Report on the Deliberation Results

March 3, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Izcargo for I.V. Infusion 10 mg
Non-proprietary Name	Pabinafusp Alfa (Genetical Recombination) (JAN*)
Applicant	JCR Pharmaceuticals Co., Ltd.
Date of Application	September 29, 2020

Results of Deliberation

In its meeting held on February 25, 2021, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients in evaluated in Japanese clinical studies, the applicant is required to conduct post-marketing clinical studies or a use-results survey covering all patients treated with the product during the re-examination period in order to keep track of information on patient characteristics and to collect data on the safety and efficacy of the product as early as possible.
3. The applicant is required to submit, on a regular basis, data and analysis results from the clinical studies and the use-results survey which are conducted to verify the efficacy and safety of the product.
4. The applicant is required to take necessary measures to ensure the proper use of the product, based on the results of an additional evaluation of the efficacy and safety of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 10, 2021
Pharmaceuticals and Medical Devices Agency

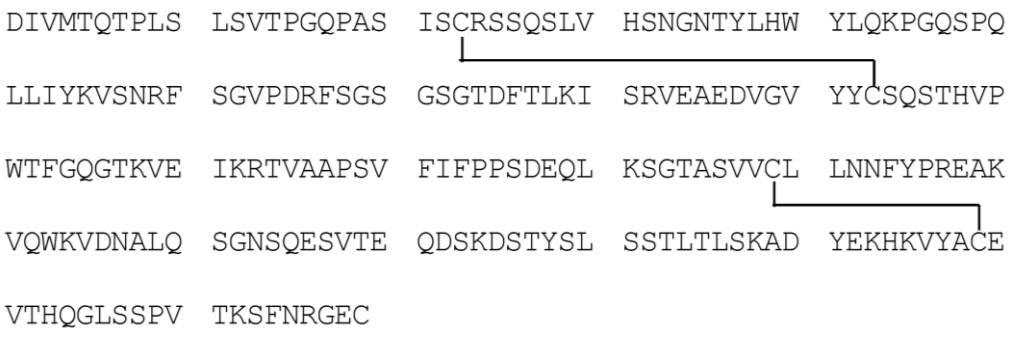
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Izcargo for I.V. Infusion 10 mg
Non-proprietary Name	Pabinafusp Alfa (Genetical Recombination)
Applicant	JCR Pharmaceuticals Co., Ltd.
Date of Application	September 29, 2020
Dosage Form/Strength	Lyophilized powder for injection: Each vial contains 12.5 mg of pabinafusp alfa (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Pabinafusp Alfa is a recombinant fusion glycoprotein (molecular weight: ca. 300,000) composed of humanized anti-human transferrin receptor monoclonal antibody and human iduronate-2-sulfatase. Pabinafusp Alfa is produced in Chinese hamster ovary cells. Pabinafusp Alfa is composed of 2 A-chains consisting of 219 amino acid residues each and 2 B-chains consisting of 975 amino acid residues each. The A-chain is the L-chain (κ-chain) of the anti-human transferrin receptor antibody, and the amino acid residues at positions 1-448, 449-450, and 451-975 in the B-chain are composed of the H-chain (γ1-chain) of the anti-human transferrin receptor antibody, a linker, and human iduronate-2-sulfatase, respectively.

Structure

Amino acid sequence and main disulfide bonds:

A-chain



B-chain

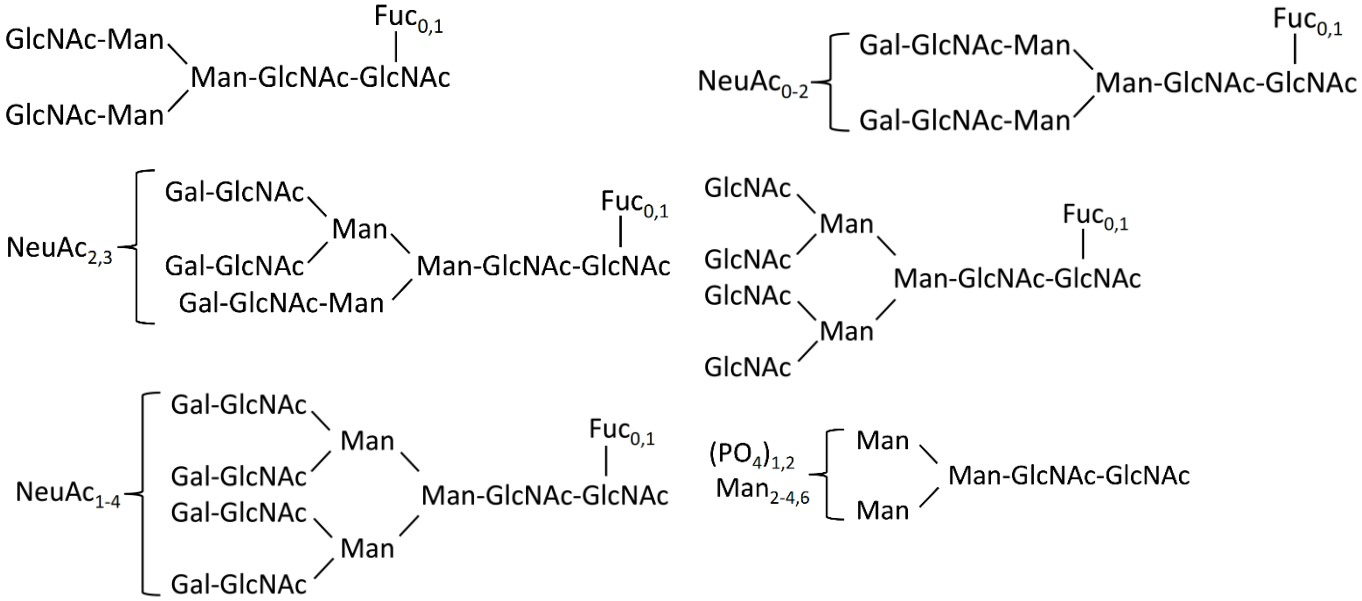
Formylglycine: B-chain C509

Glycosylation: B-chain N298, B-chain N456, B-chain N540, B-chain N569, B-chain N671, B-chain N705, B-chain N750, B-chain N938, B-chain N962

Intra-chain disulfide bond: solid line

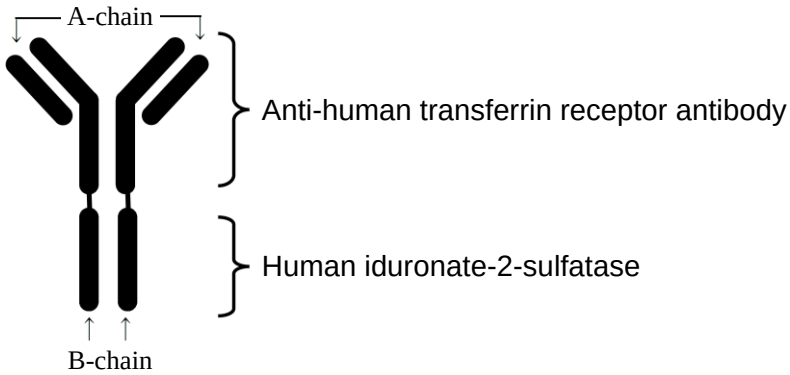
Inter-chain disulfide bond: A-chain C219–B-chain C221, B-chain C227–B-chain C227, B-chain C230–B-chain C230

Deduced structure of major glycan:



Man, mannose; GlcNAc, *N*-acetylglucosamine; NeuAc, *N*-acetylneuraminic acid, Gal, galactose; Fuc, fucose

Schema:



Molecular formula: $C_{11906}H_{18168}N_{3120}O_{3616}S_{70}$ (protein moiety)

Molecular weight: 265,110.93 (protein moiety)

Items Warranting Special Mention	SAKIGAKE designated drug (SAKIGAKE Drug Designation No. 2 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0327-1 dated March 27, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare); Orphan drug (Orphan Drug Designation No. 486 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0918-6 dated September 18, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of mucopolysaccharidosis type II, 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 long-term efficacy and other aspects of the product should be further evaluated.

Indication

Mucopolysaccharidosis type II

Dosage and Administration

The usual dosage is 2.0 mg of pabinafusp alfa (genetical recombination) per 1 kg of body weight once weekly as an intravenous infusion.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients evaluated in Japanese clinical studies, the applicant is required to conduct post-marketing clinical studies or a use-results survey covering all patients treated with the product during the re-examination period in order to keep track of information on patient characteristics and to collect data on the safety and efficacy of the product as early as possible.
3. The applicant is required to submit, on a regular basis, data and analysis results from the clinical studies and the use-results survey which are conducted to verify the efficacy and safety of the product.
4. The applicant is required to take necessary measures to ensure proper use of the product, based on the results of an additional evaluation of the efficacy and safety of the product.

Attachment

Review Report (1)

January 13, 2021

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	Izcargo for I.V. Infusion 10 mg
Non-proprietary Name	Pabinafusp Alfa (Genetical Recombination)
Applicant	JCR Pharmaceuticals Co., Ltd.
Date of Application	September 29, 2020
Dosage Form/Strength	Lyophilized powder for injection: each vial contains 12.5 mg of pabinafusp alfa (genetical recombination).

Proposed Indication

Mucopolysaccharidosis type II

Proposed Dosage and Administration

The usual dosage is 2.0 mg of pabinafusp alfa (genetical recombination) per 1 kg of body weight once weekly as an intravenous infusion.

Table of Contents

List of Abbreviations

See Appendix.

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

Izcargo is a powder for injection containing the active ingredient pabinafusp alfa (genetical recombination) (hereinafter referred to as "pabinafusp alfa"), which is a recombinant fusion protein consisting of human iduronate-2-sulfatase (hIDS) and humanized anti-human transferrin receptor 1 (hTfR) antibody. Izcargo was developed by JCR Pharmaceuticals.

Mucopolysaccharidosis type II (MPS II), also called Hunter syndrome, is an X-linked recessive genetic disorder, which is caused by a genetic deficiency in or reduced activity of iduronate-2-sulfatase (IDS), a lysosomal enzyme involved in the metabolism of glycosaminoglycans (GAGs), a type of mucopolysaccharides, leading to the cellular accumulation of specific GAGs, primarily heparan sulfate (HS) and dermatan sulfate (DS). Patients with MPS II have various symptoms such as cell hypertrophy, organomegaly, tissue damage, and organ dysfunction, which may give rise to a range of clinical manifestations including, albeit varying from patient to patient, typically, delayed psychomotor development, symptoms of neurologic regression, cardiac failure, obstructive respiratory disorder, restricted range of motion, and hepatosplenomegaly, all of which progress gradually (*Mucopolysaccharidoses Update.* [in Japanese], E-N Medix, 2011;106-10). In Japan, the prevalence of MPS II is estimated to be 1 in 90,000 to 100,000, which is considered to be similar to the incidence of MPS II reported overseas (1 in 92,000 to 1 in 16,200) (*Mol Genet Metab.* 2010;99:18-25). In the nationwide epidemiological survey in 2016, a total of 168 patients were confirmed as having MPS II (a research project funded by Health and Labor Sciences Research Grant [Research on Measures for Intractable Diseases] "Nationwide Epidemiological Survey of Lysosomal and Peroxisomal Diseases in Japan" [Fiscal year 2017 Joint Research Report; in Japanese]).

In Japan, idursulfase (genetical recombination) (whose brand name is Elaprase 6 mg for Intravenous Infusion) approved in October 2007 is currently available as an intravenous enzyme replacement therapy for MPS II. The amino acid sequence of the active ingredient idursulfase is identical to that of hIDS. However, because IDS cannot cross the blood-brain barrier, intravenous therapy with Elaprase is unlikely to be effective in the treatment of central nervous system (CNS) symptoms.

Pabinafusp alfa is designed to be delivered into not only the peripheral tissues but also the CNS after intravenous administration. The humanized anti-hTfR antibody fused with hIDS is considered to bind to TfRs expressed in the luminal cell membrane of brain microvascular endothelial cells composing the blood-brain barrier, thereby passing through brain microvascular endothelial cells via TfR-mediated transcytosis (which involves the mechanisms of uptake into the cell via endocytosis and release outside the cell via exocytosis) and further penetrating the basal lamina into neuronal cells in the brain parenchyma. Recently, the applicant filed an application for marketing approval of pabinafusp alfa based on data from studies including Study JR-141-301 conducted in Japanese patients because the study data demonstrated the efficacy and safety of pabinafusp alfa in the treatment of MPS II.

Outside Japan, an application for approval of pabinafusp alfa was filed in Brazil in December 2020, and is currently under review. As of December 2020, pabinafusp alfa has not been approved in any country or region.

Pabinafusp alfa was granted SAKIGAKE designation status (SAKIGAKE Drug Designation No. 2 of 2018 [*30 yaku*]) for the intended indication of "mucopolysaccharidosis type II" on March 27, 2018. It also has orphan drug status (Orphan Drug Designation No. 486 of 2020 [*R2 yaku*] for the intended indication of "mucopolysaccharidosis type II."

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug Substance

2.1.1 Generation and control of cell substrate

Splenocytes collected from mice immunized with hTfR were fused with mice myeloma cells to create hybridomas, from which a hybridoma clone expressing an anti-hTfR antibody that can cross the blood-brain barrier into the brain parenchyma was selected. The clone was used to determine the amino acid sequences of the variable regions in the H- and L-chains. Based on the sequences, a humanized anti-hTfR antibody was created, and gene fragments for L- and H-chains were synthesized. Gene fragments coding the H-chain of the humanized anti-hTfR antibody were attached to the synthesized hIDS gene fragments, and were cloned into the expression vector to create an expression construct for a fusion protein of the H-chain of the humanized anti-hTfR antibody and hIDS. This gene expression construct and the separately created gene expression construct of the L-chain of the humanized anti-hTfR antibody were introduced into Chinese hamster ovary (CHO) cells. The master cell bank (MCB) and working cell bank (WCB) were prepared based on a clone optimal for the production of pabinafusp alfa.

Characterization and purity testing were conducted for the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), ICH Q5B, and ICH Q5D Guidelines. The results of the characterization and purity testing demonstrated genetic stability during production. Within the range tested, no viral or non-viral adventitious agents were detected other than general endogenous retrovirus-like particles from rodent-derived cell lines.

Both MCB and WCB are stored in the gas phase above liquid nitrogen. New MCB and WCB will be prepared as necessary.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: seed culture, expanded culture, production culture, harvesting, [redacted], [redacted] chromatography, viral inactivation ([redacted] treatment), [redacted] chromatography, [redacted], [redacted] chromatography, virus removal ([redacted]), and filtration/dispensing/storage/testing.

Critical steps are [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Process validation is performed on a commercial scale for the manufacturing process of the drug substance.

2.1.3 Safety evaluation of adventitious agents

With the exception of CHO cell lines, the host cells, no raw materials of biological origin are used in the process of manufacturing the drug substance.

Purity was tested on the MCB, WCB, and CAL [see Section "2.1.1 Generation and control of cell substrate"]. Bioburden testing, mycoplasma testing, electron microscopy, and *in vitro* virus testing were performed on unprocessed bulk at commercial scale after the completion of production culture. None of the tests revealed contamination with viral or non-viral adventitious agents. The bioburden testing, mycoplasma testing, and *in vitro* virus testing on unprocessed bulk after the completion of production culture are designated as in-process controls.

A viral clearance study was performed with model viruses for the purification process of the proposed manufacturing process. The results showed that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral inactivation ([redacted] treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	≥15.15	≥10.78	≥9.14	≥5.69

a) [redacted]

2.1.4 Manufacturing process development

The major changes made to the manufacturing process during the development of the drug substance are shown below (the manufacturing processes are referred to as Processes A, B, C, D, E, F, G, and H, and the proposed commercial process). The formulation produced from the drug substance manufactured by Process D was used in the Japanese phase I/II study (JR-141-101), while those produced from the drug substances manufactured by Process H and the proposed commercial process were used in the Japanese phase II/III study (Study JR-141-301).

- Process A → Process B: [redacted], etc.
- Process B → Process C: Changes in [redacted], etc.
- Process B → Process D: Changes in [redacted], etc.
- Process C → Process E: Change in [redacted]
- Process E → Process F: Changes in [redacted], etc.
- Process F → Process G: Changes in [redacted], etc.
- Process G → Process H: Changes in [redacted], etc.
- Process H → the proposed commercial process: [redacted] of [redacted], etc.

When these changes were made to the manufacturing process, comparability was evaluated with respect to the quality attributes. The results demonstrated the comparability of pre-change and post-change drug substance.

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed.

Table 2. Evaluation items for characterization

Primary/higher-order structure	Amino acid composition, amino acid sequence, N- and C-terminal amino acid sequence, disulfide bonds, free thiol group, post-translational modification, secondary structure, tertiary structure
Physicochemical properties	Molecular weight, spectroscopic properties, electrophoresis, SE-HPLC, RP-HPLC
Carbohydrate structure	Carbohydrate composition (neutral sugar, amino sugar, sialic acid, and M6P), glycan profile, glycosylation sites
Biological properties	Enzyme activity, binding affinity for M6PR, cellular uptake activity
	Binding activity to hTfR, binding affinity for hTfR, binding affinity for FcRn, ADCC activity, CDC activity

The enzyme activity was measured using 4-nitrophenyl sulfate potassium as a substrate. The Michaelis-Menten constant (K_m) and maximum reaction velocity (V_{max}) were 32.6 mmol/L and 16.9 μmol/min/mg, respectively.

The binding activity to hTfR by enzyme-linked immunosorbent assay (ELISA) was 3.63 ng/mL (EC_{50}). The binding affinity for hTfR determined by bio-layer interferometry was 1.22×10^{-10} mol/L (K_D), and that for cation-independent mannose-6-phosphate receptor (M6PR) determined by surface plasmon resonance (SPR) was 9.22×10^{-9} mol/L (K_D).

The cellular uptake activity was measured using human fibroblasts. The results showed that pabinafusp alfa was taken up into cells in a concentration-dependent manner and that addition of mannose-6-phosphate (M6P) or the anti-hTfR antibody inhibited cellular uptake.

Antibody-dependent cellular cytotoxicity (ADCC) activity was assessed by reporter bioassay that uses the human hematopoietic cell line expressing hTfR as the target cell and the Jurkat cell line (human acute T cell leukemia cell line) as the effector cell. Pabinafusp alfa did not exhibit ADCC activity against the target cells.

Complement-dependent cytotoxicity (CDC) activity was evaluated using the human hematopoietic cell line with human serum as a complement source. Pabinafusp alfa did not exhibit CDC activity against the target cells.

The binding affinity for human neonatal Fc receptor (FcRn) was examined by SPR analysis, and the value of K_D was 1.80×10^{-6} mol/L.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization in Section “2.1.5.1 Structure and characterization,” molecular entities (Impurities A, B, C, and D) corresponding to the peaks other than the main peak identified by size exclusion

high performance liquid chromatography (SE-HPLC) were defined as product-related impurities. All the product-related impurities are controlled by the specifications for the drug substance and drug product. No product-related substances have been identified.

2.1.5.3 Process-related impurities

Host cell proteins (HCPs), host cell DNA, endotoxins, and Impurities E, F, G, H, I, J, K, and L were defined as process-related impurities. It has been confirmed that all the process-related impurities are adequately removed during the manufacturing process. HCPs are controlled by the specifications for the drug substance, while endotoxins are controlled by the specifications for the drug substance and drug product.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping, [redacted]), glycan profiles, pH, purity (SE-HPLC, HCP), bacterial endotoxins, sialic acid content, M6P content, binding activity (ELISA), enzyme activity, and assay (ultra violet-visible spectrophotometry [UV-Vis]). Among the glycan profiles, the content of bis-phosphorylated glycan peaks is controlled.

2.1.7 Stability of drug substance

Table 3 shows main stability studies for the drug substance.

Table 3. Summary of main stability studies for drug substance

	Manufacturing process	Number of batches	Storage condition	Test period	Storage package
Long-term	Process E	3	[redacted] ± [redacted]°C	[redacted] months[a)]	[redacted] cap and [redacted] container
	Proposed process	3		[redacted] months[a)]	
Stress	Process E	1	[redacted] ± [redacted]°C	[redacted] months	
		1	[redacted] ± [redacted]°C/[redacted] ± [redacted]% RH		

a) The stability testing is ongoing and will be continued for up to [redacted] months

The long-term test showed no clear change in quality attributes throughout the testing period.

The results of the stress testing showed [redacted], and [redacted].

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance when stored at [redacted] ± [redacted]°C in a [redacted] container with [redacted] cap, protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a glass vial (15 mL) containing 12.5 mg of pabinafusp alfa. Excipients contained in the drug product are sodium chloride, sucrose, sodium dihydrogen phosphate dihydrate, dibasic sodium phosphate hydrate, polyoxyethylene (160) polyoxypropylene (30) glycol, sodium hydroxide, and hydrochloric acid.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of drug solution preparation, aseptic filtration/filling, lyophilization, capping/storage/testing, and packaging/storage.

[redacted] and [redacted] have been defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

2.2.3 Manufacturing process development

A change in [redacted] was made during the development of the drug product (manufacturing processes before and after the change are defined as the previous manufacturing process and the proposed commercial process, respectively).

The comparability of the formulations was evaluated before and after the manufacturing process change, and the pre-change and post-change formulations were shown to be comparable.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (SE-HPLC, [redacted]), osmolality ratio, pH, purity (appearance, SE-HPLC), water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, binding activity (ELISA), enzyme activity, and assay (UV-Vis).

2.2.5 Stability of drug product

Table 4 shows main stability studies for the drug product.

Table 4. Summary of main stability studies for drug product

	Manufacturing process	Number of batches	Storage condition	Test period	Storage package
Long-term	Previous process[a)]	2	5 ± 3°C	36 months	Glass vial with butyl rubber stopper
	Proposed commercial process[b)]	1		36 months	
Accelerated	Previous process[a)]	2	25 ± 2°C/60 ± 5% RH	6 months	
	Proposed commercial process[b)]	1		6 months	
Stress (temperature)	Proposed commercial process[b)]	1	40 ± 2°C	3 months	
Stress (light)	Proposed commercial process[b)]	1	25 ± 2°C, overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

a) Formulation manufactured by the previous process using the drug substance manufactured by Process D or E
b) Formulation manufactured by the proposed commercial process using the drug substance manufactured by Process E

The long-term and accelerated tests showed no clear change in quality attributes throughout the testing period.

The results of the stress testing (temperature) showed [redacted] in the content of [redacted] by [redacted].

The results of the stress testing (light) demonstrated that the drug product is photolabile.

Based on the above, a shelf life of 36 months has been proposed for the drug product when stored at 2°C to 8°C without freezing in a glass vial with a butyl rubber stopper as primary packaging, in a paper box protected from light.

2.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following section, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.R.1 Content of M6P in the specifications for drug substance

There was a considerable variation in the content of M6P included in the specifications for the drug substance, and the test conditions for [redacted] required some adjustment depending on [redacted]. For these reasons, PMDA requested the applicant to consider modifying the testing method to improve variability and taking measures to maintain analytical performance.

The applicant's response:

Currently, [redacted] to reduce deviation and variation from a true value is underway. The applicant will re-evaluate the testing methods by gathering testing data on batches that will be manufactured, and will promote further discussion about how to improve the testing methods. Furthermore, the applicant will define specifications for [redacted] in order to assure the qualification of testing conditions.

PMDA accepted the applicant's explanation.

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

Studies of primary pharmacodynamics include *in vitro* investigation of cellular uptake of pabinafusp alfa, and *in vivo* investigation in mouse models of MPS II to assess the effects on GAG accumulation and on CNS symptoms. Studies of secondary pharmacodynamics include investigation of the effects of pabinafusp alfa on binding of human transferrin (hTf) to hTfR. Safety pharmacology studies include investigation of effects on the CNS, cardiovascular system, and respiratory system. No pharmacodynamic drug interaction studies were conducted.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity for TfR (CTD 4.2.1.1.1 and 4.2.1.1.3)

The binding affinity of pabinafusp alfa for the extracellular domain of human or cynomolgus monkey TfR was assessed by bio-layer interferometry. The K_D value (mean ± standard deviation [SD]; n = 3) of pabinafusp alfa was 0.122 ± 0.0035 for hTfR and 0.865 ± 0.049 nmol/L for cynomolgus monkey TfR.

3.1.1.2 Binding affinity for M6PR (CTD 4.2.1.1.4)

The binding affinity of pabinafusp alfa or idursulfase for domain 9 of M6PR was assessed by SPR. The K_D value (mean ± SD; n = 3) of pabinafusp alfa was 9.22 ± 0.03 nmol/L and that of idursulfase was 4.08 ± 0.08 nmol/L.

3.1.1.3 Cellular uptake of pabinafusp alfa in human fibroblasts (CTD 4.2.1.1.5)

To evaluate M6PR- or TfR-mediated cellular uptake of pabinafusp alfa, pabinafusp alfa 20 μg/mL was added to CCD-1076SK human fibroblast cell line in the presence of M6P and/or the humanized anti-hTfR antibody, or in the absence of both, and after 20 hours of incubation, the amount of pabinafusp alfa in cells was measured using crude lysate. The levels of cellular uptake of pabinafusp alfa (mean ± SD; n = 3) were as follows: 1165.8 ± 99.7 ng/mg protein in the absence of M6P and the humanized anti-hTfR antibody; 371.0 ± 31.8 ng/mg protein in the presence of M6P; 1109.2 ± 74.3 ng/mg protein in the presence of the humanized anti-hTfR antibody; and 51.3 ± 2.3 ng/mg protein in the presence of M6P and the humanized anti-hTfR antibody.

3.1.2 *In vivo* studies

3.1.2.1 12-week repeated dose study in hTfR KI/Ids KO mice (CTD 4.2.1.1.6)

Pabinafusp alfa (0.5, 1, 2, 5, or 10 mg/kg), idursulfase (0.5 mg/kg[1)]), or vehicle[2)] was intravenously administered to human transferrin receptor 1 gene knock in/iduronate-2-sulfatase gene knockout (hTfR KI/Ids KO) mice (5 males/group) once weekly for 12 weeks to evaluate the wet liver weight, HS and DS concentrations in peripheral tissues and other specimens, HS concentrations in cerebrospinal fluid (CSF) and the brain. At Week 12, HS and DS concentrations in all of peripheral tissues, etc. (urine, serum, heart, liver, spleen) were lower in the pabinafusp alfa group than in the vehicle group, showing a generally dose-dependent decrease. HS and DS concentrations in the idursulfase group were also lower than those in the vehicle group, and were similar to those observed in the pabinafusp alfa 0.5 to 2 mg/kg groups. At Week 12, HS concentrations in the CSF and brain were lower in the pabinafusp alfa group than in the vehicle group, showing a generally dose-dependent decrease, whereas HS concentrations in the idursulfase group did not differ significantly from those in the vehicle group. The percentage of wet liver weight to the total body weight at Week 12 was low in all of the pabinafusp alfa groups and the idursulfase group compared to the vehicle group, showing a generally dose-dependent decrease in the pabinafusp alfa group. The values in the idursulfase group, however, were similar to those in the pabinafusp alfa 1 to 2 mg/kg groups.

3.1.2.2 36-week repeated-dose study in hTfR KI/Ids KO mice (CTD 4.2.1.1.7)

hTfR KI/Ids KO mice (males) were given pabinafusp alfa (2 mg/kg), idursulfase (0.5 mg/kg[1)]), or vehicle[2)] once weekly (QW), or pabinafusp alfa (4 mg/kg) once every 2 weeks (Q2W), intravenously for 36 weeks to investigate various aspects including acquisition of Morris water maze task, HS concentrations in CSF and in the brain, wet liver weight, HS and DS concentrations in peripheral tissues and other specimens. Compared to the normal control group (wild-type mice), impaired acquisition of Morris water maze tasks was observed in

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1) 1 mg/kg of pabinafusp alfa equals to 0.5 mg/kg of idursulfase on a molecular enzyme basis.

2) Normal saline

the vehicle group of hTfR KI/Ids KO mice. Impaired acquisition did not improve in the idursulfase group (n = 12) while it improved for both dosing regimens in the pabinafusp alfa group (n = 15). Wet liver weights were similar across the vehicle, pabinafusp alfa, and idursulfase groups. The concentrations of HS and DS in peripheral tissues and other specimens (serum, heart, liver, spleen) were lower in the pabinafusp alfa and idursulfase groups than in the vehicle group, with a similar degree of decrease in the concentrations in both the pabinafusp alfa and idursulfase groups. The concentrations of HS in CSF and in the brain decreased in the pabinafusp alfa group, with a trend towards a higher degree of decrease in the 2 mg/kg QW group than in the 4 mg/kg Q2W group. In contrast, there were no decreases in HS concentrations in the idursulfase group.

The histological examinations of the brain and peripheral tissues (liver, spleen, and heart) showed that vacuolar degeneration of Purkinje cells occurred in all animals in the vehicle group (n = 8) and in the idursulfase group (n = 7), with all being moderate in severity. In the pabinafusp alfa group, on the other hand, these changes occurred in 5 of 10 animals (50.0%) in the 2 mg/kg QW group and in 7 of 10 animals (70.0%) in the 4 mg/kg Q2W group, with all being minimal in severity. Findings reported for peripheral tissues in the vehicle group (n = 8) were as follows: macrophage swelling (8 animals; minimal to mild) in the liver; macrophage swelling (8 animals; moderate) in the spleen; atrial cardiomyocyte vacuolation (8 animals; moderate), ventricular cardiomyocyte vacuolation (8 animals; minimal to mild), foam cell and inflammatory cell infiltration (8 animals; minimal to moderate), fibrosis (3 animals; minimal to mild), swelling of aortic valve interstitial cells (8 animals; minimal), swelling of pulmonary valve interstitial cells (6 animals; minimal), and swelling of tricuspid valve interstitial cells and mitral valve interstitial cells (8 animals; minimal to mild) in the heart. In the pabinafusp alfa group, however, no abnormal changes were observed in the spleen and heart, and the liver exhibited no abnormal findings other than those reported in the normal control group. In the idursulfase group, except for macrophage swelling in the liver (1 animal; minimal), the liver and spleen showed no abnormal findings other than those reported in the normal control group, and the heart showed no abnormal findings.

3.2 Secondary pharmacodynamics

3.2.1 Effects of pabinafusp alfa on hTf-hTfR binding (CTD 4.2.1.2.1)

To evaluate the effects of pabinafusp alfa on hTf-hTfR binding, pabinafusp alfa, human immunoglobulin (hIg) G1 (negative control), or an anti-hTfR polyclonal antibody (pAb) (positive control) was added at the concentration of 100 nmol/L, and the binding of hTf to hTfR was assessed by SPR. The binding response of hTf-hTfR was measured in the presence of each of the substances (pabinafusp alfa, hIgG1, and anti-hTfR pAb) or in their absence, to calculate differences in hTf-hTfR binding response (relative binding response). The hTf-hTfR binding response after addition of pabinafusp alfa or the anti-hTfR pAb was 102% and 39.4%, respectively, of the hTf-hTfR binding response after addition of the negative control, hIgG1. Pabinafusp alfa was shown to have no inhibitory activity against hTf-hTfR binding.

3.2.2 ADCC activity and CDC activity of pabinafusp alfa (CTD 4.2.1.2.2 and 4.2.1.2.3)

The ADCC activity was measured by reporter bioassay using cells expressing hTfR as target cells (human T cell leukemia cell line CCRF-CEM, human myelogenous leukemia cell line K562, or human erythroblast leukemia cell line HEL92.1.7). After adding pabinafusp alfa (0.0183-120 μg/mL) to the target cells, Jurkat

cells, a human acute T cell leukemia cell line expressing the FcγIIIa receptor, were added as effector cells, which was followed by 6 hours of incubation, and a reporter bioassay was performed. For the CDC activity, after adding pabinafusp alfa (0.0244-100 μg/mL) to CCRF-CEM cells, K562 cells, or HEL92.1.7 cells, human serum was added as a complement source, and the mixture was incubated for 4 hours. The CDC activity was evaluated using the protease activity in the supernatant of the culture as an indicator. No ADCC activity or CDC activity was detected.

3.3 Safety pharmacology

The effects of pabinafusp alfa on the central nervous system, cardiovascular system, and respiratory system were evaluated in repeated-dose toxicity studies [see Section "5.2 Repeated-dose toxicity"]. Table 5 summarizes the results.

Table 5. Summary of safety pharmacology studies

Organ system	Test system	Evaluation parameter/method	Dosage regimen of pabinafusp alfa	Route of administration	Finding	CTD
Central nervous system	Cynomolgus monkey (n = 3 to 5/sex/group)	FOB	0, 3, 10, and 30 mg/kg once weekly for 4 weeks	IV	No effects	4.2.3.2.2
	Cynomolgus monkey (n = 4 to 6/sex/group)	FOB	0, 3, 10, and 30 mg/kg once weekly for 26 weeks	IV		4.2.3.2.4
Cardiovascular system/ respiratory system	Cynomolgus monkey (n = 3 to 5/sex/group)	Electrocardiography, blood pressure, respiration rate, blood gas tension	0, 3, 10, and 30 mg/kg once weekly for 4 weeks	IV	No effects	4.2.3.2.2

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of pabinafusp alfa

The applicant's explanation:

Pabinafusp alfa is a fusion protein consisting of a humanized anti-hTfR antibody and hIDS. The humanized anti-hTfR antibody is considered to bind to TfRs expressed in the luminal cell membrane of brain microvascular endothelial cells composing the blood-brain barrier, being transported together with the TfR, passing through brain microvascular endothelial cells via transcytosis (which involves the mechanisms of uptake into the cell via endocytosis and release outside the cell via exocytosis) and further penetrating the basal lamina into neuronal cells in the brain parenchyma. In addition, after binding of pabinafusp alfa to M6PR on the cell membrane and cellular uptake via endocytosis, newly formed endosomes are thought to fuse with lysosomes and move into them (*Mol Cell Biol.* 2003;4:202-12). In patients with MPS, the type of accumulating GAG differs depending on the MPS phenotype, and CNS symptoms develops in patients with MPS phenotypes that are associated with the accumulation of HS (*Mol Genet Metab.* 2018;125:322-31). HS concentrations in CSF are high in patients with MPS-II who have intellectual disability, compared with those who do not have intellectual disability (*Mol Genet Metab Rep.* 2015;5:103-6, *J Int Errors Metab Screen.* 2015;3:e150002). These findings and other factors have suggested that HS plays a vital role in the development of CNS symptoms. The hIDS of pabinafusp alfa is considered to promote the degradation of HS in the brain parenchyma, thereby suppressing the development or progression of CNS symptoms. It has been demonstrated that pabinafusp alfa has binding affinity for M6PR and hTfR, and is taken up by human fibroblasts via the receptors. Decreases in HS and DS concentrations in peripheral tissues following administration of pabinafusp alfa 0.5 to 2 mg/kg in the 12-week repeated-dose study in hTfR KI/Ids KO mice did not differ significantly from those following

administration of idursulfase 0.5 mg/kg.[1)] The effects of pabinafusp alfa on the CNS were investigated in hTfR KI/Ids KO mice treated with intravenous pabinafusp alfa, and the results showed decreases in HS concentrations in the CSF and brain and an improvement in impaired acquisition of the Morris water maze task. The above findings suggest that pabinafusp alfa is likely to suppress the development or progression of CNS symptoms in patients with MPS II.

PMDA's view:

The primary pharmacodynamics studies included studies using hTfR KI/Ids KO mice (CTD 4.2.1.1.6 and 4.2.1.1.7), which evaluated substrate concentrations in peripheral tissues. The studies demonstrated that the enzyme activity of pabinafusp alfa is similar to that of idursulfase in peripheral tissues. The *in vitro* studies investigating the effects of pabinafusp alfa on the CNS (CTD 4.2.1.1.1, 4.2.1.1.3, 4.2.1.1.4, 4.2.1.1.5) demonstrated that pabinafusp alfa has binding affinity for TfR and M6PR, and the results suggested M6PR- or TfR-mediated cellular uptake of pabinafusp alfa. Therefore, as explained by the applicant, it is likely that pabinafusp alfa administered as an intravenous infusion is transported to the CNS tissues via TfR on the luminal cell membrane of brain microvascular endothelial cells, and that pabinafusp alfa is taken up by cells via M6PR on the cell membrane. In the studies using hTfR KI/Ids KO mice (CTD 4.2.1.1.6 and 4.2.1.1.7), HS concentrations in the brain decreased after intravenous administration of pabinafusp alfa, and histological examination of the brain also revealed decreased abnormal changes in the pabinafusp alfa groups, compared to the vehicle control group. The results of the Morris water maze test also suggest a trend towards improved acquisition after treatment with pabinafusp alfa. Given the above findings, PMDA concluded that the pharmacological action of pabinafusp alfa in peripheral tissues and the CNS following intravenous administration has been demonstrated in the non-clinical studies. The efficacy of pabinafusp alfa in humans will be discussed in Section "7.R.1 Efficacy."

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

The pharmacokinetics of pabinafusp alfa was evaluated with the results of studies in which single dose or repeated doses of intravenous pabinafusp alfa, ^{125}I-labeled pabinafusp alfa, or IDS were administered to mice or monkeys. In addition, the pharmacokinetics of repeated intravenous doses of pabinafusp alfa was investigated based on the toxicokinetics assessed in the toxicity study in monkeys. The concentrations of pabinafusp alfa and IDS in plasma and tissues and the concentrations of pabinafusp alfa in CSF were measured by electrochemiluminescence (ECL). The lower limit of quantitation (LLOQ) of pabinafusp alfa concentrations was 0.206 ng/mL (plasma and tissues) in mice, 1 to 10 ng/mL (plasma) and 0.5 ng/mL (tissues) in monkeys, while the LLOQ of IDS concentrations was 0.206 ng/mL (plasma and tissues) in mice. The LLOQ of pabinafusp alfa concentrations in CSF was 1 ng/mL in monkeys. The levels of anti-pabinafusp alfa antibodies in plasma and the inhibitory activity of anti-pabinafusp alfa antibodies against the binding of pabinafusp alfa to TfR or M6PR were measured by ECL. Radioactivity in biological samples was measured by gamma counter or quantitative whole body autoradioluminography. Results of the main studies are presented in the sections below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.3.3)

Table 6 shows the pharmacokinetic parameters of pabinafusp alfa in plasma after single-dose administration of pabinafusp alfa 1 or 5 mg/kg as an intravenous infusion over approximately 1 hour to male adult monkeys.

Table 6. Pharmacokinetic parameters of pabinafusp alfa in plasma after single-dose intravenous infusion of pabinafusp alfa

Dose (mg/kg)	N	C_{max} (μg/mL)	AUC (μg·h/mL)		$t_{1/2}$ (h)
			$AUC_{0\text{-}8\ h}$	$AUC_{0\text{-}24\ h}$	
1	2	16.1, 18.0	56.7, 59.4	—	4.30, 4.54
5	4	73.8 ± 8.17	319 ± 18.5	541, 532[a)]	6.12, 6.69[a)]

Mean ± SD; individual values for N ≤ 2; "—," not applicable
C_{max}, maximum plasma concentration; $AUC_{0\text{-}8\ h}$, area under the plasma concentration-time curve from hour 0 to 8; $AUC_{0\text{-}24\ h}$, area under the plasma concentration-time curve from hour 0 to 24; $t_{1/2}$, elimination half-life at terminal phase
a) N = 2

4.1.2 Repeated-dose studies (CTD 4.2.3.2.2, 4.2.3.2.3, 4.2.3.2.4)

Pabinafusp alfa 3, 10, or 30 mg/kg was administered once weekly for 4 weeks to adult male and female monkeys as an intravenous infusion over approximately 1 hour, and to juvenile male monkeys as an intravenous infusion over approximately 10 minutes. Table 7 shows pharmacokinetic parameters of pabinafusp alfa in plasma.

Table 7. Pharmacokinetic parameters of pabinafusp alfa in plasma after intravenous administration of pabinafusp alfa once weekly for 4 weeks

Animal species	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)		$AUC_{0\text{-}t}$ (μg·h/mL)	
				Week 1	Week 4	Week 1	Week 4
Adult monkey	3	M	3	48.4 ± 12.9	35.0 ± 14.8	418 ± 137	180 ± 108
	10		3	252 ± 66.0	161 ± 6.43	2320 ± 307	994 ± 307
	30		5	784 ± 119	662 ± 104	9100 ± 2130	5860 ± 1980
	3	F	3	45.1 ± 10.4	33.2 ± 6.75	317 ± 97.1	125 ± 53.5
	10		3	205 ± 20.6	176 ± 34.0	1980 ± 332	1110 ± 568
	30		5	699 ± 61.3	555 ± 97.7	6800 ± 933	5160 ± 1440
Juvenile monkey	3	M	3	51.9 ± 1.44	34.9 ± 4.11	212 ± 8.19	91.2 ± 24.1
	10		3	166 ± 35.7	158 ± 22.5	851 ± 117	728 ± 244
	30		5	518 ± 32.0	538 ± 31.1	3550 ± 469	3280 ± 546

Mean ± SD
C_{max}, maximum plasma concentration; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point t

In adult male and female monkeys, at Week 4, anti-pabinafusp alfa antibodies were detected in 6 of 6 animals in the 3 mg/kg group, 5 of 6 animals in the 10 mg/kg group, and 7 of 10 animals in the 30 mg/kg group. The animals which were found to have the antibodies in plasma were further examined. Inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR was detected in 6 of 6 animals (TfR) and 5 of 6 animals (M6PR) in the 3 mg/kg group, 5 of 5 animals (TfR) and 4 of 5 animals (M6PR) in the 10 mg/kg group, and 7 of 7 animals (TfR) and 7 of 7 animals (M6PR) in the 30 mg/kg group. In juvenile male monkeys, at Week 4, anti-pabinafusp alfa antibodies were detected in 3 of 3 animals in the 3 mg/kg group, 3 of 3 animals in the 10 mg/kg group, and 3 of 5 animals in the 30 mg/kg group. The animals which were found to have the antibodies in plasma were further examined. Inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR was detected in 3 of 3 animals (TfR) and 3 of 3 animals (M6PR) in the 3 mg/kg group, 3 of 3 animals (TfR) and 2 of 3 animals (M6PR) in the 10 mg/kg group, and 3 of 3 animals (TfR) and 2 of 3 animals (M6PR) in the 30 mg/kg group.

Table 8 shows pharmacokinetic parameters of pabinafusp alfa in plasma after administration of pabinafusp alfa 3, 10, or 30 mg/kg once weekly for 26 weeks as an intravenous infusion over approximately 1 hour to male and female adult monkeys.

Table 8. Pharmacokinetic parameters of pabinafusp alfa in plasma after intravenous administration of pabinafusp alfa once weekly for 26 weeks

Dose (mg/kg)	Sex	N	C_{max} (μg/mL)			AUC_{0-t} (μg·h/mL)		
			Week 1	Week 13	Week 26	Week 1	Week 13	Week 26
3	M	4	44.5 ± 4.92	27.6 ± 13.8	20.7 ± 14.0	316 ± 56.3	115 ± 89.4	113 ± 133
10		4	189 ± 24.5	104 ± 47.8	81.9 ± 47.4	1640 ± 350	526 ± 420	411 ± 454
30		6	540 ± 69.1	546 ± 77.7	432 ± 44.9	5900 ± 824	3710 ± 1130	3260 ± 985
3	F	4	42.2 ± 5.40	24.6 ± 9.04	9.68 ± 3.78	256 ± 25.6	108 ± 100	23.5 ± 13.0
10		4	169 ± 16.7	130 ± 63.8	97.1 ± 58.3	1210 ± 194	712 ± 500	599 ± 592
30		6	574 ± 79.3	442 ± 97.2	358 ± 71.7	5380 ± 990	2620 ± 1130	1870 ± 732

Mean ± SD

C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point t

At Week 12, anti-pabinafusp alfa antibodies were detected in 7 of 8 animals in the 3 mg/kg group, 8 of 8 animals in the 10 mg/kg group, and 10 of 12 animals in the 30 mg/kg group. The animals which were found to have the antibodies in plasma were further examined. Inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR was detected in 7 of 7 animals (TfR) and 6 of 7 animals (M6PR) in the 3 mg/kg group, 7 of 8 animals (TfR) and 7 of 8 animals (M6PR) in the 10 mg/kg group, and 10 of 10 animals (TfR) and 9 of 10 animals (M6PR) in the 30 mg/kg group. At Week 26, anti-pabinafusp alfa antibodies were detected in 7 of 8 animals in the 3 mg/kg group, 7 of 8 animals in the 10 mg/kg group, and 9 of 12 animals in the 30 mg/kg group. The animals which were found to have the antibodies in plasma were further examined. Inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR was detected in 7 of 7 animals (TfR) and 6 of 7 animals (M6PR) in the 3 mg/kg group, 6 of 7 animals (TfR) and 6 of 7 animals (M6PR) in the 10 mg/kg group, and 9 of 9 animals (TfR) and 9 of 9 animals (M6PR) in the 30 mg/kg group.

4.2 Distribution (CTD 4.2.2.3.1, 4.2.2.3.4, 4.2.3.2.3, 4.2.3.2.4)

A single dose of pabinafusp alfa or idursulfase 2 mg/kg was intravenously administered to male hTfR KI/Ids KO mice (n = 4/time point). Table 9 shows plasma and tissue concentrations of pabinafusp alfa and idursulfase.

Table 9. Plasma and tissue concentrations after single intravenous administration of pabinafusp alfa or idursulfase

Plasma/tissue	Pabinafusp alfa		Idursulfase	
	8 hours after administration	24 hours after administration	8 hours after administration	24 hours after administration
Plasma	1.21 ± 0.39	0.0563 ± 0.0085	0.213 ± 0.068	0.0262 ± 0.0020
Brain	0.539 ± 0.015	0.333 ± 0.011	0.00704 ± 0.00047	0.00591 ± 0.01183[b)]
Liver	7.88 ± 0.67	2.85 ± 0.33	22.7 ± 3.0	9.44 ± 1.00
Heart	1.02 ± 0.08[a)]	0.586 ± 0.072	0.563 ± 0.071	0.255 ± 0.004
Spleen	15.2 ± 1.5	8.03 ± 1.75	8.40 ± 2.62	3.29 ± 0.32

Mean ± SD; n = 4/time point

Unit: μg/mL (plasma), μg/g tissue (brain, liver, heart, and spleen)

a) n = 3

b) Detected only in 1 animal (individual value, 0.0237 μg/g tissue)

A single dose of ^{125}I-labeled pabinafusp alfa 1 mg/kg was administered as an intravenous infusion over approximately 1 hour to adult male and female monkeys (n = 1/time point). Radioactivity levels in plasma were measured at 0.33, 1, 3, 8, 24, 48, and 72 hours after the start of infusion, and radioactivity levels in the tissues were measured at 2, 8, 24, 48, and 72 hours after the start of infusion. The highest plasma radioactivity levels were observed at 1 hour after the start of infusion in both males (13.8 μg eq./mL) and females (15.1 μg eq./mL). The highest radioactivity levels in brain tissues were observed at 2 hours after the start of

infusion in both males (0.202 μg eq./mL) and females (0.278 μg eq./mL). The highest radioactivity levels were observed in most of the tissues at 2 or 8 hours after the start of infusion. The highest tissue radioactivity levels were observed in the order of the bone marrow (in males and females, 11.6 μg eq./g and 14.3 μg eq./g, respectively), the liver (5.48 and 6.76 μg eq./g, respectively), the lung (4.96 and 5.08 μg eq./g, respectively), the spleen (4.81 and 5.15 μg eq./g, respectively), the adrenal gland (2.87 and 3.35 μg eq./g, respectively), and the kidney (2.82 and 3.04 μg eq./g, respectively). At 72 hours after the start of infusion, radioactivity was detected in all tissues except for the brain and the eyeball. Radioactivity levels were higher in the liver (1.43-fold for females only), the spleen (1.56-fold for males and 1.36-fold for females), and bone marrow (5.49-fold for males and 2.86-fold for females) than in plasma.

A single dose of pabinafusp alfa 10 mg/kg was administered as an intravenous infusion over approximately 1 hour to pregnant monkeys (gestation day 139; n = 5). Pabinafusp alfa was detected in maternal plasma at 8 and 24 hours after the start of infusion, but was not detected in the plasma of the umbilical vein or umbilical artery.

Pabinafusp alfa 3, 10, or 30 mg/kg was administered as an intravenous infusion over approximately 1 hour once weekly for 26 weeks to adult male and female monkeys (n = 4/sex/group), and pabinafusp alfa 3, 10, or 30 mg/kg was administered as an intravenous infusion over approximately 10 minutes once weekly for 4 weeks to juvenile male monkeys (n = 3/group). Pabinafusp alfa concentrations in CNS tissues and CSF were measured after the final dose. Tables 10 and 11 show pabinafusp alfa concentrations in CNS tissues and CSF, respectively.

Table 10. Pabinafusp alfa concentrations in CNS tissues after repeated intravenous administration of pabinafusp alfa

Animal species	Dose (mg/kg)	Sex	N	Pabinafusp alfa concentration in CNS tissues (ng/g tissue)						
				Cerebral cortex	Hippocampus	Cerebellum	Medulla oblongata	Cervical spinal cord	Lumbar cord	Thoracic spinal cord
Adult monkey	3	M	4	11.5[a)]	12.3[a)]	ND	16.3[a)]	16.1[a)]	21.2[a)]	14.1[a)]
		F	4	ND	ND	ND	ND	ND	ND	ND
	10	M	4	ND	ND	ND	ND	14.0	19.9	18.3
		F	4	43.9[a)]	46.8[a)]	52.5[a)]	51.7[a)]	59.4[a)]	98.3[a)]	41.6[a)]
	30	M	4	55.0 ± 38.9[c)]	68.8, 70.2	60.6 ± 50.4[c)]	58.7 ± 50.1	59.7 ± 51.4	98.7 ± 60.6	52.4 ± 33.4
		F	4	ND	ND	11.8[a)]	ND	ND	10.5, 16.8[b)]	ND
Juvenile monkey	3	M	3	ND	ND	ND	ND	ND	ND	ND
	10		3	10.1[a)]	11.5[a)]	ND	13.8[a)]	10.3, 17.6[b)]	17.9 ± 10.3	13.2[a)]
	30		3	28.1 ± 25.8	39.3 ± 42.4	15.4, 36.1	41.8 ± 32.4	51.3 ± 27.3	52.4 ± 34.7	35.3 ± 26.5

Mean ± SD; individual values for N ≤ 2; ND, below the LLOQ
Measured at 48 hours after the start of final infusion
a) n = 1; b) n = 2; c) n = 3

Table 11. Pabinafusp alfa concentrations in CSF after repeated intravenous administration of pabinafusp alfa

Animal species	Dose (mg/kg)	Sex	N	Pabinafusp alfa concentration in CSF (ng/mL)		
				8 hours after the start of final infusion	48 hours after the start of final infusion[a)]	After the end of recovery period[b) c)]
Adult monkey	3	M	4	17.5[d)]	2.26[d)]	—
		F	4	ND	ND	—
	10	M	4	5.34[d)]	ND	—
		F	4	3.11, 39.0[e)]	14.1[d)]	—
	30	M	6	40.7 ± 33.4	21.4, 31.0[e)]	ND
		F	6	12.2 ± 14.9[f)]	ND	ND
Juvenile monkey	3	M	3	—	ND	—
	10		3	—	ND	—
	30		5	—	4.54[d)]	ND

Mean ± SD; individual values for N ≤ 2; ND, below the LLOQ; "—", not applicable
a) N = 3 for juvenile monkeys and N = 4 for adult monkeys
b) Measured at 4 weeks post-final dose for juvenile monkeys and 8 weeks post-final dose for adult monkeys
c) N = 2 for both juvenile and adult monkeys
d) n = 1; e) n = 2; f) n = 3

4.3 Metabolism (CTD 4.2.2.3.5 [Reference data])

A single dose of ^{125}I-labeled pabinafusp alfa 1 mg/kg was administered as an intravenous infusion over approximately 1 hour to adult male monkeys (n = 4). Unchanged pabinafusp alfa and one of its metabolites were detected in plasma. Unchanged pabinafusp alfa accounted for 91.1% (8 hours after the start of infusion) and 82.2% (24 hours after the start of infusion) of the total plasma radioactivity, while the pabinafusp alfa metabolite accounted for 9.0% (8 hours after the start of infusion) and 17.8% (24 hours after the start of infusion) of the total plasma radioactivity.

4.4 Excretion (CTD 4.2.2.3.5 [Reference data])

A single dose of ^{125}I-labeled pabinafusp alfa 1 mg/kg was administered as an intravenous infusion over approximately 1 hour to adult male monkeys (n = 4). Urinary and fecal radioactivity excreted within 24 hours after the start of infusion accounted for 57.8% and 0.7%, respectively, of the total radioactivity administered.

4.R Outline of the review conducted by PMDA

4.R.1 Distribution of pabinafusp alfa

The applicant's explanation:

In a single-dose study in male hTfR KI/Ids KO mice (CTD 4.2.2.3.1), tissue distribution of pabinafusp alfa was compared to that of idursulfase. At 8 and 24 hours after the start of infusion, idursulfase was barely detected in the brain; in contrast, pabinafusp alfa was distributed in the brain (Table 9). In the peripheral tissues, the level of pabinafusp alfa in the liver tended to be lower than that of idursulfase, while the level of pabinafusp alfa in the heart and spleen tended to be higher than that of idursulfase. Pabinafusp alfa is thought to be taken up into the cells through TfR and M6PR. In mice, the expression of TfR (TfR1) mRNA is lower in the liver than in other tissues while the expression of TfR (TfR1) is relatively high in the heart and spleen (*Blood.* 2001;98:1949-54). The content of M6P per 1 molecule of pabinafusp alfa is lower than that of idursulfase. Based on the above, M6PR-mediated uptake significantly contributes to the uptake of pabinafusp alfa into the liver while TfR-mediated uptake significantly contributes to the uptake of pabinafusp alfa into the heart and spleen. These findings are inferred to have been associated with the distribution pattern mentioned above. However, the primary pharmacodynamics studies in male hTfR KI/Ids KO mice (CTD 4.2.1.1.6 and 4.2.1.1.7) suggest that both pabinafusp alfa and idursulfase can reduce HS and DS concentrations in the peripheral tissues to a similar degree when administered at the clinical dose. Therefore, the difference in peripheral tissue distribution between pabinafusp alfa and idursulfase is unlikely to affect efficacy. The distribution of pabinafusp alfa in the CNS was evaluated in the repeated-dose toxicity studies in monkeys (CTD 4.2.3.2.3 and 4.2.3.2.4), and the results revealed that pabinafusp alfa was distributed in CNS tissues such as the brain, spinal cord, and CSF at 48 hours after the start of final infusion (Tables 10 and 11). Given that pabinafusp alfa was not detected in CSF after the end of the recovery period (4 weeks or 8 weeks after the final dose), and that no toxicity findings associated with pabinafusp alfa were noted, the risk associated with accumulation of pabinafusp alfa in the CNS is low. The results of distribution studies in monkeys (CTD 4.2.2.3.4, 4.2.2.3.5) showed that radioactivity levels were higher in bone marrow, spleen, and liver than in plasma at 72 hours after the start of infusion. On the other hand, the results from 4-week and 26-week repeated-dose toxicity studies in

monkeys (CTD 4.2.3.2.2, 4.2.3.2.3, 4.2.3.2.4) indicated no toxicity findings associated with pabinafusp alfa in these tissues.

PMDA's view:
The results of the study in male hTfR KI/Ids KO mice (CTD 4.2.2.3.1) showed that idursulfase was barely detected in the brain while pabinafusp alfa was distributed in the brain. The results of a study in monkeys (CTD 4.2.3.2.3 and 4.2.3.2.4) also showed that, albeit primarily at higher dose levels, pabinafusp alfa was distributed in the CNS. The distribution in peripheral tissues was evaluated in the study in male hTfR KI/Ids KO mice (CTD 4.2.2.3.1), and the level of pabinafusp alfa in the liver tended to be lower than that of idursulfase. However, taking into account the results of the primary pharmacodynamics study which also used male hTfR KI/Ids KO mice, the difference in peripheral tissue distribution between pabinafusp alfa and idursulfase is not significant enough to affect efficacy. The distribution of pabinafusp alfa into the CNS in humans will be discussed in Section "6.R.1 Distribution of pabinafusp alfa into the CNS in humans."

4.R.2 Effects of sex difference on the distribution of pabinafusp alfa into the CNS

In the 26-week repeated-dose toxicity study in male and female monkeys (CTD 4.2.3.2.4), there was a difference in pabinafusp alfa concentrations in the CNS between the sexes at 10 or 30 mg/kg (Table 10). PMDA asked the applicant to explain how sex differences could affect the distribution of pabinafusp alfa into the CNS.

The applicant's explanation:
In the 26-week repeated-dose toxicity study in male and female monkeys (CTD 4.2.3.2.4), the status of expression of anti-pabinafusp alfa antibodies and distribution of pabinafusp alfa into the CNS were analyzed on an individual animal basis. Pabinafusp alfa tended to be less frequently detected in the CNS both in male and female monkeys that tested positive for anti-pabinafusp alfa antibodies with inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR (Table 12). This is probably because more females with significantly high antibody titer were included in the 30 mg/kg group than in the 10 mg/kg group while fewer males with significantly high antibody titer were included in the 30 mg/kg group than in the 10 mg/kg group. Therefore, the difference in the concentrations of pabinafusp alfa in the CNS does not arise from the difference in the pharmacokinetics of pabinafusp alfa between the sexes; rather, it was likely to be attributable to the production of anti-pabinafusp alfa antibodies with significantly high antibody titer.

Table 12. The status of production of anti-pabinafusp alfa antibodies and CNS tissues in which pabinafusp alfa was detected in individual animals

Dose (mg/kg)	Sex	Animal ID	Anti-pabinafusp alfa antibodies	TfR binding inhibitory activity	M6PR binding inhibitory activity	Antibody titer	Tissues in which pabinafusp alfa was detected[a)]
10	M	21	Positive	Positive	Positive	4096	Cervical spinal cord (14.0), lumbar spinal cord (19.9), thoracic spinal cord (18.3)
		22	Positive	Positive	Positive	16384	ND
		23	Positive	Positive	Positive	131072	ND
		24	Positive	Positive	Positive	131072	ND
	F	25	Negative	—	—	—	ND
		26	Positive	Negative	Negative	4	Cerebral cortex (43.9), hippocampus (46.8), cerebellum (52.5), medulla oblongata (51.7), cervical spinal cord (59.4), lumbar spinal cord (98.3), thoracic spinal cord (41.6)
		27	Positive	Positive	Positive	8	ND
		28	Positive	Positive	Positive	32768	ND
30	M	31	Negative	—	—	—	Cerebral cortex (92.4), hippocampus (68.8), cerebellum (112), medulla oblongata (111), cervical spinal cord (121), lumbar spinal cord (160), thoracic spinal cord (92.1)
		32	Positive	Positive	Positive	512	Cerebral cortex (14.7), cerebellum (11.2), medulla oblongata (21.1), cervical spinal cord (23.2), lumbar spinal cord (118), thoracic spinal cord (37.7)
		33	Positive	Positive	Positive	4096	Medulla oblongata (10.8), cervical spinal cord (11.8), lumbar spinal cord (15.8), thoracic spinal cord (15.0)
		34	Negative	—	—	—	Cerebral cortex (57.9), hippocampus (70.2), cerebellum (58.7), medulla oblongata (91.8), cervical spinal cord (82.9), lumbar spinal cord (101), thoracic spinal cord (64.6)
	F	37	Negative	—	—	—	Cerebellum (11.8), lumbar spinal cord (16.8)
		38	Positive	Positive	Positive	16384	ND
		39	Positive	Positive	Positive	2048	lumbar spinal cord (10.5)
		40	Positive	Positive	Positive	32768	ND

"—", not applicable; ND, below the LLOQ

a) Tissues in which pabinafusp alfa was detected (pabinafusp alfa concentration; unit, ng/g tissue); tissues measured were cerebral cortex, cerebellum, hippocampus, medulla oblongata, cervical spinal cord, lumbar spinal cord, and thoracic spinal cord

The applicant explained that the difference between the sexes in trends for the distribution of pabinafusp alfa into the CNS in the 26-week repeated-dose toxicity study in male and female monkeys (CTD 4.2.3.2.4) was not due to sex differences but were caused by the production of anti-pabinafusp alfa antibodies. PMDA accepted the applicant's explanation. The effects of anti-pabinafusp alfa antibody production in humans will be further discussed in Sections "6.R.2 Effects of antibody production on pharmacokinetics and pharmacodynamics" and "7.R.2.2 Effects of antibody production."

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted repeated-dose toxicity studies and one other toxicity study (tissue cross-reactivity study).

5.1 Single-dose toxicity

Although no single-dose toxicity studies were conducted, the acute toxicity of pabinafusp alfa was evaluated based on the results obtained after the initial dose in the repeated-dose toxicity studies in adult and juvenile cynomolgus monkeys. There were no deaths or signs of acute toxicity, and the approximate lethal dose of pabinafusp alfa was determined to be >30 mg/kg (Table 13).

Table 13. Summary of data obtained after the initial dose in repeated-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female cynomolgus monkeys (4-8 years of age)	IV	0,[a)] 3, 10, 30	None	>30	4.2.3.2.2
Juvenile male cynomolgus monkeys (3-5 months of age)	IV	0,[a)] 3, 10, 30	None	>30	4.2.3.2.3
Male/female cynomolgus monkeys (2-4 years of age)	IV	0,[a)] 3, 10, 30	None	>30	4.2.3.2.4

a) Normal saline

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in adult and juvenile cynomolgus monkeys (Table 14). No deaths or changes caused by treatment with pabinafusp alfa were observed in any of the studies. In all the studies, anti-pabinafusp alfa antibodies were produced in all the pabinafusp alfa groups, and in almost all animals that tested positive for anti-drug antibodies (ADAs), inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR was observed. However, no changes associated with pabinafusp alfa were noted regardless of antibody production; therefore, the applicant considers that antibody production does not affect toxicity evaluation.

The no-observed adverse effect level (NOAEL) of pabinafusp alfa was shown to be 30 mg/kg when the drug was administered to monkeys once weekly for 26 weeks. The C_{max} and $AUC_{0\text{-}\tau}$ [3)] at the NOAEL were 557 μg/mL and 5640 μg·h/mL, respectively, which are approximately 49-fold the C_{max} (11.34 μg/mL) and 150-fold the $AUC_{0\text{-}\tau}$ (37.47 μg·h/mL) in humans at the maximum clinical dose (2 mg/kg).

Table 14. Summary of repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Major findings	NOAEL (mg/kg)	CTD
Male/female cynomolgus monkeys (4-8 years of age)	IV	4 weeks (once weekly)	0,[a)] 3, 10, 30	None[b)]	30	4.2.3.2.2
Juvenile male cynomolgus monkeys (3-5 months of age)	IV	4 weeks (once weekly)	0,[a)] 3, 10, 30	None[c)]	30	4.2.3.2.3
Male/female cynomolgus monkeys (2-4 years of age)	IV	26 weeks (once weekly)	0,[a)] 3, 10, 30	None[d)]	30	4.2.3.2.4

a) Normal saline

b) Low red blood cell count (male) in the 3 mg/kg group and low hematocrit in the 30 mg/kg group were noted; however, these were mild in severity, not associated with the dose level, and not accompanied by any change in other red blood cell parameters; therefore, these findings were not considered to be toxicologically significant.

c) Low hemoglobin, low mean corpuscular hemoglobin concentration, and high reticulocyte count were noted in the 30 mg/kg group; however, these were mild in severity and not accompanied by any change in other red blood cell parameters; therefore, these findings were not considered to be toxicologically significant.

d) High red blood cell count, high hemoglobin, and high hematocrit (male) in the 3 mg/kg group; high red blood cell count and high hematocrit (male) in the 10 mg/kg group; high red blood cell count, low mean corpuscular hemoglobin, and low mean corpuscular hemoglobin concentration (male) in the 30 mg/kg group; and low hemoglobin and low hematocrit (female) in the 30 mg/kg group were noted. All findings were mild in severity, and were not accompanied by any change in other red blood cell parameters; therefore, these findings were not considered to be toxicologically significant.

5.3 Genotoxicity

Pabinafusp alfa is a fusion protein consisting of a humanized anti-hTfR antibody and hIDS. Based on its chemical structure and mechanism of action, pabinafusp alfa is unlikely to interact directly with DNA or other chromosome components, and therefore, no genotoxicity studies were conducted.

3) Both the C_{max} and $AUC_{0\text{-}\tau}$ values represent the mean values of male and female data

5.4 Carcinogenicity

No carcinogenicity studies have been conducted.

The applicant's explanation about the carcinogenic risk of pabinafusp alfa:

Pabinafusp alfa, a fusion protein consisting of a humanized anti-hTfR antibody and hIDS, is taken up into cells through a M6PR- or TfR-mediated mechanism, hydrolyzing the 2-sulfate ester of the terminal iduronate sulfate residue in the GAGs, such as HS and DS; however, this action is not related to carcinogenicity. Furthermore, pabinafusp alfa is unlikely to inhibit iron uptake into cells via inhibition of TfR function because (1) pabinafusp alfa does not block Tf-TfR binding, although it contains a humanized anti-hTfR antibody in its structure [see Section "3.2.1 Effects of pabinafusp alfa on hTf-hTfR binding"]; and (2) no changes in red blood cell parameters or iron metabolism-related parameters suggestive of inhibition of TfR function were observed in the repeated-dose toxicity studies in cynomolgus monkeys or clinical studies of pabinafusp alfa. Additionally, none of the findings from the repeated-dose toxicity studies in cynomolgus monkeys or clinical studies of pabinafusp alfa suggest that pabinafusp alfa is carcinogenic. Given the above, there is no basis for concern that pabinafusp alfa is carcinogenic.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted for pabinafusp alfa. Pabinafusp alfa is indicated for MPS II, which is an X-linked recessive genetic disorder, mainly affecting males. There are at least 18 cases of the disease reported in female patients (*BMC Medical Genetics.* 2019:20;2-8), however, MPS II is still extremely rare in females. Based on the findings, the applicant provided the following explanation about the risk of reproductive and developmental toxicity associated with pabinafusp alfa:

- Pabinafusp alfa, a fusion protein consisting of a humanized anti-hTfR antibody and hIDS, is taken up into cells through M6PR or TfR, hydrolyzing the 2-sulfate ester of the terminal iduronate sulfate residue in the GAGs, such as HS and DS. However, this pharmacological action is identical to that of hIDS, an endogenous enzyme, and therefore pabinafusp alfa is unlikely to cause reproductive or developmental toxicity.
- In a rat study investigating the effects of a recombinant IDS, idursulfase, on pre- and postnatal development including maternal function, no findings related to reproductive or developmental toxicity were noted.
- If Tf-TfR binding is blocked in pregnant women, impaired iron transport function in the placenta will cause symptoms of iron deficiency anemia, such as increases in maternal mortality, perinatal mortality, and premature births, and low birth weight (e.g., *Lancet Glob Health.* 2018;6:e548-e554, *Nutr Rev.* 2011;69:S23-29). However, since pabinafusp alfa does not inhibit the function of TfR [see Section "3.2.1 Effects of pabinafusp alfa on hTf-hTfR binding"], the risk of such adverse events is low.
- In a single intravenous-dose study in cynomolgus monkeys in late gestation (CTD 4.2.2.3.6), pabinafusp alfa did not cross the placenta. In addition, no pabinafusp alfa-related findings in male or female reproductive organs were reported in repeated intravenous-dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2.2, 4.2.3.2.3, and 4.2.3.2.4). These results indicate that pabinafusp alfa is unlikely to affect fertility or embryo-fetal development.

- Regarding the effects of pabinafusp alfa on live pups via breast milk, biologically active pabinafusp alfa is unlikely to be absorbed by the pups. Pabinafusp alfa, which is a fusion protein, will be decomposed in the gastrointestinal organs of pups even if breast milk from the dam receiving pabinafusp alfa is ingested by the pups.

5.6 Local tolerance

The local tolerance of intravenous pabinafusp alfa was evaluated as part of repeated-dose toxicity studies. No effects of pabinafusp alfa were noted in the study; therefore, pabinafusp alfa was considered to cause no local irritation when administered intravenously.

5.7 Other toxicity study

5.7.1 Tissue cross-reactivity

The profiles of TfR expression in human and cynomolgus monkey tissues were evaluated based on the study investigating the tissue cross-reactivity of the anti-hTfR monoclonal antibody with human and cynomolgus monkey tissues. The results showed that the tissue binding profile of humans was similar to that of cynomolgus monkeys (CTD 4.2.3.7.7.1, Reference data). In the study investigating tissue cross-reactivity of pabinafusp alfa using human tissues, pabinafusp alfa bound to tissues except for the aortic endothelium, skeletal muscle, peripheral nerve, thyroid, and blood cells (CTD 4.2.3.7.7.2). Furthermore, TfR-specific binding of pabinafusp alfa was evaluated by adding an excessive amount of M6P. Pabinafusp alfa bound mainly to the following tissues: the bone marrow (bone marrow cells), cerebrum/cerebellum (vascular endothelium), colon/ileum (mucosal epithelium), eye (cornea and conjunctival epithelium), breast (acinar cells, duct epithelium), lung (alveolar epithelium, alveolar macrophage), lymph nodes (macrophage), spleen (red pulp), parathyroid glands, placenta (trophoblast cells), and uterin endometrium (glandular epithelium) (CTD 4.2.3.7.7.2). The binding profile was similar to the human tissue binding profile of the anti-hTfR monoclonal antibody; therefore, pabinafusp alfa was considered to bind to TfR-expressing tissues.

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded, from a toxicological viewpoint, that there are no particular concerns about the clinical use of pabinafusp alfa.

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

Pabinafusp alfa levels in human plasma and CSF were determined by ECL, with the LLOQs of 50 and 1 ng/mL, respectively. The anti-pabinafusp alfa antibodies and anti-IDS antibodies in human plasma, the inhibitory activity of the antibodies against the binding of pabinafusp alfa to TfR or M6PR, and the binding of IDS to M6PR were measured by ECL. HS and DS concentrations in human serum, CSF, and urine were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

6.2 Clinical pharmacology

The evaluation data submitted were the results from 2 Japanese studies (Studies JR-141-101 and JR-141-301). The reference data submitted were the results from a foreign study (Study JR-141-BR21). The results of these studies are outlined in the sections shown below. "JR-141-" is hereinafter omitted from the study identifier; for instance, "Study JR-141-101" is abbreviated as "Study 101."

6.2.1 Japanese phase I/II study (CTD 5.3.5.2.1, Study 101 [March 2017 to October 2017])

An open-label, uncontrolled study was conducted in patients with MPS II who had had prior treatment with idursulfase (target sample size, 12 subjects) to assess the pharmacokinetics, efficacy, and safety of pabinafusp alfa following multiple intravenous administration of pabinafusp alfa [see Section "7.1 Japanese phase I/II study" for the details of the study design, and efficacy and safety results].

Table 15 shows the pharmacokinetic parameters after multiple doses of pabinafusp alfa 1.0 or 2.0 mg/kg administered as an intravenous infusion over ≥3 hours once weekly for 4 weeks. Pabinafusp alfa concentrations in CSF were measured at 4 to 6 hours after the completion of the final infusion, and pabinafusp alfa was not detected in any of the subjects.

Table 15. Plasma pharmacokinetic parameters after multiple intravenous administration of pabinafusp alfa 1.0 or 2.0 mg/kg once weekly for 4 weeks

Dose (mg/kg)	N	Time point	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_d (L)	CL (L/h)
1.0	6	Baseline	4180 ± 2454	14688 ± 10504	3.083 [3.07, 5.90]	4.23, 5.56[a)]	16.357 ± 7.730[c)]	3.022 ± 1.054[c)]
		Week 3	4072 ± 1704	12858 ± 7682	3.133 [3.08, 5.12]	—	4.69, 10.12[a)]	2.53, 4.07[a)]
2.0	6	Baseline	11338 ± 6839	37474 ± 13581	3.200 [3.00, 3.72]	4.099 ± 0.513[b)]	9.272 ± 5.510[d)]	1.984 ± 0.355[d)]
		Week 3	13083 ± 9907	39187 ± 19295	3.092 [3.02, 3.55]	3.71, 5.25[a)]	9.416 ± 8.937[d)]	2.107 ± 0.722[d)]

Mean ± SD; individual values are shown for N = 2; t_{max} is median [range]; "—", not applicable
C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point t; t_{max}, time taken to reach the maximum plasma concentration;
$t_{1/2}$, elimination half-life at terminal phase; V_d, volume of distribution; CL, clearance
a) n = 2; b) n = 3; c) n = 4; d) n = 5

Anti-pabinafusp alfa antibodies[4)] and anti-IDS antibodies were measured at baseline (time point prior to the initial dose of pabinafusp alfa) and at Week 4. In Part 1, anti-pabinafusp alfa antibodies were not detected at baseline or at Week 4 while anti-IDS antibodies were detected in 1 of 2 subjects at baseline and at Week 4. Inhibitory activity against M6PR binding was not detected. In Part 2, at baseline, anti-pabinafusp alfa antibodies and anti-IDS antibodies were detected in 2 of 6 subjects and 3 of 6 subjects, respectively, in the 1.0 mg/kg group, and 1 of 6 subjects and 2 of 6 subjects, respectively, in the 2.0 mg/kg group; and at Week 4, anti-pabinafusp alfa antibodies and anti-IDS antibodies were detected in 2 of 6 subjects and 3 of 6 subjects, respectively, in the 1.0 mg/kg group, and 2 of 6 subjects and 2 of 6 subjects, respectively, in the 2.0 mg/kg group. The subjects who tested positive for anti-pabinafusp alfa antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR. At baseline, inhibitory activity against binding to TfR or M6PR was found in 2 of 2 subjects (TfR) and 2 of 2 subjects (M6PR) in the 1.0 mg/kg group, and 1 of 1 subject (TfR) and 1 of 1 subject (M6PR) in the 2.0 mg/kg group; and at Week 4, inhibitory activity against binding to TfR or M6PR was found in 2 of 2 subjects (TfR) and 2 of 2 subjects (M6PR) in the 1.0 mg/kg group,

4) In Study 301, all 3 patients who had not been previously treated with idursulfase tested positive for anti-pabinafusp alfa antibodies prior to treatment. All of them had an antibody titer of 1. In all studies, therefore, subjects who tested positive for anti-pabinafusp alfa antibodies prior to treatment and who had an antibody titer of >1 were classified as being anti-pabinafusp alfa antibody-positive.

and 2 of 2 subjects (TfR) and 1 of 2 subjects (M6PR) in the 2.0 mg/kg group. The subjects who tested positive for anti-IDS antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to M6PR. At baseline, inhibitory activity against binding to M6PR was found in 0 of 3 subjects in the 1.0 mg/kg group and 1 of 2 subjects in the 2.0 mg/kg group; and at Week 4, inhibitory activity against binding to M6PR was found in 0 of 3 subjects in the 1.0 mg/kg group and 1 of 2 subjects in the 2.0 mg/kg group.

6.2.2 Japanese phase II/III study (CTD 5.3.5.2.2, Study 301 [October 2018 to February 2020])

An open-label, uncontrolled study was conducted in patients with MPS II (target sample size, 20 subjects) to assess the efficacy and safety of pabinafusp alfa following multiple intravenous administration [see Section "7.2 Japanese phase II/III study" for details of the study design, and efficacy and safety results].

Pabinafusp alfa 2.0 mg/kg was administered as an intravenous infusion once weekly for 52 weeks.[5)] Pabinafusp alfa was detected in CSF in 1 subject (1.44 ng/mL) at Week 25 and in 2 subjects (3.10 and 1.47 ng/mL) at Week 52.[6)]

Anti-IDS antibodies were measured at baseline and anti-pabinafusp alfa antibodies at baseline and at Weeks 4, 12, 25, 38, and 52 (measured prior to administration of pabinafusp alfa for all time points). According to antibody testing in subjects who had been previously treated with idursulfase (n = 25), anti-pabinafusp alfa antibodies were detected in 5 of 25 subjects at baseline, 10 of 24 subjects at Week 25, and 10 of 24 subjects at Week 52. The subjects who tested positive for anti-pabinafusp alfa antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR. At baseline, inhibitory activity against binding to TfR or M6PR was found in 5 of 5 subjects (TfR) and 2 of 5 subjects (M6PR); at Week 25, inhibitory activity against binding to TfR or M6PR was found in 5 of 10 subjects (TfR) and 3 of 10 subjects (M6PR); and at Week 52, inhibitory activity against binding to TfR or M6PR was found in 9 of 10 subjects (TfR) and 3 of 10 subjects (M6PR). According to antibody testing in subjects who had not been previously treated with idursulfase (n = 3), no anti-pabinafusp alfa antibodies were detected at baseline, but were detected in 2 of 3 subjects at Week 25 and 2 of 3 subjects at Week 52. The subjects who tested positive for anti-pabinafusp alfa antibodies were examined for inhibitory activity on the binding of pabinafusp alfa to TfR or M6PR. Binding inhibitory activity was found in 2 of 2 subjects (TfR) and 1 of 2 subjects (M6PR) at Week 25, and 2 of 2 subjects (TfR) and 1 of 2 subjects (TfR) at Week 52.

According to antibody testing in subjects who had been previously treated with idursulfase (n = 25), anti-IDS antibodies were detected in 14 of 25 subjects at baseline. Inhibitory activity against the binding of pabinafusp alfa to M6PR was found in 2 of the 14 subjects. According to antibody testing in subjects who had not been previously treated with idursulfase (n = 3), no anti-IDS antibodies were detected at baseline.

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5) The initial dose was started at an infusion rate of approximately 8 mL/h, and the infusion rate was then increased in a stepwise fashion while ensuring subject safety. When the subject's safety had been established, the second and subsequent doses were allowed to be administered at a constant rate. For subjects who had been treated with pabinafusp alfa in Study 101, infusion was started at a constant rate. For all subjects, however, infusion at a rate of >33 mL/h was not allowed.

6) Samples collected within 4 hours after the completion of infusion were to be measured. At Week 52, pabinafusp alfa was detected in the CSF of 5 subjects. However, samples from 3 of these subjects were excluded from analysis due to blood contamination in the samples.

6.2.3 Foreign phase II study (CTD 5.3.5.2.3, Study BR21 [July 2018 to September 2019], Reference data)

An open-label, uncontrolled study was conducted in patients with MPS II (target sample size, 18 subjects) to assess the efficacy, safety, and pharmacokinetics of pabinafusp alfa following multiple intravenous administration of pabinafusp alfa [see Section "7.3 Foreign phase II study" for details of the study design, efficacy and safety results].

Table 16 shows the pharmacokinetic parameters after multiple doses of pabinafusp alfa 1.0, 2.0, or 4.0 mg/kg administered as an intravenous infusion over approximately 3 hours once weekly for 25 weeks.

Table 16. Plasma pharmacokinetic parameters after multiple intravenous administration of pabinafusp alfa 1.0, 2.0, or 4.0 mg/kg once weekly for 25 weeks

Dose (mg/kg)	N	Time point	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_d (L)	CL (L/h)
1.0	2	Baseline	331, 6310	303, 25803	2.83, 3.10	—	—	—
	3	Week 25	3983 ± 5434	26790 ± 42252	3.20 [2.58, 3.33]	11.96[a)]	10.90[a)]	0.63[a)]
2.0	2	Baseline	9400, 22300	50188, 97040	1.00, 3.50	3.16, 4.31	6.45, 11.40	1.42, 1.83
	2	Week 25	8920, 13800	43283, 54750	3.50, 3.77	3.64, 9.19	13.93, 27.56	2.08, 2.65
4.0	3	Baseline	26400 ± 3989	159349 ± 21988	4.00 [3.70, 4.02]	2.845 ± 0.494	6.839 ± 2.285	1.638 ± 0.261
	3	Week 25	16867 ± 8450	125726 ± 70261	7.17 [3.80, 10.58]	7.53[a)]	23.67[a)]	2.18[a)]

Mean ± SD; individual values are shown for N ≤ 2; t_{max} is median [range]; "—", not applicable
C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point t; t_{max}, time taken to reach the maximum plasma concentration;
$t_{1/2}$, elimination half-life at terminal phase; V_d, volume of distribution; CL, clearance
a) n =1

Anti-IDS antibodies were measured at screening and anti-pabinafusp alfa antibodies were measured at baseline and at Weeks 3, 12, and 25 (measured prior to administration of pabinafusp alfa for all time points). According to antibody testing in subjects who had been previously treated with idursulfase (n = 12), anti-pabinafusp alfa antibodies were detected in 4 of 6 subjects in the 1.0 mg/kg group, 0 of 4 subjects in the 2.0 mg/kg group, and 1 of 2 subjects in the 4.0 mg/kg group at baseline; anti-pabinafusp alfa antibodies were detected in 4 of 6 subjects in the 1.0 mg/kg group, 1 of 3 subjects in the 2.0 mg/kg group, and 1 of 1 subject in the 4.0 mg/kg group at Week 25. The subjects who tested positive for anti-pabinafusp alfa antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR. At baseline, 4 of 4 subjects (TfR) and 3 of 4 subjects (M6PR) in the 1.0 mg/kg group and 1 of 1 subject (TfR) and 1 of 1 subject (M6PR) in the 4.0 mg/kg group; at Week 25, inhibitory activity against binding to TfR or M6PR was found in 4 of 4 subjects (TfR) and 3 of 4 subjects (M6PR) in the 1.0 mg/kg group, 1 of 1 subject (TfR) and 0 of 1 subject (M6PR) in the 2.0 mg/kg group, and 1 of 1 subject (TfR) and 0 of 1 subject (M6PR) in the 4.0 mg/kg group. According to antibody testing in subjects who had not been previously treated with idursulfase (n = 8), no anti-pabinafusp alfa antibodies were detected in any of the dose groups at baseline, but were detected, at Week 25, in 2 of 2 subjects in the 1.0 mg/kg group, 0 of 1 subject in the 2.0 mg/kg group, and 5 of 5 subjects in the 4.0 mg/kg group. The subjects who tested positive for anti-pabinafusp alfa antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to TfR or M6PR. At Week 25, inhibitory activity against binding to TfR or M6PR was found in 2 of 2 subjects (TfR) and 1 of 2 subjects (M6PR) in the 1.0 mg/kg group, and 5 of 5 subjects (TfR) and 2 of 5 subjects (M6PR) in the 4.0 mg/kg group.

According to antibody testing in subjects who had been previously treated with idursulfase (n = 12), 8 of 12 subjects tested positive for anti-IDS antibodies at screening. The subjects who tested positive for anti-IDS antibodies were examined for inhibitory activity against the binding of pabinafusp alfa to M6PR. At baseline, inhibitory activity against binding to M6PR was found in 4 of 8 subjects. According to antibody testing in subjects who had not been previously treated with idursulfase (n = 8), no anti-IDS antibodies were detected at baseline.

6.R Outline of the review conducted by PMDA

6.R.1 Distribution of pabinafusp alfa into the central nervous system in humans

The applicant's explanation:

Pabinafusp alfa is delivered to the brain parenchyma through a transport mechanism mediated by hTfRs expressed on brain microvascular endothelial cells, and some portion is transported in brain interstitial fluid to CSF [see Section "3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA"]. In the study on *in vivo* distribution of pabinafusp alfa in hTfR KI/Ids KO mice and the single-dose and repeated-dose studies in monkeys, pabinafusp alfa administered as an intravenous infusion was detected in brain tissues including CSF [see Section "4.2 Distribution"]. However, pabinafusp alfa was detected in the CSF of only 3 of 42 subjects in the clinical studies.[6)] The concentrations of pabinafusp alfa detected in 2 subjects at Week 52 were 1.47 and 3.10 ng/mL, both of which are around the LLOQ. In the non-clinical study, the concentrations of pabinafusp alfa in CSF were lower than those in CNS tissues (Table 11). Given that only a trace amount of pabinafusp alfa is transported from the brain parenchyma to CSF and that CSF continues to flow and the entire CSF volume turns over every several hours (*Fluids Barriers CNS.* 2011;8:7), detection of pabinafusp alfa in CSF could have been difficult, which may have led to the low concentrations mentioned above. Table 17 shows CSF HS concentrations categorized by the presence/absence of pabinafusp alfa in CSF in Study 301. CSF HS concentrations decreased in subjects in which CSF pabinafusp alfa was not detected, to a similar extent as in the subjects with CSF in which pabinafusp alfa was detected.

Table 17. Change from baseline over time in CSF HS concentrations in subjects in whom CSF pabinafusp alfa was and was not detected in Study 301

Time point	Pabinafusp alfa was detected in CSF			Pabinafusp alfa was not detected in CSF		
	N	Mean ± SD	Median (min, max)	N	Mean ± SD	Median (min, max)
Baseline	3	4770 ± 1025	4970 (3660, 5680)	25	6089 ± 2718	5350 (2530, 15100)
Week 25	3	1960 ± 416.1	2070 (1500, 2310)	24	2408 ± 1070	2120 (1290, 5980)
Week 52	2	—	1805, 1750	20	2172 ± 1011	1930 (1100, 5450)

Unit, ng/mL; individual values are shown for N = 2; "—", not applicable

Also in Study 301, CSF HS concentrations decreased after administration of pabinafusp alfa regardless of prior treatment with idursulfase. In addition, a decrease in CSF HS concentrations is not likely to be achieved by intravenous idursulfase alone. Taking into account these findings, pabinafusp alfa is thought to be distributed into the CNS of humans.

PMDA's view:

Pabinafusp alfa was detected in CSF in as few as 3 of 42 subjects in the clinical studies. HS and DS concentrations in serum tended to remain at the same level after administration of pabinafusp alfa in subjects

who had been previously treated with idursulfase; in contrast, HS and DS concentrations in CSF decreased regardless of prior treatment with idursulfase. CSF HS concentrations decreased in subjects in which CSF pabinafusp alfa was not detected. In addition, after delivered to the brain parenchyma, pabinafusp alfa is thought to be further transported to the CSF. Taking into account these finding and the circulation rate of CSF, as well as the results of the non-clinical study, which showed that pabinafusp alfa was distributed into the CNS after being administered intravenously, the applicant's explanation is understandable in that detection of pabinafusp alfa in CSF was difficult though it was distributed into the CNS of humans.

6.R.2 Effects of antibody production on pharmacokinetics and pharmacodynamics

The applicant's explanation:

The effects of antibody production on the pharmacokinetics and pharmacodynamics of pabinafusp alfa were assessed in subjects whose data on measurement of anti-pabinafusp alfa antibodies and anti-IDS antibodies were available from Studies 101 and 301. The results are categorized by the presence/absence of anti-pabinafusp alfa antibodies or anti-IDS antibodies following intravenous administration of pabinafusp alfa 1.0 mg/kg or 2.0 mg/kg once weekly. Table 18 shows plasma pabinafusp alfa exposures (C_{max} and AUC). Table 19 shows HS and DS concentrations in serum and CSF. Table 20 shows HS and DS concentrations in serum and CSF categorized by the presence/absence of antibodies with inhibitory activity against binding to TfR or M6PR. Plasma pabinafusp alfa concentrations tended to be lower in subjects who tested positive for anti-pabinafusp alfa antibodies or anti-IDS antibodies than in subjects who tested negative for the antibodies. The serum concentrations of HS and DS tended to be higher in subjects who tested positive for anti-IDS antibodies than in subjects who tested negative for anti-IDS antibodies. These trends may be due to formation of an immune complex between the antibodies and pabinafusp alfa, which may have promoted elimination of pabinafusp alfa from the serum. However, in both Studies 101 and 301, HS and DS concentrations in serum and CSF decreased or remained at the same levels after the final dose, compared to those at baseline, regardless of ADA production or of the inhibition of the binding to TfR or to M6PR by the ADAs. Therefore, differences in changes in plasma pabinafusp alfa concentrations due to antibody production are unlikely to have a significant impact on the pharmacodynamics of pabinafusp alfa.

Table 18. Plasma pharmacokinetic parameters of pabinafusp alfa categorized by the presence/absence of ADAs[a)] (Study 101, Part 2)

Dose (mg/kg)	Parameter	Time point	Anti-pabinafusp alfa antibodies		Anti-IDS antibodies	
			Positive	Negative	Positive	Negative
1.0	C_{max} (ng/mL)	Baseline	1180, 2700 (2)	5300.0 ± 2151.9 (4)	3076.7 ± 2110.4 (3)	5283.3 ± 2635.2 (3)
		Week 3	2180, 2680 (2)	4892.5 ± 1450.6 (4)	3343.3 ± 1601.6 (3)	4800.0 ± 1762.1 (3)
	AUC_{0-t} (ng·h/mL)	Baseline	2711, 5807 (2)	19902.2 ± 8574.2 (4)	12425.7 ± 14229.5 (3)	16950.0 ± 7614.5 (3)
		Week 3	4914, 5866 (2)	16591.6 ± 6514.0 (4)	11673.2 ± 10893.3 (3)	14042.2 ± 4965.1 (3)
2.0	C_{max} (ng/mL)	Baseline	6080 (1)	12390.0 ± 7082.9 (5)	6080, 12100 (2)	12462.5 ± 8176.5 (4)
		Week 3	8240, 13200 (2)	14265.0 ± 12404.9 (4)	8240, 13200 (2)	14265.0 ± 12404.9 (4)
	AUC_{0-t} (ng·h/mL)	Baseline	15802 (1)	41808.2 ± 9468.3 (5)	15802, 45705 (2)	40833.9 ± 10639.7 (4)
		Week 3	20577, 44763 (2)	42445.1 ± 21921.0 (4)	20577, 44763 (2)	42445.1 ± 21921.0 (4)

Mean ± SD (N); individual values are shown for N ≤ 2;

C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point t;

a) Data at baseline were categorized and calculated based on the presence/absence of ADAs prior to the initial dose of pabinafusp alfa; data for other time points were categorized and calculated based on the presence/absence of ADAs throughout the study period (any subject who tested positive for the ADAs at least once was to be included in the positive category).

Table 19. HS and DS concentrations in CSF and serum categorized by the presence/absence of ADAs[a)]

Study	Test sample	Dose	Analyte	Time point	Anti-pabinafusp alfa antibodies		Anti-IDS antibodies	
					Positive	Negative	Positive	Negative
101 Part 2	CSF[b)]	1.0	HS	Baseline	4580, 5090 (2)	4505 ± 1990 (4)	4077 ± 1338 (3)	5153 ± 1848 (3)
				Week 3	3480, 4520 (2)	3080 ± 1125 (4)	3450 ± 1085 (3)	3323 ± 1243 (3)
			DS	Baseline	1010, 1780 (2)	960.0 ± 191.8 (4)	1186 ± 528.5 (3)	1024 ± 175.0 (3)
				Week 3	656, 948 (2)	768.3 ± 171.4 (4)	838.0 ± 158.8 (3)	721.0 ± 175.1 (3)
		2.0	HS	Baseline	3940, 5760 (2)	5380 ± 2185 (3)	3940, 5760 (2)	5380 ± 2185 (3)
				Week 3	2710, 4320 (2)	3338 ± 1189 (4)	2710, 4320 (2)	3338 ± 1189 (4)
			DS	Baseline	931, 933 (2)	947.3 ± 362.3 (3)	931, 933 (2)	947.3 ± 362.3 (3)
				Week 3	659, 718 (2)	862.8 ± 210.7 (4)	659, 718 (2)	862.8 ± 210.7 (4)
	Serum[c)]	1.0	HS	Baseline	958 (1)	425.8 ± 157.0 (4)	342, 958 (2)	453.7 ± 179.7 (3)
				Week 4	1100, 1110 (2)	411.3 ± 174.7 (4)	836.3 ± 465.4 (3)	448.7 ± 193.3 (3)
			DS	Baseline	946, 1260 (2)	582.0 ± 217.5 (4)	877.3 ± 421.2 (3)	634.0 ± 234.0 (3)
				Week 4	1500, 1770 (2)	641.3 ± 250.7 (4)	1231 ± 712.7 (3)	714.0 ± 250.0 (3)
		2.0	HS	Baseline	781, 1260 (2)	589.8 ± 298.6 (4)	781, 1260 (2)	589.8 ± 298.6 (4)
				Week 4	619, 837 (2)	443.5 ± 78.81 (4)	619, 837 (2)	443.5 ± 78.81 (4)
			DS	Baseline	985, 1150 (2)	601.0 ± 119.5 (4)	985, 1150 (2)	601.0 ± 119.5 (4)
				Week 4	835, 1300 (2)	613.8 ± 135.2 (4)	835, 1300 (2)	613.8 ± 135.2 (4)
301	CSF[d)]	2.0 Previously treated-subjects	HS	Baseline	5270.0 ± 1532.0 (13)	5491.7 ± 1948.7 (12)	5427.9 ± 1640.8 (14)	5310.9 ± 1875.1 (11)
				Week 25	2212.3 ± 669.9 (13)	2039.1 ± 552.3 (11)	2272.9 ± 704.3 (14)	1937.0 ± 409.4 (10)
				Week 52	2068.3 ± 782.6 (12)	1780.0 ± 394.2 (7)	2062.5 ± 805.8 (12)	1790.0 ± 307.2 (7)
			DS	Baseline	1176.5 ± 385.9 (13)	1062.2 ± 350.1 (12)	1123.5 ± 356.4 (14)	1119.3 ± 395.7 (11)
				Week 25	708.6 ± 214.4 (13)	627.8 ± 266.4 (11)	661.0 ± 225.7 (14)	686.4 ± 265.4 (10)
				Week 52	649.0 ± 327.9 (12)	506.0 ± 221.4 (7)	542.9 ± 176.0 (12)	687.9 ± 434.6 (7)
	Serum[c)]		HS	Baseline[e)]	888.2 ± 594.4 (13)	802.3 ± 692.4 (12)	1109.8 ± 736.7 (14)	512.5 ± 175.1 (11)
				Week 26[f)]	591.0 ± 310.9 (13)	477.5 ± 104.5 (11)	651.2 ± 250.9 (14)	381.9 ± 107.7 (10)
				Week 52[g)]	559.8 ± 366.3 (13)	445.0 ± 86.0 (11)	605.3 ± 321.0 (14)	369.9 ± 105.1 (10)
			DS	Baseline[e)]	1046.9 ± 601.2 (13)	818.3 ± 152.0 (12)	1131.8 ± 514.1 (14)	689.4 ± 166.2 (11)
				Week 26[f)]	1147.6 ± 600.4 (13)	959.5 ± 250.2 (11)	1277.5 ± 508.6 (14)	758.8 ± 159.8 (10)
				Week 52[g)]	1029.0 ± 580.8 (13)	877.3 ± 185.5 (11)	1143.1 ± 500.2 (14)	702.3 ± 125.8 (10)
	CSF[d)]	2.0 Treatment-naïve subjects	HS	Baseline	10710.0 ± 4336.0 (3)	—	—	10710.0 ± 4336.0 (3)
				Week 25	4156.7 ± 1962.3 (3)	—	—	4156.7 ± 1962.3 (3)
				Week 52	3256.7 ± 1911.1 (3)	—	—	3256.7 ± 1911.1 (3)
			DS	Baseline	1613.7 ± 649.6 (3)	—	—	1613.7 ± 649.6 (3)
				Week 25	796.3 ± 296.2 (3)	—	—	796.3 ± 296.2 (3)
				Week 52	575.0 ± 160.5 (3)	—	—	575.0 ± 160.5 (3)
	Serum[c)]		HS	Baseline[e)]	4996.7 ± 1765.9 (3)	—	—	4996.7 ± 1765.9 (3)
				Week 26[f)]	1101.8 ± 527.3 (3)	—	—	1101.8 ± 527.3 (3)
				Week 52[g)]	965.0 ± 473.4 (3)	—	—	965.0 ± 473.4 (3)
			DS	Baseline[e)]	4843.3 ± 2140.5 (3)	—	—	4843.3 ± 2140.5 (3)
				Week 26[f)]	1669.1 ± 892.6 (3)	—	—	1669.1 ± 892.6 (3)
				Week 52[g)]	1427.1 ± 733.8 (3)	—	—	1427.1 ± 733.8 (3)

Mean ± SD (N); individual values are shown for N ≤ 2; unit, ng/mL; "—", not applicable

a) In study 101, data at baseline were categorized and calculated based on the presence/absence of ADAs prior to the initial dose of pabinafusp alfa; data for other time points were categorized and calculated based on the presence/absence of ADAs throughout the study period (any subject who tested positive for the ADAs at least once was to be included in the positive category). In Study 301, data were categorized and calculated based on the presence/absence of ADAs throughout the study period (any subject who tested positive for the ADAs at least once was to be included in the positive category).

b) Samples collected prior to administration of pabinafusp alfa were used for measurements of the baseline data, while samples collected 4 to 6 hours after the administration of pabinafusp alfa were used for measurements at Week 3.

c) Samples collected prior to administration of pabinafusp alfa were used for measurements.

d) Samples collected prior to administration of pabinafusp alfa were used for measurements of the baseline data, while samples collected within 4 hours of the administration of pabinafusp alfa were used for measurements at Weeks 25 and 52.

e) Mean ± SD of serum HS or DS concentrations at Week −2, Week −1, and Week 0 (pre-dose).

f) Mean ± SD of serum concentrations of HS or DS at Weeks 24, 25, and 26.

g) Mean ± SD of serum concentrations of HS or DS at Weeks 50, 51, and 52.

Table 20. HS and DS concentrations in CSF and serum categorized by the presence/absence of inhibitory activity against binding to TfR or M6PR in subjects who tested positive for the ADAs[a)]

Study	Test sample	Dose (mg/kg)	Analyte	Time point	Tested positive for anti-pabinafusp alfa antibodies				Tested positive for anti-IDS antibodies	
					TfR binding inhibitory activity		M6PR binding inhibitory activity		M6PR binding inhibitory activity	
					Positive	Negative	Positive	Negative	Positive	Negative
101 Part 2	CSF[b)]	1.0	HS	Baseline	4580, 5090 (2)	—	4580, 5090 (2)	—	—	4077 ± 1338 (3)
				Week 3	3480, 4520 (2)	—	3480, 4520 (2)	—	—	3450 ± 1085 (3)
			DS	Baseline	1010, 1780 (2)	—	1010, 1780 (2)	—	—	1186 ± 528.5 (3)
				Week 3	656, 948 (2)	—	656, 948 (2)	—	—	838.0 ± 158.8 (3)
		2.0	HS	Baseline	3940, 5760 (2)	—	5760 (1)	3940 (1)	5760 (1)	3940 (1)
				Week 3	2710, 4320 (2)	—	4320 (1)	2710 (1)	4320 (1)	2710 (1)
			DS	Baseline	931, 933 (2)	—	933 (1)	931 (1)	933 (1)	931 (1)
				Week 3	659, 718 (2)	—	718 (1)	659 (1)	718 (1)	659 (1)
	Serum[c)]	1.0	HS	Baseline	958 (1)	—	958 (1)	—	—	342, 958 (2)
				Week 4	1100, 1110 (2)	—	1100, 1110 (2)	—	—	836.3 ± 465.4 (3)
			DS	Baseline	946, 1260 (2)	—	946, 1260 (2)	—	—	877.3 ± 421.2 (3)
				Week 4	1500, 1770 (2)	—	1500, 1770 (2)	—	—	1231 ± 712.7 (3)
		2.0	HS	Baseline	781, 1260 (2)	—	1260 (1)	781 (1)	1260 (1)	781 (1)
				Week 4	619, 837 (2)	—	837 (1)	619 (1)	837 (1)	619 (1)
			DS	Baseline	985, 1150 (2)	—	985 (1)	1150 (1)	985 (1)	1150 (1)
				Week 4	835, 1300 (2)	—	835 (1)	1300 (1)	835 (1)	1300 (1)
301	CSF[d)]	2.0 Previously treated-subjects	HS	Baseline	5133.6 ± 1531.5 (11)	4720, 7320 (2)	4892.0 ± 806.4 (5)	5506.3 ± 1867.2 (8)	5350, 5470 (2)	5430.8 ± 1783.5 (12)
				Week 25	2269.1 ± 717.6 (11)	1850, 1950 (2)	2240.0 ± 770.9 (5)	2195.0 ± 654.9 (8)	2680, 3290 (2)	2154.2 ± 679.5 (12)
				Week 52	2137.0 ± 846.4 (10)	1670, 1780 (2)	2194.0 ± 802.0 (5)	1978.6 ± 819.4 (7)	2640, 3340 (2)	1877.0 ± 732.8 (10)
			DS	Baseline	1221.1 ± 404.1 (11)	853, 1010 (2)	1009.2 ± 168.6 (5)	1281.1 ± 454.5 (8)	817, 899 (2)	1167.8 ± 367.2 (12)
				Week 25	724.3 ± 204.5 (11)	382, 863 (2)	795.8 ± 244.2 (5)	654.1 ± 189.4 (8)	592, 1080 (2)	631.8 ± 207.1 (12)
				Week 52	691.3 ± 343.7 (10)	361, 514 (2)	830.0 ± 435.0 (5)	519.7 ± 155.3 (7)	575, 817 (2)	512.3 ± 168.4 (10)
	Serum[c)]		HS	Baseline[e)]	918.8 ± 636.4 (11)	472, 967 (2)	1009.7 ± 556.8 (5)	812.2 ± 641.5 (8)	1093, 1240 (2)	1100.3 ± 799.8 (12)
				Week 26[f)]	615.5 ± 331.3 (11)	357, 555 (2)	651.7 ± 335.0 (5)	553.0 ± 311.9 (8)	661, 807 (2)	637.3 ± 268.3 (12)
				Week 52[g)]	573.9 ± 394.2 (11)	338, 627 (2)	584.7 ± 344.7 (5)	544.3 ± 401.7 (8)	671, 807 (2)	583.0 ± 342.3 (12)
			DS	Baseline[e)]	1086.5 ± 646.1 (11)	669, 989 (2)	1152.3 ± 556.4 (5)	981.0 ± 655.6 (8)	1050, 1070 (2)	1143.7 ± 557.9 (12)
				Week 26[f)]	1198.8 ± 641.0 (11)	747, 985 (2)	1347.5 ± 542.4 (5)	1022.6 ± 635.1 (8)	931, 1497 (2)	1288.1 ± 538.8 (12)
				Week 52[g)]	1070.1 ± 623.2 (11)	656, 949 (2)	1143.3 ± 507.8 (5)	957.5 ± 644.7 (8)	920, 1367 (2)	1143.1 ± 535.3 (12)
	CSF[d)]	2.0 Treatment-naïve subjects	HS	Baseline	10710.0 ± 4336.0 (3)	—	10710.0 ± 4336.0 (3)	—	—	—
				Week 25	4156.7 ± 1962.3 (3)	—	4156.7 ± 1962.3 (3)	—	—	—
				Week 52	3256.7 ± 1911.1 (3)	—	3256.7 ± 1911.1 (3)	—	—	—
			DS	Baseline	1613.7 ± 649.6 (3)	—	1613.7 ± 649.6 (3)	—	—	—
				Week 25	796.3 ± 296.2 (3)	—	796.3 ± 296.2 (3)	—	—	—
				Week 52	575.0 ± 160.5 (3)	—	575.0 ± 160.5 (3)	—	—	—
	Serum[c)]		HS	Baseline[e)]	4996.7 ± 1765.9 (3)	—	4996.7 ± 1765.9 (3)	—	—	—
				Week 26[f)]	1101.8 ± 527.3 (3)	—	1101.8 ± 527.3 (3)	—	—	—
				Week 52[g)]	965.0 ± 473.4 (3)	—	965.0 ± 473.4 (3)	—	—	
			DS	Baseline[e)]	4843.3 ± 2140.5 (3)	—	4843.3 ± 2140.5 (3)	—	—	—
				Week 26[f)]	1669.1 ± 892.6 (3)	—	1669.1 ± 892.6 (3)	—	—	—
				Week 52[g)]	1427.1 ± 733.8 (3)	—	1427.1 ± 733.8 (3)	—	—	—

Mean ± SD (N); individual values are shown for N ≤ 2; unit, ng/mL; "—", not applicable

a) In study 101, data at baseline were categorized and calculated based on the presence/absence of ADAs prior to the initial dose of pabinafusp alfa; data for other time points were categorized and calculated based on the presence/absence of ADAs throughout the study period (any subject who tested positive for the ADAs at least once was to be included in the positive category). In Study 301, data were categorized and calculated based on the presence/absence of ADAs throughout the study period (any subject who tested positive for the ADAs at least once was to be included in the positive category).

b) Samples collected prior to administration of pabinafusp alfa were used for measurements of the baseline data, while samples collected 4 to 6 hours after the administration of pabinafusp alfa were used for measurements at Week 3.

c) Samples collected prior to administration of pabinafusp alfa were used for measurements.

d) Samples collected prior to administration of pabinafusp alfa were used for measurements of the baseline data, while samples collected within 4 hours after the administration of pabinafusp alfa were used for measurements at Weeks 25 and 52.

e) Mean ± SD of serum concentrations of HS or DS at Week −2, Week −1, and Week 0 (pre-dose).

f) Mean ± SD of serum concentrations of HS or DS at Weeks 24, 25, and 26.

g) Mean ± SD of serum concentrations of HS or DS at Weeks 50, 51, and 52.

PMDA's view:

In Studies 101 and 301, HS concentrations in CSF and in serum tended to decrease or remain at the same levels after administration of pabinafusp alfa. The trends were seen regardless of the presence of anti-pabinafusp alfa antibodies or anti-IDS antibodies. Plasma pabinafusp alfa concentrations tended to be lower and serum HS and DS concentrations tended to be higher in subjects who tested positive for anti-pabinafusp alfa antibodies or anti-IDS antibodies than in those who tested negative for the ADAs. In Study 301, when the subjects who tested positive for anti-pabinafusp alfa antibodies or anti-IDS antibodies were examined, those in whom inhibitory activity against binding to TfR or M6PR was found tended to have higher HS and DS concentrations in serum and CSF than those in whom inhibitory activity was not found. Although the limited number of subjects who tested positive for anti-pabinafusp alfa antibodies or anti-IDS antibodies precludes a strict evaluation of the effects of the ADAs on the pharmacokinetics and efficacy of pabinafusp alfa, the antibody production associated with treatment with pabinafusp alfa may have affected plasma pabinafusp alfa concentrations and HS and DS concentrations in CSF and serum. Therefore, the package insert should include a cautionary statement to the effect that it is desirable to measure antibodies on a regular basis. In addition, the applicant should gather information concerning the effects of antibody production on the long-term efficacy and safety of pabinafusp alfa in post-marketing clinical studies and other surveillance. Effects of antibody production on safety will be discussed in Section "7.R.2.2 Effects of antibody production."

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 2 Japanese clinical studies as summarized in Table 21. The applicant also submitted the results of a foreign clinical study as reference data.

Table 21. List of clinical studies on efficacy and safety

Data	Location	Study ID	Study population	N of subjects enrolled	Summary of dosage regimen	Main endpoint
Evaluation	Japan	101	Patients with MPS II	14	Part 1: Each subject received a single dose of each of the 4 dose levels, 0.01, 0.1, 1.0, and 2.0 mg/kg as an IV infusion in the order shown, once weekly for 4 weeks Part 2: Subjects received either 1.0 or 2.0 mg/kg as an IV infusion once weekly for 4 weeks	Pharmacokinetics Efficacy Safety
	Japan	301	Patients with MPS II	28	Subjects received 2.0 mg/kg as an IV infusion once weekly for 52 weeks	Efficacy Safety
Reference	Foreign	BR21	Patients with MPS II	18	Subjects received 1.0, 2.0, or 4.0 mg/kg as an IV infusion once weekly for 25 weeks	Pharmacokinetics Efficacy Safety

The following sections provide an outline of the clinical studies.

7.1 Japanese phase I/II study (CTD 5.3.5.2.1, Study 101 [March 2017 to October 2017])

An open-label, uncontrolled study was conducted in patients with MPS II (target sample size, 12 subjects [2 subjects in Part 1, 5 subjects/group at 1.0 and 2.0 mg/kg in Part 2]) to evaluate the pharmacokinetics, efficacy, and safety of intravenous pabinafusp alfa [see Section "6.2.1 Japanese phase I/II study" for pharmacokinetics].

Key eligibility criteria were as follows:

Patients aged ≥6 years (in Part 1, limited to patients aged ≥16 years who were diagnosed as having no or mild

intellectual disability associated with MPS II [able to report their symptoms]) who had a confirmed diagnosis of MPS-II based on diagnostic methods including measurement of enzyme activity in leukocytes, plasma, and cultured skin fibroblasts, or genetic analysis; and who were on continuous pharmacotherapy with intravenous idursulfase 0.5 mg/kg once weekly for ≥12 weeks prior to the initial dose of pabinafusp alfa. Patients with a history of hematopoietic stem cell transplantation were excluded.

Both Parts 1 and 2 of this study consisted of a screening period (7-28 days) and pabinafusp alfa treatment period (4 weeks).

In Part 1, subjects received a single dose of each of the 4 dose levels of pabinafusp alfa, in the order of 0.01 mg/kg, 0.1 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, once weekly, as an intravenous infusion over ≥3 hours. In Part 2, subjects received pabinafusp 1.0 mg/kg or 2.0 mg/kg as an intravenous infusion over ≥3 hours once weekly for 4 weeks.

All 14 subjects who received pabinafusp alfa (2 subjects in Part 1; 6 subjects/group at 1.0 mg/kg and 2.0 mg/kg in Part 2) were included in the safety analysis set. The 12 subjects who were enrolled in Part 2 were included in the full analysis set (FAS), which was the primary efficacy analysis set. No subjects withdrew from the study. Of the 12 subjects enrolled in Part 2, the first subject aged <16 years enrolled was assigned to the 1.0 mg/kg group, and the rest of the subjects were randomly assigned to 1.0 mg/kg group or 2.0 mg/kg group.

Table 22 shows the data obtained in Part 2: HS concentrations in CSF, DS concentrations in CSF, HS and DS concentrations in serum, and HS, DS, and GAG concentrations in urine.

Table 22. Results for primary efficacy endpoints (Study 101, Part 2; FAS)

Item	Time point	1.0 mg/kg			2.0 mg/kg		
		N	Mean ± SD	Median (min, max)	N	Mean ± SD	Median (min, max)
HS concentration in CSF (ng/mL)	Baseline	6	4615 ± 1559	4835 (2560, 6560)	5	5168 ± 1698	4220 (3940, 7900)
	Week 3	6	3387 ± 1046	3565 (1950, 4520)	6	3397 ± 1057	2765 (2700, 5120)
DS concentration in CSF (ng/mL)	Baseline	6	1105 ± 363.1	1065 (768, 1780)	5	941.2 ± 256.3	931.0 (626, 1340)
	Week 3	6	779.5 ± 162.7	822.0 (519, 948)	6	804.7 ± 187.3	725.0 (639, 1080)
HS concentration in serum (ng/mL)	Baseline	5	532.2 ± 274.1	541.0 (247, 958)	6	733.3 ± 354.9	750.5 (329, 1260)
	Week 3	6	933.2 ± 844.9	770.5 (242, 2540)	6	543.5 ± 217.1	485.5 (335, 891)
	Week 4	6	642.5 ± 383.0	530.5 (285, 1110)	6	538.3 ± 173.4	505.5 (359, 837)
DS concentration in serum (ng/mL)	Baseline	6	755.7 ± 332.6	729.5 (426, 1260)	6	756.5 ± 263.3	670.5 (496, 1150)
	Week 3	6	878.7 ± 368.1	899.0 (372, 1310)	6	763.5 ± 300.4	671.5 (459, 1180)
	Week 4	6	972.5 ± 555.3	838.0 (423, 1770)	6	765.0 ± 295.8	694.5 (515, 1300)
HS concentration in urine (μg/mgCr)	Baseline	6	63.97 ± 47.76	51.15 (9.34, 141)	6	71.07 ± 49.83	60.50 (25.0, 162)
	Week 3	6	77.80 ± 59.13	58.45 (17.5, 167)	6	63.98 ± 45.71	50.00 (26.4, 154)
	Week 4	6	83.17 ± 64.07	63.50 (18.3, 195)	6	67.08 ± 44.47	55.15 (31.6, 155)
DS concentration in urine (μg/mgCr)	Baseline	6	28.43 ± 23.07	20.00 (3.59, 61.2)	6	28.78 ± 17.62	26.30 (12.9, 60.0)
	Week 3	6	42.82 ± 34.84	30.55 (8.42, 99.4)	6	34.05 ± 24.12	24.85 (15.9, 80.6)
	Week 4	6	48.04 ± 47.42	29.80 (9.01, 137)	6	36.12 ± 25.56	26.70 (15.2, 84.6)
GAG concentration in urine (μg/mgCr)	Baseline	6	44.64 ± 32.17	35.25 (6.74, 85.8)	6	39.47 ± 20.38	42.50 (13.2, 58.9)
	Week 3	6	53.20 ± 40.27	42.45 (10.8, 123)	6	45.38 ± 26.45	40.30 (16.3, 92.4)
	Week 4	6	64.15 ± 56.68	43.40 (11.3, 166)	6	42.80 ± 26.09	38.00 (11.9, 88.9)

Adverse events and adverse drug reactions occurred in 1 of 2 subjects and 1 of 2 subjects, respectively, in Part

1; and in Part 2, adverse events and adverse drug reactions occurred in 5 of 6 subjects and 3 of 6 subjects, respectively, in the 1.0 mg/kg group, and 3 of 6 subjects and 3 of 6 subjects, respectively, in the 2.0 mg/kg group. Adverse events occurring in ≥2 subjects were upper respiratory tract inflammation (2 subjects [1.0 mg/kg] in Part 2), pyrexia (1 subject in Part 1; 1 subject [1.0 mg/kg] and 2 subjects [2.0 mg/kg] in Part 2). Adverse drug reactions occurring in ≥2 subjects were pyrexia (1 subject in Part 1; 2 subjects [2.0 mg/kg] in Part 2).

No deaths occurred. A serious adverse event occurred in 1 subject (delirium) in the 1.0 mg/kg group in Part 2, which was classified as an adverse drug reaction. No adverse events led to treatment discontinuation.

No clinically relevant changes in vital signs or 12-lead electrocardiograms were reported.

7.2 Japanese phase II/III study (CTD 5.3.5.2.2, Study 301 [August 2018 to February 2020])

An open-label, uncontrolled study was conducted in patients with MPS II (target sample size, 20 subjects) to evaluate the efficacy and safety of intravenous pabinafusp alfa.

Key eligibility criteria were as follows:
Patients with confirmed diagnosis of MPS-II based on diagnostic methods including measurement of enzyme activity in leukocytes, plasma, and cultured skin fibroblasts, or genetic analysis. For patients on idursulfase therapy, only those who had been receiving idursulfase continuously for ≥8 weeks prior to the start of the run-in period were eligible. Patients with a history of hematopoietic stem cell transplantation were excluded.

This study consisted of a run-in period (4 weeks; 2 weeks for those with no prior treatment with idursulfase) and a study drug treatment period (52 weeks).[7)]

Subjects received pabinafusp alfa 2.0 mg/kg once weekly as an intravenous infusion. The initial dose was started at an infusion rate of approximately 8 mL/h. A stepwise increase at an infusion rate of ≤33 mL/h was allowed.

All 28 subjects who received pabinafusp alfa were included in the safety analysis set and FAS, and the FAS was the primary efficacy analysis set. One subject was withdrawn from the study due to death (hypoxic-ischaemic encephalopathy/acute respiratory failure).

Table 23 shows the change from baseline in HS concentrations in CSF at Week 52, the primary efficacy endpoint. CSF HS concentrations decreased significantly at Week 52 compared to those measured at baseline (paired t-test, $P < 0.001$).

7) Of patients who completed Study 301, those with no problems in terms of safety and from whom informed consent was obtained were enrolled in the extension study (Study 302).

Table 23. Results of HS concentrations in CSF (Study 301; FAS)

Time point	N[a)]	Mean ± SD
Baseline	27	5856 ± 2614
Week 52	27	2124 ± 882.6[b)]

a) The FAS excluded 1 subject because the data of HS concentrations in CSF following administration of pabinafusp alfa were not obtained.
b) For subjects whose data at Week 52 were not available, data from the closest time point were imputed for Week 52 data.

The results for key secondary endpoints are presented in tables and figure: HS and DS concentrations in CSF (Table 24); HS and DS concentrations in serum, HS, DS, and uronic acid concentrations in urine, liver and spleen volumes, left ventricular mass index, and 6-minute walk test distance, and data were categorized into patients with prior treatment with idursulfase and treatment naïve patients (Table 25). Figure 1 shows the results of developmental assessment (according to the Kyoto Scale of Psychological Development 2001 [KSPD]; total of the 3 domains: postural-motor, cognitive-adaptive, and language-social).

Table 24. Change in HS and DS concentrations in CSF over time (Study 301; FAS)

Parameter	Time point	N	Mean ± SD	Median (min, max)
HS concentration in CSF (ng/mL)	Baseline	28	5947.9 ± 2610.8	5315.0 (2530, 15100)
	Week 25	27	2357.8 ± 1023.5	2080.0 (1290, 5980)
	Week 52	22	2138.6 ± 968.1	1890.0 (1110, 5450)
DS concentration in CSF (ng/mL)	Baseline	28	1174.4 ± 417.6	1080.0 (491, 2270)
	Week 25	27	685.4 ± 241.6	697.0 (284, 1080)
	Week 52	22	593.4 ± 277.7	548.0 (274, 1570)

Table 25. Results for key secondary endpoints (change from baseline, Study 301; FAS)

Parameter	Time point	Prior treatment with idursulfase			No prior treatment with idursulfase		
		N	Mean ± SD	Median (min, max)	N	Mean ± SD	Median (min, max)
HS concentration in serum (ng/mL)	Baseline[a)]	25	847.0 ± 631.1	607.7 (347, 2930)	3	4997 ± 1766	4270 (3710, 7010)
	Week 26[b)]	24	539.0 ± 241.9	501.2 (220, 1290)	3	1102 ± 527.3	1100 (575, 1630)
	Week 52[c)]	24	507.2 ± 276.8	438.5 (168, 1500)	3	965.0 ± 473.4	757.7 (631, 1510)
DS concentration in serum (ng/mL)	Baseline[a)]	25	937.1 ± 452.7	821.3 (440, 2390)	3	4843 ± 2141	4037 (3220, 7270)
	Week 26[b)]	24	1061 ± 473.7	958.0 (527, 2500)	3	1669 ± 892.6	1723 (751, 2530)
	Week 52[c)]	24	959.4 ± 443.7	859.3 (538, 2480)	3	1427 ± 733.8	1333 (745, 2200)
HS concentration in urine (μg/mgCr)	Baseline	25	109.5 ± 86.9	91.90 (31.1, 414)	3	811.0 ± 466.0	1070 (273, 1090)
	Week 25	24	90.6 ± 98.6	61.80 (18.2, 451)	3	219.3 ± 102.8	161.0 (159, 338)
	Week 52	24	65.73 ± 38.5	54.30 (18.4, 171)	3	231.4 ± 122.2	287.0 (91.3, 316)
DS concentration in urine (μg/mgCr)	Baseline	25	51.4 ± 42.2	37.20 (14.6, 184)	3	270.0 ± 149.2	321.0 (102, 387)
	Week 25	24	52.3 ± 50.8	32.25 (12.0, 235)	3	127.4 ± 49.1	101.0 (97.2, 184)
	Week 52	24	41.06 ± 25.1	36.65 (9.3, 118)	3	131.0 ± 75.07	129.0 (56.9, 207)
Uronic acid concentration (mg/gCr)	Baseline	25	45.8 ± 25.7	40.60 (3.2, 108)	3	288.0 ± 31.7	300.00 (252, 312)
	Week 25	24	47.4 ± 23.5	43.15 (8.6, 116)	3	90.0 ± 54.6	59.90 (57.0, 153)
	Week 52	23	46.86 ± 17.59	42.00 (21.0, 77.3)	3	117.8 ± 70.87	86.00 (68.4, 199)
Liver volume (cm^3)	Baseline	25	814.3 ± 311.9	750.3 (372, 1893)	3	782.3 ± 155.7	774.00 (631, 942)
	Week 25	24	798.9 ± 276.7	697.1 (406, 1567)	3	603.7 ± 26.6	616.0 (573, 622)
	Week 52	24	799.7 ± 290.0	728.2 (443, 1642)	3	640.6 ± 26.7	634.0 (618, 670)
Spleen volume (cm^3)	Baseline	25	141.1 ± 66.1	129.0 (46.0, 293)	3	183.1 ± 67.4	211.0 (106, 232)
	Week 25	24	145.6 ± 64.9	128.1 (51.0, 300)	3	143.4 ± 55.3	162.0 (81, 187)
	Week 52	24	142.4 ± 68.4	117.5 (52.0, 336)	3	150.4 ± 66.0	155.0 (82.3, 214)
Left ventricular mass index (g/m^2)	Baseline	25	67.1 ± 20.9	61.0 (43.0, 135)	3	49.0 ± 26.4	60.1 (18.9, 68.0)
	Week 25	24	66.3 ± 19.9	63.1 (43.1, 125)	3	57.1 ± 13.5	53.6 (45.7, 72.0)
	Week 52	24	68.3 ± 19.5	63.2 (41.6, 122)	3	66.8 ± 12.6	72.4 (52.4, 75.7)
6-minute walk test distance (m)	Baseline	14	340.1 ± 159.2	367.5 (35.0, 590)	3	286.3 ± 95.0	316.0 (180, 363)
	Week 25	14	353.9 ± 108.1	354.0 (176, 495)	2	—	345, 367
	Week 52	14	354.5 ± 136.1	335.0 (120, 544)	1	—	401

Individual values are shown for N ≤ 2
a) Mean of the concentrations at Weeks −2, −1, and 0
b) Mean of the concentrations at Weeks 24, 25, and 26
c) Mean of the concentrations at Weeks 50, 51, and 52

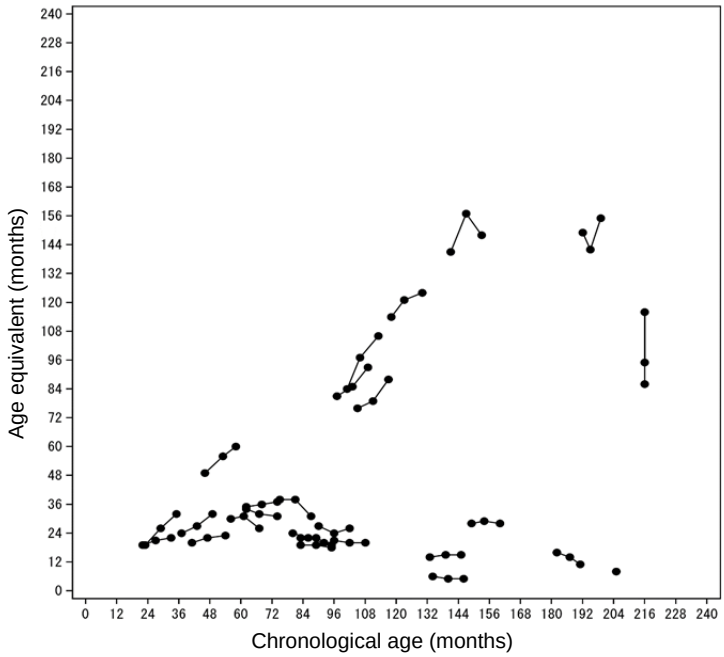

Figure 1. Change in developmental age over time (total of the 3 domains, KSPD) (FAS)

Adverse events and adverse drug reactions occurred in 28 of 28 subjects (100%) and 15 of 28 subjects (53.6%), respectively. Table 26 shows adverse events occurring in ≥3 subjects. The following adverse drug reactions

were reported: pyrexia (39.3%, 11 of 28 subjects); urticaria (10.7%, 3 of 28 subjects); chills (7.1%, 2 of 28 subject); dizziness, headache, syncope, rash, erythema, fatigue, and electrocardiogram QT prolonged (3.6%, 1 of 28 subjects for each adverse drug reaction).

Table 26. Adverse events occurring in ≥3 subjects (Study 301; safety analysis set)

Event	Pabinafusp alfa group (N = 28)
Events total	100 (28)
Pyrexia	50.0 (14)
Nasopharyngitis	46.4 (13)
Upper respiratory tract inflammation	42.9 (12)
Pharyngitis	39.3 (11)
Vomiting	25.0 (7)
Gastroenteritis	25.0 (7)
Urticaria	25.0 (7)
Skin abrasion	21.4 (6)
Rhinitis allergic	17.9 (5)
Bronchitis	17.9 (5)
Eczema	14.3 (4)
Rash	14.3 (4)
Diarrhoea	14.3 (4)
Hand-foot-and-mouth disease	14.3 (4)
Contusion	14.3 (4)
Conjunctivitis	10.7 (3)
Nausea	10.7 (3)
Influenza	10.7 (3)

Incidence, % (n); MedDRA/J ver.22.0

One subject died (hypoxic-ischaemic encephalopathy/acute respiratory failure). Serious adverse events occurred in 5 subjects (hypoxic-ischaemic encephalopathy/acute respiratory failure/upper respiratory tract inflammation; bronchitis [2 cases]/pneumonia aspiration/status epilepticus; pharyngitis streptococcal; subdural haematoma; and intraocular pressure increased in 1 subject each), and a causal relationship to pabinafusp alfa was ruled out for all these events. No adverse events led to treatment discontinuation.

No clinically relevant changes in vital signs or 12-lead electrocardiograms were reported.

7.3 Foreign phase II study (CTD 5.3.5.2.3, Study BR21 [July 2018 to September 2019], Reference data)

An open-label, uncontrolled study was conducted in patients with MPS II (target sample size, 18 subjects [6 each in the 1.0, 2.0, and 4.0 mg/kg groups[8)]]) to evaluate the pharmacokinetics, efficacy and safety of intravenous pabinafusp alfa [see Section “6.2.3 Foreign Phase II study” for the details of pharmacokinetics].

Key eligibility criteria were as follows:

Patients aged ≥0 years with confirmed diagnosis of MPS II based on diagnostic methods including measurement of enzyme activity in leukocytes and cultured skin fibroblasts, or genetic analysis, who had received no prior treatment for MPS II. Patients who had been on idursulfase therapy were also eligible if the disease condition had been stable on the therapy during the preceding 6 months. Patients with a history of hematopoietic stem cell transplantation were excluded.

8) The study enrolled 6 patients each from the 3 age groups (0 to <4 years, 4 to <8 years, and ≥8 years). Six patients in each age group were assigned to 3 treatments (2 patients/treatment/age group).

This study consisted of a run-in period (1 week) and a study drug treatment period (25 weeks).

Subjects received pabinafusp alfa 1.0, 2.0, or 4.0 mg/kg once weekly as an intravenous infusion over approximately 3 hours.

All 20 subjects who received pabinafusp alfa (8 subjects in the 1.0 mg/kg group, 5 subjects in the 2.0 mg/kg group, and 7 subjects in the 4.0 mg/kg group) were included in the safety analysis set. Of them, 19 subjects received at least 1 dose of pabinafusp alfa and had their data evaluated for efficacy at least once. They were included in the modified intention to treat (mITT) population for efficacy analysis. One subject in the 4.0 mg/kg group was withdrawn from the study due to death (respiratory arrest).

Liver and spleen volumes, left ventricular mass index, HS and DS concentrations in urine and serum in subjects with and without prior treatment with idursulfase are presented in Tables 27 and 28, respectively.

Table 27. Efficacy results in patients with prior treatment with idursulfase (Study BR21; mITT population for efficacy analysis)

Parameter	Time point	1.0 mg/kg		2.0 mg/kg		4.0 mg/kg	
		N	Measurement	N	Measurement	N	Measurement
Liver volume (cm^3)	Baseline	6	752.17 ± 208.22	4	916.75 ± 232.87	1	1078.00
	Week 25	6	673.83 ± 105.36	4	907.25 ± 217.92	1	1153.00
Spleen volume (cm^3)	Baseline	6	123.77 ± 63.04	4	188.75 ± 54.33	1	558.00
	Week 25	6	125.85 ± 52.22	4	189.25 ± 73.38	1	784.00
Left ventricular mass index (g/m^2)	Baseline	6	72.83 ± 21.77	4	86.00 ± 40.91	1	83.00
	Week 25	5	91.40 ± 42.38	4	81.48 ± 19.60	1	103.00
HS concentration in urine (mg/mgCr)	Baseline	6	253.26 ± 173.97	4	65.42 ± 22.65	1	69.60
	Week 25	6	180.78 ± 68.32	3	66.84 ± 57.24	1	32.14
DS concentration in urine (mg/mgCr)	Baseline	6	117.79 ± 61.18	4	31.38 ± 26.62	1	41.76
	Week 25	6	115.42 ± 46.72	3	29.38 ± 17.74	1	15.82
HS concentration in serum (ng/mL)	Baseline	6	2282.7 ± 1242.8	4	761.0 ± 191.5	1	978.0
	Week 25	6	1484.0 ± 436.1	3	886.7 ± 652.9	1	563
DS concentration in serum (ng/mL)	Baseline	6	2261.7 ± 958.1	4	1265.0 ± 690.2	1	1510.0
	Week 25	6	2213.3 ± 837.1	3	1303.3 ± 433.6	1	1170.0

Mean ± SD; individual values are shown for N ≤ 2

Table 28. Efficacy results in patients with no prior treatment with idursulfase (Study BR21; mITT population for efficacy analysis)

Parameter	Time point	1.0 mg/kg		2.0 mg/kg		4.0 mg/kg	
		N	Measurement	N	Measurement	N	Measurement
Liver volume (cm^3)	Baseline	2	116.00, 155.00	1	922.00	5	1263.60 ± 543.86
	Week 25	2	360.00, 973.00	1	641.00	5	994.20 ± 443.66
Spleen volume (cm^3)	Baseline	2	116.00, 155.00	1	127.00	5	283.40 ± 123.67
	Week 25	2	93.00, 106.00	1	84.00	5	228.60 ± 99.19
Left ventricular mass index (g/m^2)	Baseline	2	49.10, 58.00	1	91.60	5	134.00 ± 99.23
	Week 25	2	61.00, 89.10	1	76.70	5	116.60 ± 73.37
HS concentration in urine (mg/mgCr)	Baseline	1	41.66	1	1006.58	5	618.06 ± 340.44
	Week 25	2	46.33, 433.33	1	85.68	5	124.04 ± 92.93
DS concentration in urine (mg/mgCr)	Baseline	1	13.46	1	508.55	5	255.93 ± 156.61
	Week 25	2	22.44, 247.22	1	56.74	5	61.616 ± 49.36
HS concentration in serum (ng/mL)	Baseline	2	675.0, 4940.0	1	5390.0	5	4962.0 ± 853.0
	Week 25	2	662.0, 2310.0	1	930	5	855.0 ± 235.8
DS concentration in serum (ng/mL)	Baseline	2	1400.0, 3280.0	1	4220.0	5	3966.0 ± 1404.7
	Week 25	2	1160.0, 2780.0	1	1540.0	5	1516.0 ± 223.7

Mean ± SD; individual values are shown for N ≤ 2

Table 29 shows HS and DS concentrations in CSF.

Table 29. HS and DS concentrations in CSF (Study BR21; mITT population for efficacy analysis)

Parameter	Time point	1.0 mg/kg		2.0 mg/kg		4.0 mg/kg	
		N	Measurement	N	Measurement	N	Measurement
HS concentration in CSF (ng/mL)	Baseline	6	5120.0 ± 2036.8	4	5227.5 ± 1823.5	6	3774.2 ± 2243.1
	Week 25	8	4288.8 ± 1590.4	5	1623.0 ± 862.0	6	2365.0 ± 1603.0
DS concentration in CSF (ng/mL)	Baseline	6	1007.0 ± 238.6	4	1061.8 ± 377.9	6	870.2 ± 388.9
	Week 25	8	1189.6 ± 557.5	5	458.4 ± 196.8	6	635.5 ± 283.7

Mean ± SD

Adverse events occurred in 8 of 8 subjects in the 1.0 mg/kg group, 5 of 5 subjects in the 2.0 mg/kg group, and 7 of 7 subjects in the 4.0 mg/kg group. Table 30 shows adverse events occurring in ≥2 subjects in any group. Adverse drug reactions occurred in 4 of 8 subjects in the 1.0 mg/kg group (chills/pyrexia/headache/infusion related reaction/nausea/vomiting, dermatitis acneiform, skin plaque, and somnolence in 1 subject each), 1 of 5 subjects in the 2.0 mg/kg group (infusion related reaction), and 6 of 7 subjects in the 4.0 mg/kg group (pain/erythema/pyrexia/body temperature increased/nausea/hyperhidrosis, anaphylactic reaction/pyrexia/nausea/body temperature increased/urticaria/vomiting; urticaria; pyrexia/tremor/urticaria/vomiting; infusion related reaction; burning sensation/infusion related reaction/injection site urticaria/urticaria in 1 subject each).

Table 30. Adverse events occurring in ≥2 subjects in any group (Study BR21; safety analysis set)

Event	1.0 mg/kg (N = 8)	2.0 mg/kg (N = 5)	4.0 mg/kg (N = 7)
Events total	100 (8)	100 (5)	100 (7)
Urticaria	0 (0)	0 (0)	57.1 (4)
Pyrexia	25.0 (2)	20.0 (1)	42.9 (3)
Vomiting	12.5 (1)	0 (0)	42.9 (3)
Upper respiratory tract infection	50.0 (4)	40.0 (2)	28.6 (2)
Otitis externa	12.5 (1)	20.0 (1)	28.6 (2)
Infusion related reaction	12.5 (1)	20.0 (1)	28.6 (2)
Diarrhoea	12.5 (1)	20.0 (1)	28.6 (2)
Nausea	12.5 (1)	20.0 (1)	28.6 (2)
Asthmatic crisis	25.0 (2)	0 (0)	28.6 (2)
Nasopharyngitis	0 (0)	0 (0)	28.6 (2)
Rhinitis	0 (0)	0 (0)	28.6 (2)
Body temperature increased	0 (0)	0 (0)	28.6 (2)
Influenza	25.0 (2)	60.0 (3)	14.3 (1)
Otitis media acute	25.0 (2)	20.0 (1)	14.3 (1)
Dermatitis	37.5 (3)	0 (0)	0 (0)
Respiratory disorder	25.0 (2)	0 (0)	0 (0)

Incidence, % (n); MedDRA/J ver.22.0

One subject in the 4.0 mg/kg group died (respiratory arrest). Serious adverse events occurred in 3 subjects in the 1.0 mg/kg group (febrile convulsion, respiratory disorder, and lung infection in 1 subject each), 1 subject in the 2.0 mg/kg group (epilepsy), and 3 subjects in the 4.0 mg/kg group (respiratory arrest, vomiting, and foreign body aspiration in 1 subject each). A causal relationship to pabinafusp alfa was ruled out for all these events. No adverse events led to treatment discontinuation.

No clinically relevant changes in vital signs or 12-lead electrocardiograms were reported.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy on central nervous symptoms

7.R.1.1.1 Planning of Study 301

The applicant's explanation:

The progression of symptoms of MPS II varies significantly depending on the patient's characteristics. In addition, due to the limited number of patients, a parallel group, controlled study is unlikely to produce results that demonstrate clear efficacy. Taking into account various factors including the above, the applicant decided to design Study 301 as an open-label uncontrolled study so as to evaluate efficacy based on the individual subjects' data before and after administration of pabinafusp alfa.

Patients with any type of MPS II regardless of prior treatment with idursulfase were included in the study to ensure enrollment of a sufficient number of subjects and, at the same time, to evaluate the efficacy and safety of pabinafusp alfa in patients who had received no prior treatment with idursulfase, a currently available enzyme therapy. Given that pabinafusp alfa is of potential clinical significance in that it is expected to be effective in reducing CNS symptoms, the eligibility criteria for enrollment in Study 301 did not specify age limits or severity of MPS II, and Study 301 enrolled both patients with attenuated MPS II and those with severe MPS II. This was because the applicant considered that treatment with pabinafusp alfa should be initiated as early as possible also in younger patients in whom CNS disorder has not yet become apparent.

The efficacy endpoints were defined based on various publications. Accumulation of heparan sulfate occurs in patients with MPS I, II, III, and VII who present with CNS symptoms (*Mol Genet Metab.* 2018;125:322-31), suggesting that HS, among other mucopolysaccharides accumulating in the brain parenchyma, plays a vital role in the development of CNS symptoms. Some data have been reported in the published literature. GAG concentrations in CSF (mean ± SD) in healthy adults (n = 31) were 50.0 ± 15.5 ng/mL while the values in patients with MPS II without cognitive impairment were 373.4 ng/mL (n = 1; age range of 2-11 years), 356.8 ng/mL (n = 1; age range of 12-18 years), 619.3 ± 376.2 ng/mL (n = 4; age range of ≥18 years); in contrast, those in MPS II patients with cognitive impairment were 1540.5 ± 859.7 ng/mL (n = 19; age range of 2-11 years), indicating that GAG concentrations in CSF tended to be higher in MPS II patients with cognitive impairment than in MPS II patients without cognitive impairment (*Mol Genet Metab Rep.* 2015;5:103-6). In a different study, HS concentrations in CSF were 0.8 to 1.7 μmol/L in MPS II patients without cognitive impairment (n = 5; one patient with the highest value of 9.57 μmol/L was not included) and 2.3 to 4.3 μmol/L in MPS II patients with cognitive impairment (n = 3), indicating that HS concentrations in CSF tended to be higher in MPS II patients with cognitive impairment than in MPS II patients without cognitive impairment (*J Inborn Errors Metab Screen.* 2015;1-5). The mean of HS concentrations in CSF obtained from 9 adults who did not have MPS II was 363 ± 217 ng/mL (mean ± SD; minimum, 77.9 ng/mL and maximum, 745 ng/mL). Furthermore, in Study 101 in which data were analyzed for subjects with and without intellectual disability, baseline HS concentrations in CSF (mean ± SD) were 5895 ± 1260 ng/mL (n = 6) in subjects with intellectual disability and were 3632 ± 809.4 ng/mL (n = 5) in subjects without intellectual disability, suggesting that HS concentrations in CSF tended to be higher in subjects with intellectual disability than in patients without

intellectual disability. Additionally, the results from a non-clinical study of pabinafusp alfa in mouse models of the disease showed that HS concentrations in the brain correlate with those in CSF (CTD 4.2.1.1.6), which suggests that HS concentrations in CSF serve as a beneficial biomarker in evaluating the amount of HS accumulated in the brain. For these reasons, HS concentration in CSF was selected as the primary endpoint. While no significant elevation in DS concentrations in CSF was observed in mouse models of the disease, DS concentrations were evaluated as part of the efficacy assessment as DS is one of the substrates that accumulate in patients with MPS II. To evaluate CNS symptoms in patients with MPS II, developmental assessments were also selected as secondary endpoints to allow a comprehensive evaluation including the relationship between development and HS concentrations in CSF.

7.R.1.1.2 Decrease in HS concentrations in the central nervous system

The applicant's explanation:

HS and DS concentrations in CSF following administration of pabinafusp alfa in Study 301 are shown in Tables 23 and 24, respectively. HS concentrations in CSF decreased in all subjects while DS concentrations in CSF decreased in 26 of 27 subjects.

In a clinical study in patients with MPS II, no changes in GAG concentrations in CSF were observed in the group of patients receiving intravenous idursulfase for 6 months (*Genet Med.* 2016;18:73-81). In another clinical study in MPS II patients aged ≤18 years with cognitive impairment, total GAG concentrations and HS concentrations in CSF did not decrease in the group of patients receiving intravenous idursulfase for 52 weeks.[9)] The clinical studies of pabinafusp alfa have also confirmed that during the period of treatment with idursulfase (from 4 weeks prior to the administration of pabinafusp alfa to baseline), HS and DS concentrations in CSF remained almost constant. Furthermore, Table 31 shows changes from baseline in HS and DS concentrations in CSF in 10 subjects who participated in both Studies 101 and 301. Changes from baseline in HS and DS concentrations in CSF decreased during the period of treatment with pabinafusp alfa in both studies, but increased during the period with no treatment with pabinafusp alfa.[10)] Based on the above findings, intravenous idursulfase, the currently available enzyme replacement therapy, does not reduce HS or DS concentrations in CSF, and therefore, reductions in HS and DS concentrations in CSF in Study 301 are considered to be attributable to pabinafusp alfa.

9) https://www.shiretrials.com/-/media/files/clinical%20trials/clinicaltrialsen/clinical%20study%20reports/shire-hgt-hit-094-clinical-study-report-redact.pdf

10) A period between Week 4 of Study 101 and the initial dose in Study 301, during which only idursulfase was administered, with a mean of 466 days (range, 386-506).

Table 31. Change from baseline in HS and DS concentrations in CSF in subjects participating in both Studies 101 and 301

Item	Study	Time point of evaluation	N	Mean ± SD
HS concentration in CSF (ng/mL)	101	Baseline	9	5138.9 ± 1588.1
		Week 4	10	3594.0 ± 955.9
		Change from baseline at Week 4	9	−1447.8 ± 818.8
	301	Baseline	10	5798.0 ± 1561.4
		Week 26	9	2285.6 ± 579.8
		Change from baseline at Week 26	9	−3221.1 ± 1234.2
DS concentration in CSF (ng/mL)	101	Baseline	9	1070.9 ± 337.8
		Week 4	10	825.4 ± 156.5
		Change from baseline at Week 4	9	−273.8 ± 359.3
	301	Baseline	10	1185.4 ± 323.9
		Week 26	9	767.3 ± 185.5
		Change from baseline at Week 26	9	−410.9 ± 427.0

Mean ± SD

The efficacy results from Study 301 were analyzed by severity (19 subjects with severe MPS II and 8 subjects with attenuated MPS II). At baseline, HS concentrations in CSF (mean ± SD) were 6626 ± 2700 ng/mL in subjects with severe MPS II and 4028 ± 1098 ng/mL in subjects with attenuated MPS II. At Week 52, HS concentrations in CSF were 2294 ± 909.9 ng/mL in subjects with severe MPS II and 1721 ± 707.2 ng/mL in subjects with attenuated MPS II, showing that after the 52-week treatment with pabinafusp alfa, HS concentrations in CSF in subjects with severe MPS II decreased to a level similar to those with attenuated MPS II.

Table 32 shows changes from baseline in HS concentrations in CSF in subjects with and without prior treatment with idursulfase (25 subjects with prior treatment and 3 treatment-naïve subjects). The baseline values are lower in the subgroup with prior treatment than in the subgroup without prior treatment. On the other hand, DS concentrations in CSF decreased, albeit to a lesser extent than HS concentrations, from baseline to Week 25 and to Week 52, and the changes were similar regardless of prior enzyme replacement therapy. The inability of idursulfase to cross the blood-brain barrier was inferred to lead to no decrease in substrates in the CNS, which would produce no difference in clinical conditions between patients with and without prior idursulfase treatment. However, it turned out there was a difference in baseline values between the subgroups. The difference is partly attributable to the fact that the subgroup with prior treatment with idursulfase consisted of 8 subjects with attenuated MPS II and 17 subjects with severe MPS II, in contrast to the subgroup without prior treatment with idursulfase, which comprised 3 subjects with severe MPS II only. Table 32 shows HS concentrations in CSF in subjects with prior treatment with idursulfase by the form of MPS II (attenuated or severe). Based on the above, while baseline HS concentrations in CSF differed depending on whether the patients had received prior enzyme replacement therapy, HS concentrations in CSF decreased throughout the treatment period regardless of prior enzyme replacement therapy. This suggests that prior treatment with idursulfase does not affect the efficacy of pabinafusp alfa in reducing CNS symptoms.

Table 32. Change from baseline in HS concentrations in CSF in Study 301 by prior treatment with idursulfase

	Prior treatment with idursulfase (N = 25)			No prior treatment with idursulfase (N = 3)[a)]
	Total (N = 25)	Attenuated (N = 8)	Severe (N = 17)	
Baseline	5376 ± 1711	4028 ± 1098	5861 ± 1511	10710 ± 4336
Week 25	2133 ± 612	1764 ± 648	2318 ± 519	4157 ± 1962
Week 52	1962 ± 668	1721 ± 707	2114 ± 535	3257 ± 1911

Mean ± SD; unit, ng/mL

a) All subjects had the severe form

The HS concentrations in CSF in Study 301 can be interpreted as follows: At baseline (pre-dose) in Study 301, 7 of 8 subjects with attenuated MPS II did not have intellectual disability associated with MPS II, and baseline HS concentrations in CSF in 5 of 8 subjects with attenuated MPS II were <4000 ng/mL. In contrast, all 20 subjects with severe MPS II had baseline HS concentrations in CSF >4000 ng/mL. Therefore, reducing HS concentrations in CSF to <4000 ng/mL and maintaining the concentrations at as low as possible is likely to be an important factor to suppress the development and progression of CNS symptoms in patients with MPS II. In Study 301, HS concentrations in CSF decreased to <4000 ng/mL at Week 52 in all but 1 subject. This suggests that, pabinafusp alfa is expected to reduce HS concentrations in CSF even in patients with severe MPS II to a level similar to those in patients with attenuated MPS II, who do not manifest CNS symptoms, thereby suppressing the development and progression of CNS symptoms. Patients with MPS II suffer progressive deterioration of the CNS, which leads to reversible dysfunctions resulting in irreversible neurodegeneration, neuronal death, and eventually brain atrophy. Therefore, it is of great importance to maintain HS concentrations in CSF at low levels to prevent the progression of neurodegeneration by performing diagnosis and intervention as soon as possible.

7.R.1.1.3 Effects on development

In the developmental assessment according to the KSPD, throughout the 52-week treatment period, the age equivalents for overall domains tended to generally increase or remain at the same level although decreased age equivalent score was observed in some subjects. Figure 2 shows the results by disease severity at baseline. Age equivalents increased in all 8 subjects with the attenuated form, while they tended to remain at the same level in subjects with the severe form (n = 20).

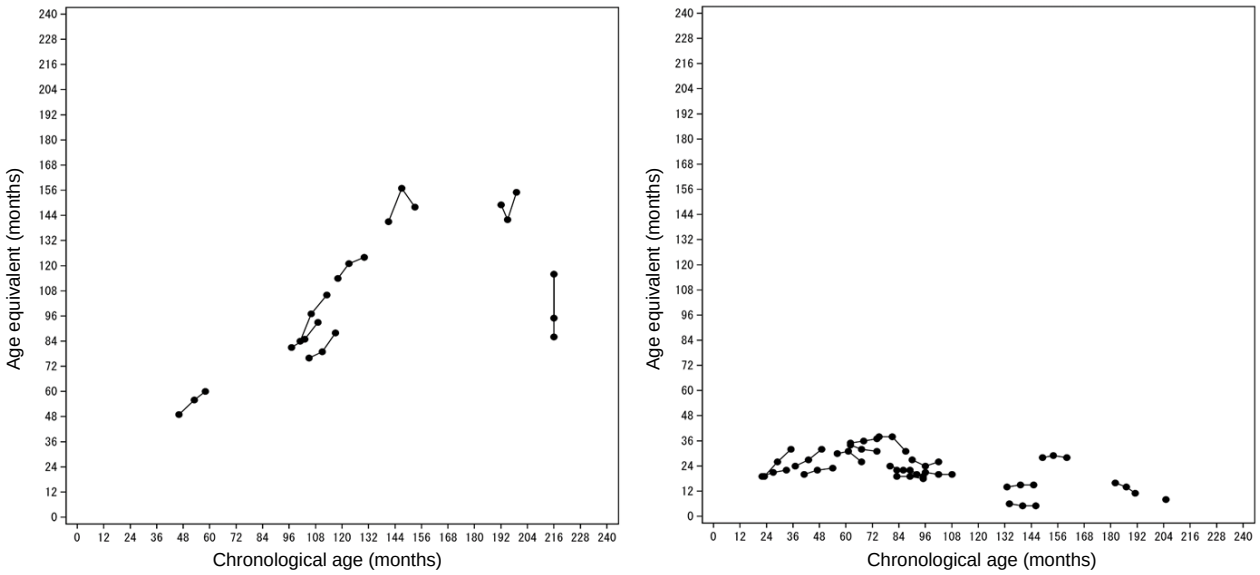

Figure 2. Change in age equivalents in individual subjects by severity (left, attenuated form; right, severe form)

Patients with the severe form were classified into 3 phases: the initial phase (aged <3 years and developmental quotient [DQ] ≥80 for all domains [according to the KSPD]), the middle phase (aged ≥3 years and ≤8 years or

DQ ≥20 for all domains, except for those classified into the initial phase), and the late phase (aged >8 years, or DQ <20 for all domains, except for those classified into the initial or middle phase). The mean gradient (mean ± SD) of the lines to be plotted between chronological age (horizontal axis) versus age equivalent (vertical axis) was calculated for each phase. The mean gradient was 0.6705 ± 0.3271 for the initial phase (n = 2, individual values are 1.083 and 0.250), −0.0802 ± 0.2199 for the middle phase (n = 11), and −0.0904 ± 0.1879 for the late phase (n = 5). The gradient tended to increase in the initial phase, while in the middle and late phases, the gradients tended to remain at the same level. The relative change in HS concentrations in CSF and that in age-equivalent scores in each subject with severe MPS II were analyzed; however, no clear relationship was identified between the increase in age-equivalent scores and decrease in HS concentrations in CSF.

Investigators' written reports on changes in clinical symptoms ("speech," "physical movement," "facial expression/liveliness," and "others") after the start of treatment with pabinafusp alfa were collected. According to the data, improvements in "speech" occurred in 13 of 26 subjects, with reported changes including increased utterances, increased conversations, and singing. The remaining 13 subjects showed no changes indicative of clear improvement. The reported changes were analyzed by disease severity. Improvements in "speech" were reported in 1 of 8 subjects with the attenuated form and 12 of 18 subjects with the severe form (2 of 2 subjects aged 0-2 years, 6 of 10 subjects aged 3-7 years, and 4 of 6 subjects aged ≥8 years). None of the subjects were reported to show clear worsening of "speech." In the category of "physical movement," changes reported include the following: "the patient's joints became more flexible," "the patient became able to walk up stairs or a slope, or walk longer distances," "muscular strength was improved," and "the patient became able to run faster." Improvements in "facial expression/liveliness" were reported in 12 of 26 subjects. Positive changes include becoming more active and a greater range of facial expressions than before. In the remaining 14 subjects, no clear changes were reported. The reported changes were analyzed disease severity. Improvements in "facial expression/liveliness" were reported in 1 of 8 subjects with the attenuated form and 11 of 18 subjects with the severe form (1 of 2 subjects aged 0-2 years, 5 of 10 subjects aged 3-7 years, and 5 of 6 subjects aged ≥8 years). As for changes classified into "others," 1 subject reported difficulties at the time of bowel movement and urination after the start of treatment with pabinafusp alfa. Other reported changes include increased calmness, less urinary and fecal incontinence, improvement in sleep, and becoming able to put on and take off shoes independently.

It has been reported that the course of age equivalents in Japanese patients with MPS II who have been receiving idursulfase differ depending on the genotypes and associated differences in residual enzyme activity; however, relatively normal development is observed in patients with any genotype in the first 24 months of life, and thereafter, gradually, the deviation from normal development becomes more noticeable. In patients with null mutations, which cause deletion or loss-of-function of IDS, age equivalents reach a plateau around 42 months of age and then show decline. Developmental quotient in patients with severe MPS II shows a rapid decline after 20 months of age, and decreases to approximately 20 at 100 months of age (*Mol Genet Metab Rep*. 2020;24:100630).

In Study 301, a patient with severe MPS II who had started receiving pabinafusp alfa at [redacted] months of age increased the age-equivalent score by 13 months after 1 year of treatment, with an increase in DQ from 84 to 94. In the study in which the natural course of patients with MPS II was followed, one of the patients with severe MPS II had the genotype ([redacted]: null mutation) identical to that of the above subject with severe MPS II treated in Study 301, and the DQ of the patient decreased from 86 to 55 during the period from 28 months to 47 months of age (*Mol Genet Metab Rep*. 2020;24:100630). With the report taken into consideration, the subject mentioned above appeared to, after treatment with pabinafusp alfa, show a favorable developmental course that was superior to the natural course of patients with severe MPS II. Furthermore, another patient with severe MPS II who started treatment with pabinafusp alfa at around [redacted] months of age, at which age equivalents are expected to start reaching a plateau in the natural course, showed an increase of age equivalent of 8 months after 1 year of treatment with pabinafusp alfa, with a DQ of 67, which remained at the same value as that at the initiation of treatment. Given that DQ shows a rapid decline after 20 months of age in the natural course, the maintenance of DQ in the subject is thought to represent the significant suppression of the deterioration that would usually occur in the natural course.

Based on the above discussions, the applicant considers that pabinafusp alfa is expected to be effective in reducing CNS symptoms.

To evaluate the efficacy of pabinafusp alfa for the treatment of CNS symptoms, in particular, neurodevelopmental disorders, long-term evaluation in subjects enrolled in Study 301 will be continued in the post-marketing clinical study to be conducted. In addition, patients with no prior pabinafusp alfa exposure will be enrolled in another planned post-marketing clinical study to continue evaluation of the long-term efficacy of pabinafusp alfa in the treatment of CNS symptoms. The participants in Study BR21 conducted in Brazil will be evaluated in an extension study. Currently, more clinical studies comparing idursulfase as a control drug are planned overseas.

PMDA's view on the efficacy of pabinafusp alfa in improving CNS symptoms based on the applicant's explanation presented in Sections 7.R.1.1.1 through 7.R.1.1.3:
At the time Study 301 was being planned, there were no approved agents expected to be effective in reducing the CNS symptoms of MPS II. Because of this and other reasons, it was unavoidable that the applicant decided to plan and conduct Study 301 only in Japan as an open-label uncontrolled study. In addition, many publications have reported that accumulation of GAGs including HS is the principal cause of CNS symptoms in patients with MPS II, and the results of non-clinical studies demonstrated that brain HS concentrations are correlated with HS concentrations in CSF; therefore, it is reasonable to use HS concentrations in CSF as one of the indicators to estimate the effect of treatment with pabinafusp alfa. Furthermore, due to the limited number of patients with MPS II and because evaluation of the efficacy of pabinafusp alfa requires assessments of not only CNS symptoms but also other systemic symptoms, inclusion of patients regardless of severity, i.e., both the severe and attenuated forms of MPS II, in the studies is also reasonable.

According to the data submitted, HS concentrations in CSF, the primary endpoint for Study 301, decreased from baseline (prior to the start of treatment with pabinafusp alfa). In addition, based on the changes in HS concentrations in subjects who participated both Studies 101 and 301, pabinafusp alfa is expected to be effective in reducing HS concentrations in the CNS. On the other hand, no pharmacotherapies, including currently available enzyme therapies, are capable of reducing HS concentrations in CSF in patients with MPS II. Based on this and other factors, it is not clear whether a decrease in HS concentrations in CSF can contribute to the improvement of clinical symptoms. In the analysis of relative change in HS concentrations in CSF and that in age equivalent scores obtained from developmental assessments, no clear relationship was identified between the increase in age equivalent scores and decrease in HS concentrations in CSF. Information on the development of patients with MPS II including the natural course of the disease is insufficient, and clinical studies conducted so far have yet to clearly demonstrate the improvement of CNS symptoms. However, CNS symptoms are thought to develop as a result of years of accumulation of GAGs; additionally, the effects of education and other factors during the developmental stage of the patients on the development of such symptoms should be taken into consideration. Taken together, it may be difficult to demonstrate that a reduction in HS concentrations in the CNS results in an immediate improvement in CNS symptoms. This could therefore have led to difficulty in acquiring data demonstrating developmental improvement during the period of Study 301.

Based on the above discussion, it may be difficult to strictly evaluate how effective pabinafusp alfa is in reducing CNS symptoms based on the data from Study 301. However, given that MPS II is a rare disease and that evaluation of the developmental effects requires long-term investigation, it can be interpreted from the currently available data from Study 301 that pabinafusp alfa should have a certain level of efficacy in the treatment of CNS symptoms. Early intervention and continuation of treatment including pharmacotherapies are considered vital for the treatment of CNS symptoms of patients with MPS II; however, there were limitations in the evaluation of CNS symptoms in Study 301. For this reason, efficacy data such as developmental assessments in patients receiving pabinafusp alfa should be collected in the post-marketing setting to continue evaluation of CNS symptoms [see Section “7.R.5 Post-marketing investigations”].

7.R.1.2 Efficacy in reduction of systemic symptoms

The applicant’s explanation:

Several secondary endpoints were specified to assess systemic symptoms of MPS II. HS and DS concentrations in serum and urine were selected because HS and DS are accumulated in systemic tissues and large amounts of HS, DS, and other GAGs are excreted in urine in patients with MPS II. Endpoints for evaluation of clinical symptoms included liver and spleen volumes, left ventricular mass index, and 6-minute walk test distance. In Study 301, the results of the endpoints were analyzed for subjects with or without prior idursulfase treatment. In subjects with prior idursulfase treatment (n = 25), serum HS concentrations (mean ± SD) were 847.0 ± 631.1 ng/mL (baseline), 539.0 ± 241.9 ng/mL (Week 26), and 507.2 ± 276.8 ng/mL (Week 52), showing a decrease throughout the study period. Serum DS concentrations were 937.1 ± 452.7 ng/mL (baseline), 1061 ± 473.7 (Week 26), and 959.4 ± 443.7 ng/mL (Week 52), showing slight increase throughout the study period, without significant changes in any subject. In contrast, in subjects with no prior idursulfase treatment (n = 3), serum

HS concentrations were 4997 ± 1766 ng/mL (baseline), 1102 ± 527.3 ng/mL (Week 26), and 965.0 ± 473.4 ng/mL (Week 52), while DS concentrations in serum were 4843 ± 2141 ng/mL(baseline), 1669 ± 892.6 ng/mL (Week 26), and 1427 ± 733.8 ng/mL (Week 52), showing significant decreases for both parameters. Liver and spleen volumes were adjusted by body weight of the patient. In subjects with prior idursulfase treatment, liver volumes were 27.17 ± 12.04 cm^3/kg (baseline), 25.99 ± 9.52 cm^3/kg (Week 26), and 24.99 ± 8.62 cm^3/kg (Week 52), while spleen volumes were 4.56 ± 2.07 cm^3/kg (baseline), 4.58 ± 1.57 cm^3/kg (Week 26), and 4.34 ± 1.56 cm^3/kg (Week 52), showing no significant changes throughout the study period. On the other hand, in subjects with no prior idursulfase treatment, liver volumes were 45.97 ± 1.60 cm^3/kg (baseline), 33.04 ± 6.77 cm^3/kg (Week 26), and 32.40 ± 4.90 cm^3/kg (Week 52), while spleen volumes were 10.55 ± 2.80 cm^3/kg (baseline), 7.39 ± 1.43 cm^3/kg (Week 26), and 7.34 ± 2.75 cm^3/kg (Week 52), showing decreases throughout the study period for both parameters.

In subjects with prior idursulfase treatment, changes from baseline in left ventricular mass index and 6-minute walk test distance were not significant, while in subjects with no prior idursulfase treatment, left ventricular mass index increased. This result, however, is affected by the data of 1 subject who had a significant increase in left ventricular mass index, and no significant changes were observed in other subjects. There were no significant changes in 6-minute walk test distance (Table 25).

Table 33 shows HS and DS concentrations in serum and urine, liver and spleen volumes, and left ventricular mass index in 10 subjects who participated in both Studies 101 and 301, indicating no significant changes from the start of treatment in Study 101 to Week 26 in Study 301.

Table 33. Results of HS and DS concentrations in serum and urine, liver and spleen volumes, and left ventricular mass index in subjects who participated in both Studies 101 and 301

Parameter	Study	Evaluation time point	N	Mean ± SD
HS concentration in serum (ng/mL)	101	Baseline	9	651.6 ± 314.0
		Week 4	10	626.1 ± 299.5
		Change from baseline at Week 4	9	−79.2 ± 187.1
	301	Baseline	10	634.6 ± 287.7
		Week 26	9	414.2 ± 204.2
		Change from baseline at Week 26	9	−215.8 ± 156.9
DS concentration in serum (ng/mL)	101	Baseline	10	773.6 ± 309.0
		Week 4	10	890.2 ± 480.2
		Change from baseline at Week 4	10	116.6 ± 232.7
	301	Baseline	10	831.5 ± 241.7
		Week 26	9	827.8 ± 335.1
		Change from baseline at Week 26	9	14.3 ± 255.5
HS concentration in urine (μg/mgCr)	101	Baseline	10	74.7 ± 47.0
		Week 4	10	82.1 ± 55.1
		Change from baseline at Week 4	10	7.5 ± 22.9
	301	Baseline	10	87.7 ± 72.4
		Week 26	9	51.6 ± 34.4
		Change from baseline at Week 26	9	−42.4 ± 60.9
DS concentration in urine (μg/mgCr)	101	Baseline	10	30.6 ± 19.8
		Week 4	10	45.3 ± 39.1
		Change from baseline at Week 4	10	14.7 ± 22.9
	301	Baseline	10	47.7 ± 40.3
		Week 26	9	32.5 ± 25.6
		Change from baseline at Week 26	9	−18.2 ± 37.0

Table 33. Results of HS and DS concentrations in serum and urine, liver and spleen volumes, and left ventricular mass index in subjects who participated in both Studies 101 and 301 (continued)

parameter	Study	Evaluation time point	N	Mean ± SD
Liver volume (cm^3)	101	Baseline	10	880.7 ± 263.9
		Week 4	10	806.4 ± 227.6
		Change from baseline at Week 4	10	−74.3 ± 98.4
	301	Baseline	10	863.6 ± 207.1
		Week 26	9	886.6 ± 214.3
		Change from baseline at Week 26	9	38.4 ± 93.1
Spleen volume (cm^3)	101	Baseline	10	168.6 ± 80.7
		Week 4	10	158.0 ± 73.4
		Change from baseline at Week 4	10	−10.7 ± 21.2
	301	Baseline	10	158.2 ± 67.6
		Week 26	9	167.3 ± 79.2
		Change from baseline at Week 26	9	15.9 ± 22.6
Left ventricular mass index (g/m^2)	101	Baseline	10	76.71 ± 17.77
		Week 4	10	76.75 ± 16.29
		Change from baseline at Week 4	10	0.05 ± 7.22
	301	Baseline	10	67.76 ± 13.27
		Week 26	9	72.67 ± 15.94
		Change from baseline at Week 26	9	5.71 ± 10.57

Mean ± SD

The above results indicate that pabinafusp alfa is effective in reducing systemic symptoms other than CNS symptoms to the similar extent to that of the currently available enzyme replacement therapy, and that pabinafusp alfa has efficacy similar to that of the currently available enzyme therapy in treatment-naïve subjects with MPS II.

PMDA's view:

In Study 301, in subjects with no prior idursulfase treatment, serum HS and DS concentrations decreased, and liver and spleen volumes tended to decrease. In subjects with prior idursulfase treatment, parameters including serum HS concentrations, serum DS concentrations, liver and spleen volumes tended to remain at the same levels from baseline. In subjects who participated in both Studies 101 and 301, no significant changes in systemic symptoms-related endpoints were observed in the pabinafusp alfa treatment periods (during participation in the two studies) and the idursulfase treatment period (period between the two studies[10)]). Although Study 301 was conducted using an open-label uncontrolled study design, which precludes a strict evaluation, the above results could support the efficacy of pabinafusp alfa in the treatment of systemic symptoms, and the degree of the therapeutic effect of pabinafusp alfa is unlikely to differ greatly from that of the currently available enzyme therapy. However, the applicant should continuously collect information about the efficacy of pabinafusp alfa in the treatment of systemic symptoms in the post-marketing setting.

7.R.2 Safety

The applicant's explanation:

Table 34 shows the summary of adverse events in Studies 101, 301, and BR21. One subject in Study 301 died (hypoxic-ischaemic encephalopathy/acute respiratory failure) and another died in the 4.0 mg/kg group in Study BR21 (respiratory arrest). A causal relationship to pabinafusp alfa was ruled out for both events.

In the pooled analysis (n = 62) of data from Studies 101, 301, and BR21, adverse events occurring in ≥10% of subjects were pyrexia (38.7%, 24 subjects), nasopharyngitis (25.8%, 16 subjects), upper respiratory tract inflammation (22.6%, 14 subjects), urticaria (21.0%, 13 subjects), pharyngitis (17.7%, 11 subjects), vomiting (17.7%, 11 subjects), influenza (14.5%, 9 subjects), upper respiratory tract infection (14.5%, 9 subjects), gastroenteritis (12.9%, 8 subject), diarrhoea (12.9%, 8 subjects), and nausea (11.3%, 7 subjects). Adverse drug reactions occurring in ≥5% of subjects were pyrexia (29.0%, 18 subjects), urticaria (14.5%, 9 subjects), and infusion related reaction (6.5%, 4 subjects). Serious adverse events occurred in 21.0% (13 subjects), of which delirium in 1 subject in the 1.0 mg/kg group in Part 2 of Study 101 was classified as an adverse drug reaction.

Table 34. Summary of adverse events in the clinical studies (safety analysis set)

		Study 101 (N = 14)	Study 301 (N = 28)	Study BR21 (N = 20)
All adverse events		64.3 (9)	100 (28)	100 (20)
All adverse drug reactions		50.0 (7)	53.6 (15)	55.0 (11)
Serious adverse events		7.1 (1)	17.9 (5)	35.0 (7)
Adverse events leading to treatment discontinuation		0 (0)	3.6 (1)	5.0 (1)
Severity	Mild	42.9 (6)	67.7 (19)	60.0 (12)
	Moderate	14.3 (2)	28.6 (8)	35.0 (7)
	Severe	7.1 (1)	3.6 (1)	5.0 (1)

Incidence, % (n)

Table 35 shows the incidence of adverse events and adverse drug reactions by timing of onset in the pooled data from Studies 101, 301, and BR21. No adverse events showed marked change in incidence with increase in the duration of treatment.

Table 35. Incidence of adverse events by timing of onset (pooled analysis of data from Studies 101, 301, and BR21; safety analysis set)

Timing of onset	Week ≥1 and Week <5 (N = 62)	Week ≥5 and Week <9 (N = 47)	Week ≥9 and Week <13 (N = 47)	Week ≥13 and Week <26 (N = 47)	Week ≥26 and Week <39 (N = 27)	Week ≥39 and Week <53 (N = 27)
Any adverse events	71.0 (44)	63.8 (30)	48.9 (23)	89.4 (42)	85.2 (23)	88.9 (24)
Any adverse drug reactions	37.1 (23)	27.7 (13)	10.6 (5)	14.9 (7)	14.8 (4)	7.4 (2)

Incidence, % (n)

No particular concerns about long-term safety have been reported in Study 302,[11)] an extension study of Study 301.

Based on the above discussions, most of the adverse events reported in the clinical studies are either events attributable to the pathology of MPS II or events that have also been reported in patients on currently available enzyme therapy, and the safety profile of pabinafusp alfa does not differ markedly from that of the currently available enzyme therapy.

PMDA's view

Based on the incidence of adverse events in the clinical studies, the safety of pabinafusp alfa is acceptable provided that appropriate cautionary advice is given regarding the adverse events, which are discussed in sections below. However, given the very limited number of patients evaluated in the clinical studies, the applicant should continuously collect post-marketing information including safety data from patients who will

11) An open-label uncontrolled study which has been conducted in patients who completed Study 301. In Study 302, patients are allowed to continue to receive pabinafusp alfa 2.0 mg/kg once weekly by intravenous infusion. Twenty-seven subjects who completed Study 301 participated in Study 302. As of November 2020, treatment was ongoing in 23 subjects. The mean total treatment duration including Study 301 is 709.6 days (range, 518-812).

be treated with pabinafusp alfa [see Section "7.R.5 Post-marketing investigations"]. Sections 7.R.2.1 and 7.R.2.2 discuss specific adverse events in greater detail.

7.R.2.1 Infusion-related reactions (including infusion-associated reaction [IAR] and anaphylaxis)

The applicant's explanation:

In the pooled analysis[12)] of data from Studies 101, 301, and BR21, the incidence of IARs[13)] by dose level was 28.6% (4 of 14 subjects) at 1.0 mg/kg, 43.6% (17 of 39 subjects) at 2.0 mg/kg, and 85.7% (6 of 7 subjects) at 4.0 mg/kg. The incidence of IARs was higher in subjects receiving 4.0 mg/kg, a dose level established only in Study BR21. No IARs led to study discontinuation in any study. In Study 101, IARs led to treatment interruption and reduction of infusion rate in 1 subject (throat irritation/urticaria). In Study 301, IARs led to treatment interruption in 2 subjects (urticaria and chills) and reduction of infusion rate in 1 subject (chills/pyrexia). In Study BR21, 5 subjects experienced IARs that led to treatment interruption or reduction of infusion rate. IARs led to both treatment interruption and reduction of infusion rate in 3 subjects (vomiting/urticaria, urticaria, and infusion related reaction; all at 4.0 mg/kg) while IARs led to treatment interruption in 4 subjects (vomiting/pyrexia, tremor/vomiting/urticaria/pyrexia, infusion related reaction, and infusion related reaction/burning sensation; all at 4.0 mg/kg).

Anaphylaxis and anaphylactic shock-related events were not reported in Studies 101 or 301, while in Study BR21, anaphylactic reaction occurred in 1 subject after the 9th dose of 4.0 mg/kg of pabinafusp alfa. Main symptoms are vomiting, somnolence, pyrexia, and tremulousness. All the symptoms resolved with treatment, and no similar events were observed after the subsequent infusions of pabinafusp alfa.

In summary, IARs and anaphylaxis and anaphylactic shock-related events occurred during treatment with pabinafusp alfa in the clinical studies. None of the events led to study discontinuation and all events were manageable with medical treatment. However, cautionary advice regarding the risk of IARs including anaphylaxis should be provided in the package insert; in addition, data on these events should be continuously collected in the post-marketing setting.

PMDA's view:

Of the hypersensitivity-related events including anaphylaxis that were reported in the clinical studies conducted in Japan and overseas, no events led to study discontinuation, and all events were manageable with treatment. The safety of pabinafusp alfa is acceptable. However, patients on treatment with pabinafusp alfa should be carefully monitored for the risk of hypersensitivity including anaphylaxis. Therefore, appropriate cautionary advice on the events should be included in the package insert. In addition, information on the incidence of these events should be collected also in the post-marketing setting.

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12) Two subjects in Part 1 of Study 101 were excluded from the analysis.

13) IARs are events defined as harmful reactions occurring in association with infusion of pabinafusp alfa (e.g., chills, pyrexia, feeling of body temperature change, nausea, and hypertension), and are classified as IARs by the investigator.

7.R.2.2 Effects of antibody production

The applicant's explanation:

The production of ADAs in subjects was investigated in the clinical studies. In Study 101 which enrolled patients with prior idursulfase treatment, 11 subjects tested negative for anti-pabinafusp alfa antibodies at baseline, and 1 of the subjects tested positive at Week 4. Three subjects tested positive for anti-pabinafusp alfa antibodies at baseline.

Study 301 included 25 subjects with prior idursulfase treatment, of whom 20 subjects tested negative for anti-pabinafusp alfa antibodies at baseline. Of the 20 subjects, 6 tested positive by Week 52. Five subjects with prior idursulfase treatment tested positive for anti-pabinafusp alfa antibodies at baseline. Of the subjects with no prior idursulfase treatment (n = 3), all tested negative for anti-pabinafusp alfa antibodies at baseline, and 2 of them tested positive by Week 52.

Study BR21 included 12 subjects with prior idursulfase treatment, of whom 7 subjects tested negative for anti-pabinafusp alfa antibodies at baseline. Of the 7 subjects, 2 tested positive by Week 26. Five subjects with prior idursulfase treatment tested positive for anti-pabinafusp alfa antibodies at baseline. Of the subjects with no prior idursulfase treatment (n = 8), all tested negative for anti-pabinafusp alfa antibodies at baseline, and 7 of them tested positive by Week 26.

Table 36 shows the incidence of IARs[13)] by anti-pabinafusp alfa antibody test result in the pooled analysis of data from Studies 101, 301, and BR21.

Table 36. Incidence of IARs by anti-pabinafusp alfa antibody test result
(Pooled analysis of data from Studies 101, 301, and BR21; safety analysis set)

	Tested negative for anti-pabinafusp alfa antibodies	Tested positive for anti-pabinafusp alfa antibodies[a)]
Total[b)]	30.8 (8/26)	55.6 (20/36)
1.0 mg/kg	20.0 (1/5)	33.3 (3/9)
2.0 mg/kg	31.6 (6/19)	55.0 (11/20)
4.0 mg/kg	— (0/0)	85.7 (6/7)

Incidence, % (n/N)
a) Any subject who tested positive for the antibodies at least once in the study period
b) The data of 2 subjects in Part 1 in Study 101 were only included in the calculation of the "total" data.

While the incidence of IARs tended to be slightly higher in subjects who tested positive for anti-pabinafusp alfa antibodies than in subjects who tested negative for anti-pabinafusp alfa antibodies, the incidence of IARs appeared to be related to the dose level of pabinafusp alfa. Therefore, from the currently available data, the applicant cannot conclude that development of anti-pabinafusp alfa antibodies affects safety. Nevertheless, it is necessary to closely monitor patients in whom anti-pabinafusp alfa antibodies are produced during treatment with pabinafusp alfa. Therefore, the package insert should include a cautionary statement to the effect that it is desirable to perform ADA testing at regular intervals because of potential antibody production in patients receiving pabinafusp alfa. In the post-marketing setting, subjects who tested positive for anti-pabinafusp alfa antibodies should be closely monitored for IARs.

PMDA's view:

In the clinical studies conducted in Japan and overseas, production of anti-pabinafusp alfa antibodies has been reported in subjects treated with pabinafusp alfa. The studies also showed that the incidence of IARs tended to be higher in subjects who tested positive for anti-pabinafusp alfa antibodies than in those who tested negative for the ADA. Based on the currently available evidence, the applicant plans to advise caution on IARs in the package insert, as with the case of drugs in the same class, and to provide a cautionary statement to the effect that it is desirable to perform ADA testing at regular intervals because of potential antibody production in patients receiving pabinafusp alfa. The applicant's plan is appropriate. Furthermore, the applicant should collect information about the effects of ADA production on the safety and efficacy of pabinafusp alfa in the post-marketing setting.

7.R.3 Clinical positioning and indication

The applicant's explanation:

Patients with the severe form of MPS II, who present with not only systemic symptoms but also CNS symptoms, are estimated to account for approximately two thirds of all patients with MPS II. Therefore, treatment that improves CNS symptoms is needed. In Japan, treatment options for patients with MPS II are enzyme replacement therapy and hematopoietic stem cell transplantation. Idursulfase has been used for enzyme replacement therapy by intravenous infusion, which has been reported to improve clinical symptoms such as hepatosplenomegaly. Because it is relatively safe, idursulfase is a first-line treatment. However, the currently available enzyme therapy cannot penetrate the blood-brain barrier, after being administered intravenously, and therefore, its efficacy in reducing CNS symptoms has not been demonstrated ("Mucopolysaccharidosis type II" in *Inborn Error of Metabolism*, 2nd ed. Book 2 [in Japanese] Nippon Rinsho. 2012;p533-8). In patients who underwent hematopoietic stem cell transplantation, decrease in accumulated GAG levels and reduction of clinical symptoms such as hepatosplenomegaly, joint contracture, respiratory symptoms have been observed. If successfully engrafted, the effect lasts for a long time; however, there are disadvantages including the following: high risks are associated with the treatment per se; a human leukocyte antigen-matched donor is needed; and improvement in CNS symptoms tends to depend on the patient's age at the time of transplantation and severity. Therefore, there is a need to establish an effective treatment for the improvement of CNS symptoms in patients with MPS II.

Pabinafusp alfa, which is a novel enzyme product administered as an intravenous infusion, is expected to cross the blood-brain barrier, suppressing the progression of not only systemic symptoms but also CNS symptoms, thereby improving these symptoms. HS concentrations in CSF before and after administration of pabinafusp alfa were measured in the clinical studies in patients with MPS II. HS concentrations in CSF decreased in all subjects at Week 3 in Study 101 and at Week 52 in Study 301. As for CNS symptoms in Study 301, age equivalent scores according to the KSPD tended to remain at the same level or improve from baseline at Week 52. The above findings suggest that pabinafusp alfa has extensive efficacy in treating a broad spectrum of CNS symptoms exhibited by patients with MPS II. The applicant also considers that the efficacy of pabinafusp alfa in treating systemic symptoms is similar to that of the currently available enzyme therapy. The results of the clinical studies indicate that the safety profile of pabinafusp alfa does not appear to differ markedly from that

of the currently available enzyme therapy. For these reasons, the applicant considered that the appropriate indication of pabinafusp alfa is "mucopolysaccharidosis type II." However, because of only limited experience with long-term use of pabinafusp alfa, its long-term efficacy and safety are yet to be known. While continuous treatment with pabinafusp alfa is expected to reduce the accumulation of substrates in the body to below a specific level, thereby maintaining the effect of treating symptoms, long-term efficacy and safety should be continuously evaluated.

PMDA's view:
Although it may be difficult to strictly evaluate the efficacy of pabinafusp alfa on the basis of data from Study 301, it can be surmised, based on the clinical study data, that pabinafusp alfa should have a certain level of efficacy in the treatment of both CNS symptoms and systemic symptoms, and its safety is acceptable [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"]. Since there are no currently available intravenous drugs that are able to improve both systemic and CNS symptoms in patients with MPS II, it is meaningful to provide access to pabinafusp alfa as a new treatment option for patients with MPS II. The proposed indication of pabinafusp alfa ("mucopolysaccharidosis type II") is acceptable. Whether it is necessary to provide a cautionary statement in the package insert to the effect that pabinafusp alfa should be considered for patients who may also require treatment of their CNS symptoms will be finalized taking into account the comments from the Expert Discussion.

7.R.4 Dosage and administration

The applicant's explanation:
A non-clinical study was conducted to determine the dosage regimen of pabinafusp alfa. The results of the non-clinical study in mouse models of MPS II demonstrated that pabinafusp alfa at 1.0 mg/kg/week and 2.0 mg/kg/week has efficacy in treating systemic symptoms to a similar extent to that achieved by idursulfase at 0.5 mg/kg/week, suggesting that pabinafusp alfa also has efficacy in reducing CNS symptoms. Accordingly, Study 101 assessed 1.0 mg/kg/week and 2.0 mg/kg/week. CSF samples were collected at baseline (pre-dose) and 4 to 6 hours post-dose at Week 3. HS concentrations in CSF decreased in all subjects in both groups, suggesting that the efficacy of pabinafusp alfa in the treatment of systemic symptoms did not differ significantly from that of the currently available enzyme therapy. However, HS concentrations in CSF tended to decrease to a greater extent in the 2.0 mg/kg/week group than in the 1.0 mg/kg/week group. In addition, HS and DS concentrations in serum and in urine tended to change in a stable manner. Safety data show that the incidence of adverse events and adverse drug reactions did not differ significantly between the two treatment groups. Based on the above results, 2.0 mg/kg/week was selected for the dosage regimen used in Study 301. The results of Study 301 showed that HS concentrations in CSF decreased in all subjects. In patients with severe MPS II, HS concentrations in CSF were maintained at <4000 ng/mL, which was defined as a boundary between the severe and attenuated forms of MPS II. The results of the developmental assessments also showed an overall trend towards increase in or maintenance of age equivalent scores. The study data demonstrated that the efficacy of pabinafusp alfa in the treatment of systemic symptoms did not differ significantly from that of the currently available enzyme therapy. In Study BR21, a foreign phase II study, the pabinafusp alfa 4.0 mg/kg group was established in addition to the 1.0 mg/kg and 2.0 mg/kg groups. Change from baseline in HS

concentrations in CSF (mean ± SD) at Week 25 was −1031.67 ± 1707.94 ng/mL at 1.0 mg/kg (n = 8), −3287.50 ± 1567.75 ng/mL at 2.0 mg/kg (n = 5), and −1409.17 ± 1173.64 ng/mL at 4.0 mg/kg (n = 6). Table 30 shows the incidence of adverse events. Although there is no marked difference among the treatment groups, the incidence of adverse drug reactions was higher in the 4.0 mg/kg group than in other groups: 50.0% (4 of 8 subjects) in the 1.0 mg/kg group, 20.0% (1 of 5 subjects) in the 2.0 mg/kg group, and 85.7% (6 of 7 subjects) in the 4.0 mg/kg group.

Based on the above, it was determined that the recommended clinical dose for pabinafusp alfa is 2.0 mg/kg/week.

PMDA's view:
Based on the efficacy and safety results of pabinafusp alfa in the clinical study data submitted [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"], the dosage and administration of pabinafusp alfa can be specified as 2.0 mg/kg once weekly as an intravenous infusion, the same as that employed in Study 301.

7.R.5 Post-marketing investigations

The applicant's explanation:
Due to the extremely limited number of patients treated with pabinafusp alfa, the applicant plans to conduct post-marketing clinical studies (Studies 302 and 401) and a use-results survey to evaluate the long-term efficacy and safety pabinafusp alfa, including efficacy in the treatment of CNS symptoms. The ongoing Study 302 (the extension study of Study 301, which was designed to allow the participants of Study 301 to receive long-term treatment with pabinafusp alfa before marketing approval) will be reclassified from an "extension study" to a "post-marketing clinical study. Study 401 will be conducted in patients in whom treatment with pabinafusp alfa will be initiated. In both studies, the observation period is from the enrollment to the completion of the study (for a maximum of 9 years) for each patient, and the registration period for Study 401 is 8 years. Efficacy evaluations will include developmental assessments including assessment using the Kyoto Scale of Psychological Development 2001, HS and DS concentrations in CSF and in serum, liver and spleen volumes, and 6-minute walk test distance. Safety evaluations will include adverse events, antibody testing, and IARs. All the patients not enrolled in the post-marketing clinical studies will be enrolled in the use-results survey for evaluation. The observation period is from the enrollment to the end of the survey period (for a maximum of 9 years) for each patient, with a registration period of 8 years. Safety evaluation will include adverse events and antibody testing, while efficacy evaluation will include developmental data or physicians' assessment, HS and DS concentrations in serum, liver volume, spleen volume, and 6-minute walk test distance. If patients in whom pabinafusp alfa treatment is initiated does not give their consent to participate in the post-marketing clinical study (Study 401), are considered to be ineligible for enrollment into the post-marketing clinical study by the investigator of the study based on the inclusion and exclusion criteria, or are not able to participate in the study due to the system of the medical institution or other reasons, then such patients will be registered in the use-results survey. However, the applicant will take measures to ensure that as many patients as possible can be enrolled in the post-marketing clinical study (Study 401), for instance, by seeking for the cooperation of the medical experts and candidate investigators of the post-marketing clinical study.

PMDA's view:

Due to the extremely limited number of patients treated with pabinafusp alfa, data on developmental assessment for patients receiving long-term treatment with pabinafusp alfa, in particular, are insufficient. The applicant, therefore, should continue to evaluate the efficacy and safety of pabinafusp alfa by collecting data over a prolonged period from as many patients as possible in the post-marketing setting. When gathering post-marketing data, developmental assessments may vary greatly depending on evaluators; therefore, the applicant plans to conduct post-marketing clinical studies to ensure that assessment is performed at a certain level. On the other hand, it is infeasible to conduct a post-marketing clinical study involving all patients who will be receiving pabinafusp alfa at sites where a certain level of assessment can be performed. Therefore, the applicant plans to conduct the use-results survey in addition to the post-marketing clinical studies to cover all the patients who will not be enrolled in the studies. The applicant's plan is understandable. However, since age equivalent will be assessed primarily based on the KSPD or similar tests in the post-marketing clinical studies (Studies 302 and 401), it is important to enroll patients who will be treated with pabinafusp alfa in the post-marketing clinical studies in so far as possible, rather than in the use-results survey. The duration of the post-marketing clinical studies and the use-results survey, the observation period, and endpoints of the studies are generally appropriate. The details of post-marketing surveillance will be finalized taking into account the comments from 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 new drug application data were subjected to a document-based compliance 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.

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

The new drug application data (CTD 5.3.5.2-2) 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.

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

On the basis of the data submitted, PMDA has concluded that pabinafusp alfa (Izcargo) has a certain level of efficacy in the treatment of MPS II, and that pabinafusp alfa has acceptable safety in view of its benefits. Pabinafusp alfa is an intravenous enzyme replacement therapy and is expected to be effective in the treatment of CNS symptoms and systemic symptoms in patients with MPS II. Pabinafusp alfa is clinically meaningful because it offers a new treatment option for patients with MPS II.

PMDA has concluded that Izcargo may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 9, 2021

Product Submitted for Approval

Brand Name	Izcargo for I.V. Infusion 10 mg
Non-proprietary Name	Pabinafusp Alfa (Genetical Recombination)
Applicant	JCR Pharmaceuticals Co., Ltd.
Date of Application	September 29, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by 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

PMDA's view:

Study 301 was conducted as an open-label uncontrolled study taking into account that there were no approved agents that show promising efficacy in treating CNS symptoms in patients with MPS II. In Study 301 which evaluated efficacy based on HS concentrations in CSF, while HS concentrations in CSF decreased after treatment with pabinafusp alfa, the results did not provide sufficient evidence for a clear improvement of CNS symptoms. However, CNS symptoms are thought to develop as a result of years of accumulation of GAGs; in addition, the effects of education and other factors during the developmental stage of the patients on the development of such symptoms should be taken into consideration. Therefore, developmental assessments require prolonged investigation. Given that MPS II is a rare disease in addition to the factors mentioned above, it can be surmised, based on the currently available results from Study 301, that pabinafusp alfa should have a certain level of efficacy in patients with MPS II presenting with CNS symptoms. Early intervention and continuation of treatment including pharmacotherapies are considered vital for the treatment of CNS symptoms in patients with MPS II. Since there were limitations in the evaluation of CNS symptoms in Study 301, efficacy data such as developmental assessments in patients receiving pabinafusp alfa should be collected in the post-marketing setting to continue evaluation of CNS symptoms. Regarding efficacy for systemic symptoms, the results of Study 301 showed a trend towards decreases in HS and DS concentrations in serum and decreases in liver and spleen volumes in subjects with no prior idursulfase treatment. In subjects with prior idursulfase treatment, these parameters tended to remain at the same levels as baseline. The findings could support the efficacy of pabinafusp alfa in the treatment of systemic symptoms, and the degree of the therapeutic effect is

unlikely to differ greatly from that of the currently available enzyme therapy.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

Most of the adverse events reported in the clinical studies are either events attributable to the pathology of MPS II or events that have also been reported during currently available enzyme therapy. Based on the results of individual analyses on IARs and antibody production, which are events of special interest, PMDA concluded that pabinafusp alfa has acceptable safety provided that appropriate measures are taken including provision of cautionary statements regarding safety.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indication

PMDA's view:

While it may be difficult to strictly evaluate the efficacy of pabinafusp alfa on the basis of data from Study 301, it can be surmised, based on the clinical study data, that pabinafusp alfa should have a certain level of efficacy in the treatment of both CNS symptoms and systemic symptoms, and safety is acceptable. Since there are no currently available intravenous drug products that are able to improve both systemic and CNS symptoms in patients with MPS II, it is meaningful to provide access to pabinafusp alfa as a new treatment option for patients with MPS II.

The indication of pabinafusp alfa may be specified as "mucopolysaccharidosis type II," as it is for other drugs in the same class. Discussion was made on whether or not it is necessary to provide a cautionary statement in the "Precautions for Indication" section in the package insert to the effect that pabinafusp alfa should be considered for patients whose CNS symptoms need improvement. Study 301 enrolled subjects including those classified as having the attenuated form, a category comprising patients with no or mild CNS symptoms, and there were no data suggestive of safety or efficacy concerns in these subjects. On the other hand, treatment with pabinafusp alfa may be unnecessary in some patients with MPS II from a medical standpoint. Taking into consideration how physicians select either pabinafusp alfa or idursulfase (genetical recombination), the package insert should include the cautionary statement mentioned above. In addition, patients eligible for pabinafusp alfa treatment are not necessarily limited to those who present with CNS symptoms. Whenever treatment of CNS symptoms is judged to be necessary based on the genotype or other information, it is appropriate to start treatment with pabinafusp alfa at an early stage.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above, and the expert advisors made the following comments:

- The package insert should include the cautionary statement to the effect that the use of pabinafusp alfa should be considered for patients whose CNS symptoms need to be treated. This is based on the following: The use of pabinafusp alfa is likely to be limited to medical institutions where there are physicians with

specialized knowledge in the diagnosis and treatment of MPS, and eligible patients can be appropriately identified based on their clinical presentation, enzyme activity and other laboratory findings, as well as genotype analysis at such medical institutions. Therefore, such physicians are unlikely to consider that pabinafusp alfa cannot be administered to patients in the stages when CNS symptoms are yet to manifest. In addition, the cautionary advice mentioned above may help reduce the excessive use of pabinafusp alfa in patients who do not need treatment with pabinafusp alfa from a medical standpoint.

- When the cautionary statement mentioned above is provided, avoid any expression that may mislead physicians into believing that pabinafusp alfa cannot be administered to patients who do not present with CNS symptoms. It is desirable to use expressions making it clear that patients including those who are likely to present with CNS symptoms or undergo progression are also eligible for treatment with pabinafusp alfa.

Based on the above discussion, PMDA asked the applicant to specify the "Precautions for Indication" section. The applicant proposed the cautionary statement shown below to avoid misunderstanding in the process of determining the eligibility of patients, and PMDA accepted the applicant's proposal.

Precautions for Indication

Pabinafusp alfa should be administered to patients in whom improvement of CNS symptoms or suppression of progression of such symptoms is considered necessary.

1.4 Dosage and administration

In Study 101, HS concentrations in CSF tended to decrease to a greater extent at 2.0 mg/kg than at 1.0 mg/kg. In addition, HS and DS concentrations in serum and in urine tended to change in a stable manner. In Study BR21, no data show that the benefit of the 4.0 mg/kg regimen was greater than that of the 2.0 mg/kg regimen. Based on these findings, the dosage and administration for pabinafusp alfa can be specified as 2.0 mg/kg as an intravenous infusion once weekly, the same as the regimen employed in Study 301.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.5 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion as set out in Section "7.R.5 Post-marketing investigations" in Review Report (1). PMDA has concluded that the risk management plan (draft) for pabinafusp alfa should include the safety and efficacy specifications presented in Table 37, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 38 through 41.

Table 37. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypersensitivity-related events (including anaphylaxis)	• Effects of antibody production	• Long-term safety
Efficacy specification		
• Long-term efficacy		

Table 38. 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 • Post-marketing clinical study (Study JR-141-302)[a)] • Post-marketing clinical study (Study JR-141-401) • General use-results survey (all-case surveillance)	• Post-marketing clinical study (Study JR-141-302)[a)] • Post-marketing clinical study (Study JR-141-401) • General use-results survey (all-case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance

a) Ongoing Study 302 will be reclassified as a post-marketing clinical study after the approval of pabinafusp alfa

Table 39. Outline of post-marketing clinical study (Study JR-141-302) (draft)

Objective	To assess long-term efficacy and safety of pabinafusp alfa
Study design	Open-label uncontrolled study
Population	Patients with MPS II
Observation period	From the start of treatment to the end of the study period (maximum of 9 years)
Planned sample size	Not specified (patients who completed Study 301)
Main survey items	Patient characteristics, status of treatment with pabinafusp alfa, HS and DS concentrations in CSF, developmental assessments (e.g., Kyoto Scale of Psychological Development 2001), HS and DS concentrations in serum, liver and spleen volumes, adverse events, ADAs

Table 40. Outline of post-marketing clinical study (Study JR-141-401) (draft)

Objective	To assess long-term efficacy and safety of pabinafusp alfa
Study design	Open-label uncontrolled study
Population	Patients with MPS II
Observation period	From the start of treatment to the end of the study period (maximum of 9 years)
Planned sample size	Not specified (patients who start treatment with pabinafusp alfa)
Main survey items	Patient characteristics, status of treatment with pabinafusp alfa, HS and DS concentrations in CSF, developmental assessments (e.g., Kyoto Scale of Psychological Development 2001), HS and DS concentrations in serum, liver and spleen volumes, adverse events, ADAs

Table 41. Outline of general use-results survey (draft)

Objective	To assess safety and efficacy of pabinafusp alfa in clinical use
Survey method	All-case surveillance (excluding participants of post-marketing clinical study)
Population	Patients with MPS II
Observation period	From the start of treatment to the end of the survey period (maximum of 9 years)
Planned sample size	All patients who receive pabinafusp alfa except for those enrolled in Study 302 or 401
Main survey items	Patient characteristics, treatment status with pabinafusp alfa, developmental assessments (e.g., Kyoto Scale of Psychological Development 2001), HS and DS concentrations in serum, liver and spleen volumes, adverse events, ADAs

2. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Since pabinafusp alfa is designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. The drug substance and drug product are both classified as powerful drugs.

Indication

Mucopolysaccharidosis type II

Dosage and Administration

The usual dosage is 2.0 mg of pabinafusp alfa (genetical recombination) per 1 kg of body weight once weekly as an intravenous infusion.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of patients evaluated in Japanese clinical studies, the applicant is required to conduct post-marketing clinical studies or a use-results survey covering all patients treated with the product during the re-examination period in order to keep track of information on patient characteristics and to collect data on the safety and efficacy of the product as early as possible.
3. The applicant is required to submit, on a regular basis, data and analysis results from the clinical studies and the use-results survey which are conducted to verify the efficacy and safety of the product.
4. The applicant is required to take necessary measures to ensure the proper use of the product, based on the results of an additional evaluation of the efficacy and safety of the product.

Appendix

List of Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AUC	Area under the plasma concentration-time curve
CAL	Cells at the limit of *in vitro* cell age used for production
CDC	Complement-dependent cytotoxicity
CSF	Cerebrospinal fluid
CL	Clearance
C_{max}	Maximum plasma concentration
DNA	Deoxyribonucleic acid
DQ	Developmental quotient
DS	Dermatan sulfate
EC_{50}	Half maximal effective concentration
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FcRn	Neonatal Fc receptor
FOB	Functional observational battery
GAG	Glycosaminoglycan
HCP	Host cell protein
[redacted]	[redacted]
hIDS	Human iduronate-2-sulfatase
hIgG1	Human immunoglobulin G1
HS	Heparan sulfate
hTf	Human transferrin
hTfR	Human transferrin receptor 1
hTfR KI/Ids KO mouse	Human transferrin receptor 1 gene knock in/iduronate-2-sulfatase gene knock out mouse
IAR	Infusion-associated reaction
ICH Q5A (R1) Guidelines	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B Guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D Guidelines	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
IDS	Iduronate-2-sulfatase
Izcargo	Izcargo for I.V. infusion 10 mg
K_D	Dissociation constant
K_m	Michaelis-Menten constant
MCB	Master cell bank
MedDRA	Medical dictionary for regulatory activities
mITT	Modified intention to treat
MPS	Mucopolysaccharidosis
M6P	Mannose-6-phosphate
M6PR	Cation-independent mannose-6-phosphate receptor
pAb	polyclonal antibody
Pabinafusp alfa	Pabinafusp Alfa (Genetical Recombination)

PMDA	Pharmaceuticals and Medical Devices Agency
[redacted]	[redacted]
RP-HPLC	Reverse phase high performance liquid chromatography
[redacted]	[redacted]
SE-HPLC	Size exclusion high performance liquid chromatography
SPR	Surface plasmon resonance
TfR	Transferrin receptor 1
t_{max}	Time taken to reach the maximum plasma concentration
$t_{1/2}$	Elimination half-life at terminal phase
UV-Vis	Ultra violet-visible spectrophotometry
V_{max}	Maximum reaction velocity
WCB	Working cell bank