Report on the Deliberation Results

May 24, 2021
Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Category	Gene therapy products, 3. Gene expression therapy product
Non-proprietary Name	Teserpaturev
Brand Name	Delytact Injection
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2020 (marketing application)

Results of Deliberation

In its meeting held on May 24, 2021, 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 product may be approved. A conditional and time-limited approval is applicable to the product. The approval conditions and the duration of approval are as follows.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with adequate knowledge and experience in treatment of malignant glioma and neurosurgical procedures who has been fully informed of results and adverse events in clinical studies of the product in an environment where appropriate measures such as monitoring and management with laboratory tests are available at a medical institution capable of responding to emergencies.
2. The applicant is required to conduct a post-marketing approval condition assessment in all the patients treated with the product until filing the marketing application after conditional time-limited approval.
3. The applicant is required, in order to ensure that the product is used in compliance with provisions for Type 1 Use approved under the "Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003)," to take necessary measures such as announcement of the provisions for use.

Duration of Approval

7 years

Review Report

May 13, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Delytact Injection
Category	Gene therapy products, 3. Gene expression therapy product
Non-proprietary Name	Teserpaturev
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a genetically engineered herpes simplex virus type 1 (strain F) in which *α47* gene and 2 *γ34.5* genes have been deleted, and the *infected cell protein* 6 (*ICP6*) gene has been inactivated by insertion of the *lacZ* gene from *Escherichia coli*.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 4 of 2017 [*29 sai*]; PSEHB/MDED Notification No. 0710-1 dated July 10, 2017, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) SAKIGAKE designation regenerative medical product (SAKIGAKE Regenerative Medical Product Designation No. 2 of 2015 [*27 sai*]; PSEHB/ELD/OMDE Notification No. 0210-4 dated February 10, 2016, by the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), SAKIGAKE comprehensive assessment consultation conducted 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 malignant glioma, and that the product has acceptable safety (see Attachment). Because information is limited at present, the applicant should continue evaluating the efficacy of the product even after the market launch.

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 approval conditions, and the conditional time-limit under Article 23-26 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Indication or Performance

Malignant glioma

Dosage and Administration or Method of Use

The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. In principle, the first and second doses are separated by 5 to 14 days, and each of the third and subsequent doses is separated from the previous dose by 4 weeks. Up to 6 doses may be administered.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with adequate knowledge and experience in treatment of malignant glioma and neurosurgical procedures who has been fully informed of results and adverse events in clinical studies of the product in an environment where appropriate measures such as monitoring and management with laboratory tests are available at a medical institution capable of responding to emergencies.
2. The applicant is required to conduct a post-marketing approval condition assessment in all the patients treated with the product until filing the marketing application after conditional time-limited approval.
3. The applicant is required, in order to ensure that the product is used in compliance with provisions for Type 1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” to take necessary measures such as announcement of the provisions for use.

Attachment

Review Report (1)

March 16, 2021

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

1. Product Submitted for Approval

Brand Name	Delytact Injection
Category	Gene therapy products, 3. Gene expression therapy product
Non-proprietary Name	Teserpaturev
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a genetically engineered herpes simplex virus type 1 (strain F) in which *α47* gene and 2 *γ34.5* genes have been deleted, and the *infected cell protein* 6 (*ICP6*) gene has been inactivated by insertion of the *lac*Z gene from *Escherichia coli*.

Proposed Indication or Performance

Malignant glioma

Proposed Dosage and Administration or Method of Use

The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. In principle, the first and second doses are separated by 1 week, and each of the third and subsequent doses is separated from the previous dose by 4 weeks.

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 proposed product

Delytact is a genetically engineered replication-competent herpes simplex virus type 1 (HSV-1). Delytact is the virus derived from HSV-1 strain F in which *γ34.5* gene[1)] and *α47* gene[2)] necessary for replication in normal cells have been deleted, and the *infected cell protein* 6 (*ICP6*) gene[3)] has been inactivated by insertion of the marker *lacZ* gene to ensure selective replication in tumor cells and enhance antitumor immunity.

Delytact, when intratumorally administered to patients with malignant glioma, is expected to exert the following effects: 1) The mutant virus selectively replicates in tumor cells and destroys the infected cells through the replication process, exerting a cytocidal effect; and 2) the administration leads to induction of tumor-responsive T cells, which activates antitumor immune response and thereby prolongs survival of patients with malignant glioma.

Delytact was designated as an orphan regenerative medical product with the intended indication or performance of "malignant glioma" dated July 10, 2017 (Orphan Regenerative Medical Product Designation No. 4 of 2017 [29 *sai*]). In addition, Delytact was designated as a regenerative medical product with the intended indication or performance of "malignant glioma" to be reviewed under the SAKIGAKE Designation System (SAKIGAKE Regenerative Medical Product Designation No. 2 of 2015 [27 *sai*]) dated February 10, 2016.

1.2 Development history, etc.

Glioma is a primary brain tumor originated from the glial cells that support neurons. Glioma is highly invasive and intractable with a very limited possibility of complete cure. On the basis of the histopathological findings and clinical malignancy, glioma is classified into any of Grades I to IV. Gliomas classified as highly malignant Grade III (anaplastic astrocytoma and anaplastic oligodendroglioma) and Grade IV (glioblastoma) lesions are referred to as malignant glioma. The annual number of individuals who are found to have primary brain tumor is estimated to be approximately 20,000 in Japan (General Rules for Clinical and Pathological Studies on Brain Tumors [in Japanese]. the fourth edition. Kanehara & Co., Ltd. 2018). When percentages of patients with brain tumor of each grade reported in Brain tumor registry in Japan by The Japan Neurosurgical Society (2005-2008) are applied to the above number, approximately 1,260 and 2,400 individuals are presumed to be annually found to have Grade III malignant glioma and Grade IV glioblastoma, respectively.

The standard of care for primary malignant glioma is multimodal therapies including surgical resection, radiotherapy (RT), and use of temozolomide (TMZ) (Practical Guidelines for Neuro-Oncology 2019 [edited by the Japan Society for Neuro-Oncology] [Japanese clinical practice guideline]). Most of the

---

1) It is the gene related to HSV-1 pathogenicity, and deletion of the *γ34.5* gene almost precludes the mutant virus from replicating in normal cells. In normal cells, viral infection induces phosphorylation of the double-stranded ribonucleic acid (RNA)-dependent protein kinase (PKR), which then phosphorylates the eukaryotic translation initiation factor-2a (eIF-2a), subsequently blocking intracellular synthesis of proteins including viral proteins. As a result, no viral replication occurs. The protein encoded by the *γ34.5* gene inhibits eIF-2a phosphorylation by antagonizing phosphorylated PKR, enabling protein synthesis and viral replication. The *γ34.5*-gene deficient HSV-1 cannot replicate in normal cells but can do in tumor cells where the phosphorylated PKR level is low.

2) The protein encoded by *α47* gene inhibits the antigen presentation-related transporter on infected cells and thereby suppresses major histocompatibility complex (MHC) class I expression on the cell surface engaged in presenting viral proteins as antigens.

3) It encodes ICP6, the large subunit of ribonucleotide reductase (RR) that is essential for viral DNA synthesis. The ICP6-inactivated mutant virus can replicate only in actively proliferating cells that express RR at a high level but not in cytostatic cells.

patients, however, experience recurrence in several months to several years after the initial treatment. Although bevacizumab (genetical recombination) and others are used for treatment of recurrent malignant glioma, no standard of care is established. In patients with Grade III and IV malignant glioma, 5-year survival rates are 43.2% to 63.3% and 15.5%, respectively, with poor outcome, leading to high demand for development of a new treatment.

Oncolytic virotherapy uses replication-competent virus that replicates selectively in tumor cells. In this therapy, tumor cells are infected with such a virus, and then destroyed through the viral innate cytocidal effect associated with its replication. Furthermore, to ensure that the virus, when intratumorally injected, can retain the replication competence at the maximum while keeping the pathogenic effect on normal tissues at the minimum, a recombinant virus in which the viral genome has been genetically modified is used.

Before development of Delytact, G207, a recombinant HSV-1, was developed through artificial genetical modification (deletion of the *γ34.5* gene and inactivation of the *ICP6* gene) (*Nat Med.* 1995;1:938-43). Delytact is a product developed by commercializing G47Δ, which was prepared through deletion of the *α47* gene from G207 by Todo, et al. of the Institute of Medical Science, The University of Tokyo. For this product, a clinical investigation was conducted in patients with RT-refractory glioblastoma as a Japanese phase I/II study, and a Japanese phase II study (Study GD01) was conducted in patients with glioblastoma in whom the tumor remained or recurred after RT with concomitant TMZ.

On the basis of the results from Study GD01, a marketing application for Delytact with the proposed indication or performance of "malignant glioma" has now been filed. Study GD01 was conducted as an investigator-initiated clinical trial under the Practical Research for Innovative Cancer Control program of the Japan Agency for Medical Research and Development.

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

Delytact is manufactured as follows: The working virus seed stock (WVSS) of Delytact is inoculated into cells expanded from the working cell bank (WCB) for manufacture of Delytact to replicate the virus followed by purification.

2.1 Drug substance

2.1.1 Generation and control of cell substrates for manufacture of drug substance

African green monkey kidney epithelial cells (Vero cells) are used for manufacture of the drug substance. Using the [redacted] Vero cells ([redacted], [redacted] [redacted], [redacted]) obtained from [redacted] by [redacted] as the original material, the master cell bank (MCB) and WCB for manufacture of the drug substance were generated from the seed cells of the [redacted] passage culture at [redacted].

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were subjected to characterization and purity tests, which were performed in accordance with the ICH Q5A (R1) guideline. Table 1 shows tests

for adventitious agents performed on the MCB (Batch [redacted], [redacted] passage), WCB (Batch [redacted], [redacted] passage), and CAL (Batch [redacted], [redacted] passage). In these tests, neither viral nor non-viral adventitious agents were detected within the range of parameters tested.

The MCB and WCB are stored in [redacted] or at [redacted]°C. The MCB and WCB are checked for [redacted], [redacted], and [redacted] at [redacted] or [redacted] to evaluate the stability during the storage period.

New MCB [redacted], new WCB will be prepared [redacted].

Table 1. Tests for adventitious agents in MCB, WCB, and CAL

Test parameter	Description or method of evaluation	MCB	WCB		CAL
				At preparation	
Retrovirus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	test	[redacted]	[redacted]	[redacted]	[redacted]
	test ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]
Adventitious virus	*In vitro* [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
	In vitro [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
	In vitro [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
	In vitro [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
	In vivo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	In vivo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	In vivo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	In vivo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vitro bovine virus	*In vitro* [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
	In vitro [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
In vitro porcine virus	*In vitro* [redacted] cells	[redacted]	[redacted]	[redacted]	[redacted]
Human virus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simian virus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bovine virus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Porcine virus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sterility	Direct inoculation method (JP)	[redacted]	[redacted]	[redacted]	[redacted]
Mycoplasma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acid-fast bacillus	EP	[redacted]	[redacted]	[redacted]	[redacted]

2.1.2 Generation and control of virus seed stocks for manufacture of drug substance

Virus seed received from [redacted] was inoculated in Vero cells ([redacted] passage) expanded from the WCB (Batch [redacted], [redacted] passage) to generate the master virus seed stock (MVSS) (Batch [redacted]) for manufacture of the drug substance. Furthermore, the MVSS was inoculated into Vero cells ([redacted] passage) expanded from the WCB to generate the WVSS (Batch [redacted]) for manufacture of the drug substance.

The MVSS and WVSS were subjected to characterization and purity tests, which were performed in accordance with the ICH Q5A (R1) guideline (Table 2). Neither viral nor non-viral adventitious agents were detected within the range of parameters tested.

The MVSS and WVSS are stored at [redacted]°C. The MVSS and WVSS are subjected to [redacted] measurement [redacted] or [redacted] to evaluate the stability during the storage period.

New MVSS [redacted], new WVSS will be prepared [redacted].

Table 2. Tests for MVSS and WVSS

Test parameter	Method of evaluation	MVSS	WVSS	
				At preparation
Retrovirus	[redacted]	[redacted]	[redacted]	[redacted]
	test			
	test ([redacted])			
Adventitious virus[*1]	*In vitro* [redacted] cells			
	In vitro [redacted] cells			
	In vitro cells			
	In vivo [redacted]			
	In vivo [redacted]			
	In vivo [redacted]			
In vitro bovine virus[*1]	*In vitro* cells			
	In vitro cells			
In vitro porcine virus[*1]	*In vitro* cells			
Human virus	[redacted]	[redacted]	[redacted]	[redacted]
Simian virus	[redacted]	[redacted]	[redacted][*2]	[redacted]
Bovine virus	[redacted]	[redacted]	[redacted]	[redacted]
Porcine virus	[redacted]	[redacted]	[redacted][*3]	[redacted]
Sterility	Direct inoculation method (JP)	[redacted]	[redacted]	[redacted]
Mycoplasma	[redacted] ([redacted])			
Acid-fast bacillus	Culturing method (EP)			
Titer	[redacted] method			
DNA sequencing of genetically modification site	[redacted] method	[redacted]	[redacted]	[redacted]
Uniformity of divided dosage units	[redacted] method ([redacted] method)	[redacted]	[redacted]	[redacted]
[redacted]	test	[redacted]	[redacted]	[redacted]
[redacted]	test			
	[redacted] method			

*1 [redacted] test
*2 [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] only
*3 [redacted] only

2.1.3 Manufacturing process

The manufacturing process of the drug substance consists of processes for cell culture, virus culture, harvest, [redacted], [redacted], [redacted], [redacted], and final filtration.

The critical process steps are defined as [redacted], [redacted], [redacted], [redacted], and [redacted]. In the harvest process, the test for virus in the unprocessed bulk harvest is performed on the [redacted] ([redacted]) of [redacted] collected in the [redacted] prepared from [redacted]. The tests include [redacted], [redacted], and [redacted].

The verification-based control strategy is constructed for the manufacturing process of the drug substance. The verification parameter specified is the [redacted] ([redacted] process).

2.1.4 Safety evaluation of adventitious agents

Table 3 shows biological raw materials used in the manufacturing process of the drug substance other than Vero cells, all of which have been confirmed to conform to the Standards for Biological Ingredients.

Table 3. Biological raw materials other than Vero cells

Raw material	Animal	Site used	Process used
Fetal bovine serum	Cattle	Blood	[redacted] and [redacted], [redacted] and [redacted], [redacted]
Trypsin	Pig	Pancreas	[redacted] and [redacted]
Casein hydrolysate	Cattle	Milk	[redacted]

Of the unprocessed harvest after the end of production culture, each manufacturing batch is subjected to tests for adventitious agents (for [redacted], [redacted], sterility, and [redacted][4]).

2.1.5 Manufacturing process development

Main changes on the manufacturing process in a course of the development of the drug substance are as shown below (relevant manufacturing processes are denoted as Process A and Process B [proposed process]). The product produced from the drug substance manufactured by Process A was used in non-clinical studies and Study GD01.

- Change from Process A to Process B (proposed process): A change of [redacted], [redacted], [redacted], [redacted], change of [redacted] (from [redacted] to [redacted]), and addition of [redacted].

In association with the above process changes, comparability evaluation on quality attributes was performed and demonstrated comparability between the pre- and post-change products [see Section 2.2.3].

2.1.6 Characterization

2.1.6.1 Structure and characterization

Table 4 shows characterization of structure and physicochemical properties, biological activities, and purity and impurities.

Table 4. Characterization items

Characterization	Test parameter
Structure and physicochemical properties	Base sequencing of genetically modification site, transmission electron microscopy, [redacted]
Biological activities	[redacted] activity, [redacted]
Purity and impurities	[redacted], Impurity A, Impurity B, Impurity C, Impurity D, Impurity E

[4] The test is performed on the [redacted] ([redacted]) of [redacted] collected in the [redacted] prepared from [redacted].

2.1.6.2 Structure and physicochemical properties

[redacted] and [redacted] have confirmed deletion of the *γ34.5* gene, insertion of the *lacZ* gene into the *ICP6* locus, and deletion of the *α47* gene. In addition, transmission electron microscopy showed [redacted].

2.1.6.3 Biological activities

On the human [redacted] cell line [redacted], a titer-dependent [redacted] effect was observed. In addition, the activity was decreased in a [redacted]-concentration-dependent manner. The tier is included in the specifications of the drug substance as a test parameter for the [redacted] activity, and the [redacted] is to be [redacted] during [redacted].

2.1.6.4 Product-related substances/Product-related impurities

Transmission electron microscopy and [redacted] revealed presence of Impurity F ([redacted], [redacted]), which were deemed as product-related impurities as with Impurity E. [redacted] and [redacted] were deemed as product-related substances. [redacted] and Impurity E are to be [redacted] during [redacted].

2.1.6.5 Process-related impurities

Process-related impurities include Impurity A, Impurity B, Impurity C, and Impurity D. Any of the process-related impurities has been confirmed to be adequately removed during the manufacturing process. In addition, Impurity A, Impurity B, and Impurity D are controlled by the specifications of the drug substance.

2.1.7 Control of drug substance

The proposed specifications for the drug substance include purity (Impurity B, Impurity A, and Impurity D), sterility, bacterial endotoxins, titer ([redacted] method) and [redacted] ([redacted]).

2.1.8 Stability of drug substance

Table 5 outlines major stability study of the drug substance.

Table 5. Outline of major stability study of drug substance

Testing	Number of batches	Storage condition	Period	Storage package
Long-term	3*1	[redacted]°C	[redacted] days	single-use bag made of [redacted], [redacted], and [redacted]*2

*1 Batches [redacted], [redacted], and [redacted]
*2 [redacted] with [redacted] and [redacted] of [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Under the long-term condition, no clear changes in quality attributes were observed in any of 3 batches throughout the period. Taking account of investigation of product process changes [see Section 2.2.3, Table 7], the shelf life of [redacted] days has been proposed for the drug substance when stored in a single-use bag made of [redacted], [redacted], and [redacted] at [redacted]°C.

2.2 Product

2.2.1 Description and composition of product and formulation development

The product is presented as an aqueous injection containing virus at 1×10^9 plaque forming unit (PFU) per vial (1 mL).

Non-active ingredients are concentrated glycerin and Dulbecco's phosphate buffered saline (DPBS), which contains potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate heptahydrate, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the product consists of processes for [redacted], filling and inspection, labeling and freezing, and packaging.

The critical process steps are defined as [redacted], [redacted], and [redacted], which are conducted in a [redacted].

The verification-based control strategy is constructed for the manufacturing process of the product. The verification parameters specified are [redacted] and [redacted] (processes for [redacted], [redacted], and [redacted]), and tests for [redacted] and [redacted] ([redacted] process).

2.2.3 Manufacturing process development

Table 6 shows main changes on the manufacturing process in a course of the development of the product (relevant manufacturing processes are denoted as Process A and Process B [proposed process]). The product produced by Process A was used in non-clinical studies and Study GD01.

Table 6. Main changes on the manufacturing process in development course of Process A and Process B

Change	Process A	Process B (proposed process)
[redacted]	[redacted]	[redacted]

In response to the process changes, Batches [redacted] to [redacted] were checked for any associated change in virus yield and process-related impurities. Batch [redacted] and subsequent batches were manufactured according to the standard operation values and target values on process parameters established through manufacture of Batches [redacted] to [redacted], and parameters specified for each process and parameters in the in-process control and specification tests were evaluated. However, [redacted] and delivery of multiple batches [redacted] occurred, and investigation activities, including [redacted], [redacted], and [redacted] were therefore continued (Table 7). The quality control strategy constructed based on manufacturing results of Batch [redacted] was optimized for each control item through manufacture of Batches [redacted] to [redacted]. Finally, the

concerned quality control strategy demonstrated certain robustness of the overall process, and thus it was determined that the quality would be endured for a certain period. Because process variable factors have not been identified at present, the intended product quality should be ensured by conducting verification for every manufacturing session.

Table 7. List of process evaluation in Batch [redacted] and subsequent batches

Batch	Intended use	Description of evaluation
[redacted]	• Process investigation • Establishment of specifications • Stability (drug substance and product)	[redacted] process Although the process was designed to perform infection at MOI of [redacted], actual MOI was found at [redacted].
[redacted]	• Process investigation • Establishment of specifications • Stability (drug substance)	[redacted] process The [redacted] in the [redacted] was found to be [redacted] than the [redacted] (standard charge-in value) and thus failed to meet the [redacted]. In addition, the [redacted] was found to be [redacted] than the [redacted] ([redacted]). A potential cause for [redacted] the [redacted] was [redacted]. As a result of these investigations, the following measures were planned for manufacture of [redacted]: • [redacted] process: [redacted], [redacted], [redacted], and [redacted] ([redacted]). • [redacted] process: [redacted] ([redacted]) [redacted], and [redacted].
[redacted]	• Process investigation • Establishment of specifications • Stability (drug substance)	[redacted] process [redacted] failed to meet the [redacted] for [redacted] (Batch [redacted] was not tested). The failure was caused by [redacted] in a packaging material of [redacted] (bag for [redacted] and [redacted] to [redacted]), indicating that [redacted] was [redacted]. The [redacted] was therefore reviewed.
[redacted]	• Process investigation • Establishment of specifications	[redacted] process The result from the [redacted] run of [redacted] test failed to meet the [redacted]. The [redacted] was [redacted] with [redacted], and the re-test was performed. The result met the [redacted]. [redacted] process The [redacted] in the [redacted] was found to be [redacted] than the [redacted] (standard charge-in value) and thus failed to meet [redacted]. In addition, the [redacted] was found to be [redacted] than the [redacted] ([redacted]). Therefore, in manufacture of Batch [redacted] and subsequent batches, the [redacted] was decided to be ≤[redacted] days ([redacted] days as the standard), and [redacted] in the formulation process including [redacted] to be more strictly controlled. It was also decided that monitoring of [redacted] should be continued to deepen understanding of process attributes and to ensure the quality consistently. [redacted] process • The [redacted] conformed to the [redacted] (a difference in [redacted] between before and after [redacted] should be ≤[redacted]%). • For the [redacted], [redacted], and [redacted], impacts on uniformity of dosage units were evaluated by measuring the [redacted]. With an analytical error of the [redacted] measurement taken into account, the batch was determined to be in a uniform state.
[redacted]	• Process investigation • Establishment of specifications	[redacted] process [redacted] vials were inspected for [redacted] state at [redacted], and of these inspected, [redacted] vials were found to have defective [redacted]. It was decided that [redacted] should be reviewed.
[redacted]	• Process investigation	[redacted] process As a corrective action on the above, the [redacted] inspection ([redacted] and [redacted]) was specified.

In association with the change from Process A to the proposed process, comparability evaluation on quality attributes was performed and demonstrated comparability between the pre- and post-change

products for all the parameters evaluated except for [redacted], which were [redacted] between the pre-change and post-change.

2.2.4 Control of product

The proposed specifications for the product include description, identification ([redacted]), pH, bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, mycoplasma, titer ([redacted] method), and [redacted] ([redacted]).

2.2.5 Stability of product

Table 8 outlines major stability study of the product.

Table 8. Outline of major stability study of product

Testing	Number of batches	Storage condition	Period	Storage package
Long-term	1*1	≤−[redacted]°C	[redacted] months	[redacted] stopper and [redacted] vial
	1*2	≤−[redacted]°C*4	[redacted] months	
	1*3*5	≤−[redacted]°C	[redacted] months*6	
Stress (temperature)	1*2	[redacted]	[redacted] days	
	1*2	[redacted]°C	[redacted] days	
	1*2	[redacted]°C	[redacted] days	
Stress (light)	1*3	2,500 lux (D65 lamp) [redacted]°C	[redacted] and 1.2 million lux•hr	

*1 Batch [redacted]
*2 Batch [redacted]
*3 Batch [redacted]
*4 After [redacted] months of storage, samples were stored at −[redacted]°C.
*5 Additional [redacted] batches will be placed in the stability study.
*6 The study will be continued to [redacted] months.

Under the long-term condition, no clear changes in parameters tested were observed in any of the 3 batches throughout the period.

Under any of the stress conditions (temperature), no clear changes were observed throughout the period.

Under all the stress conditions for photostability ([redacted] and 1.2 million lux•hr), the [redacted] was [redacted] decreased.

The above results indicated that the shelf life of 24 months has been proposed for the product when stored in [redacted] vial using a [redacted] stopper at −80°C under protection from light with a carton.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substance and the product is appropriately controlled.

3. Primary Pharmacodynamics or Tests to Support Performance and Outline of the Review Conducted by PMDA

In vitro cytocidal activity and acyclovir susceptibility tests were performed with Delytact.

The applicant submitted published literature on the *in vitro* study using G47Δ, G207, and wild-type HSV-1 (viral replication competence, cytocidal effect, preclusion of major histocompatibility complex (MHC) class I down-regulation, and stimulation of tumor-responsive T cell) and the *in vivo* study (antitumor effect in mouse tumor models) as reference information.

3.1 *In vitro* cytocidal activity test ([redacted])

The cytocidal activity of Delytact in human [redacted] cell line [redacted] was evaluated, and the cytocidal effect correlated to multiplicity of infection (MOI) was presented (Figure 1).

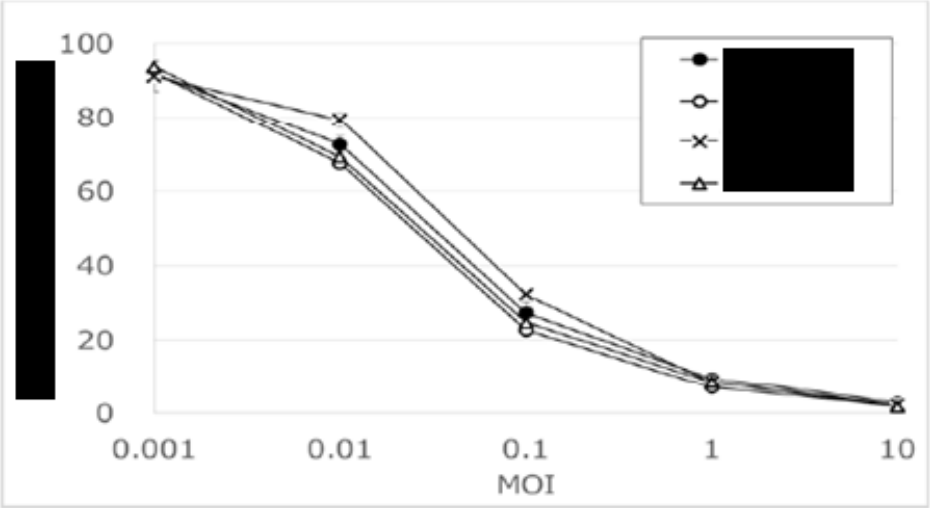

Figure 1. *In vitro* cytocidal activity: Titer dependence (Day [redacted])

3.2 Acyclovir susceptibility study ([redacted])

Acyclovir susceptibility of Delytact was evaluated using [redacted] cells. The [redacted] of G47Δ reduced in an acyclovir-concentration-dependent manner (Figure 2).

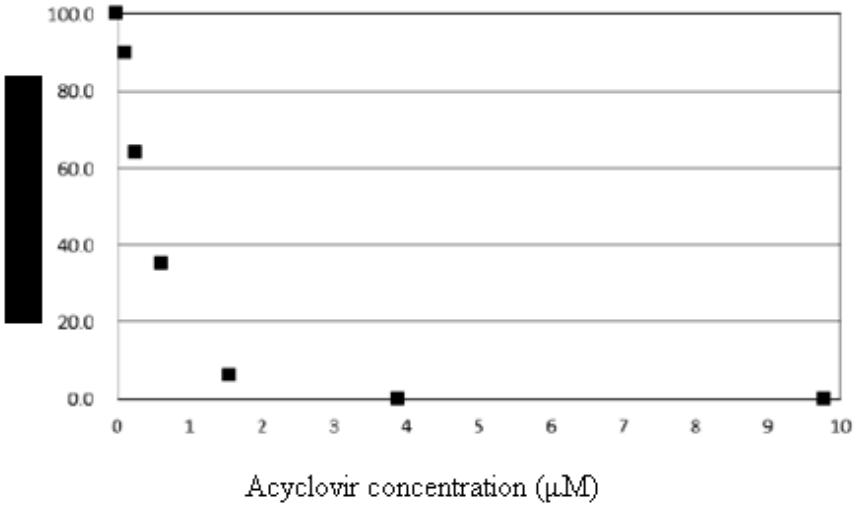

Figure 2. Acyclovir susceptibility study (Batch [redacted])

3.3 Reference data

3.3.1 *In vitro* studies

3.3.1.1 Viral replication competence in cultured cells

Various cell lines were infected with G47Δ, G207, or wild-type HSV-1, and the subsequent virus yield was measured by a plaque assay to evaluate viral replication competence. Infection with G47Δ yielded virus in human neuroblastoma cell line SK-N-SH, human glioma cell lines U87MG and U373MG, human head and neck squamous carcinoma cell line SQ20B, and human prostate cancer cell line LNCaP. In many cell lines, the virus yield of G47Δ was higher than that of G207 but lower than that of wild-type HSV-1 (*Proc Natl Acad Sci U S A.* 2001;98:6396-401 and *Clin Cancer Res.* 2005;11:7886-90).

3.3.1.2 Cytocidal effects on cultured cells

Various cell lines were infected with G47Δ or G207, and at 3 or 4 days after the infection, the cell viability was measured to evaluate the cytocidal effect. G47Δ exhibited the cytocidal activity on human glioma cell line U87MG, human malignant melanoma cell lines 624 and 888, mouse neuroblastoma cell line Neuro2a, and human prostate cancer cell lines LNCaP and DU145. In any cell line, the cytocidal activity of G47Δ was higher than that of G207 (*Proc Natl Acad Sci U S A.* 2001;98:6396-401 and *Clin Cancer Res.* 2005;11:7886-90).

3.3.1.3 Preclusion of MHC class I down-regulation in infected host cells

Various cell lines were infected with G47Δ, G207, or wild-type HSV-1, and MHC class I expression level on host cells at 24 or 48 hours after the infection was measured by flow cytometry. G47Δ precluded MHC class I down-regulation in human normal diploid fibroblast cell line Detroit 551 and human malignant melanoma cell lines 1102, 938, and 888 (3 types). In multiple cell lines, G47Δ precluded MHC class I down-regulation more strongly than G207 (*Proc Natl Acad Sci U S A.* 2001;98:6396-401).

3.3.1.4 Stimulation of tumor-responsive T cells

Various cell lines were infected with G47Δ or G207, and then cocultured with matched responding tumor-infiltrating T cell line at 37°C for 18 hours to determine the amount of interferon gamma (IFN-γ) secreted. For cell lines 1102 and 938 with high basal levels of MHC class I, the matched tumor-infiltrating T cells secreted IFN-γ in response to stimulation. The IFN-γ secretion was higher with G47Δ infection than with G207 infection (*Proc Natl Acad Sci U S A.* 2001;98:6396-401).

3.3.2 *In vivo* studies

3.3.2.1 Antitumor effect in mouse models subcutaneously transplanted with brain tumor cell lines

To nude mice subcutaneously transplanted with human glioma cell line U87MG or A/J mice subcutaneously transplanted with mouse neuroblastoma cell line Neuro2a, G47Δ, G207, or vehicle control (phosphate buffered saline [PBS] containing 10% glycerol) was intratumorally administered. Both G47Δ and G207 strongly inhibited tumor growth compared with the vehicle control. In either model, G47Δ exhibited a greater antitumor effect than G207 (*Proc Natl Acad Sci U S A.* 2001;98:6396-401).

3.3.2.2 Antitumor effect in mouse models subcutaneously transplanted with prostate cancer cell lines

To nude mice subcutaneously transplanted with human prostate cancer cell line HONDA or C57BL/6 mice subcutaneously transplanted with mouse prostate cancer cell line TRAMP-C2, G47Δ was intratumorally administered. G47Δ inhibited tumor growth in a dose-dependent manner (*Clin Cancer Res.* 2005;11:7886-90).

3.3.2.3 Antitumor effect in mouse models subcutaneously transplanted and intracerebrally transplanted with breast cancer cell line and spontaneous mammary tumor model

To C3(1)/T-Ag-transgenic mice subcutaneously transplanted with mouse breast cancer cell line M6c, G47Δ or vehicle control (PBS containing 10% glycerol) was intratumorally administered. G47Δ strongly inhibited tumor growth compared with the vehicle control. In addition, to C3(1)/T-Ag-transgenic mice intracerebrally transplanted with mouse breast cancer cell line M6c, G47Δ or vehicle control (PBS containing 10% glycerol) was intratumorally administered. G47Δ prolonged the survival compared with the vehicle control. Furthermore, to female C3(1)/T-Ag transgenic mice with spontaneous mammary tumor, G47Δ was intratumorally administered. The median survival was 5.5 weeks in the control group and 8.5 weeks in the G47Δ group, indicating that G47Δ tended to prolong the survival (*Cancer Res.* 2005;65:1532-40).

3.3.2.4 Antitumor effect in mouse model with spontaneous neurofibromatosis type 2 and mouse model subcutaneously transplanted with human schwannoma

To P0-SchΔ (39–121) line 27 transgenic mice with spontaneous neurofibromatosis type 2, G47Δ or ultraviolet-inactivated G47Δ was intratumorally administered, and the tumor volume was monitored for 4 months. The tumor volume gradually increased or remained unchanged in the control group (n = 3), while it reduced in all the animals in the G47Δ group (n = 5) (by a mean of 58.3% from baseline within 10 days post-dose) (*Hum Gene Ther.* 2006;17:20-30).

To nude mice subcutaneously transplanted with human schwannoma tissue derived from a patient with neurofibromatosis type 2 or patient with schwannoma, G47Δ or vehicle control (PBS) was intratumorally administered, and the tumor volume was monitored for 6 weeks. The tumor volume increased in all the animals in the control group (n = 3) (by a mean of 19.6% from baseline), while it reduced in all the animals in the G47Δ group (n = 5) (by a mean of 40.6% from baseline) although it transiently increased in 2 animals.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of Delytact:

The *in vitro* studies showed that G47Δ replicated in multiple cultured cell lines including the glioma cell line and exerted the cytocidal activity on these cell lines. In addition, G47Δ precluded MHC class I down-regulation in cell lines expressing MHC class I at a high level. When cocultured with G47Δ-infected cancer cell line and tumor-infiltrating T cells, IFN-γ was secreted in response to stimulation. Furthermore, the cytocidal activity of G47Δ was inhibited by acyclovir in its concentration-dependent manner.

The *in vivo* studies showed that G47Δ induced complete tumor regression in 8 of 12 model mice transplanted with glioma cell line.

As shown above, G47Δ, an active ingredient of Delytact, exhibited the strong antitumor effect on glioma cells and thus is expected to be highly effective in treatment of gliomas including glioblastoma.

On the basis of the submitted data, PMDA has concluded that there are results on indication or performance of Delytact suggesting that Delytact is capable of replicating in tumor cells and exerting the cytocidal effect on tumor tissues.

4. Disposition of the Product and Outline of the Review Conducted by PMDA

4.1 Non-clinical disposition

4.1.1 Biodistribution (4.2.2.3-1)

The applicant submitted data on biodistribution of Delytact from a single-dose biodistribution study.

A single dose of Delytact was intracerebrally administered to mice of A/J strain susceptible to HSV-1 to investigate the distribution and retention in organs (Table 9).

Table 9. Biodistribution study in mice after single intracerebral administration

Animal species	Route of administration	Evaluation timepoint	Dose	Analytical procedure
A/J mouse (weeks of age)	Intracerebral	, , and	Delytact: PFU/body*1 Control: DPBS containing 10% glycerol	To measure derived from Delytact, specimens of extracts from mouse tissues were subjected to .*2 A specific to the (and) comprising Delytact was used.

*1 When calculated per weight unit, the dose corresponds to approximately times the clinical dose on the assumption that a person weighing 60 kg receives the proposed clinical dose of 1×10^9 PFU.
*2 The detection limit is , the lower limit of quantitation is , and the quantification range is .

Measurement covered the , , , , , , , , , , , , , , , (including), (including), , , (including), (including), and .

At post-dose, Delytact-derived was detected in the injected at the highest level followed by the , , , , and (including) (Table 10). In the other tissues and organs including , , and , Delytact-derived was detected at a minimal level (<0.1% of the level at the injection site) or not detected.

At post-dose, the level of Delytact-derived in the injected was lower than that at post-dose. Then, its distribution in the and was observed.

At post-dose, Delytact-derived was detected only in the .

Table 10. Concentrations of Delytact-derived [redacted] in tissues in mice after single intracerebral administration

Tissue	Delytact-derived [redacted] ([redacted])*					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	168,000 (5/5/5)	2,380 (3/3/3)	3,290 (3/5/5)	507,000 (3/3/3)	4,660 (3/3/3)	2,430 (4/5/5)
[redacted]	2,610 (3/3/3)	297 (1/3/3)	316 (2/5/5)	2,590 (3/3/3)	693 (2/3/3)	1,720 (3/5/5)
[redacted]	195 (3/3/3)	0 (0/1/3)	0 (0/1/5)	245 (1/2/3)	0 (0/2/3)	0 (0/0/5)
[redacted]	1,300 (3/3/3)	0 (0/1/3)	0 (0/2/5)	1,120 (2/2/3)	40.0 (1/2/3)	0 (0/2/5)
[redacted]	455 (2/3/3)	0 (0/0/3)	0 (0/0/5)	203 (1/1/3)	0 (0/0/3)	0 (0/0/5)
[redacted] (including [redacted])	138 (2/3/3)	0 (0/1/3)	0 (0/2/5)	68.3 (1/3/3)	0 (0/0/3)	0 (0/0/5)

* Mean in the Delytact group. Calculated by handling any concentration below the lower limit of quantitation, if applicable, as zero (0). Numbers in parentheses indicate the "number of animals found to have [redacted] at the lower limit of quantitation or more in the tissue/number of animals found to have [redacted] at the detection limit or more in the tissue/number of all the animals tested."

4.1.2 Shedding

No non-clinical studies to evaluate shedding of Delytact have been conducted.

4.R Outline of the review conducted by PMDA

The applicant's explanation about disposition of Delytact:

When intracerebrally administered to mice of A/J strain susceptible to HSV-1 as a single dose, Delytact was mainly distributed in the central nervous system around the injection site. Delytact was not detected in the testis or ovary, and the intracerebral administration is considered to pose no risk of unintended integration of Delytact into germ-line cells.

PMDA accepted the applicant's explanation.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted data on non-clinical safety of Delytact from the single intracerebral dose biodistribution study [see Section 4.2.2.3-1] and single intracerebral dose toxicity study [see Sections 4.2.3.1-1 to 4.2.3.1-3]. No repeated-dose toxicity studies have been conducted, because in such a study, normal animals would receive injections in the brain parenchyma, of which the physical impact on the tissue was determined to complicate risk evaluation of Delytact.

5.1 Single intracerebral dose toxicity

The single intracerebral dose biodistribution study and single intracerebral dose toxicity study were conducted in mice (Table 11). Major findings in animals treated with Delytact included gliosis and perivascular infiltration of mononuclear cells at the injection site ([redacted]) and [redacted] ventricular enlargement, and deaths occurred at doses of ≥[redacted] PFU/body (when calculated per weight unit, this non-clinical dose corresponds to approximately [redacted] times the clinical dosage on the assumption that a person weighing 60 kg receives the proposed clinical dose). Because gliosis and perivascular infiltration of mononuclear cells are changes characteristic of viral infection (Pathology: A Color Atlas [in Japanese]. Medical Sciences International, Ltd. 2001;412-4, *Antiviral Res.* 2006;71:141-8, and Neurological therapeutics [in Japanese]. 2019;36:171-5), the findings in these studies are considered

attributable to infection of Delytact but not to β-galactosidase expressed from the *lacZ* gene inserted in the viral genome of Delytact as a marker.

Table 11. Single-dose toxicity

Test system	Route of administration	Observation period	Dose (PFU/body)[*1]	Major findings	Attached document
[redacted] mice (A/J)	Intracerebral	[redacted]	0 (vehicle) [redacted]	[redacted] PFU/body: Gliosis and perivascular infiltration of mononuclear cells at the injection site ([redacted]), and cerebral ventricular enlargement	4.2.2.3-1[*2]
[redacted] mice (A/J)	Intracerebral	[redacted]	0 (vehicle) [redacted] [redacted] (wild-type HSV-1)	0, [redacted] and [redacted] PFU/body: Ventricular enlargement Wild-type HSV-1: Deaths in all animals and intracerebral bleeding	4.2.3.1-1[*3]
[redacted] mice (A/J)	Intracerebral	[redacted]	0 (vehicle) [redacted] [redacted] (wild-type HSV-1)	[redacted] and [redacted] PFU/body: Death in 1 of 10 animals at each dose. Intracerebral bleeding (dead animals) and ventricular enlargement (surviving animals). Wild-type HSV-1: Deaths in 9 of 10 animals. Intracerebral bleeding and brain swelling	4.2.3.1-2[*3]
[redacted] mice (A/J)	Intracerebral	[redacted]	0 (vehicle) [redacted] [redacted] (wild-type HSV-1)	0, [redacted] and [redacted] PFU/body: Ventricular enlargement Wild-type HSV-1: Deaths in all animals. Intracerebral bleeding.	4.2.3.1-3[*3]

*1 DPBS containing 10% glycerol was used as vehicle. When calculated per weight unit, the dose of [redacted] PFU/body corresponds to approximately [redacted] times the clinical dosage on the assumption that a person weighing 60 kg receives the proposed clinical dose [1 × 10^9 PFU/body]).

*2 The biodistribution study was conducted based on Standards of Reliability of Application Data, and thus also included clinical observation, change in body weight, food consumption, blood chemistry, and histopathology ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] [including [redacted]], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] [including [redacted]], [redacted] [including [redacted]], [redacted], [redacted], [redacted] [including [redacted]], and [redacted] [including [redacted]]).

*3 All of these studies were conducted as non-GLP studies and only histological and anatomical examination on the [redacted] was conducted.

5.2. Other safety evaluation

5.2.1 Risk of integration into chromosomes

The applicant explained that as with viral genome of wild-type HSV-1, Delytact would not be integrated into host chromosomes (*Virology*. 1987;158:265-75 and *Sci Rep*. 2017;7:1507).

5.2.2 Risk of tumorigenesis and malignant transformation

The applicant's explanation:

For the following points, Delytact is unlikely to pose a risk of tumorigenesis and malignant transformation:

- The viral genome of HSV-1 is not integrated into host chromosomes and thus has no carcinogenicity (*Med Oral Patol Oral Cir Bucal*. 2015;20:e664-9, *Cancer Res*. 2001;61:8459-64, *J Am Acad Dermatol*. 1997;37:508-10, and *Assessment report: Imlygic.* European Medicines Agency. 2015).
- G207, genetically modified HSV-1, was intracerebrally administered to owl monkeys, and at 41 months after the first dose, neither abnormality in the injected cerebrum nor G207-induced cancer development was reported (*J. Virol*. 1999;73:6319-26). As with G207, Delytact cannot replicate in normal cells because of deletion of the *γ34.5* gene and inactivation of the *ICP6* gene, and thus Delytact is also considered unlikely to pose a risk of carcinogenicity as well.
- Delytact has the *lacZ* gene derived from *Escherichia coli*, and its expression product, β-galactosidase, is shown to be no genotoxic in the Ames, chromosomal aberration, or mouse micronucleus assay.

Furthermore, in a study where a single dose of β-galactosidase-producing *Papiliotrema terrestris* was intravenously administered, no toxicological findings including ones related to malignant transformation were observed (*Regul Toxicol Pharmacol*. 2018;92:213-9 and *The Australia New Zealand Food Standards Code.* Applicant A1032. Supporting Document 1, 2009).

- Although gliosis was observed in the [redacted] and around the [redacted] in the Delytact group in the single intracerebral dose biodistribution study [see Section 4.2.2.3-1], generally there are no reports that gliosis undergoes malignant transformation, and thus this finding is considered unrelated to malignant transformation (*Neuron*. 2014;81:229-48).

5.2.3 Reproductive and developmental toxicity

The applicant's explanation:

For the following points, Delytact, when intracerebrally administered, is unlikely to pose a risk of reproductive and developmental toxicity:

- Because the viral genome of HSV-1 is not integrated into host chromosomes (*Virology.* 1987;158:265-75 and *Sci Rep.* 2017;7:1507), Delytact is considered to pose no risk of unintended integration into germ-line cells.

5.2.4 Local tolerance

The applicant's explanation about local tolerance:

Although gliosis and perivascular infiltration of mononuclear cells were observed locally at the injection site ([redacted]) in the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1], both findings were mild. In addition, while the injection site in this mouse study was the brain parenchyma, Delytact is proposed to be intratumorally administered in clinical settings and thus considered unlikely to pose a risk of local irritation.

5.2.5 Safety evaluation of process-related impurities

The applicant's explanation about the safety of process-related impurities:

Clinical use of Delytact is unlikely to raise safety concerns related to the process-related impurities based on results from the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1] where a batch containing more impurities than a commercial batch of Delytact was used; and the single intracerebral dose toxicity study in mice [see Section 4.2.3.1-1 to 4.2.3.1-3] where a batch manufactured by the same process as that for the batch used in the above biodistribution study [see Section 4.2.2.3-1] was used.

5.2.6 Safety evaluation on non-active ingredients

Concentrated glycerin and DPBS, non-active ingredients of Delytact, were subjected to the safety evaluation. When calculated per brain weight unit, the dosing volume of DPBS containing 10% glycerol ([redacted] μL/body) in the vehicle control group in the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1] is approximately [redacted] times the clinical dosing volume (1 mL/body). The applicant explained that the non-active ingredients raise no safety concerns because no changes related to vehicle are observed in the vehicle group of the above study, and there are precedents where concentrated glycerin and components of DPBS have been used as excipients in intravenous drug formulations.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and review in the following sections, PMDA has concluded that Delytact raises no particular concerns about non-clinical safety.

5.R.1 Reproductive and developmental toxicity

PMDA asked the applicant to explain about a risk of reproductive and developmental toxicity of Delytact.

The applicant's explanation:
In view of the following points, Delytact, when intracerebrally administered, is unlikely to pose a risk of reproductive and developmental toxicity:

- Because the viral genome of HSV-1 is not integrated into host chromosomes (*Virology*. 1987;158:265-75 and *Sci Rep*. 2017;7:1507), Delytact is considered to pose no risk of unintended integration into germ-line cells.
- Genetical modification on the HSV-1 genes relevant to Delytact will not change the innate tropism for neurons.
- In the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1], Delytact was not detected in [redacted] or [redacted] ([redacted], [redacted], [redacted], and [redacted]).

PMDA accepted the applicant's explanation considering it as a supportive result that no histopathological changes were observed in the [redacted] in the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1].

5.R.2 Use in lactating women

PMDA asked the applicant to explain about a risk associated with Delytact in lactating women such as an effect of Delytact transferred into milk on infants.

The applicant's explanation:
Delytact, when used in lactating women, is unlikely to be transferred into milk and to affect infants because Delytact was not detected in [redacted] in the single intracerebral dose biodistribution study in mice [see Section 4.2.2.3-1].

PMDA accepted the applicant's explanation.

6. Clinical Pharmacology and Outline of the Review Conducted by PMDA

6.1 Viral shedding

In Study GD01, specimens of blood, saliva (or [redacted]), and urine from 13 patients were subjected to PCR test for Delytact-derived DNA ([redacted], [redacted], [redacted], and [redacted] after the first dose, and [redacted], [redacted], [redacted], and [redacted] after the second or subsequent dose). In this study, patients received up to 6 doses of Delytact, of which the first and second doses were separated by 7 days (range, 5-14 days), and each of the third and subsequent doses was separated from the previous dose by 4 weeks (range, 4 ± 2 weeks). Delytact was intratumorally administered in a stereotactic manner.

The Delytact-derived DNA was detected only in a blood specimen from 1 patient on the day of the first dose (post-dose), who had also provided specimens of saliva and urine with no such DNA detected. After that, it was not detected in any other specimen from this patient. The Delytact-derived DNA was not detected in any specimen from the other patients.

6.2 Anti-HSV antibody production in association with Delytact

In Study GD01, the anti-HSV antibody titer in serum (IgG and IgM) was measured using [redacted] at the time of each administration of Delytact (up to 6 doses) and at [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] after the final dose.

At baseline, 5 patients were tested negative[4)] for anti-HSV antibody in serum, and 11 patients were tested positive or false-positive (6 tested positive, 5 tested false-positive). Of 5 patients initially tested negative, all became positive after administration of Delytact. The IgG titer tended to increase after administration, reached the maximum at up to 3 months after the end of the administration, and then tended to decrease.

6.R Outline of the review conducted by PMDA

The applicant's explanation about viral shedding and anti-HSV antibody production in association with Delytact:

For viral shedding in association with Delytact, the Delytact-derived DNA was detected only in a blood specimen from 1 patient on the day of the first dose (post-dose), who had also provided specimens of saliva and urine with no such DNA detected, and after that, it was not detected in any specimen from the patient. Such DNA was not detected in any specimen from the other patients. Patients treated with Delytact are therefore considered extremely unlikely to spread Delytact into the environment and infect others through secretion and excretion.

For anti-HSV antibody production in association with Delytact, no correlations of the efficacy and safety with anti-HSV antibody titer have been observed, although the number of patients treated is limited. To date, the increased antibody titer is therefore considered unlikely to affect the efficacy and safety of Delytact.

PMDA accepted the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 1 Japanese phase II study shown in Table 12. The applicant also submitted the results of 1 Japanese phase I/II study conducted as a non-GCP compliant study as reference data.

4) IgG titer <2.0

Table 12. List of clinical studies for efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Study GD01	II	Patients with residual or recurrent glioblastoma involving 1 lesion who previously received RT and TMZ	19	Up to 6 doses of Delytact at 1×10^9 PFU are intratumorally administered. The first and second doses are separated by 7 days, and each of the third and subsequent doses is separated from the previous dose by 4 weeks.	Efficacy Safety
Reference	Japan	Clinical investiga-tion	I/II	Patients with RT-refractory glioblastoma	13 Cohort 1, 3 Cohort 2, 3 Cohort MTD, 7	Cohort 1 Up to 2 doses of Delytact at 3×10^8 PFU, separated by 5 to 14 days, are intratumorally administered. Cohorts 2 and MTD Up to 2 doses of Delytact at 1×10^9 PFU, separated by 5 to 14 days, are intratumorally administered.	Safety Dose selection Efficacy

Each clinical study is outlined below.

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.1-1 and CTD 5.3.5.1-2, Study GD01, April 2015 to April 2020)

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of Delytact in patients with residual[5)] or recurrent glioblastoma involving 1 lesion who had previously received RT and TMZ[6)] (target sample size, 30 subjects[7)]) at a single study center in Japan. Table 13 shows major inclusion and exclusion criteria.

5) A period from the end date of RT and TMZ treatments and administration of Delytact was not restricted.
6) In the protocol, a certain period between the end date of RT and administration of Delytact was not specified.
7) Because the 1-year survival rate was 40% according to the interim report of the phase I/II clinical investigation, the 1-year survival rate in this study was assumed to be 40%. A meta-analysis on a total of 16 clinical studies in patients with recurrent glioblastoma, which were initiated between 1980 and 2001, reported that the 1-year survival rate in these patients was 14% (*Neuro Oncol*. 2007;9:29-38), and the 1-year survival rate in the historical control was specified at 15%. The number of patients required to perform a test of hypothesis for the 1-year survival rate, the primary endpoint, in a single arm against the threshold of 15% with the one-sided significance level of 5% and power of 80% was calculated to be 25 (13 at the interim analysis) as the number required for the final analysis. Furthermore, to ensure adequate information, the target sample size was specified as 30.

Table 13. Major inclusion and exclusion criteria

Inclusion criteria • Patients with pathologically confirmed glioblastoma prior to enrollment • Patients with residual or recurrent tumor despite previous treatment with RT and TMZ • Patients with a lesion measuring ≥1.0 cm which was confirmed on contrast-enhanced MRI within 14 days of eligibility assessment • Patients with KPS ≥60%
Exclusion criteria • Patients with extracranial metastases • Patients with multiple intracranial lesions • Patients with tumor involving cerebral ventricle, brainstem, or posterior cranial fossa • Patients with tumor that would require administration of Delytact through cerebral ventricle • Patients with subependymal or subarachnoidal dissemination • Patients who underwent brain tumor resection or received treatment with bevacizumab within 30 days of Delytact administration

After trephining with a stereotaxic instrument, up to 6 doses[8)] of Delytact at 1×10^9 PFU were intratumorally[9)] administered[10)] at a slow rate. The first and second doses were separated by 1 week (range, 5-14 days), and each of the third and subsequent doses was separated from the previous dose by 4 weeks (range, 4 ± 2 weeks).

In this study, the primary endpoint was specified as the 1-year survival rate. A test of hypothesis was performed for the 1-year survival rate in a single arm against the threshold of 15%[11)] where a statistical significance with the one-sided significance level of 5% was required to demonstrate the efficacy of Delytact. An interim analysis was planned to decide whether the study should be terminated early for futility or for efficacy when these patients completed the 1-year follow-up period. Depending on the z statistic value (z0) calculated from the 1-year survival rate in 13 patients, the study would be terminated for futility with z0 ≤0.3163, terminated early for efficacy with z0 >2.538, or continued with z0 >0.3163 and ≤2.538. The concerned termination criteria were specified according to the Lan-DeMets procedure using O'Brien-Fleming alpha-spending function.

Of 28 patients who provided informed consent as of the interim analysis (data cutoff on June 14, 2018), 19 patients were enrolled in this study, excluding 9 patients[12)] who failed to meet the inclusion criteria

8) When any of the following (a) to (e) was met, the treatment was terminated even before the sixth dose:
(a) The target tumor becomes <1 cm.
(b) The tumor increases in size, meeting the "Progression" state specified in the tumor reduction criteria.
(c) Clinical symptoms of the patient become exacerbated.
(d) The patient does not wish to continue the treatment.
(e) For others, an investigator or sub-investigator considers that the treatment should be terminated.

9) The administration procedure was determined for each dose according to the patient's condition by an attending physician. (Actually, various procedures were applied. For example, 2 divided doses of Delytact at 1×10^9 PFU were administered to 1 lesion through 1 burr hole but in different directions or through 2 concurrently established burr holes).

10) Delytact was administered to the patient under local or general anesthesia using an MRI-guided stereotaxic technique and was administered into the current residual tumor lesion irrespective of the last injection site.

11 It was specified because in a meta-analysis on a total of 16 clinical studies in patients with recurrent glioblastoma, which were initiated between 1980 and 2001, the 1-year survival rate in these patients was 14% (*Neuro Oncol.* 2007;9:29-38).

12 Reasons for the exclusion were as follows:
Other active malignant tumors were found in 2 patients; glioblastoma was not histologically confirmed in 1 patient; "steroids were used at varied doses within 1 week of eligibility assessment" and "subependymal or subarachnoidal dissemination was found" in 1 patient; subependymal or subarachnoidal dissemination was found in 1 patient; clinical laboratory values (white blood cell, neutrophil, and platelet counts) did not meet the criteria in 1 patient; "steroids were used at varied doses within 1 week of eligibility assessment" and "multiple intracranial malignant glioma lesions were found" in 1 patient; "Karnofsky performance status (KPS) was <60%," "survival of at least 3 months was not expected," and the investigator or sub-investigator determined the condition being ineligible in 1 patient; and "KPS was <60%" and "survival of at least 3 months was not expected" in 1 patient.

or met the exclusion criteria. Of 19 patients, 16 patients were included in the full analysis set (FAS) and were also included in the efficacy analysis, excluding 3 patients[13)] who were deemed to be unevaluable.

A population of 19 patients who received at least 1 dose of Delytact was included in the safety analysis.

Table 14 shows patient characteristics and prior treatment at baseline in the FAS (n = 16).

Table 14. Patient characteristics and prior treatment at baseline (FAS, n = 16)

Item		Number of patients (%)
Median age (years) (range)		53 (25-73)
Sex	Male	13 (81.3)
	Female	3 (18.8)
KPS (%)	70-80	8 (50.0)
	90-100	8 (50.0)
Tumor location	Right frontal lobe	8 (50.0)
	Right temporal lobe	3 (18.8)
	Left frontal lobe	3 (18.8)
	Left parietal lobe	2 (12.5)
	Left temporal lobe	1 (6.3)
	Callosal splenium	1 (6.3)
Prior surgeries	Tumourectomy	15 (93.8)
	Biopsy only	1 (6.3)
Median total radiation dose (Gy) (range)		60.0 (50.4-60.0)
Prior treatment with TMZ	Yes	16 (100)
	Concomitantly used during RT only	5 (31.3)
	Continuously used during RT and after end of RT as well	11 (68.8)
Prior treatment with antineoplastic agents other than TMZ	Bevacizumab	6 (37.5)
	Carmustine	5 (31.3)
	IFN-β	1 (6.3)
Number of doses of Delytact (dose)	1	0
	2	2 (12.5)
	3	1 (6.3)
	4	2 (12.5)
	5	1 (6.3)
	6	10 (62.5)
IDH1 gene mutation[*1]	Yes	4 (25.0)
	No	12 (75.0)
Methylation of MGMT promoter region[*2]	Yes	2 (12.5)
	No	3 (18.8)
	Unknown	11 (68.8)

*1 It was not tested in this study, and thus the test was performed post hoc at the Institute of Medical Science, The University of Tokyo.
*2 It was reported according to information from the referring center (referral, etc.)

The 1-year survival rate[14)] and its z statistic value (z0) were calculated from data in 13 patients[15)] in the FAS (n = 16) in whom 1 year passed after the start of Delytact treatment (patients who died within 1 year or were found alive at 1 year of the treatment) as of the interim analysis (data cutoff on June 14, 2018). The z0 was 7.806, meeting the predetermined criterion for early termination for efficacy. The Independent Data Monitoring Committee recommended early termination for efficacy. Table 15 shows

[13] Because Delytact treatment was ongoing as of the first data cutoff (June 14, 2018), and no information on the efficacy or safety was available, these patients were handled as unevaluable subjects.
[14] In calculation of the survival rate, the numerator was the number of patients who survived at 1 year, and the denominator was the number of patients who had died or survived when 1 year passed after the start of Delytact treatment (in a censored case, patients in whom 1 year did not pass were excluded from the concerned analysis).
[15] Of the FAS, 3 patients in whom the follow-up period did not reach 1 year as of the interim analysis were excluded from the analysis on the primary endpoint.

patient characteristics and prior treatment at baseline in 13 patients included in the interim analysis, and Table 16 shows results on 1-year survival rate.

Table 15. Patient characteristics and prior treatment at baseline (FAS, n = 13)

Item		Number of patients (%)
Median age (years) (range)		53 (25-73)
Sex	Male	10 (76.9)
	Female	3 (23.1)
KPS (%)	70-80	6 (46.2)
	90-100	7 (53.8)
Tumor location	Right frontal lobe	8 (61.5)
	Right temporal lobe	2 (15.4)
	Left frontal lobe	3 (23.1)
	Left parietal lobe	1 (7.7)
	Left temporal lobe	1 (7.7)
	Callosal splenium	0
Prior surgeries	Tumourectomy	13 (100)
	Biopsy only	0
Median total radiation dose (Gy) (range)		60.0 (50.4-60.0)
Prior treatment with TMZ	Yes	13 (100)
	Concomitantly used during RT only	5 (38.5)
	Continuously used during RT and after end of RT as well	8 (61.5)
Prior treatment with antineoplastic agents other than TMZ	Bevacizumab	5 (38.5)
	Carmustine	5 (38.5)
	IFN-β	1 (7.7)
Number of doses of Delytact (dose)	1	0
	2	1 (7.7)
	3	1 (7.7)
	4	1 (7.7)
	5	1 (7.7)
	6	9 (69.2)
IDH1 gene mutation[*1]	Yes	4 (30.8)
	No	9 (69.2)
Methylation of MGMT promoter region[*2]	Yes	2 (15.4)
	No	3 (23.1)
	Unknown	8 (61.5)

*1 It was not tested in this study, and thus the test was performed post hoc at the Institute of Medical Science, The University of Tokyo.
*2 It was reported according to information from the referring center (referral, etc.)

Table 16. Interim analysis results on survival rate at 1 year after the first dose of Delytact (data cutoff on June 14, 2018)

Number of patients	13
Number of deaths (%)	1 (7.7)
1-year survival rate [95% CI*] (%)	92.3 [64.0, 99.8]

* Accurate confidence interval (CI) based on F distribution

Table 17 and Figure 3 show results on the overall survival (OS), the secondary endpoint, and the Kaplan-Meier curve of the OS in the FAS (n = 16) as of the interim analysis, respectively. The 1-year survival rate [95% confidence interval (CI)] (%) according to the Kaplan-Meier method was 85.7 [53.9, 96.2].

Table 17. Results on OS at interim analysis (FAS, data cutoff on June 14, 2018)

	FAS
Number of patients	16
Number of deaths (%)	5 (31.3)
Median [95% CI] (months)	Non-estimable [13.2, non-estimable]

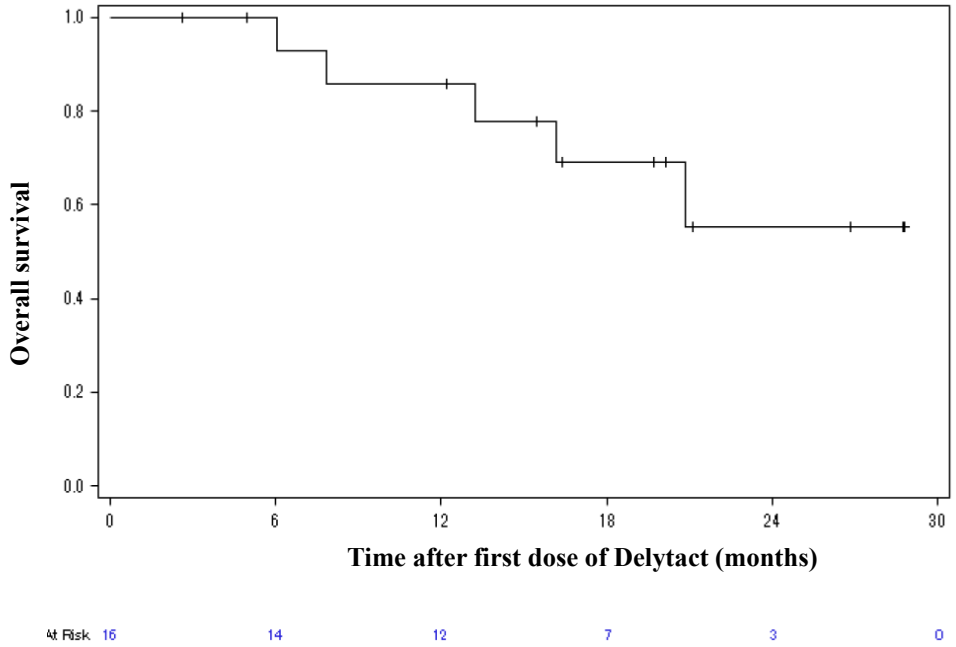

Figure 3. Kaplan-Meier curve of OS at interim analysis (FAS, data cutoff on June 14, 2018)

Deaths were reported in 12 of 19 patients (63.2%) during Delytact treatment or within 24 months after the final dose of Delytact. Except for 1 patient[16)] who was reported as death, all the patients died of disease progression, and a causal relationship to Delytact was denied for all death.

An additional analysis on OS (data cutoff on December 31, 2018) was performed in 19 patients including 3 patients who had been deemed to be unevaluable as of the interim analysis (data cutoff on June 14, 2018) although it was not prespecified. Table 18 shows patient characteristics and prior treatment at baseline in 19 patients, and Table 19 and Figure 4 show results and the Kaplan-Meier curve as of the additional analysis, respectively.

[16] A 5[redacted]-year old woman who had the underlying disease of right frontal lobe glioblastoma. She received 6 doses of Delytact, visited without any remarkable change at 15 months after the final dose, but was found dead at home 10 days later. The death was caused by an accidental factor, and no progression of glioblastoma was found. A causal relationship to Delytact was denied by the investigator.

Table 18. Patient characteristics and prior treatment at baseline (n = 19)

Item		Number of patients (%)
Median age (years) (range)		51 (25-73)
Sex	Male	15 (78.9)
	Female	4 (21.1)
KPS (%)	70-80	10 (52.6)
	90-100	9 (47.4)
Tumor location	Right frontal lobe	10 (52.6)
	Right temporal lobe	3 (15.8)
	Left frontal lobe	5 (26.3)
	Left parietal lobe	3 (15.8)
	Left temporal lobe	2 (10.5)
	Callosal splenium	1 (5.3)
Prior surgeries	Tumourectomy	17 (89.5)
	Biopsy only	2 (10.5)
Median total radiation dose (Gy) (range)		60.0 (50.4-60.0)
Prior treatment with TMZ	Yes	19 (100)
	Concomitantly used during RT only	6 (31.6)
	Continuously used during RT and after end of RT as well	13 (68.4)
Prior treatment with antineoplastic agents other than TMZ	Bevacizumab	7 (36.8)
	Carmustine	6 (31.6)
	IFN-β	1 (5.3)
Number of doses of Delytact (dose)	1	0
	2	2 (10.5)
	3	1 (5.3)
	4	2 (10.5)
	5	2 (10.5)
	6	12 (63.2)
IDH1 gene mutation[*1]	Yes	6 (31.6)
	No	13 (68.4)
Methylation of MGMT promoter region[*2]	Yes	2 (10.5)
	No	3 (15.8)
	Unknown	14 (73.7)

*1 It was not tested in this study, and thus the test was performed post hoc at the Institute of Medical Science, The University of Tokyo.
*2 It was reported according to information from the referring center (referral, etc.)

Table 19. Results on OS at additional analysis (FAS, data cutoff on December 31, 2018)

	FAS
Number of patients	19
Number of deaths (%)	8 (42.1)
Median [95% CI] (months)	21.8 [13.2, non-estimable]

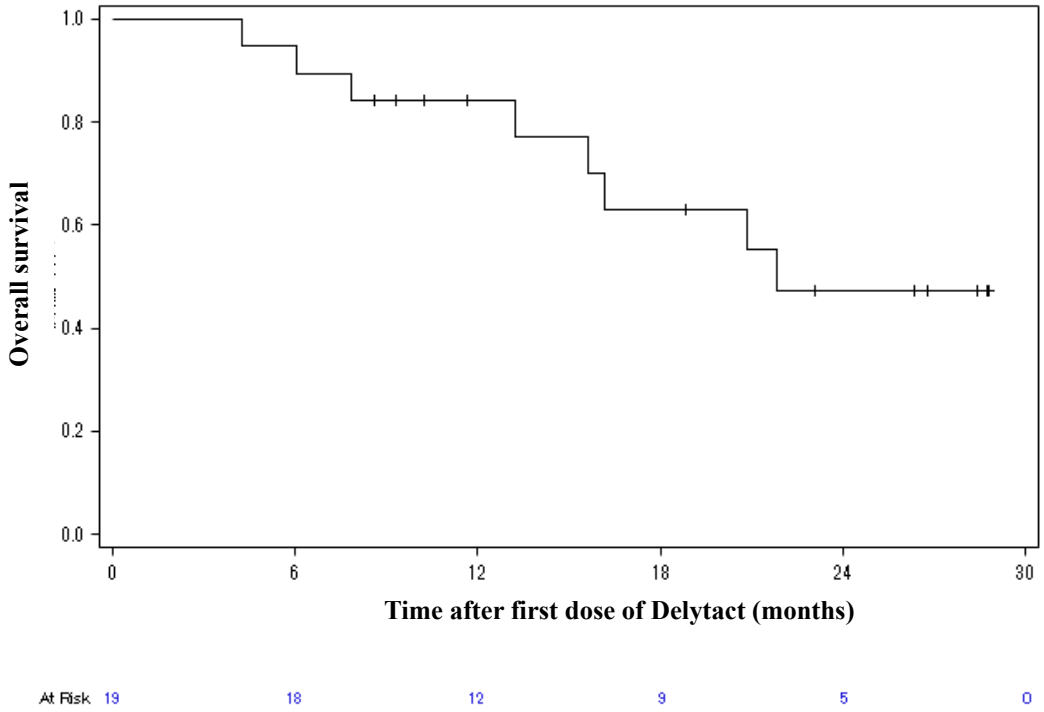

Figure 4. Kaplan-Meier curve of OS at additional analysis (FAS, data cutoff on December 31, 2018)

7.2 Reference data

7.2.1 Japanese clinical investigation

7.2.1.1 Japanese phase I/II study (CTD 5.3.5.2-1, Clinical investigation, November 2009 to [redacted] 20[redacted])

A clinical investigation was conducted in patients with RT-refractory glioblastoma[17] (target sample size, 21 patients [up to 30]) to evaluate the tolerability, safety, and other aspects of Delytact at 2 study centers in Japan as an open-label uncontrolled study.

Up to 2 doses of Delytact at 3×10^8 PFU in Cohort 1, 1×10^9 PFU in Cohort 2, and 3×10^9 PFU[18] in Cohort 3 were intratumorally administered at an interval of 5 to 14 days (7-14 days in the first patient in each cohort). Then, patients additionally received Delytact at the maximum tolerated dose (MTD) specified in Cohort 1 to 3 (Cohort MTD).

In Cohort 2, however, seizure suspected to be causally related to Delytact occurred in 3 of 3 patients (at Grade 2 for all the events), and Grade 1 pyrexia occurred in 1 of 3 patients. In light of the above, decisions were made to omit Cohort 3, to specify the dosage regimen in Cohort 2 as MTD, and to use the Cohort 2 regimen in Cohort MTD as well.

---

[17] Patients who met the following conditions were included: Glioblastoma was pathologically confirmed; a lesion measuring ≥1.0 cm was confirmed on contrast-enhanced MRI within 14 days before administration of Delytact; and KPS was ≥60% (50% for patients with low KPS due to hemiplegia caused by tumor resection). Patients meeting the following conditions were excluded:
- Patients with extracranial metastases.
- Patients with multiple intracranial lesions.
- Patients with tumor involving cerebral ventricle, brainstem, or posterior cranial fossa.
- Patients with tumor that would require administration of Delytact through cerebral ventricle.
- Patients with subependymal or subarachnoidal dissemination.

[18] Although a cohort for intratumoral doses at 3×10^9 PFU was initially planned, the Independent Data Monitoring Committee determined 1×10^9 PFU as the MTD, and thus a dose at 1×10^9 PFU was used instead of 3×10^9 PFU in this cohort.

All of 13 patients enrolled in this study (3 in Cohort 1, 3 in Cohort 2, 7 in Cohort MTD[19]) received Delytact and were included in the safety analysis.

During Delytact treatment or until the last observation, deaths occurred in 3 of 3 patients (100%) in Cohort 1 and 9 of 10 patients (90%) in Cohorts 2 and MTD all owing to disease progression, and a causal relationship to Delytact was denied.

In accordance with the World Health Organization (WHO) criteria in tumor response, objective tumor response was assessed as stable disease (SD) in 2 patients and progressive disease (PD) in 11 patients during a period up to 90 days after the second dose of Delytact.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Evaluation on 1-year survival rate in Study GD01

The applicant's explanation about rationales for specifying the primary endpoint (1-year survival rate) and threshold in Study GD01, and the efficacy of Delytact based on results from Study GD01:

In Study GD01, the primary endpoint and threshold for the efficacy were specified as "1-year survival rate" and "15%" for the reasons below:

Primary endpoint

Clinical studies in patients with glioblastoma generally use progression-free survival (PFS) or survival rate as the primary endpoint. However, it was inappropriate to assess the effectiveness of Delytact, a novel therapy, using the same response criteria (to assess PD) as those for the conventional drugs (molecular target drugs), and the survival rate determined using only death as an event was more objective than PFS determined using PD and death as events. The survival rate was therefore specified as the primary endpoint. Furthermore, the follow-up period of 1 year for the survival rate enabled identification of death events for the following reasons. The follow-up period for the survival rate was therefore specified as 1 year.

- For glioblastoma, the median duration from the initial diagnosis to death was approximately 15 months (*Cancer Epidemiol Biomarkers Prev.* 2014;23:1985-96, *J Neurooncol.* 2012;107:207-12, and *N Engl J Med*. 2005;352:987-96). In the patient population in Study GD01, the period from Delytact treatment to death is assumed to be approximately 12 months taking into account that the study is to include patients who previously received RT and TMZ with the initial diagnosis given ≥2 months ago.
- In a clinical study to evaluate the efficacy of an increased dose of TMZ in patients with glioblastoma with recurrence or progression while receiving the maintenance TMZ therapy, the median survival [95% CI] (months) was 9.3 [8.1, 10.5] (*J Clin Oncol.* 2010;28:2051-7).
- In a clinical study in patients with recurrent glioblastoma to evaluate the efficacy of a tumor treating fields (TTF) system in comparison with physician's choice chemotherapy, the median survival [95% CI] (months) was 6.6 [5.6, 7.8] in the TTF group and 6.0 [5.2, 7.4] in the physician's choice chemotherapy group (Review Report on NovoTTF-100A System on February 25, 2015).

[19] The investigation was planned to include 12 patients but included 7 patients because Study GD01 was to be initiated.

Threshold

A meta-analysis on clinical studies in patients with recurrent glioblastoma (16 studies), which were initiated between 1980 and 2001 and conducted by the North Central Cancer Treatment Group in the US and others, reported that the 1-year survival rate in these patients was 14% (*Neuro Oncol.* 2007;9:29-38). These 16 studies were intended to evaluate the efficacy of etoposide, etc., but all of these failed to demonstrate the survival benefits. In view of this failure, the concerned 1-year survival rate was considered to reflect the consequence of glioblastoma without treatment, and the threshold for the 1-year survival rate was therefore 15% in Study GD01.

Results from Study GD01

The 1-year survival rate [95% CI] (%), specified as the primary endpoint in Study GD01, was 92.3 [64.0, 99.8] in 13 patients included in the interim analysis (data cutoff on June 14, 2018), which was higher than the threshold of 15%, raising expectation for the efficacy of Delytact [see Section 7.1.1.1]. The result from the interim analysis met the predetermined criterion for early termination for efficacy, and Study GD01 was early terminated for efficacy in accordance with the recommendation from the Independent Data Monitoring Committee.

An additional analysis on OS (data cutoff on December 31, 2018) in the FAS of 19 patients including 3 patients who were deemed to be unevaluable as of the interim analysis (data cutoff on June 14, 2018) was performed. Table 19 and Figure 4 show the results on OS and the Kaplan-Meier curve [see Section 7.1.1.1].

Furthermore, an OS as of April 22, 2020 (reporting time frame of OS was counted from the date of the first dose of Delytact) was performed, although it was not scheduled. Table 20 and Figure 5 show the results on OS and the Kaplan-Meier curve.

Table 20. Results on OS (FAS, as of April 22, 2020)

	FAS
Number of patients	19
Number of events (%)	16 (84.2)
Median [95% CI] (months)	20.2 [14.5, 31.4]

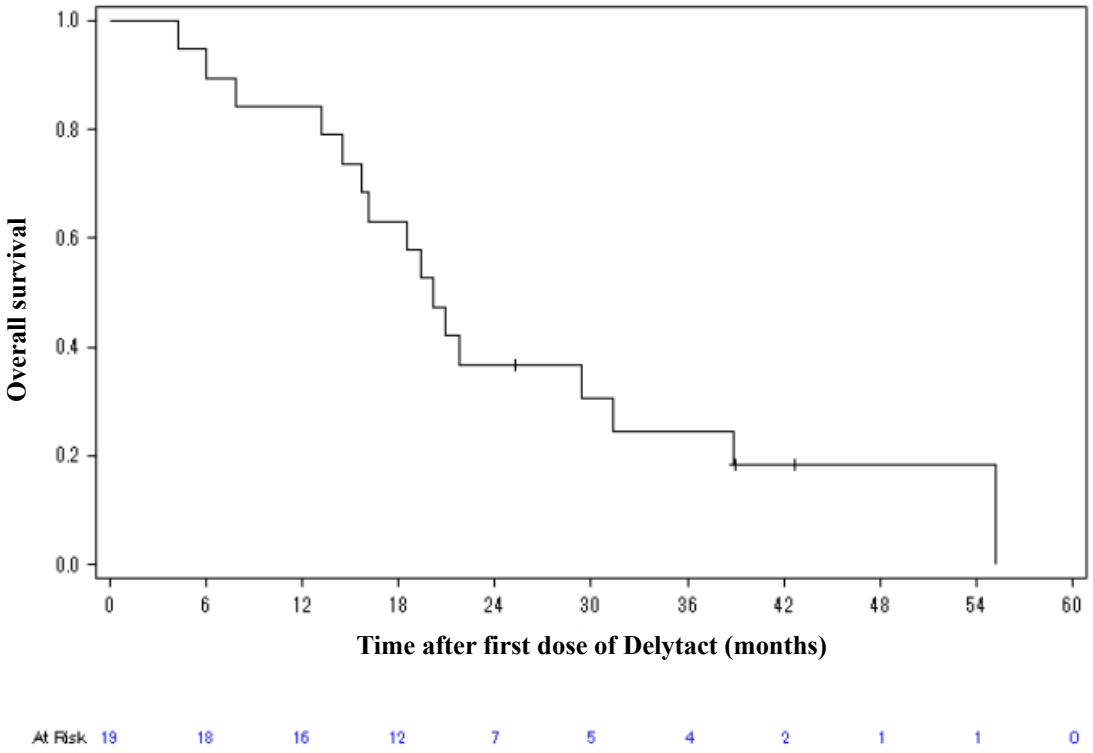

Figure 5. Kaplan-Meier curve of OS (FAS, as of April 22, 2020)

PMDA's view:

Study GD01 has the following problems, and PMDA considers it difficult to conclude that Delytact is effective solely based on the 1-year survival rate exceeding the threshold:

Problems

- Although Study GD01 is an open-label, uncontrolled study conducted only at a single study center in Japan, there are limitations in evaluation by comparing results from Study GD01 with ones from the meta-analysis on foreign clinical studies, which serve as an external control, taking into account that results on 1-year survival rate and time-to-event in Study GD01 were affected by patient characteristics.
- All of the literature used in the meta-analysis on foreign clinical studies, which provided a rationale for specifying the threshold in Study GD01, was published at least 20 years ago (1980-2001), and thus the threshold is not specified based on current clinical practices in Japan.
- Patients with glioblastoma involving mutations of the *isocitrate dehydrogenase 1 (IDH1)* gene had a relatively benign outcome (*N Engl J Med.* 2009;360:765-73). Of patients with glioblastoma, only approximately 5% are reported to have *IDH1* mutations in clinical settings, but in Study GD01, 6 of 19 patients (31.6%) had *IDH1* mutations. There are limitations in evaluation by comparison with results from the meta-analysis on foreign clinical studies where the percentage of patients with *IDH1* mutations was unknown.

In addition, the analysis method on the 1-year survival rate, the primary endpoint in Study GD01, has the following problems. In view of the design of Study GD01, which was conducted as an open-label, uncontrolled study, it cannot be denied that the analysis target was fixed based on results from the interim

analysis. Because the results may involve bias, the sponsor should have prescribed the analysis method in detail in advance.

Problems

- The patients to be included in the analysis on the 1-year survival rate were not prescribed until the Statistical Analysis Plan Version 1.2 was prepared on [redacted], 20[redacted] after the data cutoff date (June 14, 2018) for the interim analysis.
- As of data cutoff for interim analysis (June 14, 2018), the 14th patient in the order of enrollment had been died. The applicant, on the other hand, claimed that the interim analysis was planned to include the first 13 patients in the order of enrollment, and the 14th patient was excluded from the interim analysis. Neither the study protocol nor statistical analysis plan specified that the interim analysis on the primary endpoint should be performed on the first 13 patients in the order of enrollment.

PMDA, therefore, reviewed the efficacy endpoints other than OS (including the 1-year survival rate) to evaluate the efficacy of Delytact as shown in the section below.

7.R.1.2 Efficacy endpoints other than OS and evaluation results

In Study GD01, the secondary efficacy endpoints were specified as the investigator-assessed PFS and tumor reduction effect.

The disease progression events and tumor reduction criteria applied to assessment of PFS were not in accordance with the Response Assessment in Neuro-Oncology (RANO) criteria, which are widely used in clinical studies for treatment of glioblastoma, but were in accordance with the criteria originally specified based on the guideline for response assessment on immunotherapy for solid tumors (immune-related Response Criteria [irRC] [*Clin Cancer Res.* 2009;15:7412-20]) as shown in Table 21. Tables 22 and 23 show results on investigator-assessed PFS as of the interim analysis (data cutoff on June 14, 2018) and as of the additional analysis (data cutoff on December 31, 2018), respectively, and Figures 6 and 7 show respective Kaplan-Meier curves. Table 24 shows results on the tumor reduction effect.

Table 21. Tumor reduction criteria in Study GD01

CR (complete response)	Complete disappearance of target lesions in 2 consecutive MRI examinations performed approximately ≥4 weeks apart and no appearance of new lesions.
PR (partial response)	≥50% decrease in the sum of areas of target lesions compared with baseline in 2 MRI examinations performed approximately ≥4 weeks apart and no appearance of new lesions.
SD (stable disease)	Other than CR, PR, and PD
PD (progressive disease)	≥25% increase in the sum of areas of target lesions compared with that at the last MRI examination in 2 consecutive MRI examinations performed approximately ≥4 weeks apart or appearance of new lesions.

The magnetic resonance imaging (MRI) examination at 7 days after the second dose, even performed within 4 weeks after the examination at baseline, should be used in the assessment.

Table 22. Results on PFS at interim analysis (investigator's assessment, FAS, data cutoff on June 14, 2018)

	FAS
Number of patients	16
Number of events (%)	10 (62.5)
Median [95% CI] (months)	8.6 [2.6, non-estimable]

Table 23. Results on PFS at additional analysis
(investigator's assessment, FAS, data cutoff on December 31, 2018)

	FAS
Number of patients	19
Number of events (%)	14 (73.7)
Median [95% CI] (months)	4.8 [3.6, 19.6]

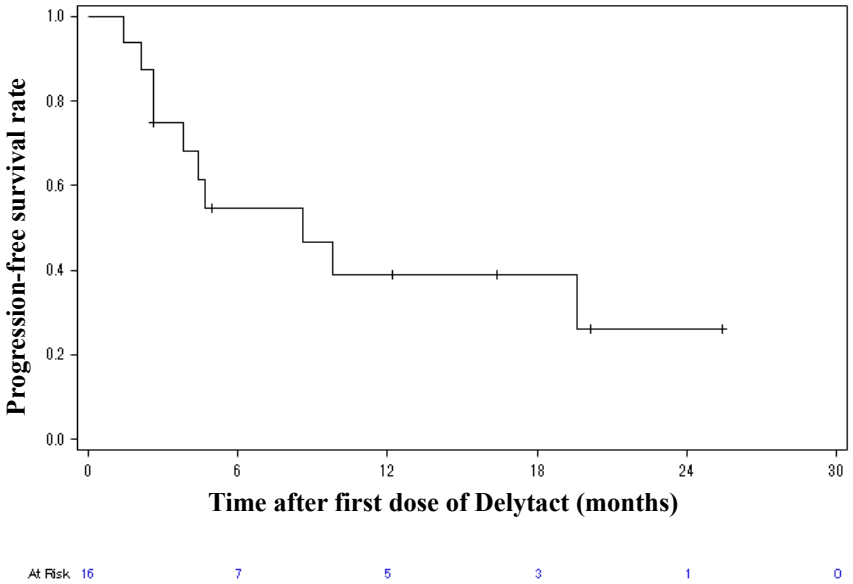

Figure 6. Kaplan-Meier curve of PFS at interim analysis (FAS, data cutoff on June 14, 2018)

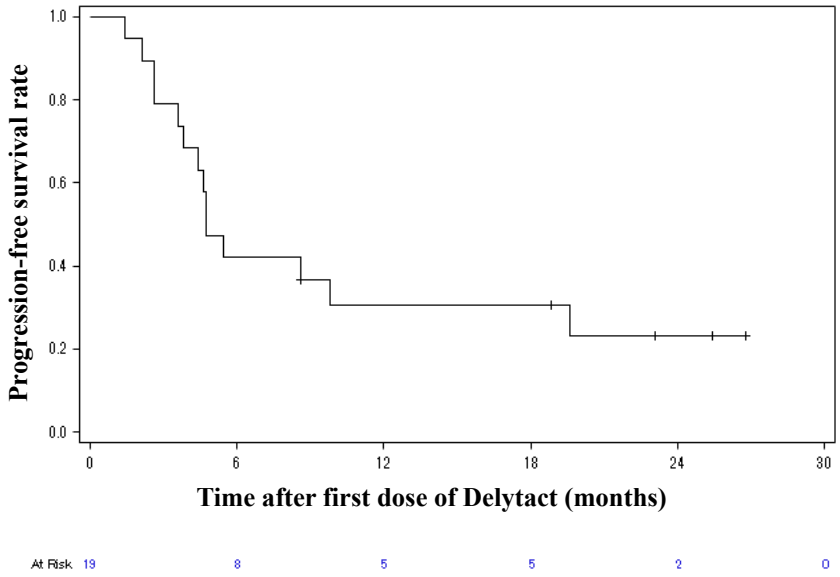

Figure 7. Kaplan-Meier curve of PFS at additional analysis (FAS, data cutoff on December 31, 2018)

Table 24. Results on tumor reduction effect at additional analysis (investigator's assessment, FAS, data cutoff on December 31, 2018)

Best overall response	Number of patients (%)
	FAS n = 19
CR	0
PR	1 (5.3)
SD	18 (94.7)
PD	0
Response (CR + PR) (response rate [95% CI])	1 (5.3 [0.1, 26.0])

PMDA's view:
PFS is a time-to-event endpoint, and it is difficult to evaluate the efficacy in Study GD01, which was conducted as an open-label, uncontrolled study, based on PFS.

Results from Study GD01 did not suggest the efficacy of Delytact in tumor reduction, in view of the response rate [95% CI] (%) of 27.6 [12.7, 47.2] in a Japanese phase II study (*Jpn J Clin Oncol.* 2012;42:887-95) of bevacizumab alone in patients with recurrent malignant glioma who had previously received RT and TMZ, the same patient population as that in Study GD01.

7.R.1.3 Assessment results on MRI images

As described in the preceding sections [Sections 7.R.1.1 and 7.R.1.2], PMDA considered it difficult to conclude that results on the predetermined primary and secondary endpoints in Study GD01 demonstrate the efficacy of Delytact.

Results on survival in Study GD01, on the other hand, are comparable to recently reported results from clinical studies in patients with glioblastoma (*N Engl J Med.* 2014;370:709-22, *Jpn J Clin Oncol.* 2012;42:887-95, etc.); development of novel therapies for glioblastoma is stagnating; and especially for recurrent glioblastoma, no highly evidenced effective therapies are available at present. PMDA, therefore, decided to evaluate images from MRI examinations (contrast-enhanced T1-weighted images and fluid-attenuated inversion-recovery [FLAIR] images) in patients in Study GD01.

Assessment results on MRI images are as follows:

- For 1 patient in whom the best overall response was assessed as partial response (PR), the FLAIR image showed an extensive hyperintense lesion, and thus assessment of PR was unacceptable.
- Of patients in whom the best overall response was assessed as SD, some (4 patients) were confirmed to maintain SD for an extended period during Delytact treatment.

Glioblastoma is malignant tumor characterized by very rapid progression, and most of the patients cannot maintain SD for an extended period. Considering that some of the patients maintained SD for an extended period in Study GD01, PMDA concluded that Delytact can be expected to have some efficacy.

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

7.R.2 Safety

As a result of the following review, PMDA considers that adverse events to which special attention should be paid in patients with residual or recurrent glioblastoma receiving Delytact alone or concomitantly with TMZ are symptoms associated with immunisation reaction, myelosuppression, seizure, brain oedema, and intracranial tumour haemorrhage.

Although attention should be paid to the above adverse events when Delytact is administered, PMDA has concluded that Delytact is tolerable provided that appropriate measures, such as monitoring and controlling of the adverse events and treatment discontinuation of Delytact, are taken by physicians with adequate knowledge and experience in treatment of glioblastoma and neurosurgical procedures.

7.R.2.1 Safety profile of Delytact

The applicant's explanation about the safety profile based on safety information of Delytact in Study GD01 (data cutoff on April [redacted], 2020) and the Japanese phase I/II study:

Table 25 outlines the safety information in Study GD01 and the Japanese phase I/II study.

Table 25. Outline of safety (Study GD01 and Japanese phase I/II study)

	Number of patients (%)	
	Study GD01 n = 19	Japanese phase I/II 1×10^9 PFU n = 10
All adverse events	19 (100)	9 (90.0)
Grade ≥3 adverse events	17 (89.5)	3 (30.0)
Adverse events leading to death	0	0
Serious adverse events	6 (31.6)	0
Adverse events leading to treatment discontinuation	1 (5.3)	0

Table 26 shows adverse events reported by ≥3 patients in Study GD01.

Table 26. Adverse events reported by ≥3 patients (Study GD01)

SOC PT (MedDRA/J ver.21.0)	Number of patients (%) n = 19	
	All Grade	Grade ≥3
All adverse events	19 (100)	17 (89.5)
General disorders and administration site conditions		
Pyrexia	18 (94.7)	1 (5.3)
Pain	8 (42.1)	0
Oedema peripheral	3 (15.8)	0
Gastrointestinal disorders		
Nausea	14 (73.7)	0
Vomiting	13 (68.4)	1 (5.3)
Constipation	8 (42.1)	0
Dysphagia	5 (26.3)	1 (5.3)
Diarrhoea	4 (21.1)	0
Stomatitis	4 (21.1)	0
Investigations		
Lymphocyte count decreased	14 (73.7)	12 (63.2)
White blood cell count decreased	12 (63.2)	4 (21.1)
Weight decreased	10 (52.6)	3 (15.8)
Platelet count decreased	9 (47.4)	0
Neutrophil count decreased	8 (42.1)	3 (15.8)
White blood cell count increased	4 (21.1)	0
Liver function test increased	3 (15.8)	0
Nervous system disorders		
Headache	13 (68.4)	0
Brain oedema	12 (63.2)	5 (26.3)
Depressed level of consciousness	9 (47.4)	3 (15.8)
Seizure	9 (47.4)	1 (5.3)
Hemiparesis	8 (42.1)	5 (26.3)
Hemiplegia	7 (36.8)	4 (21.1)
Sensory disturbance	4 (21.1)	0
Dysarthria	3 (15.8)	0
Hemianopia homonymous	3 (15.8)	0
Injury, poisoning and procedural complications		
Wound complication	13 (68.4)	0
Fall	7 (36.8)	0
Contusion	3 (15.8)	0
Infections and infestations		
Upper respiratory tract infection	7 (36.8)	0
Gastroenteritis	3 (15.8)	0
Vascular disorders		
Hypotension	8 (42.1)	0
Hypertension	4 (21.1)	3 (15.8)
Metabolism and nutrition disorders		
Decreased appetite	8 (42.1)	3 (15.8)
Hyponatraemia	5 (26.3)	2 (10.5)
Hypernatraemia	4 (21.1)	2 (10.5)
Musculoskeletal and connective tissue disorders		
Back pain	5 (26.3)	0
Arthralgia	3 (15.8)	0
Muscular weakness	3 (15.8)	2 (10.5)
Musculoskeletal pain	3 (15.8)	0
Pain in extremity	3 (15.8)	0
Cardiac disorders		
Sinus bradycardia	6 (31.6)	0
Sinus tachycardia	3 (15.8)	1 (5.3)
Psychiatric disorders		
Insomnia	6 (31.6)	0
Respiratory, thoracic and mediastinal disorders		
Pneumonia aspiration	4 (21.1)	0
Pneumonitis	3 (15.8)	0
Skin and subcutaneous tissue disorders		
Decubitus ulcer	3 (15.8)	0
Renal and urinary disorders		
Urinary incontinence	5 (26.3)	0
Blood and lymphatic system disorders		
Anaemia	5 (26.3)	0

Table 27 shows adverse events reported by ≥2 patients in the Japanese phase I/II study

Table 27. Adverse events reported by ≥2 patients (Japanese phase I/II study)

SOC PT (MedDRA/J ver.21.0)	Number of patients (%)			
	Cohort 1 n = 3		Cohorts 2 and MTD n = 10	
	All Grade	Grade ≥3	All Grade	Grade ≥3
All adverse events	3 (100)	1 (33.3)	9 (90.0)	3 (30.0)
General disorders and administration site conditions				
Pyrexia	2 (66.6)	0	6 (60.0)	0
Gastrointestinal disorders				
Nausea	1 (33.3)	0	3 (30.0)	0
Vomiting	3 (100)	0	3 (30.0)	1 (10.0)
Investigations				
White blood cell count decreased	0	0	4 (40.0)	1 (10.0)
Haemoglobin decreased	0	0	2 (20.0)	0
Nervous system disorders				
Headache	3 (100)	0	5 (50.0)	1 (10.0)
Seizure	1 (33.3)	0	3 (30.0)	0
Injury, poisoning and procedural complications				
Wound complication	0	0	2 (20.0)	0
Metabolism and nutrition disorders				
Decreased appetite	1 (33.3)	0	2 (20.0)	0
Skin and subcutaneous tissue disorders				
Pruritus	0	0	2 (20.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Intracranial tumour haemorrhage	1 (33.3)	0	2 (20.0)	0

Serious adverse events reported in Study GD01 were pyrexia in 3 patients (15.8%), and death, cerebral infarction, hemiplegia, syncope, urinary tract infection, post procedural infection, and subcutaneous abscess in 1 patient (5.3%) each. A causal relationship to Delytact could not be ruled out for pyrexia in 1 patient. Of patients treated with Delytact, 12 patients (disease progression in 11 patients and death in 1 patient) died. An adverse event leading to treatment discontinuation was post procedural infection in 1 patient (5.3%), for which a causal relationship to Delytact was denied.

A serious adverse event in the Japanese phase I/II study was lymphocyte count decreased in 1 patient (33.3%) in Cohort 1, for which a causal relationship to Delytact was denied. Neither adverse events leading to death nor adverse events leading to treatment discontinuation occurred.

PMDA's view:
In Study GD01 and the Japanese phase I/II study, serious adverse events occurred, but the event for which a causal relationship to Delytact could not be ruled out was pyrexia only, and no adverse events leading to death occurred. In light of the above, Delytact at 1×10^9 PFU is tolerable provided that appropriate measures, such as monitoring of the adverse events, differential diagnoses or controlling in consideration of adverse drug reactions due to excessive immune reactions, and treatment discontinuation of Delytact, are taken by physicians with adequate knowledge and experience in treatment of glioblastoma and neurosurgical procedures.

In the following sections, PMDA reviewed the safety information with the focus on the adverse events that frequently occurred in Study GD01.

7.R.2.2 Symptoms associated with immunisation reaction

The applicant's explanation about symptoms associated with immunisation reaction in patients receiving Delytact:

Events classified in "pyrexia," "brain oedema," and "hypersensitivity" of the preferred terms (PTs) in the Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) were identified as symptoms associated with immunisation reaction.

Table 28 shows occurrence of symptoms associated with immunisation reaction in Study GD01 and the Japanese phase I/II study.

Table 28. Occurrence of symptoms associated with immunisation reaction (Study GD01 and Japanese phase I/II study)

PT (MedDRA/J 21.0)	Number of patients (%)			
	Study GD01 n = 19		Japanese phase I/II n = 13	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Symptoms associated with immunisation reaction	19 (100)	6 (31.6)	8 (61.5)	0
Pyrexia	18 (94.7)	1 (5.3)	8 (61.5)	0
Brain oedema	12 (63.2)	5 (26.3)	0	0
Hypersensitivity	2 (10.5)	0	0	0

Table 29 shows details of the patients who experienced serious symptoms associated with immunisation reaction. In the Japanese phase I/II study, no serious symptom associated with immunisation reaction occurred.

Table 29. List of patients who experienced serious symptoms associated with immunisation reaction (Study GD01)

Age	Sex	PT (MedDRA/J 21.0)	Grade	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
4	Male	Pyrexia	2	2	Yes	6	Resolved	Yes
4	Male	Pyrexia	1	6	No	5	Resolved	No
6	Male	Pyrexia	2	1	No	199	Resolved	Yes

In Study GD01, there were no symptoms associated with immunisation reaction that led to death or treatment discontinuation.

In Study GD01,[20)] the median time to the first onset of a symptom associated with immunisation reaction (range) was 11.0 (2-93) days.

Of events of hypersensitivity in 2 patients, 1 event was hypersensitivity to the MRI contrast medium, and the other one was allergy to TMZ, and for either event, a causal relationship to Delytact was denied.

PMDA's view:

In Study GD01, pyrexia frequently occurred in patients who received Delytact, including serious pyrexia for which a causal relationship to Delytact could not be ruled out, and thus attention should be paid to

[20] In the Japanese phase I/II study, median time to the first onset of event was not calculated because information on the date of the first dose of Delytact was not collected. Hereinafter the same.

symptoms associated with immunisation reaction when Delytact is administered. Therefore, information about incidences of symptoms associated with immunisation reaction and measures at the onset in clinical studies should be appropriately presented to healthcare professionals to raise caution, using the package insert, etc.

7.R.2.3 Myelosuppression

The applicant's explanation about myelosuppression in patients receiving Delytact:
Events classified in "haematopoietic cytopenias" in MedDRA/J Standardised MedDRA Query (SMQ) (Broad) were identified as myelosuppression.

Table 30 shows incidences of myelosuppression in Study GD01 and the Japanese phase I/II study.

Table 30. Occurrence of myelosuppression (Study GD01 and Japanese phase I/II study)

PT (MedDRA/J 21.0)	Number of patients (%)			
	Study GD01 n = 19		Japanese phase I/II n = 13	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Myelosuppression	19 (100)	14 (73.7)	8 (61.5)	2 (15.4)
Lymphocyte count decreased	14 (73.7)	12 (63.2)	2 (15.4)	1 (7.7)
White blood cell count decreased	12 (63.2)	4 (21.1)	4 (30.8)	1 (7.7)
Platelet count decreased	9 (47.4)	0	0	0
Neutrophil count decreased	8 (42.1)	3 (15.8)	0	0
Anaemia	5 (26.3)	0	0	0
Reticulocyte count decreased	1 (5.3)	0	0	0
Haemoglobin decreased	0	0	2 (15.4)	0

Of Grade ≥3 adverse events in Study GD01, a causal relationship to Delytact could not be ruled out for lymphocyte count decreased in 5 patients (26.3%), and white blood cell count decreased and neutrophil count decreased in 1 patient (5.3%) each.

In Study GD01, there was no myelosuppression that was serious, led to death, or led to treatment discontinuation.

In Study GD01, the median time to the first onset of myelosuppression (range) was 7.0 (2-129) days.

A serious adverse event in the Japanese phase I/II study was lymphocyte count decreased in 1 patient (7.7%), for which a causal relationship to Delytact was denied.

PMDA's view:
In Study GD01, myelosuppression frequently occurred in patients who received Delytact, including Grade ≥3 myelosuppression for which a causal relationship to Delytact could not be ruled out, and thus attention should be paid to myelosuppression when Delytact is administered. Therefore, information about incidences of myelosuppression and measures at the onset in clinical studies should be appropriately presented to healthcare professionals to raise caution, using the package insert, etc.

7.R.2.4 Seizure

The applicant's explanation about seizure in patients receiving Delytact:
Events classified in "seizure" of the PT in MedDRA/J were identified as seizure.

Table 31 shows incidences of seizure in Study GD01 and the Japanese phase I/II study.

Table 31. Incidences of seizure (Study GD01 and Japanese phase I/II study)

PT (MedDRA/J 21.0)	Number of patients (%)			
	Study GD01 n = 19		Japanese phase I/II n = 13	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Seizure	9 (47.4)	1 (5.3)	4 (30.8)	0

Of 9 patients who experienced seizure in Study GD01, a causal relationship to Delytact was denied for the events in 6 patients, which was caused by exacerbation of disease, effect of the surgery, and exacerbation of brain oedema.

In Study GD01 and the Japanese phase I/II study, there was no seizure that was serious, led to death, or led to treatment discontinuation.

In Study GD01, the median time to the first onset of seizure (range) was 63.0 (1-277) days.

PMDA's view:
In Study GD01, seizure occurred, and thus attention should be paid to seizure when Delytact is administered. Therefore, information about incidences of seizure and measures at the onset in clinical studies should be appropriately presented to healthcare professionals to raise caution, using the package insert, etc.

7.R.2.5 Brain oedema

The applicant's explanation about brain oedema in patients receiving Delytact:
Events classified in "brain oedema" of the PT in MedDRA/J were identified as brain oedema.

Table 32 shows incidences of brain oedema in Study GD01. In the Japanese phase I/II study, no events of brain oedema occurred.

Table 32. Incidences of brain oedema (Study GD01 and Japanese phase I/II study)

PT (MedDRA/J 21.0)	Number of patients (%) n = 19	
	All Grade	Grade ≥3
Brain oedema	12 (63.2)	5 (26.3)

Of 12 patients who experienced brain oedema in Study GD01, a causal relationship to Delytact was denied for the events in 9 patients, which was caused by exacerbation of disease in any patient. There was no brain oedema that was serious, led to death, or led to treatment discontinuation.

In Study GD01, the median time to the first onset of brain oedema (range) was 94.5 (16-801) days.

PMDA's view:
In Study GD01, brain oedema occurred, and thus attention should be paid to brain oedema when Delytact is administered. Therefore, information about incidences of brain oedema and measures at the onset in clinical studies should be appropriately presented to healthcare professionals to raise caution, using the package insert, etc.

7.R.2.6 Intracranial tumour haemorrhage

The applicant's explanation about intracranial tumour haemorrhage in patients receiving Delytact:
Events classified in "intracranial tumour haemorrhage" of the PT in MedDRA/J were identified as intracranial tumour haemorrhage.

Table 33 shows details of patients who experienced intracranial tumour haemorrhage in Study GD01 and the Japanese phase I/II study.

Table 33. List of patients who experienced intracranial tumour haemorrhage (Study GD01 and Japanese phase I/II study)

Age	Sex	PT (MedDRA/J 21.0)	Grade	Seriousness	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
Study GD01									
6[redacted]	Female	Intracranial tumour haemorrhage	1	Non-serious	1	No	15	Resolved	Yes
6[redacted]	Male	Intracranial tumour haemorrhage	1	Non-serious	2	No	29	Resolved	Yes
		Intracranial tumour haemorrhage	1	Non-serious	5	No	51	Not resolved	No
Japanese phase I/II									
70s	Female	Intracranial tumour haemorrhage	1	Non-serious	Unknown	Yes	Unknown	Unknown	No
50s	Female	Intracranial tumour haemorrhage	1	Non-serious	Unknown	Yes	Unknown	Unknown	No
40s	Female	Intracranial tumour haemorrhage	1	Non-serious	Unknown	Yes	Unknown	Unknown	No

In Study GD01, the median time to the first onset of intracranial tumour haemorrhage (range) was 17.5 (1-34) days.

PMDA's view:
In Study GD01, intracranial tumour haemorrhage occurred, and thus attention should be paid to intracranial tumour haemorrhage when Delytact is administered. Therefore, information about incidences of intracranial tumour haemorrhage and measures at the onset in clinical studies should be appropriately presented to healthcare professionals to raise caution, using the package insert, etc.

7.R.2.7 Others

The following are details of depressed level of consciousness and syncope, nerve paralysis, cerebral infarction, pneumonitis, post procedural haemorrhage, and post procedural infection and subcutaneous abscess that occurred in patients receiving Delytact in Study GD01 and Japanese phase I/II study. Although a causal relationship to Delytact was denied for all of the events, considering the mechanism of action and route of administration of Delytact, PMDA concluded that the applicant should continue collecting the relevant information even after the market launch and, if any new finding becomes available, provide the information to healthcare professionals appropriately.

7.R.2.7.1 Depressed level of consciousness and syncope

The applicant's explanation about depressed level of consciousness and syncope in patients receiving Delytact:

Events classified in "depressed level of consciousness," "syncope," and "altered state of consciousness" of the PTs in MedDRA/J were identified as depressed level of consciousness and syncope.

Table 34 shows incidences of depressed level of consciousness and syncope in Study GD01. In the Japanese phase I/II study, there was no depressed level of consciousness and syncope.

Table 34. Incidences of depressed level of consciousness and syncope (Study GD01)

PT (MedDRA/J 21.0)	Number of patients (%) n = 19	
	All Grade	Grade ≥3
Depressed level of consciousness and syncope	10 (52.6)	6 (31.6)
Depressed level of consciousness	9 (47.4)	3 (15.8)
Syncope	2 (10.5)	2 (10.5)
Altered state of consciousness	1 (5.3)	1 (5.3)

Table 35 shows details of a patient who experienced serious depressed level of consciousness in Study GD01.

Table 35. List of patients who experienced symptoms associated with serious depressed level of consciousness and syncope (Study GD01)

Age	Sex	PT (MedDRA/J 21.0)	Grade	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
5[redacted]	Male	Syncope	3	2	No	2	Resolved	-

There was no depressed level of consciousness or syncope that led to death or treatment discontinuation. In Study GD01, the median time to the first onset of depressed level of consciousness or syncope (range) was 116.0 (10-646) days.

7.R.2.7.2 Nerve paralysis

The applicant's explanation about nerve paralysis in patients receiving Delytact:

Events classified in "hemiparesis," "hemiplegia," "cranial nerve disorder," "IIIrd nerve disorder," and "VIth nerve disorder" of the PTs in MedDRA/J were identified as nerve paralysis.

Table 36 shows incidences of nerve paralysis in Study GD01 and the Japanese phase I/II study.

Table 36. Incidences of nerve paralysis (Study GD01)

PT (MedDRA/J 21.0)	Number of patients (%)			
	Study GD01 n = 19		Japanese phase I/II n = 13	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Nerve paralysis	14 (73.7)	9 (47.4)	2 (15.3)	1 (7.7)
Hemiparesis	8 (42.1)	5 (26.3)	0	0
Hemiplegia	7 (36.8)	4 (21.1)	0	0
IIIrd nerve disorder	1 (5.3)	1 (5.3)	0	0
VIth nerve disorder	0	0	1 (7.7)	0
Cranial nerve disorder	0	0	1 (7.7)	1 (7.7)

Table 37 shows details of a patient who experienced serious nerve paralysis in Study GD01. In the Japanese phase I/II study, no serious events occurred.

Table 37. List of patients who experienced symptoms associated with serious nerve paralysis (Study GD01)

Age	Sex	PT (MedDRA/J 21.0)	Grade	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
5[redacted]	Male	Hemiplegia	3	6	No	337	Not resolved	No

There was no nerve paralysis that led to death or treatment discontinuation.

In Study GD01, the median time to the first onset of nerve paralysis (range) was 112.5 (2-536) days.

7.R.2.7.3 Cerebral infarction

The applicant's explanation about cerebral infarction in patients receiving Delytact:
Events classified in "cerebral infarction" of the PT in MedDRA/J were identified as cerebral infarction.

Table 38 shows details of patients who experienced cerebral infarction in Study GD01. In the Japanese phase I/II study, no cerebral infarction occurred.

Table 38. List of patients who experienced cerebral infarction (Study GD01)

Age	Sex	PT (MedDRA/J 21.0)	Grade	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
5[redacted]	Male	Cerebral infarction	3	2	No	386	Not resolved	No
6[redacted]	Male	Cerebral infarction	2	2	No	481	Not resolved	No
		Cerebral infarction	2	2	No	466	Not resolved	No

In Study GD01, the median time to the first onset of cerebral infarction (range) was 136.5 (12-261) days.

7.R.2.7.4 Pneumonitis

The applicant's explanation about pneumonitis in patients receiving Delytact:
Events classified in "pneumonitis" of the PT in MedDRA/J were identified as pneumonitis.

Table 39 shows details of patients who experienced pneumonitis in Study GD01. In the Japanese phase I/II study, no pneumonitis occurred.

Table 39. List of patients who experienced pneumonitis (Study GD01)

Age	Sex	PT (MedDRA/ J 21.0)	Grade	Seriousness	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
6[redacted]	Female	Pneumonitis	2	Non-serious	6	No	21	Resolved	No
6[redacted]	Male	Pneumonitis	2	Non-serious	5	No	54	Not resolved	No
4[redacted]	Male	Pneumonitis	2	Non-serious	6	No	11	Resolved	No

In Study GD01, the median time to the first onset of pneumonitis (range) was 558.0 (540-573) days.

7.R.2.7.5 Post procedural haemorrhage

The applicant's explanation about post procedural haemorrhage in patients receiving Delytact:
Events classified in "post procedural haemorrhage" of the PT in MedDRA/J were identified as post procedural haemorrhage.

Table 40 shows incidences of post procedural haemorrhage in Study GD01. In the Japanese phase I/II study, no post procedural haemorrhage occurred.

Table 40. List of patients who experienced post procedural haemorrhage (Study GD01)

Age	Sex	PT (MedDRA/ J 21.0)	Grade	Seriousness	Time to onset (nth dose)	Causal relationship to Delytact	Duration (days)	Outcome	Re-administration
4[redacted]	Male	Post procedural haemorrhage	1	Non-serious	6	No	30	Resolved	No
6[redacted]	Male	Post procedural haemorrhage	1	Non-serious	2	No	17	Resolved	No

In either patient, the applicable event was postoperative haemorrhage associated with the surgery, and its causal relationship to Delytact was ruled out.

In Study GD01, the median time to the first onset of intracranial tumour haemorrhage (range) was 309.0 (127-491) days.

7.R.2.7.6 Post procedural infection and subcutaneous abscess

The applicant's explanation about serious adverse events of post procedural infection and subcutaneous abscess in 1 patient each in Study GD01:
A patient discontinued Delytact after receiving 2 doses owing to serious post procedural infection, which was considered attributable to foreign matters (bone fragment, titanium plate, and Gore-Tex) left during an operation performed by the previous surgeon, and thus for which a relationship to Delytact was denied. However, a causal relationship to the surgery for Delytact treatment cannot be ruled out for this serious event. The other serious event of subcutaneous abscess was considered attributable to wound infection

associated with craniotomy performed after the end of Delytact treatment, and thus its relationship to Delytact was denied. The concerned serious event is unrelated to the surgery for Delytact treatment as well.

7.R.3 Clinical positioning and indication or performance

The "Indication or Performance" and "Precautions Concerning Indication or Performance" sections for Delytact were proposed as shown below.

Indication or Performance	Precautions Concerning Indication or Performance
Malignant glioma	Appropriate patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of Delytact.

According to results of the review in Sections "7.R.1 Efficacy" and "7.R.2 Safety" as well as the sections described below, PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections of Delytact should be specified as shown below.

Underline denotes additions.

Indication or Performance	Precautions Concerning Indication or Performance
Malignant glioma	• Delytact should be used in patients who previously received radiation therapy and temozolomide • Appropriate patients must be selected by physicians with a full understanding of the information about tissue types of patients enrolled in the clinical studies presented in the "Clinical Studies" section and of the efficacy and safety of Delytact.

7.R.3.1 Clinical positioning and intended population

Clinical practice guidelines in and outside of Japan and representative textbooks about brain tumor were found to have no reference to Delytact.

The applicant's explanation about clinical positioning and intended population of Delytact:
While conventional treatment of glioblastoma have been surgery, RT, and drug therapy, Delytact is a novel treatment modality with an unprecedented mechanism of action not found in any treatment.

In Study GD01 in patients with residual or recurrent glioblastoma who had previously received RT and TMZ, the survival rate at 1 year after the start of Delytact treatment was suggested to show efficacy in comparison with results from conventional treatment, and thus Delytact is considered to potentially offer a new treatment option to patients with glioblastoma.

Taking into account the review on the following (a) and (b) that might affect the efficacy evaluation in Study GD01, the applicant considers that Delytact is recommended for the patient population in Study GD01, which demonstrated the efficacy of Delytact.

(a) Influence of pseudo-progression[21)]

Pseudo-progression is defined as a "phenomenon of first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy" (*J Clin Oncol.* 2010;28:1963-72) and which likely results from transiently increased permeability of the tumor vasculature by irradiation. For the following reasons, Study GD01 appropriately excluded patients presenting pseudo-progression:

- Patients with MRI images suspected of pseudo-progression (patients without tumor cells and patients with lesion associated with non-specific inflammatory and oedema in tumor) were not enrolled because they did not meet the inclusion criterion of "residual or recurrent glioblastoma" for this study.
- Not only just before the first dose of Delytact but also just before each of the subsequent doses, all the patients underwent biopsy to confirm presence of histopathologically viable tumor cells during the treatment irrespective of whether 3 months (a period during which findings suspected of pseudo-progression likely occur) passed after the end of chemoradiotherapy. None of the biopsy specimens presented any histopathological finding indicative of pseudo-progression.

(b) *IDH1* gene mutation and influence of the gene mutation on methylation of O6-methylguanine-DNA methyltransferase (MGMT) promoter region

Table 41 and Figure 8 show results from an additional analysis on and the Kaplan-Meier curve of OS by *IDH1* gene mutation,[22)] respectively, in Study GD01.

Table 41. Results from additional analysis on OS by *IDH1* gene mutation (FAS, data cutoff on December 31, 2018)

	With gene mutation	Without gene mutation
Number of patients	6	13
Number of events (%)	1 (16.7)	7 (53.8)
Median [95% CI] (months)	Non-estimable [6.0, non-estimable]	20.9 [13.2, non-estimable]

[21] The Japanese clinical practice guideline describes pseudo-progression as follows:
Pseudo-progression is a pathological condition characterized by an increased size of contrast-enhanced lesion without clinical deterioration at the start of the treatment under the Stupp protocol (protocol consisting of surgical resection of glioblastoma followed by adjuvant radiotherapy plus oral TMZ, given concomitantly with and after RT [*N Engl J Med.* 2005;352:987-96 and *Lancet Oncol.* 2009;10:459-66]) and a histological finding of the isolated tissue mainly indicative of necrosis. Pseudo-progression results in a decreasing trend of tumor size at 3 months after chemoradiotherapy, allowing discrimination from true progression. On the contrary, discrimination from true progression would be particularly difficult within 3 months after that.

[22] *IDH1* gene mutation was not checked in Study GD01 but was checked post hoc at the Institute of Medical Science, The University of Tokyo.

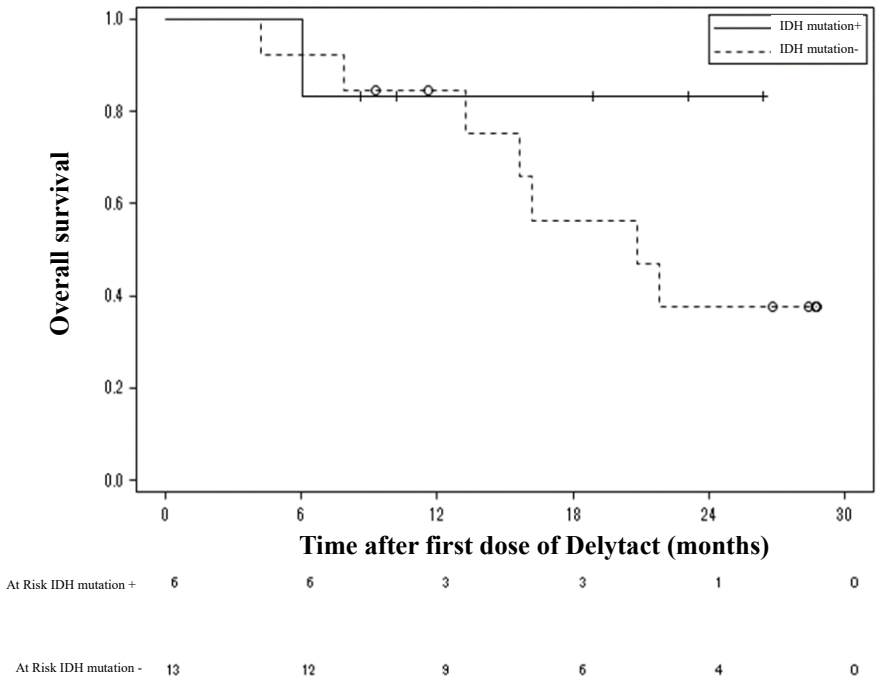

Figure 8. Kaplan-Meier curve of OS at additional analysis by *IDH1* gene mutation (FAS, data cutoff on December 31, 2018)

Table 42 and Figure 9 show results from an additional analysis on and the Kaplan-Meier curve of OS with and without methylation of MGMT promoter region, respectively, in 5 patients[23)] with the methylation status identified (2 patients with methylation, 3 patients without methylation).

Table 42. Results from additional analysis on OS with and without methylation of MGMT promoter region (5 patients, data cutoff on December 31, 2018)

	With methylation	Without methylation
Number of patients	2	3
Number of events (%)	1 (50.0)	2 (66.7)
Median [95% CI] (months)	Non-estimable [15.6, non-estimable]	20.9 [6.0, non-estimable]

[23] Because the examination was not performed at Institute of Medical Science, The University of Tokyo, the status was identified based on the information from the referring center (referral, etc.).

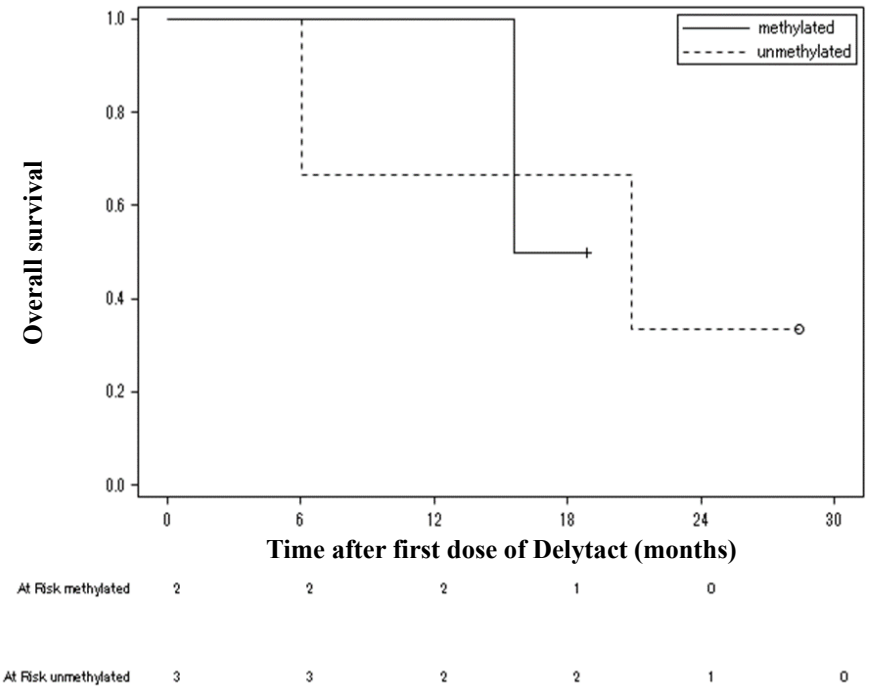

Figure 9. Kaplan-Meier curve of OS with and without methylation of MGMT promoter region at additional analysis (5 patients, data cutoff on December 31, 2018)

On the basis of the above results, the applicant considers that Delytact is expected to show efficacy irrespective of the status of *IDH1* gene mutation or methylation of MGMT promoter.

In addition, even for patients meeting (a) to (e) in Table 43, who were excluded from Study GD01, Delytact is recommended.

Table 43. Reasons for exclusion from Study GD01 and for recommendation of Delytact

Excluded patients	Reason for exclusion	Reason for recommendation of Delytact
(a) Patients with Grade III malignant glioma according to WHO classification	• The study was to evaluate the efficacy and safety of Delytact in patients with glioblastoma (Grade IV according to WHO classification), which is the most common and highly malignant glioma, as the historical control.	• To Grade III malignant glioma, treatment similar to that of glioblastoma is applied. • Pathologically, the criteria for distinguishing glioblastoma from anaplastic astrocytoma, Grade III malignant glioma, in terms of an extent of differentiation are not clearly defined.
(b) Patients with extracranial metastases	• In such patients, who are assumed to have cerebrospinal fluid dissemination, the survival is 2.7 to 3.4 months (*J Neurosurg.* 1994;80:834-9 and *J Korean Neurosurg Soc.* 2011;49:334-8) of which the period may not be long enough to evaluate the efficacy and safety of Delytact. • The lesion to be measured cannot be identified owing to widely distributed foci, precluding assessment of the tumor reduction effect.	In view of the mechanism of action (tumor-specific cytocidal effect and antitumor effect mediated by antitumor immune response), Delytact is expected to be effective.
(c) Patients with multiple intracranial lesions of malignant glioma	• Such multiple lesions were considered to complicate the efficacy evaluation of Delytact.	
(d) Patients with subependymal or subarachnoidal lesion	• Such patients have a risk of spinal dissemination through cerebrospinal fluid, and as with patients in (b), their survival may not be long enough to evaluate the efficacy and safety of Delytact.	
(e) Patients with tumor involving cerebral ventricle, brainstem, or posterior cranial fossa or with tumor that would require administration of Delytact through cerebral ventricle	• The administration of Delytact through cerebral ventricle poses a risk of normal pressure hydrocephalus. • The brainstem has a center of functions supporting life. • Stereotactic surgery on the posterior cranial fossa requires the patient to lie prone under general anesthesia.	In view of the mechanism of action (tumor-specific cytocidal effect and antitumor effect mediated by antitumor immune response), Delytact is expected to be effective. In addition, normal pressure hydrocephalus can be managed by shunting.

Treatment strongly recommended for adult patients with primary glioblastoma based on scientific evidence is Stupp protocol only, and the Japanese clinical practice guideline instructs that after the surgery, TMZ maintenance treatment should be given concomitantly with and after RT (standard treatment). The applicant considers that the standard treatment with RT and TMZ should be provided even when Delytact is used, and for the following reasons, at least concomitant use of Delytact with TMZ maintenance treatment is recommended: In Study GD01, 16 of 19 patients received Delytact while being on TMZ maintenance treatment, and the results suggested the efficacy in comparison with the Historical Data; and in view of the mechanism of action, Delytact, when administered at the beginning of treatment, is expected to show efficacy for an extended period.

In addition to the standard treatment, bevacizumab, nimustine hydrochloride (nimustine), and carmustine implant for intracranial use are "recommended without scientific evidence (Recommendation Grade C1)" in the Japanese clinical practice guideline. Delytact is expected to offer an additional treatment option to patients for whom bevacizumab and carmustine implant for intracranial use are not recommended (patients with glioblastoma of whom survival is not expected to be prolonged with bevacizumab, patients without any space available for carmustine implant for intracranial use

owing to partial tumor resection, etc.), and nimustine may be concomitantly used in patients ineligible for TMZ because of allergy.

Furthermore, Study GD01 included patients who had previously received RT and TMZ, but for the following reasons, Delytact is expected to show efficacy irrespective of prior treatment, and thus the applicant considers that the prior treatment may not have to be defined in the "Indication or Performance."

- In view of the mechanism of action, Delytact is expected to exert an antitumor effect irrespective of prior treatment.
- Study GD01 included patients (n = 10) who had previously received bevacizumab or carmustine implant for intracranial use in addition to TMZ. The median OSs [95% CI] (months) in patients (n = 10) with the concerned prior treatment and patients (n = 9) without that estimated by the Kaplan-Meier method were non-estimable [4.2, non-estimable] and 20.9 [7.9, non-estimable], respectively (data cutoff on December 31, 2018), and thus Delytact can be expected to show efficacy even in patients refractory to prior treatment.

Study GD01 and clinical investigation, on the other hand, did not include children, and no clinical study results in children are available. Although Delytact may be expected to show efficacy in pediatric patients in view of the mechanism of action, the applicant considers that the safety in pediatric patients has not been established.

On the basis of the above, the proposed "Indication or Performance" of Delytact was specified as "malignant glioblastoma." Furthermore, to provide information about patients in Study GD01 to healthcare professionals appropriately, the following statements will be added to the "Precautions Concerning Indication or Performance" section, which has been planned to have the statement "Appropriate patients must be selected by physicians with a full understanding of the information presented in the 'Clinical Studies' section and of the efficacy and safety of Delytact" in the package insert with details of patients in Study GD01 (prior treatment, exclusion criteria, etc.) being described in the "Clinical Studies" section:

- The efficacy and safety of Delytact in patients without prior chemoradiotherapy have not been established.
- The efficacy and safety of Delytact administered into the infratentorial lesion have not been established.

PMDA's view:

Evaluation on time to event such as survival in Study GD01 is affected by patient characteristics, and the efficacy evaluation in comparison with external control has limitations. Study GD01 is a single-center clinical study, and thus the efficacy and safety of Delytact should be evaluated at multiple centers, and it is necessary to construct the system for such an evaluation promptly.

In Study GD01, on the other hand, SD was maintained for an extended period in some patients with glioblastoma, which is characterized by rapid progression hardly allowing extended maintenance of SD. In light of this result, a certain level of efficacy of Delytact is expected [see Section 7.R.1.3]. PMDA considers it possible to position Delytact as a new treatment option for patients with glioblastoma.

Concerning patients in (a) in Table 43 that the applicant proposed as the potential intended population of Delytact, the pivotal study results were from Study GD01 that included patients with glioblastoma, and Delytact should be recommended to patients with glioblastoma. However, there is little need to limit the "Indication or Performance" of Delytact to glioblastoma, considering that the number of patients with Grade III malignant glioma according to WHO classification is very small with the available treatment options limited in addition to the above applicant's explanation.

Concerning patients in (b) to (e) in Table 43, attending physicians may be given room to choose Delytact or not for these patients according to location of the lesion and patient's condition, except for patients requiring an intrathecal administration, because treatment options for these patients are very limited, and complications such as normal pressure hydrocephalus can be managed by neurosurgeons. Accordingly, there is little need to exclude patients in (b) to (e) in Table 43 from the "Indication or Performance" of Delytact although the applicant should inform healthcare professionals that these patients were excluded from clinical studies by stating this in the "Clinical Studies" and other sections in the package insert.

Study GD01 included patients who had previously received RT and TMZ, the Japanese clinical practice guideline recommends RT and TMZ for treatment of malignant glioma, but there is not enough evidence to support use of Delytact in preference to RT and TMZ. Use of Delytact is not recommended in preference to RT and TMZ at present. For patients who have a residual or recurrent lesion even after receiving RT and TMZ and are in need of a new treatment, it is considered acceptable to allow use of Delytact, a novel treatment modality, because treatment options are limited.

No clinical studies in children have been conducted so far, and use of Delytact in children is not recommended. The applicant should consider collecting data necessary to propose use of Delytact in children promptly, in light of the limited treatment options for children as with those for adults.

PMDA therefore has concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" of Delytact should be specified as shown below.

Indication or Performance	Precautions Concerning Indication or Performance
Malignant glioma	• Delytact should be used in patients who previously received radiation therapy and temozolomide • Appropriate patients must be selected by physicians with a full understanding of the information about tissue types of patients enrolled in the clinical studies presented in the "Clinical Studies" section and of the efficacy and safety of Delytact.

7.R.4 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" of Delytact were specified as shown below.

Dosage and Administration or Method of Use	Precautions Concerning Dosage and Administration or Method of Use
The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. In principle, the first and second doses are separated by 1 week, and each of the third and subsequent doses is separated from the previous dose by 4 weeks.	• Symptoms associated with immunisation reaction may occur just after administration of Delytact. Continuous use of Delytact should be carefully considered in light of benefits and risks. • The efficacy and safety of Delytact administered in >6 doses have not been established. • For concomitant use of temozolomide, if any, its necessity should be carefully considered by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of Delytact. In addition, physicians should thoroughly read the package insert of the concomitant drug. • Delytact should be intratumorally administered using a stereotaxic technique. Delytact should be thawed under protection from light and, after being thawed, administered immediately. If it has to be stored after being thawed out of necessity, it should be stored at 2°C to 8°C under protection from light because of its susceptibility to light and used within 24 hours. In addition, the residual fluid should be appropriately discarded.

As a result of the review in Sections "7.R.1 Efficacy" and "7.R.2 Safety" as well as the sections described below, PMDA concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" of Delytact should be specified as shown below.

Underline denotes additions.

Dosage and Administration or Method of Use	Precautions Concerning Dosage and Administration or Method of Use
The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. ~~In principle,~~ The first and second doses are separated by ~~1 week~~ 5 to 14 days, and each of the third and subsequent doses is separated from the previous dose by 4 weeks. Up to 6 doses may be administered.	~~• Symptoms associated with immunisation reaction may occur just after administration of Delytact. Continuous use of Delytact should be carefully considered in light of benefits and risks.~~ ~~• The efficacy and safety of Delytact administered in >6 doses have not been established.~~ ~~• For concomitant use of temozolomide, if any, its necessity should be carefully considered by physicians with a full understanding of the information presented in the "Clinical Studies" section and of the efficacy and safety of Delytact. In addition, physicians should thoroughly read the package insert of the concomitant drug.~~ • As the other concomitant antineoplastic agent, if any, temozolomide should be used. • Each dosage is intended to target the whole tumor lesion in the brain. To ≥2 sites where necessary, the dosage should be administered in divided doses. • No results from a clinical study where Delytact was intratumorally administered by means other than a stereotaxic technique are available. • No results from a clinical study where Delytact was administered into the infratentorial lesion are available. • Delytact should be thawed under protection from light and, after being thawed, administered immediately. If it has to be stored after being thawed out of necessity, it should be stored at 2°C to 8°C under protection from light ~~because of its susceptibility to light~~ and used within 24 hours. In addition, the residual fluid should be appropriately discarded.

7.R.4.1 Dosage and administration or method of use of Delytact

The applicant's explanation about the rationale for specifying the "Dosage and Administration or Method of Use" of Delytact:

Dose of Delytact

In the Japanese phase I/II study, the safety was confirmed in patients who received Delytact at 1×10^9 PFU per treatment session, and thus in Study GD01, the dose of Delytact was specified at 1×10^9 PFU per treatment session. In Study GD01, 15 of 19 patients received Delytact at 1×10^9 PFU for 1 lesion in divided doses, which were injected into 2 sites through 1 puncture or through 2 punctures. Even after the market launch, Delytact should be administered as done in Study GD01. Although Delytact has not been administered to patients with multiple intracranial lesions, the dosage of 1×10^9 PFU may be administered to multiple lesions in divided doses based on experience with divided doses for 1 lesion.

The applicant therefore plans to include in the "Dosage and Administration or Method of Use" the statement to the effect that 1 mL (1×10^9 PFU) should be intratumorally administered in each treatment session; to add the following content to the "Precautions Concerning Dosage and Administration or Method of Use"; and to provide the information about the divided-dose method in clinical studies to healthcare professionals appropriately using labeling materials.

- Each dosage is intended to target the whole tumor lesion in the brain. To ≥2 sites where necessary, the dosage should be administered in divided doses.

Dosing interval and number of doses of Delytact

In the Japanese phase I/II study, a tissue specimen was collected during the second dose to evaluate the efficacy of the first dose, and the interval between the first and second doses was specified as 5 to 14 days. In Study GD01, the interval between the first and second doses was specified as 5 to 14 days as done in the Japanese phase I/II study. In addition, because Delytact was presumed to disappear within 4 weeks, the interval between each of the third and subsequent doses and the previous dose was specified as 4 weeks.

Results from non-clinical studies indicated that the efficacy of Delytact was expected to increase with the increasing number of doses. In view of the average survival of patients with glioblastoma, patients were assumed capable of receiving approximately 6 doses of Delytact and thus the maximum number of doses was specified as 6 in Study GD01. In view of the cytocidal effect and antitumor immune response expected for Delytact, the applicant considers it important to ensure that Delytact is delivered throughout the whole tumor by multiple doses. In post-marketing cases where 6 doses are not enough to deliver Delytact throughout the whole tumor, options to receive the seventh and subsequent doses are considered clinically meaningful for patients who are in the stable disease condition after 6 doses.

In light of the above, the "Dosage and Administration or Method of Use" will have the statement "In the standard regimen, the first and second doses are separated by 1 week, and each of the third and subsequent doses up to the sixth dose is separated from the previous dose by 4 weeks." Furthermore, to the "Precautions Concerning Dosage and Administration or Method of Use," the following statement is added:

- The efficacy and safety of Delytact administered in >6 doses have not been established.

Administration procedure of Delytact

Because the stereotaxic technique is generally used in neurosurgical procedure to reach the needle to an intracerebral point at coordinates, the administration procedure in Study GD01 was limited to this technique. The applicant, however, considered it possible to administer Delytact into the brain by procedures other than the stereotaxic technique such as a visual-guided procedure and thus planned to include in the "Precautions Concerning Dosage and Administration or Method of Use" the statement to the effect that Delytact should be intratumorally administered using a stereotaxic technique or other procedures.

Concomitant use of Delytact with antineoplastic agents other than TMZ

- Bevacizumab
  Patients must undergo incision of the head to receive Delytact, use of bevacizumab, which is known to delay wound healing, was prohibited in Study GD01. Considering its pharmacological action, bevacizumab, however, is unlikely to weaken the efficacy of Delytact, and thus there may be cases where concomitant use of bevacizumab with Delytact is considered.
- Nimustine
  Nimustine is used as a substitute for TMZ in patients who are not able to use TMZ, and thus there may be cases where concomitant use of nimustine with Delytact is considered.
- Carmustine implant for intracranial use
  A carmustine implant for intracranial use, if it remains in the resection space, may affect the route of administration of Delytact, and thus it is not recommended for patients who are scheduled to receive Delytact.

PMDA's view:
PMDA considered it acceptable to specify the "Dosage and Administration or Method of Use" based on the condition in Study GD01. However, there are no results from clinical studies to evaluate the efficacy and safety of Delytact administered in >6 doses, and it is not appropriate to administer Delytact in >6 doses at present. The following point should be clearly specified in the "Dosage and Administration or Method of Use."

- Up to 6 doses of Delytact may be administered.

The above applicant's explanation about the "Precautions Concerning Dosage and Administration or Method of Use" is understandable but Delytact has never been administered by procedures other than the stereotaxic technique, thus, such information should be clearly noted. In addition, no results from a clinical study where Delytact was administered into the infratentorial lesion are available, and especially administration into the brain stem is anticipated to pose a very high risk. The administration into the brain stem should be carefully considered. Concomitant use of Delytact with an antineoplastic agent other than TMZ is not acceptable because the efficacy and safety remain unknown. The statement "Symptoms associated with immunisation reaction may occur just after administration of Delytact. Continuous use of Delytact should be carefully considered in light of benefits and risks." is a general caution for adverse events, and thus there is little need to include such statement in the "Precautions Concerning Dosage and Administration or Method of Use" section.

Taking account of the above, PMDA has concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" of Delytact should be as shown below.

Dosage and Administration or Method of Use	Precautions Concerning Dosage and Administration or Method of Use
The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. The first and second doses are separated by 1 week (5-14 days), and each of the third and subsequent doses is separated from the previous dose by 4 weeks. Up to 6 doses may be administered.	• As the other concomitant antineoplastic agent, if any, temozolomide should be used. • Each dosage is intended to target the whole tumor lesion in the brain. To ≥2 sites where necessary, the dosage should be administered in divided doses. • No results from a clinical study where Delytact was intratumorally administered by means other than a stereotaxic technique are available. • No results from a clinical study where Delytact was administered into the infratentorial lesion are available. • Delytact should be thawed under protection from light and, after being thawed, administered immediately. If it has to be stored after being thawed out of necessity, it should be stored at 2°C to 8°C under protection from light and used within 24 hours. In addition, the residual fluid should be appropriately discarded.

8. Risk Analysis and Outline of the Review Conducted by PMDA

8.1 Post-marketing investigations

The applicant's explanation about post-marketing investigations of Delytact:

Because currently available information on the efficacy and safety of Delytact is limited, the applicant will conduct a use-results comparison survey (Table 44) to further evaluate the efficacy and safety of Delytact after the market launch by comparing information in patients receiving Delytact with information in patients not receiving it.

Table 44. Outline of use-results comparison survey (draft)

Objective	To confirm the efficacy and safety of Delytact in patients with malignant glioma. In addition, to compare Delytact with the conventional treatment (control group) by investigating the applicable efficacy data retrospectively.
Survey method	All-case surveillance system
Population	• Delytact group: All the patients who have received Delytact • Control group: All the patients who were diagnosed with malignant glioma (primary or recurrent) during a certain period of time, 2 years back from the date of the first dose of Delytact (i.e., a period of 6 months, starting from 2 years and 6 months before the date of the first dose to 2 years before the date of the first dose) at survey centers to which Delytact was delivered
Survey period	7 years from approval date
Follow-up period	• Delytact group: Period from the date of diagnosis of malignant glioma (date of primary or recurrent diagnosis)[*1] to 2 years after the first dose of Delytact. The follow-up is censored at 2 years after the first dose of Delytact in patients who survive ≥2 years after the first dose where applicable. • Control group: 2 years from the date of diagnosis of malignant glioma (date of primary or recurrent diagnosis)
Efficacy endpoints	Primary endpoint OS (from the date of diagnosis of malignant glioma [date of primary or recurrent diagnosis] to death [from any cause]) Secondary endpoints Factors affecting OS: Timing of the first dose of Delytact (<3 months or ≥3 months after end of chemoradiotherapy), number of doses of Delytact, category of lesion at the time of diagnosis with malignant glioma (single or multiple), prognostic factors of malignant glioma according to the Recursive Partitioning Analysis (tissue type [Grade], age, KPS, extent of resection, mental status, duration of neurologic symptom, overall radiation dose, neural function [capable of working or not], methylation of MGMT promoter, and *IDH1/2* gene mutation [yes or no], etc.)
Method of efficacy evaluation	• Perform the following analysis on each of primary glioblastoma[*2] and recurrent glioblastoma[*3]: Conduct a trend score matching so that the Delytact and control groups include the same number of patients (1:1) and perform a logrank test with the two-sided significance level of 5% on OS in the sample population. Calculate the median survival, and 1-year and 2-year survival rate by the Kaplan-Meier method, and 95% CI according to the Greenwood's formula. Calculate the hazard ratio using the Cox proportional hazards model and 95% CI of the ratio. The matching factors are 10 factors affecting prognosis of malignant glioma. • In the Delytact group, perform the following analysis on each of primary glioblastoma, recurrent glioblastoma, primary anaplastic oligodendroglioma, recurrent anaplastic oligodendroglioma, primary anaplastic astrocytoma, and recurrent anaplastic astrocytoma: To identify factors potentially affecting OS, perform univariate and multivariate analyses using the Cox proportional hazards model, and calculate the hazard ratio and its 95% CI for each factor. • Perform the following analysis on each of Grade III anaplastic oligodendroglioma and anaplastic astrocytoma: Conduct a trend score matching so that the Delytact and control groups include the same number of patients (1:1), and calculate the median survival, and 1-year and 2-year survival rate in the sample population OS by the Kaplan-Meier method, and 95% CI according to the Greenwood's formula. Calculate the hazard ratio using the Cox proportional hazards model and 95% CI of the ratio. The matching factors are the same 10 factors as those for glioblastoma.
Safety survey items	• Incidences of reported adverse drug reactions and infections by type • Incidences of reported serious adverse events • Factors affecting safety • Safety specifications: Symptoms associated with immunisation reaction, neurologic symptoms such as seizure, transient lymphocyte count decreased, hypersensitivity such as anaphylaxis, procedural adverse events, reduced effectiveness of Delytact due to antiherpesvirus drugs, normal pressure hydrocephalus, and autoimmune diseases involving the central nervous system

Target sample size	Target sample size of patients with glioblastoma • Delytact group: A total of 250 patients with glioblastoma including 150 patients with primary lesion and 100 patients with recurrent lesion • Control group: A total of 500 patients with glioblastoma including 300 patients with primary lesion and 200 patients with recurrent lesion Rationale for establishment: The 2-year survival rates in patients with primary glioblastoma and in patients with recurrent glioblastoma receiving conventional treatment are presumed to be [redacted]%[*4] and [redacted]%,[*5] respectively. On the assumption that the 2-year survival rate in patients receiving Delytact is [redacted]% higher than that in patients receiving conventional treatment, the sample size was estimated for a logrank test to compare survival between the Delytact and control groups at the sample size ratio of [redacted] for the follow-up period of 2 years with the two-sided significance level of [redacted]% and power of [redacted]%. The estimation indicated that the Delytact group was required to include 148 patients with primary glioblastoma and 97 patients with recurrent glioblastoma. For matching patient characteristics between the Delytact and control groups, the sample size of the control group was planned to be twice that of the Delytact group. The matching factors are 10 factors affecting prognosis of malignant glioma (tissue type [Grade], age, KPS, extent of resection, mental status, duration of neurologic symptom, overall radiation dose, neural function [capable of working or not], methylation of MGMT promoter, and *IDH1/2* gene mutation [yes or no]). Target sample size of patients with Grade III malignant glioma (anaplastic oligodendroglioma and anaplastic astrocytoma): • Delytact group: 30 to 50 patients with anaplastic oligodendroglioma and 30 to 50 patients with anaplastic astrocytoma • Control group: 60 to 100 patients with anaplastic oligodendroglioma and 60 to 100 patients with anaplastic astrocytoma Rationale for establishment: The 2-year survival rates in patients with anaplastic oligodendroglioma and in patients with anaplastic astrocytoma receiving conventional treatment are presumed to be [redacted]%[*6] and [redacted]%,[*7] respectively. On the assumption that the 2-year survival rate in patients receiving Delytact is [redacted]% higher than that in patients receiving conventional treatment, the sample size was determined[*8] to be 30 to 50. On the assumption that the survival function has an exponential distribution, simulation was performed [redacted] times. The simulations revealed that in the survey with each of the groups including [redacted], [redacted], and [redacted] patients, the probability of the point estimate of the hazard ratio in the proportional hazards model being determined to be <1 was [redacted]%, [redacted]%, and [redacted]% for anaplastic oligodendroglioma and [redacted]%, [redacted]%, and [redacted]% for anaplastic astrocytoma, respectively. For matching patient characteristics between the Delytact and control groups, the sample size of the control group was planned to be twice that of the Delytact group. The matching factors are the same 10 factors as those for glioblastoma.

*1 The "date of diagnosis of malignant glioma" for patients with primary lesion is the date on which the diagnosis of malignant glioma is given by the survey investigator for the first time. The "date of diagnosis of malignant glioma" for patients with recurrent lesion is the date on which the diagnosis of recurrence is given by the survey investigator based on a documented increase in tumor size (both ≥20% and ≥5 mm [absolute value] increase in sum of tumor diameters) after chemoradiotherapy, appearance of a new tumor in diagnostic imaging such as MRI without any tumor increase in comparison with the image at the start of initial chemoradiotherapy, or malignant transformation (from Grade III malignant glioma to glioblastoma).

*2 The control group should include patients who have not responded to the initial chemoradiotherapy in terms of tumor size.
The Delytact group should include patients who have not responded to the initial chemoradiotherapy in terms of tumor size and then received Delytact.

*3 The control group should include patients in whom the tumor size has increased in comparison with the size at the start of initial chemoradiotherapy (both ≥20% and ≥5 mm [absolute value] increase in sum of tumor diameters) or a new tumor has appeared in diagnostic imaging such as MRI without any tumor increase in comparison with the image at the start of initial chemoradiotherapy.
The Delytact group should include patients who have been given a diagnosis of recurrence for the first time at ≥3 months after the initial chemoradiotherapy and then received Delytact.

*4 *N Engl J Med.* 2014;370:709-22

*5 *Neuro Oncol.* 2015;17:1504-13

*6 *J Neurooncol.* 2015;122:111-9

*7 *Neuro Oncol.* 2017;19:252-8

*8 The Delytact group should include patients with anaplastic oligodendroglioma or anaplastic astrocytoma who have received Delytact at ≥3 months after the initial chemoradiotherapy. Because Grade III malignant glioma has a higher survival rate than Grade IV (glioblastoma), the survival rate has not been investigated by status of the primary or recurrent lesion. Patients with the primary lesion and patients with the recurrent lesion will be pooled for the analysis.

On the primary efficacy endpoint (comparison between groups), an analysis with confounding factors adjusted by a trend score model is planned. Taking account of the reports on prognostic factors of malignant glioma (*J Natl Cancer Inst.* 1993;85:704-10 and *Radiother Oncol.* 2018;129:347-51), 10 factors (tissue type [Grade], age, Karnofsky performance status [KPS], extent of resection, mental status, duration of neurologic symptom, overall radiation dose, neural function [capable of working or not],

methylation of MGMT promoter, and *IDH1/2* gene mutation [yes or no]) are specified as confounding factors affecting prognosis of malignant glioma and also survey items.

The applicant will carefully select survey centers during an early post-marketing phase, and approximately [redacted] survey centers mainly including institutions of [redacted] are expected to participate in the survey. Malignant glioma, the indication of Delytact, is estimated to develop in approximately 2,000 people as glioblastoma and in approximately 1,000 people as Grade III malignant glioma annually. The control group is planned to consist of all the patients who were diagnosed with malignant glioma (primary or recurrent) during a certain period of time, 2 years back from the date of the first dose of Delytact (i.e., a period of 6 months, starting from 2 years and 6 months before the date of the first dose to 2 years before the date of the first dose) at survey centers to which Delytact was delivered. Data on conventional treatment are to be collected in a retrospective manner.

For patients with a lesion involving the lower brainstem (cerebellum, midbrain, pons, and medulla oblongata), no clinical study results are available at present, but the applicant plans to conduct a post-marketing clinical study (Table 45) to evaluate the safety and efficacy in this patient population, because their treatment options are very limited, and the population size is remarkably small.

Table 45. Outline of post-marketing clinical study (draft)

Objective	To evaluate the safety of Delytact, the primary endpoint, in patients with malignant glioma involving the lower brainstem (cerebellum, midbrain, pons, and medulla oblongata) and the efficacy.
Survey method	Post-marketing clinical study
Population	Patients with malignant glioma involving the lower brainstem (cerebellum, midbrain, pons, and medulla oblongata)
Study period	7 years from approval date
Follow-up period	2 years
Efficacy endpoint and method of evaluation	• OS (period from the end of radiation therapy for patients with primary lesion or diagnosis of recurrence for patients with recurrent lesion to death [from any cause]): Calculate the median survival and 1-year survival rate by the Kaplan-Meier method, and 95% CI according to the Greenwood's formula. Calculate the hazard ratio using the Cox proportional hazards model and 95% CI of the ratio. • 1-year survival rate: Calculate the point estimate and the precise 95% CI.
Safety endpoint	• Adverse events and adverse drug reactions • Adverse events and adverse drug reactions leading to discontinuation of Delytact • Safety specifications: Symptoms associated with immunisation reaction, neurologic symptoms such as seizure, transient lymphocyte count decreased, hypersensitivity such as anaphylaxis, procedural adverse events, reduced effectiveness of Delytact due to antiherpesvirus drugs, normal pressure hydrocephalus, and autoimmune diseases involving the central nervous system
Target sample size	Delytact group (Grade III malignant glioma and glioblastoma): 14 patients Rationale for establishment: On the assumption that the 1-year survival rate in patients with Grade III malignant glioma and in patients with glioblastoma in the control group (target sample size, 21 patients corresponding to the external comparative control data collected in a retrospective manner) is [redacted]%[*1] and [redacted]%,[*2] and the survival function has an exponential distribution, simulation was performed [redacted] times. The simulations revealed that in the study with each of the groups including [redacted] to [redacted] patients, the probability of the point estimate of the hazard ratio in the proportional hazards model being determined to be <1 was [redacted]% to [redacted]% for Grade III malignant glioma and [redacted]% to [redacted]% for glioblastoma. In view of the limited number of patients with malignant glioma involving the lower brainstem in addition to the above simulation result, the sample size was specified as 14.

*1 *J Neurol Sci.* 2015;353:92-7 and *BMC Cancer.* 2014;14:115
*2 *J Neurooncol.* 2019;145:479-86

Data from the above use-results comparison survey and post-marketing clinical study will be registered in the electronic data capture (EDC) system internally constructed and administered by the applicant.

8.R Outline of the review conducted by PMDA

PMDA's view:

Since clinical experience with Delytact is limited, the applicant should continuously confirm the efficacy and safety of Delytact even after the market launch.

In the use-results comparison survey, the control group is planned to consist of all the patients who were diagnosed with malignant glioma (primary or recurrent) during a certain period of time, 2 years back from the date of the first dose of Delytact (i.e., a period of 6 months, staring from 2 years and 6 months before the date of the first dose to 2 years before the date of the first dose) at survey centers to which Delytact was delivered. Use of the non-randomized control group, however, has limitations in ensuring fair comparison between the groups, and such a control group would not provide the information comparable to those from a prospective study in terms of quality and volume. The survey should be essentially conducted in a randomized, double-blind, parallel-group design. When Delytact becomes available in clinical settings, on the other hand, evaluation in a randomized controlled design is likely to be impractical. PMDA, therefore, considers it inevitable to evaluate the efficacy and safety of Delytact by comparing retrospective data in the control group collected from patients in whom Delytact is indicated but not received Delytact, as presented by the applicant, on condition that the plan ensures further fair comparison between the groups and thereby objective evaluation and assessment.

For the efficacy, the therapeutic goal in patients with malignant glioma eligible for Delytact is considered to prolong the survival. PMDA, therefore, considers it appropriate to specify OS as the primary efficacy endpoint.

For the safety, in view of the review in Section "7.R.2 Safety," the safety specifications should additionally include "myelosuppression," "brain oedema," and "intracranial tumour haemorrhage" to collect the information.

The follow-up periods for the efficacy and safety endpoints presented by the applicant are considered appropriate in view of feasibility of follow-up in the study population.

In patients with a lesion involving the lower brainstem (cerebellum, midbrain, pons, and medulla oblongata), of whom the number is very limited, results on the safety and efficacy should be obtained in the post-marketing clinical study for evaluation.

For details of the use-results comparison survey and post-marketing clinical study, PMDA will make a final conclusion, taking account of comments raised in the Expert Discussion on the efficacy and safety evaluation of Delytact.

9. Regulations on Type-1 Use of Living Modified Organisms under Article 4 of the Act on Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms ("the Cartagena Act")

The use of Delytact is classified as Type-1 Use of Living Organisms under Article 4 of the Cartagena Act, and the Regulations on Type-1 Use of Living Modified Organisms has been approved (Approval number, 14-36V-0002).

10. Results of Compliance Assessment Concerning the Application Data and Conclusion Reached by PMDA

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

The inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Delytact is expected to have a certain level of efficacy in the treatment of malignant glioma, and that Delytact has acceptable safety in view of its benefits. Although the information on the efficacy and safety of Delytact is limited at present, PMDA considers it meaningful to provide Delytact to clinical settings as a treatment option for patients with malignant glioma.

PMDA has concluded that Delytact may be approved if Delytact is not considered to have any particular problems based on comments from the Expert Discussion, with the following condition and time limit under Article 23-26 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices: The applicant is required to continue evaluating the efficacy of Delytact and to further collect the safety information until a certain time limit after the market launch. For the time limit under the concerned article, PMDA will make a conclusion taking account of details of the post-marketing survey (preparation period for sales, patient enrollment period, follow-up period for each patient, and preparation period for application, etc.) and comments raised in the Expert Discussion.

Review Report (2)

May 13, 2021

Product Submitted for Approval

Brand Name	Delytact Injection
Non-proprietary Name	Teserpaturev
Applicant	Daiichi Sankyo Company, Limited
Date of Application	December 28, 2020

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

As a result of the review in Section "7.R.1 Efficacy" of the Review Report (1), PMDA considered it difficult to derive the conclusion only from results on the predetermined primary and secondary efficacy endpoints in Study GD01 that Delytact demonstrated the efficacy, because its study design and threshold setting have problems. As shown by MRI imaging, on the other hand, SD was maintained for an extended period in some patients with glioblastoma, which is characterized by rapid progression hardly allowing extended maintenance of SD. In light of this result, Delytact is expected to have certain level of efficacy.

Information about the efficacy of Delytact available at present, however, is very limited, and thus the efficacy should be continuously evaluated also after the market launch [see Sections "7.R.3 Clinical positioning and indication or performance" and "8.R Outline of the review conducted by PMDA" of the Review Report (1)].

The PMDA's conclusion that Delytact is expected to have certain level of efficacy was supported by the expert advisors at the Expert Discussion. The following comments on information to be additionally provided were raised from the expert advisors:

- Results on long-term SD are likely to be affected by the patient characteristics as with those on OS, and thus results from Study GD01, in which the study population was narrowed down by various criteria, potentially led to overestimation of the efficacy of Delytact.

- Delytact is expected to be a new treatment modality for malignant glioma, but currently available results do not show the efficacy superior to that of the other treatment options, and the efficacy of Delytact can be clarified only by the post-marketing assessment. Accordingly, information about results from Study GD01 should be appropriately provided to healthcare professionals to avoid excessive expectations for the efficacy of Delytact.

Taking account of the comments from the Expert Discussion, PMDA requested the applicant to provide information about results from Study GD01 to healthcare professionals appropriately using materials, etc., as the information about the efficacy of Delytact available is limited. The applicant responded that they would take appropriate measures, and thus PMDA accepted the applicant's explanation.

1.2 Safety

As a result of the review in Section "7.R.2 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention in patients with residual or recurrent glioblastoma during use of Delytact alone or combination with TMZ are symptoms associated with immunisation reaction, myelosuppression, seizure, brain oedema, and intracranial tumour haemorrhage.

Although attention should be paid to the above adverse events when Delytact is administered, PMDA has concluded that Delytact is tolerable provided that appropriate measures, such as monitoring and controlling of the adverse events and treatment discontinuation of Delytact, are taken by physicians with adequate knowledge and experience in treatment of glioblastoma and neurosurgical procedures.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments on information to be additionally provided were raised from the expert advisors:

- Administration of Delytact involves an invasive injection procedure of multiple brain punctures, and actually in Study GD01, a number of adverse events associated with the injection procedure occurred. Therefore, the applicant should provide information of not only the risks of Delytact itself, but also details of the Delytact injection procedure and its associated risks to healthcare professionals.

Taking account of the comments from the Expert Discussion, PMDA requested the applicant to provide the following information to healthcare professionals appropriately using materials, etc.: Involvement of an invasive injection procedure of multiple brain punctures for administration of Delytact, details of the injection procedure, and its associated risks. The applicant responded that they would take appropriate actions, and PMDA accepted.

1.3 Clinical positioning and indication or performance

As a result of the review in Section "7.R.3 Clinical positioning and indication or performance" of the Review Report (1), PMDA has concluded that the "Clinical Studies" section of the package insert should include details of the patients enrolled in Study GD01, and the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections of Delytact should be established as described in the corresponding sections of the Review Report (1).

The following comments were raised from the expert advisors at the Expert Discussion:

- Of malignant glioma, it would be appropriate to use Delytact for Grade IV glioblastoma.
- Concerning Grade III malignant glioma, Delytact may be considered only for patients with recurrent lesion in whom its benefits are considered to outweigh the risks, taking into account that patients with Grade III malignant glioma survive longer than patients with glioblastoma, the efficacy of Delytact shown in Study GD01 is limited, and treatment with Delytact involves an invasive injection procedure of multiple brain punctures.

In view of the above comments from expert advisors and expert advisors' comments on the administration site in Section "1.4 Dosage and administration or method of use," PMDA has concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections of Delytact should be modified as shown below to establish these sections. For the use of Delytact in patients with Grade III malignant glioma, PMDA requested the applicant to provide information to healthcare professionals appropriately using materials, etc., which require them to weigh the benefits and risks carefully, taking the presence of a recurrent lesion into account.

Indication or Performance

Malignant glioma

Precautions Concerning Indication or Performance

- Delytact should be used in patients who received prior treatment with radiation therapy and temozolomide
- Appropriate patients must be selected by physicians who carefully weigh the benefits and risks with a full understanding of the efficacy and safety of Delytact and information presented in the "Clinical Studies" section including characteristics of patients (presence of glioblastoma, tumor location, etc.) enrolled in the clinical study and the possibility of up to 6 brain punctures.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.4 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections of Delytact should be as specified in the corresponding sections of the Review Report (1).

The above conclusion of PMDA was supported at the Expert Discussion. The following comments on matters to be additionally considered were raised from the expert advisors:

- The procedure has not been established for administration into the brainstem, and adverse events such as haemorrhage, if any, are highly likely to become severe or fatal. Accordingly, administration into the brainstem is considered to pose an extremely high risk.

In view of the above comments from expert advisors, PMDA requested the applicant to establish the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections of Delytact as shown below:

Dosage and Administration or Method of Use

The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. In principle, the first and second doses are separated by 5 to 14 days, and each of the third and subsequent doses is separated from the previous dose by 4 weeks. Up to 6 doses may be administered.

Precautions Concerning Dosage and Administration or Method of Use

- As the other concomitant antineoplastic agent, if any, temozolomide should be used.
- Each dosage is intended to target the whole tumor lesion in the brain. To ≥2 sites where necessary, the dosage should be administered in divided doses.
- No results from a clinical study where Delytact was administered by means other than a stereotaxic technique are available.
- No results from a clinical study where Delytact was administered into the infratentorial lesion are available, and the use of Delytact should be carefully determined after due consideration of the risk of complications, etc. associated with the injection procedure. Administration into the brainstem lesion should be avoided because it poses an extremely high risk.
- Delytact should be thawed under protection from light and, after being thawed, administered immediately. If it has to be stored after being thawed out of necessity, it should be stored at 2°C to 8°C under protection from light and used within 24 hours. The residual fluid should be appropriately discarded.

1.5 Post-marketing approval condition assessment plan (draft)

The applicant submitted draft plans of a use-results comparison survey to compare information between all patients receiving Delytact and patients not receiving Delytact in order to further evaluate the efficacy and safety of Delytact after the market launch, and a post-marketing clinical study in patients with a lesion involving the lower brainstem.

As a result from the review in Section “8 Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA,” PMDA has concluded that the post-marketing safety specifications should additionally include “myelosuppression,” “brain oedema,” and “intracranial tumour haemorrhage.”

The above conclusion of PMDA was supported at the Expert Discussion. The following comments on matters to be additionally considered were raised from the expert advisors:

- For comparison of OS between groups, the number of events required to ensure power of predesigned hypothesis test should be specified for each group in the protocol.

In view of the above comments and the following corrections presented by the applicant, PMDA has concluded that the applicant should appropriately conduct a post-marketing approval condition assessment through the use-results comparison survey in Table 46 and the post-marketing clinical study in Table 47.

Major corrections

- The necessary number of events is specified for each group.
- In the safety specifications, "pyrexia," "brain oedema," "haemorrhage," and "infection" are added, and "symptoms associated with immunisation reaction," "hypersensitivity such as anaphylaxis," "reduced effectiveness of Delytact due to antiherpesvirus drugs," and "procedural adverse events" are deleted. In addition, "neurologic symptoms such as seizure" and "transient lymphocyte count decreased" are changed to "seizure" and "cytopenia," respectively.

Table 46. Outline of use-results comparison survey (draft)

Objective	To evaluate the efficacy and safety of Delytact in patients with malignant glioma. In addition, to compare Delytact with the conventional treatment (control group) by investigating the applicable efficacy data retrospectively.
Survey method	All-case surveillance system
Population	• Delytact group: All the patients who have received Delytact • Control group: All the patients who were diagnosed with malignant glioma during a certain period of time, 2 years back from the date of the first dose of Delytact (i.e., a period of 6 months, starting from 2 years and 6 months before the date of the first dose to 2 years before the date of the first dose) at survey centers to which Delytact was delivered
Survey period	7 years from approval date
Follow-up period	• Delytact group: Period from the date of diagnosis of malignant glioma (date of primary or recurrent[*1] diagnosis) to 2 years after the first dose of Delytact. For patients who survive >2 years after the first dose, follow-up will be continued until the end of the survey period. • Control group: 2 years from the date of diagnosis of malignant glioma (date of primary or recurrent[*1] diagnosis). For patients who survive >2 years after the date of diagnosis of malignant melanoma, follow-up will be continued until the end of the survey period as a prospective survey.
Major efficacy endpoint and method of evaluation	OS (from the date of diagnosis[*1] of malignant glioma to death [from any cause]): For each population of patients with primary glioblastoma[*2] and patients with recurrent glioblastoma,[*3] conduct a trend score matching[*4] so that the Delytact and control groups include the same number of patients (1:1), and perform a log-rank test with the two-sided significance level of 5% on OS in the sample population. For patients with Grade III malignant glioma (anaplastic oligodendroglioma and anaplastic astrocytoma),[*5] conduct a trend score matching as done for patients with glioblastoma, and check whether the point estimate of the hazard ratio of OS in the sample population calculated using the Cox proportional hazards model is <1.
Safety specifications	Pyrexia, brain oedema, cytopenia, seizure, haemorrhage, infection, normal pressure hydrocephalus, and autoimmune diseases involving the central nervous system
Target sample size	Target sample size of patients with glioblastoma • Delytact group: A total of 250 patients with glioblastoma including 150 patients with primary lesion and 100 patients with recurrent lesion • Control group: A total of 500 patients with glioblastoma including 300 patients with primary lesion and 200 patients with recurrent lesion Rationale for establishment: The 2-year survival rates in patients with primary glioblastoma and in patients with recurrent glioblastoma receiving conventional treatment are presumed to be [redacted]%[*6] and [redacted]%,[*7] respectively. On the assumption that the 2-year survival rate in patients receiving Delytact is [redacted]% higher than that in patients receiving conventional treatment, the sample size was estimated for a log-rank test to compare survival between the Delytact and control groups at the sample size ratio of [redacted]:[redacted] during the follow-up period of 2 years with the two-sided significance level of [redacted]% and power of [redacted]%. Taking account of the necessary number of events, 82 patients and 104 patients should be assigned to the Delytact and control groups, respectively, for patients with primary glioblastoma, and 68 patients and 83 patients should be assigned to the Delytact and control groups, respectively, for patients with recurrent glioblastoma. Target sample size of patients with Grade III malignant glioma • Delytact group: 30 to 50 patients with anaplastic oligodendroglioma and 30 to 50 patients with anaplastic astrocytoma • Control group: 60 to 100 patients with anaplastic oligodendroglioma and 60 to 100 patients with anaplastic astrocytoma Rationale for establishment: The 2-year survival rates in patients with anaplastic oligodendroglioma and in patients with anaplastic astrocytoma receiving conventional treatment are presumed to be [redacted]%[*8] and [redacted]%,[*9] respectively. On the assumption that the 2-year survival rate in patients receiving Delytact is [redacted]% higher than that in patients receiving conventional treatment, the number of events necessary to achieve

	the probability of the point estimate of the hazard ratio being <1 is >[redacted]% was determined using simulations. Of patients with anaplastic oligodendroglioma, 1 patient and 6 patients should be assigned to the Delytact and control groups, respectively, and of patients with anaplastic astrocytoma, 6 patients and 10 patients should be assigned to these groups.

*1 The "date of diagnosis of malignant glioma" for patients with recurrent lesion is the date on which the diagnosis of recurrence is given by the survey investigator based on a documented increase in tumor size (both ≥20% and ≥5 mm [absolute value] increase in sum of tumor diameters) after chemoradiotherapy in comparison with the size at the start of initial chemoradiotherapy, appearance of a new tumor in diagnostic imaging such as MRI without any tumor increase in comparison with the image at the start of initial chemoradiotherapy, or malignant transformation (from Grade III malignant glioma to glioblastoma).
*2 The control group should include patients who have not responded to the initial chemoradiotherapy in terms of tumor size.
The Delytact group should include patients who have not responded to the initial chemoradiotherapy in terms of tumor size and then received Delytact.
*3 The control group should include patients who have been given a diagnosis of recurrence (except for malignant transformation) for the first time at ≥3 months after the initial chemoradiotherapy. Recurrence is defined as a case where the tumor size has been increased in comparison with the size at the start of initial chemoradiotherapy (both ≥20% and ≥5 mm [absolute value] increase in sum of tumor diameters) or a new tumor has appeared in diagnostic imaging such as MRI without any tumor increase in comparison with the image at the start of initial chemoradiotherapy.
The Delytact group should include patients who have been given a diagnosis of recurrence (except for malignant transformation) for the first time at ≥3 months after the initial chemoradiotherapy and then received Delytact. Recurrence is defined as done in the control group.
*4 Factors used for trend score matching estimation are 10 factors affecting prognosis of malignant glioma (tissue type [Grade], age, KPS, extent of resection, mental status, duration of neurologic symptom, overall radiation dose, neural function [capable of working or not], methylation of MGMT promoter, and *IDH1/2* gene mutation [yes or no])
*5 The Delytact group should include patients who have received Delytact at ≥3 months after the initial chemoradiotherapy.
*6 *N Engl J Med.* 2014;370:709-22
*7 *Neuro Oncol.* 2015;17:1504‐13
*8 *J Neurooncol.* 2015;122:111-9
*9 *Neuro Oncol.* 2017;19:252-8

Table 47. Outline of post-marketing clinical study (draft)

Objective	To evaluate the efficacy and safety of Delytact in patients with malignant glioma involving the lower brainstem (mainly cerebellum)
Survey method	Post-marketing clinical study
Population	Delytact group: Patients with malignant glioma involving the lower brainstem (mainly cerebellum) Control group: Of patients included in the control group in the use-results comparison survey, patients with malignant glioma involving the lower brainstem
Study period	7 years from approval date
Follow-up period	During the study period or until death
Major efficacy endpoint and method of evaluation	OS (from the date of diagnosis of malignant glioma [date of primary or recurrent diagnosis] to death [from any cause]): Check whether the point estimate of the hazard ratio calculated using the Cox proportional hazards model is <1.
Safety specifications	Pyrexia, brain oedema, cytopenia, seizure, haemorrhage, infection, normal pressure hydrocephalus, and autoimmune diseases involving the central nervous system
Target sample size	Delytact group: 14 patients Rationale for establishment: The 1-year survival rate in the control group for Grade III malignant glioma and glioblastoma (patients who serve an external comparative control group in the use-results comparison survey and have a lesion involving the lower brainstem are to be included [target sample size, 21 patients]) is presumed to be [redacted]%[*1] and [redacted]%.[*2] On the assumption that the 1-year survival rate in the Delytact group is [redacted]% higher than that in the conventional treatment group, the number of events necessary to achieve the probability of the point estimate of the hazard ratio being <1 is >[redacted]% was determined using simulations. Of patients with Grade III malignant glioma, 2 patients and 3 patients should be assigned to the Delytact and control groups, respectively, and of patients with glioblastoma, 3 patients and 5 patients should be assigned to these groups.

*1 *J Neurol Sci.* 2015;353:92–7 and *BMC Cancer.* 2014;14:115
*2 *J Neurooncol.* 2019;145:479-86

1.6 Others

1.6.1 Designation as designated regenerative medical product

On the basis of "Concept for designation of biological products and specified biological products as well as designated regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated

November 5, 2014), PMDA has concluded that Delytact need not be designated as a designated regenerative medical product for the following reasons:

- All animal-derived materials used in manufacture of Delytact conform to the Standards for Biological Ingredients, and thus their risk of causing infections is deemed negligible.
- Vero cells used for manufacture of the drug substance are considered unlikely to retain pathogenic viruses as documented by extensive virus testing in cell substrates (MCB, WCB, and CAL), virus seed stocks (MVSS and WVSS), and unprocessed harvest after the end of production culture.
- The types of living organisms susceptible to Delytact are considered to be the same as those susceptible to wild-type HSV-1. HSV-1 can infect humans, which are its natural hosts, but has not been reported to infect or spread through other mammals, plants, or microorganisms in the natural world.
- Delytact is designed to replicate selectively in tumor cells and to be replication incompetent in normal cells except for some cultured normal cells in a laboratory. Delytact is therefore considered unlikely to be directly transmitted to the third party horizontally. In addition, Delytact is susceptible to acyclovir as with wild-type HSV-1.
- Delytact is a genetically modified HSV-1 of which the genome has 4 distant mutations (in 3 genes), and thus a risk of spontaneous [redacted] from Delytact by genetic recombination is deemed negligible. Furthermore, test for [redacted] is specified as a [redacted], each lot of Delytact will not be released until absence of [redacted] is confirmed.

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

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

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

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

The application data (CTD 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of its review, PMDA has concluded that the product may be approved after modifying the indication or performance and dosage and administration or method of use as shown below, with the following conditions, and the conditional time-limit under Article 23-26 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, provided that a cautionary statement is given in the package insert, and information on proper use is disseminated after

the market launch. The time limit under the concerned article should be 7 years, and the product need not be designated as a designated regenerative medical product.

Indication or Performance

Malignant glioma

Dosage and Administration or Method of Use

The usual adult dosage is 1 mL (1×10^9 PFU) of Delytact administered intratumorally. In principle, the first and second doses are separated by 5 to 14 days, and each of the third and subsequent doses is separated from the previous dose by 4 weeks. Up to 6 doses may be administered.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with adequate knowledge and experience in treatment of malignant glioma and neurosurgical procedures who has been fully informed of results and adverse events in clinical studies of the product in an environment where appropriate measures such as monitoring and management with laboratory tests are available at a medical institution capable of responding to emergencies.
2. The applicant is required to conduct a post-marketing approval condition assessment in all the patients treated with the product until filing the marketing application after conditional time-limited approval.
3. The applicant is required, in order to ensure that the product is used in compliance with provisions for Type 1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” to take necessary measures such as announcement of the provisions for use.

Appendix

List of Abbreviations

Application	Marketing application
[redacted]	[redacted]
Bevacizumab	Bevacizumab (genetical recombination)
[redacted]	[redacted]
CAL	Cell at the limit of in vitro cell age
Cartagena Act	Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms
CR	Complete response
Delytact	Delytact Injection
DNA	Deoxyribonucleic acid
DPBS	Dulbecco's phosphate buffered saline
[redacted]	[redacted]
EDC	Electronic data capture
EP	European Pharmacopoeia
[redacted]	[redacted]
FAS	Full analysis set
FLAIR	Fluid-attenuated inversion-recovery
G207	Genetically engineered HSV-1 with deficient *γ34.5* gene and inactivated *ICP6* gene
G47Δ	Genetically engineered HSV-1 with deficient *γ34.5* gene and *α47* gene and inactivated *ICP6* gene
[redacted]	[redacted]
HSV	Herpes simplex virus
[redacted]	[redacted]
IDH	Isocitrate dehydrogenase
IFN-β	Interferon beta
IFN-γ	Interferon gamma
ICP6	Infected cell protein 6
Japanese clinical practice guideline	Practical Guidelines for Neuro-Oncology 2019 (edited by the Japan Society for Neuro-Oncology)

JP	Japanese Pharmacopoeia
KPS	Karnofsky performance status
MCB	Master cell bank
[redacted]	[redacted]
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MGMT	O6-Methylguanine-DNA Methyltransferase
MHC	Major histocompatibility complex
MOI	Multiplicity of infection
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MVSS	Master virus seed stock
Nimustine	Nimustine hydrochloride
OS	Overall survival
[redacted]	[redacted]
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
[redacted]	[redacted]
PD	Progressive disease
PFS	Progression-free survival
PFU	Plaque forming unit
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
[redacted]	[redacted]
PT	Preferred term
RT	Radiotherapy
[redacted]	[redacted]
[redacted]	[redacted]
RNA	Ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SD	Stable disease
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SMQ	Standardised MedDRA queries
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
[redacted]	[redacted]
TMZ	Temozolomide
[redacted]	[redacted]
[redacted]	[redacted]
USP	United States Pharmacopeia
Vero cells	African green monkey kidney epithelial cells
WCB	Working cell bank
WHO	World Health Organization
WVSS	Working virus seed stock
[redacted]	[redacted]