Report on the Deliberation Results

August 29, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Neffy Nasal Spray 1 mg
	Neffy Nasal Spray 2 mg
Non-proprietary Name	Adrenaline (JAN*)
Applicant	Alfresa Pharma Corporation
Date of Application	November 29, 2024

Results of Deliberation

In its meeting held on August 22, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 6 years. The drug product is classified as a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, such as implementing training prior to delivery of the product to ensure that the product will be prescribed and used only by a physician who fully understands the safety and efficacy of the product and is capable of providing patients with appropriate and sufficient instructions on the use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 15, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Neffy Nasal Spray 1 mg Neffy Nasal Spray 2 mg
Non-proprietary Name	Adrenaline
Applicant	Alfresa Pharma Corporation
Date of Application	November 29, 2024
Dosage Form/Strength	Nasal spray solution: each container (0.1 mL) contains 1 mg or 2 mg of adrenaline
Application Classification	Prescription drug, (3) Drug with a new route of administration
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy as adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The product is not classified as a biological product or a specified biological product. The drug product is classified as a powerful drug.

The safety and efficacy of the product in clinical use should be further evaluated in post-marketing surveillance, etc.

Indication

Adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others (for use only in individuals with a history of anaphylaxis or at a high risk of anaphylaxis)

Dosage and Administration

The usual dosage is a single intranasal dose of adrenaline 1 mg for patients weighing <30 kg and a single intranasal dose of adrenaline 2 mg for patients weighing ≥30 kg.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, such as implementing training prior to delivery of the product to ensure that the product will be prescribed and used only by a physician who fully understands the safety and efficacy of the product and is capable of providing patients with appropriate and sufficient instructions on the use of the product.

Attachment

Review Report (1)

July 4, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Neffy Nasal Spray 1 mg Neffy Nasal Spray 2 mg
Non-proprietary Name	Adrenaline
Applicant	Alfresa Pharma Corporation
Date of Application	November 29, 2024
Dosage Form/Strength	Nasal spray solution: each container (0.1 mL) contains 1 mg or 2 mg of adrenaline

Proposed Indication

Adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others (for use only in individuals with a history of anaphylaxis or at a high risk of anaphylaxis)

Proposed Dosage and Administration

The usual dosage is intranasal administration of adrenaline 1 mg for patients weighing 15 kg to <30 kg and intranasal administration of adrenaline 2 mg for patients weighing ≥30 kg.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by respiratory or cardiovascular symptoms that may be life-threatening (*Anaphylaxis Guidelines.* 2022. [in Japanese] Anaphylaxis Committee, Japanese Society of Allergology; hereinafter referred to as the Japanese Anaphylaxis Guidelines). The guidelines state that first-line therapy for anaphylaxis is adrenaline, and if anaphylaxis is diagnosed or strongly suspected, adrenaline should be intramuscularly injected immediately. In Japan, Epipen Injection 0.15 mg and Epipen Injection 0.3 mg (hereinafter referred to as Epipen) have been approved as self-administered intramuscular injections for the adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others. In addition, multiple other adrenaline injections have been approved for different indications, such as for adjunctive treatment for acute hypotension or shock associated with various diseases and conditions.

Neffy Nasal Spray 1 mg and Neffy Nasal Spray 2 mg (hereinafter referred to as "Neffy"), a nasal spray solution containing adrenaline as an active substance, were developed to provide easily self-administered adjunctive treatment for anaphylactic reactions.

In Japan, the clinical development of Neffy began in [redacted] 20[redacted]. Recently, the applicant filed an application for the marketing approval based on Japanese and foreign clinical study results. As of May 2025, Neffy 1 mg and 2 mg formulations have been approved in the US, and EURneffy 2 mg formulation has been approved in Europe.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance (adrenaline) is listed in the Japanese Pharmacopoeia (JP). Adrenaline is registered in the master file (MF) (MF registration No. [redacted]) and used in the manufacture of approved formulations. During the review process, microbial limits were established for the specifications of the drug substance [see Section 2.R.1].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a nasal spray solution, each container (0.1 mL) contains 1.0 mg or 2.0 mg of the drug substance. The drug product contains the following excipients: dodecyl maltoside (DDM), disodium edetate hydrate, benzalkonium chloride concentrated solution 50, sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising of the following steps: Acceptance inspection, dissolution [redacted], [redacted], mixing/pH adjustment/making up to a constant volume/filtration, filling/capping, assembly/packaging/labeling/storage, and testing/storage. [redacted], [redacted], and [redacted]

[redacted] are defined as critical steps. In-process control parameters and control values have been established for [redacted] and [redacted].

The quality control strategy has been formulated based on the following investigations (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters based on quality risk assessment

Table 1. Outline of the control strategy for the drug product

CQA	Control method
Strength	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Identification (identity)	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process
[redacted]	Manufacturing process
Related substances and impurities	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
pH	Manufacturing process, specifications
Osmolality	Manufacturing process
Uniformity of dosage units (spray volume uniformity)	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process
[redacted]	Manufacturing process
[redacted]	Manufacturing process
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description ([redacted]), identification (high performance liquid chromatography [HPLC], ultraviolet-visible spectroscopy), pH, purity (related substances [HPLC, ultra high performance liquid chromatography (UHPLC)], [redacted] [HPLC]), uniformity of dosage units (spray volume uniformity), [redacted], [redacted], microbial limits, [redacted] (HPLC), and assay (HPLC). [redacted], [redacted], and [redacted] were established during the review process.

2.2.4 Stability of drug product

Table 2 summarizes the main stability studies that have been conducted on the drug product.

In the long-term study, for the [redacted] mg formulation, multiple [redacted] deviated from the specifications at [redacted] months. For the [redacted] mg formulation, an increasing tendency in [redacted] was noted. Although [redacted] had not deviated from the specifications at [redacted] months, given [redacted], the results suggest that [redacted] is likely to deviate from the specifications in future manufacturing batches.

The results of the accelerated study indicated that both formulations were stable.

The results of a photostability study showed that the formulations in a container fitted with a nasal spray pump were photostable.

Table 2. Main stability studies (drug product)

Formulation specification	Study	Primary batch	Temperature	Humidity	Storage package	Storage period
1 mg	Long-term	3 commercial batches	25°C	60% RH	Glass vial + [redacted] rubber stopper	36 months
	Accelerated		40°C	75% RH		6 months
2 mg	Long-term	3 commercial batches	25°C	60% RH		36 months
	Accelerated		40°C	75% RH		6 months

Based on the above results, a shelf life of 24 months was proposed for both formulations when packaged in a glass vial and [redacted] rubber stopper, fitted with a nasal spray pump as the primary package at room temperature.

2.R Outline of the review conducted by PMDA

Based on the submitted data and discussions below, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.R.1 Addition of preservative

Neffy is a single-use nasal spray solution. The applicant's explanation about the necessity of adding benzalkonium chloride concentrated solution 50 to the single-use formulation as a preservative:

Dodecyl maltoside has been added to Neffy to promote absorption of adrenaline. To assess the formulation design, a preservative effectiveness study was conducted. In solutions without benzalkonium chloride concentrated solution 50, specimens inoculated with [redacted] or [redacted] exhibited a decrease in DDM content at [redacted] months. To minimize microbial contamination during manufacture, microbial limits were controlled through the establishment of drug substance specifications. In addition, [redacted] and [redacted] are to be performed. However, these measures are not sufficient to prevent the decomposition of DDM by microorganisms. For this reason, benzalkonium chloride concentrated solution 50 needs to be added to stabilize DDM.

PMDA accepted the applicant's explanation.

2.R.2 New excipient

The amount of disodium edetate hydrate contained in the drug product exceeds the maximum amount used previously for intranasal administration; therefore, disodium edetate hydrate is classified as a new excipient. Dodecyl maltoside, another excipient contained in the drug product, is also classified as a new excipient because it has not previously been used via any route of administration.

2.R.2.1 Specifications and stability

PMDA concluded that there are no particular problems with the specifications and stability of disodium edetate hydrate, a JP-compliant product. On the other hand, DDM is controlled by the specifications outlined in the

Attachment. Based on the submitted data, PMDA concluded that there are no particular problems with the specifications and stability of these new excipients.

2.R.2.2 Safety

The applicant's explanation about the safety of disodium edetate hydrate:

The oral lethal dose 50% (LD_{50}) for rats was 2,000 to 2,800 mg/kg (Chemicals Evaluation and Research Institute, Japan [CERI] *Hazard Assessment Report "Ethylenediaminetetraacetic acid."* [in Japanese] 2006, p13, Chemical Assessment and Research Center, CERI); therefore, there are no toxicity concerns when systemic exposure is considered. In a single intranasal dose toxicity study of Neffy in rats [see Section 5.1], nasal bleeding was the only finding in the control group animals[1)] receiving vehicle containing disodium edetate hydrate. No significant changes were noted in the administration site. Based on the considerations described above, it is concluded that there are no significant safety concerns associated with disodium edetate hydrate at the proposed dosage regimen of Neffy.

The applicant's explanation about the safety of DDM:

In a 2-week repeated intranasal dose toxicity study in rats, nasal cavity inflammation associated with DDM treatment was noted following intranasal administration of DDM [redacted]% (200 μg/[redacted] μL) and [redacted]% (400 μg/[redacted] μL) every other day (7 doses total); however, the effects appeared to be reversible. The no-observed-effect level (NOEL) was determined to be [redacted]% (80 μg/[redacted] μL). In a skin irritation study in rabbits, following subcutaneous administration of DDM [redacted]% (15 mg/[redacted] mL) once weekly (2 doses total), minor to severe subacute inflammation was observed at the administration site, suggesting that DDM is a skin irritant. In an intranasal dose carcinogenicity study in rats, following administration of the minimum dose level of DDM [redacted]% (0.1 mg/[redacted] μL) once daily, inflammation, squamous cell hyperplasia, and squamous metaplasia were noted at the administration site; however, following administration of DDM [redacted]% (3.0 mg/[redacted] μL), the maximum dose level once daily, carcinogenicity was not detected. In other studies,[2)] no particular changes were noted. While DDM has not been used previously in pharmaceutical products approved in Japan, DDM has been used as an excipient for nasal drops approved in other countries. It is considered that the above findings support the safety of Neffy containing [redacted]% DDM at the proposed dosage.

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1) Vehicle ([redacted]% disodium edetate hydrate, [redacted]% benzalkonium chloride, and [redacted]% DDM-containing physiological saline [pH[redacted]]) was administered.

2) Results from the following studies were also submitted:
A 13-week repeated intranasal dose toxicity study in dogs (DDM, maximum [redacted]% [330 μg/[redacted] μL], administered intranasally once daily); a 8-day intravenous dose study in rats (DDM, maximum 10 mg/kg/dose, administered once weekly, as an 24-hour continuous IV infusion [total of 2 doses]); an intravenous dose escalating toxicity study in dogs (1-10 mg/kg/dose or 10-400 mg/kg/dose of DDM, administered by escalating doses, once weekly, as an 24-hour continuous IV infusion [4 or 7 doses in total]); a reverse mutation assay; an *in vitro* chromosome aberration assay; an intravenous dose embryo-fetal developmental toxicity study in rats (DDM 30 mg/kg/day was administered as an 24-hour continuous IV infusion from gestational days 6 to 17); and a skin sensitization test in guinea pigs using the maximization method ([redacted]% DDM administered intradermally)

PMDA's view:
Based on the previous use of disodium edetate hydrate in approved pharmaceutical products in addition to the applicant's explanation, it was concluded that there are no significant safety concerns.

In addition to the applicant's explanation, considering that Neffy is intended for intermittent use as adjunctive treatment for anaphylactic reactions and based on the available human safety data for Neffy [see Section 7.R.3], it was concluded that there are no significant safety concerns for DDM at the highest estimated intranasal dose level ([redacted] mg when administered twice daily), as derived from the DDM concentration in Neffy ([redacted]%) and the proposed dosage regimen [see Section 7.R.5]. However, in a rat intranasal carcinogenicity study, squamous cell hyperplasia and squamous metaplasia considered to be associated with chronic damage were noted in the nasal cavity at concentrations ([redacted]%) lower than the DDM concentration in Neffy ([redacted]%). These findings suggest that the safety of DDM remains unclear when intranasal doses are repeatedly administered to humans. Accordingly, the use of DDM should be limited to specific conditions in which repeated administration is not expected to result in the accumulation of local tissue damage, such as with the proposed use of Neffy, and this should not be regarded as establishing a general precedent.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Adrenaline is widely used in the treatment of anaphylaxis. Adrenaline is known to exert the following effects on anaphylactic symptoms: α_1 receptor-mediated vasoconstrictive effects and mucosal edema suppressing effects, β_1 receptor-mediated increased ventricular contractility and increased heart rate, β_2 receptor-mediated suppression of further mediator release from mast cells and bronchodilation effects (*World Allergy Organ J.* 2008;1:S18-26, *World Allergy Organ J.* 2011;4:13-37).

When the application for a new route of administration was filed, a study was conducted in dogs to evaluate the pharmacokinetics of adrenaline administered intranasally [see Section 4.1.2]. In the study, cardiovascular effects were also studied; however, the effectiveness of adrenaline by intranasal administration on anaphylactic reactions was not evaluable in the test system used in the study.

3.R Outline of the review conducted by PMDA

No studies specifically evaluating the pharmacology of intranasal adrenaline had been conducted when the present application was filed. However, PMDA concluded that additional non-clinical pharmacology studies on intranasal adrenaline are not necessary for the following reasons: Absorption after intranasal administration of adrenaline has been evaluated [see Section 4.1]; and the pharmacological effects of blood adrenaline are already well understood.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The present application involves a new route of administration. Data from studies including single-dose studies of adrenaline in rats and dogs were submitted as absorption and metabolism data. Data from the main studies are outlined in the following sections.[3)]

The concentrations of adrenaline in plasma were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS) (lower limits of quantitation, 0.1 ng/mL).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.3.1-1)

Table 3 shows the plasma adrenaline pharmacokinetic parameters following a single intranasal dose of adrenaline 0, 0.2, 0.4, or 0.8 mg to rats. Within the dose levels studied, the C_{max} and $AUC_{0\text{-}240min}$ increased dose-dependently. There was no consistent tendency in adrenaline exposure between the sexes.

Table 3. Pharmacokinetic parameters of plasma adrenaline following single dose administration

Dose (mg)	Sex	N	C_{max} (ng/mL)	$AUC_{0\text{-}240min}$ (ng·min/mL)	t_{max} (min)
0 [a)]	Male	3 per group[b)]	1.25	223	30
	Female		1.84	277	15
0.2	Male		161	3,440	15
	Female		47.3	2,230	15
0.4	Male		162	5,980	15
	Female		165	6,870	15
0.8	Male		656	26,500	30
	Female		326	17,600	15

Mean; t_{max}, median

a) Vehicle ([redacted]% disodium edetate hydrate, [redacted]% benzalkonium chloride, and [redacted]% DDM-containing physiological saline [pH[redacted]])

b) Number of animals per timepoint; the values were calculated based on the mean adrenaline concentration at each timepoint

4.1.2 Single-dose study (CTD 4.2.1.1-2 [reference data])

In an unconscious state under anesthesia,[4)] a single intranasal dose of adrenaline 1.0 mg was administered to anaphylaxis-noninduced dogs (pretreated with 1.2 mL/kg of physiological saline) and anaphylaxis-induced dogs (pretreated with 1.2 mL/kg of 0.25% Tween 80). Table 4 shows the plasma pharmacokinetic parameters based on baseline-corrected values taking into account endogenous adrenaline.

In this study, no anaphylaxis-induced or adrenaline-untreated control group was established, and the time course of endogenous adrenaline concentrations in anaphylaxis-induced dogs was not evaluated. The applicant explained that in its preliminary study, plasma adrenaline C_{max} was 473 pg/mL[5)] following administration of vehicle control to anaphylaxis-induced dogs in an unconscious state under anesthesia, while the plasma

3) Among data from studies on intranasal adrenaline submitted as absorption data, the dosing interval was defined as at least 2 days, which may have increased the absorption for the second dose of intranasal adrenaline [see Section 6.R.3], making it difficult to interpret the results. For this reason, the data are not included in this Review Report. The applicant submitted metabolism data from *in vitro* studies, in which metabolism by CYP1A2, CYP2C9, and CYP3A4, which were considered to be present in nasal mucosa, was evaluated. It was suspected that there was a high likelihood that adrenaline was degraded not due to the CYP enzymes but due to the experimental system. Accordingly, data were not included in this Review Report.

4) In the preliminary study, adrenaline pharmacokinetics was evaluated in dogs in a conscious state or unconscious state under anesthesia following single intranasal dose or single intramuscular dose administration of adrenaline. The result revealed that fluctuation of blood adrenaline was greater in conscious dogs; therefore, it was decided that the study was to be implemented in unconscious animals under anesthesia.

5) In the preliminary study, anaphylaxis was induced 5 minutes before the administration of vehicle control, and the t_{max} was observed 15 minutes after administration of vehicle control. The values were not corrected with baseline values.

adrenaline concentration in anaphylaxis-induced dogs in this study significantly exceeded the preliminary study concentration, a result indicating the absorption of intranasally administered adrenaline.

Table 4. Pharmacokinetic parameters[a)] of plasma adrenaline following administration of a single dose of adrenaline 1.0 mg[b)]

Anaphylaxis[c)]	N	C_{max} (pg/mL)	$AUC_{0\text{-}45min}$ (pg·min/mL)	t_{max} (min)
Non-induced	14 per group[d)]	998 (126)	24,300 (144)	7.50 [2.50, 45.0]
Induced		2,420 (169)	28,900 (267)	5.00 [2.50, 45.0]

Geometric mean (% geometric coefficient of variation [CV]); t_{max}, median [range]

a) Pharmacokinetic parameters were calculated using the plasma adrenaline concentration (anaphylaxis-noninduced, 50.0 pg/mL; anaphylaxis-induced, 274 pg/mL) 4 minutes after administration of physiological saline or 0.25% Tween 80 (3 minutes before adrenaline administration) as the baseline value.

b) A formulation containing disodium edetate hydrate, benzalkonium chloride, sodium pyrosulfite, and DDM

c) Anaphylaxis-induced dogs vs non-induced dogs were evaluated using the same animals with ≥7 day-interval between the test periods. In each period, adrenaline was administered to a different nostril.

d) 10 males and 4 females

4.R Outline of the review conducted by PMDA

Based on the submitted non-clinical pharmacokinetic data, PMDA concluded that the *in vivo* behavior of intranasally administered adrenaline can be reasonably characterized.

5. Toxicology and Outline of the Review Conducted by PMDA

The toxicology results of adrenaline from a single intranasal dose toxicity study in rats and an eye irritation study in rabbits were submitted. Given that adrenaline is an endogenous substance, and that its systemic toxicity profile in humans is well known from the long-term clinical data of approved adrenaline injections, no other study data were submitted for the present application.

5.1 Single-dose toxicity

A single intranasal dose toxicity study was conducted in rats (Table 5). At adrenaline ≥0.2 mg, necrosis, ulcers, inflammation, or bleeding was noted at the administration sites, i.e., nose and nasal cavity. These changes, not observed in the vehicle control group, were considered to be adrenaline-associated changes; however, they were not determined to be toxicities because of their low severity, limited distribution, and reversibility. The non-observed adverse effect level (NOAEL) was determined to be 0.8 mg.

The mean blood exposure (males and females) at an adrenaline dose of 0.8 mg was 433 ng/mL (C_{max}) and 21,900 ng·min/mL ($AUC_{0\text{-}240min}$). The dose per nasal cavity surface area at adrenaline 0.8 mg was 3.2-fold[6)] that of the intranasal dose of adrenaline 4 mg, which represents the maximum expected human dose of Neffy when administered twice daily.

[6)] The dose of adrenaline per nasal cavity surface area was calculated as 0.08 mg/cm^2 in rats assuming a nasal cavity surface area of 10 cm^2 for rats (*J Anat.* 1982;135:83-8); 0.025 mg/cm^2 in humans assuming a nasal cavity surface area of 160 cm^2 for humans (*Curr Drug Deliv.* 2012;9:566-82).

Table 5. Summary of single toxicity study in rats

Test system	Route of administration	Dose[a] (mg)	Major findings[b]	NOAEL (mg)	CTD
Male/female rats (SD)	Intranasal	Adrenaline 0,[c] 0,[d] 0.2, 0.4, 0.8	At ≥0 mg,[d] nasal bleeding At ≥0.2 mg, acute inflammation of the nasal cavity, nasal cavity necrosis At ≥0.4 mg, nasal ulcer, nasal inflammation (neutrophilic) At 0.8 mg, minor increase in blood fibrinogen Reversibility: reversible in all cases	0.8	4.2.3.1-1

a) Physiological saline 80 μL, vehicle 80 μL, or adrenaline (10 mg/mL) 20, 40, or 80 μL was to be administered to the right and left nostrils, (half the amount for each nostril). In each nostril, 10 μL per dose was to be administered, and administration was to be continued until the specified volume was reached.
b) The animals were kept for 2 or 15 days after single dose administration, and then underwent necropsy.
c) Physiological saline
d) Vehicle ([redacted]% disodium edetate hydrate, [redacted]% benzalkonium chloride, and [redacted]% DDM-containing physiological saline [pH[redacted]])

5.2 Local tolerance

An eye irritation study in rabbits was conducted to evaluate the effects if Neffy enters the eye (Table 6). While transient dilation of the pupil, which is caused by the pharmacological action of adrenaline, was observed, no other adverse effects were noted, indicating that tolerability was satisfactory.

Table 6. Summary of eye irritation study

Test system	Test method	Major findings	CTD
Male/female rabbits (NZW)	A single dose of adrenaline 0 [a] or 1 mg [b] was instilled into either the right or left eye, and eye irritation was evaluated.	At 30 minutes and 1 hour after instillation, dilation of the pupil was observed, which subsided at 6 hours post-instillation. Not considered to be an eye irritant.	4.2.3.6-1 Reference data

a) Vehicle ([redacted]% disodium edetate hydrate, [redacted]% benzalkonium chloride, and [redacted]% DDM-containing physiological saline [pH[redacted]]) 100 μL was to be administered.
b) Adrenaline (10 mg/mL) 100 μL was to be administered.

5.R Outline of the review conducted by PMDA

Based on the submitted toxicity data, PMDA concluded that local toxicity following intranasal administration of adrenaline had been adequately evaluated.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Biopharmaceutic evaluation data including results from relative bioavailability studies were submitted. The main study results are summarized in the following sections.[7] No bioequivalence studies were conducted between the 1 mg and 2 mg commercial formulations.

Plasma adrenaline concentrations were determined by LC-MS/MS (lower limit of quantitation, 11.0 pg/mL[8] or 20.0 pg/mL). Unless otherwise specified, dose levels were expressed as adrenaline dose levels.

[7] In addition to data from Study EPI 11B, data from 4 clinical studies that evaluated intranasal administration of adrenaline or intramuscular injection of adrenaline to healthy adults (Studies EPI 01, EPI 02, EPI 06, and EPI 11) were also submitted as data relating to biopharmaceutic studies. However, given that the formulation used in Study EPI 01 differs significantly from the formulations used in subsequent clinical studies, and that in Studies EPI 02, EPI 06, and EPI 11, the dosing interval was specified as 24 hours, which may have increased the intranasal absorption in the administration of the second intranasal dose [see Section 6.R.3], making interpretation difficult, the data are not included in this Review Report. Meanwhile, data from Study EPI 12, which were submitted as clinical pharmacology data, are presented in this section in accordance with the type of study.
[8] Study EPI JP02, Study EPI 18, and Study EPI 10 Part 2

6.1.1 Foreign phase I study (CTD 5.3.1.1-5, Study EPI 11B [March 2021 to April 2021])

A randomized, open-label, 5-treatment, 5-period crossover study was conducted in 2 cohorts in healthy non-Japanese adults (26 subjects total, 13 subjects/cohort) to evaluate relative bioavailability. Subjects received a single intranasal dose of formulations containing different concentrations of adrenaline and DDM, or a single intramuscular dose of Symjepi[9)] (Cohort 1) or Epipen (Cohort 2) 0.3 mg. The relative bioavailability of adrenaline compared with Symjepi or Epipen is shown in Table 7 and Figure 1.[10)]

Following intranasal administration of adrenaline, no clear dose-exposure relationship was observed in Cohort 1. In contrast, in Cohort 2, exposure tended to increase with increasing adrenaline dose, and the highest C_{max} and AUC_{0-t} were observed with the adrenaline 2.0 mg (0.30% DDM) formulation. There was no marked difference in t_{max} between the adrenaline formulations. In terms of efficacy, administration of adrenaline 2.0 mg resulted in plasma adrenaline concentrations comparable to those observed with Symjepi. From a safety perspective, the C_{max} was not expected to exceed that of Epipen. Based on these findings, the applicant selected 2.0 mg as the adult dosage of Neffy.

Table 7. Pharmacokinetic parameters[a)] of plasma adrenaline following single dose administration

Cohort	Route of administration	Formulation[b)]	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	Geometric mean ratio [90% CI] vs intramuscular administration[c)]	
							C_{max}	AUC_{0-t}
1	Intra-muscular	Symjepi 0.3 mg	12	318 (61.4)	17,100 (60.0)	30.0 [6.00, 45.0]		
	Intranasal[d)]	Adrenaline 1.3 mg (0.25% DDM)	13	202 (153)	12,600 (112)	30.0 [15.0, 120]	0.5902 [0.4146, 0.8401]	0.6883 [0.4972, 0.9530]
		Adrenaline 1.5 mg (0.25% DDM)	13	171 (73.9)	11,100 (61.9)	20.0 [2.00, 90.0]	0.5019 [0.3526, 0.7146]	0.6042 [0.4364, 0.8366]
		Adrenaline 1.5 mg (0.30% DDM)	13	366 (115)	19,200 (119)	20.0 [13.0, 60.0]	1.0723 [0.7533, 1.5265]	1.0454 [0.7551, 1.4474]
		Adrenaline 1.8 mg (0.30% DDM)	12	221 (84.4)	14,100 (71.9)	25.0 [6.00, 60.0]	0.6955 [0.4861, 0.9952]	0.8223 [0.5911, 1.1439]
2	Intra-muscular	Epipen 0.3 mg	9	537 (43.3)	14,200 (40.1)	6.00 [2.00, 6.00]		
	Intranasal[d)]	Adrenaline 1.0 mg (0.25% DDM) (batch 1)[e)]	12	142 (85.6)	9,830 (67.9)	25.0 [2.00, 120]	0.2625 [0.1651, 0.4175]	0.6688 [0.4226, 1.0586]
		Adrenaline 1.0 mg (0.25% DDM) (batch 2)[e)]	11	183 (90.5)	8,970 (110)	12.0 [2.00, 45.0]	0.3473 [0.2161, 0.5581]	0.6367 [0.3979, 1.0188]
		Adrenaline 1.5 mg (0.30% DDM)	12	267 (69.4)	13,900 (90.0)	15.0 [2.00, 60.0]	0.4938 [0.3105, 0.7854]	0.9473 [0.5985, 1.4993]
		Adrenaline 2.0 mg (0.30% DDM)	12	391 (63.3)	21,800 (73.0)	20.0 [4.00, 60.0]	0.7272 [0.4576, 1.1555]	1.5017 [0.9495, 2.3752]

Geometric mean (% geometric CV); t_{max}, median [range]

a) Pharmacokinetic parameters were evaluated based on plasma concentrations up to 120 minutes post-dose

b) The adrenaline nasal formulation used in Study EPI 11B is different from the commercial formulation

c) The ratio of adrenaline vs Symjepi 0.3 mg (Cohort 1) or Epipen 0.3 mg (Cohort 2)

d) In each treatment by intranasal administration, adrenaline was administered to the right and left nostril alternately. An interval of at least 12 days was specified for ipsilateral nostril administration.

e) Batches 1 and 2 are formulations of different manufacturing batches

9) A prefilled syringe of adrenaline approved in the US as a formulation that allows self-administration to treat allergic reactions (Type I) including anaphylaxis. The product is not approved in Japan.

10) The following subjects were excluded from the pharmacokinetic analysis population: subjects to whom the formulation was accidentally administered intravenously instead of intramuscularly (4 subjects treated with Epipen 0.3 mg whose C_{max} >1,000 pg/mL and $t_{max} \leq 4$ min); subjects whose C_{max} or AUC_{0-t} value was determined to be abnormal (values that were determined to be statistically significant at two-sided significance level of 5% in the Grubbs test: 1 subject each for Symjepi 0.3 mg; adrenaline 1.8 mg [0.30% DDM]; adrenaline 1.0 mg [0.25% DDM, batch 1]; adrenaline 1.0 mg [0.25% DDM, batch 2]; adrenaline 1.5 mg [0.30% DDM]; and adrenaline 2.0 mg [0.30% DDM]). A supplementary analysis was performed on subjects including those mentioned above. The pharmacokinetic results tended to be similar to those of the primary analysis.

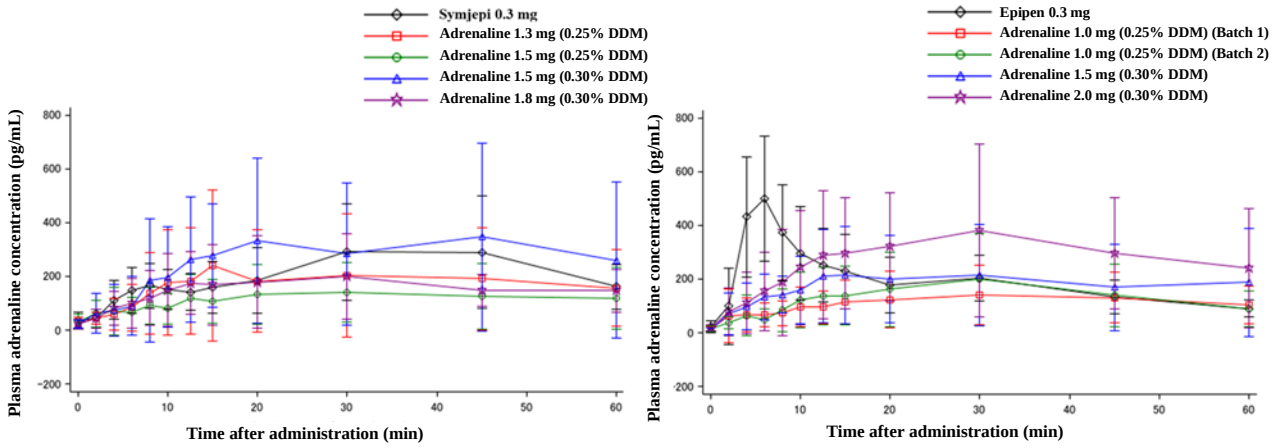

Figure 1. Time course of plasma adrenaline concentrations up to 60 minutes after single dose administration (arithmetic mean ± standard deviation)

6.1.2 Foreign phase I study (CTD 5.3.4.2-5, Study EPI 12 [January 2021 to March 2021])

A randomized, open-label, 4-treatment, 4-period crossover study was conducted in 36 adult non-Japanese patients with Type I systemic allergy. In the study, the plasma adrenaline pharmacokinetics was evaluated following administration of a single intranasal dose of formulations containing different concentrations of DDM or a single intramuscular dose of Symjepi or Epipen 0.3 mg. The results are presented in Table 8.[11)]

The pharmacokinetics data showed that, following intranasal administration of adrenaline 1.0 mg, C_{max} and AUC_{0-t} were comparable between the 0.25% DDM and 0.35% DDM formulations, whereas t_{max} was shorter for the 0.35% DDM formulation.

The above results suggest that a certain level of absorption of adrenaline can be achieved by intranasal administration when DDM is included at concentrations of ≥[redacted]%. The applicant also explained that because [redacted] was observed in the formulation in the stability study of Neffy, a DDM concentration of [redacted]% was selected for the commercial formulation to ensure that the DDM concentration can be maintained within the expiration period.

[11)] The following subjects were excluded from the pharmacokinetic analysis population: subjects to whom the formulation was accidentally administered intravenously instead of intramuscularly (7 subjects treated with Epipen 0.3 mg and 1 subject treated with Symjepi 0.3 mg whose C_{max} >1,000 pg/mL and t_{max} ≤4 min); subjects whose C_{max} or AUC_{0-t} value was determined to be abnormal (values that were determined to be statistically significant at two-sided significance level of 5% in the Grubbs test: 1 subject treated with Symjepi 0.3 mg, 1 subject treated with adrenaline 1.0 mg [0.35% DDM]); and subjects in whom medication error occurred (10 subjects treated with Epipen 0.3 mg, 6 subjects treated with Symjepi 0.3 mg). A supplementary analysis was performed on subjects including those mentioned above. The pharmacokinetic results tended to be similar to those of the primary analysis.

Table 8. Pharmacokinetic parameters [a)] of plasma adrenaline following single dose administration

Route of administration	Formulation	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)
Intranasal[b)]	Adrenaline 1.0 mg (0.25% DDM)	18	187 (54.6)	16,800 (68.0)	34.5 [2.00, 120]
	Adrenaline 1.0 mg (0.35% DDM)[c)]	17	205 (73.3)	15,600 (84.4)	21.0 [6.00, 90.0]
Intra-muscular	Symjepi 0.3 mg	34	391 (52.8)	22,600 (36.6)	30.0 [4.00, 90.0]
	Epipen 0.3 mg	29	458 (52.3)	23,400 (38.7)	15.0 [3.00, 154]

Arithmetic mean (%CV); $t_{max,}$ median [range]

a) Pharmacokinetic parameters were evaluated based on plasma concentrations up to 240 minutes post-dose

b) Data when the first intranasal dose of adrenaline was administered. When the second or subsequent intranasal doses of adrenaline were administered, intranasal absorption may increase if the dosing interval is short [see Section 6.R.3]. Therefore, only data for the first intranasal adrenaline dose were used.

c) For the subject in whom C_{max} was observed prior to administration of adrenaline, the plasma adrenaline concentration prior to the first adrenaline dose was to be handled as the lower limit of quantitation.

6.2 Clinical pharmacology

Clinical pharmacology data including results from the studies in healthy adults, patients with systemic allergy, and other populations were submitted. Table 9 summarizes the main clinical pharmacology studies conducted using the commercial formulation, and data are presented in the following sections.[12)] Unless otherwise specified, dose levels are expressed as adrenaline dose levels.

[12)] The applicant submitted data from other pharmacology studies that evaluated pharmacokinetics and pharmacodynamics following administration of an intranasal dose of adrenaline or an intramuscular dose of adrenaline to healthy adults or adult patients with seasonal allergic rhinitis.

Table 9. Summary of main clinical pharmacology studies

Study ID	Study population	Main objective	Dosage regimen
EPI 15	Healthy non-Japanese adults	Comparison of pharmacokinetics and pharmacodynamics of adrenaline after administration of a single dose (Part 1) or 2 doses (Part 2) of Neffy 2.0 mg, Epipen 0.3 mg, etc.	**Single dose** • Neffy 2.0 mg • Epipen 0.3 mg • Adrenalin[a)] 0.3 mg
			2 doses • Neffy 2.0 mg (contralateral nostril) • Neffy 2.0 mg (ipsilateral nostril) • Epipen 0.3 mg
EPI JP02	Healthy Japanese adults	Comparison of pharmacokinetics and pharmacodynamics of adrenaline after administration of Neffy 2.0 mg or Adrenalin[a)] 0.3 mg	**Single dose** • Neffy 2.0 mg • Adrenalin[a)] 0.3 mg
EPI 14	Adult non-Japanese patients with rhinitis associated with upper respiratory tract infection	Comparison of pharmacokinetics and pharmacodynamics of adrenaline after administration of Neffy 2.0 mg under normal nasal conditions and in subjects with rhinitis	**Single dose** <u>Normal state</u> • Neffy 2.0 mg <u>Rhinitis</u> • Neffy 2.0 mg
EPI 16	Adult non-Japanese patients with seasonal allergic rhinitis		**Single dose** <u>Normal state</u> • Neffy 2.0 mg • Adrenalin[a)] 0.3 mg • Adrenalin[a)] 0.5 mg <u>Rhinitis</u> • Neffy 2.0 mg
EPI 18			**2 doses** <u>Normal state</u> • Neffy 2.0 mg (contralateral nostril) • Adrenalin[a)] 0.3 mg <u>Rhinitis</u> • Neffy 2.0 mg (contralateral nostril) • Neffy 2.0 mg (ipsilateral nostril) • Adrenalin[a)] 0.3 mg
EPI 10	Pediatric non-Japanese patients with systemic allergy	Exploratory study of optimal dosage for pediatric patients by body weight category	**Single dose** <u>Body weight ≥15 kg and <30 kg</u> • Neffy 0.65 mg • Neffy 1.0 mg <u>Body weight ≥30 kg</u> • Neffy 1.0 mg • Neffy 2.0 mg

a) An adrenaline 1 mg/mL vial formulation approved in the US for the indication of treatment of allergic reactions (Type I) including anaphylactic reactions. The product is not approved in Japan.

6.2.1 Foreign phase I study (CTD 5.3.4.1-2, Study EPI 15 [July 2021 to September 2021])

A randomized,[13)] open-label, 3-treatment, 3-period crossover study was conducted in healthy non-Japanese adults (target sample size, 42 subjects) in each of the 2 parts[14)] established to evaluate the pharmacokinetics and pharmacodynamics of Neffy.

In Part 1 (Periods 1 through 3), subjects received a single intranasal dose of Neffy 2.0 mg or a single intramuscular dose of Epipen or Adrenalin[15)] 0.3 mg. In Part 2 (Periods 4 through 6), subjects received either 2 intranasal doses of Neffy 2.0 mg administered into the same nostril or to opposite nostrils, or 2 intramuscular doses of Epipen 0.3 mg, administered 10 minutes apart.[16)]

[13)] In Part 2, subjects were randomized to one of the following 2 treatment sequences. In Period 5, subjects were to receive Epipen 0.3 mg intramuscularly, i.e., left anterolateral thigh followed by right anterolateral thigh.
- Neffy 2.0 mg intranasally (right/left nostrils) → Epipen 0.3 mg intramuscularly (left/right anterolateral thighs) → Neffy 2.0 mg intranasally (right nostril twice)
- Neffy 2.0 mg intranasally (right nostril twice) → Epipen 0.3 mg intramuscularly (left/right anterolateral thigh) → Neffy 2.0 mg intranasally (right/left nostril)

[14)] Throughout Part 1 and Part 2, participants received the study drugs in a 6-treatment and 6-period design.

[15)] An adrenaline 1 mg/mL vial formulation approved in the US for the emergency treatment of allergic reactions (Type I) including anaphylaxis. The product is not approved in Japan.

[16)] The dosing interval was specified as 24 hours in Part 1 and ≥6 days in Part 2, with a between-part interval of ≥12 days. In Part 2, the study drugs were administered intranasally in Period 4 and Period 6, and intramuscularly in Period 5, which ensured a dosing interval of ≥12 days for intranasal administration.

All 59 subjects[17)] who received the study drug were included in the safety analysis population, and 58 subjects were included in the pharmacokinetic and pharmacodynamic analysis populations.[18)]

The results of plasma adrenaline pharmacokinetics and pharmacodynamics in Part 1 and Part 2 are presented in Table 10 and Figure 2 to Figure 4.

The pharmacokinetic results show that in the single-dose regimens, C_{max} was lower and t_{max} was delayed following administration of Neffy 2.0 mg compared with Epipen 0.3 mg while the AUC_{0-t} was higher. In the 2-dose regimens, the C_{max} and AUC_{0-t} were higher and t_{max} was delayed following administration of Neffy 2.0 mg compared with Epipen 0.3 mg (Table 10).

The pharmacodynamic results show that in both single and 2-dose regimens, change from baseline in systolic blood pressure (SBP) to maximum observed effect (ΔSBP E_{max}) and change from baseline in pulse rate (PR) to maximum observed effect (ΔPR E_{max}) were greater and t_{Emax} was delayed following administration of Neffy 2.0 mg compared with Epipen 0.3 mg (Table 10). The results for changes from baseline in SBP and PR showed increases from shortly after administration of Neffy 2.0 mg, comparable to or greater than those with Epipen 0.3 mg (Figure 3 and Figure 4).

In Part 2, there were no clear pharmacokinetic/pharmacodynamic differences between ipsilateral or contralateral intranasal administration of two Neffy 2.0 mg doses.

Based on the findings, the applicant explained that pharmacodynamic effects similar to those of Epipen can be expected after single-dose or 2-dose administration of Neffy 2.0 mg.

[17)] Including 5 subjects who were re-enrolled.

[18)] Sample preparation errors occurred in 13 subjects. These subjects received the study drug and were included in the pharmacokinetic and pharmacodynamic analysis populations, but were not included in the analysis. In addition, the following subjects were excluded from the pharmacokinetic and pharmacodynamic analyses: subjects to whom the formulation was administered intravascularly where it was supposed to be administered intramuscularly (C_{max} >1,000 pg/mL and t_{max} ≤4 min: in Part 1, 7 subjects treated with Epipen 0.3 mg and 1 subject treated with intramuscular Adrenalin 0.3 mg; in Part 2, 2 subjects treated with Epipen 0.3 mg); subjects whose C_{max} or AUC_{0-t} value was determined to be abnormal (values that were determined to be statistically significant at a two-sided significance level of 5% in the Grubbs test: in Part 2, 3 subjects treated with Neffy 2.0 mg [right/left nostril] and 3 subjects treated with Epipen 0.3 mg). A supplementary analysis was performed on subjects including those mentioned above, and the results tended to be similar to the results of this analysis.

Table 10. Pharmacokinetic and pharmacodynamic parameters of plasma adrenaline following administration of a single dose and 2 doses[a)]

Part	Formulation	Administration site	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	ΔSBP E_{max}(mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
Part 1 (single dose)	Neffy 2.0 mg	Intranasal (left nostril)	42	481 (76.0)	43,500 (69.4)	30.0 [6.00, 150]	23.6 (64.8) 25.0 [1.00, 116]	17.3 (62.7) 19 [1.00, 116]
	Epipen 0.3 mg	Intramuscular (left anterolateral thigh)	35	612 (58.4)	30,900 (37.1)	8.00 [2.00, 45.0]	15.6 (59.4) 10.0 [1.00, 116]	11.7 (64.9) 11.0 [2.00, 115]
	Adrenalin 0.3 mg	Intramuscular (right anterolateral thigh)	41	309 (53.2)	29,000 (42.1)	45.0 [4.00, 90.0]	12.0 (81.5) 20.0 [1.00, 116]	9.73 (88.0) 29.0 [1.00, 117]
Part 2 (2 doses)	Neffy 2.0 mg	Intranasal (right/left nostril)	36	805 (69.2)	72,500 (61.4)	30.0 [6.00, 150]	28.5 (48) 29.0 [2.00, 116]	21.0 (57.1) 34.5 [1.00, 116]
	Neffy 2.0 mg	Intranasal (right/right nostril)	39	992 (75.3)	86,000 (60.5)	30.0 [4.00, 150]	29.1 (46.0) 28.0 [6.00, 85.0]	22.9 (44.3) 40.0 [1.00, 116]
	Epipen 0.3 mg	Intramuscular (left/right thigh anterolaterally)	37	719 (43.3)	49,900 (38.7)	15.0 [0.00, 360]	19.2 (44.9) 14.0 [1.00, 85.0]	17.3 (52.4) 26.0 [1.00, 116]

Arithmetic mean (%CV); t_{max} and $t_{Emax,}$ median [range]

a) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 360 minutes post-dose and 120 minutes post-dose, respectively.

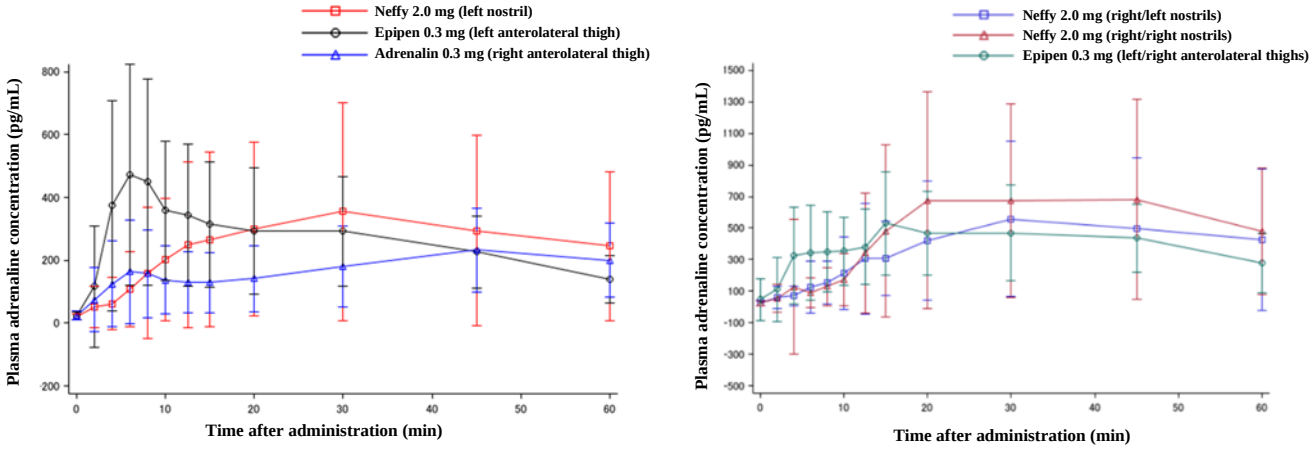

Figure 2. Time course of plasma adrenaline concentrations up to 60 minutes following single-dose (left) or 2-dose administration (right) (arithmetic mean ± standard deviation)

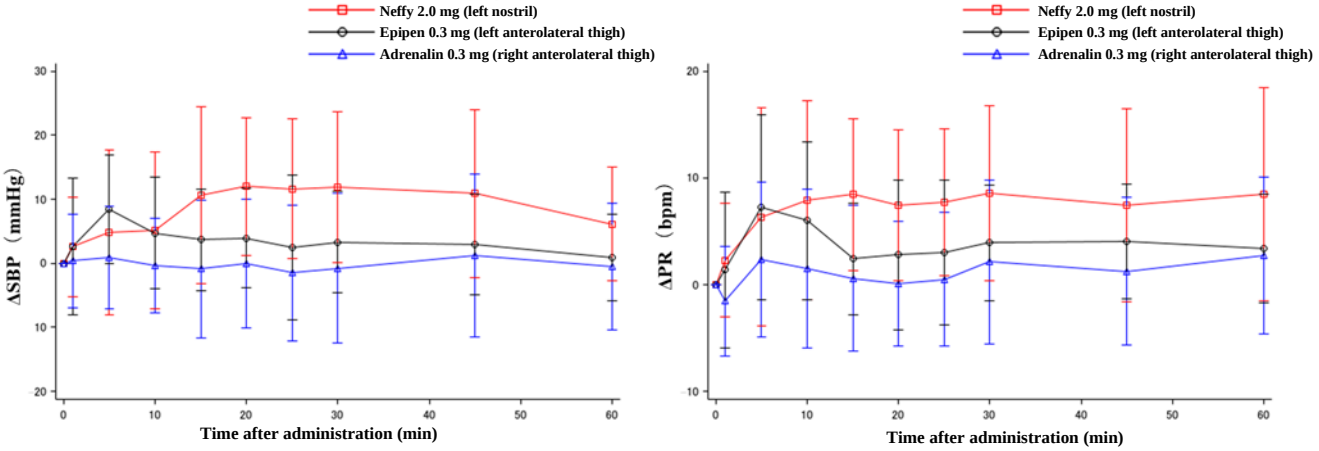

Figure 3. Changes over time from baseline in SBP (left) and PR (right) up to 60 minutes following single-dose administration (arithmetic mean ± standard deviation)

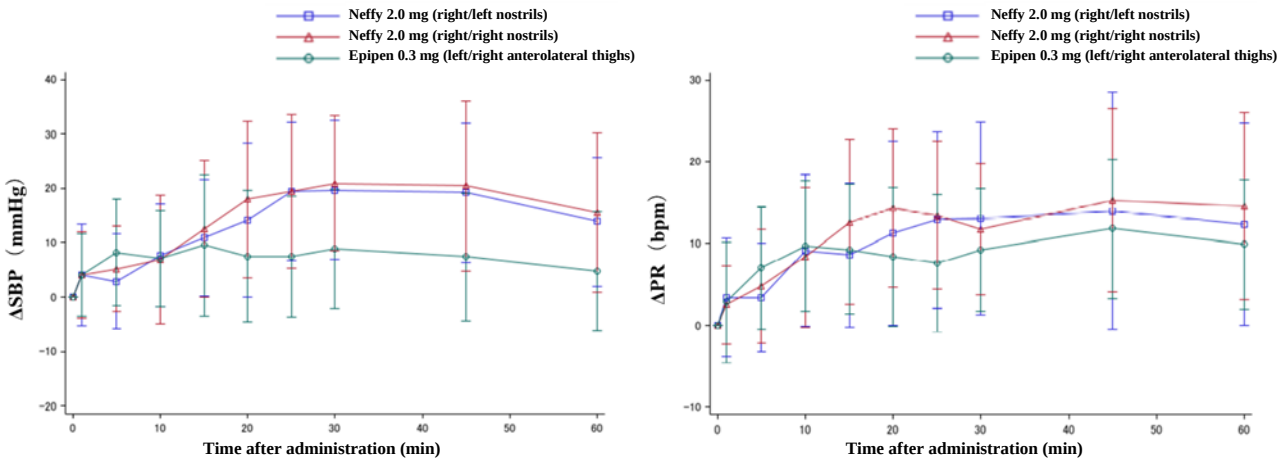

Figure 4. Changes over time from baseline in SBP (left) and PR (right) up to 60 minutes following 2-dose administration (arithmetic mean ± standard deviation)

Table 11 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 11. Incidence of adverse events (safety analysis population)

Part	Part 1 (single dose administration)			Part 2 (2-dose administration)		
Formulation	Neffy 2.0 mg	Epipen 0.3 mg	Adrenalin 0.3 mg	Neffy 2.0 mg (right/left nostril)	Neffy 2.0 mg (right nostril twice)	Epipen 0.3 mg
N	56	55	55	39	39	42
All adverse events	3 (5.4)	2 (3.6)	0	6 (15.4)	4 (10.3)	1 (2.4)
Adverse drug reactions	2 (3.6)	2 (3.6)	0	4 (10.3)	3 (7.7)	1 (2.4)
Adverse events occurring in ≥2 subjects in any group						
Vomiting	2 (3.6)	0	0	1 (2.6)	0	0
Headache	0	0	1 (1.8)	1 (2.6)	3 (7.7)	0

n (%) MedDRA ver.22.0

6.2.2 Foreign phase I study (CTD 5.3.4.1-1, Study EPI JP02 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, 2-treatment, 2-period crossover study was conducted outside Japan in healthy Japanese adults (target sample size, 12 subjects) to evaluate the pharmacokinetics and pharmacodynamics of Neffy.

In this study, subjects received a single intranasal dose of Neffy 2.0 mg or a single intramuscular dose of Adrenalin 0.3 mg.[19)]

All 13 subjects who received the study drug were included in the safety analysis population and pharmacokinetic/pharmacodynamic analysis populations.[20)]

[19)] For each treatment, a dosing interval of 24 hours was specified.
[20)] In Period 1, after study drug administration, 1 subject discontinued the study without plasma adrenaline concentration being measured. This subject was included in the pharmacokinetic and pharmacodynamic analysis populations, but was not included in the analysis.

The results of plasma adrenaline pharmacokinetics and pharmacodynamics are presented in Table 12, Figure 5, and Figure 6.

The pharmacokinetic results show that the C_{max} and $AUC_{0\text{-}t}$ were higher and t_{max} was observed earlier in the Neffy group than in the Adrenalin 0.3 mg group (Table 12).

The pharmacodynamic results show that ΔSBP E_{max} and ΔPR E_{max} were greater in the Neffy 2.0 mg group than in the Adrenalin 0.3 mg group. The t_{Emax} was comparable or earlier compared with the Adrenalin 0.3 mg group (Table 12). In terms of changes from baseline in SBP and PR over time, administration of Neffy 2.0 mg resulted in increases exceeding those observed with intramuscular Adrenalin 0.3 mg from the early phase after dosing (Figure 6).

Table 12. Pharmacokinetic and pharmacodynamic parameters[a)] of plasma adrenaline following single dose administration

Formulation	Administration site	N	C_{max} (pg/mL)	$AUC_{0\text{-}t}$ (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
Neffy 2.0 mg	Intranasal (left nostril)	12	814 (105.67)	56,782 (79.6)	20.0 [15.0, 120.0]	27 (42.1) 25 [1, 55]	20 (44.4) 16 [1, 55]
Adrenalin 0.3 mg	Intramuscular (right anterolateral thigh)	12	268 (31.5)	30,644 (36.4)	45.0 [15.0, 360.0]	7 (89.3) 25 [1, 40]	12 (64.8) 25[5, 55]

Arithmetic mean (%CV); t_{max} and t_{Emax}, median [range]

a) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 360 minutes post-dose and 120 minutes post-dose, respectively.

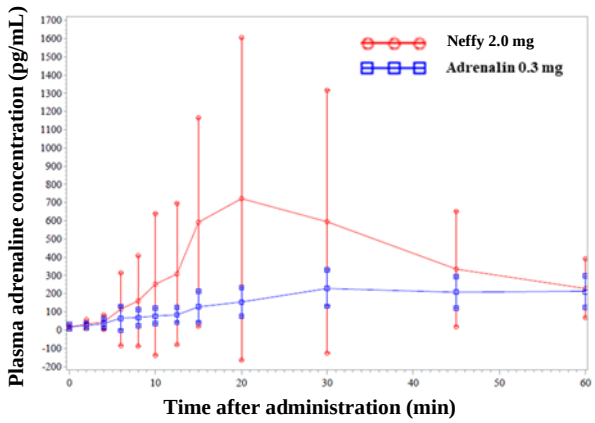

Figure 5. Time course of plasma adrenaline concentrations up to 60 minutes following single-dose administration (arithmetic mean ± standard deviation)

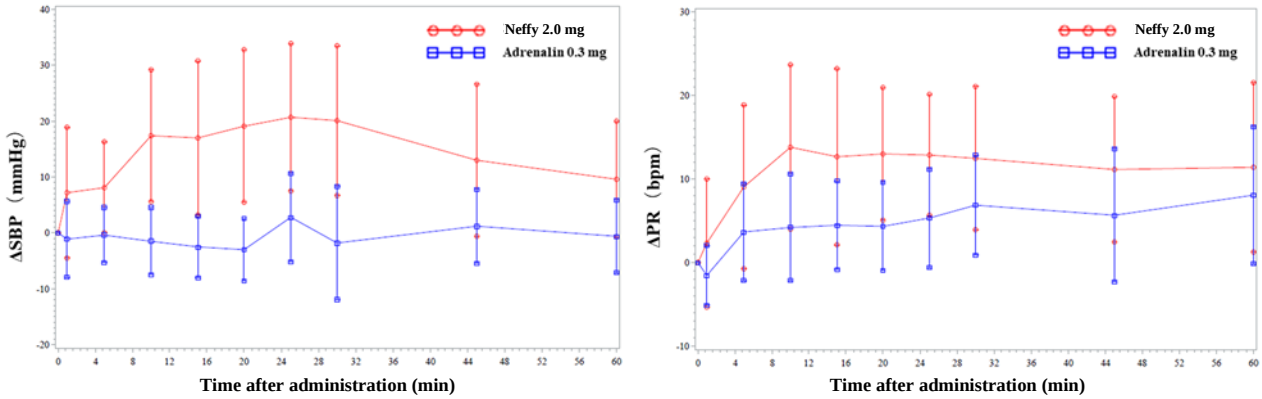

Figure 6. Changes over time from baseline in SBP (left) and PR (right) up to 60 minutes following single-dose administration (arithmetic mean ± standard deviation)

Table 13 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 13. Incidence of adverse events (safety analysis population)

Formulation	Neffy 2.0 mg	Adrenalin 0.3 mg
N	13	12
All adverse events	6 (46.2)	0
Adverse drug reactions	6 (46.2)	0
Adverse events occurring in ≥2 subjects in either group		
Nasal discomfort	3 (23.1)	0
Headache	2 (15.4)	0

n (%) MedDRA ver.22.0

6.2.3 Foreign phase I study (CTD 5.3.4.2-7, Study EPI 14 [August 2021 to March 2022])

An open-label study consisting of 2 periods was conducted to evaluate the pharmacokinetics and pharmacodynamics of Neffy in adult non-Japanese patients with rhinitis associated with upper respiratory tract infection (target sample size, 20 subjects).

In Period 1, a single intranasal dose of Neffy 2.0 mg was administered into the left nostril of subjects who contracted upper respiratory tract infection and presented with rhinitis[21)] (characterized by nasal mucosa oedema and nasal congestion). In Period 2,[22)] a single intranasal dose of Neffy 2.0 mg was administered into the right nostril of subjects who recovered from upper respiratory tract infection under normal nasal conditions.

All 21 subjects who received the study drug were included in the safety analysis population and pharmacokinetic/pharmacodynamic analysis populations.[23)]

The results of plasma adrenaline pharmacokinetics and pharmacodynamics for each treatment are presented in Table 14, Figure 7, and Figure 8.

The pharmacokinetic results show that the C_{max} and AUC_{0-t} were slightly lower in subjects with rhinitis associated with upper respiratory tract infection than in those with normal nasal conditions; however, no clear differences in pharmacokinetic parameters were noted (Table 14).

The pharmacodynamic results indicate that ΔSBP E_{max}, ΔPR E_{max}, t_{Emax}, and changes from baseline in SBP and PR were similar under both normal nasal conditions and rhinitis conditions associated with upper respiratory tract infection (Table 14 and Figure 8).

[21)] Confirmed upper respiratory tract infection and a TNSS score of ≥5 with a congestion score of ≥2 before treatment with Neffy
[22)] Period 1 and Period 2 were implemented ≥1 week apart to allow patients to recover from upper respiratory tract infection before entering Period 2.
[23)] In Period 2, the patient with missing data at 15 minutes post-dose of Neffy 2.0 mg (normal nasal condition) was excluded from the pharmacokinetic and pharmacodynamic analyses.

Table 14. Pharmacokinetic and pharmacodynamic parameters[a)] of plasma adrenaline following single dose administration of Neffy under the normal nasal conditions vs rhinitis conditions associated with upper respiratory tract infection

Nasal condition (administration site)	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
Rhinitis associated with upper respiratory tract infection (left nostril)	21	490 (67.2)	58,700 (60.9)	45.0 [1.60, 150]	20.9 (64.1) 45.1 [10.2, 90.6]	17.2 (55.5) 25.4 [5.10, 88.1]
Normal (right nostril)	16	570 (56.1)	64,400 (53.4)	45.7 [9.90, 150]	19.9 (61.8) 45.2 [0.00, 106]	16.4 (50.2) 30.4 [5.00, 106]

Arithmetic mean (%CV); t_{max} and $t_{Emax,}$ median [range]

a) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 240 minutes post-dose and 120 minutes post-dose, respectively.

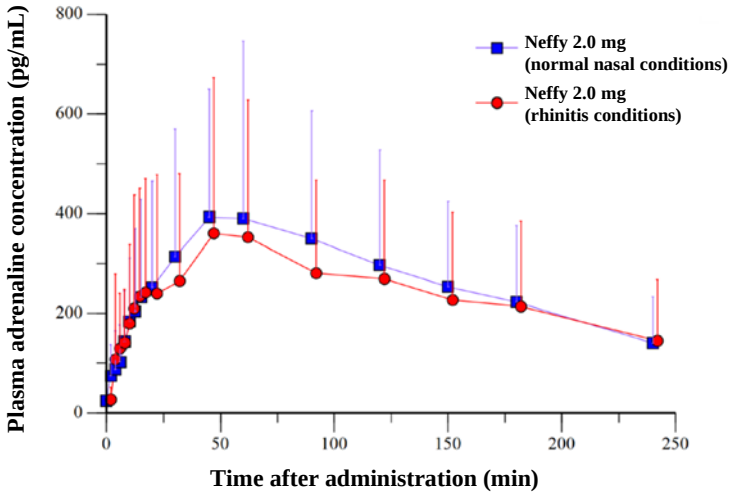

Figure 7. Time course of plasma adrenaline concentrations up to 240 minutes following single-dose administration of Neffy in normal nasal conditions or rhinitis conditions associated with upper respiratory tract infection (arithmetic mean + standard deviation)

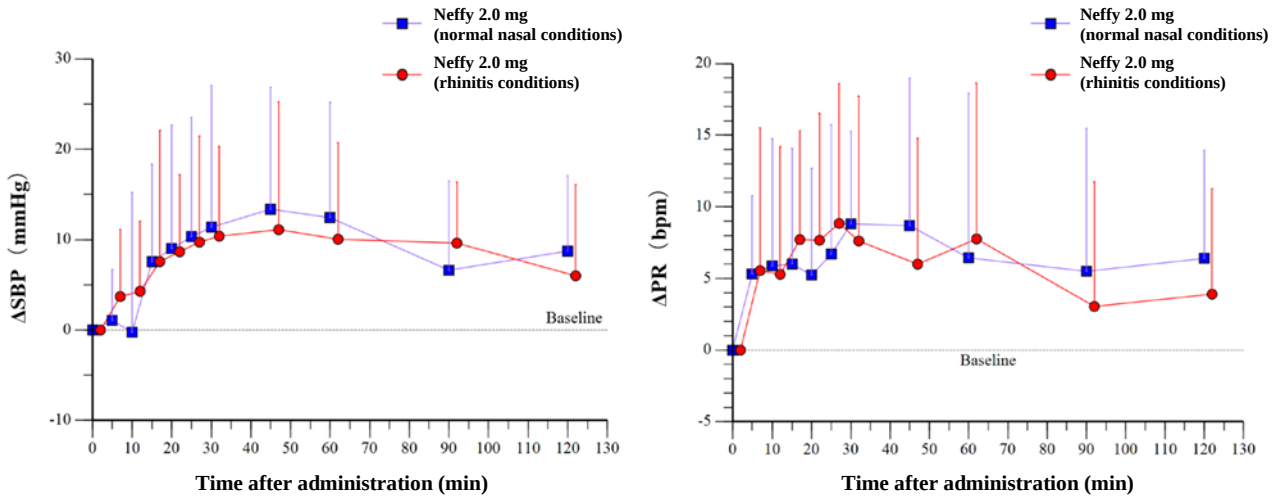

Figure 8. Changes over time from baseline in SBP (left) and PR (right) up to 120 minutes following single-dose administration of Neffy in normal nasal conditions or rhinitis conditions associated with upper respiratory tract infection (arithmetic mean + standard deviation)

Table 15 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 15. Incidence of adverse events (safety analysis population)

Formulation	Neffy 2.0 mg	
Nasal condition	Rhinitis	Normal
N	21	17
All adverse events	11 (52.4)	11 (64.7)
Adverse drug reactions	11 (52.4)	11 (64.7)
Adverse events occurring in ≥2 subjects in either group		
Headache	7 (33.3)	2 (11.8)
Nasal discomfort	4 (19.0)	10 (58.8)
Nausea	4 (19.0)	1 (5.9)
Feeling jittery	2 (9.5)	3 (17.6)
Dizziness	2 (9.5)	1 (5.9)
Lacrimation increased	2 (9.5)	0
Rhinorrhoea	0	2 (11.8)
Throat irritation	0	2 (11.8)

n (%) MedDRA ver.22.0

6.2.4 Foreign phase I study (CTD 5.3.4.2-8, Study EPI 16 [December 2021 to February 2022])

A randomized,[24] open-label, 4-treatment, 4-period crossover study was conducted in adult non-Japanese patients with seasonal allergic rhinitis[25] (target sample size, 36 subjects) to evaluate the pharmacokinetics and pharmacodynamics of Neffy.

In Period 1, a single intranasal dose of Neffy 2.0 mg was administered into the left nostril under normal nasal conditions.[26] In Period 2 and Period 3, subjects received a single intramuscular dose of Adrenalin 0.3 mg or 0.5 mg. In Period 4, subjects underwent a nasal allergen challenge to induce the development of rhinitis[27] and received a single intranasal dose of Neffy 2.0 mg into the right nostril.[28]

All 36 subjects who received the study drug were included in the safety analysis population and pharmacokinetic/pharmacodynamic analysis populations.[29]

The results of plasma adrenaline pharmacokinetics and pharmacodynamics under each treatment are presented in Table 16, Figure 9, and Figure 10.

The pharmacokinetic results show that the C_{max} and AUC_{0-t} were lower and t_{max} was earlier following administration of Neffy under rhinitis conditions compared with normal nasal conditions (Table 16).

[24] Subjects were randomized to one of the following 2 treatment sequences:
- Neffy 2.0 mg (normal nasal) → intramuscular Adrenalin 0.3 mg → intramuscular Adrenalin 0.5 mg → Neffy 2.0 mg (after a nasal allergen challenge)
- Neffy 2.0 mg (normal nasal) → intramuscular Adrenalin 0.5 mg → intramuscular Adrenalin 0.3 mg → Neffy 2.0 mg (after a nasal allergen challenge)

[25] Eligible patients were those who had
(1) history of seasonal allergy; (2) a positive skin prick test or a positive intradermal test for allergens within 12 months prior to enrollment; and (3) a TNSS score of ≥5 and a congestion score of ≥2 after a nasal allergen challenge at screening.

[26] Absence of evident oedema or nasal congestion (a TNSS score of ≤2 and a congestion score of ≤1) was to be confirmed before study drug treatment.

[27] Rhinitis conditions (a TNSS score of ≥5 and a congestion score of ≥2) were to be confirmed before study drug treatment.

[28] For each treatment, a dosing interval of 24 hours was specified.

[29] Patients with missing data necessary to calculate pharmacokinetic parameters (C_{max} and t_{max}) were excluded from the pharmacokinetic analysis: 1 subject in the Neffy 2.0 mg (rhinitis) group, 4 subjects in the Adrenalin 0.3 mg group, and 4 subjects in the Adrenalin 0.5 mg group. These patients were also excluded from the pharmacodynamic analysis except for the 1 subject in the Adrenalin 0.5 mg group.

The pharmacodynamic results show that ΔSBP E_{max} and ΔPR E_{max} were small following administration of Neffy under rhinitis conditions compared with normal nasal conditions and t_{Emax} was observed earlier (Table 16). The increases from baseline in SBP and PR were smaller under rhinitis conditions compared with normal nasal conditions except for immediately post-dose (Figure 10).

Table 16. Pharmacokinetic and pharmacodynamic parameters[a)] of plasma adrenaline following single dose administration to subjects with normal nasal conditions or rhinitis induced by nasal allergen challenge

Formulation	Nasal condition	Administration site	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
Neffy 2.0 mg	Rhinitis	Intranasal (right nostril)	33	309 (66.2)	23,500 (69.1)	6.00 [2.00, 90.0]	15.0 (84.5) 19.0 [1.00, 120]	10.8 (114) 4.00 [1.00, 119]
	Normal	Intranasal (left nostril)	36	491 (65.2)	37,100 (66.1)	20.0 [2.00, 120]	20.8 (80.6) 26.0 [1.00, 120]	18.5 (75.9) 25.0 [1.00, 178]
Adrenalin 0.3 mg		Intramuscular (left anterolateral thigh)	31	283 (54.9)	27,700 (37.5)	45.0 [4.00, 60.0]	13.4 (70.9) 19.0 [1.00, 123]	11.1 (73.3) 44.0 [2.00, 120]
Adrenalin 0.5 mg		Intramuscular (right anterolateral thigh)	31[b)]	452 (81.1)	42,400 (40.2)	45.0 [4.00, 360]	15.2 (62.3) 30.0 [1.00, 120]	13.6 (54.0) 19.5 [1.00, 122]

Arithmetic mean (%CV); t_{max} and t_{Emax}, median [range]

a) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 360 minutes post-dose and 120 minutes post-dose, respectively.

b) The pharmacodynamic analysis on 32 subjects was summarized.

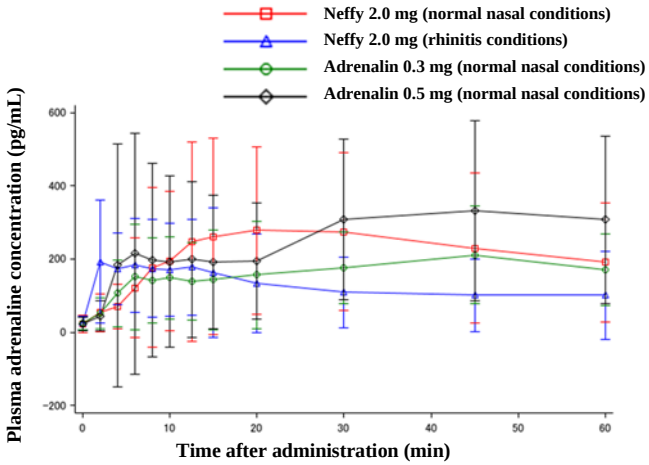

Figure 9. Time course of plasma adrenaline concentrations up to 60 minutes following single-dose administration under the normal nasal conditions or rhinitis induced by nasal allergen challenge (arithmetic mean ± standard deviation)

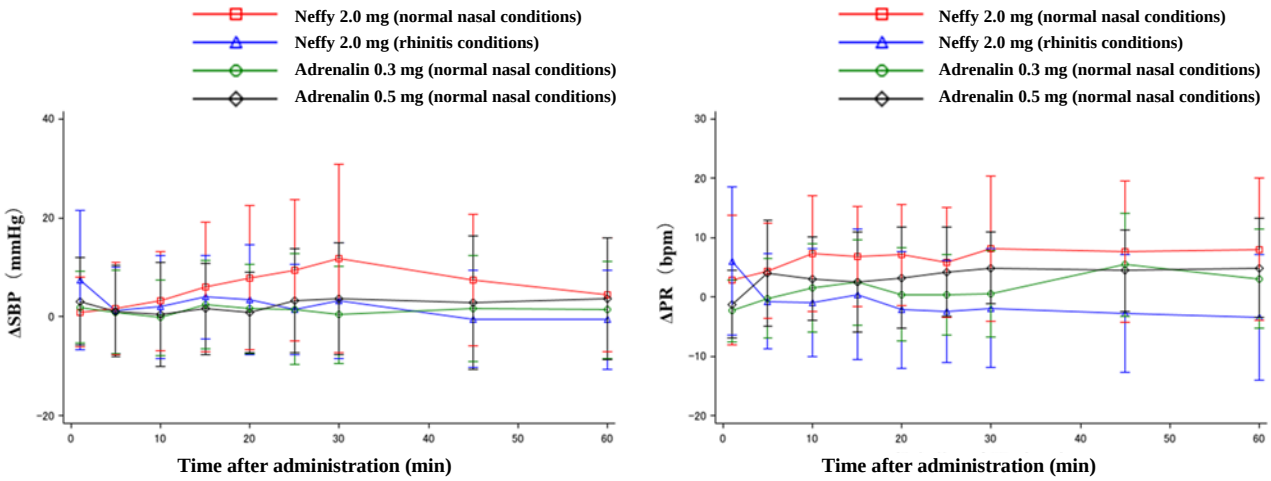

Figure 10. Changes over time from baseline in SBP (left) and PR (right) up to 60 minutes following single-dose administration under normal nasal conditions or rhinitis induced by nasal allergen challenge (arithmetic mean ± standard deviation)

Table 17 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 17. Incidence of adverse events (safety analysis population)

Formulation	Neffy 2.0 mg		Adrenalin 0.3 mg	Adrenalin 0.5 mg
Nasal condition	Rhinitis	Normal	Normal	Normal
N	34	36	35	35
All adverse events	1 (2.9)	9 (25.0)	0	1 (2.9)
Adverse drug reactions	0	8 (22.0)	0	0
Adverse events occurring in ≥2 subjects in any group				
Headache	0	5 (13.9)	0	0
Dizziness	0	2 (5.6)	0	0

n (%) MedDRA ver.22.0

6.2.5 Foreign phase I study (CTD 5.3.4.2-10, Study EPI 18 [October 2023 to December 2023])

A randomized, open-label, 2-treatment, 2-period crossover study was conducted followed by open-label studies consisting of Periods 3, 4, and 5, in adult non-Japanese patients with seasonal allergic rhinitis (target sample size, 46 subjects)[25)] to evaluate the pharmacokinetics and pharmacodynamics of Neffy.

In Periods 1 and 2, under normal nasal conditions, subjects received 2 intranasal doses of Neffy 2.0 mg 10 minutes apart into opposite nostrils,[30)] or 2 intramuscular doses of Adrenalin 0.3 mg 10 minutes apart. In Periods 3, 4, and 5, subjects underwent a nasal allergen challenge to induce the development of rhinitis.[31)] In Period 3, subjects received 2 intramuscular doses of Adrenalin 0.3 mg 10 minutes apart; in Period 4, 2 intranasal doses of Neffy 2.0 mg administered 10 minutes apart into opposite nostrils; and in Period 5, 2 intranasal doses of Neffy 2.0 mg administered 10 minutes apart into the same nostril.[32)]

All 43 subjects who received the study drug were included in the safety analysis population and pharmacokinetic/pharmacodynamic analysis populations.

The results of plasma adrenaline pharmacokinetics and pharmacodynamics for each treatment are presented in Table 18, Figure 11, and Figure 12.

The pharmacokinetic results show that the C_{max} and $AUC_{0\text{-}t}$ were comparable or higher and t_{max} was earlier in subjects receiving 2 Neffy doses (left nostril followed by right nostril; right nostril twice) than in those receiving intramuscular Adrenalin 0.3 mg regardless of nasal condition (Table 18).

[30)] Although no criteria were specified for TNSS to determine whether nasal conditions are normal, the evaluation of TNSS prior to study drug treatment indicated that no subjects had rhinitis (TNSS ≥5 and congestion score ≥2).

[31)] Although no criteria were specified for TNSS to determine whether rhinitis conditions are present, the evaluation of TNSS prior to study drug treatment indicated that rhinitis conditions (TNSS ≥5 and congestion score ≥2) were present in 24 subjects (57.1%) in the intramuscular Adrenalin 0.3 mg group (left/right anterolateral thighs), 24 subjects (60.0%) in the Neffy 2.0 mg intranasal group (left/right nostrils), and 28 subjects (68.3%) in the Neffy 2.0 mg intranasal group (right nostrils twice).

[32)] Each dose was separated by a 24-hour washout period for Periods 1 to 3, and by a 3-week washout period for Periods 3 to 5.

The pharmacodynamic results show that ΔSBP E_{max} and ΔPR E_{max} were greater in subjects receiving 2 Neffy doses (left nostril followed by right nostril; right nostril twice) than in those receiving intramuscular Adrenalin 0.3 mg regardless of nasal condition (Table 18). The changes from baseline in SBP and PR were greater in subjects receiving 2 Neffy doses (left nostril followed by right nostril; right nostril twice) than in those receiving intramuscular Adrenalin 0.3 mg (Figure 12).

Table 18. Pharmacokinetic and pharmacodynamic parameters[a)] of plasma adrenaline when 2 doses of the study formulation were administered to subjects under normal nasal conditions or subjects with rhinitis induced by nasal allergen challenge

Formulation	Nasal condition	Administration site	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
Neffy 2.0 mg	Rhinitis	Intranasal (left/right nostrils)	40	581 (68.8)	35,723 (102.8)	15.0 [2, 152]	18 (68.2) 16 [1, 120]	22 (45.1) 11 [1, 121]
Neffy 2.0 mg		Intranasal (right nostril twice)	41	852 (73.7)	66,424 (80.6)	20.0 [2, 150]	21 (48.1) 26 [1, 120]	22 (46.2) 16 [1, 121]
Adrenalin 0.3 mg		Intramuscular (left/right anterolateral thigh)	42	495 (47.0)	42,821 (31.4)	45.0 [6, 150]	13 (65.1) 30 [1, 121]	14 (47.5) 28 [1, 120]
Neffy 2.0 mg	Normal	Intranasal (left/right nostrils)	43	1,064 (89.5)	68,230 (98.5)	20.0 [4, 180]	29 (53.5) 19 [1, 120]	24 (49.2) 16 [1, 120]
Adrenalin 0.3 mg		Intramuscular (left/right anterolateral thigh)	42	420 (66.5)	37,311 (42.5)	55.0 [8, 122]	14 (65.5) 38 [1, 120]	14 (63.9) 45 [1, 121]

Arithmetic mean (%CV); t_{max} and $t_{Emax,}$ median [range]

a) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 240 minutes post-dose and 120 minutes post-dose, respectively.

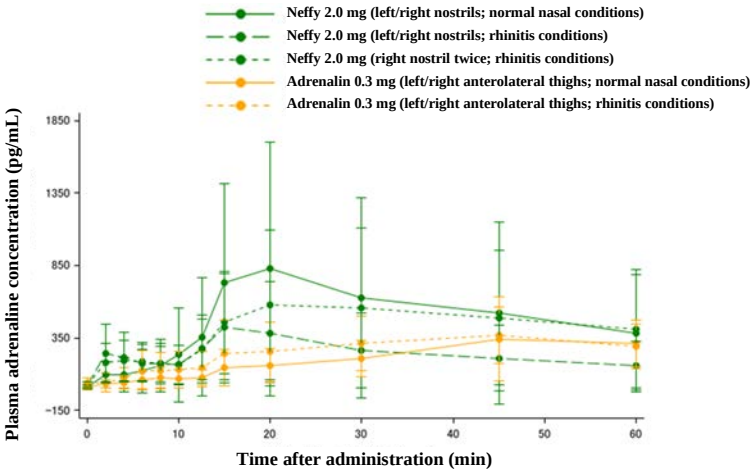

Figure 11. Time course of plasma adrenaline concentrations up to 60 minutes following 2-dose administration under normal nasal conditions or rhinitis induced by nasal allergen challenge (arithmetic mean ± standard deviation)

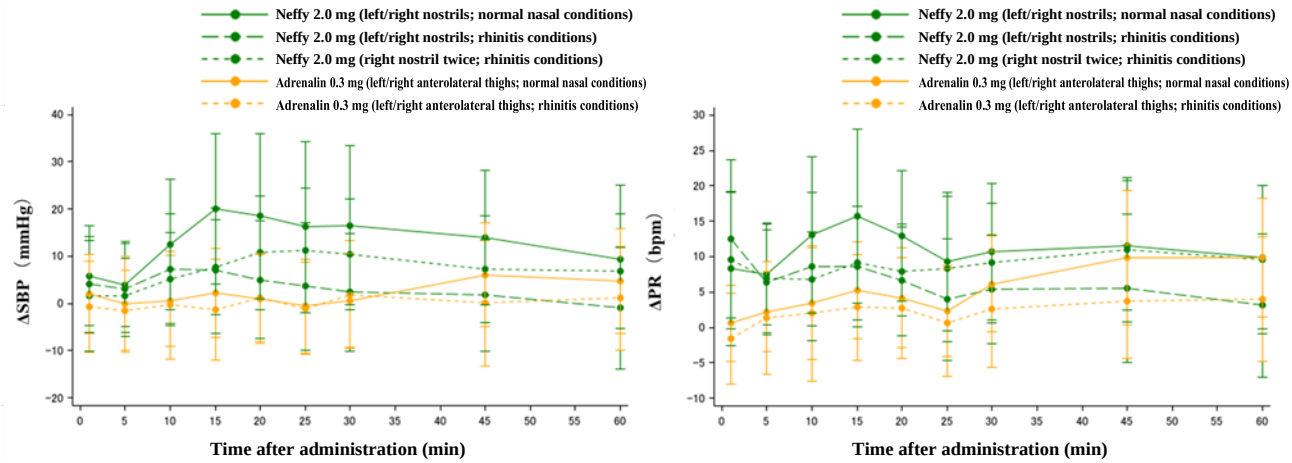

Figure 12. Changes over time from baseline in SBP (left) and PR (right) up to 60 minutes following 2-dose administration under normal nasal conditions or rhinitis induced by nasal allergen challenge (arithmetic mean ± standard deviation)

Table 19 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 19. Incidence of adverse events (safety analysis population)

Formulation	Neffy 2.0 mg (left/right nostrils)	Neffy 2.0 mg (right nostril twice)	Adrenalin 0.3 mg	Neffy 2.0 mg (left/right nostrils)	Adrenalin 0.3 mg
Nasal conditions	Rhinitis			Normal	
N	40	41	42	43	40
All adverse events	16 (40.0)	15 (36.6)	9 (21.4)	31 (72.1)	19 (45.2)
Adverse drug reactions	15 (37.5)	14 (34.1)	8 (19.0)	30 (69.8)	17 (40.5)
Adverse events occurring in ≥2 subjects in any group					
Throat irritation	1 (2.5)	1 (2.4)	2 (4.8)	14 (32.6)	3 (7.1)
Nasal discomfort	5 (12.5)	4 (9.8)	0	9 (20.9)	4 (9.5)
Headache	6 (15.0)	6 (14.6)	1 (2.4)	7 (16.3)	3 (7.1)
Tremor	4 (10.0)	0	0	4 (9.3)	1 (2.4)
Rhinorrhoea	0	0	0	4 (9.3)	0
Feeling jittery	3 (7.5)	5 (12.2)	3 (7.1)	3 (7.0)	3 (7.1)
Nasal pruritus	0	0	0	3 (7.0)	1 (2.4)
Sneezing	0	0	0	2 (4.7)	1 (2.4)
Nasal congestion	0	0	0	2 (4.7)	0
Gingival pain	1 (2.5)	2 (4.9)	0	1 (2.3)	0
Injection site pain	0	0	1 (2.4)	0	2 (4.8)

n (%) MedDRA ver.22.0

6.2.6 Foreign phase I study (CTD 5.3.4.2-1, Study EPI 10 [July 2020 to [redacted] 20[redacted]])

An open-label study was conducted in pediatric non-Japanese patients aged ≥4 years with systemic allergy[33)] to evaluate the pharmacokinetics and pharmacodynamics of Neffy in 2 cohorts.

In Cohort 1, pediatric patients weighing ≥15 kg to <30 kg received a single intranasal dose of Neffy 0.65 mg and those weighing ≥30 kg received a single intranasal dose of Neffy 1.0 mg. In Cohort 2, pediatric patients weighing ≥15 kg to <30 kg received a single intranasal dose of Neffy 1.0 mg, and those weighing ≥30 kg received a single intranasal dose of Neffy 2.0 mg.

[33)] Patients with past history of severe systemic Type I allergy caused by exposure to an antigen (food, insects, venom, or drug) requiring treatment with an adrenaline formulation.

All 80 subjects [34)] who received the study drug were included in the safety analysis population and pharmacokinetic/pharmacodynamic analysis populations.[35)]

The results of plasma adrenaline pharmacokinetics and pharmacodynamics for each treatment are presented in Table 20, Figure 13, and Figure 14.

The pharmacokinetic results show that plasma adrenaline concentrations over time following administration of Neffy 1.0 mg to pediatric patients weighing ≥15 kg to <30 kg differed from those of Neffy 2.0 mg to pediatric patients weighing ≥30 kg. The t_{max} was observed earlier in those weighing ≥15 kg to <30 kg, while the C_{max} and AUC_{0-t} were similar between the body weight groups (Table 20 and Figure 13).

The pharmacodynamic results show that following administration of Neffy 1.0 mg to pediatric patients weighing ≥15 kg to <30 kg or Neffy 2.0 mg to those weighing ≥30 kg, ΔSBP E_{max} and ΔPR E_{max} were comparable between the body weight groups. Changes from baseline in SBP and PR over time were generally similar between the groups (Table 20 and Figure 14).

Table 20. Pharmacokinetic and pharmacodynamic parameters[a), b)] of plasma adrenaline following single dose administration

Body weight	Dose (mg)	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
≥15 kg to <30 kg	0.65	11 [c)]	534 (58.7)	21,800 (49.8)	12.5 [2.50, 30.3]	12.3 (43.5) 30.5 [10.0, 120]	15.7 (118) 15.0 [5.00, 91.0]
	1.0	21	651 (64.2)	35,100 (57.3)	20.0 [2.50, 61.5]	13.4 (44.6) 20.0 [11.0, 122]	18.5 (63.5) 25.0 [4.00, 120]
≥30 kg	1.0	25 [d)]	253 (66.2)	14,000 (52.9)	20.1 [7.50, 122]	7.81 (97.7) 30.0 [5.00, 124]	13.8 (73.0) 20.0 [5.00, 124]
	2.0	21	690 (100)	40,200 (92.8)	29.5 [2.90, 120]	12.2 (67.4) 25.0 [14.0, 90.0]	16.9 (64.1) 44.0 [5.00, 120]

Arithmetic mean (%CV); t_{max} and t_{Emax}, median [range]

a) Although formulations containing different concentrations of DDM (0.25%-0.35%) were used between and within the dose levels, the difference in the DDM concentration range was not considered to have a significant impact on the pharmacokinetics, and the results obtained with different formulations were pooled for the analysis.

b) Pharmacokinetic and pharmacodynamic parameters were evaluated based on measurement data obtained up to 120 minutes post-dose.

c) The sample size for the pharmacokinetic analysis. The pharmacodynamic analysis on 12 subjects was summarized.

d) The sample size for the pharmacokinetic analysis. The pharmacodynamic analysis on 26 subjects was summarized.

[34)] Including 18 subjects who participated in Cohort 1 (single intranasal dose of Neffy 0.65 mg to patients weighing ≥15 kg and <30 kg, Neffy 1.0 mg to those weighing ≥30 kg) and re-enrolled in Cohort 2 (single intranasal dose of Neffy 1.0 mg to patients weighing ≥15 kg and <30 kg, Neffy 2.0 mg to those weighing ≥30 kg).

[35)] One patient in the Neffy 1.0 mg (≥30 kg) whose data were all below the lower limit of detection and 1 subject in the Neffy 0.65 mg group (≥15 kg and <30 kg) whose pharmacokinetic sampling measurements were missing for the most part were excluded from the pharmacokinetic analysis.

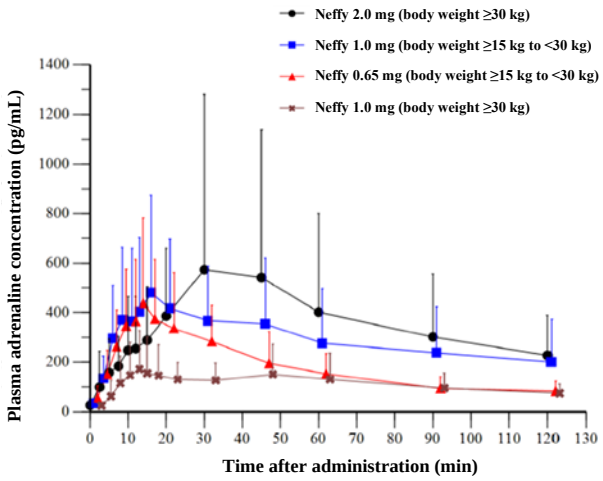

Figure 13. Time course of plasma adrenaline concentrations up to 120 minutes following single-dose administration (arithmetic mean + standard deviation)

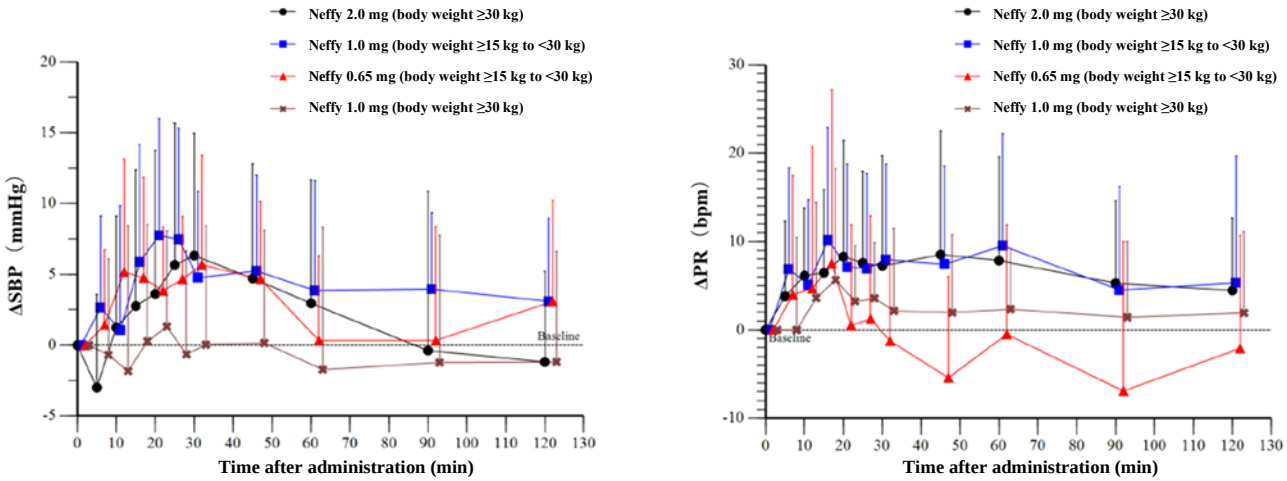

Figure 14. Changes over time from baseline in SBP (left) and PR (right) up to 120 minutes following single-dose administration (arithmetic mean + standard deviation)

Table 21 summarizes the overall incidence of adverse events, and the incidence of adverse drug reactions and main adverse events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 21. Incidence of adverse events (safety analysis population)

Body weight	≥15 kg to <30 kg		≥30 kg	
Dose	0.65 mg	1.0 mg	1.0 mg	2.0 mg
N	12	21	26	21
All adverse events	6 (50.0)	11 (52.4)	12 (46.2)	14 (66.7)
Adverse drug reactions	2 (16.7)	10 (47.6)	9 (34.6)	12 (57.1)
Adverse events occurring in ≥2 subjects in any group				
Nasal discomfort	1 (8.3)	1 (4.8)	5 (19.2)	4 (19.0)
Rhinorrhoea	1 (8.3)	1 (4.8)	3 (11.5)	4 (19.0)
Intranasal paraesthesia	0	0	0	4 (19.0)
Sneezing	0	0	2 (7.7)	3 (14.3)
Paraesthesia	0	2 (9.5)	1 (3.8)	2 (9.5)
Rhinalgia	0	1 (4.8)	2 (7.7)	2 (9.5)
Epistaxis	1 (8.3)	0	0	2 (9.5)
Fatigue	0	0	0	2 (9.5)
Feeling jittery	0	0	0	2 (9.5)
Nasal congestion	0	4 (19.0)	0	1 (4.8)
Oropharyngeal pain	0	1 (4.8)	2 (7.7)	1 (4.8)
Throat irritation	2 (16.7)	1 (4.8)	0	1 (4.8)
Lacrimation increased	0	0	2 (7.7)	1 (4.8)
Upper respiratory tract congestion	0	3 (14.3)	0	0
Dry throat	0	2 (9.5)	0	0
Nasal dryness	0	2 (9.5)	0	0
Nasal mucosal disorder	0	0	5 (19.2)	0
Taste disorder	0	0	2 (7.7)	0
Ocular hyperaemia	0	0	2 (7.7)	0

n (%) MedDRA ver.22.0

6.2.7 Japanese phase III study (CTD 5.3.5.2-1, Study EPI JP03 [July 2023 to August 2023])

An open-label, uncontrolled, single-center study was conducted in Japan in Japanese patients with oral food challenge (OFC)-induced anaphylaxis symptoms (Grade ≥2 as per the Japanese Anaphylaxis Guidelines) [see Section 7.1]. All 15 subjects were included in the pharmacodynamic analysis population. Changes over time from baseline in SBP, diastolic blood pressure (DBP), and PR (ΔSBP, ΔDBP, and ΔPR, respectively) following administration of a single intranasal dose of Neffy 1.0 mg to patients weighing ≥15 kg to <30 kg and a single intranasal dose of Neffy 2.0 mg to those weighing ≥30 kg are presented in Figure 15. It was considered that the initial decreases in DBP and SBP following administration in both groups reflect a β_2 receptor-mediated effect, and the subsequent increase in SBP reflects an α_1 receptor-mediated pharmacological effect of adrenaline.

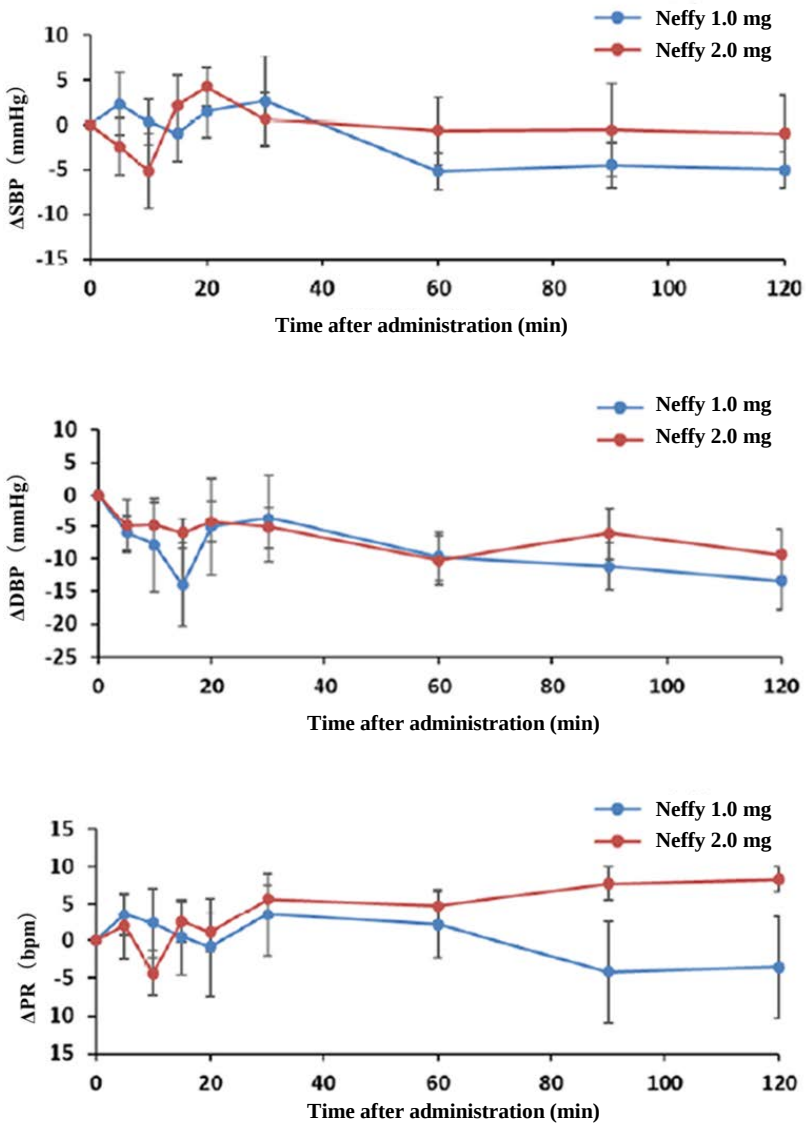

Figure 15. Changes from baseline in SBP (top), DBP (middle), and PR (bottom) up to 120 minutes following single-dose administration of Neffy (arithmetic mean ± standard error)

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetics and pharmacodynamics of Neffy

The applicant's explanation about the pharmacokinetics and pharmacodynamics of Neffy including comparison with Epipen, a formulation used in Japan for the adjunctive treatment of anaphylaxis:

Based on the information available at the start of development of Neffy, the pharmacokinetics of intramuscular adrenaline injections including Epipen vary significantly, making it difficult to demonstrate the pharmacokinetic equivalence of Neffy and Epipen. In addition, it was considered that no pharmacokinetic parameters that could be used as efficacy and safety indicators for adrenaline in anaphylaxis treatment had been identified. Therefore, for the comparison of pharmacokinetics of Neffy and Epipen it was decided to focus on a comprehensive assessment of pharmacokinetic parameters (C_{max}, $AUC_{0\text{-}t}$, and t_{max}) as well as the time course of plasma adrenaline concentrations. To compare the pharmacodynamics of both formulations, SBP and PR, which reflect α_1- and β_1-adrenaline receptor stimulation, were selected as efficacy pharmacodynamic markers [see Section 7.R.1].

In studies in adults, although the pharmacokinetics (C_{max}, $AUC_{0\text{-}t}$, t_{max}, and the time course of plasma adrenaline concentrations) of Neffy differ from those of Epipen after both single and 2-dose administrations, the pharmacodynamic indicators (ΔSBP E_{max} and ΔPR E_{max}) following both single and 2-dose administration of Neffy 2.0 mg were comparable to or exceeded those observed after treatment with Epipen 0.3 mg [see Section 6.2.1]. In the 2-dose administration, the exposure to Neffy 2.0 mg was higher than that to Epipen 0.3 mg, while the adverse events that occurred following the 2-dose administration were mild in severity in all cases.

Since no clinical studies have been conducted to compare the pharmacokinetics and pharmacodynamics of Neffy and Epipen in Japanese subjects, the results from 2 different studies were compared. Table 22 shows the results of plasma adrenaline pharmacokinetics and pharmacodynamics following single intramuscular administration of Epipen 0.3 mg to adult Japanese subjects in Study EPI JP01[36)] and those following single intranasal administration of Neffy 2.0 mg in Study EPI JP02. Although the C_{max}, $AUC_{0\text{-}t}$, and t_{max} of Neffy differ from those of Epipen, the pharmacodynamic indicators (ΔSBP E_{max} and ΔPR E_{max}) following administration of Neffy were comparable to or exceeded those after treatment with Epipen.

Table 22. Pharmacokinetic and pharmacodynamic parameters[a)] of plasma adrenaline following single dose administration

Study	Formulation	Administration site	N	C_{max} (pg/mL)	$AUC_{0\text{-}t}$ (pg·min/mL)	t_{max} (min)	ΔSBP E_{max} (mmHg) t_{Emax} (min)	ΔPR E_{max} (bpm) t_{Emax} (min)
EPI JP02	Neffy 2.0 mg	Intranasal (left nostril)	12	814 (105.7)	56,782 (79.6)	20.0 [15.0, 120.0]	27 (42.1) 25 [1, 55]	20 (44.4) 16 [1, 55]
	Adrenalin 0.3 mg	Intramuscular (right anterolateral thigh)	12	268 (31.5)	30,644 (36.4)	45.0 [15.0, 360.0]	7 (89.3) 25 [1, 40]	12 (64.8) 25 [5, 55]
EPI JP01	Epipen 0.3 mg	Intramuscular (left anterolateral thigh)	30	676 (46.4)	49,400 (23.4)	10.0 [2.00, 45.0]	11.9 (50.1) 22.5 [5, 360]	16.2 (45.4) 30.0 [5, 360]
	Adrenalin 0.3 mg	Intramuscular (left anterolateral thigh)	35	549 (33.1)	56,500 (19.7)	45.0 [4.00, 60.0]	7.57 (58.7) 25.0 [0, 240]	16.7 (31.8) 60.0 [5, 360]

Arithmetic mean (%CV); t_{max} and t_{Emax}, median [range]

a) Pharmacokinetic parameters were evaluated based on measurement data obtained up to 360 minutes post-dose (Study EPI JP02) and 480 minutes post-dose (Study EPI JP01). Pharmacodynamic parameters were evaluated based on measurement data obtained up to 120 minutes post-dose in both Studies EPI JP02 and EPI JP01.

The pharmacokinetic parameters following intranasal administration of Neffy 2.0 mg, either as single-dose administration (adult Japanese and non-Japanese subjects) or 2-dose administration (adult non-Japanese subjects), showed a higher C_{max} and $AUC_{0\text{-}t}$ and earlier t_{max} compared with intramuscular Adrenalin 0.3 mg. The indicators of pharmacodynamic parameters (ΔSBP E_{max} and ΔPR E_{max}) following single-dose or 2-dose administration of Neffy 2.0 mg were greater than that observed with intramuscular Adrenalin 0.3 mg [see Sections 6.2.1, 6.2.2, and 6.2.4 for single-dose; Section 6.2.5 for 2-dose administration].

Study EPI 10 evaluated the dosage regimen of Neffy by body weight category in non-Japanese pediatric patients with systemic allergy [see Section 6.2.6]. When Neffy 1.0 mg was intranasally administered to pediatric patients weighing ≥15 kg to <30 kg and Neffy 2.0 mg was intranasally administered to those weighing ≥30 kg, the adrenaline exposures tended to be higher compared with those in adult patients receiving intranasal dose of Neffy 2.0 mg. However, there were no safety concerns. Although the ΔSBP E_{max} tended to be smaller

[36)] A crossover study conducted in adult Japanese subjects with seasonal allergic rhinitis to evaluate the pharmacokinetics, etc. following administration of single intranasal or intramuscular dose of adrenaline.

in pediatric subjects than in adult subjects, a certain level of pharmacodynamic effect was noted [see Sections 6.2.1 and 6.2.2].

Based on the pharmacokinetic and pharmacodynamic results described above, it is considered that Neffy can be expected to have efficacy and safety similar to Epipen in the treatment for anaphylactic reactions.

PMDA considers that while the pharmacokinetic profile of Neffy is not similar to that of Epipen in adults, the pharmacodynamic data demonstrated that the physiological effects of adrenaline achieved in treatment with Neffy were approximately similar to or greater than those with Epipen. The applicant's explanation about the administration to pediatric patients is considered reasonable.

The conclusion on the efficacy and safety of Neffy in the treatment of anaphylactic reactions will be made based on the results from Study EPI JP03 and safety data from clinical pharmacology studies [see Sections 7.R.2 and 7.R.3].

6.R.2 Administration of Neffy under rhinitis conditions

The applicant's explanation about the administration of Neffy under rhinitis conditions:

In Study EPI 14, which was conducted in patients with upper respiratory tract infection, the pharmacokinetic and pharmacodynamic profiles of Neffy under normal nasal conditions were similar to those under rhinitis conditions [see Section 6.2.3]. In Studies EPI 16 and EPI 18, which were conducted in patients with seasonal allergic rhinitis, there were decreases in C_{max} and AUC_{0-t} under rhinitis conditions compared to normal conditions following single-dose or 2-dose administration of Neffy, and there were also decreases in ΔSBP E_{max} and ΔPR E_{max} [see Sections 6.2.4 and 6.2.5]. In Studies EPI 16 and EPI 18, nasal mucosa permeability may have increased due to nasal oedema, leading to faster absorption under rhinitis conditions compared with normal nasal conditions. Conversely, it is also possible that pharmacodynamic effects decreased as a result of reduced absorption of Neffy due to rhinorrhoea. However, even under rhinitis conditions, the C_{max}, AUC_{0-t}, ΔSBP E_{max}, and ΔPR E_{max} following intranasal administration of Neffy were generally similar to or greater than those observed with treatment with intramuscular Adrenalin 0.3 mg, which is used as treatment for anaphylactic reactions in other countries. In Study EPI 16, following single-dose administration of Neffy to subjects with seasonal allergic rhinitis, the increase in ΔPR E_{max} was smaller than that with intramuscular Adrenalin, except immediately post-dose, although the variability was high. Therefore, the overall pharmacodynamic effects of Neffy were considered similar to those of intramuscular Adrenalin 0.3 mg and Adrenalin 0.5 mg (containing adrenaline 0.5 mg), which is the maximum daily dose for adults.

Based on the above, no concerns regarding efficacy have been identified associated with the use of Neffy in patients with rhinitis; therefore, no specific restrictions are considered necessary for patients with rhinitis.

PMDA's view:

Study EPI 14 was conducted in patients with upper respiratory tract infection, and Studies EPI 16 and EPI 18 were conducted in patients with seasonal allergic rhinitis. The results from these studies did not show consistent

pharmacokinetic responses to Neffy under rhinitis conditions. It is therefore difficult to clearly assess the effects of rhinitis conditions on the pharmacokinetics and pharmacodynamics of Neffy. However, even if the exposure to Neffy was low under rhinitis conditions when Neffy was administered, given that its pharmacodynamic effects were demonstrated to be comparable to those of the intramuscular adrenaline formulation approved in other countries for the indication of anaphylactic reactions (not approved in Japan), PMDA concluded that it is not necessary to limit the use of Neffy to patients with rhinitis.

6.R.3 Increase in intranasal absorption by administration of Neffy

The applicant's explanation about the change in nasal mucosa after administration of Neffy:

In the crossover studies (e.g., Study EPI 03) in the early development phase of Neffy, when intranasal administration was repeated to the same nostril with short dosing intervals, the amount of adrenaline absorbed tended to increase (Table 23). After this phenomenon was revealed, the protocols of the subsequent studies specified a dosing interval of ≥12 days for cases in which Neffy was administered to the same nostril. In Study EPI 15, which specified a dosing interval of ≥12 days, the effects of dosing time on plasma adrenaline concentrations were evaluated. The results are presented in Table 24. For dosing intervals of ≥12 days,[37)] no increase in absorption was detected at the next administration of Neffy. Although the cause of the phenomenon is not clear, it has been suggested that DDM changes mucosal viscosity and membrane fluidity, loosening intercellular junctions, thereby promoting drug absorption (*Headache*. 2018;58:676-87). Therefore, it is considered possible that changes in nasal mucosa caused by DDM did not disappear completely in a short period of time, increasing intranasal absorption when subsequent doses were administered.

Based on the discussions above, because intranasal formulations including Neffy may increase systemic absorption during the 2 weeks following administration, cautionary statements will be included in the Interactions section of the package insert. Since Neffy is an emergency treatment drug for anaphylaxis, it is assumed that its use will be infrequent; therefore, it is unlikely that Neffy will be re-administered to a patient within a short period of time.

Table 23. Pharmacokinetic parameters following intranasal administration of Neffy with a dosing interval of 2 days or 4 days (Study EPI 03)[a), b)]

Number of doses	Dosing timepoint[c)]	N	C_{max} (pg/mL)	$AUC_{0\text{-}t}$ (pg·min/mL)	t_{max} (min)
1 dose[d)]	First dose	42	284 (79.1)	25,700 (59.6)	30.0 [2.0, 150]
	Second dose (2 days post-dose)	13	572 (59.7)	41,300 (58.6)	20.0 [10.0, 30.0]
	Second dose (4 days post-dose)	13	356 (54.5)	33,600 (41.2)	20.0 [8.0, 45.0]

Arithmetic mean (%CV); t_{max}, median [range]

a) Study EPI 03 is a crossover study consisting of 5 periods with the following dosage regimens: a single intranasal dose of Neffy 1.0 mg (left nostril); 2 intranasal doses of Neffy 1.0 mg (left/right nostrils); single intramuscular dose of Adrenalin 0.3 mg; single intramuscular dose of Adrenalin 0.5 mg; and 2 intramuscular doses of Adrenalin 0.3 mg. The dosing interval between periods was ≥24 hours.

b) Pharmacokinetic parameters were evaluated based on measurement data obtained up to 480 minutes post-dose.

c) First dose: data from patients whose first dose was a single intranasal dose of Neffy 1.0 mg (left nostril);
Second dose: data from patients who received 2 intranasal doses of Neffy 1.0 mg (left/right nostrils) followed by a single intranasal dose of Neffy 1.0 mg 2 days or 4 days later in Study EPI 03.

d) In Study EPI 03, 1.0 mg formulation containing [redacted]% DDM was used.

[37)] The actual dosing interval was 12 days for all participants.

Table 24. Pharmacokinetic parameters following intranasal administration of Neffy with 12-day dosing intervals (Study EPI 15, Part 2)[a), b)]

Number of doses	Administration site	Dosing timepoint	N	C_{max} (pg/mL)	AUC_{0-t} (pg·min/mL)	t_{max} (min)
2 doses	Right/left nostrils	First dose	21	931.05 (108.2)	70,569.63 (61.8)	30.0 [11.0, 150.0]
		Second dose	18	1,086.94 (79.2)	104,039.39 (80.0)	30.0 [6.0, 60.0]
	Right nostril twice	First dose	18	1,044.06 (70.2)	96,446.74 (52.1)	30.0 [12.0, 150.0]
		Second dose	21	946.67 (81.7)	76,999.53 (69.0)	20.0 [4.0, 120.0]

Arithmetic mean (%CV); t_{max}, median [range]

a) In Periods 4 through 6 in Study EPI 15, Part 2, subjects were to receive study drugs according to one of the following treatment sequences, and a dosing interval of ≥12 days was established in Periods 4 and 6. This analysis was performed on the supplementary analysis population [see footnote 18], which includes patients who were excluded from the primary analysis. Treatment data in Period 4 were summarized as the data for first dose and treatment data in Period 6 were summarized as the data for the second dose.

- Neffy 2.0 mg intranasally (right/left nostrils) → Epipen 0.3 mg intramuscularly (left/right anterolateral thighs) → Neffy 2.0 mg intranasally (right nostril twice)
- Neffy 2.0 mg intranasally (right nostril twice) → Epipen 0.3 mg intramuscularly (left/right anterolateral thighs) → Neffy 2.0 mg intranasally (right/left nostrils)

b) Pharmacokinetic parameters were evaluated based on measurement data obtained up to 360 minutes post-dose.

PMDA accepted the applicant's explanation about the inclusion of cautionary statements in the package insert regarding an increase in intranasal absorption after administration of Neffy.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results data from the study shown in Table 25.

Table 25. Clinical study data on efficacy and safety

Location	Study ID	Phase	Study population	Subjects enrolled	Summary of dosage regimen	Main endpoint Primary endpoint
Japan	EPI JP03	III	Patients with OFC-induced anaphylaxis symptoms (Grade ≥2 as per the Japanese Anaphylaxis Guidelines)	(1) 6 (2) 9	(1) Patients weighing ≥15 kg to <30 kg Single intranasal administration of Neffy 1.0 mg (2) Patients weighing ≥30 kg Single intranasal administration of Neffy 2.0 mg	Efficacy, safety, and pharmacodynamics **Proportion of patients whose main symptom improved at 15 minutes post-dose, or if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment.**

7.1 Japanese phase III study (CTD 5.3.5.2-1, Study EPI JP03 [July 2023 to August 2023])

An open-label, uncontrolled, single-center study was conducted in Japan in Japanese patients with OFC-induced anaphylaxis symptoms (Grade ≥2 [moderate symptoms] as per the Japanese Anaphylaxis Guidelines) (Table 26) (target sample size, approximately 15 subjects [38)]) to evaluate the efficacy, safety, and pharmacodynamics of Neffy.

38) The study was to enroll ≥5 patients weighing ≥15 kg to <30 kg and ≥5 patients weighing ≥30 kg.

Table 26. Key inclusion/exclusion criteria

Inclusion criteria

Eligibility criteria for OFC

1. Patients aged ≥4 years to ≤55 years
2. Patients weighing ≥15 kg at pre-OFC examination on the day of study drug treatment
3. Patients scheduled for an OFC test in an inpatient setting

Criteria for study drug treatment

1. Occurrence of gastrointestinal, respiratory, or cardiovascular symptoms classified Grade ≥2 as per the Japanese Anaphylaxis Guidelines induced by OFC

Exclusion criteria

1. Patients with past nasal bone fracture, severe nasal damage, past history of nasal disease, nasal conditions that may prevent administration of nasal spray, abuse of nasal decongestant, or sleep apnea
2. Patients who used a transnasal medication within 14 days prior to study drug treatment
3. Patients with past history of myocardial infarction, or abnormal cardiovascular findings including clinically significant electrocardiographic abnormalities
4. Patients with mucosal inflammatory disorders (e.g., pemphigus, Sjogren's syndrome, and sinusitis fungal)
5. Patients with poorly controlled asthma or angioedema
6. Patients who used systemic agents containing adrenaline- or noradrenaline, ephedrine-containing formulations, herbal medicines with bronchodilating, anti-allergic, or anti-inflammatory effects, such as Bakumondoto and Shoseiryuto, within 7 days prior to study drug administration.
7. Patients who were treated with a histamine H_1 receptor antagonist, leukotriene receptor antagonist, inhaled β_2 agonist, or systemic corticosteroid within 3 days prior to study drug treatment.

This study consisted of a screening phase (up to 120 days) and an open-label phase (1 day; the day of study drug treatment). The OFC test was performed in an inpatient setting in the open-label phase in patients eligible for OFC in accordance with the "Oral Food Challenge Guidelines 2020" Health, Labour and Welfare Sciences Research Grants (Research on Immunologic and Allergic Diseases Program, Research Area of Diseases and Disabilities: Establishment of standard implementation procedure for oral food challenge tests). Of the eligible patients, those in whom gastrointestinal, respiratory, or cardiovascular symptoms (classified Grade ≥2 as per the Japanese Anaphylaxis Guidelines) were induced by the OFC were to receive Neffy 1.0 mg (≥15 kg to <30 kg) or Neffy 2.0 mg (≥30 kg) administered as a single intranasal dose. Patients were to receive the standard of care if symptoms did not improve or worsen, and the (principal or sub) investigator considered alternative treatment to be necessary.

All 15 patients with allergies, aged 6 to 17 years, who were enrolled in this study received the study drug and completed the study. These patients were included in the efficacy and safety analysis populations. The main symptoms induced by the OFC were all Grade 2, and there were no reports of Grade 3 (severe) symptoms.

Table 27 shows the results for the primary efficacy endpoint, the proportion of patients whose main symptom improved at 15 minutes post-dose, or if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment [for the definition of the primary efficacy endpoint, see Section 10].

Table 27. Proportion of patients whose main symptom improved at 15 minutes post-dose, or if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment (efficacy analysis population)

	Neffy 1.0 mg N = 6	Neffy 2.0 mg N = 9	Total N = 15
Proportion of patients whose main symptom improved	83.3 (5/6)	66.7 (6/9)	73.3 (11/15)

% (n/N)

Adverse events occurred in 4 of 6 subjects (66.7%) in the Neffy 1.0 mg group and 6 of 9 subjects (66.7%) in the Neffy 2.0 mg group. Adverse events occurred in 10 of 15 subjects (66.7%) in total. Reported adverse events

are presented in Table 28. Aside from the adverse events determined to be induced by the OFC,[39] other adverse events occurred in 2 of 6 subjects (33.3%) in the Neffy 1.0 mg group and 5 of 9 subjects (55.6%) in the Neffy 2.0 mg group. Adverse events occurred in 7 of 15 subjects (46.7%) in total.

Adverse drug reactions occurred in 1 of 6 subjects (16.7%) in the Neffy 1.0 mg group and 5 of 9 subjects (55.6%) in the Neffy 2.0 mg group. Adverse drug reactions occurred in 6 of 15 subjects (40.0%) in total. It was determined that none of these adverse drug reactions were OFC-induced events.

There were no deaths, serious adverse events, or adverse events that led to treatment discontinuation.

Table 28. Incidence of adverse events reported (safety analysis population)

Event	Neffy 1.0 mg (N = 6)	Neffy 2.0 mg (N = 9)	Total (N = 15)
All adverse events	4 (66.7)	6 (66.7)	10 (66.7)
Tremor	0	3 (33.3)	3 (20.0)
Cough	0	2 (22.2)	2 (13.3)
Nasal mucosal disorder	1 (16.7)	1 (11.1)	2 (13.3)
Erythema	1 (16.7)	1 (11.1)	2 (13.3)
Rash	2 (33.3)	0	2 (13.3)
Dyspnoea	0	1 (11.1)	1 (6.7)
Intranasal hypoaesthesia	0	1 (11.1)	1 (6.7)
Nasal crusting	0	1 (11.1)	1 (6.7)
Nasal discomfort	0	1 (11.1)	1 (6.7)
Oropharyngeal pain	0	1 (11.1)	1 (6.7)
Pharyngeal hypoaesthesia	0	1 (11.1)	1 (6.7)
Rhinalgia	0	1 (11.1)	1 (6.7)
Headache	0	1 (11.1)	1 (6.7)
Hypoaesthesia	0	1 (11.1)	1 (6.7)
Urticaria	0	1 (11.1)	1 (6.7)
Hypoaesthesia oral	0	1 (11.1)	1 (6.7)
Chills	0	1 (11.1)	1 (6.7)
Pain	0	1 (11.1)	1 (6.7)
Tachycardia	0	1 (11.1)	1 (6.7)
Abdominal pain	1 (16.7)	0	1 (6.7)
Eyelid oedema	1 (16.7)	0	1 (6.7)
Ocular hyperaemia	1 (16.7)	0	1 (6.7)

n (%) MedDRA version 22.0

[39] Of all adverse events reported, the following were determined to be OFC-induced adverse events: rash (2 subjects), erythema (1 subject), eyelid oedema (1 subject), and ocular hyperaemia (1 subject) in the Neffy 1.0 mg group; cough (1 subject), erythema (1 subject), dyspnoea (1 subject), hypoaesthesia (1 subject), and urticaria (1 subject) in the Neffy 2.0 mg group.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan for Neffy

The applicant's explanation about the development plan for Neffy:

Adrenaline has long been used as a drug of choice for the treatment of Type I hypersensitivity reactions including anaphylaxis. Since the approval of the first adrenaline auto-injector product in 1987 in the US and in 1994 in Europe, multiple products have been approved. In 2003, Epipen was approved in Japan as an adjunctive treatment drug for anaphylactic reactions. However, given that conducting a randomized, placebo-controlled study intended to evaluate a drug used to treat systemic allergic reactions in patients at an increased risk of anaphylaxis is unethical and unfeasible, studies involving patients to evaluate efficacy have not been conducted for any adjunctive treatment drug approved in and outside Japan for anaphylaxis. In addition, no other types of clinical studies have been conducted for many products (*Cochrane Database Syst Rev*. 2008; CD006312, *BMC Pediatr*. 2014;14:158).

Adrenaline auto-injectors and pre-filled syringes used outside medical institutions generally have the same dosage regimen across countries and regions: Usually, intramuscular adrenaline 0.3 mg/dose to patients weighing ≥30 kg, or intramuscular adrenaline 0.15 mg/dose to patients weighing ≥15 kg. Based on the data from clinical studies of Neffy as well as published data, the pharmacokinetics of intramuscular adrenaline formulations[40)] approved in the US and Europe including Epipen, and vial formulations used in medical institutions were investigated. The median t_{max} (range, 5-45 minutes) and mean C_{max} (range, 244-753 pg/mL) following intramuscular adrenaline 0.3 mg varied considerably between formulations. Nevertheless, despite such differences in pharmacokinetics, all of these adrenaline formulations have been approved as effective treatments for anaphylactic reactions.

Based on the above, it was decided to conduct clinical studies of Neffy in patients weighing ≥15 kg. In the development of Neffy in the US and Europe, its efficacy and safety were assessed based on the fact that Neffy's pharmacokinetic parameters (C_{max}, $AUC_{0\text{-}t}$, and t_{max}) and plasma adrenaline concentration-time profiles of Neffy fell within the range observed for intramuscular adrenaline formulations already approved in the US and Europe.

Conversely, in the development of Neffy in Japan, since Epipen is the only adjunctive treatment of anaphylaxis that can be self-administered and is currently used domestically, it was important to demonstrate the similarity in pharmacokinetics and pharmacodynamics between Neffy and Epipen. However, based on the pharmacokinetic data for Neffy available at the start of development in Japan, it was considered difficult to demonstrate pharmacokinetic equivalence between Neffy and Epipen. Therefore, in addition to known information on adrenaline, the efficacy of Neffy for anaphylaxis was evaluated, taking also account of the viewpoints shown below. It was decided to evaluate safety based on results of the clinical studies on Neffy.

[40)] Data for Epipen from the clinical studies of Neffy, treatment data for Symjepi and Adrenalin, literature data on Epipen and Auvi-Q (an intramuscular or subcutaneous adrenaline auto-injector product approved in the US for the treatment of Type I allergic reactions including anaphylaxis. The product is not approved in Japan).

1) Pharmacodynamic data of Neffy from clinical studies

Among adrenaline's pharmacological effects, the critical physiological responses in the treatment of anaphylaxis include increased vasoconstriction, elevated blood pressure, decreased bronchial mucosal oedema, enhanced myocardial contractility, elevated heart rate, bronchial smooth muscle relaxation, increased bronchodilation, inhibition of plasma exudation, and decreased mast cell mediator release. These effects are mediated by the α_1, β_1, and β_2 adrenergic receptors [see Section 3]. In the development of Neffy, SBP and PR were selected as pharmacodynamic efficacy markers, as they allow evaluation of the Neffy's stimulating effects on α_1 and β_1 adrenergic receptors. In clinical studies, DBP was also included in the pharmacodynamic endpoints because adrenaline also affects DBP due to its vasodilation effects mediated via the β_2 adrenergic receptor. However, because DBP was considered to be affected by differences in the route of administration (i.e., intramuscular or intranasal administration),[41)] it was decided to focus the evaluation primarily on SBP and PR. Effects such as bronchial smooth muscle relaxation, increased bronchodilation, coronary vasodilation, inhibition of plasma exudation, and decreased mast cell mediator release cannot be measured by the above indicators. However, given that these are responses mediated by the β_2 adrenergic receptor, which has a higher affinity for adrenaline compared with the α_1 and β_1 adrenergic receptors, these β_2-mediated pharmacodynamic responses can be inferred where α_1 and β_1-mediated effects are observed.

2) Data for OFC in Japanese patients

As described above, because it is difficult to conduct randomized, placebo-controlled studies in patients who develop anaphylaxis, Study EPI JP03 was conducted to investigate the therapeutic effect of Neffy by assessing its efficacy and safety when administered to patients in whom Grade ≥2 (moderate) anaphylaxis symptoms were induced during an oral food challenge (OFC). Study EPI JP03 was planned as an open-label, uncontrolled study with a target sample size of approximately 15 patients, taking feasibility into account. The study population comprised adults and pediatric patients weighing ≥15 kg, who are considered to represent the intended population for use of this drug in real-world clinical practice. The primary efficacy endpoint and the dosage regimen for Study EPI JP03 are as follows:

- Primary efficacy endpoint

The primary efficacy endpoint in Study EPI JP03 was defined, based on the following factors, as the proportion of patients whose main symptom improved at 15 minutes post-dose, or if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment [for the definition of the primary efficacy endpoint, see Section 10].

- Neffy has been developed as a drug for adjunctive treatment of anaphylaxis until the patient can receive medical attention. Assuming that the time from the administration of Neffy to ambulance arrival is approximately 15 minutes,[42)] the evaluation timepoint was set at 15 minutes post-dose, or at the last

[41)] In clinical pharmacodynamic studies of Neffy, while DBP tended to decrease following administration of intramuscular adrenaline, DBP tended to increase at early timepoints following intranasal administration of Neffy. The applicant considers that this difference may be attributable to differences in the vasodilatory effects of adrenaline on skeletal muscle, depending on the router of administration: intramuscular administration delivers adrenaline directly to local skeletal muscle, whereas with intranasal administration, a portion of the systemically circulating adrenaline acts on skeletal muscle.

[42)] It has been suggested that the mean time required for an ambulance to arrive at the site of an emergency (time to arrival after receiving an emergency phone call) is approximately 10.0 minutes (Fire and Disaster Management Agency 2024: Current status of emergency/rescue services: I. Emergency services [in Japanese] https://www.fdma.go.jp/publication/rescue/items/kkkg_r06_01_kyukyu.pdf [last accessed on July 4, 2025]).

assessment timepoint prior to initiation of the alternative treatment if such treatment occurred within 15 minutes.

- The measure for the primary endpoint to evaluate the treatment effect of Neffy was defined as the proportion of patients whose main OFC-induced (Grade ≥2) anaphylaxis symptom is decreased by ≥1 level from baseline. Since Neffy is an adjunctive treatment for anaphylactic reactions, it is important for patients to receive appropriate medical treatment after arrival at the Emergency Department; therefore, alleviation of anaphylaxis symptoms, that is, a ≥1-level reduction (improvement) in grade, is meaningful. In addition, anaphylaxis is a systemic reaction, and its symptoms can manifest in multiple organs; however, the timing of onset and resolution of organ symptoms vary from patient to patient. Accordingly, for the efficacy evaluation of Neffy, the primary endpoint focused on the main symptom. The main symptom was defined, considering its appropriateness as an initial manifestation of an anaphylactic reaction and its severity, as the symptom with the highest grade among Grade ≥2 cardiovascular symptoms, respiratory symptoms, and gastrointestinal symptoms. [for the definition of the primary efficacy endpoint, see Section 10].

- Dosage regimen

A single intranasal dose of Neffy 1.0 mg for patients weighing ≥15 kg to <30 kg and a single intranasal dose of Neffy 2.0 mg for those weighing ≥30 kg were selected as the dosage regimen for Study EPI JP03 based on the following factors.

- When Neffy 2.0 mg was intranasally administered to healthy non-Japanese and Japanese adults, the pharmacokinetic parameters and plasma adrenaline concentration-time profiles were within the range observed following intramuscular administration of 0.3 mg adrenaline using Epipen or another adrenaline intramuscular formulation approved in the US and Europe [see Sections 6.1.1, 6.2.1, and 6.2.2].
- The recommended dose levels of intramuscular adrenaline formulations for anaphylactic reactions in Japan are the same as those in other countries (Japanese Anaphylaxis Guidelines, *World Allergy Organ J.* 2020;13:100472).
- When Neffy 1.0 mg or Neffy 2.0 mg was intranasally administered to pediatric patients with allergies weighing ≥15 kg to <30 kg and ≥30 kg, respectively, although exposure tended to be higher than that observed in adults receiving Neffy 2.0 mg, no safety concerns were identified [see Section 6.2.6].

PMDA's view:

Adrenaline has long been used in the emergency treatment for anaphylactic reactions in and outside Japan, and its efficacy is well established.

Neffy has been developed as an adjunctive treatment for anaphylaxis and is positioned similarly to the already approved product Epipen; however, Neffy can be administered more easily. Accordingly, when evaluating the efficacy and safety of Neffy based on the pharmacokinetic and pharmacodynamic results, it is important to demonstrate similarity in pharmacokinetic and pharmacodynamic profiles between Neffy and Epipen. However, the pharmacokinetic profile of Neffy does not match that of Epipen due to a difference in route of

administration and other factors; in addition, the criteria for the determination of pharmacodynamic similarity are difficult to define in advance.

Similarly to adrenaline formulations including Epipen, due to ethical issues, etc., the applicant considers that it is difficult to conduct a randomized, placebo-controlled study. The applicant's explanation is regarded as reasonable. In addition, with respect to Study EPI JP03, which was conducted for the development of Neffy in Japan, when taking feasibility into account, the proposed patient population, primary efficacy endpoint, and dosage regimen are understandable.

Based on the above, in the present review, the efficacy and safety of Neffy as an adjunctive treatment for anaphylaxis were comprehensively evaluated by PMDA, taking into account the known data on adrenaline, together with pharmacokinetic and pharmacodynamic results on Neffy from clinical pharmacology studies and data from Study EPI JP03 concerning the effect of Neffy on the mitigation of anaphylaxis symptoms.

7.R.2 Efficacy

The applicant's explanation about the efficacy of Neffy:

Table 27 shows the results for the primary efficacy endpoint in Study EPI JP03, the proportion of patients whose main symptom improved at 15 minutes post-dose, or, if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment. Symptoms improved by ≥1 level in 11 of 15 patients (73.3%). Figure 16 shows the time course change in all other Grade 2 symptoms after administration of Neffy other than the main symptom. A trend towards a decrease in symptom grade was observed at the first evaluation timepoint, 5 minutes post-dose, except for cardiovascular symptoms[43)] in 1 patient. An alternative treatment was initiated within 15 minutes post-dose in 1 patient, who received a β_2 agonist for respiratory symptoms. In this patient, before the administration of the β_2 agonist, respiratory symptoms had tended to improve.[44)]

[43)] Because the Japanese Anaphylaxis Guidelines does not define Grade 1 (mild) in the severity classification of cardiovascular symptoms, when symptoms disappear, it was recorded as a reduction from Grade 2 cardiovascular symptoms (improvement).

[44)] A Grade 2 cardiovascular symptom and a respiratory symptom were observed after OFC, and the cardiovascular symptom was determined to be the main symptom. At the timepoint 30 minutes post-dose, the main symptom had improved. Although the respiratory symptoms improved by 1 level at the timepoint 5 minutes after administration of Neffy, β_2 agonist was administered 8 minutes after administration of Neffy, and symptoms disappeared at the timepoint 15 minutes after administration of Neffy.

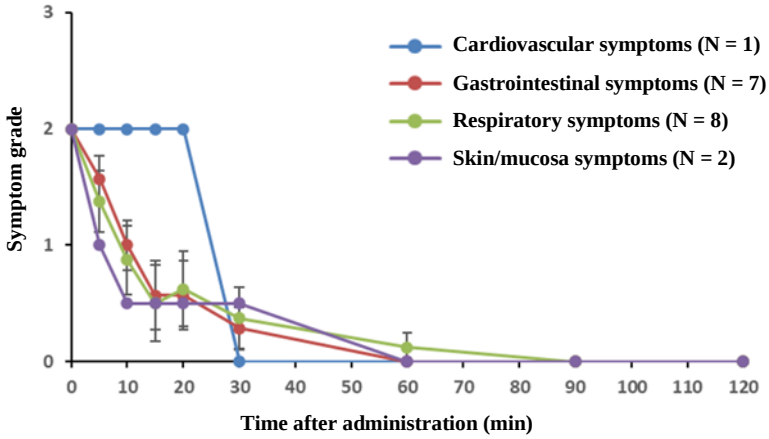

Figure 16. Time course changes in Grade 2 symptoms following administration of Neffy (arithmetic mean ± standard error)

Except for 1 patient in whom a biphasic reaction was observed at 2 hours and 45 minutes after the administration of Neffy, no patients required additional administration of adrenaline. It has been reported that a certain proportion of patients with food-induced anaphylaxis experience biphasic reactions (*J Allergy Clin Immunol Pract.* 2021;9:3717-27).

In Study EPI JP03, OFC-induced anaphylaxis symptoms improved following intranasal administration of Neffy. Although the pharmacokinetic profile of Neffy differs from that of Epipen, in the clinical pharmacology study (Study EPI 15), there were increases in SBP and PR following intranasal administration of Neffy 2.0 mg, comparable to or greater than those observed following intramuscular administration of Epipen 0.3 mg. Given these and other factors, it is expected that Neffy has efficacy comparable to that of Epipen.

PMDA's view:
Study EPI JP03 was conducted as an open-label, uncontrolled study, and thus the evaluation has inherent limitations. However, given the following factors, it is considered that the study results suggest a certain level of efficacy of Neffy in alleviating anaphylaxis symptoms.

- In Study EPI JP03, anaphylactic reactions were induced using a standard approach in accordance with the Oral Food Challenge Guidelines 2020 and the Japanese Anaphylaxis Guidelines. Therefore, the study design was considered capable of providing a reasonable evaluation of efficacy and safety.
- In Study EPI JP03, the primary efficacy endpoint, the proportion of patients whose main symptom improved at 15 minutes post-dose, or if an alternative treatment was initiated within 15 minutes post-dose, at the last assessment timepoint prior to initiation of the alternative treatment, was 73.3% (11 of 15 subjects), indicating that symptoms improved in some patients by ≥1 level. Most patients required no alternative treatment within the 15-minute period after administration of Neffy, and only 1 patient received alternative treatment.

In addition, although the pharmacokinetic profile of Neffy differs from that of Epipen, Neffy exerts pharmacodynamic effects comparable to Epipen [see Section 6.R.1], and the efficacy of adrenaline for

anaphylaxis is well known. Based on a comprehensive assessment of these factors, PMDA concluded that Neffy as an adjunctive treatment for anaphylaxis can be expected to be effective.

However, since no data are available on the use of Neffy as adjunctive treatment of anaphylactic reactions outside medical institutions, the applicant is required to assess the efficacy in clinical practice via post-marketing surveillance, etc., and provide information to healthcare professionals as necessary.

The PMDA's conclusion above will be further discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of Neffy:

Common adverse events that occurred in the Japanese phase III study (Study EPI JP03) [see Section 7.1] and clinical pharmacology studies [see Sections 6.2.1 through 6.2.6] are presented in Table 11, Table 13, Table 15, Table 17,Table 19,Table 21, and Table 28. There were no deaths or serious adverse events in any of the studies.

(1) The safety of Neffy administered intranasally, and (2) the safety of Neffy in pediatric patients weighing ≥15 kg and older patients are discussed below.

(1) Safety of Neffy administered intranasally

Administration site-related adverse events that occurred in patients receiving intranasal dose(s) of Neffy included nasal discomfort, throat irritation, and rhinorrhoea (Table 29). All these events were non-serious, and the majority of events were mild (172 mild events; 10 moderate events). All events resolved except for 6 mild events for which outcomes are unknown. Nasal discomfort is a commonly observed adverse event associated with nasal drops. No effects on olfaction were observed in any of the studies.

The above findings suggest that there have been no major administration site-related safety problems when Neffy is administered intranasally.

Table 29. Administration site-related adverse events[a)] (safety analysis population)

Study	N	Administration site-related adverse events[a)]
Clinical pharmacology studies 8 studies[b)]	541 [c)]	Nasal discomfort (59 events); throat irritation (27 events); rhinorrhoea (21 events); rhinalgia, sneezing (8 events each); nasal congestion, epistaxis (7 events each); oropharyngeal pain (6 events); nasal mucosal disorder (5 events); intranasal paraesthesia, nasal pruritus (4 events each); pharyngeal paraesthesia, dry throat, upper respiratory tract congestion (3 events each); upper-airway cough syndrome, nasal dryness (2 events each); pharyngeal hypoaesthesia, increased upper airway secretion (1 event each)
EPI JP03	15	Cough,[d)] nasal mucosal disorder (2 events each); pharyngeal hypoaesthesia, dyspnoea,[d)] oropharyngeal pain, intranasal hypoaesthesia, rhinalgia, nasal discomfort, nasal crusting (1 event each)

a) MedDRA System organ class (SOC) "Respiratory, thoracic and mediastinal disorders" MedDRA ver.22.0
b) Data from clinical pharmacology studies that used the commercial formulation were aggregated (Studies EPI 10, EPI 13, EPI 14, EPI 15, EPI 16, EPI 17, EPI 18, and EPI JP02).
c) In each study, participants were counted as 1 subject in each treatment period.
d) Cough and dyspnoea (1 subject each) were determined to be OFC-induced adverse events.

There were no other adverse events that were likely to cause clinical problems, compared with approved intramuscular adrenaline formulations. A cautionary statement regarding known adverse events associated with

approved intramuscular adrenaline formulations will be included in the Adverse Reactions section of the package insert.

(2) Safety of Neffy in pediatric patients weighing ≥15 kg and older patients

Regarding the safety of Neffy in pediatric patients weighing ≥15 kg, common adverse events reported in Studies EPI JP03 and EPI 10, in which Neffy was administered to pediatric patients with allergies (Table 21 and Table 28), were also reported in clinical studies conducted in adults. In Study EPI JP03, tremor occurred in 20.0% (3 of 15) of subjects, which was higher than in other clinical studies. However, this adverse event is consistent with the expected pharmacological effects of adrenaline, and is therefore not considered unique to pediatric patients.

The adverse events occurring after intramuscular administration of adrenaline to pediatric patients (*J Allergy Clin Immunol.* 1998;101:33-7, *J Allergy Clin Immunol.* 2002;109:171-5) are similar to those reported in adult patients, indicating no significant differences in the safety profile of adrenaline between children and adults. Additionally, in the use-results survey for Epipen (*Japanese Journal of Allergology.* 2013;62:144-54), no clinically significant adverse drug reactions occurred when Epipen was used in patients over a wide age range.[45)] These findings suggest that there are no particular safety concerns in the use of Neffy in pediatric patients.

Regarding the safety of Neffy in older patients, no clinical study data in patients aged ≥65 years are available. However, given that no clinically significant adverse drug reactions occurred in the use-results survey of Epipen mentioned above, significant problems are not expected to occur following intranasal administration of Neffy to older individuals. Nonetheless, as some older individuals have higher sensitivity to adrenaline, as with already approved intramuscular adrenaline formulations, cautionary statements to the effect that Neffy should be administered with caution depending on the patient's condition will be included in the Precautions concerning patients with specific backgrounds section of the package insert.

PMDA's view:

Although it should be noted that clinical study data on Neffy are limited, the submitted clinical study data indicate that there are no safety concerns that may cause problems in clinical use even though there have been reports of administration site-related adverse events following intranasal administration of Neffy. Similar to Epipen, an existing adjunctive treatment for anaphylaxis, increased vigilance is needed for cardiovascular- and psychiatric and nervous system-related adverse events when using Neffy. PMDA concluded that the safety of Neffy is acceptable for pediatric patients weighing ≥15 kg as well as for elderly patients, provided that appropriate monitoring of patients following administration of Neffy and interventions, including emergency transfer if necessary, are implemented.

[45)] A total of 449 subjects were included in the safety analysis population. The youngest and the oldest age groups consisted of patients aged 0 to 3 years and patients aged ≥80 years, respectively.

However, Neffy was administered to only a limited number of patients in clinical studies. In addition, available clinical study data in patients experiencing anaphylaxis are confined to intranasal administration during hospital-based OFC tests. Taking these into considerations, the applicant is required to continue to collect safety data on Neffy in clinical use via post-marketing surveillance, etc. and provide information to healthcare professionals as necessary.

The PMDA's conclusion above will be further discussed at the Expert Discussion.

7.R.4 Clinical positioning and indication

PMDA's view on the clinical positioning and indication of Neffy:

Based on the submitted data and discussions in Sections 7.R.2 and 7.R.3, as well as the existing treatment algorithm for anaphylaxis, Neffy, similar to Epipen, an approved self-injectable intramuscular adrenaline formulation, can be positioned as one of the adjunctive treatments for an anaphylactic reaction. The indication of Neffy should be the same as the proposed indication, "adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others (for use only in individuals with a history of anaphylaxis or at a high risk of anaphylaxis)."

Neffy is intended to be used as adjunctive treatment for anaphylaxis in emergency situations, and cannot be a substitute for treatment at the medical institutions. Based on past knowledge on the treatment of anaphylaxis with adrenaline, it can be anticipated that there will be cases where anaphylactic symptoms are resistant to adrenaline, or cases where adrenaline is ineffective if not used appropriately. Therefore, prior to prescribing Neffy, it is essential for the physician to give instructions to the patient on the correct use of the product, etc. to ensure that the patient can self-administer the product properly. Furthermore, Neffy can only be prescribed after confirming that the patient, caregiver, or other appropriate representatives have understood how to use the product, etc. It is also important to instruct patients to seek medical attention immediately after using Neffy to receive appropriate care. Therefore, a cautionary statement to this effect should be included in the Warnings section of the package insert.

The following cautionary statements should be included in the Precautions Concerning Indication section of the package insert, equivalent to that provided for Epipen:

- Anaphylactic reactions are progressive in nature and initial symptoms may differ from patient to patient (e.g., numbness, discomfort, swelling of the lips, feeling unwell, nausea, vomiting, abdominal pain, urticaria, coughing fit). Before prescribing Neffy, the physician must ask if the patient has had prior anaphylactic episodes, as well as initial symptoms, and give appropriate instructions to the patient, caregiver, or other appropriate representatives regarding when and how to use the product.
- The following should be used as guides to ensure that Neffy is used at the right time.
    - When the initial symptoms appear but before the onset of anaphylactic shock
    - When an allergen that previously caused anaphylaxis is inadvertently ingested and the patient experiences noticeable abnormal symptoms

- Because Neffy increases myocardial oxygen demand, the use of Neffy should be avoided in cases of cardiogenic shock or haemorrhagic/traumatic shock.

The PMDA's conclusion above will be further discussed at the Expert Discussion.

7.R.5 Dosage and administration

Based on the submitted data, discussions in Sections 6.R.1, 7.R.2, and 7.R.3, PMDA concluded that, as adjunctive treatment for anaphylactic reactions, the intranasal administration of Neffy at 1 mg of adrenaline per dose to patients weighing ≥15 kg to <30 kg or 2 mg of adrenaline per dose to patients weighing ≥30 kg, can be expected to provide a certain level of efficacy, with acceptable safety.

Moreover, PMDA evaluated the use of Neffy in patients weighing <15 kg and the potential for 2-dose administration of Neffy as described below:

(1) Administration of Neffy to patients weighing <15 kg

For Epipen, in certain life-threatening situations, administration in dosages slightly exceeding the recommended intramuscular dosage of 0.01 mg/kg may be justified. Accordingly, in the Precautions Concerning Dosage and Administration section of the package insert, a cautionary statement states that the necessity of administering doses of Epipen exceeding 0.01 mg/kg should be carefully determined on a case-by-case basis by closely monitoring the patient's symptoms, giving the highest priority to saving the life of the patient (Review Report of "Epipen Injection 0.15 mg and Epipen Injection 0.30 mg" dated February 4, 2005).

PMDA asked the applicant to explain the administration of Neffy to patients weighing <15 kg.

The applicant's explanation:

In the development of Neffy, patients weighing ≥15 kg were selected as the intended patient population [see Section 7.R.1] using the dosage regimen of Epipen as a reference. In the clinical studies of Neffy, the lower limit of body weight among patients who received Neffy 1.0 mg was 16 kg (Study EPI JP03), and no clinical studies were conducted in patients weighing <15 kg. In addition, in Study EPI 10 conducted in non-Japanese pediatric patients with systemic allergies, the exposure was higher in the lower body weight group when an identical dose level was administered to different body weight groups (Table 20). Based on this and other factors, Neffy 1 mg may result in an overdose if administered to patients weighing <15 kg. However, although increased vigilance for the occurrence of adverse drug reactions is required and the decision to administer Neffy should be made cautiously based on close monitoring of the patient, it is appropriate to allow administration of Neffy to patients weighing <15 kg based on the following: Neffy is intended for use in emergency settings; and a use-results survey and other data for Epipen,[46)] have reported use in patients weighing <15 kg or those aged ≤3 years without the occurrence of serious adverse drug reactions.

[46)] According to the use-results survey of Epipen, 0.15 mg formulation of Epipen was administered to patients aged 0 to 3 years (N = 10, unknown body weight) who presented with anaphylactic reactions, and no serious adverse drug reactions were reported in these patients (*Japanese Journal of Allergology.* 2013;62:144-54). In a patient aged 2 years and 7 months weighing 12 kg developed an anaphylactic reaction. The anaphylactic reaction

PMDA's view:

The efficacy and safety of Neffy in patients weighing <15 kg have not been evaluated, and administration of Neffy 1.0 mg may result in an overdose of adrenaline. However, Neffy is intended as an adjunctive treatment to preserve life until the patient can be taken to the hospital by ambulance. Taking into account experience with the use of Epipen, it is considered that in emergency life-threatening situations such as anaphylactic shock, where immediate intervention is necessary, the clinical benefits of allowing administration of Neffy to patients weighing <15 kg outweigh the potential risks, provided that the patient subsequently receives medical attention and appropriate medical care. However, as with Epipen, careful attention must be paid to the occurrence of adverse drug reactions when administering Neffy to patients weighing <15 kg. Cautionary statements to the following effect should be included in the Precautions Concerning Dosage and Administration section of the package insert, equivalent to those provided for Epipen: Increased vigilance is needed such as monitoring for adverse drug reactions, and the use of a standard adrenaline injection should also be considered; whether Neffy needs to be administered should be determined carefully after closely monitoring the patient's symptoms, giving the highest priority to the saving of life.

(2) Two-dose administration of Neffy

The Japanese Anaphylaxis Guidelines state that because the effect of adrenaline is short-lived, if anaphylactic symptoms are refractory to treatment, repeated administration of adrenaline every 5 to 15 minutes is recommended.

PMDA asked the applicant to provide an explanation regarding the possibility that a second dose of Neffy may be needed if the patient experiencing an anaphylactic reaction responds inadequately to the first dose or if symptoms worsen, as well as the safety of the second dose in clinical use.

The applicant's explanation:

Neffy is intended as an adjunctive treatment during the onset of anaphylaxis until the patient can reach a medical institution. While cases requiring a second administration are expected to be uncommon, situations may occur where a second dose of Neffy may be required, such as when a patient's location is remote from a medical institution and access to medical care is delayed.

The safety of 2-dose administration of Neffy was evaluated in Studies EPI 15 and EPI 18 conducted in healthy non-Japanese adults and adult patients with seasonal allergic rhinitis, respectively [see Sections 6.2.1 and 6.2.5]. In these studies, subjects were to receive 2 doses of Neffy 10 minutes apart. While the exposure following administration of 2 doses of Neffy was higher than that of 2 doses of Epipen (Table 10 and Table 18), all the adverse events reported in these studies were mild. There were no reports of death, serious adverse events, or adverse events that led to treatment discontinuation. These results suggest that there are no significant safety

improved after administration of the Epipen 0.15 mg formulation, and no adverse events occurred (Journal of the Japanese Association of Rural Medicine. 2016;65:862-86).

concerns associated with 2-dose administration of Neffy. It is considered that the second dose of Neffy can be administered whenever deemed necessary.

In Study EPI 15, the pharmacokinetic/pharmacodynamic profiles following administration of 2 doses of Neffy to the same nostril were comparable to those to different nostrils. In Study EPI 18, under rhinitis conditions, the exposure following administration of 2 doses of Neffy to the same nostrils was higher than that to different nostrils, with a higher pharmacodynamic response when administered to the same nostril (Table 18, Figure 11, and Figure 12). For this reason, when 2 doses of Neffy are administered, a higher exposure and higher pharmacodynamic response can be obtained by administering to the same nostril twice. Conversely, even when 2 doses of Neffy are administered to different nostrils, the exposure and pharmacodynamic response were comparable to or higher than those of intramuscular Adrenalin 0.3 mg; therefore, no particular recommendation is necessary regarding to which nostril the second dose should be administered.

PMDA's view:
Regarding 2 doses of Neffy, there are no clinical study data on patients when Neffy was administered twice for a single anaphylactic reaction. However, no particular safety concerns were identified when 2 intranasal doses were administered 10 minutes apart in studies including Studies EPI 15 and EPI 18, which were conducted in healthy non-Japanese adults and adult patients with seasonal allergic rhinitis, respectively. Based on the results, the safety of 2-dose administration of Neffy is considered acceptable. Taking into account that Neffy is intended for the use in emergency settings and that early treatment for anaphylaxis is critical, PMDA concluded that a second dose of Neffy can be administered whenever necessary. However, for patients in whom an additional dose of Neffy may be required, it is important that physicians provide instructions at the time of prescribing regarding the situations and symptoms that warrant an additional dose. The applicant is required to include a cautionary statement to this effect in the Precautions Concerning Dosage and Administration section of the package insert.

The PMDA's conclusions on dosage regimens, including administration of Neffy in patients weighing <15 kg and 2-dose administration of Neffy, as well as the details of the Precautions Concerning Dosage and Administration section as discussed above will be further discussed at the Expert Discussion.

7.R.6 Self-administration

The applicant's explanation about the efficacy and safety of self-administration of Neffy:
In Study EPI JP03 conducted in Japanese patients, the study drug was administered by physicians. No data for Neffy administered by Japanese patients or caregivers have been obtained. However, based on the following factors, it is considered that Neffy can be administered by patients or caregivers appropriately in Japan:

- Neffy is a nasal formulation product designed to allow easy administration.
- The sprayer device used for Neffy has already been used for other drugs approved in the US.
- It is considered that Neffy can be administered appropriately even outside medical institutions by practicing using the training device provided for the product. The device, in conjunction with sufficient

information provided by the physician before actual use, would allow patients and caregivers to familiarize themselves with the procedure.

In Study EPI 17,[47)] a phase I study in adult non-Japanese patients with Type I allergy, after training using a training device, Neffy was self-administered. No significant administration errors occurred.[48)]

PMDA's view:
During the development of Neffy, no data have been obtained on the use of Neffy under the conditions anticipated in clinical use, that is, self-administration of Neffy by Japanese patients or their caregivers at the time of onset of an anaphylactic reaction. However, given that Neffy is a nasal spray solution that is relatively easy to administer, PMDA concluded that Neffy can be self-administered provided that (i) appropriate training programs are implemented for patients and caregivers at the time of dispensing, (ii) Neffy is used by patients whom the physician has determined to be capable of self-administering Neffy correctly, and (iii) appropriate measures to optimize safe use including the provision of patient-directed education materials are implemented. However, the applicant is required to collect safety and efficacy-related data following administration of Neffy to Japanese patients or caregivers via the post-marketing surveillance, etc. and provide the data obtained to healthcare professionals in an appropriate manner.

The PMDA's conclusion above will be further discussed at the Expert Discussion.

7.R.7 Implementation system for proper use

The applicant's explanation about the implementation system for proper use of Neffy:
If Neffy is not administered appropriately, it may result in a lack of efficacy, overdose, or other issues. Therefore, in order to promote appropriate use, the applicant plans to establish an appropriate internal framework and, after consultation with the relevant academic societies (The Japanese Society of Allergology, Japanese Society of Pediatric Allergy and Clinical Immunology, and Japanese Association for Acute Medicine), to implement safety measures equivalent to those for Epipen, as outlined below.

(1) Measures for physicians/medical institutions
For healthcare professionals, in addition to the package insert, the applicant will appropriately provide information and issue alerts regarding the proper use of Neffy by using educational materials for healthcare professionals (proper use guide) that describe the overall framework of the applicant's measures to promote the proper use of Neffy, correct administration methods, and what patients and caregivers need to receive instructions on.

[47)] A randomized, open-label 2-treatment, 2-period crossover study in adult non-Japanese patients with Type I allergy. Patients who completed the self-administration training program were to self-administer a single intranasal dose of Neffy 2.0 mg or healthcare professionals were to administer a single intramuscular dose of Adrenalin 0.3 mg to patients. The results of pharmacodynamic effects (ΔSBP E_{max} and ΔPR E_{max}) for self-administered Neffy 2.0 mg were comparable to or greater than those for Adrenalin 0.3 mg administered by healthcare professionals.

[48)] Inappropriate cases were identified in some patients among 42 patients who self-administered Neffy based on the video records of self-administration: the tip of the nozzle of the sprayer device was not inserted into the nose properly (tip only [1 subject], about a half [8 subjects], and undeterminable [2 subjects]), the nozzle was not kept at the right angle (not straight [8 subjects] and undeterminable [2 subjects]). After administration of Neffy, 10 subjects experienced rhinorrhoea.

For physicians who wish to prescribe Neffy, viewing a video regarding proper use of Neffy is mandatory for prescriber registration. Physician registration will only be granted to those who pass the confirmation test.

Regarding distribution management, when receiving orders from medical institutions and pharmacies, the pharmaceutical distributors can deliver Neffy only after confirming, in collaboration with the applicant, that the prescribing physician is a registered prescriber for Neffy.

(2) Measures for patients

Prior to prescribing Neffy, the registered prescribers will obtain informed consent from patients, caregivers, or other appropriate representatives. The following explanations and instructions will be provided:

- The physician should explain how and when to correctly use Neffy, possible adverse drug reactions that may occur when using Neffy, and other information using the educational materials for patients and a training device so that patients, caregivers, or other appropriate representatives can gain a clear understanding of the illness and are able to use Neffy correctly. The patients/caregivers, etc. should also be instructed to regularly practice the use of Neffy using the training device to ensure proper administration.
- The physician should instruct patients to write the name of the prescribing physician and emergency contact information on the patient card included in product box, and carry the card together with the product at all times to enable a prompt response in emergency situations.
- Since Neffy is an adjunctive treatment for anaphylactic reactions, patients should be instructed to always seek medical attention after using Neffy. In addition, to allow healthcare professionals to confirm the administration status of Neffy after its use, patients should be instructed to show the used product to healthcare professionals.
- Patients/caregivers, etc. should be instructed to enroll in a notification service that provides notification prior to the expiration date of the product. They should also be instructed to take expired products to the prescribing medical institution, and obtain a new prescription before the expiration date.

With respect to informed consent and training using the practice device described in (2), cautionary statements will be provided in the Warnings section of the package insert. Guidance on presenting the used product to the healthcare professionals after administration will be included in the Important precautions section of the package insert.

Information materials such as educational materials for healthcare professionals and those for patients will be posted on the company’s web site.

PMDA’s view:

Since Neffy is designed to be self-administered by patients/caregivers, etc. outside medical institutions, it is extremely important to ensure that Neffy is used properly. The measures for proper use of Neffy proposed by the applicant are generally similar to those implemented for Epipen, an approved product, and there are no

significant problems with the measures; however, the appropriateness of these measures, including the need for any additional measures to optimize safety should be further discussed at the Expert Discussion.

7.R.8 Post-marketing investigations

The applicant plans to conduct a post-marketing general use-results survey to collect data on the real-world use, safety, and efficacy of Neffy when administered outside medical institutions to patients experiencing anaphylactic reactions.

PMDA's view:

As discussed in Section 7.R.3, based on the submitted clinical study data, Neffy has acceptable safety if administered appropriately. However, no data are currently available on the use of Neffy outside medical institutions in patients who developed anaphylactic reactions. Therefore, PMDA concluded that the safety and efficacy of Neffy in clinical use should be investigated via post-marketing surveillance, etc. and information obtained should be provided promptly to healthcare professionals.

The PMDA's conclusion above will be further discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that efficacy of Neffy is expected as adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others, and Neffy has acceptable safety in view of its benefits. The drug product is classified as a powerful drug. Neffy is considered to be clinically meaningful because it offers a new adjunctive treatment option for anaphylactic reactions. The dosage regimen, the internal framework for ensuring proper use, and post-marketing investigations, etc. should be further evaluated.

PMDA considers that Neffy may be approved if Neffy is not considered to have any particular problems based on comments from the Expert Discussion.

10. Other

Definitions of efficacy endpoints and other items in clinical studies are shown below.

Item	Definition
TNSS	The total score calculated as the sum of patient-rated scores for 4 nasal symptoms (nasal congestion, rhinorrhoea, nasal itching, and sneezing), each assessed on a scale ranging from 0 (absent) to 3 (severe).
Congestion score	The score for nasal congestion as assessed by the patient on a scale ranging from 0 (absent) to 3 (severe).
Main symptom	Among gastrointestinal, respiratory, or cardiovascular symptoms of Grade ≥2 as per the Japanese Anaphylaxis Guidelines, the symptom with the highest grade. If symptoms of the same grade are observed in different organs, the main symptom was to be selected in the following priority: cardiovascular, respiratory, and gastrointestinal symptoms.
Improvement	A decrease of at least one grade in the severity of symptoms in each organ as per the Japanese Anaphylaxis Guidelines compared to baseline.
Proportion of patients whose main symptom improved	The proportion of patients whose main symptom decreased by ≥1 level in grade as per the Japanese Anaphylaxis Guidelines compared to baseline.

Review Report (2)

August 8, 2025

Product Submitted for Approval

Brand Name	Neffy Nasal Spray 1 mg Neffy Nasal Spray 2 mg
Non-proprietary Name	Adrenaline
Applicant	Alfresa Pharma Corporation
Date of Application	November 29, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, safety, clinical positioning, indication, dosage and administration, and self-administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the efficacy, safety, clinical positioning, indication, dosage and administration, and self-administration of Neffy presented in Review Report (1). The expert advisers also made the following comments:

- While it is appropriate to add a cautionary statement to the effect that for patients weighing <15 kg, whether administration of Neffy is necessary should be carefully determined on a case-by-case basis after closely monitoring the patient's symptoms, giving the highest priority to saving the life of the patient; however, whether to administer Neffy to younger patients and/or low-body-weight patients should be determined with even greater caution.
- In some cases, such as being in areas far from medical institutions, administration of Neffy twice may be required. In such cases, to achieve higher exposure in patients requiring two doses, it is appropriate for the second dose of Neffy to be administered into the same nostril.

Based on the discussion at the Expert Discussion, PMDA concluded as follows: The dosage and administration of Neffy should be "the usual dosage is a single intranasal dose of adrenaline 1 mg for patients weighing <30 kg and a single intranasal dose of adrenaline 2 mg for patients weighing ≥30 kg"; and cautionary statements regarding the administration of Neffy to patients weighing <15 kg and 2-dose administration of Neffy should be included in the Precautions Concerning Dosage and Administration section of the package insert.

The applicant considers that no particular recommendation is necessary regarding which nostril the second dose of Neffy should be administered into [see Section 7.R.5 of Review Report (1)]. However, PMDA considers that where a second dose is administered, it is advisable to administer Neffy into the same nostril, and concluded that a cautionary statement to this effect should be included in the Precautions Concerning Dosage and Administration section of the package insert based on the following factors:

- The clinical study data suggest that a higher exposure of adrenaline can be expected when Neffy is administered repeatedly into the same nostril.
- Due to the change in the nasal mucosa caused by DDM, the systemic absorption of intranasally administered formulations may increase for several days after administration of Neffy. If another intranasal formulation is used concurrently, its pharmacokinetics may be affected; therefore, it is advisable to administer Neffy into only one nostril.

Based on the above discussions and evaluation, PMDA concluded that cautionary statements to the following effect should be included in the Precautions Concerning Dosage and Administration section of the package insert.

- As a general principle, the Neffy 1 mg formulation should be used in patients weighing ≥15 kg. If the Neffy 1 mg formulation is administered to patients weighing <15 kg, patients should be closely monitored for the occurrence of adverse drug reactions or other problems, and the use of a standard adrenaline injection should also be considered. Whether administration of Neffy 1 mg to patients weighing <15 kg is necessary should be determined carefully on a case-by-case basis after closely monitoring the patient's symptoms, giving the highest priority to saving the life of the patient.
- Where a second dose is administered, it is preferable to administer Neffy into the same nostril as the first dose. Patients who are expected to require an additional dose of Neffy should be instructed at the time of dispensing regarding the situations and symptoms that indicate the need for an additional dose.

PMDA instructed the applicant as follows: (i) specify the dosage and administration as discussed above, and establish the Precautions Concerning Dosage and Administration section in the package insert; and (ii) provide cautionary statements regarding the administration of Neffy to patients weighing <15 kg and 2-dose administration of Neffy, including whether to administer Neffy to younger patients and/or low-body-weight patients, using the educational materials for healthcare professionals and for patients.

The applicant agreed to follow these instructions.

1.2 Implementation system for proper use, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions on the implementation system for proper use, and post-marketing investigations presented in Review Report (1). The expert advisers also made the following comments:

- It is extremely important to establish an appropriate implementation system to promote proper use in preparation for the product launch.

- Regarding the planned general use-results survey, it is important to develop a suitable system for information provision and to provide the obtained survey results to healthcare professionals promptly.

In view of the discussion in Section "7.R.8 Post-marketing investigations" in Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that (i) the risk management plan (draft) for Neffy should include the safety and efficacy specifications presented in Table 30, and (ii) the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and the additional risk minimization activities presented in Table 31. PMDA requested the applicant to conduct post-marketing surveillance to evaluate these issues.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Pulmonary oedema • Dyspnoea • Cardiac arrest	• Misuse during administration	• Safety in out-of-hospital use
Efficacy specification		
• Efficacy in clinical use		

Table 31. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	• General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate the educational material for users (Neffy Guidebook) • Organize and disseminate the educational material for healthcare professionals (Proper use guide for Neffy nasal spray solution) • Development of an internal framework for proper use management

The applicant explained that a general use-results survey will be conducted to assess the safety and efficacy of Neffy in clinical use as shown in Table 32.

Table 32. Outline of general use-results survey (draft)

Objective	To assess the safety and efficacy of Neffy in clinical use
Survey method	Continuous survey method
Population	Patients who developed anaphylaxis and used Neffy
Observation period	Until the day following administration of Neffy
Planned sample size	100 subjects
Main survey items	• Safety specification: pulmonary oedema, dyspnoea, cardiac arrest, misuse during administration, safety in out-of-hospital use • Efficacy specification: efficacy in clinical use • Patient characteristics (e.g., age, body weight, history of adrenaline use) • Administration status of Neffy (allergen that triggered anaphylaxis, severity of anaphylaxis, nasal congestion/discharge before administration, other treatments after administration of Neffy) • Data on misuse, malfunction • Adverse events • Efficacy

PMDA accepted these actions and considers that the applicant is required to provide collected data to healthcare professionals in an appropriate and timely manner.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed dosage and administration, and indication as shown below, with the following approval conditions. Since the product is a drug with a new route of administration, the re-examination period is 6 years.

Indication

Adjunctive treatment for anaphylactic reactions caused by bee venom, foods, drugs, and others (for use only in individuals with a history of anaphylaxis or at a high risk of anaphylaxis)

(No change made to the proposed text)

Dosage and Administration

The usual dosage is a single intranasal ~~administration~~ dose of adrenaline 1 mg for patients weighing ~~15 kg to~~ <30 kg and a single intranasal ~~administration~~ dose of adrenaline 2 mg for patients weighing ≥30 kg.

(The underlined words are added to the proposed text; the strikethrough words are deleted from the proposed text)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to take necessary measures, such as implementing training prior to delivery of the product to ensure that the product will be prescribed and used only by a physician who fully understands the safety and efficacy of the product and is capable of providing patients with appropriate and sufficient instructions on the use of the product.

Appendix

List of Abbreviations

Adrenalin	Adrenalin®
AUC_{0-t}	Area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-x\ min}$	Area under the concentration-time curve from time zero to x minutes
Auvi-Q	AUVI-Q®
bpm	Beats per minute
CERI	Chemicals Evaluation and Research Institute, Japan
CI	Confidence interval
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ΔDBP	Change from baseline DBP
DDM	Dodecyl maltoside
E_{max}	Maximum observed effect
Epipen	Epipen Injection 0.15 mg, Epipen Injection 0.3 mg
HPLC	High performance liquid chromatography
Japanese Anaphylaxis Guidelines	Anaphylaxis Guidelines. 2022. [in Japanese] Anaphylaxis Committee, Japanese Society of Allergology
JP	Japanese Pharmacopoeia
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LD_{50}	Lethal dose 50
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MF	Master file
Neffy	Neffy Nasal Spray 1 mg Neffy Nasal Spray 2 mg
NZW	New Zealand White
OFC	Oral food challenge
Oral Food Challenge Guidelines 2020	Oral Food Challenge Guidelines 2020. Health, Labour and Welfare Sciences Research Grants (Research on Immunologic and Allergic Diseases Program, Research Area of Diseases and Disabilities: Establishment of standard implementation procedure for oral food challenge tests)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Pulse rate
ΔPR	Change from baseline PR
RH	Relative humidity
SBP	Systolic blood pressure
ΔSBP	Change from baseline SBP
SD	Sprague Dawley
Symjepi	SYMJEPI™
t_{Emax}	Time of maximum observed effect
t_{max}	Time to maximum plasma concentration
TNSS	Total nasal symptom score
Tween 80	Polysorbate 80
UHPLC	Ultra high performance liquid chromatography