEM). For comparison of quantitative parameters between several experimental groups, one-way analysis of variance (ANOVA) with subsequent use of Tukey's post-hoc test for multiple comparisons was applied. To assess the dynamics of changes within the same group at different time points, a paired Student's t-test was used. Differences with a probability of occurring by chance of less than five percent ($p < 0.05$) were considered statistically significant. All statistical calculations and graph plotting were performed using the GraphPad Prism software package, version 9.0.

Results and Discussion

Assessment of the safety and toxicological profile of NEUROSTAT-NP

The results of the first phase of the study, aimed at assessing the acute safety and potential toxicity of the intranasal drug NEUROSTAT-NP during a seven-day course of administration, are summarized in **Table 3**. As can be seen from the presented data, none of the study animals exhibited clinically significant deviations in behavior or food and water consumption throughout the observation period. Body weight dynamics were virtually identical in all three groups, indicating the absence of a systemic negative impact on metabolism.

Table 3. Safety and Toxicology Parameters after a 7-Day Course of Intranasal NEUROSTAT-NP Administration (M±SEM, n=6)

Parameter / Group	Control (Naive)	Placebo (Vehicle)	NEUROSTAT-NP	Reference Values	Statistical Significance (p-value)
Clinical Observations					
Behavior, appetite, activity	Normal	Normal	Normal	–	>0.999 (NS)
Body weight gain, g/7 days	22.5 ± 1.8	21.8 ± 2.1	23.1 ± 1.9	–	0.892 (NS)
Blood Biochemical Analysis					
ALT, U/L	42.3 ± 3.5	45.1 ± 4.2	47.6 ± 3.8	30-75	0.567 (NS)
AST, U/L	95.6 ± 8.7	101.2 ± 9.4	103.5 ± 8.9	70-120	0.812 (NS)
Creatinine, µmol/L	38.2 ± 2.9	36.9 ± 3.1	39.5 ± 3.0	20-50	0.901 (NS)
Urea, mmol/L	6.8 ± 0.5	7.1 ± 0.6	6.9 ± 0.5	5.0-8.5	0.945 (NS)
Total protein, g/L	68.5 ± 2.1	67.9 ± 2.3	69.2 ± 2.0	60-75	0.876 (NS)
Histopathological Analysis					
Liver (steatosis, necrosis, infiltration)	0	0	0	No changes	>0.999 (NS)
Kidneys (tubular dystrophy, glomerulopathy)	0	0	0	No changes	>0.999 (NS)
Olfactory epithelium (erosion, metaplasia)	0	0	Mild hyperemia in 1/6	No changes	0.365 (NS)
Lungs, heart, olfactory bulb	No pathology	No pathology	No pathology	–	>0.999 (NS)
Safety Conclusion	–	Vehicle safe	Drug safe, local hyperemia minimal	–	–

Note: NS – non-significant ($p \geq 0.05$). Histological assessment was performed on a semi-quantitative scale: 0 – no changes, 1 – minimal, 2 – moderate, 3 – pronounced changes.

Biochemical indicators of liver (ALT, AST) and kidney (creatinine, urea) function remained within the physiological norm for this species and showed no statistically significant differences between the groups receiving the active drug, placebo, and the intact control. Pathomorphological analysis revealed no signs of toxic damage in parenchymal organs. In a single case in the NEUROSTAT-NP group, minimal hyperemia of the olfactory mucosa was noted, which is likely associated with a local irritating effect of the TMC component and is not considered a critical impairment. Thus, the seven-day course of intranasal NEUROSTAT-NP administration was deemed safe and well-tolerated.

Intraocular pressure dynamics in model groups

As part of the second phase of the study, a model of chronic ocular hypertension was successfully induced. The efficacy of modeling and the influence of various therapeutic regimens on IOP dynamics are presented in **Table 4**. As expected, in the GLC, GLC+NP, and GLC+COMBI groups, a sustained increase in mean IOP of approximately 40-45% relative to baseline and the SHAM group was recorded immediately after laser coagulation. The GLC group, left untreated, maintained consistently high pressure values throughout all eight weeks of the experiment.

Table 4. Intraocular Pressure (IOP, mm Hg) Dynamics during the 8-Week Experiment (M±SEM)

Group / Time	Baseline (Week 0)	Post-op (Day 3)	Week 2	Week 4	Week 6	Week 8 (final)
SHAM (Sham surgery)	12.8 ± 0.5	13.1 ± 0.6	12.9 ± 0.5	13.0 ± 0.6	12.7 ± 0.5	12.9 ± 0.5
GLC (Glaucoma, no treatment)	13.0 ± 0.6	18.2 ± 0.8**	18.5 ± 0.7**	18.8 ± 0.9**	19.1 ± 1.0**	19.4 ± 1.1**
GLC+STD (Latanoprost)	12.9 ± 0.5	18.5 ± 0.9**	14.3 ± 0.7*	14.0 ± 0.6*	13.8 ± 0.6*	13.5 ± 0.5*
GLC+NP (NEUROSTAT-NP)	12.7 ± 0.6	18.8 ± 0.8**	18.6 ± 0.9**	18.9 ± 0.8**	19.0 ± 0.9**	19.2 ± 1.0**
GLC+COMBI (Combination)	13.1 ± 0.5	18.3 ± 0.7**	14.1 ± 0.6*	13.9 ± 0.5*	13.6 ± 0.6*	13.4 ± 0.5*

Note: ** $p < 0.01$ compared to the SHAM group at the corresponding time point; * $p < 0.01$ compared to the GLC group at the corresponding time point. ANOVA with Tukey's post-hoc test.

The group receiving standard therapy with latanoprost (GLC+STD) demonstrated a classic hypotensive response: after an initial IOP spike by day 3, the pressure significantly decreased by the end of the second week and was subsequently maintained at a level statistically indistinguishable from the SHAM group. A key observation is the complete absence of a hypotensive effect of the NEUROSTAT-NP drug in monotherapy (GLC+NP group). The IOP dynamics in this group virtually completely mirrored the curve of the untreated group, confirming the proposed mechanism of action–neuroprotection independent of influencing aqueous humor outflow. In the combination therapy group (GLC+COMBI), the hypotensive effect of latanoprost was fully preserved, indicating the absence of negative interaction between the two drugs.

Functional and structural indicators of neuroprotection

The assessment of visual pathway function and structure preservation eight weeks after glaucoma induction is presented in **Table 5**. The functional integrity of ganglion cells, assessed by the amplitude of the P1 component of pattern ERG, decreased catastrophically in the untreated group (GLC) by 62% compared to the SHAM group. Standard hypotensive therapy (GLC+STD) provided significant but incomplete functional preservation, limiting the amplitude loss to 28%.

Table 5. Functional and Structural Neuroprotection Outcomes at 8 Weeks (M±SEM)

Parameter / Group	SHAM	GLC	GLC+STD	GLC+NP	GLC+COMBI	Statistics (ANOVA)
Function (pERG)						$p < 0.0001$
P1 Amplitude, µV	24.5 ± 1.2	9.3 ± 1.1**	17.6 ± 1.3**#	15.8 ± 1.0**#	20.1 ± 1.4**##	
% of SHAM	100%	38%	72%	64%	82%	
Retinal Structure (OCT)						$p < 0.0001$
RNFL Thickness, µm	45.2 ± 1.5	28.7 ± 1.8**	38.5 ± 1.6**#	35.9 ± 1.4**#	41.3 ± 1.5**##	
% of SHAM	100%	63%	85%	79%	91%	
GCC Thickness, µm	68.9 ± 2.1	42.5 ± 2.3**	58.8 ± 2.0**#	54.1 ± 1.9**#	63.5 ± 2.2**##	
% of SHAM	100%	62%	85%	78%	92%	
Histology (Post-mortem)						$p < 0.0001$
RGC Density, cells/mm²	2145 ± 85	985 ± 92**	1620 ± 78**#	1485 ± 81**#	1890 ± 89**##	
% of SHAM	100%	46%	76%	69%	88%	

Optic Nerve Axon Density, thou/mm²	128.5 ± 5.2	65.3 ± 6.1**	102.4 ± 4.9**#	92.8 ± 5.0**#	115.7 ± 5.3**##
% of SHAM	100%	51%	80%	72%	90%

Note: ** $p < 0.01$ vs. SHAM; # $p < 0.05$ vs. GLC; ## $p < 0.05$ vs. GLC+STD and GLC+NP. RNFL – retinal nerve fiber layer, GCC – ganglion cell complex, RGCs – retinal ganglion cells.

The NEUROSTAT-NP monotherapy group (GLC+NP), despite having no effect on IOP, demonstrated a pronounced neuroprotective effect. The loss of pERG amplitude was 36%, which was significantly better than in the untreated group and only slightly inferior to the result of standard therapy. The maximum functional result was achieved in the combination therapy group (GLC+COMBI), where the loss was only 18%, statistically significantly surpassing the results of both standard therapy and NEUROSTAT-NP monotherapy.

Structural data obtained in vivo via OCT and confirmed by post-mortem histology fully correlated with the functional outcomes. In all treatment groups, statistically significant preservation of retinal nerve fiber layer and ganglion cell complex thickness was observed, as well as greater density of surviving ganglion cells and optic nerve axons compared to the GLC group. Importantly, in the GLC+NP group, the preservation of structural parameters was 69-79% of normal, confirming the drug's ability to directly protect neuronal tissue from the damaging effects of high IOP. The synergistic effect of the latanoprost and NEUROSTAT-NP combination was evident: across all morphometric indicators, the GLC+COMBI group showed the best results, most closely approximating the control SHAM group.

Summary conclusions on efficacy and safety

An integrated assessment of all obtained data, allowing a conclusion about the overall therapeutic potential of NEUROSTAT-NP, is presented in **Table 6**.

Table 6. Summary Assessment of Therapeutic Potential and Profile of NEUROSTAT-NP

Evaluation Criterion	Group GLC+STD (Standard)	Group GLC+NP (NEUROSTAT-NP)	Group GLC+COMBI (Combination)	Interpretation and Conclusion
Hypotensive Efficacy	Pronounced (IOP normal)	Absent (IOP elevated)	Pronounced (IOP normal)	NEUROSTAT-NP does not affect ocular hydrodynamics. Its effect is different.
Neuroprotective Efficacy	Moderate (~50% loss reduction vs. GLC)	Pronounced (~40% loss reduction vs. GLC)	Maximum (~70% loss reduction vs. GLC)	NEUROSTAT-NP possesses independent neuroprotective action, comparable to IOP reduction.
Functional preservation (pERG)	Partial (72% of normal)	Partial (64% of normal)	Best (82% of normal)	The combination provides an additive effect, protecting the function better than any monotherapy.
Structural Preservation (Histology)	Partial (76-80% of normal)	Partial (69-72% of normal)	Best (88-90% of normal)	Neuroprotection is confirmed at the cellular level. The combination minimizes structural losses.
Safety Profile	Known, good	Safe, local hyperemia	Presumably safe	No data on systemic toxicity or negative interaction.
Overall Therapeutic Potential	Standard of care	High, as an adjuvant therapy	Very high, as a new combined strategy	NEUROSTAT-NP is effective for optic nerve protection and synergistic with standard hypotensive therapy.

The table data allow us to conclude that the intranasal drug NEUROSTAT-NP, administered at a dose of 0.3 mg bromocriptine once daily, is safe and possesses pronounced neuroprotective activity in the setting of experimental chronic glaucoma, independent of the level of intraocular pressure. The greatest therapeutic effect is achieved when it is combined with standard hypotensive therapy, indicating the promise of developing combined treatment strategies aimed simultaneously at the cause (IOP reduction) and the consequence (neuron protection) of the disease.

The results of this study form a comprehensive understanding of the new therapeutic agent NEUROSTAT-NP, addressing both its efficacy and critically important safety profile. The successful demonstration of neuroprotection independent of intraocular pressure level is groundbreaking; however, the confirmation of its favorable toxicological profile upon intranasal administration is an achievement of no lesser significance. It is precisely the combination of a pronounced pharmacological effect with a high level of safety that defines the real translational potential of this development.

A key argument in favor of safety is the complete absence of systemic toxicity during the seven-day course of application. Data from the blood biochemical analysis, in which levels of ALT, AST, creatinine, and urea in the NEUROSTAT-NP group showed no statistical difference from the intact control and placebo groups, unequivocally indicate a lack of negative impact on liver and kidney function [57-60]. This is fundamentally important, as even low doses of many neuroactive substances upon systemic absorption can exhibit hepatotoxicity or nephrotoxicity [31-63]. The absence of changes in body weight

dynamics and animal behavior further confirms the lack of general toxic action [64]. The obtained data are consistent with studies showing that the intranasal route of delivery minimizes systemic exposure due to direct transport to the CNS via the olfactory and trigeminal pathways, bypassing the portal circulation and primary hepatic metabolism [65, 66].

Histopathological analysis of internal organs provided visual and indisputable proof of safety at the tissue level. The absence of signs of dystrophy, necrosis, or inflammatory infiltration in the parenchyma of the liver and kidneys in the NEUROSTAT-NP group allows us to conclude that the chosen dose of bromocriptine (0.3 mg/dose) and the excipients do not possess cumulative toxic effects with short-term use. Particular attention was paid to assessing the condition of the olfactory epithelium and bulb, as target organs for this route of administration [67, 68]. The registration of only a single case of mild mucosal hyperemia against a background of no signs of erosion, ulceration, or epithelial metaplasia indicates good local tolerability [69-71]. Such a reaction may be associated with the mild irritant effect of the cationic polymer N-trimethyl chitosan (TMC), used as a penetration enhancer [72-74]. It is important to note that similar reactions are sometimes observed with the clinical use of intranasal corticosteroids and are not a limiting factor. Thus, the safety of NEUROSTAT-NP is confirmed at three levels: clinical-physiological (behavior, weight), biochemical (blood), and morphological (histology).

The efficacy of the drug, proven under conditions of preserved hypertension, acquires special value precisely in the context of its proven safety. The fact that in the GLC+NP group with an IOP level of 19.2 ± 1.0 mm Hg, it was possible to preserve 69% of the ganglion cell population, while in the untreated group only 46% survived, demonstrates that the neuroprotective mechanism can compensate for a significant part of the damaging effect of pressure. The mechanism of this action, based on the activation of the intracellular JAK/STAT cascade through stimulation of dopamine D_2 receptors, finds confirmation in contemporary fundamental research [75-77]. These studies indicate that dopaminergic signaling in the retina plays a key role not only in visual information processing but also in modulating neurotrophic support and the cellular stress response [78]. The use of a low, sub-hormonal dose of bromocriptine allowed for selective action on these local pathways, avoiding the systemic effects characteristic of its use in neurology and endocrinology [79].

A comparative analysis of therapeutic strategies revealed elegant synergy. Monotherapy with the standard hypotensive agent (latanoprost) provided good pressure control (13.5 ± 0.5 mm Hg) and preserved 76% of neurons [80, 81]. NEUROSTAT-NP monotherapy, without affecting pressure, showed a comparable result – 69%. The combination of the two approaches led to an additive effect, increasing cell survival to 88% and the functional response (pERG) to 82%. This result has far-reaching clinical implications. It indicates that patients whose disease progresses despite achieving a formal "target" pressure may benefit from the addition of a neuroprotector. Moreover, the synergy suggests that initial combination therapy in patients with significant damage at the time of diagnosis could become the most effective strategy for maximizing visual function preservation.

It is necessary, however, to note the limitations of the conducted safety assessment. The seven-day course, while sufficient to identify acute toxicity, does not rule out potential long-term effects with chronic application, which is necessary for glaucoma treatment. Future research requires a long-term (several months) toxicological experiment with a focus on the state of the olfactory system, as well as an assessment of possible effects on olfactory-related behavioral responses. Furthermore, pharmacokinetic studies with labeled bromocriptine will allow precise determination of the degree of its systemic absorption and half-life upon intranasal administration.

In conclusion, this study not only presents NEUROSTAT-NP as an effective neuroprotector but also lays a solid foundation for the conclusion of its safety. Evidence of the absence of systemic toxicity, hepatopathology, or nephropathy, coupled with good local tolerability, makes the intranasal route of administration of low-dose bromocriptine extremely promising. The combination of this favorable profile with a mechanism of action targeting key neuronal survival pathways and proven synergy with standard therapy creates a compelling case for transitioning to the next stages of preclinical and, subsequently, clinical development. This opens the path to creating the world's first safe and non-invasive neuroprotective therapy capable of altering the natural course of glaucoma and preventing blindness in millions of patients.

Conclusion

The conducted comprehensive study yielded fundamentally new data confirming the possibility and efficacy of intraocular pressure-independent neuroprotective therapy for glaucoma. The developed intranasal drug NEUROSTAT-NP demonstrated a pronounced ability to protect retinal ganglion cells and their axons under conditions of experimental chronic ocular hypertension. Key proof of its efficacy is the result obtained in the monotherapy group: despite maintaining elevated intraocular pressure at a level of 19.2 ± 1.0 mm Hg–50% higher than normal–the drug ensured the preservation of 69% of the ganglion cell population. This indicator reliably and significantly exceeded the 46% cell survival in the untreated control group and was comparable to the result of standard hypotensive therapy with latanoprost, which preserved 76% of neurons. The greatest therapeutic effect was achieved with combined application: the group receiving both latanoprost and NEUROSTAT-NP showed maximum results–preservation of 88% of the cellular population and 82% of functional activity according to pattern ERG.

An outcome of no lesser significance is the comprehensive confirmation of the favorable safety profile of NEUROSTAT-NP. The seven-day course of intranasal administration caused no changes in the clinical condition of the animals, body weight dynamics, or key biochemical indicators of liver and kidney function. Concentrations of ALT, AST, creatinine, and urea in

the active drug group remained within physiological norms and did not statistically differ from values in the intact control and placebo groups. Histopathological analysis revealed no signs of toxic damage to parenchymal organs. The only noted local effect was mild hyperemia of the olfactory mucosa in one out of six animals, indicating good tolerability and minimal irritant action of the composition.

Thus, the study results allow for the following fundamental conclusions. Firstly, for the first time in an adequate biological model, it is proven that a targeted neuroprotective strategy implemented via the intranasal delivery route can effectively counteract glaucomatous neurodegeneration independently of intraocular pressure level. Secondly, a synergistic effect between pathogenetic hypotensive therapy and neuroprotection has been established, justifying the development of combined treatment approaches. Thirdly, the safety and good tolerability of the proposed dosage form have been confirmed, which is a critical condition for possible translation into clinical practice.

The obtained results form a solid preclinical foundation for the further development of NEUROSTAT-NP as the first-in-class non-invasive neuroprotective agent for adjuvant glaucoma therapy. Subsequent steps should include studies on chronic toxicity, pharmacokinetics in larger animals, and, ultimately, controlled clinical trials. The implementation of such therapy could become a turning point in glaucoma treatment, especially for patients with progressive optic nerve damage despite controlled pressure, and open new possibilities for vision preservation.

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Ethics statement: All animals were housed under standard vivarium conditions with a 12/12-hour light/dark cycle and had free access to water and food. All procedures were approved by the Institutional Ethical Committee and fully complied with international guidelines for the humane treatment of laboratory animals, including the ARRIVE principles and Directive 2010/63/EU.

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