Report on the Deliberation Results

November 21, 2018
Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Classification	Human cell product 2. Human-derived somatic stem cell product
Nonproprietary Name	Human (autologous) bone marrow-derived mesenchymal stem cells
Brand Name	Stemirac for Injection
Applicant	Nipro Corporation
Date of Application	June 29, 2018 (Application for marketing approval)

Results of Deliberation

In its meeting held on November 21, 2018, the Committee on Regenerative Medicine Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The Committee's decision:

The product may be approved within the framework of conditional and time-limited approval. The following conditions and time-limit should apply.

Conditions of Approval

1. The product should be used only for patients considered eligible for the treatment and only under the supervision of a specialist with sufficient knowledge and experience in diagnosis and treatment of spinal cord injury at medical institutions fully capable of emergency care where patients are appropriately monitored and managed by vital sign check and laboratory test, etc.
2. The applicant is required to conduct an approval condition-based post-marketing evaluation in all patients treated with the product during the period after the conditional and time-limited approval until reapplication for marketing approval.

Time Limit of the Approval

7 years

Review Report

November 12, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Stemirac for Injection
Classification	Human cell product 2. Human-derived somatic stem cell product
Nonproprietary Name	Human (autologous) bone marrow-derived mesenchymal stem cells
Applicant	Nipro Corporation
Date of Application	June 29, 2018

Shape, structure, ingredients, quantities, or definition

The product is a regenerative medicine product. Its primary constituent part is mesenchymal stem cells (MSCs). MSCs are isolated from the patient's bone marrow fluid, cultured *in vitro*, and cryopreserved in a bag. The secondary constituent part of the product comprises a blood collection kit and a bone marrow collection kit to be used at a medical institution for the collection and transportation of the patient's peripheral blood and bone marrow fluid.

Application classification (1-1) New regenerative medical product

Items Warranting Special Mention

SAKIGAKE designation regenerative medical product (SAKIGAKE Regenerative Medical Product Designation No. 1 of 2015 [*27 sai*]; PSEHB/PED Notification No. 0210-4 dated February 10, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare); the product underwent SAKIGAKE comprehensive evaluation consultation for regenerative medical products.

Reviewing Office Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product is expected to have a certain level of efficacy in the treatment of neurological symptoms and functional disorders associated with spinal cord injury, and that the product has acceptable safety (see Attachment). Given the only limited data available at present, the efficacy of the product must be verified by further evaluation after the marketing approval.

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following conditions. The approval should be conditional and time-limited in accordance with Article 23-26 of "the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics."

Indication or Performance

Improvement of neurological symptoms and functional disorders associated with spinal cord injury only in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C

Dosage and Administration or Method of Use

Bone marrow aspiration should be aimed to be performed within 31 days after spinal cord injury, according to the systemic condition, etc. of the patient. Once produced, the product should be administered at the earliest time possible.

Procedures for the collection of source materials of Stemirac

(1) Patient's peripheral blood is collected. The collected peripheral blood is put into a container (Nipro Celltry for serum) enclosed in the blood collection kit. After being tightly sealed, the container holding peripheral blood is transported to a facility designated by the marketing authorization holder.

(2) Patient's bone marrow fluid is collected. The collected bone marrow fluid is put into a container (Nipro Celltry for bone marrow), and the bone marrow fluid diluent DMEM, enclosed in the bone marrow collection kit, is added to be mixed. After being tightly sealed, the container holding bone marrow fluid is transported to a facility designated by the marketing authorization holder.

Procedures for the administration of Stemirac to the patient

The product is administered by intravenous drip infusion at a rate of 0.7 to 1.0 mL/min, as 0.5×10^8 to 2.0×10^8 autologous bone marrow-derived MSCs (maximum dose, 3.34×10^6 cells per kg body weight) while being diluted ≥3-fold with physiological saline.

Conditions of Approval

1. The product should be used only for patients considered eligible for the treatment and only under the

supervision of a specialist with sufficient knowledge and experience in diagnosis and treatment of spinal cord injury, at medical institutions fully capable of emergency care where patients are appropriately monitored and managed by vital sign check and laboratory test, etc.

2. The applicant is required to conduct an approval condition-based post-marketing evaluation in all patients treated with the product during the period after the conditional and time-limited approval until reapplication for marketing approval.

Attachment

Review Report (1)

September 20, 2018

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.

Product Submitted for Approval

Brand Name	Stemirac for Injection
Classification	Human cell product 2. Human-derived somatic stem cell product
Nonproprietary Name	Human (autologous) bone marrow-derived mesenchymal stem cells
Applicant	Nipro Corporation
Date of Application	June 29, 2018

Shape, Structure, Ingredients, Quantities, or Definition

The product is a regeneration medical product. Its primary constituent part is mesenchymal stem cells (MSCs). MSCs are isolated from the patient's bone marrow fluid, cultured *in vitro*, and cryopreserved in a bag. The secondary constituent part of the product comprises a blood collection kit and a bone marrow collection kit to be used at a medical institution for the collection and transportation of the patient's peripheral blood and bone marrow fluid.

Proposed Indication or Performance

Improvement of neurological symptoms and functional disorders associated with spinal cord dysfunction

Proposed Dosage and Administration or Method of Use

Bone marrow aspiration should be aimed to be performed within 31 days after spinal cord injury, according to the systemic condition, etc. of the patient. Once produced, the product should be administered at the earliest time possible.

Procedures prior to the production of Stemirac

(1) Patient's bone marrow fluid is collected. The collected bone marrow fluid is put into a container (Nipro Celltry for bone marrow), and the bone marrow fluid diluent DMEM, enclosed in the bone marrow collection kit, is added to be mixed. After being tightly sealed, the container holding bone marrow fluid is transported to a facility designated by the marketing authorization holder.

(2) Patient's peripheral blood is collected. The collected peripheral blood is put into a container (Nipro Celltry for serum) enclosed in the blood collection kit. After being sealed, the container holding peripheral blood is transported to a facility designated by the marketing authorization holder.

Procedures for the administration of Stemirac to the patient

The product is administered by intravenous drip infusion as 0.5×10^8 to 2.0×10^8 autologous bone marrow-derived MSCs (maximum dose, 3.34×10^6 cells per kg body weight) while being diluted ≥3-fold with physiological saline.

Table of Contents

List of Abbreviations

See appendix.

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

1.1 Outline of the product submitted

Stemirac is a human somatic stem cell product. Its (1) primary constituent part is cryopreserved cells developed from MSCs present in bone marrow fluid, which is collected from the patient. MSCs are cultured for growth *in vitro*, suspended in cryopreservation fluid containing patient's own serum, and cryopreserved. The (2) secondary constituent part of the product comprises (i) a blood collection kit for the collection of patient's peripheral blood and (ii) a bone marrow collection kit for the collection of patient's bone marrow fluid, both of which are also used for the transportation of collected materials to a designated facility for the production of Stemirac.

The product is indicated for spinal cord injury. In most cases, spinal cord injury is intractable and causes serious and persistent dysfunction, affecting regions controlled by the spinal cord below the level of injury site. Injury of the upper cervical spinal cord may lead to respiratory disorder or quadriplegia (*Orthopedic knowledge update Spine.* American Academy of orthopaedic surgeons; 2012.187-95). In Japan, there are ≥100,000 patients with spinal cord injury, including approximately 5000 new patients per year. The major causes of the injury are traffic accident, fall from a height, and sports injury *(Orthopedic knowledge update Spine.* American Academy of orthopaedic surgeons; 2012.187-95, *Nihon Sekizuishogai Igakkai Zasshi [The journal of the Japan Medical Society of Spinal Cord Lesion]*. 2005;18:271-274). In Japan, age distribution of patients with spinal cord injury is characterized by bimodal peaks in young generation and in the elderly (*Nihon Sekizuishogai Igakkai Zasshi [The journal of the Japan Medical Society of Spinal Cord Lesion]*. 2005;18:71-274).

The constituent cells of the product have been confirmed to have the capacity for migration, neurotrophic factor secretion, immunomodulation, and differentiation. After being administered, the cells accumulate at the injury site, where they exhibit nerve-protecting effect mediated by neurotrophic factors, etc. and improve neurological symptoms associated with spinal cord injury by multiple mechanisms including immunomodulation, differentiation into nerve cells, etc. As with pharmaceutical products, Stemirac is expected to exhibit therapeutic effects by its pharmacological mechanism. The product is administered by intravenous drip infusion.

Stemirac was designated as a breakthrough product under the SAKIGAKE Designation System for regenerative medicinal products on February 10, 2016, for the planned indication or performance of "improvement of neurological symptoms and functional disorders associated with spinal cord injury," according to "Experimental implementation of the SAKIGAKE Designation System for medical devices, *in vitro* diagnostics, and regenerative medical products" (PFSB/ELD/OMDE Notification No. 0701-1 dated July 1, 2015, issued by the Counsellor of the Minister's Secretariat, the Ministry of Health, Labour and Welfare (Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products) (SAKIGAKE Regenerative Medical Product Designation No. 1 of 2015 [*27, sai*]).

1.2 History of development

Spinal cord injury is classified into (i) primary injury directly caused by external force such as tissue crush injury, bleeding, or axonotmesis and (ii) secondary injury that progresses over several months after injury, such as ischemia, inflammation, and delayed neuronal cell death. In the treatment of spinal cord injury, the prevention of progression of these secondary injury and the preservation of remaining functions are critical.

The current standard treatments for spinal cord injury are surgical treatments such as reduction, decompression, fixation, etc. of the spine during the acute phase and rehabilitation (*Handb Clin Neurol. 2012*;109:105-130). As a drug therapy, sodium methylprednisolone succinate is administered intravenously in bulk. However, its clinical benefit has not been fully recognized (*Orthopedic knowledge update Spine.* American Academy of orthopaedic surgeons; 2012.187-95). These treatments lead to little progress in neurological function with poor outcomes, and the demand for a new treatment option is growing.

In the past, injured central or cerebral nerves were thought to be unrestorable. However, since late 1970s, the transplantation of neural cells such as oligodendrocytes and Schwann cells induced the re-myelination in injured central nerves of demyelinated animals (e.g., *Ann N Y Acad Sci.* 1987;495:71-85, *Nature. 1977*;266: 68-9). The transplantation of neuronal stem cells into animals with spinal cord injury induced re-myelination and differentiation into nerve cells, leading to the recovery of neurological functions (*Exp Neurol.* 2001;167:27-39). These outcomes demonstrated the possibility that injured nerve tissues are regenerated by cell transplantation. Honmou et al. of Sapporo Medical University, the developers of Stemirac, reported that the transplantation of rat bone marrow-derived MSCs into the injury site of demyelinated rats induced the re-myelination of demyelinated nerve axons (*Glia.* 2001;35:26-34). The intravenous administration of MSCs to rats with spinal cord injury caused MSC accumulation to the injury site, suppression of spinal cord tissue necrosis, neurotrophic factor secretion, and differentiation to neural cells, resulting in significant recovery of motor function (*Brain Res.* 2010;1343:226-35). In 2006, Honmou et al. began a clinical research to investigate the effect of intravenous administration of autologous bone marrow-derived MSCs to patients with cerebral infarction during the subacute phase (*Brain.* 2011;134:1790-1807). Then, an investigator-initiated clinical study in patients with cerebral infarction and another investigator-initiated phase II study (Study STR01-03) in patients with spinal cord injury began at Sapporo Medical University. Study STR01-03 suggested the efficacy of the product with an acceptable safety profile. The applicant introduced the technology related to the product from Sapporo Medical University, and filed the current application for marketing approval of the regenerative medicine product based on the results of Study STR 01-03.

2 Manufacturing Method and Specifications and Outline of the Review Conducted by PMDA

The primary constituent part is MSCs collected from the bone marrow fluid of the patient, grown in adhesive dishes, suspended in cryopreservation fluid, and filled in a cryopreservation bag to be stored frozen. The cell culture medium and the cryopreservation fluid used in these processes contain patient's own serum.

The secondary constituent part comprises a blood collection kit and a bone marrow collection kit used for the collection of patient's peripheral blood and bone marrow fluid from the patient, both of which are also used for transportation of collected materials to a designated facility for the production of Stemirac. Each of the blood collection kit and the bone marrow collection kit contains a sterilized container (medical device Nipro Celltry). In addition, the bone marrow collection kit includes DMEM for bone marrow dilution.

2.1 Manufacturing procedures

2.1.1 Manufacturing process

The manufacturing process of Stemirac involves the production of (i) the suspension of autologous bone marrow MSCs, the primary constituent part, and (ii) the secondary constituent part of the product.

2.1.1.1 Manufacturing method of the primary constituent part

The manufacturing processes of the autologous bone marrow MSC suspension are acceptance of patient's peripheral blood, serum separation, preparation of [redacted], acceptance of patient's bone marrow fluid, [redacted], filling, capping, freezing, testing, packaging/labeling, and storage. [redacted] were identified as the critical processes.

2.1.1.2 Manufacturing process of secondary constituent part

The manufacturing processes of the blood collection kit are acceptance of the components, packaging/labeling/storage, and testing. The bone marrow collection kit, the other secondary constituent part, manufactured through the production of DMEM for bone marrow dilution (reconstitution, sterile filtration, filling, test for foreign matters in the solution, labeling/packaging, inspection/storage), acceptance, packaging/labeling/storage, and testing.

2.1.2 In-process control test

Table 1 shows the in-process control tests during the production of the autologous bone marrow MSC suspension, the primary constituent part. The patient's peripheral blood is the source material of serum, which is to be contained in the cell culture medium for the production of the primary constituent part and in the cryopreservation fluid. Peripheral blood is collected from the patient for multiple times, and the maximum volume for each collection is 400 mL. A total of approximately 1000 mL of the peripheral blood is collected. A total of 20 to 50 mL of the patient's bone marrow fluid, the source material of the product, is collected from the iliac bone of the patient. The collected peripheral blood and bone marrow fluid are put in the respective kits for transportation to the designated production site.

[1)] To be conducted if the total cell count in the first passage is below the control limit.

Table 1. In-process control tests of autologous bone marrow mesenchymal stem cell suspension

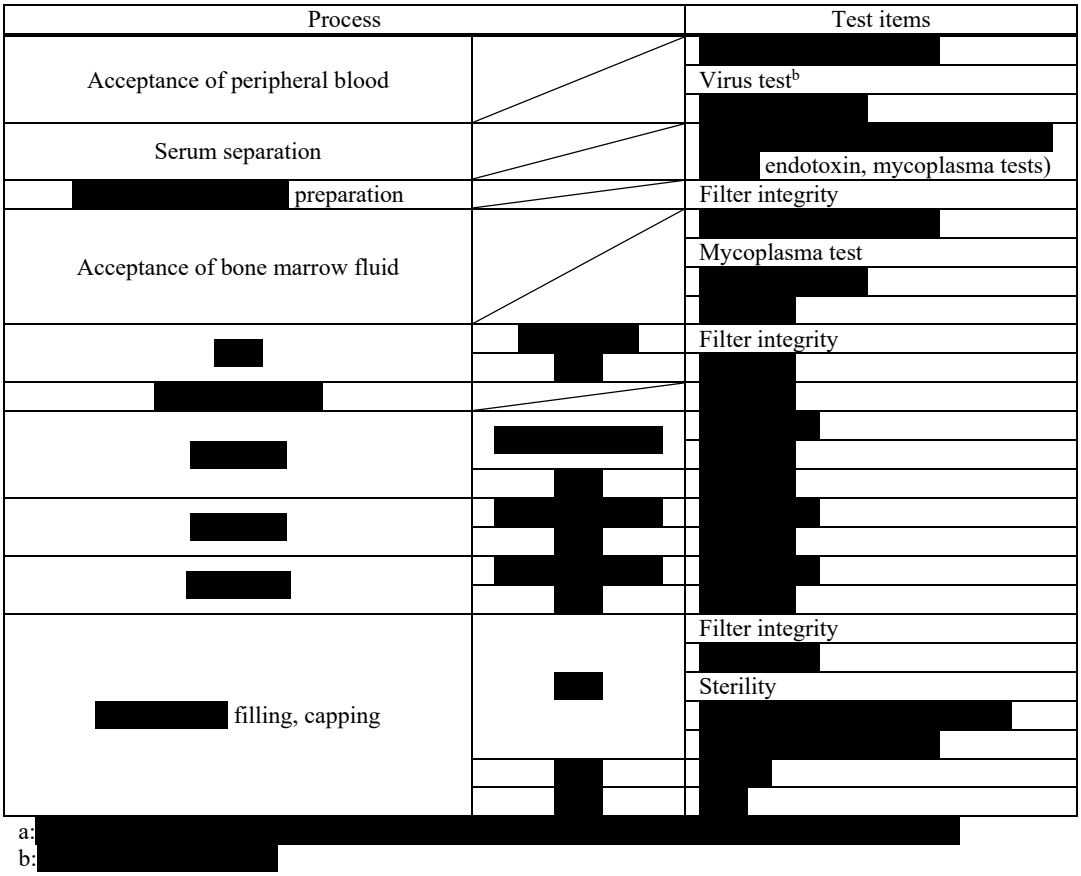

Table 2 shows the in-process control tests in the manufacturing process of bone marrow diluent DMEM enclosed in the bone marrow collection kit, a secondary constituent part.

Table 2 In-process control tests of bone marrow collection kit (bone marrow diluent DMEM)

Process	Test item
Sterile filtration	Filter integrity
Filling	

2.2 Safety evaluation of adventitious infectious agents

2.2.1 Peripheral blood and bone marrow fluid

The acceptance of patient's peripheral blood and the bone marrow fluid depends on the record of history-taking at the medical institution and serological test or nucleic acid-amplification test for viruses, etc. (HBV, HCV, HIV-1, HIV-2, HTLV-1, parvovirus B19, and *Treponema pallidum*). Mycoplasma testing is performed at the production site. All source substances conform to the Standard for Biological-Materials (Notification No. 210 issued by the Ministry of Health, Labour and Welfare, dated May 20, 2003).

2.2.2 Biological materials other than peripheral blood and bone marrow fluid

Table 3 shows biological materials other than peripheral blood and bone marrow fluid of patients used in the production of the primary constituent part.

Table 3. Biological materials other than peripheral blood and bone marrow fluid of patients used in the manufacture of the primary constituent part

Source material		Animal	Site	Processes in which the material is used
Heparin sodium		Pig	Intestinal mucosa	[redacted]
Trypsin-EDTA solution	Trypsin	Pig	Pancreas	[redacted] filling, capping [redacted]
	Lactose	Cow	Milk	
	Trypsin Activator	Pig	Pancreas	

Heparin sodium used is a pharmaceutical product approved for marketing in Japan.

Trypsin powder is the source material of trypsin-EDTA solution and is derived from the spleen of healthy pigs. All biological materials conform to the Standard for Biological-Materials (Notification No. 210 issued in 2005 by the Ministry of Health, Labour and Welfare).

2.3 History of the manufacturing process development

Main changes made in the manufacturing methods during the development of the main construct are as follows.

- Method A to B: [redacted]
- Method B to C: [redacted]
- Method C to the proposed manufacturing method: [redacted], [redacted], [redacted], [redacted], [redacted]

Equivalency in quality attributes was evaluated before and after each change in the manufacturing method, which confirmed the quality equivalency and homogeneity of the primary constituent part throughout the manufacturing process development. The primary constituent part produced by Method B was used in the clinical study[2)] in 8 patients (STR0103-03, STR0103-04, STR0103-05, STR0103-06, STR0103-07, STR0103-09, STR0103-10, and STR0103-11) and the primary constituent part produced by Method C was used in the same clinical study in 5 patients (STR0103-12, STR0103-14, STR0103-15, STR0103-16, and STR0103-17) [see Section 7.1].

2.4 Characterization

Table 4 shows the characterization conducted on the primary constituent part [see Sections 4.1-4.4].

2) Study STR01-03

Table 4 Specification for characterization

Surface antigen	FCM (cell surface antigen phenotype)
Migration	FCM (expression of migration-related receptors and adhesion factors), migration assay, quantitative RT-PCR (gene expression of adhesion/ invasion-associated factors)
Secretion of neurotrophic factors, etc.	ELISA (expression of humoral factors), quantitative RT-PCR (gene expression of humoral factor)
Immunomodulation	ELISA and quantitative RT-PCR (expression of immunomodulatory factors), FCM (cell surface antigen phenotype)
Differentiation	Differentiation potencies of osteoblasts, adipocytes, chondrocytes, and neural cells

2.5 Evaluation of the manufacturing process

2.5.1 Removal of process-related impurities

The residual amount of process-related impurities was evaluated based on [redacted] in [redacted] process. Table 5 shows the estimated residual amounts in the final product of [redacted], and [redacted], components contained in the cell culture medium used in the manufacturing process. The residual amount of antibiotics (penicillin-streptomycin) in the final product for the clinical study was measured, and the following results were obtained: penicillin, [redacted] units[3)] (mean [redacted] units) and streptomycin [redacted] μg (mean [redacted] μg). In the proposed manufacturing method, antibiotics are added to the cell culture medium only [redacted] [see Section 2.3], the residual amount of the each component in the commercial product is therefore expected to be lower than that in the product for the clinical study. Because of the extremely low safety concerns of the residual amount of each impurity, no control parameters are set for process-related impurities.

Table 5. Estimated residual amount of process-related impurities

Process-related impurities, their types and components	Estimated residual amount (mg) in 40 mL study product
[redacted]	[redacted]

2.5.2 Verification

Variation factors in the manufacturing process of the primary constituent part have not been clearly identified at present. In order to ensure the intended quality of every product, a verification-based quality control strategy was established. The strategy comprises process parameters and the in-process control tests for the potential risks due to varying quality attributes of the peripheral blood and the bone marrow fluid, and the specifications and tests for the primary constituent part shown in Table 6. The characteristics required for the

[3)] Value calculated as [redacted]μg/unit

product include [redacted]

2.6 Control of the product

Tables 6 and 7 show the specification for the primary and secondary constituent parts, respectively.

No reference material is set for either constituent part.

Table 6. Specification for the primary constituent part

Test item		Testing method
Appearance, description		Visual inspection
[redacted]		[redacted]
[redacted]		[redacted]
Cell surface antigen analysis	[redacted]-positive	FCM
	[redacted]-positive	
	[redacted]-positive	
	[redacted]-negative	
	[redacted]-negative	
	[redacted]-positive	
	[redacted]-positive	
Sterility		Rapid test for microorganisms
Endotoxin test		Japanese Pharmacopoeia
Mycoplasma test		Japanese Pharmacopoeia

Table 7. Specification for the secondary constituent part

Second construct		Test item
Blood collecting kit		Appearance
Bone marrow collecting kit	Bone marrow diluent DMEM	Appearance
		Description
		[redacted]
		[redacted]
		Endotoxin
		Sterility
		[redacted]
		Volume collected
		Foreign insoluble matter
		Insoluble particulate matter
		[redacted]

2.R Outline of the review conducted by PMDA

Stemirac is produced from the patient's autologous peripheral blood and bone marrow fluid. Considering extremely limited production experience during the development phase and little knowledge about the manufacturing process in the present situation, the reduction of quality variation among products is a critical task in quality control. The applicant's verification plan includes quality risk assessment-based items which are necessary for controlling potential critical quality attributes related to clinical efficacy, i.e., cell surface antigen phenotype showing the characteristic feature of MSCs, the secretion of neurotrophic factors and immunomodulatory factors in response to inflammatory cytokines, and adhesion factors related to migratory capacity. This verification-based production control will help manage quality variation among products, and thus the proposed quality control strategy is acceptable. Data on the various quality attributes

of the product in post-marketing production should be collected, and critical quality attributes should be identified based on data on clinical benefit and safety.

3 Stability and Outline of the Review Conducted by PMDA

3.1 Stability of the primary constituent part

Table 8 shows the outline of the stability tests of the primary constituent part.

Table 8. Outline of the stability tests of the primary constituent part

	Number of batches	Storage condition	Testing period	Storage form
Long-term testing	3	-80 ± 5°C	3 months	Cell cryopreservation bag with polyethylene tubing
Stress test	1	[redacted]	[redacted]	

In the long-term testing and the stress test, no clear changes were observed in the quality attributes throughout the test period.

Accordingly, the shelf-life of the primary constituent part was determined as 3 months when stored in a cryopreservation bag with a polyethylene tube attached at ≤-80°C.

3.2 Stability of dosing suspension

The primary constituent part of Stemirac is thawed before dosing. The stability of the thawed dosing suspension was evaluated using [redacted] as the index. Table 9 shows the outline of the test.

Table 9. Outline of the stability test of the dosing suspension

Number of batches	Storage condition	Thawing condition	Evaluation time points	Storage form
3	30 ± 2°C	Rapid thawing in water bath at 37°C	0, 0.25, 0.5, 0.75, 1.0, and 2.0 hours	Cell cryopreservation bag with a polyethylene tube

[redacted] at 30 ± 2°C was ≥[redacted]% at 2 hours after thawing.

Accordingly, it was determined that the administration of the primary constituent part should be started immediately after thawing at 37°C and completed within 1 hour after thawing.

3.3 Stability of the secondary constituent part

Table 10 shows the outline of the stability tests of the bone marrow diluent DMEM contained in the bone marrow collection kit, a secondary constituent.

Table 10. Outline of the stability tests of secondary constituent part

	Number of batches	Storage condition	Test period	Storage condition
Long-term testing	3	5 ± 3°C	12 months	Syringe (polypropylene syringe barrel + butyl rubber gasket)
Accelerated testing	3	25°C/60% RH	6 months	

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

Accordingly, the shelf-life of a bone marrow collection kit was determined as 1 year when stored at 5 ± 3°C. The shelf-life of a blood collection kit was determined as 3 years when stored in a cool and dry place out of direct sunlight, in accordance with the shelf life of the sterilized container (medical device Nipro Celltry).

3.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA accepted the storage method and the shelf-lives of the primary and secondary constituent parts, and the results of the stability evaluation of the dosing suspension.

4 Indication or Performance and Outline of the Review Conducted by PMDA

Studies on the indication or performance were conducted using the test samples (referred to as "MSCs derived from patients" in this section) obtained, according to the manufacturing method, by cultivating surplus cells from those produced for the clinical study, unless specified otherwise.

4.1 Migratory capacity of cells (attached data 4-1)

4.1.1 Expression of chemokine receptors and growth factor receptors

The expression of chemokine receptors ([redacted] types) and growth factor receptors ([redacted] types) was investigated by flow cytometry (FCM). There were no chemokine receptors commonly expressed in MSCs derived from 3 patients. In contrast, growth factor receptors, i.e., EGFR, HGFR, NGFR, and Tie2 were expressed in MSCs derived from all 3 patients.

4.1.2 Migratory capacity toward chemokines and growth factors

Migratory capacity toward chemokines and growth factors was investigated by transwell migration assy. Using the culture medium with or without adding each chemokine ([redacted] types) or growth factor ([redacted] types), the relative migratory ratio was calculated from the number of cells that migrated through the membrane. The MSCs derived from 3 patients showed that the relative migratory ratio tended to increase in the presence of each of these chemokines and growth factors. Chemokine MCP-1 ([redacted] fold) and growth factor EGF ([redacted] fold) showed a particularly high migratory ratio.

4.1.3 Expression of adhesion factors and invasion-associated factors

Changes in the expressions of adhesion factor (*ITGA4* and *ITGB1*) genes and invasion-associated factor (*MMP1*, *MMP2*, *TIMP*1 and *TIMP2*) genes in MSCs in response to inflammatory cytokines ([redacted]) were investigated by real-time reverse transcription polymerase chain reaction (RT-PCR). In the MSCs derived from 3 patients, all of these factors were expressed without inflammatory cytokine stimulation. In contrast, [redacted] only *MMP1* ([redacted] fold, [redacted] fold, respectively) was expressed in response to inflammatory cytokine stimulation.

The expression of adhesion factors ([redacted] types) was investigated by FCM. A total of 7 types of adhesion factors (NCAD, CD44, NCAM, ALCAM, ITGAV, ITGA4, and ITGB1) were identified in MSCs derived from 3 patients.

4.2 Expression and secretion of humoral factors such as neurotrophic factors (attached data 4-2)

Gene expression and secretion of neurotrophic factors and other humoral factors ([redacted]) and their changes induced by inflammatory cytokine stimulation ([redacted]) were investigated using MSCs derived from 3 patients.

The investigation of gene expression by real-time RT-PCR showed the expression of all factors without stimulation, and inflammatory cytokine stimulation increased *NGF* expression ([redacted] fold and [redacted] fold, respectively) by [redacted].

The investigation by enzyme linked immunosorbent assay (ELISA) showed the secretion of proBDNF, matureBDNF, VEGF, PlGF, and HGF without stimulation, and inflammatory cytokine stimulation increased the secretion of [redacted], VEGF, and HGF.

4.3 Immunomodulatory activity (attached data 4-3)

4.3.1 Expression and secretion of immunomodulatory factors

Gene expression and secretion of immunomodulatory factors (*TSG-6*, *CX3CL1*, and *TGF-β1*) and their changes by inflammatory cytokine stimulation ([redacted]) were investigated using MSCs derived from 3 patients.

Immunomodulatory factor expression was investigated by real-time RT-PCR identified all genes expressed without stimulation, and inflammatory cytokine stimulation increased the expression of [redacted] TSG-6 and increased the expression of [redacted] CX3CL1. *TGF-β* level did not change in the presence of any stimulation.

Immunomodulatory factor secretion was investigated by ELISA. No TSG-6 secretion was observed in any conditions tested, including no stimulation. CX3CL1 secretion was not observed without stimulation, but markedly increased by[redacted]. TGF-β1 secretion was observed without stimulation and the secretion level did not change by inflammatory cytokine stimulation.

4.3.2 Suppressive macrophage induction

TSG-6, CX3CL1, and TGF-β1 secreted from MSCs are believed to induce the differentiation of phagocytes such as macrophages and microglia from activated form (M1) to suppressed form (M2), leading to the suppression of cell death (*Stem Cells.* 2012;30:044-53, *Neurobiol Dis.* 2013;58:249-57, etc.). The activity to

induce the differentiation of [redacted]-stimulated [redacted] cells from M1 (CD86-positive, CD163-negative) to M2 (CD86-negative, CD163-positive) was investigated by FCM. Co-culturing of MSCs derived from 3 patients and [redacted] cells resulted in decreased M1-form [redacted] cell count and increased M2-form [redacted] cell count.

4.4 Differentiation into nerve cells (attached data 4-4)

The capacity of MSCs to differentiate into nerve cells was investigated by real-time RT-PCR, immunostaining, and Nissl staining

MSCs derived from 3 patients were cultivated for 24 hours in a neurodifferentiation-inducing medium, and the expression of a nerve cell marker *MAP2* was investigated by real-time RT-PCR. The expression increased in all samples tested. The expression of markers of neural stem cells (SOX2 and nestin) and nerve cells (neurofilament) was investigated by immunostaining. SOX2 and nestin were expressed before the induction of neurodifferentiation, and neurofilament was expressed at 24 hours after the induction. MSCs were investigated for the presence of Nissl bodies, organelles specifically found in nerve cells, by Nissl staining. Nissl bodies were identified at 24 hours after the induction of neurodifferentiation.

MSCs obtained from 1 patient formed spheres. After 7-day cultivation in the neurodifferentiation induction medium, neurite-like processes were developing on the spheres. The expression of the markers of neuronal stem cells (nestin) and nerve cells (neurofilament) was investigated by immunostaining. Nestin-positive cells were identified in the spheres. The neurite-like cells on the spheres were nestin-negative and neurofilament-positive.

4.5 *In vivo* evaluation of the action mechanism of MScs

No *in vivo* studies were conducted on the action mechanism of the product. The applicant discussed the mechanism of action based on published literature on MSCs, and provided the following explanation.

4.5.1 Effect on motor function (reference data 4-A-1)

A single dose of rat MSCs was intravenously administered to a rat model of spinal cord injury (at 6 hours, 1, 3, 7, 10, 14, 21, or 28 days after spinal cord injury), and time-course change in the hind-limb motor function was evaluated up to 42 days after injury using Basso-Beattie-Bresnahan (BBB) score. Improved motor function was observed at all observation time points in the group receiving rat MSCs as compared with the vehicle group. The sooner the treatment was given after injury, the greater the motor function improved (*Brain Res.* 2010;1343:226-35).

4.5.2 Effect on nerve functions (reference data 4-A-10)

Mouse MSCs were transplanted into the spinal cord of a rat model of demyelination (induced by X ray irradiation followed by the administration of ethidium bromide 3 days later). The spinal cord was isolated

after 21 days for electrophysiological evaluation. Results showed recovery of nerve conduction velocity (*J Neurosci.* 2002;22:6623-30).

4.5.3 Accumulation at the injured site (reference data 4-A-1)

A single dose of LacZ-labeled rat MSCs (LacZ-rMSC) was administered intravenously to a rat model of spinal cord injury (6 hours, 1, 3, 7, 10, 14, 21, or 28 days after spinal cord injury). The spinal cord was isolated at 1 week after administration. Immunostaining of the frozen sections of the spinal cord identified LacZ-rMSCs accumulated at and around the injury site (*Brain Res.* 2010;1343: 226-35) [see Section 5.2].

4.5.4 Secretion of neurotrophic factors (reference data 4-A-1)

A single dose of MSCs was administered intravenously to a rat model of spinal cord injury (6 hours, 1, 3, 7, 10, 14, 21, or 28 days after spinal cord injury), and BDNF secretion in the spinal cord was evaluated at 3 days after administration. BDNF concentration was higher in rats receiving MSCs than in the vehicle group, at all measuring time points (*Brain Res.* 2010;1343:226-35).

4.5.5 Immunomodulatory effect (reference data 4-A-1 and 4-A-2)

A single dose of MSCs was administered intravenously to a rat model of spinal cord injury (6 hours, 1, 3, 7, 10, 14, 21, or 28 days after spinal cord injury). Necropsy of rats at 42 days after injury showed suppression of the formation of necrotic cavities at the site of the lesion (*Brain Res.* 2010; 343:226-35). Rat MSCs or the vehicle was administered to a rat model of spinal cord injury at 7 days after the injury. A week later, immediately after the administration of a single intravenous dose of Evans blue to the rats, leakage of Evans blue from the blood-spinal cord barrier around the injury site was evaluated. The leakage was lower in the group receiving rat MSCs than in the vehicle group (*Exp Neurol.* 2015;267:152-64).

4.5.6 Differentiation into nerve cells (reference data 4-A-1)

A single dose of rat MSCs was administered to a rat model of spinal cord injury, and frozen sections of the spinal cord were prepared a week later. Immunostaining of the sections showed part of MSCs accumulated at the injury site were positive for NeuN, a marker of nerve cells, or for GFAP, a marker of glia cells (*Brain Res.* 2010;1343:226-35).

4.R Outline of the review conducted by PMDA

The applicant's explanation about the action mechanism of an intravenous dose of the product on the recovery of neural function after spinal injury:

Intravenously injected MSCs are expected to migrate around the injury site in response to growth factors and chemokines, thereby secreting invasion factors such as MMP and TIMP to infiltrate into the injury site [see Sections 4.1 and 4.5.3]. MSCs are also expected to exhibit a nerve-protective effect by secreting neurotrophic factors and immunomodulatory factors at the injury site [see Sections 4.2, 4.3, 4.5.4, and 4.5.5]. Furthermore, MSCs have capacity to differentiate into nerve cells, the occurrence of which was observed at the injury site

[see Sections 4.4 and 4.5.6]. These biological and pharmacological characteristics of MSCs is expected to help recover motor activity and neural function affected by spinal cord injury [see Sections 4.5.1 and 4.5.2].

PMDA's view:
The data submitted suggest the promising effects of MSCs with their variety of biological and pharmacological characteristics that help recover motor and neural functions after spinal cord injury. The applicant should continue to source knowledge from research papers, etc. about new biological and pharmacological characteristics of MSCs, and new findings should be communicated to healthcare professionals appropriately.

5 Pharmacokinetics of the Product and Outline of the Review Conducted by PMDA
The pharmacokinetic data of Stemirac submitted were the results of a pharmacokinetic study on GFP-labeled rat MSCs in rats and the study on the accumulation of LacZ-labeled rat MSCs at the site of spinal cord injury in rats.

5.1 Pharmacokinetics in normal rats (attached data 5-a)
MSCs isolated from the bone marrow of GFP-transgenic rats (GFP-rMSCs) were cultivated and administered as a single intravenous dose to the femur of female rats. The distribution of GFP-rMSCs was monitored in blood immediately after administration, and in the liver, kidney, heart, lung, spleen, pancreas, salivary gland, stomach, brain, spinal cord, thyroid, ovary, muscle, bone marrow fluid, blood, and urine at 2 and 24 hours and 1, 2, 3, and 4 weeks after administration, using a confocal laser microscope. GFP-rMSC was distributed in the spleen and lung at 2 hours after administration. GFP-rMSCs in the lung became undetectable at 1 week after administration. In the spleen, GFP-rMSCs was detectable up to 4 weeks after administration only sporadically. No GFP-rMSC was detected in other organs, blood, and urine.

5.2 Accumulation at the site of injury in a rat model of spinal cord injury (reference data 4-A-1)
A single intravenous dose of LacZ-labeled rat MSCs (LacZ-rMSCs, 1.0×10^6 cells) was administered to the femur of a rat model of spinal cord injury. A week later, the cross section of the immunostained spinal cord including the injury site was monitored with a confocal microscope. The accumulation of LacZ-rMSCs was detected at and around the injury site of the spinal cord (*Brain Res.* 2010;1343:226-35).

5.R Outline of the review conducted by PMDA
The applicant's explanation about the pharmacokinetics of the product:
Following an intravenous dose of MSCs to normal rats, MSCs were distributed in the lung and spleen, but not in other tissues, bone marrow fluid, or urine. The result suggests that MSCs are degraded mainly in the spleen. Intravenous MSCs administered to a rat model of spinal cord injury are mostly eliminated as in normal animals. The results however suggested that some MSCs accumulate at the site of spinal cord injury. MSCs may have migrated due to the attraction effect of inflammation at the injury site, but a precise mechanism of the accumulation remains unclear.

Approximately 5.5% of rat MSCs administered to a rat model of spinal cord injury were found to accumulate at the injury site (*Neuroscience.* 2016;335:221-231). This suggests that the product administered to patients with spinal cord injury partly accumulates at the injury site and otherwise are distributed as described in Section 5.1.

PMDA accepted the explanation of the applicant about the pharmacokinetics of the product.

6 Nonclinical Safety and Outline of the Review Conducted by PMDA

The nonclinical safety data of Stemirac submitted included the results of a general toxicity study in dogs (including the evaluation of the effect on the central nervous system, respiratory system, and cardiovascular system), a karyotyping study, and a soft agar colony formation assay.

6.1 General toxicity (including the effect on the central nervous system, respiratory system, and cardiovascular system) (attached data 6-a)

A single-dose toxicity study was conducted in dogs as shown in Table 11. The product caused no toxicological change or had no effect on the central nervous system, respiratory system, or cardiovascular system.

Table 11. Single dose toxicity study (including the evaluation of the effect on the central nervous, respiratory, and cardiovascular systems)

Study system	Route of administra-tion	Dose (cells/kg)	Main findings	Attached data
Male and female dogs (beagle)	intravenous	0, 3.34×10^6	Adhesion of the lung and thoracic cavity wall and localized inflammation of the lung were observed in males of 3.34×10^6 cells/kg group. These change were considered spontaneous, based on intensity and frequency. FOB was measured within 6 hours post-dose, and respiratory rate, ECG, heart rate, blood pressure, and body weight were measured up to 6 hours post-dose and on the day before necropsy performed at 2 weeks post-dose. No product-induced abnormalities were observed at any time point.	6-a

6.2 Other safety (tumorigenicity)

6.2.1 Soft agar colony formation assay (attached data 6-a-4, 6-a-5, 6-a-6)

Cells were obtained from the product cultured for [redacted] passages, inoculated on soft agar plates, and cultivated for 2 weeks. No colonies with anchorage-independent growth were observed.

6.2.2 Karyotyping (attached data 6-a-1, 6-a-2, 6-a-3)

P1-cultured cells or cells obtained from the product cultured for [redacted] passages were subjected to counting of chromosomes and karyotyping by G-band staining. The cells comprising the product maintain the normal karyotype without transformation.

6.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that there are no particular concerns about the nonclinical toxicity of the product.

7 Clinical Study and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 1 Japanese phase II study shown in Table 12.

Table 12. Clinical study on the efficacy and safety

Data cate -gory	Region	Study	Phase	Study patients	Number enrolled	Outline of dosage and administration	Main endpoints
Evalu -ation	Japan	STR01-03	II	Patients with cervical cord injury diagnosed as ASIA Impairment Scale of A, B, or C	17	A single dose of MSCs (0.5×10^8 - 2.0×10^8 cells/body [$\leq 3.34 \times 10^6$ cells/kg])	Efficacy Safety

The outline of the clinical study was as follows.

7.1 Japanese clinical study

7.1.1 Japanese phase II study (attached data 7-1: Study STR01-03 [[redacted], [redacted], [redacted]])

An open-label, uncontrolled study was conducted in 1 study site involving patients with cervical cord injury graded as A, B, or C of American Spinal Injury Association Impairment Scale (AIS)[4)] at the primary enrollment (before the collection of peripheral blood and bone marrow fluid, the source materials of Stemirac) and at the secondary enrollment (before the administration of Stemirac) to investigate the efficacy and safety of the product. The target sample size was 10 (≥5, ≤20) patients for each AIS grade of A, B, and C.

The main inclusion criteria at the primary enrollment were 1) within 14 days after suffering spinal cord injury, 2) main injury at the cervical cord, 3) partial injury identified by diagnostic imaging, 4) AIS grade of A, B, or C, and 5) 20 through 70 years of age. The main inclusion criteria at the secondary enrollment were 1) being able to undergo Stemirac treatment within 54 days after spinal cord injury, 2) readiness of Stemirac for clinical study that meets shipping standards, and 3) AIS grade of A,B, or C. Patients were required to meet all these criteria.

The methods for collecting peripheral blood and bone marrow fluid from patients, dosage, and method use of the product were as follows.

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4) A 5-grade evaluation of the level of severity rated on a scale of A to E
A, Complete paralysis (complete loss of motor and sensory functions at segments S4-5);
B, Paresis (complete loss of motor function below the neurological level, sensory function including that at segments S4-5 is preserved);
C, Paresis (motor function is preserved below the neurological level, and less than half of key muscles in the paralyzed region have functional strength of MMT (manual muscle test) grade ≥3 (able to move against gravity).
D, Paresis (motor function is preserved below the neurological level, and more than half of key muscles in the paralyzed region have functional strength of MMT grade ≥3 (able to move against gravity).
E, Normal (both motor and sensory functions are normal)

Collection of patient's peripheral blood and bone marrow fluid

Bone marrow fluid (≤60 mL) was collected from the iliac bone, etc. Peripheral blood was collected in multiple times to prepare autologous serum to be used for cell culture. Autologous serum was prepared for the primary culture of Stemirac, then, the inoculation of bone marrow fluid was started. Approximately 1000 mL of peripheral blood was required.

Dosage and administration or method of use

Immediately after thawing, the product (containing 0.5×10^8 - 2.0×10^8 MSCs/body [maximum dose, 3.34×10^6 cells/kg]) was administered intravenously as a single dose over 30 minutes.

Peripheral blood was collected from all 17 patients eligible for the primary enrollment, and bone marrow fluid was collected from 15 patients.[5)] A total of 13 patients[6)] met the inclusion criteria and did not meet the exclusion criteria for the secondary enrollment. These 13 patients received treatment with Stemirac and were included in the efficacy analysis population. The safety analysis population included the 17 patients eligible for the primary enrollment and the 13 eligible for the secondary enrollment.

Table 13 shows the characteristics of 13 patients included in the efficacy analysis population. All had traumatic spinal cord injury and were eligible for the final evaluation on Day 220. There were only 2 patients with AIS B. According to the applicant, the target sample size of 5 subjects seemed difficult to achieve for patients with AIS B due to a limited number of patients. Based on the treatment results in patients with AIS A or C, Stemirac treatment was expected to have efficacy in patients with AIS B as well. The applicant therefore terminated the study before the number of patients with AIS B reached the target sample size.

5) A total of 2 patients discontinued the study due to suspected hematologic disease (myelodysplastic syndrome) (Patient ID STR0103-01) and a high level of anti-hepatitis B virus antibody (Patient ID STR0103-02).

6) A total of 2 patients discontinued due to chromosomal abnormality of peripheral blood (Patient ID STR0103-08) and pyrexia, precluding the administration of the clinical study product within 54 days (Patient ID STR0103-13).

Table 13. Patient characteristics (efficacy analysis population)

Patient ID	AIS		Age	Sex	Injury site	Type of injury	History of surgery	Days from injury	
	Before primary enrollment[a]	Immediate-ly before treatment[b]						To surgery	To treatment
STR0103-03	A	A	34	Male	C5	Fracture dislocation	Nil	-	47
STR0103-04	A	A	56	Female	C5	No bone injury	Posterior decompression	1	49
STR0103-05	C	C	47	Male	C5	No bone injury	Nil	-	47
STR0103-06	C	C	58	Male	C4	No bone injury	Nil	-	49
STR0103-07	B	B	23	Male	C5	Fracture	Posterior fixation	2	54
STR0103-09	C	C	36	Male	C4	No bone injury	Posterior decompression	13	53
STR0103-10	C	C	52	Male	C5	No bone injury	Posterior decompression	2	46
STR0103-11	C	C	55	Male	C4	No bone injury	Nil	-	52
STR0103-12	B	B	43	Male	C5	No bone injury	Posterior decompression	1	51
STR0103-14	A	A	65	Male	C4	No bone injury	Posterior decompression	0	43
STR0103-15	A	A	66	Male	C4	No bone injury	Nil	-	54
STR0103-16	A	A	55	Male	C3	Fracture	Posterior decompression + posterior fixation	16	51
STR0103-17	A	A	21	Male	C4	Fracture dislocation	Posterior fixation)	2	43

[a] Evaluated within 14 days after spinal cord injury
[b] Evaluated before the secondary enrollment and within 7 days before treatment with the study product

The primary efficacy endpoint was the percentage of patients who achieved ≥1 grade improvement in AIS at 220 (± 14) days after spinal cord injury from immediately before (≤7 days before) the day of treatment (40 ± 14 days after injury). No hypothesis on efficacy was set in advance.

The secondary efficacy endpoints were (i) the percentage of patients who achieved ≥2 grade improvement in AIS at 220 (± 14) days after spinal cord injury from immediately before (≤7 days before) the day of treatment (40 ± 14 days after injury); (ii) changes in the score of each item (motor function/sensory function [light touch, pin-prick test]) and total score of ISCSCI-92[7)] (*Paraplegia.* 1994;32:70-80, *Spinal Cord.* 1997;35:266-74) at 220 (± 14) days after spinal cord injury from immediately before (≤7 days before) the day of treatment (40 ± 14 days after injury); and (iii) change in the total score of SCIM-III[8)] (*Disabil Rehabil.* 2007;29:1926-33) at 220 days (± 14) after spinal cord injury from immediately before (≤7 days before) the day of treatment (40 ± 14 days after injury).

7) Consists of motor function score and sensory function (light-touch and pin-prick sensations) score. Motor function score is a total of the MMT of the representative key muscle groups at 10 segments from C5 to T1 and from L2 to S1. The normal score is 100, which is the sum of the scores of the right and left half of the body (50 each). For sensory function, light-touch sensation and pin-prick sensation at the representative key sensory sites in 28 segments from C2 to S4-5 are counted as 0 (compete loss), 1 (partial loss), or 2 (normal), and the sum of the counts is calculated (normal total score = 112).
8) Spinal Cord Independence Measure evaluating disability in (i) self-care (subtotal, 0–20), (ii) respiration and sphincter management (subtotal, 0–40), and (iii) mobility (subtotal, 0–40) in the 100-point scale

Table 14 shows efficacy data of each patient.

Table 14. Efficacy data of each patient

Patient ID	AIS immediately before treatment[a]	AIS at 220 days after injury	Change in AIS			ISCSCI-92					SCIM-III				
						Change at 220 days after injury from immediately before treatment				Total score at 220 days after injury	Total change at 220 days after injury from immediately before treatment	At 220 days after injury			
			No change	1-grade improvement	2-grade improvement	Motor function	Light touch sensation	Pin-prick sensation	Total			Total score	Self-care (subtotal)	Respiration and sphincter man agement (subtotal)	Movement (subtotal)
STR0103-03	A	C	-	-	●	18	23	26	67	120	4	14	1	10	3
STR0103-04		C	-	-	●	13	44	47	104	149	9	11	0	10	1
STR0103-14		B	-	●	-	0	16	10	26	54	2	4	0	4	0
STR0103-15		B	-	●	-	3	19	11	33	61	2	4	0	4	0
STR0103-16		B	-	●	-	5	20	13	38	66	3	5	0	4	1
STR0103-17		A	●	-	-	0	8	6	14	24	0	0	0	0	0
STR0103-07	B	C	-	●	-	7	1	4	12	183	17	21	2	10	9
STR0103-12		D	-	-	●	57	48	47	152	277	2	12	0	10	2
STR0103-05	C	D	-	●	-	56	21	10	87	252	76	86	15	34	37
STR0103-06		D	-	●	-	51	6	4	61	220	24	34	2	21	11
STR0103-09		D	-	●	-	47	0	0	47	219	65	77	17	33	27
STR0103-10		D	-	●	-	36	38	36	110	286	67	77	14	36	27
STR0103-11		D	-	●	-	39	6	6	51	224	82	92	18	36	38

[a] Evaluated before the secondary enrollment and within 7 days before treatment with the clinical study product.

Table 15 shows the percentage of patients achieving ≥1 grade improvement in AIS. Of 13 patients in the efficacy analysis population, 12 showed ≥1 grade improvement, except 1 patient with AIS A (Patient ID STR0103-17).

Table 15. Percentage of patients achieving ≥1 grade improvement in AIS 220 days after spinal cord injury from immediately before treatment

AIS immediately before treatment	Number of patients (Number of patients with ≥1 grade improvement/number of patients analyzed)	Percentage of patients with ≥1 grade improvement [95% CI] (%)
A	5/6	83.3 [43.7, 97.0]
B	2/2	100 [34.2, 100.0]
C	5/5	100 [56.6, 100.0]
Total	12/13	92.3 [66.7, 98.6]

Table 16 shows the percentage of patients achieving ≥2 grade improvement in AIS. A total of 3 patients, namely STR0103-03 and STR0103-04 (both from AIS Grade A to C) and STR0103-12 (from AIS Grade B to D), achieved ≥2 grade improvement.

Table 16. Percentage of patients achieving ≥2 grade improvement in AIS 220 days after spinal cord injury from immediately before treatment

AIS immediately before treatment	Number of patients (Number of patients with ≥2 grade improvement/number of patients analyzed)	Percentage of patients with ≥2 grade improvement [95% CI] (%)
A	2/6	33.3 [9.7, 70.0]
B	1/2	50.0 [9.5, 90.6]
C	0/5	0.0 [0, 43.5]
Total	3/13	23.1 [8.2, 50.3]

Table 17 shows changes in the score of each item (motor function/sensory function [light-touch sensation, pin-prick sensation]) and the total score of ISCSCI-92. The mean score of each item (motor function/sensory function [light-touch sensation, pin-prick sensation]) and the mean total score increased at 220 (± 14) days after spinal cord injury, regardless of AIS A, B, or C.

Table 17. Change in the score of ISCSCI-92 at 220 days after spinal cord injury from immediately before treatment

AIS immediately before treatment	Item	Change (mean ± SD)	95% CI
A (N = 6)	Motor function	6.5 ± 7.4	-1.3, 14.3
	Light-touch sensation	21.7 ± 12.1	9.0, 34.3
	Pin-prick sensation	18.8 ± 15.4	2.7, 35.0
	Total score	47.0 ± 33.0	12.3, 81.7
B (N = 2)	Motor function	32.0 ± 35.4	-285.7, 349.7
	Light-touch sensation	24.5 ± 33.2	-274.1, 323.1
	Pin-prick sensation	25.5 ± 30.4	-247.7, 298.7
	Total Score	82.0 ± 99.0	-807.4, 971.4
C (N = 5)	Motor function	45.8 ± 8.3	35.5, 56.1
	Light-touch sensation	14.2 ± 15.4	-4.9, 33.3
	Pin-prick sensation	11.2 ± 14.3	-6.6, 29.0
	Total	71.2 ± 26.7	38.0, 104.4
All patients (A + B + C) (N = 13)	Motor function	25.5 ± 22.6	11.9, 39.2
	Light-touch sensation	19.2 ± 15.8	9.7, 28.8
	Pin-prick sensation	16.9 ± 16.5	7.0, 26.9
	Total	61.7 ± 41.5	36.6, 86.8

N: Number of patients analyzed

Table 18 shows the change in total SCIM-III scores. The mean total score increased at 220 (± 14) days after spinal cord injury, regardless of AIS A, B, or C.

Table 18. Change in total SCIM-III score at 220 days after spinal cord injury from immediately before treatment

AIS immediately before treatment	Change (mean ± SD)	95% CI
A (N = 6)	3.3 ± 3.1	0.1, 6.6
B (N = 2)	9.5 ± 10.6	-85.8, 104.8
C (N = 5)	62.8 ± 22.8	34.5, 91.1
All patients (A + B + C) (N = 13)	27.2 ± 32.4	7.6, 46.7

The safety endpoint was the collection of all adverse events that occurred after the primary enrollment and before the end of the final evaluation (at 220 [± 14] days after spinal cord injury).

Adverse events occurred in 100% (17 of 17) of patients before Stemirac treatment and in 100% (13 of 13) of patients after treatment. A total of 362 adverse events were observed (200 events before treatment, 162 events after treatment). Table 19 shows adverse events occurring in ≥20% of patients. No deaths or serious adverse events occurred.

Table 19. Adverse events observed in ≥20% of patients

Adverse events observed after treatment (N = 17)			Adverse events observed after treatment (N = 13)		
Event	Number of patients	Percentage	Event	Number of patients	Percentage
Urinary tract infection	12	70.6	Erythema	5	38.5
Dermatitis contact	11	64.7	Dermatitis contact	5	38.5
Weight decreased	10	58.8	Drug-induced liver injury	5	38.5
Dry skin	8	47.1	Seborrhoeic dermatitis	4	30.8
Drug-induced liver injury	7	41.2	Haemorrhage subcutaneous	4	30.8
Pneumonia	5	29.4	Fall	4	30.8
Rhinitis allergic	4	23.5	Skin exfoliation	3	23.1
Depression	4	23.5	Excessive granulation tissue	3	23.1
Catheter site injury	4	23.5	Erythema	3	23.1
Hepatic function abnormal	4	23.5	Catheter site injury	3	23.1
Pleural effusion	4	23.5			
Muscle spasms	4	23.5			
Erythema	4	23.5			
Pain	4	23.5			

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Anaemia (Grade 2; 2 events in 2 patients) following peripheral blood collection and puncture site pain (Grade 1; 1 event in 1 patient) following bone marrow fluid collection were causally related to the collection of peripheral blood or bone marrow fluid, or to the administration of the product.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of the product:

The product, while accumulating at the site of spinal cord injury, exhibits its neurotrophic and protective actions mediated by the secretion of neurotrophic factors and anti-inflammatory action. These actions are expected to suppress the progression of the secondary injury of the spinal cord after acute phase treatment and promote the recovery of neural function. The product is thus expected to be recognized as a new treatment option for patients with neurological symptoms and functional disorders associated with spinal cord injury.

PMDA's view:

Given the characteristics of MSCs described in the data on indication or performance [see Section "4. Indication or Performance and Outline of the Review Conducted by PMDA"] and the results of the clinical study, the product can be a new treatment option for patients with spinal cord injury with persisting neurological symptoms and functional disorders aiming to suppress the progression of the secondary injury and promote the recovery of neural function.

7.R.2 Efficacy

7.R.2.1 Appropriateness of the design of the clinical study

PMDA's view:

Study STR01-03 was an uncontrolled study. The possibility cannot be excluded that there were factors other than the effect of Stemirac (spontaneous recovery, effect of rehabilitation, etc.) affecting the results, and the available data are limited. For the evaluation of the efficacy of the product, control data should have been obtained for comparison against the clinical course with the standard therapy.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the justification for the efficacy endpoints of Study STR01-03:

The product is expected to improve the neurological symptoms and functional disorders associated with spinal cord injury. AIS and ISCSCI-92 are major indices for comprehensive evaluation of functional disorders presenting as neurological symptoms after spinal cord injury. AIS is often used in published articles and for the evaluation of a long-term natural course of symptoms. Therefore, AIS was used as the primary endpoint. ISCSCI-92 helps evaluate precisely neurological symptoms related to motor function and sensory function (light-touch sensation and pin-prick sensation). SCIM-III is a practical index of functional disorders that helps evaluate important issues for patients with spinal cord injury such as respiratory control, bedsore prevention, outdoor mobility, and riding in a car. Accordingly, ISCSCI-92 and SCIM-III were used as the secondary endpoints.

The time point of efficacy evaluation was 220 days after spinal cord injury. This was decided by referring to published literature, according to which the outcome of patients with spinal cord injury on the standard therapy almost stabilizes 6 months after injury (*J Neurosurg.* 1993;79:500-507), which is around Day 180 post-dose of Stemirac.

PMDA's view:

The efficacy endpoints and the evaluation timing in Study STR01-03 are acceptable for the exploratory evaluation of the efficacy of the product for patients with spinal cord injury.

7.R.2.3 Results of efficacy evaluation

The applicant's explanation about the efficacy of the product:

Prior to a discussion on the efficacy results of Study STR01-03, a research was conducted as per Table 20 on the prognosis of neurological function in patients with spinal cord injury who received the standard treatment. The research focused on changes in AIS from 1 month after spinal cord injury, because the time from injury to treatment was close to that in Study STR01-03.

Table 20 Outline of the method used for data search

Database	Pubmed
Search period	[redacted], [redacted]
Keywords	spinal cord injury AND ASIA AND prognosis
Narrowing condition	Articles on the AIS-based evaluation of spinal cord injury at 30 days and 1 year after injury

As a result, reports from Scivoletto, et al (*Arch Phys Med Rehabil.* 2004;85:485-9, *Front Hum Neurosci.* 2014;8:1-11) were only available and relevant. Table 21 shows the characteristics, etc. of patients with spinal cord injury evaluated in this reference article and in Study STR01-03. The degree of improvement in AIS in Study STR01-03 was greater than that in patients receiving the standard treatment reported in the article (Table 22). This indicates that the severity of symptoms decreased following the treatment with Stemirac.

Table 21 Comparison of results between the report of Scivoletto et al. and Study STR01-03

		Report of Scivoletto et al.		Study STR01-03	
Evaluation index		AIS		AIS	
Evaluation timing	Early phase	30 days after injury		40 ± 14 days after injury	
	Late phase	1 year after injury		220 ± 14 days after injury	
Age (mean ± SD)		50.4 ± 19.3		47.0. ± 14.7	
AIS at early phase evaluation		AIS A, 84 patients AIS B, 19 patients	AIS C, 129 patients AIS D, 52 patients	AIS A, 6 patients AIS B, 2 patients	AIS C, 5 patients AIS D, no patient
Injury site		Cervical cord injury, 81 patients Thoracic cord injury, 147 patients Lumbar cord injury, 54 patients		Cervical cord injury, 13 patients	

Table 22 Change in AIS grade after 1 year from 30 days after injury (report of Scivoletto et al.)

AIS at 30 days after injury	Percentage 1 year after injury				
	AIS A	AIS B	AIS C	AIS D	AIS E
A	95.2	0	2.4	2.4	0
B	0	52.6	21.1	26.3	0
C	0.8	0	44.2	53.5	1.6
D	1.9	0	0	96.2	1.9

The results of Study STR01-03 also showed a tendency toward improvement in ISCSCI-92 (motor function and sensory function) and SCIM-III in patients with AIS A, B, or C, demonstrating improved functional disorders and neurological symptoms in these patients.

A patient (STR0103-17) with AIS A was not able to experience improvement in AIS and SCIM-III. The patient had cervical cord injury secondary to fracture dislocation at C4. The spinal cord continued to be compressed without being reduced over 2 days after injury, resulting in the spread of edema from the brain stem throughout the entire spinal cord. In contrast, another patient (STR0103-16) had only fracture, and the other (STR0103-03) had fracture and dislocation which was promptly reduced. They showed favorable recovery despite AIS A immediately before treatment.

PMDA's view on the efficacy of the product:
Study STR01-03 was an exploratory study conducted at a single study site and yielded limited data due to no control group and the limited number of subjects, etc. Given a limited number of patients with AIS B in the clinical setting, it would be difficult to have patients sufficient for the target sample size. Even so, the early termination of the study was rather inappropriate. The report of Scivoletto et al. presented by the applicant shows different patient characteristics in their study from those in Study STR01-03; more than half of participated patients had non-traumatic spinal cord injury, and some had injury of spinal cord other than

cervical cord. In addition, there are limitations to the efficacy evaluation of the product because of limited comparability of the external comparison with the study data from Scivoletto, et al.

However, 12 of 13 patients experienced ≥1 grade improvement in AIS in Study STR01-03, including 2 grade improvement achieved by 2 of 6 patients with AIS A spinal cord injury that is unlikely to cure spontaneously. These results suggest the efficacy of Stemirac. Also, ISCSCI-92 and SCIM-III scores increased in 13 and 12 patients, respectively, out of 13 patients after treatment with the product, although the extent of improvement differed among patients, showing improved activities of daily lives in many patients. Thus, the results of Study STR01-03 indicate that the product is effective to a certain extent for neurological symptoms and functional disorders associated with spinal cord injury. However, the fact should be noted that neither AIS nor SCIM-III improved in 1 patient (STR0103-17) with AIS A spinal cord injury due to fracture dislocation, and the possibility cannot be ruled out that the severity of injury affects the efficacy of the product. A relationship between the efficacy of the product and patient characteristics, such as AIS in the early post-injury phase, site or type of injury, a history of surgery, etc. should be further evaluated based on post-marketing data collected.

Thus, Stemirac is expected to have a certain level of efficacy. Still, the investigation should be continued because of the limited data currently available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of the product:

In Study STR01-03, there were no deaths or other serious adverse events. Adverse events causally related to the collection of peripheral blood or bone marrow fluid or the administration of the product were anaemia (Grade 2, 2 events in 2 patients) due to peripheral blood collection and puncture site pain (Grade 1, 1 event in 1 patient) due to bone marrow fluid collection.

Adverse events newly occurring after the use of Stemirac in ≥20% of patients were subcutaneous haemorrhage in 30.8% (4 of 13) of patient, seborrhoeic dermatitis in 30.8% (4 of 13) of patient, and fall in 23.1% (3 of 13) of patients, all of which were characteristic to patients with spinal cord injury. The following are the reasons for the occurrence of these events and the judgment on a causal relationship to the product:

- Haemorrhage subcutaneous (4 events in 4 patients) was considered due to bruise, and its causal relation to the product was ruled out for all patients.
- Seborrhoeic dermatitis (4 events in 4 patients) was attributable to inability to remove lipids adhering to the face, etc. due to paralysis, and its causal relationship to the product was ruled out for all patients.
- Fall (7 events in 3 patients) occurred in their daily activity lives or during rehabilitation and was not accompanied by dizziness, etc. A causal relationship of the events to the product was ruled out for all of the patients.

Adverse events which occurred in <20% of patients before Stemirac treatment and ≥20% of patients after treatment were skin exfoliation (23.1%, 3 of 13) and excessive granulation tissue (23.1%, 3 of 13). The following are the reasons for the occurrence of these events and their causal relationship to the product.

- Skin exfoliation (5 events in 3 patients) was accompanied by the use of tapes and diapers, and a causal relationship to the collection of peripheral blood or bone marrow fluid or Stemirac treatment was ruled out.
- Excessive granulation tissue (3 events in 3 patients) was caused by the insertion of a cannula for a purpose other than Stemirac treatment. A causal relationship to the collection of peripheral blood or bone marrow fluid or Stemirac treatment.

These results demonstrated the safety of the product in patients with spinal cord injury. However, because of the current limited data, safety data of the product should be further collected in the post-marketing setting.

As of August 2018, all 13 patients who had been treated with Stemirac in Study STR01-03 were in good condition (2.0 to 4.3 years after injury), without any noteworthy diseases.

PMDA asked the applicant to explain risks associated with peripheral blood collection, bone marrow fluid, or intravenous infusion of the product, with a concern for the systemic condition of patients with spinal cord injury.

The applicant explained as follows, noting that these risks would be highlighted in the package insert.

(a) Risks associated with the collection of peripheral blood and bone marrow fluid

In addition to anemia following peripheral blood collection and puncture site pain observed following bone marrow fluid collection in Study STR01-03, the collection of peripheral blood or bone marrow fluid may involve the following risks.

In patients with spinal cord injury, the impaired autonomic nervous system causes the instability of hemodynamics and may pose a risk of hypotension. There is no use experience of Stemirac in the following patient groups, and the collection of peripheral blood or bone marrow fluid may aggravate their symptoms: patients with serious systemic condition due to endocrine metabolic disease, cardiovascular disease, respiratory disease, gastrointestinal disease, severe multiple injuries, multiple organ failure, etc; patients with serious intracranial lesions, severe constriction of major vessels, dissecting aortic aneurysm, severe arteriosclerotic changes, severe calcification, etc; and patients with severe spinal and spinal cord diseases (osteoporosis, spinal cord tumor, spinal vascular malformation, syringomyelia, etc.). In addition, there may be a risk of bleeding from the punctuation site in patients with poorly controlled blood pressure.

(b) Risks associated with the intravenous administration of the product

Pulmonary embolism, thrombus formation, etc. have been reported as risks associated with the intravenous administration of cells. These are the likely risks in patients with spinal cord injury because they often have enhanced blood coagulability. Also, the possibility cannot be completely ruled out that cancer may relapse due to the immunomodulatory effect of the product and the effect of factors secreted by the product, and that infection may occur or become aggravated due to the immunomodulatory effect of the product. In addition, the following risks cannot be totally excluded: hypersensitivity (including anaphylaxis) caused by the use of antibiotics, animal-derived materials, etc; infection due to the use of human- or animal-derived materials or source materials; and ectopic tissue formation due to MSCs' potential to differentiate into various types of cells.

PMDA's view on the safety of the product:
In Study STR01-03, adverse events causally related to the collection of peripheral blood or bone marrow fluid or the administration of Stemirac were anaemia (grade 2, 2 events in 2 patients) due to peripheral blood collection and puncture site pain (grade 1, 1 event in 1 patient) due to bone marrow fluid collection. All these events were non-serious. There were no other adverse events for which causal relatioship to the collection of peripheral blood or bone marrow fluid or the administration of Stemirac could not be ruled out. These results suggest that the product is well tolerated in patients with spinal cord injury. However, because the product's safety data are limited, relevant data should be further collected in the post-marketing setting. New findings should be communicated to healthcare professionals in an appropriate manner. The applicant's explanation about the risks associated with the collection of peripheral blood or bone marrow fluid, or the intravenous administration of Stemirac, with a concern for the systemic condition of patients with spinal cord injury, and their risk reduction effort through highlighting these risks in the package insert are appropriate. In order to prevent the risk of pulmonary embolism, thrombus formation, etc., in particular, healthcare professionals should be informed of the importance of the infusion rate, and the product should be used at medical institutions fully capable of emergency care whereat the patient condition is managed and monitored appropriately by vital sign check and laboratory test, etc. To prevent the risk of anemia associated with peripheral blood collection, the procedure to obtain a source material for the production of Stemirac, information on blood collection interval and the required total volume should be provided in the package insert, etc. A blood collection plan should be designed in light of the patent's age, body weight, systemic condition, etc. Blood should be collected where the patient condition is managed and monitored appropriately by vital sign check and laboratory test, etc.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.4 Indication or performance

The applicant's justification for the indication or performance:
Study STR01-03 showed improvement in indicators such as AIS and ISCSCI-92 for neurological symptoms and SCIM-III for functional disorders following Stemirac treatment. Therefore, the indication or performance

of the product of "improvement of neurological symptoms and functional disorders associated with spinal cord injury" is appropriate.

The applicant's view, in relation to indication or performance, on the use of Stemirac in (a) pediatric patients, (b) patients with AIS D, and (c) patients with spinal cord injury other than cervical cord injury:

(a) Use of the product in pediatric patients

Table 23 outlines a literature search conducted to investigate the safety of the product in pediatric patients, which was not investigated in Study STR01-03.

Table 23. Outline of the method used for data search

Database	Pubmed
Search period	[redacted]
Keywords	(clinical trial OR clinical test)AND(cell therapy OR cell transplantation) AND (safety OR risk) AND (child OR children)
Narrowing condition	Articles on the use of MSCs in children

Table 24 shows the age of children, dosage regimen of MSCs, and adverse events reported in each article extracted. All articles reported about patients treated with autologous bone marrow-derived MSCs.

Table 24. Clinical results following MSC treatment in children

Article	Method of administration	Disease	Age (Years)	Body weight (kg)	Number of treatment	Number of cells (cells/kg)	Treatment-related adverse events	Remark
Proc Natl Acad Sci U S A. 2002;99: 8932-37	i.v. drip infusion	Osteogenesis imperfecta	3	N/A	2	1×10^6	Not occurred	-
						5×10^6	Not occurred	-
		Osteogenesis imperfecta	4	N/A	2	1×10^6	Not occurred	-
						4.37×10^6	Not occurred	-
		Osteogenesis imperfecta	2	N/A	2	1×10^6	Not occurred	-
						1×10^6	Not occurred	-
		Osteogenesis imperfecta	3	N/A	2	1×10^6	Not occurred	-
						2.85×10^6	Not occurred	-
		Osteogenesis imperfecta	3	N/A	2	1×10^6	Not occurred	-
						5×10^6	Not occurred	-
		Osteogenesis imperfecta	3	N/A	2	1×10^6	Not occurred	-
						5×10^6	Not occurred	Urticaria caused by anti-fetal calf serum antibody
Bone Marrow	dr ip in fu	Metachromatic leukodystrophy	5	13	1	2×10^6	Occurred	Mild pyrexia not requiring treatment

Article	Method of administration	Disease	Age (Years)	Body weight (kg)	Number of treatment	Number of cells (cells/kg)	Treatment-related adverse events	Remark
Transplant. 2002;30:215-22		Hurler's syndrome	5	23	1	4×10^6	Not occurred	-
		Hurler's syndrome	6	20	1	10×10^6	Not occurred	-
		Metachromatic leukodystrophy	7	21	1	10×10^6	Not occurred	-
		Hurler's syndrome	5	18	1	10×10^6	Not occurred	-
Transplantation. 2006;81:1390-7	i.v. drip infusion	GVHD	8	N/A	2	2×10^6 1×10^6	Not occurred	-
		GVHD	12	N/A	2	0.7×10^6 1.3×10^6	Not occurred	-
Blood Cells Mol Dis. 2008;40:25-32	i.v. drip infusion	Haemophagocytic syndrome	14	72.5	3	Total, 0.4×10^6	Not occurred	-
		GVHD	9	39	1	2×10^6	Not occurred	-
		GVHD	14	37.5	1	0.4×10^6	Not occurred	-
		GVHD	4	15	1	3.0×10^6	Not occurred	-
Lancet. 2008;71:1579-86	i.v. drip infusion	GVHD	Mean, 22 (0.5-64)	N/A	1-5	$0.4\text{-}9.0 \times 10^6$	Not occurred	25 children out of total 55 patients
Biol Blood Marrow Transplant. 2014;20:229-35	i.v. drip infusion	GVHD	Mean, 8.6 (0.2-17.5)	Mean, 32.1	Twice weekly for 4 weeks	2×10^6	Not occurred	75 patients

N/A, No information available

The above literature search did not identify any adverse event specific to children, suggesting that the safety risk is low when the product is administerd according to the dosage and administration or method of use proposed for the product, i.e., “a single dose intravenous administration at the dose of 0.5×10^8 to 2.0×10^8 cells/body (maximum dose, 3.34×10^6 cells/kg body weight).”

At the same time, the collection of peripheral blood, while necessary for the production of Stemirac, may pose a potential risk of anemia due to children’s smaller circulating blood volume. The volume and the intervals of peripheral blood collection should be controlled according to the patient’s condition, body weight, laboratory value (hemoglobin level), etc. The package insert and other written materials will hightlight the importance of paying attention to the onset or aggravation of anemia at blood colletion for the use of the product in patients with low body weight, such as children. The risks associated with peripheral blood collection in children is reduced to an acceptable level by these precautions. According to the Guidelines of the Japan Society for Hematopoietic Cell Transplantation, up to 12% of the circulating blood

(10 mL/kg) may be collected at a time from the peripheral blood of a child for autologous blood donation. There are no further restrictions on the volume of blood, body weight, age, etc. for autologous blood donation (*Guidelines of the Japan Society for Hematopoietic Cell Transplantation. vol. 2*, Iyaku Journal Co., Ltd.;2015. p.115).

According to the Guidelines of the Japan Society for Hematopoietic Cell Transplantation, children aged ≥1 and ≤15 years are eligible for bone marrow donation. In clinical practice, the volume of bone marrow fluid to be collected for hematopoietic cell transplantation is 10 to 15 mL/kg (*Guidelines of the Japan Society for Hematopoietic Cell Transplantation. vol. 2*, Iyaku Journal Co., Ltd.;2015. p.114 and 117). Therefore, the volume of bone marrow fluid (up to 50 mL) required for the production of Stemirac is within the acceptable range from the aspect of the associated risk. However, bone marrow fluid is collected from the children's iliac bone as in adults, and risks of iliac osteomyelitis, septic shock, or sacroiliac joint injury (due to the penetration of the needle through the iliac bone) following bone marrow fluid collection remain. These risks will be highlighted in the package insert for risk reduction.

The product is intended for the improvement of neurological symptoms and functional disorders associated with spinal cord injury through nerve protection by neutrotrophic factor secretion, cavitation suppression by immuomodulation, stabilization of the blood-spinal cord barrier, etc. Given this action mechanism, the efficacy of Stemirac is unlikely to be affected by the age of patients.

After spinal cord injury, patients are forced to live with residual disability for years. The use of the product in children thus is of high social significance and is accepable from the risk-and-benefit point of view.

(b) Use of the product in patients with AIS D

In Study STR01-03, Stemirac improved neurological symptoms in all patient groups with AIS A, B, and C consistently. SCIM-III showed marked improvement particularly in patients with AIS C, demonstrating a high clinical significance. The product is therefore expected to have efficacy in patients with AIS D as well, a patient population excluded from Study STR01-03.

(c) Use of the product in patients with spinal cord injury other than cervical cord injury

Spinal cord injury accompanies disorders of nerve function directly caused by the primary injury such as tissue crushing, bleeding, axonotmesis, etc., and the secondary injury including ischemia, inflammation, delayed-onset neuronal cell death, etc. (*Front Cell Neurosci.* 2016;10:98). Regardless of the site affected, disorder develops through the same mechanism. The product administered intravenously accumulates at the injury site, improves neurological symptoms and functional disorders by protectiing nerves through the secretion of neurotrophic factor, etc., suppressing cavitation through its immunomoduratory effect, and stabilizing the blood spinal cord barrier. Given this action mechanism, the efficacy of the product is unlikely to be injurysite-specific. Similarly, possible adverse events following Stemirac treatment are unlikely to be injury site-specific, and the safety risks posed by Stemirac for the treatment of cervical cord injury and those

for spinal cord injury affecting non-cervical regions are expected to be the same. Accordingly, defining the indication of the product, regardles of the injury site, as spinal cord injury is appropriate.

PMDA's view on indication or performance:
As discussed in Section 7.R.2, the product is expected to have a certain level of efficacy in treating neurological symptoms and functional disorders associated with spinal cord injury, based on the results of Study STR01-03, despite limited data.

PMDA's view on the use of product in the context of indication or performance in (a) in pediatric patients, (b) patients with AIS D, (c) patients with spinal cord injury other than cervical cord injury, and (d) patients with non-traumatic spinal cord injury:
(a) Use in pediatric patients
Pediatric use of Stemirac was not investigated in Study STR01-03. Despite that, the applicant's literature search identified no concerns specific to the use of bone marrow-derived MSCs in children, and the pediatric use of the product according to the proposed dosage and administration or usage method is thus acceptable. However, patients are required to undergo the collection of peripheral blood and bone marrow fluid, a substantial volume of which must be obtained within a given time frame to produce Stemirac. The procedures will expose pediatric patients to a high risk, due to their smaller volume of circulating blood than adults. In order to minimize such risk, general guidelines for the total volume of peripheral blood and bone marrow fluid and a standard collection schedule should be clearly presented in the "Precautions for Indication or Administration Method" section of the package insert. The section should also advise that the use of the product in children must be determined carefully in light of the patient's age, body weight, systemic condition, etc. Then, blood collection and bone marrow fluid collection must be performed while patient condition is monitored and managed appropriately through vital sign check, laboratory tests, etc.
In the post-marketing setting, safety and efficacy data of the product in children should be collected for evaluation.

(b) Use in patients with AIS D
AIS D is defined as "paresis (motor function is preserved below the neurological level, and no less than half of key muscles in the paralyzed region have functional strength of the manual muscle test (MMT) Grade ≥3." This patient population have a relatively good condition than other patients with spinal cord injury, albeit a variety of symptoms.

However, the clinical benefit of Stemirac in patients with AIS D is unknown because of no use experience in Study STR01-03. Therefore, the product should be indicated for patients with AIS A, B, or C. The efficacy and safety of the product in patients with AIS D should be investigated in another clinical study.

(c) Use in spinal cord injury other than cervical cord injury

Although there are no use experiences of Stemirac for spinal cord injury affecting non-cervical regions, the expected action mechanism of the product is not dependent on the injury site in the spinal cord. Study STR01-03 demonstrated a certain level of efficacy of the product on neurological symptoms and functional disorders associated with spinal cord injury. The use of product for spinal cord injury affecting non-cervical regions is unlikely to pose additional safety concerns. Therefore, the indication of the product does not need to be limited to cervical cord injury. In the post-marketing setting, the efficacy and safety data should be collected by injury site for evaluation.

(d) Use of the product for non-traumatic spinal cord injury

In Study STR01-03, all patients receiving Stemirac treatment had traumatic spinal cord injury. The efficacy and safety of the product in patients with non-traumatic spinal cord injury is unclear because the cause of non-traumatic spinal cord injury is different from that of traumatic spinal cord injury, and there is no use experience of the product for the treatment of non-traumatic spinal cord injury. Therefore, the use of the product should be limited for the treatment of traumatic spinal cord injury. This should be clearly stated in the "Indication or Performance" section to ensure the proper use of the product.

Thus, the indication or performance of Stemirac should be defined as "Improvement of neurological symptoms and functional disorders associated with spinal cord injury in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C."

The above conclusion will be discussed at the Expert Discussion.

7.R.5 Dosage and administration or method of use

The proposed dosage and administration or method of use:

Bone marrow aspiration should be aimed to be performed within 31 days after spinal cord injury, according to the systemic condition, etc. of the patient. Once produced, the product should be administered at the earliest time possible.

Procedures prior to the production of Stemirac

(1) Patient's bone marrow fluid is collected. The collected bone marrow fluid is put into a container (Nipro Celltry for bone marrow), and the bone marrow fluid diluent DMEM, enclosed in the bone marrow collection kit, is added to be mixed. After being tightly sealed, the container holding bone marrow fluid is transported to a facility designated by the marketing authorization holder.

(2) Patient's peripheral blood is collected. The collected peripheral blood is put into a container (Nipro Celltry for serum) enclosed in the blood collection kit. After being tightly sealed, the container holding peripheral blood is transported to a facility designated by the marketing authorization holder.

Procedures for the administration of Stemirac to the patient

The product is administered by intravenous drip infusion at a rate of 0.7 to 1.0 mL/min, as 0.5×10^8 to 2.0×10^8 autologous bone marrow-derived MSCs (maximum dose, 3.34×10^6 cells per kg body weight) while being diluted ≥3 fold with physiological saline.

The applicant's justification for the dosage and administration or method of use of the product:
The dosage regimen of the product in the clinical study (STR01-03) was "a single intravenous dose of 0.5×10^8 to 2.0×10^8 cells/body (maximum dose, 3.34×10^6 cells/kg)," which was determined based on the results of studies on the number of effective cells among bone marrow-derived mesenchymal cells and the number of times of administration in model animals (*Exp Neurol.* 2006;199:56-66, *Brain Res.* 2008;1236:30-8, *Brain Res.* 2010;1343:226-35, etc.), and on the results of the single dose toxicity study in dogs [see Section 6.1]. Study STR01-03, in which the product was administered intravenously as a single dose within the specified range of the number of cells, revealed no relationship between the number of administered cells and efficacy or no serious adverse events. No adverse events such as vascular pain were observed when the product was administered while being diluted ≥3 fold with physiological saline. The proposed dosage regimen are therefore considered appropriate.

In terms of the appropriateness of infusion rate based on the product's cell density, the potential risks attributable to the infusion rate are local irritation due to change in osmotic pressure and embolism and thrombus formation. These risks are discussed below.

(a) Local irritation due to change in osmotic pressure
The cell density of the final product is [redacted] to [redacted] cells/mL, and 1 to 2 bags of the final product, each containing 20 mL of cell suspension, are supplied for each patient. The product is administered at a rate of up to 1.0 mL/min, while being diluted with physiological saline, which is added at the rate of 2.0 mL/min through a tube connected along the drip infusion line. The osmotic pressure of the product is approximately [redacted] mOsm, and the osmotic pressure of the dosing solution diluted 3 fold with physiological saline, the worst diluting condition, is approximately [redacted] mOsm. Since the limit of the osmotic pressure of a solution that can be administered through the peripheral vein is considered to be 800 to 1000 mOsm/kg H_2O (*Guidelines for Parenteral and Enteral Nutrition. 3rd Ed*, Shorinsha;2013. p33-4), the above procedures for administration is appropriate. In Study STR01-03, the product was administered at a rate of 0.7 to 1 mL/min, and no adverse events such as vascular pain were observed.

(b) Embolism and thrombus formation
In a single dose toxicity study in dogs, the product was administered under the condition equivalent to the maximum cell administration rate in clinical use (cell suspension containing 5.0×10^6 cells /mL per bag was administered at the rate of 1.0 mL/min). Results showed no abnormalities such as embolism and thrombus formation. In Study STR01-03, no adverse events related to cell density of the dosing suspension were observed. A caution statement is to be presented in the "Precautions for Dosage and Administration or Method of Use" section to the effect that "out of concern for potential risks of embolism, thrombus formation,

and intravascular haemolysis posed by intravenous administration of cells, the infusion rate should not exceed 1.0 mL/min."

In Study STR01-03, the product was administered at a rate of 0.7 to 1.0 mL/min. It took an average of 48 minutes to administer the content of 2 bags and an average 25 minutes per bag. The stability of the product has been demonstrated up to 2 hours after thawing. The "Precautions for Dosage and Administration or Method of Use" section notes that "the product should be thawed at 37°C as specified by the marketing authorization holder, and the thawed suspension should not be stored and should be administered immediately within 1 hour after thawing."

Based on the above, the applicant considers that the infusion rate is appropriate.

The Study STR01-03 required the study product be administered within 54 days after spinal cord injury. The product administered within this time frame showed efficacy without any serious adverse event. In clinical practice, however, it often takes a long time before the actual procedure is started to treat spinal cord injury. For this reason, strictly restricting the dosing timing to within 54 days after injury, as per the Study STR01-03, is rather impractical. Therefore, the "Dosage and Administration or Method of Use" section will define the timing of bone marrow fluid collection, instead of the dosing timing, because these timings are closely linked. Based on the dosing timing (43-54 days after injury) and experience in production of Stemirac (median time for cell cultivation, approximately [redacted] days; time for the quality test of the finished product, [redacted] days), bone marrow fluid collection timing was defined as approximately 31 days after injury, and the dosing timing of suspension as the earliest time possible after production.

PMDA's view on Dosage and Administration or Method of Use:
Given the results of the nonclinical studies and Study STR01-03, the dosage regimen or method of use of suspension should be described as "a single dose intravenous administration at 0.5×10^8 to 2.0×10^8 cells/body (maximum dose, 3.34×10^6 cells/kg)" as proposed by the applicant. The proposed infusion rate is also acceptable. However, to ensure the safety of intravenous infusion and the stability of the thawed suspension, the guideline for the infusion rate should be presented in the "Dosage and Administration or Method of Use" section.

As specified in the "Dosage and Administration or Method of Use" section, the maximum dose depends on body weight, and therefore Stemirac may not always be consumed completely. Cautionary advice should be given against inadvertent overdosing in the "Precautions for Dosage and Administration or Method of Use" section. Further, healthcare professionals should be informed of how to prepare dosing suspension for partial use appropriately through written materials.

Stemirac is an autologous cell-based product that requires a certain time to be produced. As the applicant points, when the dosing timing in clinical practice is strictly defined as within 54 days in the "Dosage and

Administration or Method of Use" section following the Study STR01-03, a possible scenario is that the product is not ready to be administered to the patient within the specified time frame. In this point of view, and based on their production experience and treatment results during the clinical study, the applicant has made a proposal to give a guideline for the timing of bone marrow fluid collection, which is closely linked to the timing of the administration of Stemirac suspension, as within 31 days after injury and to advise that the dosing suspension should be administered the earliest time possible after production. This proposal is acceptable.
Accordingly, the "Dosage and Administration or Method of Use" section may be described as proposed by the applicant, with the additional guideline for infusion rate.

The above conclusion will be discussed at the Expert Discussion.

7.R.6 Qualifications for medical institutions and doctors using Stemirac

Qualifications for medical institutions and doctors handling the product listed by the applicant:

- Specialists in spinal cord injury (specialists in neurosurgery, orthopedic surgery, neurology [cerebral neurology], or emergency medicine or anesthesiology)
- Medical institutions capable of safe and hygienic bone marrow and peripheral blood collection
- Doctors who have attended a training seminar organized by the marketing authorization holder
- Medical institutions capable of malignant tumor testing or have test results available
- General medical institutions accommodating emergency care, or medical institutions prepared for emergency care by allying with a hospital accommodating such service

PMDA's review:

The qualifications for medical institutions and doctors proposed by the applicant are generally acceptable in the context of the proper use of the product in clinical practice. The final conclusion on the appropriateness of these requirements are to be made based on the actual practice in the treatment of spinal cord injury in Japan. Because the collection of autologous peripheral blood and bone marrow fluid is essential to produce Stemirac, the total volumes of peripheral blood and bone marrow fluid required and a standard time schedule for these procedures should be communicated to healthcare professionals through the package insert, a seminar, etc. so as to ensure the proper use of the product.

The clinical study on Stemirac was conducted only in an exploratory manner involving a small number of patients and yielded limited efficacy data. Therefore, efficacy data should be collected in the post-marketing setting for further evaluation. The efficacy evaluation should be conducted based on baseline and post-dose AIS, etc. by an evaluator well-trained for evaluation based on these scales. A majority of patients are expected to be transferred from an acute phase hospital to a rehabilitation hospital during the course of treatment. Cooperation should be established between them to collect efficacy and safety data for a specific time period. Patient eligibility criteria for the treatment, product properties, administration method,

precautions for use, etc. should be communicated to doctors appropriately at a training seminar and via written materials. Stemirac must be handled by doctors who have acquired such knowledge.

The above conclusion will be discussed at the Expert Discussion.

8 Risk Analysis and Outline of the Review Conducted by PMDA

8.1 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan of the product:

Because of the limited information available on the efficacy and safety of the product obtained from Study STR01-03, a comparative use results survey will be conducted to further evaluate the efficacy and safety of the product in the post-marketing setting. Data will be analyzed by comparison between patients who use the product and those who do not (Table 25).

Table 25. Outline of the post-marketing comparative use results survey (draft)

Objective	Evaluation of the efficacy and safety of Stemirac
Survey method	All-case surveillance
Population	Patients with spinal cord injury in acute to subacute phase
Observation period	12 months after injury
Efficacy survey items	Primary endpoint • Percentage of patients with AIS A achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury Secondary endpoints • Percentage of patients with AIS A achieving ≥2 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Percentage of patients with AIS B or C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Percentage of the sum of patients with AIS A, B, and C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ±7 days) after injury (based on Cochran-Mantel-Haenszel test stratified by "AIS A" and "sum of AIS B and C") • Mean change in the sum of ISCSCI-92, SCIM-III, and SF36 scores at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Change in the level of injury site (ISCSCI-92) at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury
Safety survey items	Anemia, puncture site pain during bone marrow fluid collection, and other malfunctions and adverse events; causal relationship to Stemirac and incidence of each malfunction or adverse event
Population	Patients enrolled in the survey are defined as ITT population. All patients in ITT population except the following are defined as the full analysis set (FAS). FAS is the main population for the efficacy and safety analyses. Observation on patients excluded from FAS continues. Patients excluded from FAS: (Stemirac group) Patients withdrawn before function evaluation including AIS at week 6 to 8 (49 ± 7 days) after injury, patients undergone function evaluation including AIS at week 6 to 8 (49 ± 7 days) after injury but withdrawn before treatment with Stemirac (Control group) Patients withdrawn before function evaluation including AIS at week 6 to 8 (49 ± 7 days) after injury
Target sample size	Target number of analyzable patients 49 patients each in the Stemirac and control groups (17 patients with AIS A, 32 patients with AIS B or C; all suffering cervical cord injury, aged 20 to 70 years). The target sample size is to be re-defined based on the results of the interim analysis. Justification for the target sample sizes • According to Scivoletto, et al., the standard treatment improved AIS by 1 grade in 4.8% of patients with AIS A at 30 days after injury. In Study STR01-03, Stemirac improved AIS by 1 grade in 83.3% of patients with AIS A. In light of these outcomes, when the percentage of patients achieving ≥1 grade improvement in AIS is obtained by [redacted] test, conservatively assuming the estimated percentage of improvement by the standard treatment to be [redacted]%, the estimated percentage of improvement by Stemirac [redacted]%, 2-sided significance level of [redacted]%, and a power of test [redacted]%, 17 each of patients with AIS A are required for both the Stemirac and control groups.

	• Similarly, when the percentage of patients achieving ≥1 grade improvement in AIS in patients with AIS B or C is obtained by [redacted] test, conservatively assuming the estimated percentage of improvement by the standard treatment to be [redacted]%, the estimated percentage of improvement by Stemirac [redacted]%, 2-sided significance level [redacted]%, and a power of test [redacted]%, 32 each of patients with AIS B or C are required for both the Stemirac and control groups. • In each stratum of "AIS A" and "sum of AIS B and C," when a power of [redacted]% is obtained as above and each stratum shows a tendency toward favorable efficacy of Stemirac, the power of Cochran-Mantel-Haenszel test, if used, will be sufficient because it exceeds the power of test in each stratum. Based on the above reasons, the target sample size was set as 49 (17 patients with AIS A and 32 patients with AIS B or C) for both the Stemirac and control groups.
	Expected necessary number of patients to be enrolled 113 in the Stemirac group, 120 in the control group (even where patients of these necessary numbers are enrolled, if these numbers do not satisfy the target number of analyzable patients, i.e., 49 per group, the survey is to be continued until this is achieved.) Justification for the expected necessary number of patients to be enrolled The expected necessary number of patients was determined so that the target numbers of analyzable patients is achieved. Assuming the rate of withdrawal to be [redacted]% in the Stemirac group and [redacted]% in the control group, and considering the possibility of enrollment of patients with AIS D, patients with spinal cord injury other than cervical cord injury, and patients aged <20 years or >70 years, the necessary number of patients was calculated based on the results of the epidemiological survey of spinal cord injury (*Paraplegia.* 1995;33:183-8). The calculation yielded the required number of patients of 113 for the Stemirac group and 120 for the control group
Timing of analysis	Interim analysis: When the number of analyzable patients reaches [redacted] in both Stemirac and control groups (AIS Grade A ≥[redacted] patients, the sum of AIS Grade B and C ≥[redacted] patients) Final analysis: When data from the survey sheets of all enrolled patients are finalized.

The efficacy survey items were selected aiming to evaluate the improvement of neurological symptoms and functional disorders associated with spinal cord injury. In addition to AIS, ISCSCI-92, and SCIM-III used in the clinical study, SF36 was selected as a comprehensive scale for health-related QOL to evaluate the efficacy of Stemirac in a multifaceted manner. As many functional tests as possible are planned to be performed immediately after injury (within 7days), including AIS, followed by functional tests at 6 to 8 weeks (49 ± 7 days) after injury, by which AIS grading will be confirmed. The functional tests will be performed again at a 6-month (180 ± 30 days) interval after injury, which is considered long enough for Stemirac treatment to exert its effect, according to the results of Study STR01-03. AIS will be evaluated using video imaging. The Central Assessment Committee will finalize the AIS assessment by checking the results from each medical institution against video images taken at evaluation, so that the evaluation and assessment are objective.

The safety survey items selected are a causal relationship and the incidences of malfunctions and adverse events including anemia and puncture site pain at bone marrow fluid collection, which are the risks of Stemirac identified in the clinical study. Hypersensitivity (including anaphylaxis) is caused by antibiotics and animal-derived materials used during the production of Stemirac, and it has been identified as an important potential risk, although did not occur in Study STR01-03. Accordingly, hypersensitivity-related data will be collected as well. Further, the safety of Stemirac in children is an important missing information, and is to be collected in the survey. The safety survey is scheduled to be conducted at 6 to 8 weeks (49 ± 7 days), 6 months (180 ± 30 days), and 12 months (360 ± 30 days) after injury. Only life/death status will be checked at 12 months after injury.

8.R Outline of the review conducted by PMDA

PMDA's view:

Because of the limited clinical use experience, continuous monitoring of the efficacy and safety of Stemirac is essential in the post-marketing setting. The applicant proposes a survey designed with a control group of patients who are eligible for Stemirac treatment but do not receive it, and efficacy and safety are evaluated by the comparison of functional outcomes between the Stemirac group and the control group. However, it is possible that the condition of spinal cord injury improves spontaneously. Comparison with a non-randomized control group has a risk of bias in selection. Some of the evaluation indices of the survey are subjective. Considering these points, efficacy and safety should ideally be evaluated by randomized, double-blind, parallel group comparison. Even so, in practice, randomized comparison-based evaluation will be difficult to conduct once Stemirac becomes available for clinical use. After all, the applicant proposal, prospective comparison with the control group of patients who are eligible for Stemirac treatment but do not receive it, is the only possible alternative way to evaluate Stemirac's efficacy and safety, on the premise that objectivity of evaluation or assessment is assured by increasing comparability between the groups.

The efficacy objective of the treatment of patients with spinal cord injury, the target patients of Stemirac, is to improve various neurological symptoms associated with spinal cord injury and improve the activity of daily living. Because the survey is not designed for randomized, double-blind comparison, it requires higher objectivity of evaluation or assessment as mentioned earlier. In this respect, the primary endpoint should be "the percentage of patients with AIS A achieving ≥2 grade improvement in AIS," which refers to motor function improvement for treatment outcome, instead of "the percentage of patients with AIS A achieving ≥1 grade improvement in AIS," which refers to partial improvement in sensory function. Because AIS is not meant for the evaluation of the activity of daily living, the results of SCIM-III, the functional disorder index, should also be referred to assess the clinical significance of Stemirac.

Besides the proposed identified safety risks (anemia and puncture site pain at bone marrow fluid collection), important potential risk (hypersensitivity including anaphylaxis), and important missing information (safety in children), the following potential risks, although which did not occur in Study STR01-03, should be added in the safety survey items to collect data in the planned use results comparative survey.

- Occurrence of hypersensitivity to antibiotics and animal-derived source materials used for the production of Stemirac, and the risk of infection caused by human- or animal-derived source materials
- Risk of ectopic tissue formation due to the pluripotency of MSCs that constitute Stemirac
- Risks of pulmonary embolism, thrombus formation, etc. caused by cells administered intravenously
- Effect of Stemirac's immunomodulatory activity and secretion factors on concurrent or past diseases (onset or aggravation of infection, relapse of cancer, etc.)

In addition, reasons for not being able to produce Stemirac despite success in obtaining peripheral blood and/or bone marrow fluid should be gathered, if any of such cases.

The applicant's proposal on the timing of the survey on efficacy and safety items is appropriate, judging from the time period required for the stabilization of outcome of spinal cord injury and the feasibility of follow-up for patients enrolled in the comparative use results survey.
The results of the clinical study are currently available from only a single site. Therefore, it is critical to further evaluate the efficacy and safety of Stemirac at multiple centers, and the implementation of such study needs to be organized immediately.

The details of the post-marketing use results survey will be finalized, taking account of the comments raised in the Expert Discussion.

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

9.1 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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.

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

The new drug application data (7-1) were subjected to an on-site GCP[9)] inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

10 Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that the product is expected to have a certain level of efficacy in the treatment of neurological symptoms and functional disorders associated with spinal cord injury, and that the product has acceptable safety in view of its benefits. Despite limited information on the efficacy and safety, it is of significance to introduce the product to the clinical setting as a treatment option for patients with spinal cord injury.

PMDA has concluded that the product may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion, with the conditions that require further efficacy confirmation and safety data collection for a certain time period in the post-marketing setting and a

9) At the time of the submission of Stemirac for approval as a regenerative medicine, the Ministerial Ordinance on GCP for Regenerative Medical Products had not been enforced, and the Ministerial Ordinance on GCP for Drugs e was applied to the clinical study.

time limit in accordance with Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The time limit according to the Article will be determined based on the post-marketing surveillance plan (time for pre-launch preparation, patient enrollment, observation of each patient, application preparation, etc.), and comments raised in the Expert Discussion.

Review Report (2)

November 9, 2018

Product Submitted for Approval

Brand Name	Stemirac for Injection
Nonproprietary Name	Human (autologous) bone marrow-derived mesenchymal stem cells
Applicant	Nipro Corporation
Date of Application	June 29, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA concluded that the product is expected to have a certain level of efficacy in patients with spinal cord injury with persisting neurological symptoms and functional disorders, based on the results of a Japanese phase II study (STR01-03) conducted in patients with cervical cord injury assessed as Grade A, B, or C of American Spinal Injury Association Impairment Scale (AIS) to investigate the efficacy and safety of the product.

Because of the limited efficacy information available at present, the efficacy of the product should be further evaluated in the post-marketing setting [Section “7.R.2.3 Results of efficacy evaluation” in Review Report (1)].

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

After reviewing adverse events observed in Study STR01-03, PMDA concluded that the product is tolerated in patients with spinal cord injury. Because of the limited safety information available at present, safety data should be continuously collected in the post-marketing setting, and new findings should be provided appropriately to healthcare professionals. The risks associated with the collection of peripheral blood or bone marrow fluid and the risks of pulmonary embolism, thrombus formation, etc. associated with the

intravenous administration of the product should be highlighted in the package insert. The product should be used at medical institutions fully capable of emergency care whereat the collection of blood or bone marrow fluid and the administration of the product are performed while the patient condition is managed and monitored appropriately by vital sign check and laboratory test, etc. In order to minimize the risks of anemia, hypotension, etc. associated with peripheral blood collection, general guidelines for the total volume of peripheral blood required and a standard collection schedule should be presented in the package insert. Blood collection should be scheduled appropriately in light of the patient's age, body weight, systemic conditions, etc [Section "7.R.3 Safety" of Review Report (1)].

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Indication or performance

As a result of its review in Section "7.R.4 Indication or performance" in Review Report (1), PMDA concluded that the indication, or performance of the product should be set be as follows.

Indication or Performance

Improvement of neurological symptoms and functional disorders associated with spinal cord injury in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) Grade A, B, or C

For the production of Stemirac, substantial volumes of peripheral blood and bone marrow fluid need to be collected within a given time frame, and this will pose a greater risk to pediatric patients due to smaller volume of circulating blood than in adults. The "Precautions for Dosage and Administration or Method of Use" section of the package insert should highlight that whether to use the product for children be decided carefully in light of the patient's age, body weight, systemic condition, etc.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to set indication or performance as above, along with the advice on the use of the product in children, i.e., whether to use should be carefully decided in light of the patient's age, body weight, systemic condition, etc.

The applicant responded appropriately to the above instructions, and PMDA accepted the actions taken.

1.4 Dosage and administration or method of use

As a result of its review in Section "7.R.5 Dosage and administration or method of use" in Review Report (1), PMDA concluded that a guideline for the infusion rate should be added to the proposed description of the "Dosage and Administration or Method of Use" section of the package insert, in the viewpoint of the safety of intravenous administration and the stability of thawed product. The maximum dose of the product is

determined based on per kg body weight, and using up of dosing suspension in a bag may lead to overdosing depending on patients' body weight. This risk should be highlighted in the "Precautions for Dosage and Administration or Method of Use" section of the package insert, and how to prepare the dosing suspension for partial use should be communicated to health professionals appropriately, using written materials, etc.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to give the above cautionary advice in the package insert and to communicate the details of how to prepare dosing suspension for partial use to healthcare professionals in an appropriate manner using written materials.

The applicant responded appropriately and explained that the "Dosage and Administration or Method of Use" section would be revised as follows.

Dosage and Administration or Method of Use

Bone marrow aspiration should be aimed to be performed within 31 days after spinal cord injury, according to the systemic condition, etc. of the patient. Once produced, the product should be administered at the earliest time possible.

Procedures for the collection of source materials of Stemirac

(1) Patient's peripheral blood is collected. The collected peripheral blood is put into a container (Nipro Celltry for serum) enclosed in the blood collection kit. After being tightly sealed, the container holding peripheral blood is transported to a facility designated by the marketing authorization holder.

(2) Patient's bone marrow fluid is collected. The collected bone marrow fluid is put into a container (Nipro Celltry for bone marrow), and the bone marrow fluid diluent DMEM, enclosed in the bone marrow collection kit, is added to be mixed. After being tightly sealed, the container holding bone marrow fluid is transported to a facility designated by the marketing authorization holder

Procedures for the administration of Stemirac to the patient

The product is administered by intravenous drip infusion at a rate of 0.7 to 1.0 mL/min, as 0.5×10^8 to 2.0×10^8 autologous bone marrow-derived MSCs (maximum dose, 3.34×10^6 cells per kg body weight) while being diluted ≥3-fold with physiological saline.

PMDA accepted the revised "dosage and administration or method use."

1.5 Qualifications for medical institutions and doctors using use Stemirac

As a result of its review in Section "7.R.6 Qualifications for medical institutions and doctors using Stemirac" in Review Report (1) in relation to the proper use of the product in clinical practice, PMDA generally accepts the qualifications proposed by the applicant. Also, PMDA concluded that the total volumes of the peripheral blood and the bone marrow fluid necessary for the production of Stemirac and a standard collection schedule,

eligibility criteria for the treatment, properties of the product, administration method, precautions for use, etc. should be communicated appropriately via the package insert, written materials, and training seminar, and that Stemirac must be handled by doctors who have acquired such knowledge.

Approval condition-based post-marketing evaluation is to be conducted before the expiry of the approval of Stemirac, and it requires AIS evaluation, etc. The evaluation must be conducted appropriately by well-trained evaluators at baseline and post dose. A majority of patients are expected to be transferred from an acute phase hospital to a rehabilitation hospital during the course of treatment. Both parties should establish Cooperation should be established between them to collect efficacy and safety data for a specific time period, not only at the time of treatment but also during the subsequent follow up period.

Regarding the qualifications for medical institutions and doctors for the use of Stemirac, the following comments were raised by expert advisors at the Expert Discussion.

- Given the real clinical practice in Japan, the involvement of an orthopedist or a neurosurgeon who has sufficient knowledge and experience in the treatment of spinal cord injury in the field of spinal surgery, is essential.
- For the collection of peripheral blood and the bone marrow fluid required for the production of Stemirac, coordination with a hematologist with sufficient knowledge and experience in bone marrow collection and transplantation, peripheral blood stem cell transplantation, etc. is important.

Other conclusions of PMDA were supported by the expert advisors.

Based on the comments raised in the Expert Discussion, PMDA concluded that the qualifications for medical institutions and doctors for the use of Stemirac proposed by the applicant need the following addition: (i) involvement of an orthopedist or a neurosurgeon with sufficient knowledge and experience in the treatment of spinal cord injury (mandatory), and (ii) coordination with a hematologist with sufficient knowledge and experience in bone marrow collection and transplantation, peripheral blood stem cell transplantation, etc.

Based on the above, PMDA instructed the applicant to set qualifications for medical institutions and doctors for the use of Stemirac according to its conclusions. In response, the applicant modified the qualifications by reflecting PMDA's instruction.

- Surgeons familiarized with the diagnosis and treatment of spinal cord injury, namely, specialists in neurosurgery or orthopedic surgery
- Doctors who have attended a training seminar organized by the marketing authorization holder
- Medical institutions well-prepared for prompt and appropriate actions against adverse events in coordination with hematologists with expert knowledge and skills in bone marrow fluid and peripheral blood collection (to be guided or assisted when tackling adverse events associated with these procedures)
- Medical institutions capable of safe and hygienic bone marrow and peripheral blood collection

- Medical institutions capable of malignant tumor testing or have test results available
- General medical institutions accommodating emergency care, or medical institutions prepared for emergency care by allying with a hospital accommodating such service

PMDA accepted the above proposal.

The applicant's further explanation:
In the approval condition-based post-marketing evaluation, efficacy will be evaluated by the central assessment committee, using video images. The applicant will confirm the feasibility of AIS evaluation, etc. including video imaging at each facility using Stemirac. Two or more doctors who have attended a training seminar organized by the marketing authorization holder will be responsible for the evaluation at baseline and post dose of Stemirac. PMDA accepted the explanation of the applicant.

1.6 Approval condition-based post-marketing evaluation plan (draft)
PMDA's conclusion on the post-marketing investigations as a result of the review in Section "8.1 Post-marketing investigations" of Review Report (1):

- Because of the limited information available on the efficacy and safety of the product, an approval condition-based post-marketing evaluation should be conducted to evaluate the efficacy and safety of the product continuously in the post-marketing setting.
- Efficacy evaluation should preferably be conducted in a form of a randomized, comparative study between a group treated with Stemirac and another group untreated. However, such study will be practically infeasible once the product is approved for marketing and made available in the clinical setting. Given this situation, there will be no alternative way to evaluate the efficacy and safety of Stemirac in an approval condition-based post-marketing evaluation, on the premise that the objectivity of evaluation and assessment is maintained by increasing comparability between the groups, but in a form of a comparative use results survey with a control group of patients not receiving Stemirac despite their eligibility, to collect data prospectively for comparison against patients treated with Stemirac, as proposed by the applicant.
- In the approval condition-based post-marketing evaluation, the primary endpoint should be "the percentage of patients with AIS A showing ≥2 grade improvement in AIS," which evaluates motor function improvement.
- In addition to the proposed identified risks (anemia and puncture site pain at bone marrow fluid collection), important potential risk (hypersensitivity including anaphylaxis), and important missing information (safety in children), the following potential risks should be subjected to data collection as safety survey items.
  - ✓ Occurrences of hypersensitivity to antibiotics and animal-derived source materials used for the production of Stemirac, and the risk of infection caused by human- or animal-derived source materials
  - ✓ Risk of ectopic tissue formation due to the pluripotency of MSCs that constitute Stemirac

- ✓ Risk of pulmonary embolism, thrombus formation, etc. caused by cells administered intravenously
- ✓ Effect of Stemirac's immunomodulatory activity and secretion factors on concurrent or past diseases (occurrence or aggravation of infection, relapse of cancer, etc.)

- Reasons for not being able to produce Stemirac despite success in obtaining peripheral blood and/or bone marrow fluid should be gathered, if any of such cases.
- The proposed timing of the survey of efficacy and safety evaluation is appropriate, judging from the time period required for the stabilization of outcome of spinal cord injury and the feasibility of follow-up for patients enrolled in the comparative use results survey.

The above opinions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- The assessment of neurological symptoms at the respective medical institutions should be performed by ≥2 doctors.
- Collected data must be valid for the analysis of a relationship between the dosing timing and efficacy of Stemirac.
- It is important to ensure the comparability between both groups remains acceptable. If the sample size is planned to be adjusted as a result of the interim analysis, a procedure for the adjustment should be strictly determined in advance.
- Data on allodynia in the course of motor function recovery should be collected.

Based on the comments raised in the Expert Discussion, PMDA instructed the applicant to review the approval condition-based post-marketing evaluation plan.

The applicant submitted the outline of the approval condition-based post-marketing evaluation plan shown in Table 26, and provided the following explanation.

Table 26. Outline of the approval condition-based post-marketing evaluation (draft)

Objective	Evaluation of the efficacy and safety of Stemirac
Survey method	All-case surveillance
Population	Patients with traumatic spinal cord injury with AIS Grade A, B, or C at enrollment in acute to subacute phase
Observation period	12 months after injury
Survey period	Until the re-submission of an approval application after conditional and term-limited approval
Efficacy survey items	Cohort 1, Patients with AIS Grade A at 6 to 8 weeks (49 ± 7 days) after injury Primary endpoint • Percentage of patients achieving ≥2 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury Main secondary endpoints • Percentage of patients achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Mean change in the total scores of ISCSCI-92, SCIM-III, and SF36, and change in the level of injury (ISCSCI-92) at 180±30 days from 6 to 8 weeks (49±7 days) after injury Cohort 2, Patients with AIS Grade B or C at 6 to 8 weeks (49 ± 7 days) after injury Primary endpoint Percentage of patients with AIS Grade B or C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury Main secondary endpoints • Mean change in the sum of ISCSCI-92, SCIM-III, and SF36 scores and change in the level of injury

	(ISCSCI-92) in patients with AIS Grade B or C at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Percentage of patients with AIS Grade B achieving ≥1 grade improvement in AIS, and percentage of patients with AIS Grade B achieving ≥2 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Percentage of patients with AIS Grade C achieving ≥1 grade improvement in AIS at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Mean change in the sum of ISCSCI-92, SCIM-III, and SF36 scores and change in the level of injury (ISCSCI-92) in patients with AIS Grade B at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury • Mean change in the sum of ISCSCI-92, SCIM-III, and SF36 scores and change in the level of injury (ISCSCI-92) in patients with AIS C at 180 ± 30 days from 6 to 8 weeks (49 ± 7 days) after injury
Safety survey items	Anemia, puncture site pain during bone marrow fluid collection, and other malfunctions and adverse events; causal relationship to Stemirac and incidence of each malfunction or adverse event
Population	Patients enrolled in the surveillance are included in ITT population. FAS is used as the main population for efficacy analyses. Secondary analyses are performed in ITT population. The safety analysis population is the ITT population excluding those without any safety data. FAS is defined as the population of patients in whom all of the following criteria are met. Stemirac group: • Patients who are enrolled in the surveillance, have peripheral blood and bone marrow fluid collected, and are treated with Stemirac • Patients who have the result of AIS evaluation at 6 to 8 weeks (49 ± 7 day) after injury Control group • Patients enrolled in the surveillance • Patients who have the result of AIS evaluation at 6 to 8 weeks (49 ± 7 day) after injury The primary endpoint is analyzed in 2 separate cohorts; cohort 1 consisting of patients with cervical cord injury aged 20 to 70 years with AIS Grade A in FAS and cohort 2 consisting of patients with cervical cord injury aged 20 to 70 years with AIS Grade B or C in FAS.
Target sample size	Target number of analyzable patients (FAS) <u>Cohort 1</u> Patients with cervical cord injury aged 20 to 70 years with AIS Grade A at week 6 to 8 after injury: 27 in the Stemirac group, 54 in the control group. If the number of patients enrolled in the control group reaches the target sample size before that in the Stemirac group does, further enrollment of up to 81 patients was accepted in the control group, aiming at the ratio of the Stemirac group to the control group of 1 to 3. Justification for the target sample size According to Scivoletto, et al., the standard treatment improved AIS by 2 grades in 4.8% of patients with AIS Grade A at 30 days after injury. In Study STR01-03, Stemirac improved AIS by ≥2 grades in 33.3% of patients with AIS Grade A. In light of these outcomes, when the percentage of patients achieving ≥2 grade improvement in AIS is obtained by [redacted] test, conservatively assuming the estimated percentage of improvement to be [redacted]% in the control group and [redacted]% in the Stemirac group, 2-sided significance level [redacted]%, the power of test [redacted]%, and the assignment ratio [redacted], 27 and 54 patients with AIS Grade A, respectively, are required for the Stemirac group and the control group. <u>Cohort 2</u> Patients with cervical cord injury aged 20 to 70 years with AIS Grade B or C at week 6 to 8 after cervical cord injury: 63 in the Stemirac group, 125 in control group. If the number of patients enrolled in the control group reaches the target sample size before that in the Stemirac group does, further enrollment of up to 189 patients was accepted in the control group, aiming at the ratio of the Stemirac group to the control group of to 3. Justification for the target sample size Similarly to Cohort 1, when the percentage of patients achieving ≥1 grade improvement in AIS in patients with AIS B or C is obtained by [redacted] test conservatively assuming the estimated percentage of improvement by the standard treatment to be [redacted]% and the estimated percentage of improvement by Stemirac [redacted]%, 2-sided significance level [redacted]%, and the power of test [redacted]%, 63 and 125 patients with AIS Grade B or C are required for the Stemirac group and the control group, respectively.
	Expected necessary numbers of patients to be enrolled 198 in the Stemirac group, 414 in the control group Justification for the expected necessary number of patients to be enrolled The expected necessary number of patients was determined so that the target number of analyzable patients is achieved. Assuming the rate of withdrawal to be [redacted]% in the Stemirac group and [redacted]% in the control group, considering the possibility of enrollment of patients ineligible for the analysis of the primary endpoint, the necessary number of patients was calculated based on the results of the epidemiological survey of spinal cord injury (*Paraplegia.* 1995;33:183-8). The calculation yielded the required number of patients of 108 for the Stemirac group and 227 for the control group in Cohort 1, and 198 for the

	Stemirac group and 414 for the control group in Cohort 2. Accordingly, the expected necessary number of patients to be enrolled was set at 198 in the Stemirac group and 414 in the control group.
Timing of analysis	Interim analysis Cohort 1 When the number of patients enrolled (FAS) reaches ■ in the Stemirac group and ■ in the control group. Cohort 2 When the number of patients enrolled (FAS) reaches ■ in the Stemirac group and ■ in the control group. Final analysis: At the completion of surveys on all efficacy-related items until 6 months after injury are completed with the target number of analyzable patients (FAS) of each cohort. Check for life/death status at 12 months after injury is to be continued after the final analysis.

- According to Scivoletto et al (*Arch Phys Med Rehabil.* 2004;85:485-9, *Front Hum Neurosci.* 2014;8:1-11), patients with AIS A will have different prognosis from that of patients with AIS B or C at week 6 to 8 (49 ± 7 days) after injury. Therefore, patients with AIS A will be separated from the cohort of patients with AIS B or C, and efficacy will be evaluated in the hypothesis test-based number of patients.
- The primary endpoint in Cohort 1 (AIS A) will be the percentage of patients showing ≥2 grade improvement in AIS, and that in Cohort 2 (AIS B or C) the percentage of patients showing ≥1 grade improvement in AIS. According to Scivoletto et al (*Arch Phys Med Rehabil 2004; 85: 485-9, Front Hum Neurosci 2014; 8: 1-11*), the percentage of patients showing ≥1 grade improvement in AIS after receiving the standard treatment is expected to be similar between those with AIS B and those with AIS C. Therefore, the primary endpoint in Cohort 2 (AIS B or C) will be calculated as the percentage of the sum of patients with AIS B and C achieving the target improvement. In patients with AIS B or C, ≥1 grade improvement in AIS indicates improved motor function. Thus, the objectivity of the evaluation is ensured by the visual assessment of the patient's motor function based on video imaging.
- The interim analysis will be conducted to investigate the comparability between the Stemirac group and the control group. There will be no revision of the number of patients. Instead, the following plans will be added.
  - ✓ In the interim analysis, the independent monitoring committee will evaluate bias in patient characteristics between the groups and possible factors affecting the improvement in AIS.
  - ✓ The independent monitoring committee will review the record of efficacy endpoints and possible confounding factors. When non-uniformity is observed in the distribution of possible confounding factors, the independent monitoring committee will investigate the necessity of performing the final analysis with such confounding factors taken into account. The independent monitoring committee will make recommendation to the department of the sponsor responsible for the management of the post-marketing surveillance based on the above investigation.
  - ✓ The department responsible for the management of the surveillance will instruct the department responsible for the conduct of the surveillance to take necessary measures. The department responsible for management of the surveillance will not disclose the results of the interim analysis and the details of the recommendation to the department responsible for conduct of the surveillance or the medical institutions.
- The analyses in both Cohorts 1 and 2 will require patients to be enrolled for approximately 5 years.

- The following potential risks will be included in the safety specifications, and relevant information will be collected in the comparative use results survey to be conducted.
  - ✓ Occurrences of hypersensitivity to antibiotics and animal-derived source materials used in the manufacture process of the product, and the risk of infection caused by human- or animal-derived source materials
  - ✓ Risk of ectopic tissue formation due to the pluripotency of MSCs that constitute Stemirac
  - ✓ Risk of pulmonary embolism, thrombus formation, etc. caused by cells administered intravenously
  - ✓ Effect of Stemirac's immunomodulatory activity and secretion factors on concurrent or past diseases (occurrence or aggravation of infection, relapse of cancer, etc.)
- Reasons for not being able to produce Stemirac despite success in obtaining peripheral blood and/or bone marrow fluid should be gathered, if any of such cases.
- Neurological symptoms are to be assessed by ≥2 doctors at each medical institution.
- Collected data must be valid for the analysis of a relationship between the dosing timing and efficacy of Stemirac.
- Information on allodynia during recovery of motor function will be collected.

PMDA's view on the outline of the approval condition-based post-marketing evaluation (draft):
Due to the expected different clinical courses of spinal cord injury, the applicant plans to conduct the efficacy evaluation assigning patients with AIS B or C to a separate cohort from that of patients with AIS A and determining the number of patients for each cohort by hypothesis testing. These plans of the applicant are acceptable. The primary endpoint for Cohort 2 (AIS B or C), the percentage of patients achieving ≥1 grade improvement in AIS in combined patients with AIS B or C to evaluate motor function improvement, is also acceptable. Yet, the efficacy of Stemirac for each AIS B and C should also be explained based on the secondary endpoints, the results of separate analyses in patients with AIS B and C and based on SCIM-III, etc., the indices for functional disorders.

PMDA accepted the draft of approval condition-based post-marketing evaluation and response by the applicant.

2. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved with the modified descriptions of Indication or Performance and Dosage and Administration or Method of Use shown below and the following conditions of approval, provided that necessary cautionary advice is given in the package insert and information concerning the proper use of the product is disseminated appropriately in the post-marketing setting. This is conditional and time-limited approval in accordance with Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The time limit according to said Article is 7 years, and the product need not be classified as a specified regenerative medical product.

Indication or Performance

Improvement of neurological symptoms and functional disorders associated with spinal cord injury in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C

Dosage and Administration or Method of Use

Bone marrow aspiration should be aimed to be performed within 31 days after spinal cord injury, according to the systemic condition, etc. of the patient. Once produced, the product should be administered at the earliest time possible.

Procedures for the collection of source materials of Stemirac

(1) Patient's peripheral blood is collected. The collected peripheral blood is put into a container (Nipro Celltry for serum) enclosed in the blood collection kit. After being tightly sealed, the container holding peripheral blood is transported to a facility designated by the marketing authorization holder.

(2) Patient's bone marrow fluid is collected. The collected bone marrow fluid is put into a container (Nipro Celltry for bone marrow), and the bone marrow fluid diluent DMEM, enclosed in the bone marrow collection kit, is added to be mixed. After being tightly sealed, the container holding bone marrow fluid is transported to a facility designated by the marketing authorization holder.

Procedures for the administration of Stemirac to the patient

The product is administered by intravenous drip infusion at a rate of 0.7 to 1.0 mL/min, as a dose of 0.5×10^8 to 2.0×10^8 autologous bone marrow-derived MSCs (maximum dose, 3.34×10^6 cells per kg body weight) while being diluted ≥3-fold with physiological saline.

Conditions of Approval

1. The product should be used only for patients considered eligible for the treatment and only under the supervision of a specialist with sufficient knowledge and experience in diagnosis and treatment of spinal cord injury, at medical institutions fully capable of emergency care where patients are appropriately monitored and managed vital sign check and laboratory test, etc.
2. The applicant is required to conduct an approval condition-based post-marketing evaluation in all patients treated with the product during the period after the conditional and time-limited approval until reapplication for marketing approval.

List of Abbreviations

[redacted]	[redacted]
AIS	American Spinal Injury Association Impairment Scale
ALCAM	Activated leukocyte cell adhesion molecule
ASIA	American Spinal Injury Association
BDNF	Brain-derived neurotrophic factor
CI	Confidence interval
CX3CL1	Fractalkine
DMEM	Dulbecco's Modified Eagle's Medium
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELISA	Enzyme linked immunosorbent assay
FAS	Full analysis set
FCM	Flow cytometry
FOB	Functional observational battery
GFP-rMSC	MSC cultivated from the bone marrow of GFP gene-transgenic mice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HGFR	Hepatocyte growth factor receptor
HIV	Human immunodeficiency virus
HTLV	Human T-cell leukemia virus
ISCSCI-92	International Standards for Neurological and Functional Classification of Spinal Cord Injury 1992 version
ITGA4	Integrin 4
ITGAV	Integrin V
ITGB1	Integrin β1
ITT	Intent-to-treat
LacZ-rMSC	LacZ-labeled rat MSC
MAP2	Microtubule-associated protein 2
MCP-1	Monocyte chemoattractant protein-1
MMP1	Matrix metalloproteinase1
MMP2	Matrix metalloproteinase2
MMT	Manual muscle test
MSC	Mesenchymal stem cell
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCAD	Neural cadherin
NCAM	Neural cell adhesion molecule
NGF	Nerve growth factor
NGFR	Nerve growth factor receptor
PMDA	Pharmaceuticals and Medical Devices Agency

PlGF	Placental growth factor
RT-PCR	Reverse transcription polymerase chain reaction
SCIM	Spinal cord independence measure
Sapporo Medical University	Sapporo Medical University, the public university of Hokkaido
TGF-β1	Transforming growth factor-β1
TIMP1	Metallopeptidase inhibitor 1
TIMP2	Metallopeptidase inhibitor 1
TSG-6	TNF-stimulated gene-6
Tie2	Receptor-type tyrosine kinase Tie2
VEGF	Vascular endothelial growth factor