Report on the Deliberation Results

September 8, 2009

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Rasuritek 1.5 mg for I.V. Infusion Rasuritek 7.5 mg for I.V. Infusion
[Non-proprietary name]	Rasburicase (Genetical Recombination) (JAN*)
[Applicant]	Sanofi-aventis K.K.
[Date of application]	February 26, 2008

[Results of deliberation]
In the meeting held on August 31, 2009, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

Review Report

August 19, 2009

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Rasuritek 1.5 mg for I.V. Infusion Rasuritek 7.5 mg for I.V. Infusion
[Non-proprietary name]	Rasburicase (Genetical Recombination)
[Applicant]	Sanofi-aventis K.K.
[Date of application]	February 26, 2008

[Dosage form/Strength]
Injection: Each vial contains 1.5 or 7.5 mg of Rasburicase (Genetical Recombination)

[Application classification] Prescription drug (1) Drug with a new active ingredient

[Amino acid sequence]

									10										20
CH_3CO-	Ser	Ala	Val	Lys	Ala	Ala	Arg	Tyr	Gly	Lys	Asp	Asn	Val	Arg	Val	Tyr	Lys	Val	His	Lys
									30										40
Asp	Glu	Lys	Thr	Gly	Val	Gln	Thr	Val	Tyr	Glu	Met	Thr	Val	Cys	Val	Leu	Leu	Glu	Gly
									50										60
Glu	Ile	Glu	Thr	Ser	Tyr	Thr	Lys	Ala	Asp	Asn	Ser	Val	Ile	Val	Ala	Thr	Asp	Ser	Ile
									70										80
Lys	Asn	Thr	Ile	Tyr	Ile	Thr	Ala	Lys	Gln	Asn	Pro	Val	Thr	Pro	Pro	Glu	Leu	Phe	Gly
									90										100
Ser	Ile	Leu	Gly	Thr	His	Phe	Ile	Glu	Lys	Tyr	Asn	His	Ile	His	Ala	Ala	His	Val	Asn
									110										120
Ile	Val	Cys	His	Arg	Trp	Thr	Arg	Met	Asp	Ile	Asp	Gly	Lys	Pro	His	Pro	His	Ser	Phe
									130										140
Ile	Arg	Asp	Ser	Glu	Glu	Lys	Arg	Asn	Val	Gln	Val	Asp	Val	Val	Glu	Gly	Lys	Gly	Ile
									150										160
Asp	Ile	Lys	Ser	Ser	Leu	Ser	Gly	Leu	Thr	Val	Leu	Lys	Ser	Thr	Asn	Ser	Gln	Phe	Trp
									170										180
Gly	Phe	Leu	Arg	Asp	Glu	Tyr	Thr	Thr	Leu	Lys	Glu	Thr	Trp	Asp	Arg	Ile	Leu	Ser	Thr
									190										200
Asp	Val	Asp	Ala	Thr	Trp	Gln	Trp	Lys	Asn	Phe	Ser	Gly	Leu	Gln	Glu	Val	Arg	Ser	His
									210										220
Val	Pro	Lys	Phe	Asp	Ala	Thr	Trp	Ala	Thr	Ala	Arg	Glu	Val	Thr	Leu	Lys	Thr	Phe	Ala
									230										240
Glu	Asp	Asn	Ser	Ala	Ser	Val	Gln	Ala	Thr	Met	Tyr	Lys	Met	Ala	Glu	Gln	Ile	Leu	Ala
									250										260
Arg	Gln	Gln	Leu	Ile	Glu	Thr	Val	Glu	Tyr	Ser	Leu	Pro	Asn	Lys	His	Tyr	Phe	Glu	Ile
									270										280
Asp	Leu	Ser	Trp	His	Lys	Gly	Leu	Gln	Asn	Thr	Gly	Lys	Asn	Ala	Glu	Val	Phe	Ala	Pro
									290										300
Gln	Ser	Asp	Pro	Asn	Gly	Leu	Ile	Lys	Cys	Thr	Val	Gly	Arg	Ser	Ser	Leu	Lys	Ser	Lys
301																			
Leu																			

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from the use of this English version.

Molecular formula: $C_{6092}H_{9523}N_{1668}O_{1848}S_{28}$
Molecular mass:136,605
Chemical name:
A tetrameric protein composed of four subunits (a molecular mass of 136,605), each consisting of an N-terminal-acetylated 301-amino acid polypeptide ($C_{1523}H_{2383}N_{417}O_{462}S_7$; a molecular mass of 34,151.19), produced by a genetically modified *Saccharomyces cerevisiae* strain that expresses urate oxidase cDNA cloned from a strain of *Aspergillus flavus*

[Items warranting special mention] None

[Reviewing office] Office of New Drug V

Review Results

August 19, 2009

[Brand name]	Rasuritek 1.5 mg for I.V. Infusion Rasuritek 7.5 mg for I.V. Infusion
[Non-proprietary name]	Rasburicase (Genetical Recombination)
[Applicant]	Sanofi-aventis K.K.
[Date of application]	February 26, 2008

Results of review

Based on the submitted data, it has been determined that the efficacy and safety of the product for the indication of "hyperuricemia associated with cancer chemotherapy" was demonstrated.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]
Hyperuricemia associated with cancer chemotherapy

[Dosage and administration]
The usual dosage is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is up to 7 days.

Review Report (1)

July 17, 2009

I. Product Submitted for Registration

[Brand name] Rasuritek 1.5 mg for I.V. Injection
Rasuritek 7.5 mg for I.V. Injection
[Non-proprietary name] Rasburicase (Genetical Recombination)
[Applicant] Sanofi-aventis K.K.
[Date of application] February 26, 2008
[Dosage form/Strength]
Injection: Each vial contains 1.5 or 7.5 mg of Rasburicase (Genetical Recombination)
[Proposed indication]
Treatment and prophylaxis of acute hyperuricemia associated with the treatment of hematological malignancies
[Proposed dosage and administration]
The usual dosage for adults and children is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is 5 days as a rule.
[Items warranting special mention] None

II. Summary of the Submitted Data and the Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted in this application and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.1 Drug overview

Rasburicase (Genetical Recombination) (hereinafter referred to as rasburicase) is a recombinant urate oxidase formed after the gene cloned from *Aspergillus flavus* is inserted and expressed in a modified *Saccharomyces cerevisiae* strain. Rasburicase is a tetrameric protein made up of four subunits of 301 amino acids. Rasburicase converts uric acid to more soluble allantoin, which is readily excreted by the kidneys, and thus improves hyperuricemia.

1.2 Development history etc.

Outside Japan, a phase I study in healthy adults (TDR2681) was initiated in May 1995. Then, phase II studies in patients with malignant lymphoma or leukemia (ACT2694 [children and adults], ACT2511 [children and adults]) were initiated in March 1996 and a phase III, randomized, allopurinol-controlled, comparative study in pediatric patients with malignant lymphoma or leukemia (EFC2975) was started in November 1996.

An application for the approval of rasburicase including the pivotal data from Study EFC2975 was filed overseas and the drug was approved in the EU in February 2001 (under the centralized procedure) and in the US in July 2002. The indication at the time of approval was "treatment and prophylaxis of acute hyperuricemia, in order to prevent acute renal failure, in patients with hematological malignancy with a high tumor burden and at risk of a rapid tumor lysis or shrinkage at initiation of chemotherapy" in the EU and "ELITEK is indicated for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid" in the US.

The recommended dosage and dose regimen was 0.20 mg/kg administered once daily for 5 to 7 days in the EU and 0.15 or 0.20 mg/kg as a single daily dose for 5 days in the US. In the EU, the recommended duration of treatment was changed from “5 to 7 days” to “up to 7 days” in August 2006.

In December 2008, based on the results from a phase III study in adult patients with leukemia, malignant lymphoma, and solid tumor malignancies (EFC4978), a supplemental application for an adult indication was filed in the US and is currently under review. As of June 2009, rasburicase has been approved in 55 countries or regions including Europe and the US.

In Japan, a phase I study in healthy adult subjects (TDU4730) was initiated in [redacted] 20[redacted] after rasburicase was approved in the EU. Following the completion of this study, a phase II study in adult patients with malignant lymphoma or leukemia (ARD5290) was started in [redacted] 20[redacted] and a phase II study in pediatric patients with hematological malignancies (ACT5080) in [redacted] 20[redacted].

The applicant positioned Japanese study ACT5080 as a bridging study and foreign studies ACT2694 and ACT2511 as the studies to be bridged and concluded that bridging was established with these studies. Then, the applicant has filed a new drug application for rasburicase and submitted a clinical data package containing the pivotal data from a foreign phase III study (EFC2975) to be extrapolated into Japan, in support of this application.

With a view to preventing medical accidents, the applicant has decided to modify the proposed brand names from “Rasuritek 1.5 mg for I.V. Injection” and “Rasuritek 7.5 mg for I.V. Injection” to “Rasuritek 1.5 mg for I.V. Infusion” and “Rasuritek 7.5 mg for I.V. Infusion.”

2. Data relating to quality

2.A Summary of the submitted data

Rasburicase is a recombinant tetrameric protein composed of four subunits, each consisting of an N-terminal-acetylated 301-amino acid polypeptide ($C_{1523}H_{2383}N_{417}O_{462}S_7$; 34151.19 Da), produced in yeast (*S. cerevisiae*) transfected with the cDNA coding for urate oxidase from *A. flavus*. It has no intermolecular disulfide bonds.

2.A.1) Manufacturing process for the drug substance

2.A.1).(1) Establishment of cell banking system

A shuttle vector that contains the DNA replication mechanisms of yeast and *Escherichia coli* [redacted] was constructed by inserting [redacted] gene containing the full-length urate oxidase cDNA prepared from *A. flavus* cultured under the urate oxidase expression condition (medium containing uric acid) into [redacted] prepared from a yeast and *E. coli* shuttle vector [redacted].

[redacted] ([redacted]) strain that does not produce endogenous urate oxidase was prepared from ATCC standard strain [redacted] and then transformed into [redacted] prototrophic strain using the expression vector [redacted]. A single colony ([redacted] strain) was selected and a master cell bank (MCB) was prepared from [redacted] strain and a working cell bank (WCB) was prepared from the MCB.

2.A.1).(2) Characterization and control of cell banks

The MCB was characterized when it was established (See the table below). The MCB is stored at [redacted] facilities [redacted]. If contingencies arise, the [redacted] at the time will be characterized as the MCB and qualified and then a new WCB will be prepared from this MCB. The stability of the MCB is confirmed by characterization studies to be performed when a new WCB is prepared.

A new WCB is prepared from the MCB in the same manner as the current WCB and then the new WCB is characterized (the table below) and qualified. The WCB is stored [redacted]. The stability of the WCB during storage has been assessed by viable cell count, microscopy, and restriction enzyme cleavage pattern of plasmid and the frequency of plasmid elimination and the stability for [redacted] years has been confirmed.

Cells cultured beyond the limit of *in vitro* cell age (additional [redacted] passages) for the production of rasburicase (CAL) have also been tested and the stability of the expression system has been demonstrated (See the table below).

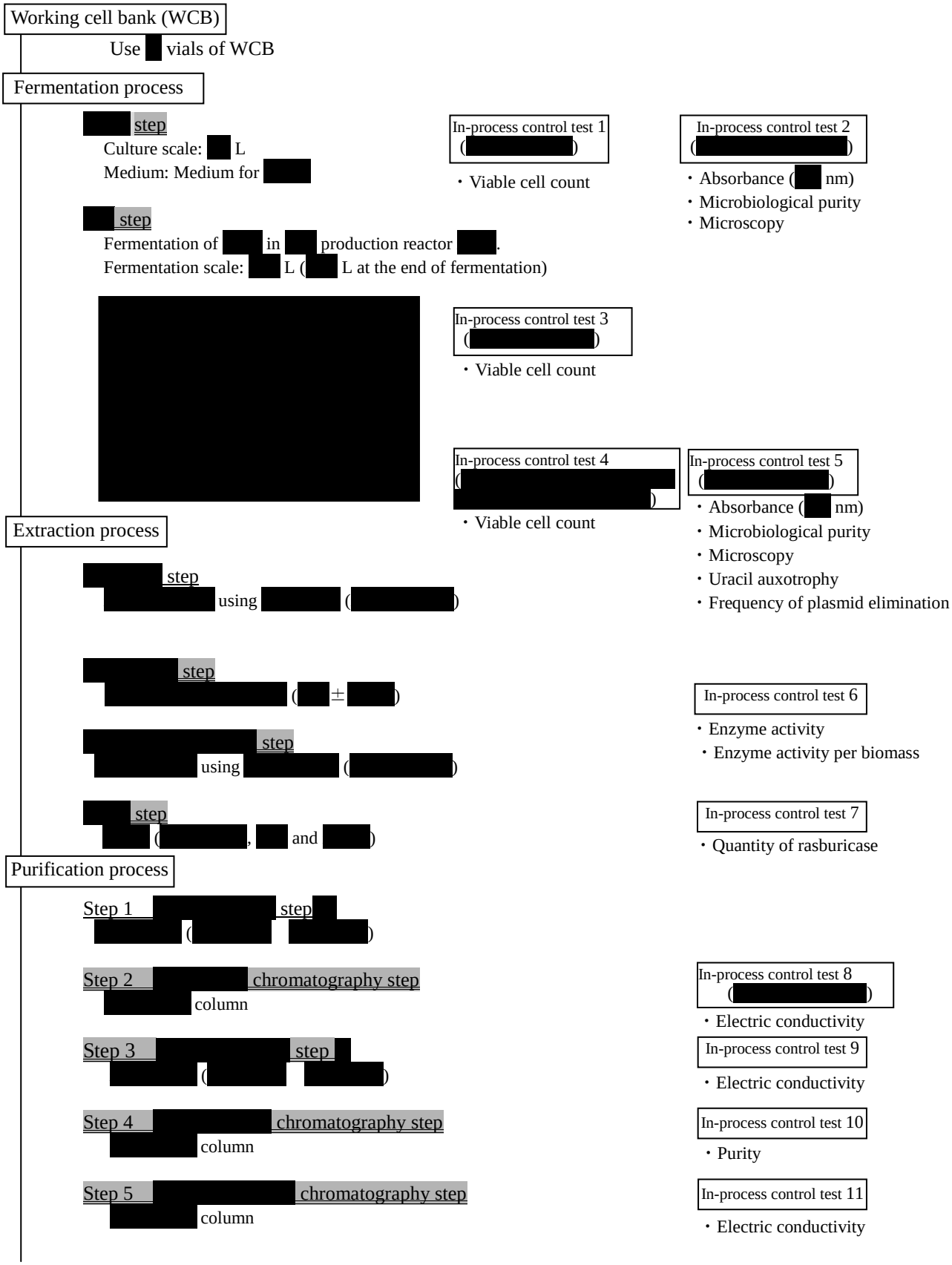
Tests for cell banks and CAL and test results

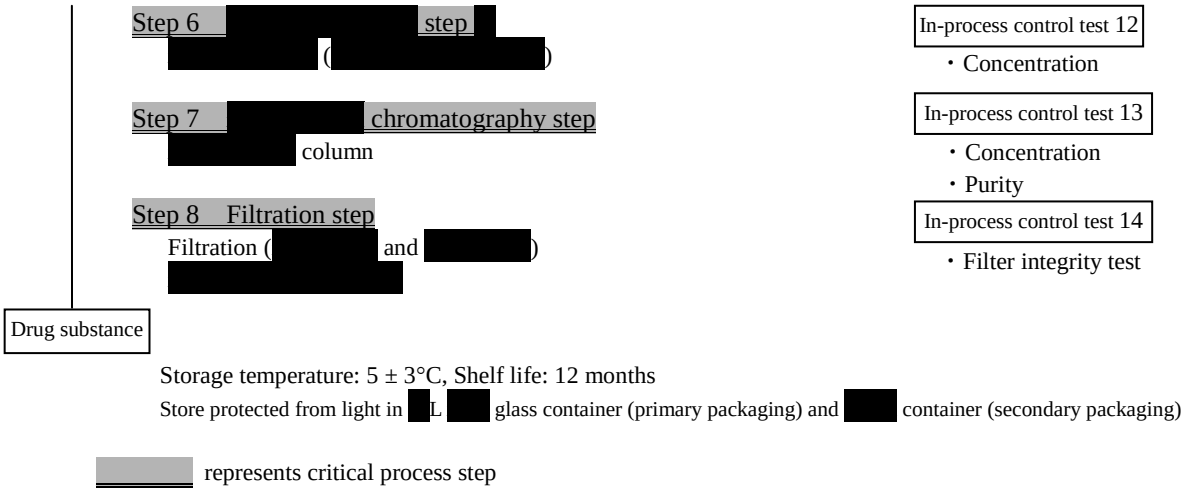
Tests	Acceptance criteria	MCB	WCB	CAL
Appearance	[redacted] tube made of [redacted] tightly stoppered with [redacted] containing approximately [redacted] mL [redacted]	Pass	Pass	Test not required
Microbiological purity	Microbial [redacted] is not detected.	Pass	Pass	Pass
Viable cell count (CFU/mL)	WCB: ≥ 10[redacted] CFU/mL	[redacted]×10[redacted]	[redacted]×10[redacted]	[redacted]×10[redacted]
Microscopy	Yeast population of [redacted]	Pass	Pass	Pass
[redacted] auxotrophy	Cells are [redacted] auxotrophic	Pass	Pass	Pass
Protease-negative colonies (%)	WCB, CAL: ≥ [redacted]%	> [redacted]	> [redacted]	> [redacted]
Mating type	[redacted]	[redacted]	[redacted]	[redacted]
Restriction enzyme cleavage pattern of plasmid	MCB: [redacted] is within the range of ± [redacted]% of [redacted] WCB, CAL: [redacted] is identical to MCB	Pass	Pass	Pass
Plasmid DNA sequence	MCB: Identical to [redacted] *1 CAL: Identical to MCB	Identical	—*2	Identical
Frequency of plasmid elimination (%)	WCB, CAL: ≤ [redacted]%	< [redacted]	< [redacted]	[redacted]
Plasmid copy number	[redacted]	[redacted]	—*2	[redacted]
Rasburicase production	MCB: Urate oxidase activity is detected	Detected	Test not required	Test not required
Average mass of the content	WCB: The average mass of the contents of [redacted] [redacted] tubes is within the range of [redacted] to [redacted] g.	Test not required	[redacted] g	Test not required
Mass variation of the content	WCB: Pass*3	Test not required	Pass	Test not required
Enzyme activity (EAU/mL)*4	[redacted]	Test not required	Test not required	[redacted]
Turbidity of culture fluid	CAL: ≥ [redacted] ([redacted])	Test not required	Test not required	[redacted]
Reverse mutation to [redacted] prototrophy*5	[redacted]	Test not required	Test not required	< [redacted]/[redacted]×10[redacted]

*1: [redacted] of [redacted] at [redacted] sites including amino acid substitutions in [redacted] are taken into consideration.
*2: Test is omitted because the genetic stability has been demonstrated with CAL.
*3: (a) The masses of individual contents are within the range of [redacted]% to [redacted]% of the average mass of the content. Or (b) when only [redacted] samples fail to meet (a) and the masses of the contents of these samples are within the range of [redacted]% to [redacted]% of the average mass, the average mass of the content is calculated with additional [redacted] [redacted] tubes. The masses of individual contents of ≤ [redacted] samples are outside the range of [redacted]% to [redacted]% of the average mass and no individual content of [redacted] tube is outside the range of [redacted]% to [redacted]% of the average mass.
*4: 1 EAU corresponds to the enzyme amount that converts 1 μmol of uric acid into allantoin per minute in [redacted] buffer solution (pH [redacted], [redacted]°C).
*5: Test procedure is similar to test for [redacted] auxotrophy. Using a minimal medium (agar medium) containing no [redacted], the proportion of cells reverted to [redacted] prototrophy per mL of sample is determined.

2.A.1).(3) Manufacturing process

The manufacturing process for the drug substance is as follows.


Working cell bank (WCB)
Use [redacted] vials of WCB
Fermentation process
[redacted] step
Culture scale: [redacted] L
Medium: Medium for [redacted]
In-process control test 1
([redacted])
・Viable cell count
In-process control test 2
([redacted])
・Absorbance ([redacted] nm)
・Microbiological purity
・Microscopy
[redacted] step
Fermentation of [redacted] in [redacted] production reactor [redacted].
Fermentation scale: [redacted] L ([redacted] L at the end of fermentation)
[redacted]
In-process control test 3
([redacted])
・Viable cell count
In-process control test 4
([redacted])
・Viable cell count
In-process control test 5
([redacted])
・Absorbance ([redacted] nm)
・Microbiological purity
・Microscopy
・Uracil auxotrophy
・Frequency of plasmid elimination
Extraction process
[redacted] step
[redacted] using [redacted] ([redacted])
[redacted] step
[redacted] ([redacted] ± [redacted])
In-process control test 6
・Enzyme activity
・Enzyme activity per biomass
[redacted] step
[redacted] using [redacted] ([redacted])
[redacted] step
[redacted] ([redacted], [redacted] and [redacted])
In-process control test 7
・Quantity of rasburicase
Purification process
Step 1 [redacted] step
[redacted] ([redacted])
Step 2 [redacted] chromatography step
[redacted] column
In-process control test 8
([redacted])
・Electric conductivity
Step 3 [redacted] step
[redacted] ([redacted])
In-process control test 9
・Electric conductivity
Step 4 [redacted] chromatography step
[redacted] column
In-process control test 10
・Purity
Step 5 [redacted] chromatography step
[redacted] column
In-process control test 11
・Electric conductivity



Process validation of the commercial-scale manufacturing process for the drug substance was carried out, which confirmed the following points.

For the fermentation process, in-process control tests 1 to 5 were performed and evaluated, which confirmed that all parameters were within the process limits. There were also no marked lot-to-lot differences in the growth curve during fermentation.

For the extraction and purification processes, in-process control tests 6 to 14 were performed and evaluated. As a result, all parameters were within the process limits, demonstrating the robustness of the manufacturing process. A bacterial challenge test (, ×10 CFU) on membrane used in Step 8 (filtration step) was performed at a small scale, which confirmed the performance of the membrane.

In the purification process, the lifespan of membrane filters has been assured by the monitoring of crude extract of , of solution, and of membrane filters, and in-process control tests, and the lifespan of column resins by in-house in-process controls in each process step (rate of , measurement, coefficient).

Yeast-derived proteins (SCP), which are process-related impurities, were shown to be removed primarily by chromatography step (Step), chromatography ( ) step (Step), and chromatography step (Step) and yeast-derived DNA was shown to be removed primarily by chromatography step (Step). Process-related impurity A and Process-related impurity B were demonstrated to be removed in the purification process.

The crude extract obtained from the extraction process and the intermediates in the purification steps (Steps 1-7) were assessed for stability and these were all stable for days at ± °C.

2.A.1).(4) Safety evaluation of adventitious agents

Bactopeptone (bovine-derived gelatin [bones, connective tissue, skin] sourced from France or South America, e.g. Argentina and Brazil; a digestive enzyme derived from porcine pancreas is used for digestion of gelatin) was used in the medium for the preparation of the MCB. These use raw materials from healthy herds and the bovine-derived materials have been confirmed to meet the conditions provided in “Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Ingredients” (Administrative Notice dated

March 27, 2009).

The risk of viral infections from the medium for the preparation of the MCB has been reduced by autoclaving ([redacted]°C, [redacted] minutes) before use. No raw materials of human or animal origin have been used in the preparation of the WCB and subsequent manufacturing processes.

2.A.1).(5) Manufacturing process development (Comparability)
The drug substance in early development was produced at [redacted] plant ([redacted]) and commercial-scale lots of drug substance were used in toxicity studies and clinical studies. For drug substance [redacted], the production site was changed from [redacted] plant to [redacted] plant ([redacted]) and [redacted] of WCB, [redacted] in the fermentation process ([redacted] step), [redacted], [redacted], and [redacted] in the extraction process, [redacted] and [redacted] in the purification process, and [redacted] of [redacted] were [redacted]. Based on comparisons of the cell growth curve, cellular genetic stability ([redacted], [redacted]), physicochemical properties (primary structure, higher-order structure), and the results of in-process control tests, lot analysis, and stability studies, it has been confirmed that the drug substances before and after the production site change are comparable.

2.A.2) Drug substance
2.A.2).(1) Structure/Composition
The drug substance was characterized by the following tests.

i) Physicochemical properties
(i) Molecular mass of the subunit (SDS-polyacrylamide gel electrophoresis [SDS-PAGE], electrospray ionization mass spectrometry [ESI])
- SDS-PAGE (reducing, non-reducing) yielded a band close to the theoretical molecular mass of the subunit and indicated that no intermolecular disulfide bonds are present.
- The molecular mass of the subunit as determined by ESI matched the theoretical mass.

(ii) Amino acid sequence (N-terminal amino acid sequence, C-terminal amino acid sequence, complete amino acid sequence, cysteine residues, post-translational modifications)
- Its failure to undergo Edman degradation and N-terminal mass spectrometry analysis revealed that the monomer is N-terminal acetylated.
- The C-terminal sequence was confirmed by carboxypeptidase P hydrolysis.
- The peptide fragments obtained from trypsin digestion were separated by reverse-phase chromatography (RPC) and identified by amino acid compositional analysis, matrix-assisted laser desorption ionization (MALDI), and amino acid sequence analysis (Edman sequencing). As a result, the primary structure was confirmed.
- The primary structure was confirmed by peptide mapping after cyanogen bromide digestion.
- Ellman's colorimetry and amino acid sequence analysis after trypsin or cyanogen bromide digestion confirmed that the subunit contains three cysteine residues (positions 35, 103, and 290) and that none of the cysteine residues form intramolecular disulfide bonds.

(iii) Molecular structure (X-ray crystallography, electrospray ionization/time-of-flight mass spectrometry [ESI/TOFMS], size exclusion chromatography [SEC])
- X-ray crystallography showed that like the subunits of a natural uricase, the conformation of rasburicase is a tetramer, where two dimers are superimposed face-to-face. It was also confirmed that while intramolecular disulfide bonds are formed in a natural uricase, rasburicase has no intramolecular disulfide bonds.
- The molecular mass of rasburicase as determined by ESI/TOFMS and SEC matched the theoretical mass of a tetramer.

(iv) Other physicochemical properties

- The drug substance had an ultraviolet-visible absorption spectrum with a peak at about [redacted] nm, typical of proteins.
- The isoelectric point (pI) of the major band as measured by isoelectric focusing (IEF) matched the theoretical value (pI, 7.6) and the presence of three minor bands (pI, 7.7, 7.3, 7.2) was confirmed. The specific activities and molecular masses of the major and minor bands (four bands) as measured by zymography and mass spectrometry were similar.

ii) Biological activity (enzyme activity)

- Enzyme activity was determined based on the reduction of uric acid. The mean K_m was [redacted] μmol/L, the mean V_{max} was [redacted] μmol/L/min, and the mean specific activity was [redacted] EAU/mg.

2.A.2).(2) Product-related substances

- [redacted] IEC-fractionated peaks were classified into Product-related substance 1 ([redacted] peak having a relative retention time of [redacted]), Product-related substance 2 (a peak having a relative retention time of about [redacted]), and Product-related substance 3 ([redacted] peak having a relative retention time [redacted] that of Product-related substance [redacted]), according to the relative retention time to the main peak.
- [redacted] IEC-fractionated peaks all had a molecular mass of a tetramer as determined by SEC and their specific activities were [redacted] to [redacted] EAU/mg.
- [redacted] IEC-fractionated peaks were analyzed by IEF. As a result, the pI values of Product-related substances 1, 2, and 3 were [redacted] to [redacted], [redacted] to [redacted], and [redacted] to [redacted], respectively.
- [redacted] IEC-fractionated peaks were found to have a molecular mass corresponding to or close to the main peak by RPC/MS.
- [redacted] IEC-fractionated peaks were analyzed by immunoradiometric assay (IRMA). As a result, the immunological properties of these fractions were comparable.
- SEC revealed a peak with a value close to the theoretical molecular mass of [redacted]mer, which had comparable enzyme activity to the desired product ([redacted] EAU/mg). Thus, this peak ([redacted]mer) was identified as Product-related substance B.

2.A.2).(3) Impurities

i) Process-related impurities

- SCP, yeast-derived DNA, and impurities derived from fermentation/extraction/purification process (Process-related impurity A, Process-related impurity B) were detected.

ii) Product-related impurities

- Based on RPC relative retention times, 5 minor peaks were detected. The contents of Product-related impurities 1, 2, 4, and 5 were ≤ [redacted]% and the content of Product-related impurity 3 was around [redacted]% to [redacted]%, as determined by RPC.
- SDS-PAGE revealed trace [redacted] near 62 kDa.
- SEC detected high molecular weight proteins larger than [redacted]mer.

2.A.2).(4) Drug substance specification

The proposed specifications for the drug substance are description (appearance), identification (peptide map, enzyme activity), pH, purity (appearance of solution, SDS-PAGE [product-related impurities including [redacted]mer], IEC [the main peak, Product-related substances 1-3], SEC [Product-related substance B, high molecular weight proteins], RPC [Product-related impurities 1-5, total product-related impurities], SCP [enzyme-linked immunosorbent assay]), bioburden, bacterial endotoxins, specific activity, and assay (SEC).

2.A.2).(5) Stability of the drug substance

Using 3 lots of drug substance produced at the commercial scale, long-term testing (5 ± 3°C, 12

months, a glass container, a silicon seal, a plastic cap) and accelerated testing (25 ± 2°C/60 ± 5%RH, 6 months, a glass container, a silicon seal, a plastic cap) were performed. Using [redacted] lots of drug substance placed in glass wide-mouthed bottles, photostability stress testing (200 W·h/m^2, 1.2 million lx·h) was conducted. The test attributes were description (appearance), identification (peptide map, enzyme activity, IEC, SEC), pH, purity (appearance of solution, SDS-PAGE, IEC, SEC, RPC), bioburden, bacterial endotoxins, enzyme activity, specific activity, assay (SEC), and leak test (description, identification, bioburden, bacterial endotoxins, and leak test were not included in the attributes for photostability testing).

At the long-term storage condition, up to [redacted]% decrease in the main peak and up to [redacted]%, [redacted]%, [redacted]%, and [redacted]% increases in Product-related substances 1, 2, and 3 and Product-related impurity 3, respectively, were observed. There were no marked changes in other attributes tested. At the accelerated storage condition of 25 ± 2°C for 6 months, the main peak was substantially decreased after [redacted] months of storage and Product-related substances 2 and 3 and Product-related impurity 3 were increased after [redacted] months of storage. In the photostability study, there were a substantial decrease in the main peak and increases in Product-related substances 2, 3, and B and Product-related impurities 1 and 3.

Based on the above, a shelf life of “12 months” has been proposed for the drug substance when stored “at 5 ± 3°C, protected from light,” in a glass container with a silicon seal and a plastic cap.

2.A.3) Drug product
2.A.3).(1) Formulation development
The drug product (1.5 mg drug product, 7.5 mg drug product) is presented as a freeze-dried powder in glass vials.

Each vial of the 1.5 mg drug product contains 1.5 mg rasburicase (as an active ingredient), 15.9 mg L-alanine and 10.6 mg D-mannitol (as stabilizers), and 12.6 to 14.3 mg dibasic sodium phosphate hydrate (as a buffer). The diluent for reconstitution (1 mL) is provided in a glass ampule and each ampule contains 1.0 mg polyoxyethylene (160) polyoxypropylene (30) glycol (as a solubilizer) and an appropriate quantity of water for injection.

The 7.5 mg drug product is different from the 1.5 mg drug product only in fill weights. Each vial of the 7.5 mg drug product contains 7.5 mg rasburicase, 79.5 mg L-alanine and 53.0 mg D-mannitol (as stabilizers), and 63.0 to 71.5 mg dibasic sodium phosphate hydrate (as a buffer). Each ampule of the diluent for reconstitution (5 mL) contains 5.0 mg polyoxyethylene (160) polyoxypropylene (30) glycol (as a solubilizer) and an appropriate quantity of water for injection.

Overages of 10% and 25% are used in each vial of the 1.5 mg drug product and each ampule of the diluent (1 mL), respectively. Overages of 3% and 8% are used in each vial of the 7.5 mg drug product and each ampule of the diluent (5 mL), respectively.

2.A.3).(2) Drug product formulation process
The manufacturing process for the drug product is as follows.

Drug solution preparation process:
After [redacted] is added with [redacted] and agitated/dissolved ([redacted]), [redacted] is transferred to [redacted]. After [redacted] of [redacted] are added and agitated with [redacted] and [redacted] ([redacted]), [redacted] is added and agitated. After [redacted] transferred to [redacted] is added and agitated, [redacted] ± [redacted]°C and [redacted].

Pre-filtration process: [redacted] is [redacted] filtrated with [redacted] μm membrane filter.
Sterile filtration process: The solution is filtrated with [redacted] μm membrane filter.
Vial filling process: Sterile-filtrated [redacted] is filled into glass vials and the vials are partially stoppered with chlorobutyl rubber stoppers.
Freeze-drying process: Partially stoppered vials are freeze-dried and fully stoppered.
Capping process: Fully stoppered vials are sealed with aluminium caps.
Labeling and packaging process: Vials are labeled and packaged with the diluent for reconstitution.

In the manufacturing process for the drug product, the sterile filtration process, vial filling process, and freeze-drying process have been defined as critical process steps and the in-process controls include [redacted] in [redacted], [redacted] of [redacted], and bioburden for the drug solution preparation process, filter integrity test (before and after filtration), [redacted], and bioburden for the pre-filtration process, filter integrity test (before and after filtration) for the sterile filtration process, [redacted] for the vial filling process, [redacted] ([redacted], [redacted], [redacted], [redacted]) for the freeze-drying process, and [redacted] and visual inspection ([redacted]) for the capping process.

The manufacturing process for the reconstitution diluent is as follows:

Solution preparation process:
Polyoxyethylene (160) polyoxypropylene (30) glycol is added to water for injection and dissolved to prepare [redacted].
Sterile filtration process: [redacted] is filtrated with [redacted] μm membrane filter.
Ampule filling process: The solution is filled into glass ampules and [redacted] with [redacted].
Sterilization process: Ampules after [redacted] are sterilized by autoclaving.
Labeling and packaging process: Ampules are labeled and packaged with the drug product.

In the manufacturing process for the reconstitution diluent, the ampule filling process and sterilization process have been defined as critical process steps and the in-process controls include agitation [redacted] for the solution preparation process, filter integrity test (before and after filtration) for the sterile filtration process, filling [redacted] for the ampule filling process, autoclave parameters ([redacted], [redacted]) for the sterilization process, and leak test and visual inspection ([redacted]) after the end of the sterilization process.

2.A.3).(3) Drug product specification
The proposed specifications for the drug product include description (appearance), identification (enzyme activity), pH, purity (appearance of solution, SDS-PAGE [product-related impurities including a dimer], IEC [the main peak, Product-related substances 1-3], SEC [Product-related substance B, high molecular weight proteins], RPC [Product-related impurities 1-5, total product-related impurities]), water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, dissolution time (macroscopic observation), enzyme activity, and assay (SEC).

The proposed specifications for the reconstitution diluent include description (appearance), identification (qualitative test for the solubilizer), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, and sterility.

2.A.3).(4) Stability of the drug product
Using 3 lots each of the 1.5 mg and 7.5 mg drug products produced at the commercial scale, long-term testing (5 ± 3°C, 36 months, a glass vial, a rubber stopper) and accelerated testing (25 ± 2°C/60 ± 5%RH, 6 months, a glass vial, a rubber stopper) were performed. Using 1 lot of the 1.5 mg drug product, photostability stress testing (200 $W \cdot h/m^2$, 1.2 million lx·h, a glass vial, a

rubber stopper) was performed. The attributes tested for the drug product were description (appearance), identification (enzyme activity, IEC, SEC), pH, purity (appearance of solution, SDS-PAGE, IEC, SEC, RPC), water content, bacterial endotoxins, foreign insoluble matter, insoluble particulate matter, sterility, dissolution time, enzyme activity, assay (SEC), and leak test (description, identification, water content, bacterial endotoxins, insoluble particulate matter, sterility, dissolution time, and leak test were not included in the attributes for photostability testing).

At the long-term storage condition, there were up to [redacted]% decrease in the main peak and up to [redacted]%, [redacted]%, and [redacted]% increases in Product-related substances 2 and 3 and Product-related impurity 3, respectively, for the 1.5 mg drug product and up to [redacted]% decrease in the main peak and up to [redacted]% and [redacted]% increases in Product-related substances 2 and 3, respectively, for the 7.5 mg drug product. No marked changes were observed for other attributes tested. At the accelerated storage condition of 25 ± 2°C for 6 months, a decrease in the main peak and increases in Product-related substances 2, 3, and B and Product-related impurity 3 were observed for both the 1.5 mg and 7.5 mg drug products. In the photostability study, a substantial increase in Product-related substance B was noted.

Using 3 lots each of the diluents for the reconstitution of the 1.5 mg and 7.5 mg drug products, long-term testing (25 ± 2°C/60%RH, 48 months, a glass ampule) and accelerated testing (40 ± 2°C/75%RH, 6 months, a glass ampule) were performed. The attributes tested for the diluent were description, appearance of solution, identification (qualitative test for the solubilizer), bacterial endotoxins, foreign insoluble matter, insoluble particulate matter, sterility, and leak test (bacterial endotoxins, insoluble particulate matter, and sterility were not included in the attributes for accelerated testing). There were no changes in the attributes tested for the diluents during storage.

Based on the above, a shelf life of “36 months” for the drug product when stored at “5 ± 3°C, protected from light” in glass vials with rubber stoppers and a shelf life of “48 months” for the diluent when stored at “room temperature” have been proposed.

2.A.4) Reference materials

The primary reference material is a material produced similarly to [redacted] and further purified by [redacted], [redacted], [redacted], [redacted], and [redacted], which is stored at ≤ [redacted]°C and retested every [redacted] years. The working reference material is a material produced similarly to [redacted] and diluted with [redacted] to adjust the rasburicase concentration to [redacted] to [redacted] mg/mL, which is stored at ≤ [redacted]°C and retested every [redacted] years.

The reference material for SEC is prepared from a sample of drug substance stored at [redacted]°C where the content of Product-related substance B has been increased to [redacted]% to [redacted]% ([redacted] times the upper specification limit for the drug substance). The reference material for IEC is prepared from a sample of drug substance degraded when stored at [redacted]°C. These reference materials are both stored at ≤ [redacted]°C. The retest period is [redacted] years.

The specifications for the primary reference material, working reference material, reference material for SEC, and reference material for IEC are presented in the following table.

Specifications for the primary reference material, working reference material, reference material for SEC, and reference material for IEC

	Primary reference material	Working reference material	Reference material for SEC	Reference material for IEC
Specifications	Description	Description	Description	Description
	Identification ・Enzyme activity	Identification ・Enzyme activity ・Peptide map ・IEC ・SEC	Identification ・SEC	Identification ・IEC ・SEC
	—*	pH	—*	—*
	Purity ・SDS-PAGE Product-related impurities (including [redacted]mer) ・IEC Main peak Product-related substances 1-3 ・SEC Product-related substance B High molecular weight proteins ・RPC Product-related impurities 1-5 Total product-related impurities	Purity ・Appearance of solution ・SDS-PAGE Product-related impurities (including [redacted]mer) ・IEC Main peak Product-related substances 1-3 ・SEC Product-related substance B High molecular weight proteins ・RPC Product-related impurities 1-5 Total product-related impurities	Purity ・SEC Product-related substance B High molecular weight proteins	Purity ・IEC Main peak Product-related substances 1-3
	Assay ・Protein content ・Enzyme activity ・Specific activity	Assay ・Rasburicase content	Assay ・Rasburicase content	Assay ・Rasburicase content
	—*	Enzyme activity	—*	—*
	—*	Specific activity	—*	—*

*: Not included in the specifications.

2.B Outline of the review by PMDA

As a result of the following reviews, PMDA concluded that the quality of the drug product to be marketed is adequately controlled.

2.B.1) [redacted]mer (Product-related substance B)

PMDA asked the applicant to explain the safety of [redacted]mer, including its antigenicity, and the reason for classifying it as a product-related substance.

The applicant responded as follows:
Since [redacted]mer has enzyme activity comparable to the desired product, it has been classified as a product-related substance. Although the antigenicity of [redacted]mer alone has not been studied, as [redacted]mer is composed of tetramers, i.e. the desired product, and a tetramer was positive in the passive cutaneous and active systemic anaphylaxis tests in guinea pigs, the possibility that [redacted]mer shows antigenicity can not be ruled out. However, since the NOAEL dose (10 mg/kg/day) determined from a rat repeat-dose toxicity study of a tetramer contains about [redacted] times higher level of [redacted]mer than does the proposed clinical dose (0.2 mg/kg/day), [redacted]mer has been qualified.

While [redacted]mer is considered a product-related substance due to its enzyme activity comparable to the desired product, the content of [redacted]mer is controlled by specification. Thus, PMDA accepted the response.

2.B.2) Drug substance specifications

2.B.2).(1) Specification for SCP

The SCP content of most drug substance lots is around [redacted] ppm.

PMDA asked the applicant to explain the necessity of lowering the proposed specification limit for SCP content ([redacted] ppm), taking account of the SCP contents, the results of safety assessment, e.g. adverse events, and the manufacturing history of the drug substance lots used in clinical studies.

The applicant responded as follows:
The SCP content of the drug substance used in the drug product for clinical studies was [redacted] to [redacted] ppm. In clinical studies in patients (ACT5080, ARD5290, ACT2511, ACT2694, EFC2975, PKM6638), the incidence and severity of allergic reactions (hypersensitivity), which are adverse events associated with rasburicase requiring attention for safety reasons, were not related to the SCP content. In Study ACT5080, a subject with anti-SCP antibodies detected at baseline (1 of 30 subjects) received rasburicase, but experienced no hypersensitivity-related events during the study period.

In [redacted] lots of drug substance produced between 19[redacted] and 20[redacted] at [redacted] plant, the SCP content ranged from [redacted] to [redacted] ppm and the mean + 3σ value was [redacted] ppm. Therefore, a specification limit of ≤ [redacted] ppm is justified and there is no need to lower the proposed specification limit for SCP content.

The incidence and severity of allergic reactions (hypersensitivity) were not related to the SCP content in the clinical studies using the drug product manufactured from the drug substance containing [redacted] to [redacted] ppm of SCP, although the drug substance containing SCP at its upper specification limit ([redacted] ppm) has not been used in clinical studies. Taking account of this finding and the manufacturing history, PMDA accepted the response. During the period covered by Periodic Safety Update Report (PSUR) (from February 23, 2001 to August 31, 2007), the estimated number of patients exposed to rasburicase was 26,041 children and 24,779 adults and 22 anaphylaxis-related adverse events were reported, but a warning about the development of severe hypersensitivity including anaphylactic shock has been included in the warnings section of the proposed package insert. Thus, PMDA concluded that an appropriate measure has been taken.

2.B.2).(2) [redacted]mer
In purity test, the bands other than the major band or bands at oligomer positions (at multiples of the molecular weight of the major band) on SDS-PAGE are considered as product-related impurities.

PMDA asked the applicant to explain the reason for not considering the bands at oligomer positions as product-related impurities.

The applicant responded as follows:
Although the band at [redacted]mer position detected on SDS-PAGE was not classified as a product-related impurity, as its enzyme activity has not been confirmed, it has been decided to consider it as a product-related impurity. The results of SDS-PAGE from the long-term and accelerated stability studies of the drug substance were also reviewed. As a result, [redacted]mer was detected at the long-term storage condition and a slight increase was observed at the accelerated storage condition. Therefore, it has been decided to include [redacted]mer detected by SDS-PAGE in the specification and control it. Therefore, a limit test for [redacted]mer ([redacted]mer content, ≤ [redacted]%) will be included as part of purity tests in the specifications for drug substance and drug product.

PMDA accepted the response.

2.B.3) Specification setting for drug substance and drug product and shelf life
Despite that there were substantial changes in the levels determined by IEC (the main peak,

Product-related substances 2 and 3) and the levels determined by RPC (Product-related impurity 3, total product-related impurities) in the long-term stability studies of drug substance and drug product, the acceptance criteria that would qualify such changes have been established. PMDA asked the applicant to provide the rationale for determining that all changes are within acceptable ranges and then explain the reasons for proposing the above acceptance criteria and the shelf lives of 12 months and 36 months for drug substance and drug product, respectively, taking account of the results of clinical studies and the manufacturing history overseas.

The applicant responded as follows:
(a) The acceptance criteria for drug substance and drug product were established using "mean +3σ+ change" ("mean − 3σ + change" for the main peak), taking account of the changes observed in the release testing of 100 lots of drug substance ([redacted] plant) and 20 lots of drug product ([redacted] plant [redacted], 1.5 mg drug product) and the long-term stability studies (drug substance, 12 months; drug product, 36 months).

(b)
・In the drug substance lots used in the drug products for clinical studies (ARD5290, ACT5080, ACT2511, ACT2694, EFC2975, PKM6638), the content of the main peak on IEC was [redacted]% to [redacted]%, the content of Product-related substance 1 was [redacted]% to [redacted]%, the content of Product-related substance 2 was [redacted]% to [redacted]%, the content of Product-related substance 3 was [redacted]% to [redacted]%, the content of Product-related substance B was < [redacted]%, the content of Product-related impurity 2 was < [redacted]% to [redacted]%, the content of Product-related impurity 3 was [redacted]% to [redacted]%, and the content of total product-related impurities was [redacted]% to [redacted]%. In the drug product lots manufactured from these drug substance lots, the content of the main peak was [redacted]% to [redacted]%, the content of Product-related substance 1 was [redacted]% to [redacted]%, the content of Product-related substance 2 was [redacted]% to [redacted]%, the content of Product-related substance 3 was [redacted]% to [redacted]%, the content of Product-related substance B was [redacted]% to [redacted]%, the content of Product-related impurity 2 was < [redacted]% to [redacted]%, the content of Product-related impurity 3 was [redacted]% to [redacted]%, and the content of total product-related impurities was [redacted]% to [redacted]%. There were no differences among these clinical studies for the response rate (the proportion of patients with controlled plasma uric acid levels [responders]) or the percent reduction in uric acid at 4 hours following the first dose of rasburicase and severe hypersensitivity was not reported in any of these studies.
・The drug product used in Study EFC2975 was manufactured from the drug substance stored for 12 months after manufacture, but there were no efficacy or safety problems in this study.
・Although no clinical study using the drug product stored for 36 months (the proposed shelf life) has been conducted, in Study ACT2511, the drug product stored for up to 30 months was used and there were no efficacy or safety problems.

Based on the above, it has been determined that the maximum changes in the main peak (drug substance, [redacted]% decrease; drug product, [redacted]% decrease), Product-related substance 2 (drug substance, [redacted]% increase; drug product, [redacted]% increase), Product-related substance 3 (drug substance, [redacted]% increase; drug product, [redacted]% increase), Product-related impurity 3 (drug substance, [redacted]% increase; drug product, [redacted]% increase), and total product-related impurities (drug substance, [redacted]% increase; drug product, [redacted]% increase) observed after 12 months of storage of drug substance and 36 months of storage of drug product are within acceptable ranges.

(c) Since the NOAEL dose of 10 mg/kg/day determined from a rat repeat-dose toxicity study contains approximately [redacted] to [redacted] times higher levels of individual product-related substances and product-related impurities than does the proposed clinical dose (the upper specification limits), these product-related substances and impurities have been qualified.

Although the contents of the main peak on IEC, product-related substances, and product-related

impurities changed substantially during the storage of drug substance and drug product, there were no efficacy or safety problems in the clinical studies using the drug product produced from the drug substance stored for 12 months after manufacture or the drug product stored for up to 30 months and individual product-related substances and product-related impurities at their upper specification limits have been qualified by a rat repeat-dose toxicity study. Thus, PMDA concluded that there are no problems with the proposed acceptance criteria. PMDA also accepted the proposed shelf lives of 12 months and 36 months for drug substance and drug product, respectively.

2.B.4) Specifications for 7.5 mg drug product

The acceptance criteria for Product-related substance 3 (IEC) and Product-related substance B and high molecular weight proteins (SEC) (the specifications for purity) are wider for the 7.5 mg drug product compared to the 1.5 mg drug product.

PMDA asked the applicant to provide the justification of the above specifications.

The applicant responded as follows:
The results of lot analyses and stability studies were reviewed. As a result, it has been concluded that the same acceptance criteria should be used for both formulations. The same acceptance criteria as for the 1.5 mg drug product will be set for the 7.5 mg drug product.

PMDA accepted the response. There will be no change to the proposed shelf life (36 months) associated with the changes to the specifications for the 7.5 mg drug product.

3. Non-clinical data

3.1 Pharmacology studies

3.1.A Summary of the submitted data

One primary pharmacodynamic study report as the evaluation data and 1 primary pharmacodynamic study report as the reference data were submitted. Three safety pharmacology study reports and 3 other study reports were submitted as the evaluation data.

3.1.A.1) Primary pharmacodynamics

Rasburicase (urate oxidase) is an enzyme that catalyzes the oxidation of uric acid into allantoin and hydrogen peroxide (H_2O_2).

$$\text{Uric acid} + O_2 + 2H_2O \xrightarrow[\text{urate oxidase}]{} [\text{5-hydroxyisourate}] \xrightarrow[\text{nonenzymatic decomposition}]{} \text{allantoin} + CO_2 + H_2O_2$$

3.1.A.1).(1) Biochemical characterization

The biochemical properties and uricolytic activity of rasburicase [see "2.A.2).(1) Structure/Composition"] were compared to those of a natural *A. flavus* uricase (Boehringer Mannheim) reported in the literature (*Biochem J* 1980;187:727-32) (the table below). As a result, there were some differences in the biochemical parameters between rasburicase (measured values) and the natural uricase (values reported in the literature).

Comparison between rasburicase and natural uricase

Biochemical parameters	Natural uricase (values reported in the literature)	Rasburicase
Enzyme structure	Tetramer	Tetramer
Molecular mass (kDa)	130	136.7
Molecular mass of monomer (kDa)	32	34.2
Specific activity (EAU/mg)	16.9	[redacted]
Isoelectric point	NA	7.6
K_m (μmol/L)	NA	[redacted] [95% CI [redacted]]
V_{max} (μmol/L/min)	NA	[redacted] [95% CI [redacted]]

NA: not available, 95% CI: 95% confidence interval

Like other natural uricase, the uricolytic activity of rasburicase is competitively inhibited by 8-azaxanthine, which is similar in structure to uric acid (*Biophy Chem* 1995;54:229-35).

3.1.A.1).(2) Plasma uric acid lowering effect of rasburicase (Report 083005Z)

An *in vivo* primary pharmacodynamic study of rasburicase was conducted in chickens, where the plasma uric acid lowering effect of a non-recombinant uricase (Brand name: Uricozyme, Sanofi-Synthelabo) and of uricase obtained from *Candida utilis* has been confirmed (*J Pharmacol Exp Ther* 1981; 219: 352-4, *J Pharm Pharmacol* 1984; 36: 354-5).

Following a single intravenous administration of rasburicase 0.04, 0.2, or 1 mg/kg to female chickens (n = 6 per group), plasma uric acid levels at pre-dose and 0.5, 1, 2, and 4 hours post-dose were assessed (the table below).

The plasma uric acid $AUC_{0.5\text{-}4h}$ was significantly reduced in the 0.2 and 1 mg/kg groups compared to the vehicle control group. The plasma uric acid level was significantly reduced at 2 and 4 hours post-dose in the 0.2 mg/kg group and at all timepoints after administration in the 1 mg/kg group. The applicant explained that the plasma uric acid lowering effect of rasburicase has been demonstrated *in vivo* at doses that are not substantially different from the proposed clinical dose.

Effect of rasburicase on plasma uric acid in chickens

Dose (mg/kg)	Plasma uric acid $AUC_{0.5\text{-}4h}$ (mg·h/dL)	Plasma uric acid (mg/dL)				
		Pre-dose	0.5 hours	1 hour	2 hours	4 hours
Vehicle	6.8 ± 1.1	2.3 ± 0.3	1.7 ± 0.2	1.7 ± 0.4	2.0 ± 0.6	2.2 ± 0.4
0.04	6.0 ± 1.2	2.3 ± 0.3	1.6 ± 0.3	1.3 ± 0.4	1.9 ± 0.5	1.8 ± 0.4
0.2	5.0 ± 0.9**	2.4 ± 0.6	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.3*	1.6 ± 0.2**
1	3.9 ± 0.4**	2.3 ± 0.4	0.6 ± 0.3**	0.6 ± 0.4**	1.1 ± 0.1**	1.6 ± 0.3*

Mean ± standard deviation (SD)

*: $P < 0.05$, **: $P < 0.01$ (significant difference from the vehicle control group, Dunnett's test [a two sided 5% significance level])

3.1.A.2) Safety pharmacology

In safety pharmacology studies, the dose of rasburicase was 1.5 mg/kg, which is approximately 7-fold the proposed clinical dose.

3.1.A.2).(1) Effects on the central nervous system (Report SNX0070)

Following a single intravenous administration of rasburicase 1.5 mg/kg or placebo (alanine, mannitol, disodium phosphate dodecahydrate) to male mice (n = 8 per group), the effects of rasburicase on general symptoms/behaviour (Irwin test) and body temperature were assessed. There were no noteworthy findings at 5, 15, 30, 60, and 120 minutes after the administration of rasburicase compared to placebo.

3.1.A.2).(2) Effects on the cardiovascular system (Report CVR0135)
Following a single intravenous administration of rasburicase 1.5 mg/kg to anesthetized male beagle dogs (n = 5), mean blood pressure, carotid and femoral blood flows and corresponding vascular resistances, stroke volume, total peripheral resistance, and dP/dt_{max} were measured at pre-dose and 5, 15, 30, 60, 90, and 120 minutes post-dose. There were slight increases in heart rate (a maximum of 12% increase at 90 and 120 minutes post-dose) and corresponding decreases in stroke volume (a maximum of 11% decrease at 90 minutes post-dose) from pretreatment. The applicant discussed that these changes were not related to rasburicase as increased heart rate associated with the vasodilating action of halothane, which was used as an anesthetic, has been reported (*Circ Res* 1974; 34: 155-67).

3.1.A.2).(3) Effects on the renal/urinary system (Report ION0365)
Following a single intravenous administration of rasburicase 1.5 mg/kg or placebo (alanine, mannitol, disodium phosphate dodecahydrate) to saline-loaded male rats (n = 10 per group), urinary volume and urinary electrolytes etc. were measured. Rasburicase had no effects on urine flow rate, pH, glomerular filtration rate (creatinine clearance), free water clearance, and urinary concentrations and excretion fractions of Na^+, K^+, and Cl^-.

3.1.A.2).(4) Effects on the respiratory system
Although the effects of rasburicase on the respiratory system have not been studied, there were no findings of abnormal respiration (irregular respiration or gasping respiration) in the mouse study assessing the effects of rasburicase on general symptoms/behaviour and no effects of rasburicase 50 mg/kg on respiration were observed in rat single-dose and 1-month repeat-dose toxicity studies.

3.1.A.3) Others (Reports MIH0050, MIH0081, MIH0082)
As antineoplastic drugs are used during or after administration of rasburicase in a clinical setting, the effects of rasburicase on antineoplastic drugs that are used for the treatment of hematological malignancies and allopurinol that is expected to be used as supportive therapy were studied *in vitro*.

After a reaction solution containing each concomitant drug (7.5 μmol/L) was added and reacted with rasburicase (3 μg/mL) or control (inactivated rasburicase) at 37°C for 30 minutes, the drug concentration was determined by HPLC-UV, HPLC-FLUO, or LC-MS/MS. After the reaction, the mean drug concentration ratio of rasburicase to control was calculated (the table below). As a result, there were no major differences in the drug concentration after reaction between rasburicase and control. Thus, the applicant explained that rasburicase was shown to have no effects on the concentrations of the drugs tested.

Effects of rasburicase on antineoplastic drug concentration

Drug	Concentration ratio vs. control (%)[*1]
6-mercaptopurine[*2]	104
Methotrexate[*2]	104
Cytarabine[*2]	95.4
Methylprednisolone[*3]	99.7
Vincristine[*3]	98.5
Thioguanine[*3]	96.1
Allopurinol[*3]	100
Etoposide[*3]	102
Daunorubicin[*3]	96.4
Cyclophosphamide[*4]	99.2

*1: (Mean drug concentration in rasburicase group/mean drug concentration in control group) × 100
*2: n = 2, *3: n = 6, *4: n = 6 in rasburicase group, n = 5 in control group

3.1.B Outline of the review by PMDA

As a result of the following review, PMDA concluded that although non-clinical studies have not investigated the relationship between the pharmacokinetics (PK) and pharmacodynamics (PD) (plasma uric acid levels) of rasburicase and it is difficult to infer this relationship in clinical use, rasburicase has been shown to have uricolytic activity also *in vivo*.

Cardiac findings have been observed in a safety pharmacology study, and cardiac events including tachycardia and congestive cardiac failure have also been reported in clinical studies. Thus, PMDA considers that caution is needed when administering rasburicase.

3.1.B.1) *In vivo* pharmacology study

At the time of regulatory submission, only a published article on an *in vivo* pharmacology study using a non-recombinant uricase instead of rasburicase was submitted as a primary pharmacodynamics study (as the reference data).

PMDA asked the applicant to explain the reason for considering that the data from a pharmacology study of a non-recombinant uricase instead of rasburicase can be extrapolated into rasburicase.

The applicant responded as follows:
Since the biochemical properties of rasburicase are not identical to those of a non-recombinant uricase due to the influences of the manufacturing process, it was considered necessary to confirm the pharmacological action of rasburicase also *in vivo*, and another pharmacology study in chickens was conducted. The results from this study are submitted as the evaluation data [see "3.1.A.1).(2) Plasma uric acid lowering effect of rasburicase (Report 083005Z)"].

Based on the newly submitted data from the *in vivo* primary pharmacodynamics study, PMDA confirmed that although the secondary structure and specific activity of rasburicase are not identical to those of a non-recombinant uricase, rasburicase has enzyme activity also *in vivo*. PMDA considers that a pharmacology study should have been designed to enable potency comparison with other uricase and allopurinol.

3.2 Pharmacokinetic studies

3.2.A Summary of the submitted data

The pharmacokinetics (PK) of rasburicase and the effects of rasburicase on drug-metabolizing enzymes were evaluated preclinically in rats and baboons and the effects of different formulations on PK in baboons.

3.2.A.1) Analytical methods

Rasburicase concentrations in rat and baboon plasma were determined by a sandwich immunoradiometric assay (IRMA) using solid-phase mouse anti-rasburicase antibody and ^{125}I-labeled mouse anti-rasburicase antibody.

Anti-rasburicase antibodies in rats were determined by an enzyme-linked immunosorbent assay (ELISA) using solid phased rasburicase and peroxidase-labeled anti-rat immunoglobulin antibody.

3.2.A.2) Absorption

3.2.A.2).(1) Single-dose administration

Following a single intravenous administration of rasburicase 0.3, 0.9, or 3 mg/kg to male and female rats, plasma rasburicase concentrations were determined (the table below). The plasma

rasburicase concentration back extrapolated to time of injection (C_0) and AUC increased dose-proportionally and CL and Vd were almost constant regardless of dose. There were no gender-related differences in PK.

PK parameters following a single intravenous administration of rasburicase in rats

Dose (mg/kg)	Gender	C_0 *1 (μg/mL)	C_1 *2 (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2\beta}$ (h)	CL (mL/h/kg)	Vd (mL/kg)
0.3	Males	5.42	2.61 ± 0.38	10.6	1.61	28	66
	Females	6.55	2.84 ± 0.16	11.7	1.57	26	58
0.9	Males	13.0	8.67 ± 0.10	33.4	1.86	27	72
	Females	16.5	8.32 ± 0.45	33.7	1.85	27	71
3	Males	58.2	35.3 ± 2.50	144	1.87	21	56
	Females	48.4	29.3 ± 0.45	119	1.83	25	67

Mean ± SD, n = 3 rats per sampling point, *1: Extrapolated value, *2: Plasma rasburicase concentration at 1 hour post-dose

The 0.15, 0.45, and 1.5 mg/kg intravenous doses of rasburicase were administered sequentially with an interval of 4 days between each dose to male baboons and plasma rasburicase concentrations were determined (the table below). The applicant explained that the PK of rasburicase were linear over the dose range tested.

PK parameters following a single intravenous administration of rasburicase in baboons

Dose (mg/kg)	C_0 * (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2\beta}$ (h)	CL (mL/h/kg)	Vd (mL/kg)
0.15	2.61 ± 0.60	15.3 ± 3.47	3.40 ± 0.63	10 ± 2	50 ± 16
0.45	9.88 ± 1.26	45.0 ± 8.94	3.31 ± 0.13	10 ± 2	49 ± 13
1.5	24.8 ± 4.15	129 ± 21.8	3.70 ± 0.98	12 ± 2	62 ± 9

Mean ± SD, n = 3

3.2.A.2).(2) Repeated-dose administration

Following repeated intravenous administration of rasburicase 0.3, 0.9, or 3 mg/kg/day for 29 to 34 days to male and female rats, PK on the last day of administration were determined (the table below). Although a high inter-animal variability in plasma rasburicase concentrations was observed, C_0 and $AUC_{0\text{-}24}$ increased dose-dependently. The applicant explained that there were no remarkable gender-related differences in the PK parameters.

PK parameters on the last day of 1-month repeated intravenous administration of rasburicase in rats

Dose (mg/kg/day)	Gender	C_0 * (μg/mL)	$AUC_{0\text{-}24}$ (μg·h/mL)
0.3	Males	2.82	8.91
	Females	3.09	8.08
0.9	Males	18.2	41.9
	Females	18.4	36.7
3	Males	61.1	210
	Females	71.9	147

n = 2 rats per sampling point

Anti-rasburicase antibodies were detected in 15 of 20 rats in the rasburicase 0.3 mg/kg group, 16 of 20 rats in the rasburicase 0.9 mg/kg group, and 19 of 20 rats in the rasburicase 3 mg/kg group. The applicant discussed that although there was no apparent relationship between the dose or plasma rasburicase concentration and anti-rasburicase antibody titer, the possibility that plasma rasburicase concentrations were affected by anti-rasburicase antibodies can not be ruled out.

Following repeated intravenous administration of rasburicase 1, 3, or 10 mg/kg/day for 2 weeks to male and female rats, plasma rasburicase concentrations and the proportion of rats with anti-rasburicase antibodies on the last day of administration were as shown in the following table. Plasma rasburicase concentrations increased dose-proportionally and there were no

gender-related differences. The applicant explained that as the plasma rasburicase concentrations in the 3 mg/kg group after repeated administration were similar to those after a single dose, repeated administration of rasburicase did not result in accumulation over the dose range tested (1-10 mg/kg) and there were no apparent differences in the plasma rasburicase concentration according to the presence or absence of anti-rasburicase antibodies.

Plasma rasburicase concentrations and the proportion of rats with anti-rasburicase antibodies on the last day of 2-week intravenous administration of rasburicase in rats

Dose (mg/kg/day)	0	1	3	10
Plasma rasburicase concentration at 1 hour after the end of administration (μg/mL)				
Males	0	12.1 ± 1.27	39.0 ± 1.95	124 ± 7.34
Females	0	11.2 ± 0.95	34.8 ± 5.18	119 ± 31.9
Proportion of rats with anti-rasburicase antibodies*				
Males	0/3 (ND)	0/3 (ND)	1/3 (1/650)	1/3 (1/450)
Females	0/3 (ND)	1/3 (1/250)	0/3 (ND)	1/3 (1/140)

Mean ± SD, n = 3, *: Antibody titer in rat with anti-rasburicase antibodies in parentheses

3.2.A.3) Distribution

Tissue distribution of rasburicase has not been studied. The applicant explained that a tissue distribution study of rasburicase is of little significance for the following reasons:

(a) "Tissue concentrations of radioactivity and/or autoradiography data using radiolabeled proteins may be difficult to interpret due to rapid *in vivo* metabolism or unstable radiolabeled linkage. Care should be taken in the interpretation of studies using radioactive tracers incorporated into specific amino acids because of recycling of amino acids into non-drug related proteins/peptides" ("Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" [PMSB/ELD Notification No. 326 dated February 22, 2000]). Therefore, it was considered difficult to appropriately evaluate the results of a tissue distribution study using radiolabeled rasburicase.

(b) As mice, rats, and baboons used in toxicity studies possess endogenous urate oxidase activity, the tissue distribution of rasburicase can not be determined based on the enzyme activity of rasburicase.

3.2.A.4) Metabolism and excretion

Referring to "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PMSB/ELD Notification No. 326 dated February 22, 2000), the applicant explained that a metabolism study of rasburicase can be omitted.

The applicant explained that when rasburicase 1, 5, or 10 μg/L was added to rat and baboon plasma *in vitro*, rasburicase was stable for 24 hours at room temperature, indicating that rasburicase is not degraded in rat or baboon plasma.

3.2.A.5) Pharmacokinetic interactions

3.2.A.5).(1) Effects of rasburicase on liver drug metabolizing enzymes

Using the microsomes prepared from the livers of rats (0.3, 0.9, 3 mg/kg/day) and baboons (0.136, 0.346, 1.500 mg/kg/day) following repeated intravenous administration of rasburicase for 1 month, rat CYP1A, 2B, 2C, 2E, and 3A activities and baboon CYP1A, 2A, 2C, 2E, and 3A activities were measured. In rats, only CYP2C activity slightly increased in female rats treated with 3 mg/kg of rasburicase. In baboons, there were no effects on liver CYP isozymes. Following repeated administration of rasburicase, there were little changes in rat and baboon liver weights.

3.2.A.5).(2) Effects of rasburicase on metabolism of other drugs

The effects of rasburicase on the metabolism of antineoplastic drugs were investigated [see "3.1.A.3) Others"].

3.2.A.6) Relative bioavailability study

While the formulation for clinical studies and the proposed commercial formulation contain poloxamer 188 as a solubilizer, a poloxamer 188-free formulation was used in some of the non-clinical studies.

Following a single intravenous administration of rasburicase 1.5 mg/kg to male baboons in a crossover design (a 14-day washout interval), the effects of poloxamer 188 on PK were investigated (the table below). The applicant explained as follows: The results of crossover ANOVA revealed no significant effects of the sequence, period, test animal, or formulation on AUC_{inf} and the 90% CI for the AUC_{inf} ratio of the two formulations was 0.92 to 1.12, which fell within the range of 0.8 to 1.25. Thus, the bioavailabilities of the two formulations are equivalent.

PK parameters following single intravenous administration of poloxamer 188-free or poloxamer 188-containing formulation (rasburicase 1.5 mg/kg) in baboons

PK parameter	Poloxamer 188-free (Water for injection)	Poloxamer 188-containing (0.1% poloxamer solution)
C_0 (μg/mL)	36.1 ± 5.14	32.3 ± 3.35
AUC_{inf} (μg·h/mL)	186 ± 13.0	190 ± 27.8
$t_{1/2\beta}$ (h)	3.88 ± 0.68	3.18 ± 0.84
CL (L/h/kg)	0.008 ± 0.001	0.008 ± 0.001
Vd (L/kg)	0.046 ± 0.011	0.036 ± 0.005

Mean ± SD, n = 4

3.2.A.7) Applicant's discussions

The Vd of rasburicase in rats and baboons was small, i.e. about 60 to 70 mL/kg in rats and about 50 to 60 mL/kg in baboons, which were almost comparable to V_Z in humans (70.3-89.5 mL/kg) [see "4.2.A.1) Healthy adult subjects"]. The Vd of rasburicase was approximately twice the plasma volume in rats and was almost equal to the plasma volume in baboons, which were equivalent to the intravascular volume. Thus, the applicant discussed that as rasburicase has a high molecular mass (approximately 136 kDa), its distribution is almost limited to the intravascular space.

A publication on a different uricase, i.e. ^{3}H-labeled *Candida utilis* uricase intravenously administered to mice (*Bioconjug Chem* 1999; 10: 638-46) has reported that radioactivity was distributed mainly to the liver, kidneys, and lungs. Rasburicase has been shown to be stable in rat and baboon plasma *in vitro* [see "3.2.A.4) Metabolism and excretion"]. It has also been reported that when a different uricase, i.e. *C. utilis* uricase was incubated with rat plasma at 37°C for 24 hours, ≥ 90% of the uricase activity was maintained (*Chem Pharm Bull* 1990; 38: 2053-6).

The applicant discussed that although distribution, metabolism, and excretion studies of rasburicase have not been conducted, it is inferred from the above results and findings that rasburicase is distributed primarily to the intravascular space, partly taken up into tissues like the liver and kidneys, and degraded by protease and eliminated.

3.2.B Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concluded that the applicant's discussions on absorption, distribution, metabolism, and excretion and pharmacokinetic interactions of rasburicase are acceptable.

3.2.B.1) Reason for not conducting a tissue distribution study of rasburicase

The applicant explained that one of the reasons for not conducting a tissue distribution study of rasburicase was the difficulty of appropriately evaluating the results of a tissue distribution study using radiolabeled rasburicase [see "3.2.A.3) Distribution"]. PMDA asked the applicant to specifically explain what brought them to this conclusion.

The applicant responded as follows:

The $t_{1/2\beta}$ of rasburicase, a recombinant protein, was approximately 2 hours in rats and approximately 4 hours in baboons, showing rapid elimination. Therefore, like other proteins, rasburicase is likely to be hydrolyzed *in vivo* to small peptides and amino acids. Thus, radiolabeled amino acids may be incorporated into endogenous substances and the obtained data will be difficult to interpret. In addition, (a) As the volume of distribution of rasburicase in rats and baboons was almost equivalent to the plasma volume [see "3.2.A.7) Applicant's discussions"] and rasburicase has a high molecular mass, its distribution is almost confined to the intravascular space with limited distribution in other tissues, (b) The pharmacological target site for rasburicase is blood (blood uric acid), and (c) There were no serious organ/tissue-specific toxicities of rasburicase in toxicity studies. On the basis of these considerations, a tissue distribution study of rasburicase was not conducted.

PMDA accepted the response, considering as follows:

Although the results of a tissue distribution study in a relevant animal species are useful for predicting potential toxicities in clinical use etc., as rasburicase is distributed primarily to the intravascular space, a tissue distribution study of rasburicase is not essential at present.

3.3 Toxicology studies

3.3.A Summary of the submitted data

3.3.A.1) Single-dose toxicity

Mice and rats received single intravenous doses of up to 15 mg/kg and up to 50 mg/kg (75 times and 250 times the proposed clinical dose of 0.2 mg/kg, respectively) of rasburicase, respectively. No deaths occurred and there were no abnormalities in clinical observations, body weight, or necropsy findings and the approximate lethal dose was determined to be ≥ 15 mg/kg in mice and ≥ 50 mg/kg in rats. Anti-rasburicase antibodies were detected in rats at 10, 20, and 50 mg/kg at 1 to 2 weeks post-dose.

3.3.A.2) Repeat-dose toxicity

Rats and baboons received repeated intravenous doses of up to 50 mg/kg/day and up to 1.5 mg/kg/day (250 times and 7.5 times the proposed clinical dose of 0.2 mg/kg, respectively) of rasburicase, respectively, for 1 month. As toxicity findings, mild anemia combined with increased hematopoiesis was noted in rats at 20 and 50 mg/kg/day (100 times and 250 times the proposed clinical dose, respectively) and the no observed adverse effect level (NOAEL) was determined to be 10 mg/kg/day in rats and 1.5 mg/kg/day in baboons. Follicular hyperplasia in the spleen and Peyer's patches of the ileum was considered to be a physiological response to a foreign protein. Rasburicase was immunogenic in rats and baboons and anti-rasburicase antibodies were detected at 0.3 to 50 mg/kg/day and at 0.14 to 1.5 mg/kg/day, respectively, at 2 to 4 weeks after the initiation of rasburicase. As the duration of treatment with rasburicase is approximately 5 days in a clinical setting, a repeat-dose toxicity study of > 1 month duration has not been conducted.

Based on the above results, the applicant explained as follows:

Although the definite cause of anemia combined with increased hematopoiesis observed in rats is unknown, as rasburicase enzymatically converts uric acid to allantoin and hydrogen peroxide, it may have been attributable to the exposure of erythrocytes to hydrogen peroxide. Hydrogen

peroxide is converted in the presence of iron to highly reactive hydroxyl radicals, which are considered to cause oxidative injury to lipids, proteins, and nucleic acids (*Am J Surg* 1991; 161: 488-503). Hydrogen peroxide leads to erythrocyte injury (hemolysis and methemoglobinemia) in patients with a genetic deficiency of enzymes responsible for scavenging hydrogen peroxide (*Free Radicals in Biology.* Vol V. [Academic Press, 1982] p.115-60). Based on the above, it seems that anemia observed in rats was associated with erythrocyte injury due to high-dose rasburicase resulting in an increased hydrogen peroxide concentration exceeding the capability of the endogenous hydrogen peroxide scavenging mechanisms (glutathione peroxidase etc.).

In humans, there is a concern about similar effects in patients with a genetic deficiency of enzymes that remove hydrogen peroxide, e.g. glucose-6-phosphate dehydrogenase (G6PD) and glutathione peroxidase. On the other hand, in patients with normal concentrations of these enzymes, the following defense mechanisms against hydrogen peroxide function adequately ([redacted]).

- Enzymes, e.g. G6PD and glutathione peroxidase, can decompose hydrogen peroxide faster (≥ 25 times) than the formation of hydrogen peroxide via rasburicase.
- Many of antioxidant small molecules and proteins can scavenge hydrogen peroxide or its reaction by-products.

The AUC of rasburicase at the NOAEL dose for a repeat-dose toxicity study (anemia) in adult rats was approximately 9.7 times the AUC in adult patients (576-833 μg·h/mL in adult rats, 59.3 μg·h/mL in adult patients). Likewise, the AUC in neonatal rats was approximately 31 times the AUC in pediatric patients (975-1230 μg·h/mL in neonatal rats, 31.5 μg·h/mL in pediatric patients).

Based on the above, the influences of hydrogen peroxide generated via rasburicase are unlikely to become a safety problem in both children and adults. However, rasburicase has been contraindicated in patients with a genetic deficiency of enzymes responsible for scavenging hydrogen peroxide (G6PD etc.) and patients with other cellular metabolic abnormalities causing hemolytic anemia.

3.3.A.3) Genotoxicity

A bacterial Ames test, a mammalian cell gene mutation assay (mouse lymphoma), an unscheduled DNA synthesis assay (rat hepatocytes), an *in vitro* chromosomal aberration assay (human lymphocytes), and an *in vivo* chromosomal aberration assay (a rat micronucleus assay) were performed, all of which produced negative results.

3.3.A.4) Reproductive and developmental toxicity

Rasburicase had no effects on reproductive performance, fertility, and early (preimplantation) embryonic development in male and female rats, up to the highest dose of 10 mg/kg/day. The NOAELs for general toxicity, copulation, and fertility (males and females) in parent animals and early embryonic development were all determined to be 10 mg/kg/day.

Pregnant rats received repeated intravenous doses of up to 50 mg/kg/day of rasburicase (250 times the proposed clinical dose of 0.2 mg/kg) from gestation day 6 through gestation day 17 and pregnant rabbits received repeated intravenous doses of up to 20 mg/kg/day of rasburicase (100 times the proposed clinical dose of 0.2 mg/kg) from gestation day 6 through gestation day 19. In a dose-finding study in rabbits, up to 50 mg/kg/day of rasburicase (250 times the proposed clinical dose) was administered. Rasburicase produced embryonic/fetal toxicities in rats and rabbits. The maternal effects in rats were decreases in body weight gain (transient

decreases in the 50 mg/kg/day group) only.

In rabbits, maternal body weight and food consumption were reduced at all dose levels (2, 10, 20, 50 mg/kg/day, including a dose-finding study). Death or moribund condition (euthanization) occurred at ≥ 2 mg/kg/day and abortions occurred at 10, 20, and 50 mg/kg/day.

As embryo/fetal effects, heart and blood vessel anomalies only were observed in 1 fetus at 50 mg/kg/day in rats. Meanwhile, in rabbits, rasburicase increased post-implantation loss, the number of dead fetuses, and the number of resorptions and decreased the number of live fetuses and fetal body weight. Rasburicase also affected fetal skeletal development and anomalies in the heart and great vessels were observed at ≥ 2 mg/kg/day.

Based on the above results, the applicant explained as follows:
Rasburicase is teratogenic in rats and rabbits. However, as rasburicase is indicated for the treatment of hyperuricemia associated with malignant tumors and is intended to be used in combination with cytotoxic antineoplastic drugs and many of these drugs cause embryo-fetal toxicity/teratogenicity, the embryo-fetal toxicities/teratogenicity of rasburicase observed in rabbits and rats will not affect the clinical use of rasburicase.

The following caution statement will be included in "5. Use during Pregnancy, Delivery or Lactation" of "Precautions" in the proposed package insert for rasburicase: "the drug should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment."

3.3.A.5) Neonatal toxicity
Rasburicase was well tolerated in neonatal rats. The highest dose in 1-month intravenous toxicity studies was 50 mg/kg/day (250 time the proposed clinical dose of 0.2 mg/kg). Since the toxicity findings observed in neonatal rats were anemia combined with increased hematopoiesis at 20 and 50 mg/kg/day and female rats exhibited increased spleen weights (about 39%) at 50 mg/kg/day, the NOAEL was determined to be 10 mg/kg/day. These effects were similar to those observed in adult rats. Although body weight loss (up to 9%) and reduced body weight gain were noted in males receiving 50 mg/kg/day, there were no apparent gender-related differences in PK. The immunogenicity of rasburicase was very low in neonatal rats unlike adult rats, which was considered attributed to an immature immune system in neonatal rats (*Environ Health Perspect* 2003; 111: 579-83, *Br Defects Res* 2003; B.68: 321-34).

The applicant explained as follows:
The toxicological profile of rasburicase in neonatal rats was similar to that in adult rats and new toxicities are unlikely to emerge in pediatric patients. When the exposure at the clinical dose in children was compared to the exposure at the NOAEL dose (10 mg/kg) in neonatal rats, the AUC in neonatal rats (≥ 975 μg·h/mL) was ≥ 31 times higher than the AUC in pediatric patients (31.5 μg·h/mL).

3.3.A.6) Local tolerance
Rasburicase administered intravenously, intra-arterially, and perivenously was well tolerated locally in rabbits and rasburicase had also no irritant effects on the skin or eyes.

3.3.A.7) Antigenicity
Rasburicase was immunogenic in rats (adult and neonatal rats), rabbits, baboons, and guinea pigs. Plasma anti-rasburicase antibodies were detected in rats, rabbits, and baboons and active systemic anaphylaxis and passive cutaneous anaphylaxis were induced in guinea pigs.

As rasburicase is not a human-derived protein, it can induce hypersensitivity also in humans. Therefore, the applicant explained that a single course of treatment (a 5-day repeated administration) is recommended in order to prevent possible allergic reactions.

3.3.A.8) Hemolytic potential
Rasburicase at 0.0817 to 0.30 mg/mL caused no hemolysis of human whole blood.

3.3.A.9) Carcinogenicity
No carcinogenicity study has been performed as rasburicase has been tested negative for genotoxicity and the treatment duration in a clinical setting does not exceed 7 days.

3.3.B Outline of the review by PMDA

3.3.B.1) Doses for a single-dose toxicity study
PMDA asked the applicant to explain the rationale for selecting 50 mg/kg as the highest dose for a rat single-dose toxicity study (TXA0857).

The applicant responded as follows:
Prior to the conduct of Study TXA0857, a rat single-dose toxicity study at a dose of 15 mg/kg of rasburicase (75 times the proposed clinical dose of 0.2 mg/kg) (TXA313) was carried out. However, as this study could not detect any apparent toxicity, 10, 20, and 50 mg/kg (50, 100, and 250 times the proposed clinical dose, respectively) were chosen for Study TXA0857.

In Study TXA0857, the exposure to rasburicase (AUC_{0-24}) at 50 mg/kg was 3800 to 4040 μg·h/mL. As the AUC_{0-24} at 0.2 mg/kg was 59.3 to 65.2 μg·h/mL in Japanese adult patients (Study ADR5290) and 31.5 to 38.1 μg·h/mL in Japanese pediatric patients (Study ACT5080), the AUC_{0-24} at 50 mg/kg in rats was 58 times the AUC_{0-24} in Japanese adult patients and 100 times the AUC_{0-24} in Japanese pediatric patients. Based on the above, as the systemic exposure at 50 mg/kg in Study TXA0857 was ≥ 50 times higher than that at the proposed clinical dose, the 50 mg/kg dose was considered appropriate for a single-dose toxicity study.

PMDA accepted the applicant's response.

3.3.B.2) Anti-rasburicase antibodies
The applicant explained as follows:
In a rat 1-month repeat-dose toxicity study (TSA1178), 19 of 20 rats in the control group were strongly positive (≥ 1.00 AU [absorption unit]) for anti-rasburicase antibodies in plasma at Week 5. In an additional study (DIV0902), a cutoff value of 15% (B/B0 = 15%, B0: absorbance of positive control, B: absorbance of sample) was chosen and no positive results were obtained. Thus, the positive results in the control group in Study TSA1178 were false-positive.

PMDA asked the applicant to explain why anti-rasburicase antibodies were detected in the control group in Study TSA1178.

The applicant responded as follows:
The cause of strongly positive results for anti-rasburicase antibodies in 19 of 20 rats in the control group in Study TSA1178 was investigated and examined. As a result, the possibility of errors in the experimental procedure (rasburicase mistakenly administered to the control group or mix-ups of plasma samples) was excluded. It is known that an ELISA for antibodies can produce false positive responses and an additional study to evaluate the anti-rasburicase antibody assay (DIV0902) confirmed that it produces false positive responses. Based on the above, the positive results for anti-rasburicase antibodies in the control group in Study TSA1178 were determined to be false positive responses.

However, as the definite cause for the detection of anti-rasburicase antibodies in the control group was unknown and various changes associated with the placement of an intravenous access port were observed in Study TSA1178, another rat 1-month repeat-dose toxicity study (TSA1220) was conducted. In Study TSA1220, the above-mentioned cutoff value was used and none of the rats in the control group were positive for antibodies. Thus, it was considered possible to assess the human safety margin (exposure) in this study.

PMDA accepted the applicant's response, i.e., although the cause of positive results for anti-rasburicase antibodies in the control group in Study TSA1178 is unknown, as positive results for anti-rasburicase antibodies in the control group were not reproduced in Study TSA1220, it is possible to assess the human safety margin (exposure) in Study TSA1220.

Based on the above review, PMDA concluded as follows:
Since rasburicase is a recombinant urate oxidase formed after the gene cloned from *A. flavus* is inserted and expressed in a modified *S. cerevisiae* strain, it is expected to be immunogenic in humans and may cause allergic reactions. The healthcare professionals need to be adequately cautioned about potential risks, e.g. anaphylactic shock.

Although embryo-fetal toxicities and anomalies in the heart and associated vascular system were observed in rats and rabbits, as rasburicase is intended to be used in patients with potentially life-threatening malignant tumors, using rasburicase for hyperuricemia associated with cancer chemotherapy during pregnancy is acceptable if the maternal benefits outweigh the possible risks to the fetus.

4.1 Biopharmaceutic studies

4.1.A Summary of the submitted data

4.1.A.1) Analytical methods

4.1.A.1).(1) Assay for quantitation of rasburicase

Rasburicase in human plasma was quantitated by RIA (DOH0017 or DOH0089) or ELISA. Solid-phase mouse anti-rasburicase antibody and ^{125}I-labeled mouse anti-rasburicase antibody were used in the RIA and horse radish peroxidase (HRP) was used as the probe in the ELISA.

4.1.A.1).(2) Assay for quantitation of allantoin in urine

Allantoin in urine was separated and quantitated by LC-MS/MS.

4.1.A.1).(3) Detection method for anti-rasburicase antibodies

Anti-rasburicase antibodies in human plasma were qualitatively (0, +, ++, +++) assessed by an ELISA using solid phased rasburicase and peroxidase-labeled anti-human immunoglobulin antibody. The effects of the presence of anti-rasburicase antibodies on the uricolytic activity of rasburicase were investigated.

4.1.A.1).(4) Assay for quantitation of plasma uric acid

In a foreign phase I study (TDR2681), plasma uric acid was determined via the amount of hydrogen peroxide produced during the decomposition of uric acid by rasburicase by measuring a quinoneimine chromogen formed in the presence of hydrogen peroxidase. In other clinical studies, clinical laboratory test values at the trial sites were used.

The applicant explained as follows:
The agreement of plasma uric acid measurements obtained by commonly used assays at medical institutions between Japan and the US was evaluated. As a result, as the uric acid assays used in Japan and the US are considered to be equivalent, plasma uric acid measurements can be

compared between Japan and foreign countries.

4.1.A.1).(5) Assay for quantitation of anti-SCP antibodies in serum
Anti-SCP antibodies in serum were quantitated using a commercial kit "QUANTA LiteÔ ASCA (*S. cerevisiae*) IgG ELISA."

4.2 Clinical pharmacology studies

4.2.A Summary of the submitted data

Human PK and PD (plasma uric acid levels over time and urinary excretion of allantoin) of rasburicase were studied in healthy adult subjects and pediatric and adult patients with hematological malignancies.

In all studies, rasburicase was to be administered intravenously over 30 minutes (or 25-35 minutes).

4.2.A.1) Healthy adult subjects

4.2.A.1).(1) Japanese phase I study (Study TDU4730; Studied period, [redacted] to [redacted] 20[redacted])

Following a single intravenous dose of placebo or 0.05, 0.10, 0.15, or 0.20 mg/kg of rasburicase to 32 healthy adult male subjects, plasma rasburicase concentrations, plasma uric acid levels, urine allantoin levels, and the incidence of anti-rasburicase antibodies were determined (the table below). When dose proportionality was assessed using the power model, C_{max} was proportional to the dose while AUC_{inf} was slightly less than proportional to the dose. On the other hand, $t_{1/2Z}$ and V_Z were independent of the dose. The applicant explained that although the effect of the dose on CL was statistically significant, there was no trend towards an increase or a decrease of CL with increasing dose.

PK parameters following single doses of rasburicase in Japanese healthy adult subjects

Dose (mg/kg)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	CL (mL/h/kg)	V_Z (mL/kg)	$t_{1/2Z}$ (h)
0.05	1070 ± 177	23500 ± 3790	2.17 ± 0.392	78.8 ± 17.6	25.1 ± 2.84
0.10	2270 ± 204	46100 ± 4120	2.20 ± 0.205	70.3 ± 6.48	22.2 ± 1.59
0.15	3070 ± 434	53900 ± 9630	2.88 ± 0.619	89.5 ± 17.2	21.7 ± 1.42
0.20	4600 ± 1070	79100 ± 20100	2.68 ± 0.724	86.8 ± 22.9	22.8 ± 4.43

Mean ± SD, n = 6

Plasma uric acid levels demonstrated a dose-dependent rapid decline and plasma uric acid levels at 4 to 24 hours post-dose were kept below 5% of the baseline levels at ≥ 0.15 mg/kg. The time for plasma uric acid to return towards baseline was prolonged with increasing dose.

The urinary excretion rate of allantoin was highest at 0 to 8 hours post-dose in all rasburicase groups.

Anti-rasburicase antibodies were detected in 10 of 24 subjects at 30 days post-dose. Of which, 1 subject in the 0.20 mg/kg group had a positive antibody response even at 6 months post-dose, but was tested negative at 1 year post-dose.

4.2.A.1).(2) Foreign phase I study (Study TDR2681; Studied period, [redacted] to [redacted] 19[redacted])

Following single (0.05, 0.10, 0.15, or 0.20 mg/kg) or multiple (0.10, 0.15, or 0.20 mg/kg, once daily for 5 days) intravenous doses of rasburicase to 28 healthy adult male subjects, plasma rasburicase concentrations, plasma uric acid levels, and the incidence of anti-rasburicase antibodies were determined (the table below). The single-dose AUC_{0-24} and C_{max} and the AUC_{0-24} and C_{max} on Day 5 of multiple dosing were almost dose-proportional, suggesting dose proportionality. The V_z value was similar to the circulating blood volume. The single-dose

AUC_{inf} was comparable to the AUC_{0-24} on Day 5 of multiple dosing, indicating that a steady-state had been reached by Day 5. CL remained unchanged after multiple dosing. The applicant discussed that the PK of rasburicase is linear over the dose range tested.

PK parameters after single or multiple doses of rasburicase in foreign healthy adult subjects

	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL (mL/h/kg)	V_Z (mL/kg)	$t_{1/2Z}$ (h)
Single dose	0.05	964 ± 60.2	13100 ± 1470	22200 ± 4630	2.31 ± 0.399	59.3 ± 6.04	18.1 ± 2.36
	0.10	1690 ± 383	17700 ± 3690	27300 ± 5770	3.81 ± 0.945	103 ± 29.9	18.6 ± 1.41
	0.15	2600 ± 223	31200 ± 1920	47800 ± 5850	3.17 ± 0.409	86.7 ± 9.02	19.0 ± 1.30
	0.20	3580 ± 363	47000 ± 3750	69500 ± 3650	2.88 ± 0.154	75.4 ± 4.76	18.1 ± 0.519
Multiple doses							
Day 1	0.10	2240 ± 273	26500 ± 4180	NA	NA	NA	NA
	0.15	3620 ± 456	37200 ± 5450	NA	NA	NA	NA
	0.20	3680 ± 1530	43900 ± 14500	NA	NA	NA	NA
Day 5	0.10	2760 ± 383	29300 ± 4080	NA	3.47 ± 0.499	95.3 ± 33.0	18.7 ± 4.25
	0.15	4840 ± 635	47700 ± 8290	NA	3.21 ± 0.553	89.1 ± 15.8	19.3 ± 2.12
	0.20	6010 ± 663	65000 ± 7420	NA	3.11 ± 0.392	78.7 ± 31.1	17.2 ± 5.26

Mean ± SD, NA: Not calculated, n = 4

After a single dose of rasburicase, plasma uric acid levels demonstrated a dose-dependent rapid decline. At ≥ 0.15 mg/kg, plasma uric acid levels fell to below the lower limit of quantitation (0.5 mg/dL) within 4 hours post-dose, which was maintained until 24 hours post-dose. Plasma uric acid levels during multiple dosing were also kept below the lower limit of quantitation.

Anti-rasburicase antibodies were detected in 19 of 28 subjects (single-dose, 9 of 16 subjects; multiple doses, 10 of 12 subjects) by 43 days following rasburicase administration and the incidence of anti-rasburicase antibodies was higher after multiple dosing compared to single dosing. At 43 days after rasburicase administration, 18 of 28 subjects (single-dose, 10 subjects; multiple doses, 8 subjects) were positive for inhibition of uricolytic activity (inhibition rate, 7.5%-45%) and 15 of these 18 subjects were concurrently tested positive for anti-rasburicase antibodies. At 16 months after administration, 12 of these 15 subjects were tested for anti-rasburicase antibodies and only 1 subject had positive antibodies and this subject was tested positive also for inhibition of enzyme activity.

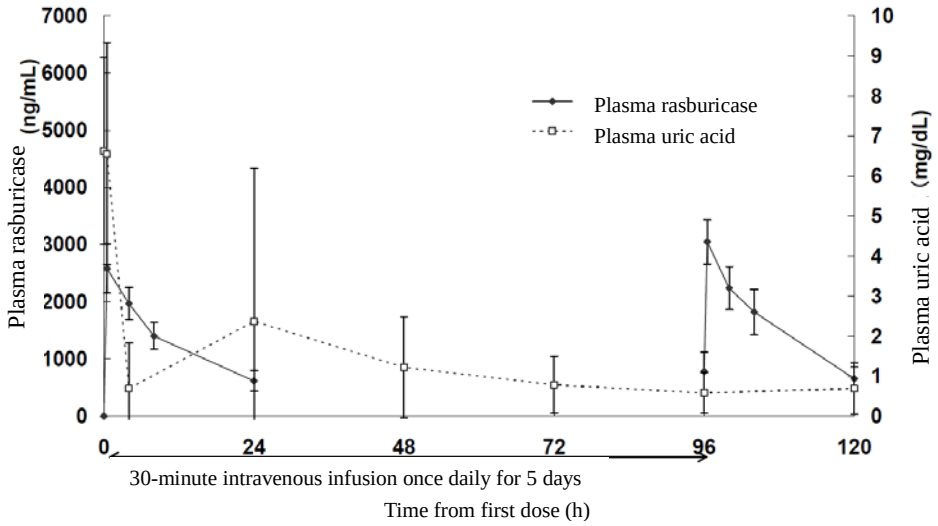
4.2.A.2) Pediatric cancer patients

4.2.A.2).(1) Japanese phase II study (Study ACT5080; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Rasburicase 0.15 or 0.20 mg/kg was intravenously administered once daily for 5 days to 30 pediatric patients with newly diagnosed hematological malignancies (20 patients included in PK analysis). Plasma rasburicase concentrations, plasma uric acid levels, and the incidence of anti-rasburicase antibodies were determined (PK parameters in cancer patient studies including this study are presented in "4.2.A.4) Discussion on PK and PD in Japanese and foreign subjects").

The PK of rasburicase and plasma uric acid levels were as shown in the following figure. Plasma uric acid levels rapidly declined after the initiation of rasburicase and remained low until 24 hours after the last dose in both the 0.15 and 0.20 mg/kg groups.

At 1 month after rasburicase administration, 28 of 30 patients were tested for anti-rasburicase antibodies and 1 patient had a positive result, but became negative at 6 months after administration.



Plasma rasburicase concentrations and plasma uric acid levels over time in Japanese pediatric patients treated with rasburicase (0.20 mg/kg)

4.2.A.2).(2) Foreign phase II study (Study ACT2694; Studied period, March 1996 to October 1997)

Rasburicase 0.15 or 0.20 mg/kg was intravenously administered once daily for 5 to 7 days to 133 pediatric patients with leukemia or malignant lymphoma (30 patients included in PK analysis). Plasma rasburicase concentrations, plasma uric acid levels, urine allantoin levels, and the incidence of anti-rasburicase antibodies were determined.

Concerning the PK of rasburicase, the applicant discussed that the Day 5 to Day 2 trough concentration (C_{min}) ratio indicated that a steady-state had been reached by Day 2.

Concerning the PD of rasburicase, plasma uric acid levels rapidly declined after the initiation of rasburicase and remained low until 24 hours after the last dose in both the 0.15 and 0.20 mg/kg groups. The applicant explained that the urinary excretion of allantoin was higher after the administration of rasburicase compared to baseline.

By 28 days following rasburicase administration, 121 of 133 patients were tested for anti-rasburicase antibodies and 2 of 12 patients in the rasburicase 0.15 mg/kg group and 15 of 109 patients in the rasburicase 0.20 mg/kg group had positive results.

4.2.A.2).(3) Foreign phase II study (Study ACT2511; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])

Rasburicase 0.15 mg/kg was intravenously administered once daily for 5 to 7 days to 107 pediatric and adult patients with leukemia or malignant lymphoma (10 pediatric patients included in PK analysis). Plasma rasburicase concentrations, plasma uric acid levels, urine allantoin levels, and the incidence of anti-rasburicase antibodies were determined.

Concerning the PD of rasburicase, the applicant explained that plasma uric acid levels and urine allantoin over time were similar to those in Study ACT2694.

By 28 days following rasburicase administration, 97 of 107 patients were tested for anti-rasburicase antibodies and 7 patients had positive results.

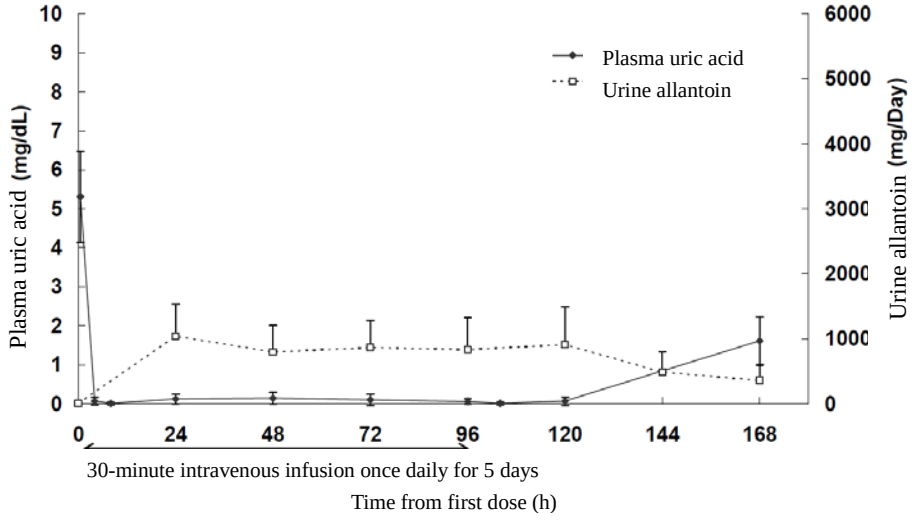
4.2.A.3) Adult cancer patients

4.2.A.3).(1) Japanese phase II study (Study ARD5290; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Rasburicase 0.15 or 0.20 mg/kg was intravenously administered once daily for 5 days to 50 adult patients with leukemia or malignant lymphoma (21 patients included in PK analysis). Plasma rasburicase concentrations, plasma uric acid levels, urine allantoin levels, and the incidence of anti-rasburicase antibodies were determined.

Concerning the PK of rasburicase, the applicant discussed that the trough concentrations (C_{min}) from Day 2 to Day 5 indicated that a steady-state had been reached by Day 2.

Concerning the PD of rasburicase, plasma uric acid levels declined within 4 hours after the initiation of rasburicase and remained low until 24 hours after the last dose in both the 0.15 and 0.20 mg/kg groups. Plasma uric acid levels and urine allantoin over time were as shown in the following figure and the applicant explained that the urinary excretion of allantoin was higher after the administration of rasburicase compared to baseline.



Plasma uric acid levels and urinary excretion of allantoin over time in Japanese adult patients treated with rasburicase (0.20 mg/kg) for 5 days

Anti-rasburicase antibodies were positive in 0 of 25 patients in the 0.15 mg/kg group and 0 of 24 patients in the 0.20 mg/kg group at 8 days after the initiation of rasburicase and in 2 of 25 patients in the 0.15 mg/kg group and 3 of 25 patients in the 0.20 mg/kg group at 29 days. Among the 2 patients in the 0.15 mg/kg group and 3 patients in the 0.20 mg/kg group who were tested positive at 29 days, 2 patients in the 0.20 mg/kg group had positive antibodies at 6 months, of whom 1 patient became negative at 1 year and the other patient was lost to follow-up.

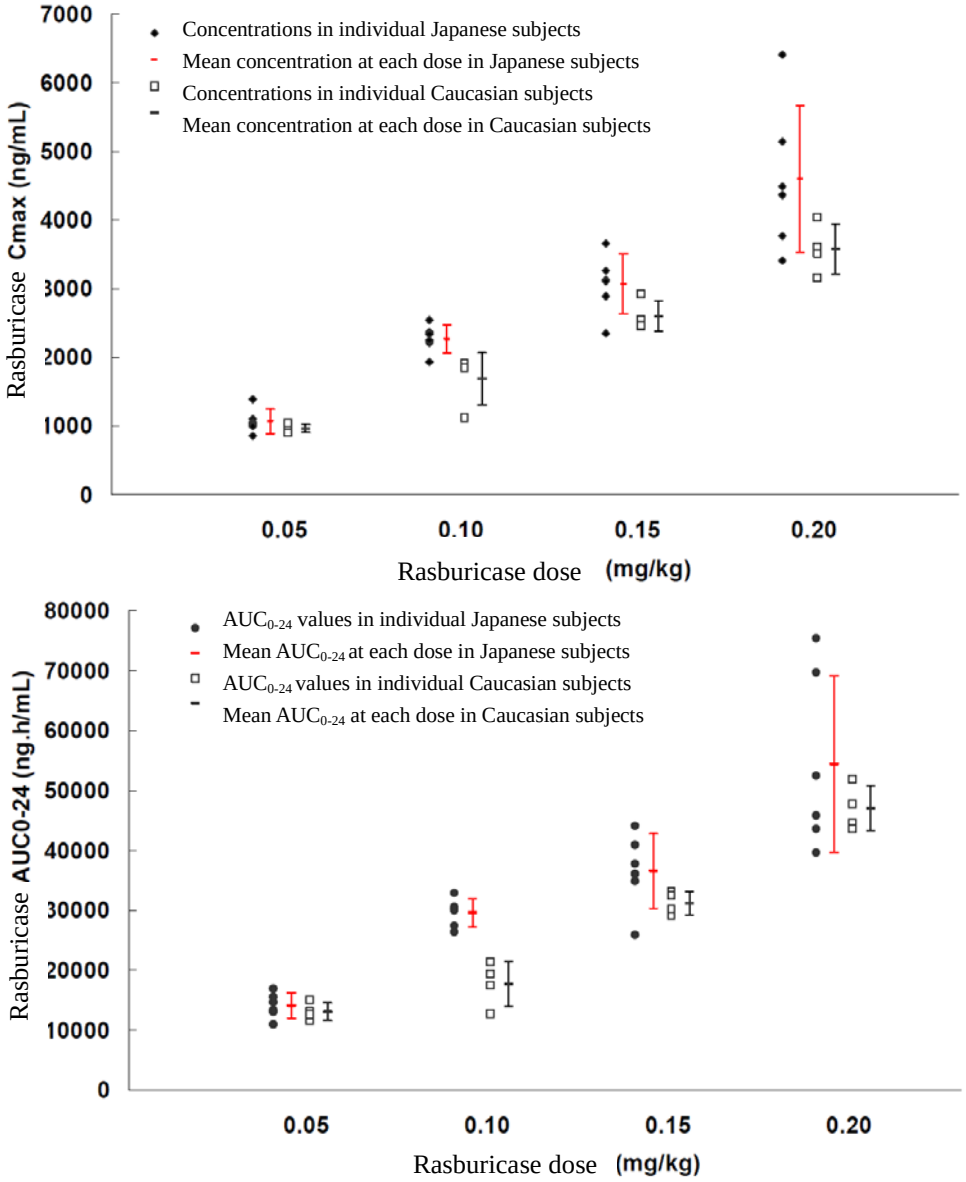
4.2.A.3).(2) Foreign PK study (Study PKM6638; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Rasburicase 0.15 or 0.20 mg/kg was administered for 5 days to 25 adult patients with leukemia or malignant lymphoma. Plasma rasburicase concentrations and plasma uric acid levels were determined.

Concerning the PD of rasburicase, the applicant explained that plasma uric acid levels rapidly declined after the initiation of rasburicase and remained low until 24 hours after the last dose in both the 0.15 and 0.20 mg/kg groups.

4.2.A.3).(3) Foreign phase III study (Study EFC4978; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])
Adult patients with leukemia, malignant lymphoma, or solid tumor malignancies were to receive (a) 0.20 mg/kg of rasburicase for 5 days (rasburicase group), (b) 0.20 mg/kg of rasburicase from Day 1 through Day 3 followed by 300 mg of oral allopurinol from Day 3 through Day 5 (rasburicase/allopurinol group), or (c) 300 mg of oral allopurinol for 5 days (allopurinol group). The PK of rasburicase were determined in 8 patients in the rasburicase group.

4.2.A.4) Discussion on PK and PD in Japanese and foreign subjects
4.2.A.4).(1) Healthy adult subjects
The single-dose C_{max} and AUC_{0-24} of rasburicase increased dose-dependently in Japanese and foreign healthy adult subjects (the figure below).



Relationship between single-dose C_{max} (top) or AUC_{0-24} (bottom) and dose of rasburicase in Japanese and foreign healthy adult subjects

The ratios of PK parameters of rasburicase (Japanese/foreign subjects) are presented in the following table. The applicant discussed that although C_{max}, $t_{1/2Z}$, and AUC_{inf} and AUC_{0-24} at 0.10 mg/kg were higher in Japanese subjects, as the differences between Japanese and foreign subjects were small for AUC_{inf}, AUC_{0-24}, and CL at the doses other than 0.10 mg/kg, the observed racial differences in the PK parameters are of little clinical relevance.

Single-dose PK parameters of rasburicase in Japanese and foreign subjects

Dose (mg/kg)	Japanese subjects/foreign subjects ratio [90% CI]			
	0.05	0.10	0.15	0.20
C_{max} *1	1.22 [1.12, 1.33]			
AUC_{inf} *2	1.06 [0.87, 1.29]	1.71 [1.41, 2.09]	1.12 [0.92, 1.36]	1.11 [0.91, 1.35]
AUC_{0-24} *2	1.07 [0.89, 1.29]	1.69 [1.41, 2.03]	1.16 [0.97, 1.39]	1.13 [0.94, 1.35]
$t_{1/2z}$ *1	1.24 [1.16, 1.32]			
V_z *2	1.31 [1.07, 1.60]	0.70 [0.57, 0.86]	1.02 [0.83, 1.25]	1.12 [0.91, 1.37]
CL *2	0.94 [0.77, 1.15]	0.59 [0.48, 0.72]	0.90 [0.74, 1.09]	0.90 [0.74, 1.10]

*1: As the dose-by-race interaction was not significant, the data from all dose groups were pooled for analysis.
*2: The dose-by-race interaction was significant (two-way ANOVA, $P < 0.05$).
Japanese subjects (n = 6), foreign subjects (n = 4)

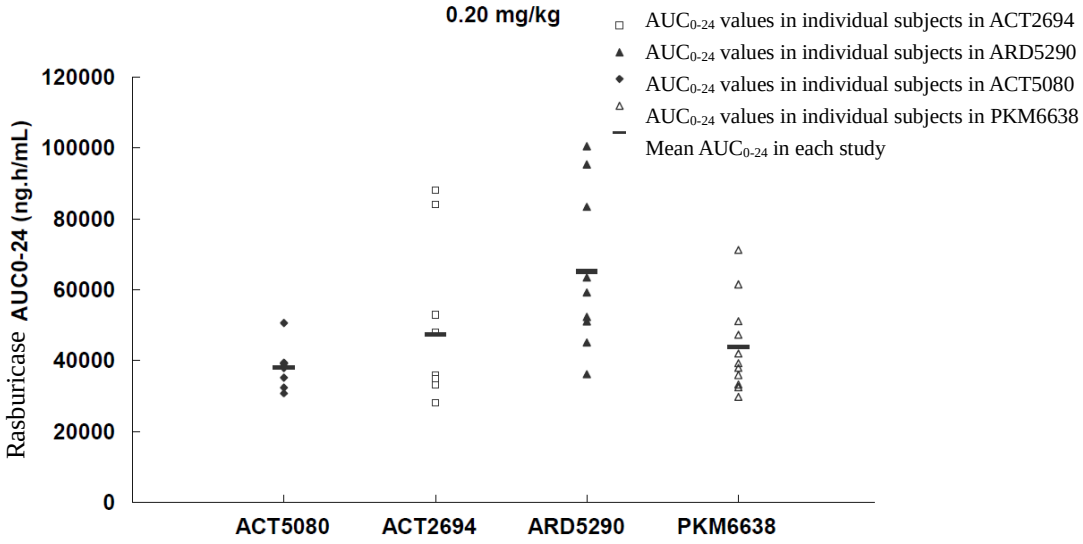
4.2.A.4).(2) Cancer patients

PK parameters, the distribution of AUC_{0-24} values, and plasma uric acid levels over time in Japanese and foreign patients with hematological malignancies administered 0.15 or 0.20 mg/kg of rasburicase once daily for 5 days were as follows. The applicant discussed that AUC_{0-24} values and plasma uric acid levels over time showed that the PK and PD of rasburicase are almost similar between Japanese and foreign patients.

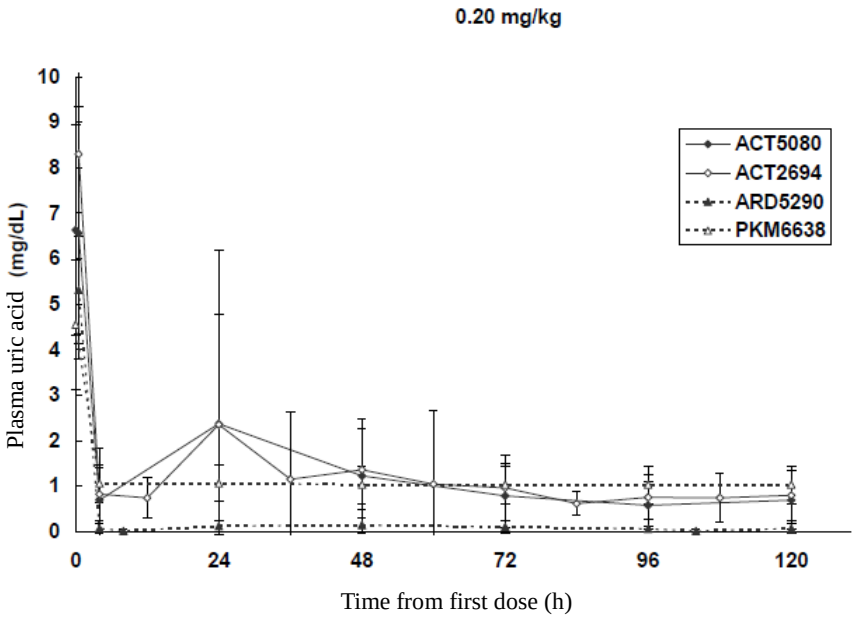
PK parameters in Japanese and foreign patients administered 0.15 or 0.20 mg/kg of rasburicase once daily for 5 days (Japanese children in Study ACT5080, Japanese adults in Study ARD5290, foreign children in Studies ACT2511 and ACT2694, foreign adults in Study PKM6638)

Study	Dose (mg/kg)	Day 1		Day 5		$t_{1/2Z}$ (h)
		C_{eoi} (ng/mL)	AUC_{0-24} (ng·h/mL)	C_{eoi} (ng/mL)	AUC_{0-24} (ng·h/mL)	
ACT5080	0.15	2160 ± 512	28200 ± 7270	2490 ± 373	29700 ± 6460	11.6 ± 4.96*1
	(n)	(10)	(10)	(10)	(10)	(10)
	0.20	2580 ± 432	31500 ± 4540	3050 ± 383	38100 ± 5640	11.2 ± 3.06*1
	(n)	(10)	(9)	(9)	(9)	(9)
ACT2694	0.15	3130 ± 787	32900 ± 8540	3360 ± 390	34400 ± 9050	16.0 ± 6.34*2
	(n)	(11)	(11)	(10)	(9)	(8)
	0.20	3880 ± 1020	45200 ± 18900	4500 ± 1150	47300 ± 21700	21.1 ± 12.0*2
	(n)	(19)	(18)	(15)	(10)	(14)
ACT2511	0.15	2790 ± 729	28000 ± 7520	3500 ± 792	31700 ± 6630	17.4 ± 3.95*2
	(n)	(10)	(9)	(10)	(10)	(7)
ARD5290	0.15	3734 ± 1081	45653 ± 7544	3948 ± 710	48210 ± 9660	22.5 ± 5.8*1
	(n)	(11)	(11)	(11)	(11)	(11)
	0.20	4239 ± 1556	59333 ± 15849	5126 ± 1468	65154 ± 22713	16.1 ± 5.6*1
	(n)	(10)	(10)	(9)	(9)	(9)
PKM6638	0.15	2280 ± 652	30700 ± 10900	2200 ± 815	33400 ± 10100	15.7 ± 6.71*1
	(n)	(13)	(12)	(9)	(9)	(9)
	0.20	2630 ± 1200	39300 ± 9840	3100 ± 970	43800 ± 13000	19.7 ± 5.37*1
	(n)	(12)	(12)	(11)	(11)	(11)

Mean ± SD, C_{eoi}: Plasma concentration at the end of an intravenous infusion
*1: Values on Day 5, *2: Values on Day 5, 6, or 7



Distribution of AUC_{0-24} values on Day 5 in Japanese and foreign patients administered rasburicase (0.20 mg/kg) once daily for 5 days (Japanese children in Study ACT5080, Japanese adults in Study ARD5290, foreign children in Study ACT2694, foreign adults in Study PKM6638)



Plasma uric acid levels over time in Japanese and foreign patients administered rasburicase (0.20 mg/kg) once daily for 5 days (Japanese children in Study ACT5080, Japanese adults in Study ARD5290, foreign children in Study ACT2694, foreign adults in Study PKM6638)

4.2.A.5) The applicant's discussion on the PK of rasburicase and background factors

The applicant explained as follows:

Based on the data from Japanese and foreign clinical studies in patients with hematological malignancies (ACT5080, ARD5290, ACT2511, ACT2694, PKM6638), the effects of background factors on the PK of rasburicase were examined. As a result, as there were no apparent effects of the background factors of age, body weight, gender, abnormal renal function tests, and abnormal liver function tests on the PK parameter (AUC_{0-24}), dose adjustment based on these background factors is not required.

4.2.B Outline of the review by PMDA

4.2.B.1) PK and PD of rasburicase in Japanese and foreign subjects

The applicant explained that the PK parameters and PD of rasburicase are almost similar between Japanese and foreign subjects [see "4.2.A.4) Discussion on PK and PD in Japanese and foreign subjects"].

PMDA's view on the PK and PD (plasma uric acid levels over time) of rasburicase in Japanese and foreign subjects is as follows:
In pediatric cancer patients, there were no apparent differences in AUC_{0-24} between Japanese and foreign patients and plasma uric acid levels over time were similar between Japanese and foreign patients.

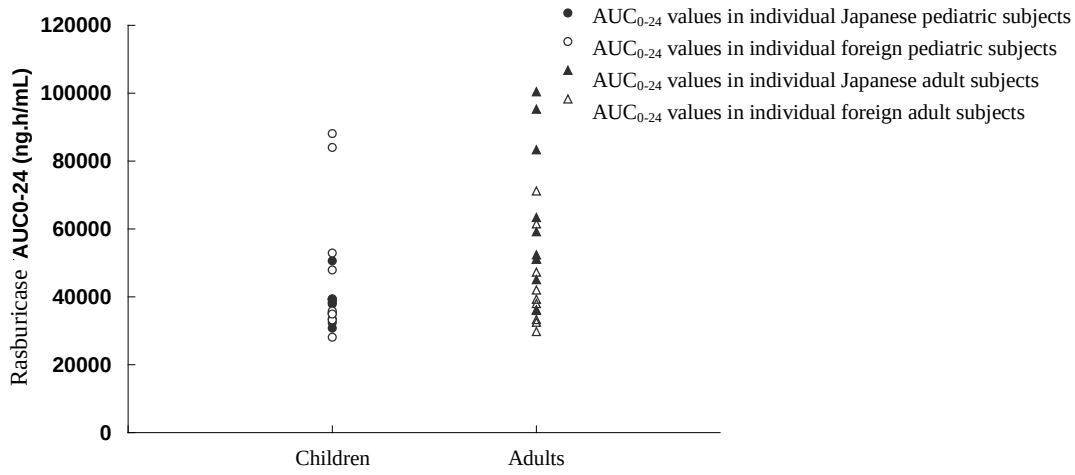
In adult cancer patients, AUC_{0-24} tended to be higher in Japanese patients than in foreign patients. In Japanese patients with a trend towards higher AUC_{0-24}, plasma uric acid levels remained lower throughout the treatment period compared with foreign patients. In both Japanese and foreign patients, plasma uric acid levels were kept far below the efficacy threshold used for clinical studies. In healthy adults, although AUC_{inf} at 0.10 mg/kg tended to be higher in Japanese subjects than in foreign subjects, as this trend was not consistent with the results in other dose groups (0.05, 0.15, 0.20 mg/kg), there should be no apparent differences between Japanese and foreign subjects. Based on the above, there have been no marked differences in the PK and PD of rasburicase between Japanese and foreign subjects, in both children and adults.

4.2.B.2) PK and PD of rasburicase in children and adults

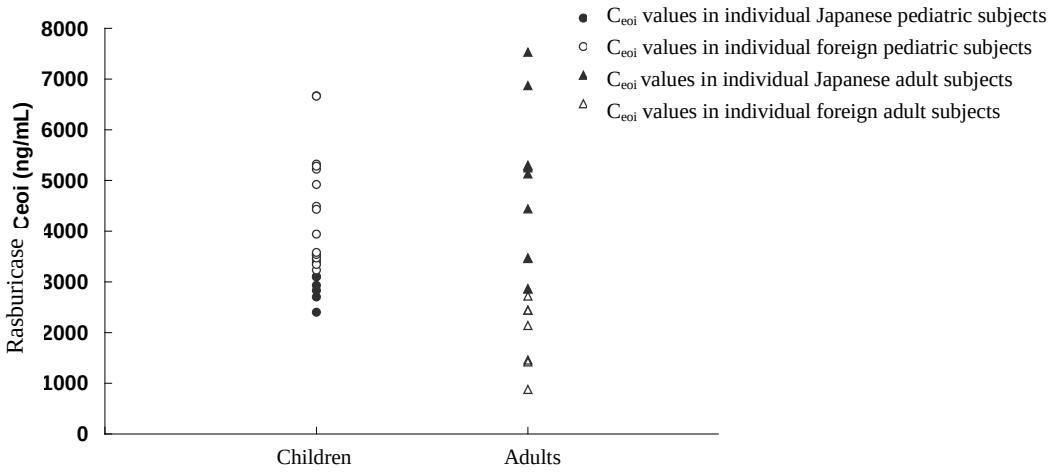
Comparisons of the PK of rasburicase between children and adults have been discussed based only on AUC_{0-24}.

PMDA asked the applicant to discuss PK and PD differences between children and adults, taking also account of the results of comparisons of PK parameters other than AUC_{0-24} and plasma uric acid levels over time, etc.

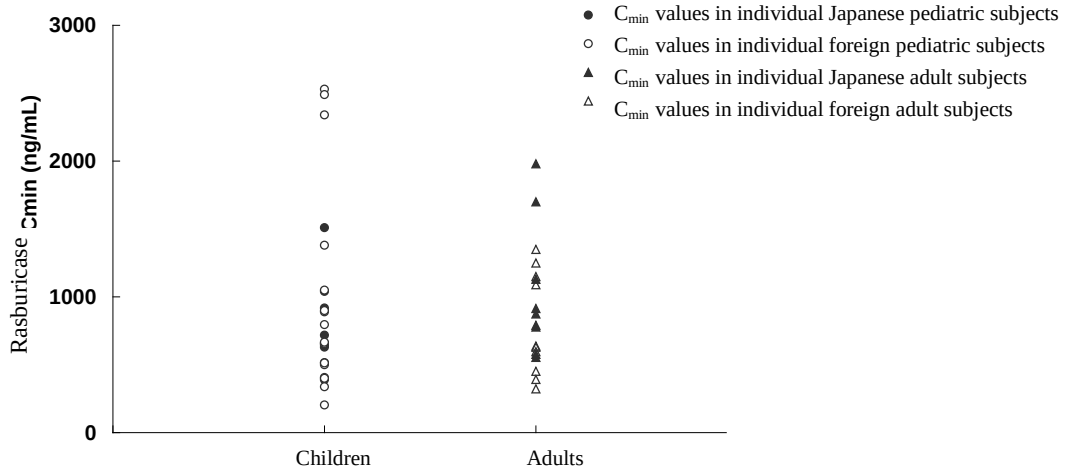
The applicant responded as follows:
Based on the results from Studies ACT5080 (Japanese children), ARD5290 (Japanese adults), ACT2694 (foreign children), and PKM6638 (foreign adults), the distributions of AUC_{0-24}, C_{eoi}, and C_{min} values on Day 5 (considered to have reached a steady-state) were compared (the figures below). As a result, the variation range of each PK parameter was similar between children and adults. Plasma rasburicase concentrations over time in individual subjects were also similar between children and adults, i.e. slow elimination after an intravenous infusion.



$AUC_{0\text{-}24}$ on Day 5 (rasburicase 0.20 mg/kg) in children and adults



C_{eoi} on Day 5 (rasburicase 0.20 mg/kg) in children and adults



C_{min} on Day 5 (rasburicase 0.20 mg/kg) in children and adults

The PD endpoint of plasma uric acid levels remained low from 4 hours after the first dose until 24 hours after the last dose (Day 5) in both children and adults as shown in the figure in "4.2.A.4)(2) Cancer patients," although the plasma uric acid levels in Japanese adults (Study ARD5290) remained even slightly lower than those in other studies at 0.20 mg/kg.

The above results indicate that there are no PK or PD differences between children and adults.

PMDA considers as follows:
In the foreign population, there have been no apparent differences in PK or PD (plasma uric acid levels over time) between pediatric and adult cancer patients. In the Japanese population, $AUC_{0\text{-}24}$ tended to be higher in adults than in children. Although plasma uric acid levels remained lower throughout the treatment period in adults compared to children, plasma uric acid levels were kept far below the efficacy threshold used for clinical studies, in both children and adults. Based on the above, there have been no marked differences in the PK or PD of rasburicase between children and adults, in both the Japanese and foreign populations.

Comparisons of the PK and PD of rasburicase between children and adults have so far been assessed with a limited number of patients. Thus, it is also necessary to continue to collect information including publications and appropriately provide information when new findings become available.

4.2.B.3) Effects of anti-rasburicase antibodies on PK
In Studies PKM6638 and EFC4978, antibody assay was to be performed after a quantitative assay for anti-rasburicase antibodies was established. The results of anti-rasburicase antibody assay in these studies submitted after filing the application were as follows.

In Study PKM6638, anti-rasburicase antibody production was assessed up to 6 months after rasburicase administration in 12 patients each in the 0.15 and 0.20 mg/kg groups. No anti-rasburicase antibodies were detected in the 0.15 mg/kg group. In the 0.20 mg/kg group, 2 patients developed IgG antibodies and 1 patient developed neutralizing antibodies. In Study EFC4978, anti-rasburicase antibody production was assessed up to 18 months after rasburicase administration in 91 patients in the rasburicase group, 91 patients in the rasburicase/allopurinol

group, and 90 patients in the allopurinol group. Neutralizing antibodies were detected in 2 patients in the rasburicase group, IgG antibodies and neutralizing antibodies were detected in 8 patients and 3 patients, respectively, in the rasburicase/allopurinol group, and IgG antibodies and neutralizing antibodies were detected in 2 patients each in the allopurinol group.

PMDA asked the applicant to explain the possible effects of anti-rasburicase antibodies on the PK of rasburicase.

The applicant responded as follows:
Anti-rasburicase antibody production was assessed within 1 week after the initiation of rasburicase in Japanese study TDU4730 and foreign study TDR2681 (multiple dosing) involving healthy adult subjects and Study ARD5290 involving Japanese adult patients and 0 of 24 subjects, 1 of 12 subjects, and 0 of 49 subjects, respectively, were tested positive for antibodies within 1 week after the initiation of rasburicase. In these studies and other studies involving healthy adult subjects or patients, the time to detection of anti-rasburicase antibodies was about 2 weeks or more after the initiation of rasburicase. Among 26 patients in Studies PKM6638 and EFC4978, CL_{SS} was compared between anti-rasburicase antibody positive cases (quantitative assay [2 patients], qualitative assay [2 patients]) and negative cases (22 patients). As a result, the distribution of CL_{SS} was similar between the two groups. Based on the above, anti-rasburicase antibodies are unlikely to affect the PK of rasburicase during treatment with rasburicase (about 5 days).

PMDA considers as follows:
Because anti-rasburicase antibodies were detected in a limited number of subjects during the PK assessment period, the submitted study results have not defined the relationship between anti-rasburicase antibodies and the PK of rasburicase. A relatively higher incidence of anti-rasburicase antibodies has been reported at $\geq$ 2 weeks after the initiation of rasburicase, but in clinical practice, rasburicase may be readministered after 2 weeks from the drug initiation. Thus, patients should be selected for rasburicase retreatment, taking also account of the presence or absence of anti-rasburicase antibodies.

4.3 Clinical efficacy and safety

4.3.A Summary of the submitted data

As the efficacy and safety evaluation data, the results from a total of 14 studies including 3 Japanese clinical studies and 11 foreign clinical studies were submitted. As the reference data, the results from 1 foreign clinical study were submitted.

List of clinical studies

Category *		Region	Study	Phase	Study population	Age	No. of subjects treated† (N)	Dosage and dose regimen	Main endpoints
Efficacy	Safety								
—	○	Japan	TDU4730	I	Healthy adult male subjects	≥ 20 years and ≤ 35 years	32	Single dose of placebo or rasburicase 0.05, 0.10, 0.15, 0.20 mg/kg	Safety, PK, Antibodies, Uricolytic activity
○	○		ACT5080	II	Newly diagnosed hematological malignancies at high risk for TLS	< 18 years	30	0.15 or 0.20 mg/kg once daily for 5 days	Efficacy, Safety, PK, Antibodies
○	○		ARD5290	II	Newly diagnosed or relapsed malignant lymphoma or acute leukemia	≥ 18 years and < 75 years	50	0.15 or 0.20 mg/kg once daily for 5 days	Efficacy, Safety, PK, Antibodies
—	○	Overseas	TDR2681	I	Healthy adult male subjects	≥ 18 years and ≤ 35 years	28	Single dose: 0.05, 0.10, 0.15, 0.20 mg/kg Multiple doses: 0.10, 0.15, 0.20 mg/kg, once daily for 5 days	Safety, PK, Antibodies
○	○		ACT2694	II	Malignant lymphoma or leukemia	≤ 21 years	131	Dose validation phase: the initial dose of 0.15 mg/kg could be increased to 0.20 or 0.25 mg/kg as needed in an ascending-dose scheme Accrual phase: the dose that was effective in 14 consecutive patients in the dose validation phase (If needed, dosing every 12 hours was permitted during the first 48 hours of chemotherapy), for 5-7 days	Efficacy, Safety, PK, Antibodies
○	○		ACT2511	II	Malignant lymphoma or leukemia	No age limits	107	Dose validation phase: the initial dose of 0.15 mg/kg could be increased to 0.20 or 0.25 mg/kg as needed in an ascending-dose scheme Accrual phase: the dose that was effective in 14 consecutive patients in the dose validation phase (If needed, dosing every 12 hours was permitted during the first 48 hours of chemotherapy), for 5-7 days	Efficacy, Safety, PK, Antibodies
○	○		EFC2975	III	Malignant lymphoma or leukemia	≤ 21 years	52	Rasburicase: 0.20 mg/kg once daily for 5-7 days (If hyperuricemia persisted or the patient was at risk of TLS, dosing every 12 hours was permitted during the first 48-72 hours of chemotherapy) Allopurinol: 100-800 mg (according to standard medical practice) orally administered for 5-7 days	Efficacy, Safety, Antibodies
△	○		EFC4982	II	Previously untreated non-Hodgkin's lymphoma	≥ 18 years and < 80 years	100	0.20 mg/kg once daily for 3-7 days (If hyperuricemia persisted or the patient was at risk of TLS, dosing every 12 hours was permitted during the first 72 hours of chemotherapy)	Efficacy, Safety, Antibodies
△	○		EFC4983	II	Relapsing non-Hodgkin's lymphoma	≥ 18 years	33	0.20 mg/kg once daily for 4-7 days (Rasburicase was to be started within 24 hours before initiation of chemotherapy combined with or not with immunotherapy [rituximab] and continued at least during the first 3 days of chemotherapy [4 days in total])	Efficacy, Safety, Antibodies

△	○		EFC5339	IV	Malignant lymphoma /leukemia /solid tumor malignancies at their first relapse or refractory disease	No age limits	94	0.20 mg/kg once daily for 5 days	Efficacy, Safety, Antibodies
△	○		PKM6638	PK study	Leukemia or malignant lymphoma	≥ 18 years	25	0.15 or 0.20 mg/kg once daily for 5 days	Efficacy, Safety, PK, Antibodies
—	○		LTS3025	II	Malignant lymphoma, leukemia, multiple myeloma, or bulky solid tumors	No age limits	82	0.20 mg/kg once daily for 1-7 days (If hyperuricemia persisted or the patient was at risk of TLS, dosing every 12 hours was permitted during the first 72 hours of chemotherapy)	Safety, Antibodies
—	○		LTS3256	Safety study (compassionate use)			278		
—	○		LTS3257				1069		
△	△		EFC4978	III	Leukemia, malignant lymphoma, or solid tumor malignancies at risk for hyperuricemia and TLS	≥ 18 years	275	Rasburicase group: 0.20 mg/kg once daily for 5 days Allopurinol group: 300 mg orally administered for 5 days Rasburicase/allopurinol group: rasburicase from Day 1 through Day 3 followed by allopurinol from Day 3 through Day 5	Efficacy, Safety, PK, Antibodies

*: ○Evaluation data, △Reference data, †: No. of subjects who received at least one dose of study drug, TLS: tumor lysis syndrome

Individual studies are summarized below. The main adverse events excluding deaths observed in individual clinical studies are presented in "4.4 Adverse events observed in clinical studies" and PK and PD results are presented in "4.1 Biopharmaceutic studies" or "4.2 Clinical pharmacology studies."

Japanese clinical studies

1) Japanese phase I study (Study TDU4730; Publication, None; Studied period, [redacted] to [redacted] 20[redacted])

An open-label study was conducted at a single center in Japan to evaluate the PK, PD, safety, and tolerability of single ascending doses of rasburicase in healthy adult male subjects aged between 20 and 35 years (target number of cases of 32).

A single dose of 0.05, 0.10, 0.15, or 0.20 mg/kg of rasburicase was to be intravenously administered over 30 minutes.

All of 32 subjects enrolled into this study (8 subjects in the placebo group, 6 subjects each in the rasburicase 0.05 mg/kg, 0.10 mg/kg, 0.15 mg/kg, and 0.20 mg/kg groups) received study drug and were included in the safety analysis.

Regarding safety, there were no deaths reported during the study period.

Based on the results of safety analysis, it was concluded that the tolerability of single doses of 0.05 to 0.20 mg/kg of rasburicase (as a 30-minute intravenous infusion) in Japanese healthy adult male subjects was demonstrated.

2) Japanese phase II study (Study ACT5080; Publication, None; Studied period, June 2005 to April 2006)

A multicenter, open-label, randomized study was conducted at 21 centers in Japan to evaluate the efficacy and safety of rasburicase in patients aged < 18 years with newly diagnosed

hematological malignancies presenting with hyperuricemia (> 7.5 mg/dL in patients aged ≥ 13 years; > 6.5 mg/dL in patients aged < 13 years) or newly diagnosed hematological malignancies presenting with high tumor burden [Note 1] (target number of cases of 30).

Rasburicase 0.15 or 0.20 mg/kg was to be intravenously administered over 25 to 35 minutes once daily for 5 days.

Of 31 subjects enrolled into this study, 30 subjects excluding 1 subject who did not meet the inclusion criteria were randomized and received rasburicase (15 subjects per group) and were included in the efficacy and safety analyses.

The primary efficacy endpoint was the proportion of responders among subjects who received at least one dose of rasburicase (the response rate) and subjects were classified as "responders" if the plasma uric acid endpoint (≤ 7.5 mg/dL in patients aged ≥ 13 years; ≤ 6.5 mg/dL in patients aged < 13 years) was achieved within 48 hours from the initiation of rasburicase and maintained until 24 hours after the last administration of rasburicase. Subjects who did not complete a 5-day treatment for reasons other than hyperuricemia were classified as unevaluable cases and were not included in the calculation of the response rate.

The response rate was 93.3% (14 of 15 subjects) [95% CI, 68.1-99.8] in the 0.15 mg/kg group and 100% (14 of 14 subjects) [95% CI, 76.8-100.0] in the 0.20 mg/kg group. One subject in the 0.20 mg/kg group was classified as an unevaluable case as this subject was found to meet the withdrawal criteria after receiving the first dose (the subject had not met the inclusion criterion regarding white blood cell count at baseline) and withdrawn from the study.

Regarding safety, there were no deaths reported during the study period (up to 33 days after the last dose of rasburicase). One subject in the 0.15 mg/kg group died after being withdrawn from the study. This subject was a 15-year-old patient with acute leukemia who developed brain herniation, brain oedema, and cerebral haemorrhage on Day 3 of rasburicase treatment. The subject was withdrawn from the study for ethical considerations (the absence of brainstem reflexes was confirmed) at 3 days after the completion of the 5-day treatment period and died 6 days later (14 days after the initiation of rasburicase). A causal relationship to study drug was denied for all events.

Note 1:
(a) Clinical Stage IV (adapted from Murphy classification) non-Hodgkin's lymphoma (NHL), (b) Clinical Stage III (adapted from Murphy classification) NHL with at least one lymph node or mass > 5 cm in diameter or LDH ≥ 3 times the upper limit of normal, (c) Acute leukemia with a peripheral white blood cell count ≥ 50 000/mm^3 or LDH ≥ 3 times the upper limit of normal

3) Japanese phase II study (Study ARD5290; Publication, None; Studied period, April 2003 to June 2004)
A multicenter, open-label, randomized study was conducted at 8 centers in Japan to evaluate the efficacy and safety of rasburicase in patients aged ≥ 18 and < 75 years with newly diagnosed or relapsed malignant lymphoma or acute leukemia [Note 2] (target number of cases of 50). In this study, hyperuricemia was defined as a plasma uric acid concentration of ≥ 8.0 mg/dL.

Rasburicase 0.15 or 0.20 mg/kg was to be intravenously administered over 30 minutes once daily for 5 days.

All of 50 subjects enrolled into this study were randomized and received rasburicase (25 subjects per group) and were included in the efficacy and safety analyses.

The primary efficacy endpoint was the response rate, which was defined in the same manner as that of Japanese Study ACT5080. Subjects who did not complete a 5-day treatment were to be classified as nonresponders.

The response rate was 100% (25 of 25 subjects) [95% CI, 86.3-100.0] in the 0.15 mg/kg group and 96.0% (24 of 25 subjects) [95%CI, 79.6-99.9] in the 0.20 mg/kg group. One subject in the 0.20 mg/kg group was classified as a nonresponder because the subject was withdrawn from the study due to the occurrence of a serious adverse event (hepatic enzyme increased) before completing the 5-day treatment.

Regarding safety, there were no deaths reported during the study period (up to 33 days after the last dose of rasburicase).

Note 2:
(a) Acute leukemia with a peripheral white blood cell count ≥ 20 000/mm^3, (b) Clinical Stage ≥ III (the Ann Arbor staging system with Cotswolds modifications) malignant lymphoma or Clinical Stage ≥ II malignant lymphoma with bulky disease (a nodal mass ≥ 10 cm in maximum dimension or a mediastinal mass with a maximum width > one-third of the internal transverse diameter of the thorax at the level of T5/6 interspace), (c) Malignant lymphoma or acute leukemia, without regard to classification or morphology, with a uric acid level ≥ 8.0 mg/dL and LDH ≥ twice the upper limit of normal

Foreign clinical studies

1) Foreign phase I study (Study TDR2681; Publication, *Proc Am Assoc Cancer Res* 1996; 37: 214 [abstract]; Studied period, [redacted] to [redacted] 19[redacted])

All of 28 foreign healthy adult male subjects enrolled into this study (a single dose, 16 subjects; multiple doses, 12 subjects) received rasburicase and there were no deaths reported during the study period.

2) Foreign phase II study (Study ACT2694; Publication, *Blood* 1998; 92 (Supple 1): 1998; Studied period, March 1996 to October 1997)

A multicenter, open-label study was conducted at 22 centers overseas to evaluate the efficacy and safety of rasburicase in patients aged ≤ 21 years with leukemia or malignant lymphoma with large systemic tumor burden and at risk for hyperuricemia induced by either malignancy or chemotherapy[Note 3] (target number of cases of ≥ 90 [≥ 14 cases for the dose validation phase, ≥ 76 cases for the accrual phase]). In this study, hyperuricemia was defined as a serum or plasma uric acid concentration of > 8 mg/dL.

Rasburicase was to be intravenously administered over 30 minutes for 5 to 7 days. In the dose validation phase, the initial dose of 0.15 mg/kg was to be increased to 0.20 mg/kg and then to 0.25 mg/kg in an ascending-dose scheme (the dose was to be increased unless 14 consecutive patients responded to treatment). The dose that was effective in 14 consecutive patients in the dose validation phase was to be selected for the accrual phase. The duration of treatment depended on each patient's clinical status. If needed, dosing every 12 hours was permitted during the first 48 hours of chemotherapy.

In the dose validation phase, 12 patients received rasburicase in the 0.15 mg/kg group. As 1 patient was a nonresponder, the dose was increased to 0.20 mg/kg according to the ascending-dose scheme. In the 0.20 mg/kg group, all of 22 enrolled patients received rasburicase. Excluding 1 patient withdrawn from the study due to adverse events (bronchospasm and dyspnoea for which a causal relationship to rasburicase could not be denied) after receiving

the first dose of rasburicase and 1 patient who died (respiratory depression for which a causal relationship to rasburicase was denied) after receiving rasburicase for 5 days, 20 patients were included in analyses and the effective dose was determined to be 0.20 mg/kg. A total of 98 patients were enrolled in the accrual phase and 87 patients excluding 11 unevaluable patients were included in analyses.

Patients were classified as "responders" if the plasma uric acid endpoint (≤ 6.5 mg/dL in patients aged < 13 years, ≤ 7.5 mg/dL in patients aged ≥ 13 years) was achieved within 48 ± 2 hours from the initiation of rasburicase and maintained until 24 hours after the last administration of rasburicase and no other antihyperuricemic agent was needed to achieve this endpoint. The primary efficacy endpoint was the plasma uric acid response rate (the proportion of responders in the efficacy analysis population). The efficacy results were as shown in the following table.

Efficacy results

	Dose	Response rate [n/N (%)]
Dose validation phase	0.15 mg/kg	11/12 (91.7)
	0.20 mg/kg	19/20 (95.0)
Accrual phase	0.20 mg/kg	83/87 (95.4)

Regarding safety, there were 2 deaths (1 case of respiratory depression, 1 case of fungal pneumonia) reported during the study period (up to 28 days after the initiation of rasburicase), but a causal relationship to study drug was denied for both cases.

Note 3:
(a) Clinical Stage ≥ III small non-cleaved cell (Burkitt's or non-Burkitt's type) NHL, (b) B-cell leukemia of Burkitt's type (L3 morphology according to the FAB classification), (c) Acute lymphocytic leukemia (ALL) with a white blood cell count ≥ 50 000/mm^3, (d) ALL with clinical, radiological, and laboratory evidence of a large systemic tumor burden that is considered by the investigator to be at risk for severe hyperuricemia during tumor lysis, without regard to white blood cell count, (e) Clinical Stage ≥ III lymphoblastic lymphoma with clinical, radiological, and laboratory evidence of a large systemic tumor burden that is considered by the investigator to be at risk for severe hyperuricemia during tumor lysis, (f) Malignant lymphoma or leukemia, without regard to classification or morphology, with a uric acid level ≥ 8.0 mg/dL and creatinine or LDH ≥ twice the upper limit of normal

3) Foreign phase II study (Study ACT2511; Publication, *Proc Am Assoc Cancer Res* 1997; 38: 223; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])
A multicenter, open-label study was conducted at 12 centers overseas to evaluate the efficacy and safety of rasburicase in patients at risk for hyperuricemia induced by either malignancy ((a) Clinical Stage ≥ III non-Hodgkin's lymphoma [NHL], (b) Clinical Stage ≥ II NHL with LDH ≥ twice the upper limit of normal or a mass ≥ 10 cm in diameter, (c) Acute lymphocytic leukemia [ALL], (d) Acute nonlymphocytic leukemia) or chemotherapy (target number of cases of 90 [14 cases for the dose validation phase, 76 cases for the accrual phase]).

The same dosage and dose regimen as for Study ACT2694 was chosen.

The ascending-dose scheme in the dose validation phase was also the same as for Study ACT2694. As all of 20 patients enrolled in the dose validation phase received and responded to 0.15 mg/kg of rasburicase, 0.15 mg/kg was selected for the accrual phase. In the accrual phase, 87 of 88 enrolled patients received at least one dose of rasburicase and 84 patients excluding unevaluable patients were included in the efficacy analysis.

The primary efficacy endpoint was the plasma uric acid response rate (the proportion of responders in the efficacy analysis population; the definition of responders was the same as for Study ACT2694) and the efficacy results were as shown in the following table. Three unevaluable patients were excluded.

Efficacy results

Dose group		Response rate [n/N (%)]
Dose validation phase	0.15 mg/kg	20/20（100）
Accrual phase	0.15 mg/kg	83/84（98.8）
Total		103/104（99.0）

Regarding safety, there were 3 deaths (1 case of pneumonia, 1 case of acute renal failure/ pulmonary oedema, 1 case of abdominal pain) reported during the study period (up to 28 days after the initiation of rasburicase). A causal relationship to study drug could not be denied for the case of acute renal failure/pulmonary oedema only.

4) Foreign phase III study (Study EFC2975; Publication, *Blood* 1998; 92 (Supple 1): 680a. Abstract 2801; Studied period, November 1996 to December 1997)

A multicenter, randomized, open-label, comparative study was conducted at 6 centers overseas to evaluate the efficacy and safety of rasburicase in patients aged ≤ 21 years with leukemia or malignant lymphoma ((a) Clinical Stage ≥ III NHL, (b) ALL with a white blood cell count≥ 25000/mm^3, (c) Leukemia or malignant lymphoma with a baseline serum uric acid level ≥ 8.0 mg/dL) (target number of cases of 50 [25 cases in the rasburicase group, 25 cases in the allopurinol group]). In this study, hyperuricemia was defined as a serum or plasma uric acid level of ≥ 8.0 mg/dL.

Rasburicase 0.20 mg/kg was to be intravenously administered over 30 minutes once daily in the rasburicase group. In the allopurinol group, allopurinol was to be orally administered daily according to standard medical practice or in-hospital chemotherapy plan (according to the US labeling, the minimum effective dosage was 100 to 200 mg daily and the maximal recommended dosage was 800 mg daily). The duration of treatment was 5 to 7 days in both groups.

Fifty-two patients enrolled into this study (27 patients in the rasburicase group, 25 patients in the allopurinol group) were included in the intent-to treat (ITT) population for efficacy analysis. All of the 52 patients received study drug and were included in the safety analysis.

The primary efficacy endpoint for the study, i.e. the plasma uric acid $AUC_{0\text{-}96}$ (the area under the curve of the serial plasma uric acid levels from the start of study drug until 96 hours) was 128.1 ± 70.3 mg·h/dL in the rasburicase group and 328.5 ± 129.3 mg·h/dL in the allopurinol group (one way analysis of variance, $P < 0.0001$).

Regarding safety, 2 patients in the allopurinol group died (1 case of meningitis/sepsis/cerebral haemorrhage/coagulation disorder/brain herniation/brain oedema, 1 case of intracranial haemorrhage) during the study period (up to 14 days after the initiation of rasburicase), but a causal relationship to study drug was denied for both cases.

5) Foreign phase II study (Study EFC4982; Publication, *J Clin Oncol* 2003; 21: 4402-6; Studied period, May 2001 to ■ 2002)

A multicenter, open-label study was conducted at 14 centers overseas to evaluate the efficacy (the prophylaxis and treatment of hyperuricemia related to tumor lysis syndrome [TLS] and the protection of renal function) and safety of rasburicase in patients aged ≥18 and < 80 years with

previously untreated aggressive NHL (including diffuse large B cell, peripheral T-cell, immunoblastic, Burkitt's type, anaplastic large cell lymphomas, and transformation of indolent lymphomas) at high risk for hyperuricemia (Target number of cases of 100).

Rasburicase 0.20 mg/kg was to be intravenously administered over at least 30 minutes once daily for 3 to 7 days.

The study enrolled 100 patients, of whom 94 patients excluding 6 patients (adverse events [3 patients], death [1 patient], protocol violations [1 patient], others [1 patient]) completed the scheduled treatment. All of the 100 patients were included in the efficacy and safety analyses.

Efficacy analysis showed that all patients including those who were hyperuricemic at baseline had normalized plasma uric acid levels (the table below).

Results of uric acid control

		Hyperuricemic at baseline [n/10 (%)]	Non-hyperuricemic at baseline [n/88 (%)]	Missing [n/2 (%)]	All [n/100 (%)]
Patients with normalized uric acid levels (< 8.0 mg/dL)*	All patients	10 (100)	88 (100)	2 (100)	100 (100)
	Patients treated with rasburicase for at least 3 days	9 (90.0)	85 (96.6)	1 (50.0)	95 (95)

"A complete response" was defined as normalization of uric acid, creatinine, potassium, and phosphorus levels and "a minor response" was defined as normalization of plasma uric acid levels, but no change or worsening of other biochemical parameters. The response rate was 95.0% (95 of 100 patients) (including 91 of 100 patients with "a complete response" [91.0%] and 4 of 100 patients with "a minor response" [4.0%]). However, based on the clinical judgment of the investigator, patients with a normal plasma uric acid level were classified as having "a complete response" even with abnormal values of some of the other biochemical parameters.

Regarding safety, there were 3 deaths during the study period (up to 4 weeks after the last dose of rasburicase) including 1 death during the treatment period (gastrointestinal haemorrhage) and 2 deaths during the follow-up period (4 weeks after the last dose) (1 case of respiratory failure/collapse, 1 case of cardiac failure/marrow hypoplasia). Eight patients died after the follow-up period (the cause of death was unknown except for 1 case of septic shock). A causal relationship to study drug was denied for all deaths.

6) Foreign phase II study (Study EFC4983; Publication, None; Studied period, July 2002 to January 2005)

A multicenter, open-label study was conducted at 14 centers overseas to evaluate the efficacy and safety of rasburicase in 2 populations of patients aged ≥ 18 years, previously treated or not with urate oxidase (pre-treated group and naïve group), with relapsing aggressive NHL and at risk of TLS presenting with hyperuricemia (a plasma uric acid level of ≥ 8 mg/dL) and/or bulky disease (> 5 cm in diameter) (target number of cases of 100).

Rasburicase 0.20 mg/kg was to be intravenously administered over at least 30 minutes once daily for 4 to 7 days.

All of 33 patients enrolled into the study (10 patients in the pre-treated group, 23 patients in the naïve group) received rasburicase and were included in the efficacy and safety analyses.

Patients were classified as "responders" if their plasma uric acid levels obtained during

treatment returned to normal range (< 8 mg/dL) and were maintained during at least 4 consecutive days or until the end of treatment. The response rate was 100% (10 of 10 patients) in the pretreated group and 87.0% (20 of 23 patients) in the naïve group. One failure patient in the naïve group was a responder according to the plasma uric acid criteria (decreased from 411 μmol/L to 0 μmol/L), but was classified as a failure due to elevated creatinine. The other failure patient had a clinically significant decrease in plasma uric acid (decreased from 375 μmol/L to 12 μmol/L) after 3 doses of rasburicase, but was classified as a failure because he was lost to follow-up. One patient in the naïve group was unevaluable due to withdrawal from the study.

Regarding safety, 1 patient in the pre-treated group and 6 patients in the naïve group died during the study period (including the post-follow-up period). Of whom, 1 patient in the pre-treated group and 1 patient in the naïve group (pulmonary alveolar haemorrhage and disease progression, respectively) died during the follow-up period (4 weeks after the last dose), which were both reported to be due to the deterioration of the primary disease, and 5 patients in the naïve group (1 case of cardiac arrest, 1 case of progression of the primary disease, 3 cases of unknown cause) died after the follow-up period. A causal relationship to study drug was denied for all deaths.

The applicant explained as follows:
Although this study was carried out based on a post-marketing commitment with the European Medicines Agency (EMEA), the target accrual of 50 patients per group could not be reached within a 29-month recruitment period ([redacted] 20[redacted] to December 20[redacted]) and taking into account that any major safety problem or a loss of therapeutic effect was not identified, this clinical study was terminated after obtaining agreement from the EMEA as of [redacted], 20[redacted].

7) Foreign phase IV study (Study EFC5339; Publication, None; Studied period, March 2004 to July 2006)
A multicenter, open-label study was conducted at 16 centers overseas to evaluate the efficacy and safety of rasburicase in 2 populations of patients with lymphoma/leukemia/solid tumor malignancies, those previously treated with a uricolytic agent and those not previously treated with a uricolytic agent at their first relapse or refractory disease (target number of cases of 170).

The study population was initially adult patients only (≥ 18 years of age), but the first protocol amendment after the initiation of the study ([redacted], 20[redacted]) allowed the inclusion of children and the inclusion criterion for age was amended.

Rasburicase 0.20 mg/kg was to be intravenously administered over 30 minutes once daily for 5 days. If plasma uric acid levels exceeded 7.5 mg/dL after 5 days of treatment, prolongation of the treatment was allowed to a maximum of 7 days.

All of 94 patients enrolled into the study (9 patients in the pre-treated group, 85 patients in the naïve group) received rasburicase and were included in the efficacy and safety analyses.

Patients were classified as “responders” if their plasma uric acid levels decreased to ≤ 7.5 mg/dL within 48 hours from the initiation of rasburicase and were maintained until 48 hours after the last administration of rasburicase and the proportion of responders (the response rate) was the primary endpoint.

Response rate (mITT population*)

	Pre-treated group			Naïve group		
	Children (N = 6)	Adults (N = 3)	Total (N = 9)	Children (N = 10)	Adults (N = 75)	Total (N = 85)
Responders (Response rate, n (%) [95%CI])	5 (83.3) [35.9, 99.6]	3 (100) [29.2, 100.0]	8 (88.9) [51.7, 99.7]	10 (100) [69.1, 100.0]	67 (89.3) [80.0, 95.3]	77 (90.6) [82.3, 95.8]

*: Patients who received at least one dose of study drug

Regarding safety, 59 patients died during the study period (up to 30 days after the last dose of rasburicase) or during the follow-up period and a causal relationship to study drug was denied for all deaths. Of these, 8 adult patients only died within 30 days of the last dose of rasburicase, due to the deterioration of the primary disease (3 patients) and sepsis, neutropenic sepsis, pneumonia/hypoxia, neutropenic infection leading to respiratory failure, and venoocclusive disease (1 patient each).

The applicant explained as follows:
Although this study was carried out based on a post-marketing commitment with the US Food and Drug Administration (FDA), the target accrual of 85 pre-treated patients could not be reached within a 28-month recruitment period ([redacted] 20[redacted] to [redacted] 20[redacted]) and taking into account that any major safety problem or a loss of therapeutic effect was not identified, as of [redacted], 20[redacted], this clinical study was terminated after obtaining agreement from the FDA, based on the request of the Independent Data Monitoring Committee and the applicant.

8) Foreign PK study (Study PKM6638; Publication, None; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])
Three patients in the 0.15 mg/kg group died during the study period (including the post-follow-up period), but a causal relationship to study drug was denied for all deaths. Of whom, 2 patients died within 30 days of the last dose of rasburicase (1 case of deterioration of the primary disease, 1 case of lung infiltration).

9) Foreign phase II study (Study LTS3025; Publication, *Med Ped Oncol* 1998; 31: 274; Studied period, [redacted] 19[redacted] to [redacted] 19[redacted])
During the study period (up to 1 week after the last dose of rasburicase), 3 of 82 patients died (1 case of acute renal failure/hypotension, 1 case of respiratory failure, 1 case of cardiac arrest). A causal relationship to study drug was denied for all events except for respiratory failure.

10) Foreign safety study (Study LTS3256; Publication, *ASCO* 2002, Abstract 2187; Studied period, [redacted] 19[redacted] to [redacted] 20[redacted])
During the study period (including the post-follow-up period), 19 of 278 patients (6.8%) died, but a causal relationship to rasburicase was denied for all deaths. Of whom, 17 patients died within 30 days of the last dose of rasburicase.

11) Foreign safety study (Study LTS3257; Publication, *Leukemia* 2005; 19: 34-38 etc.; Studied period, January 1999 to September 2002)
During the study period (including the post-follow-up period), 79 of 1069 patients (7.4%) died, but a causal relationship to rasburicase was denied for all deaths.

12) Foreign phase III study (Study EFC4978; Publication, None; Studied period, April 2004 to December 2007)
When rasburicase was approved in the US in July 2002, a post-marketing commitment study designed to assess the comparative efficacy and safety of single agent rasburicase, single agent allopurinol, and sequential rasburicase and allopurinol in adult patients was requested by the FDA. This study was conducted to meet this request and for an additional adult indication in the

US.

A multicenter, randomized, open-label, three-arm, parallel-group, comparative study was conducted at 18 centers overseas to compare the adequacy of control of plasma uric acid concentration and the safety profile of single agent rasburicase (rasburicase group) vs. single agent allopurinol (allopurinol group) vs. sequential treatment with rasburicase followed by allopurinol (rasburicase/allopurinol group) in patients aged ≥ 18 years with leukemia, malignant lymphoma, or solid tumor malignancies at risk for hyperuricemia and TLS (target number of cases, 92 cases per group, 276 cases in total).

Rasburicase 0.20 mg/kg was to be intravenously administered over 30 minutes once daily for 5 days in the rasburicase group and allopurinol 300 mg/day was to be orally administered for 5 days in the allopurinol group. In the rasburicase/allopurinol group, the same dose as given to the single agent group was used for rasburicase and allopurinol, respectively and rasburicase was administered from Day 1 through Day 3 followed by allopurinol from Day 3 through Day 5.

In this study, 280 patients (94 patients in the rasburicase group, 93 patients in the rasburicase/allopurinol group, 93 patients in the allopurinol group) were randomized and included in the ITT population. Of whom, 275 patients who received study drug (92 patients in the rasburicase group, 92 patients in the rasburicase/allopurinol group, 91 patients in the allopurinol group) were included in the mITT population for efficacy and safety analyses.

Patients were classified as "responders" if their plasma uric acid levels were ≤ 7.5 mg/dL from 48 hours after the initiation of study drug through 48 hours after the last administration of study drug and the primary efficacy endpoint was the response rate. As the difference in the response rate between the rasburicase and allopurinol groups [95.305% CI] was 21.0 [8.6, 32.7] and the lower one-sided 97.65% confidence limit was larger than 0 (a pre-defined value), rasburicase was shown to be superior to allopurinol. The response rates were as shown in the following table.

Response rates (mITT population)

	Rasburicase (N = 92)	Allopurinol (N = 91)	Rasburicase/Allopurinol (N = 92)
Responders n (%) [95% CI]	80 (87.0) [78.3, 93.1]	60 (65.9) [55.2, 75.5]	72 (78.3) [68.4, 86.2]
Nonresponders n (%)	12 (13.0)	31 (34.1)	20 (21.7)
Failed to control uric acid	0	10 (11.0)	0
Anti-hyperuricemic treatment extended beyond 5 days	0	4 (4.4)	6 (6.5)
Missing uric acid samples	12 (13.0)	17 (18.7)	14 (15.2)
Estimated difference in Response Rate [95.305% CI] (%) [95.305% CI], *P*-value	21.0 [8.6, 32.7], *P* = 0.0009 —		— 12.3 [-0.9, 25.0], *P* = 0.0632

Regarding safety, 112 patients (38 of 94 patients in the rasburicase group, 36 of 93 patients in the rasburicase/allopurinol group, 38 of 93 patients in the allopurinol group) died during the study period (including the post-follow-up period). Of whom, 30 patients (13 of 92 patients in the rasburicase group, 7 of 92 patients in the rasburicase/allopurinol group, 10 of 91 patients in the allopurinol group) died within 30 days of the last dose of study drug and a causal relationship to study drug was denied for all cases [Note by PMDA: Deaths during the study period and deaths within 30 days of the last dose of study drug were counted in the ITT population and the mITT population, respectively].

Causes of deaths within 30 days of the last dose of study drug

	Rasburicase (N = 92) [n (%)]	Rasburicase/Allopurinol (N = 92) [n (%)]	Allopurinol (N = 91) [n (%)]
All-cause deaths	13 (14.1)	7 (7.6)	10* (11.0)
Neutropenic sepsis	4 (4.3)	1 (1.1)	3 (3.3)
Multi-organ failure	2 (2.2)	0	1 (1.1)
Respiratory failure	1 (1.1)	1 (1.1)	1 (1.1)
Acute myeloid leukaemia (disease progression)	1 (1.1)	0	0
Adverse drug reaction	1 (1.1)	0	0
Myocardial infarction	1 (1.1)	0	0
Neutropenic infection	1 (1.1)	0	0
Subdural haemorrhage	1 (1.1)	0	0
Systemic mycosis	1 (1.1)	0	0
Pulmonary haemorrhage	0	2 (2.2)	0
Disease progression	0	1 (1.1)	1 (1.1)
Death (cause of death, others/unknown)	0	1 (1.1)	0
Subdural haematoma	0	1 (1.1)	0
Cardio-respiratory arrest	0	0	1 (1.1)
Completed suicide	0	0	1 (1.1)
Lobar pneumonia	0	0	1 (1.1)
Sepsis	0	0	1 (1.1)
TLS	0	0	1 (1.1)

*: As adverse events with a fatal outcome, “multi-organ failure” and “TLS” were documented for the same patient.

4.3.B Outline of the review by PMDA

4.3.B.1) Data for review

The applicant explained about the clinical development of rasburicase in Japan and its regulatory strategy as follows:

The clinical development of rasburicase in Japan was planned and conducted with a view to the use of foreign clinical data based on a bridging strategy. A Japanese phase II study (ACT5080) was positioned as a bridging study and foreign phase II studies (ACT2694, ACT2511) were positioned as the studies to be bridged and a clinical data package containing a foreign phase III study (EFC2975) was submitted for registration. However, as the daily dosing frequency and duration of treatment were not identical between the bridging study and the studies to be bridged, the similarity of clinical study data between Japan and overseas was assessed after excluding the subjects in the studies to be bridged who were not treated with the same dosage regimen as in Japanese Study ACT5080 (administered once daily for 5 days).

Differences between the number of subjects in the efficacy analysis population and the bridging analysis population in bridging study and studies to be bridged

Location	Study	Dose (mg/kg)	Efficacy analysis population	Bridging analysis population
Japan	ACT5080	0.15	15	15
		0.20	15	15
Overseas	ACT2511	0.15	107 (Dose validation phase, 20; Accrual phase, 87)	37
	ACT2694	0.20	119 (Dose validation phase, 22; Accrual phase, 97)	63

PMDA’s view on the above regulatory strategy for rasburicase is as follows:

Due to a number of differences regarding the daily dosing frequency, duration of treatment, and inclusion/exclusion criteria etc., only a portion of subjects enrolled into the foreign clinical studies were identified to assess the similarity of clinical study data between Japan and overseas. This is not considered appropriate. However, the submitted clinical study data etc. confirmed the following points and based on “Ethnic Factors in the Acceptability of Foreign Clinical Data” (PMSB/ELD Notification No. 672 dated August 11, 1998), rasburicase was characterized as insensitive to ethnic factors. Therefore, it has been decided to conduct a regulatory review based on the submitted data containing a foreign phase III study.

(a) There have been no apparent differences between Japan and overseas for the PK and PD of

rasburicase, which are considered important for predicting and expecting its therapeutic efficacy, based on its mode of action [see "4.2.B.1) PK and PD of rasburicase in Japanese and foreign subjects"].
(b) Japanese and foreign clinical studies of rasburicase have suggested similar efficacy results [see "4.3.B.2) Efficacy"] and also as to safety, there have been no adverse events specific to Japanese subjects [see "4.3.B.3) Safety"].

The above direction of review will be discussed at the Expert Discussion.

4.3.B.2) Efficacy
PMDA evaluated plasma uric acid levels over time, the response rate, the prevention of renal impairment, and the prevention of TLS as follows. As a result, PMDA concluded that the efficacy of rasburicase has been demonstrated.

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

4.3.B.2).(1) Endpoint
Recognition of risk and prevention are the most important steps in the management of TLS (*Harrison's Principles of Internal Medicine* 17th edition [McGraw-Hill Professional, 2008], *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 8th edition [Lippincott Williams & Wilkins, 2008]) and among symptomatic treatment against TLS, the management of hyperuricemia plays a central role in the prevention of acute renal failure associated with TLS (*DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 8th edition [Lippincott Williams & Wilkins, 2008]). Since cancer chemotherapy can be completed following appropriate management of hyperuricemia, the efficacy endpoint of achieving a sufficient reduction in blood uric acid is appropriate. However, as the clinical purpose of the control of blood uric acid levels is to prevent acute renal failure associated with TLS, it is important to evaluate the efficacy of rasburicase in terms of renal protection, etc.

4.3.B.2).(2) Plasma uric acid levels over time
In a foreign phase III study (EFC2975), the primary efficacy endpoint of the plasma uric acid $AUC_{0\text{-}96}$ was significantly lower in the rasburicase 0.20 mg/kg group compared to the allopurinol group ($P < 0.0001$). The percent reductions in plasma uric acid at 4 hours after the first dose of rasburicase in this study and other studies were as shown in the following tables.

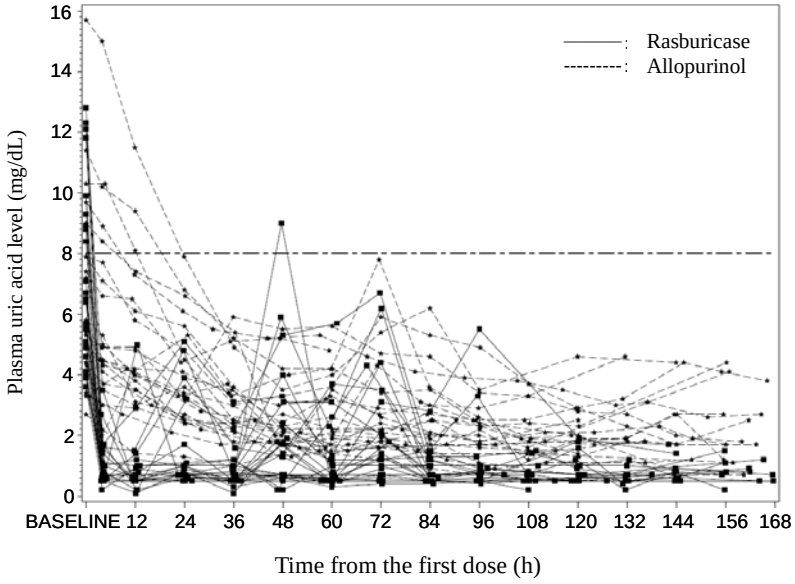
Summary of plasma uric acid levels (pediatric patients)

	Study	Dose (mg/kg)	No. of cases analyzed (N)	Baseline plasma uric acid level (mg/dL)	Plasma uric acid level at 4 hours after the first dose (mg/dL)	Percent reduction in uric acid at 4 hours after the first dose (%)
Japan	ACT5080	0.15	15	7.69	1.62	-84.79
		0.20	15	6.61	0.61	-92.86
Overseas	ACT2511	0.15	90	4.60	0.48	-90.09
	ACT2694	0.15	12	6.94	2.23	-74.27
		0.20	117	7.61	1.25	-86.00
	EFC2975	0.20	27	7.16	0.99	-86.00
		Allopurinol	25	6.39	5.68	-11.81
	Foreign studies combined	0.15	102	4.88	0.70	-88.13
		0.20	144	7.53	1.20	-86.00

Summary of plasma uric acid levels (adult patients)

	Study	Dose (mg/kg)	No. of cases analyzed (N)	Baseline plasma uric acid level (mg/dL)	Plasma uric acid level at 4 hours after the first dose (mg/dL)	Percent reduction in uric acid at 4 hours after the first dose (%)
Japan	ARD5290	0.15	25	5.20	0.33	-95.11
		0.20	25	5.59	0.15	-97.65
Overseas	ACT2511	0.15	17	6.36	2.28	-77.85
	ACT2694	0.20	2	7.10	0.90	-86.78
		0.20	92	5.67	0.64	-88.12
	EFC4978	0.20/Allopurinol	92	5.42	0.69	-87.62
		Allopurinol	91	6.01	5.32	-13.70

Plasma uric acid levels over time in individual subjects in Study EFC2975 were as shown in the following figure.



Time course of plasma uric acid levels up to 168 hours after the first dose (Study EFC2975)

Based on the above, PMDA confirmed that (a) rasburicase is expected to degrade uric acid *in vivo* in humans, (b) rasburicase provides control of plasma uric acid more rapidly than allopurinol (plasma uric acid levels are rapidly reduced following the initial dose of rasburicase and remain low), and (c) 0.15 mg/kg and 0.20 mg/kg of rasburicase produce similar plasma uric acid lowering effects.

4.3.B.2).(3) Response rate

"Responders" in Japanese and foreign clinical studies were defined as shown in the following table. The applicant explained that as the definition of responders for foreign clinical studies included a criterion restricting the use of other antihyperuricemic agents and the concomitant use of other antihyperuricemic agents was prohibited in Japanese clinical studies, the rule on the use of other antihyperuricemic agents during the efficacy assessment period was the same in Japan and overseas.

Definition of responders in Japanese and foreign clinical studies

Study	Study population	Definition of responders
ACT5080	Japanese pediatric patients	The plasma uric acid endpoint (≤ 7.5 mg/dL in patients aged ≥ 13 years, ≤ 6.5 mg/dL in patients aged < 13 years) was achieved within 48 hours from initiation of rasburicase and maintained until 24 hours after the last administration (Day 5) of rasburicase
ARD5290	Japanese adult patients	The plasma uric acid endpoint (≤ 7.5 mg/dL) was achieved within 48 hours from initiation of rasburicase and maintained until 24 hours after the last administration (Day 5) of rasburicase
ACT2694 ACT2511	Foreign pediatric and adult patients	・ The plasma uric acid endpoint (≤ 7.5 mg/dL in patients aged ≥ 13 years, ≤ 6.5 mg/dL in patients aged < 13 years) was achieved within 48 ± 2 hours from initiation of rasburicase and maintained until 24 hours after the last administration of rasburicase ・ No other antihyperuricemic agent was needed to achieve the above endpoint
EFC2975	Foreign pediatric patients	Although the response rate was not included as an endpoint, the data were analyzed using the same definition as for Studies ACT2694 and ACT2511.
EFC4978	Foreign adult patients	・ The plasma uric acid endpoint (≤ 7.5 mg/dL) was maintained from Day 3 through Day 7 ・ No other antihyperuricemic treatment extended beyond 5 days to achieve the above endpoint

The response rates in these studies were as shown in the following tables. The applicant explained the reason for a lower response rate in Study EFC4978 compared to other studies as follows: The definition of responders required the plasma uric acid endpoint to be maintained until "48 hours after the last administration," which was 24 hours longer and the definition of nonresponders was more stringent (patients with consecutive missing values were to be classified as nonresponders, etc.) in this study than in other studies.

Summary of response rates (pediatric patients)

	Study	Dose (mg/kg)	No. of cases analyzed (N)	Response rate [n/N (%)]
Japan	ACT5080	0.15	15	14/15 (93.3)
		0.20	15	14/14 (100)
Overseas	ACT2511	0.15	90	87/88 (98.9)
	ACT2694	0.15	12	11/12 (91.7)
		0.20	117	101/106 (95.3)
	EFC2975	0.20	27	21/23 (91.3)
		Allopurinol	25	13/14 (92.9)
	Foreign studies combined	0.15	102	98/100 (98.0)
		0.20	144	122/129 (94.6)

Summary of response rates (adult patients)

	Study	Dose (mg/kg)	No. of cases analyzed (N)	Response rate [n/N (%)]
Japan	ARD5290	0.15	25	25/25 (100)
		0.20	25	24/25 (96.0)
Overseas	ACT2511	0.15	17	16/16 (100)
	ACT2694	0.20	2	1/1 (100)
	EFC4978	0.20	92	80/92 (87.0)
		0.20/Allopurinol	92	72/92 (78.3)
		Allopurinol	91	60/91 (65.9)

The definition of "unevaluable cases" that affects the calculation of response rates and the handling of unevaluable cases in analyses were not identical in these studies. Although these points should be noted when comparing the response rate among the different studies, PMDA confirmed that these studies except for Study EFC4978 achieved similarly good response rates at both 0.15 and 0.20 mg/kg, regardless of children or adults and of Japan or overseas. For Study EFC4978, taking into account that a trend towards a higher response rate in the rasburicase group than in the allopurinol group was suggested, PMDA considers that the efficacy of rasburicase has been shown also in this study.

On the other hand, there were a total of 11 nonresponders in the rasburicase groups in the clinical studies intended primarily to evaluate efficacy (6 cases in Study ACT2694 [1 case in the 0.15 mg/kg group, 5 cases in the 0.20 mg/kg group], 1 case in Study ACT2511 [0.15 mg/kg group], 2 cases in Study EFC2975 [0.20 mg/kg group], 1 case in Study ACT5080 [0.15 mg/kg group], 1 case in Study ARD5290 [0.20 mg/kg group]).

The applicant explained about the nonresponders as follows:
Except for 1 patient withdrawn from the study due to a serious adverse event during the treatment period (hepatic enzyme increased) in Japanese Study ARD5290, the other 10 cases were: (a) the plasma uric acid level was high at baseline, which was reduced after the initiation of rasburicase, but did not fall below the threshold within 48 hours from the initiation of rasburicase or (b) regardless of the plasma uric acid level at baseline, the plasma uric acid level was reduced sufficiently after the initiation of rasburicase, but rose above the threshold at ≥ 48 hours from the initiation of rasburicase.

Although "the nonresponders" included patients with a transient increase in plasma uric acid and those with plasma uric acid levels rising again at > 144 hours after the end of treatment, PMDA confirmed that plasma uric acid levels tended to decline for a certain period of time after the initiation of rasburicase in all the nonresponders.

4.3.B.2).(4) Renal protection
Acute renal failure may occur when uric acid crystals precipitate in the renal tubules as a consequence of an acute rise in plasma uric acid. The precipitation of calcium phosphate crystals caused by the release of intracellular phosphate with cell lysis may further worsen renal impairment.

In a foreign phase III study (EFC2975), among the renal impairment adverse events/laboratory metabolic abnormalities (hyperkalemia, blood creatinine increased, urine β2 microglobulin increased, urine output decreased, etc.) and TLS-related adverse events (hyperuricemia, hyperkalemia, hyperphosphatemia, hypercalcemia, acidosis) (the table below), there were no events assessed as causally related, no serious renal impairment adverse events, or no renal impairment adverse events leading to rasburicase discontinuation/interruption in either group. In this study, 1 of 25 subjects in the allopurinol group was reported to have acute renal failure requiring hemodialysis while none of the subjects in the rasburicase group had acute renal failure or required hemodialysis.

Renal impairment adverse events and TLS-related adverse events (Study EFC2975)

	Rasburicase 0.20 mg/kg (N = 27) [n (%)]	Allopurinol (N = 25) [n (%)]
Renal impairment adverse events	10 (37.0)	7 (28.0)
Haematuria	5 (18.5)	2 (8.0)
Oliguria	3 (11.1)	1 (4.0)
Renal disorder	1 (3.7)	0
Acute renal failure	0	1 (4.0)
Anuria	0	1 (4.0)
TLS-related adverse events	13 (48.1)	12 (48.0)
TLS	1 (3.7)	3 (12.0)
Hypercalcaemia	0	1 (4.0)

In Study EFC4978, a total of 6 subjects required hemodialysis (2 subjects each [2.2%] in the rasburicase, rasburicase/allopurinol, and allopurinol groups).

Renal impairment adverse events and TLS-related adverse events (Study EFC4978)

	Rasburicase 0.20 mg/kg (N = 92) [n (%)]		Rasburicase/Allopurinol (n = 92) [n (%)]		Allopurinol (N = 91) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Renal impairment adverse events	24 (26.1)	5 (5.4)	25 (27.2)	8 (8.7)	18 (19.8)	2 (2.2)
Blood creatinine increased	7 (7.6)	1 (1.1)	8 (8.7)	0	9 (9.9)	0
Hyperkalaemia	7 (7.6)	1 (1.1)	5 (5.4)	2 (2.2)	4 (4.4)	1 (1.1)
Proteinuria	6 (6.5)	0	7 (7.6)	0	8 (8.8)	0
Acute renal failure	2 (2.2)	2 (2.2)	5 (5.4)	5 (5.4)	2 (2.2)	2 (2.2)
Renal failure	2 (2.2)	2 (2.2)	1 (1.1)	1 (1.1)	0	0
Oliguria	2 (2.2)	1 (1.1)	0	0	0	0
Blood urea nitrogen/creatinine ratio increased	1 (1.1)	0	0	0	0	0
Urinary retention	1 (1.1)	0	1 (1.1)	0	0	0
Urine flow decreased	1 (1.1)	0	0	0	0	0
Blood urea increased	0	0	2 (2.2)	1 (1.1)	0	0
Renal impairment	0	0	1 (1.1)	0	0	0
TLS-related adverse events	11 (12.0)	4 (4.3)	6 (6.5)	3 (3.3)	11 (12.1)	4 (4.4)
Hyperkalaemia	7 (7.6)	1 (1.1)	5 (5.4)	2 (2.2)	4 (4.4)	1 (1.1)
Acidosis	2 (2.2)	1 (1.1)	0	0	2 (2.2)	0
Hypercalcaemia	2 (2.2)	1 (1.1)	0	0	1 (1.1)	0
TLS	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	5 (5.5)	4 (4.4)

The applicant explained about renal impairment following rasburicase administration as follows:
In Studies EFC2975 and EFC4978, although Grade ≥ 3 events or serious events were slightly fewer in the rasburicase group compared to the allopurinol group, there were no major differences between the rasburicase and allopurinol groups for renal impairment adverse events, TLS-related adverse events, and dialysis status. However, the two drugs have different modes of action and rasburicase is more likely to prevent renal impairment, e.g. acute renal failure, and help avoid dialysis by reducing blood uric acid levels more rapidly than allopurinol.

PMDA considers as follows:
As blood uric acid levels can be controlled by rasburicase, the prevention of renal impairment such as acute renal failure associated with TLS and avoidance of dialysis can be expected. However, the clinical significance of the rate of blood uric acid reduction (a rapid decline) as claimed by the applicant is unknown and based on the submitted data, the difference in the rate of decline between rasburicase and allopurinol is not clear. As the clinical purpose of blood uric acid control is to prevent acute renal failure associated with TLS, it is necessary to continue to collect post-marketing information on the prevention of renal impairment.

4.3.B.2).(5) Prevention of TLS
In the clinical studies submitted, TLS as an adverse event was not defined in the protocols and the onset of TLS as an adverse event was determined by the investigator or sub-investigator based on the patient's symptoms and laboratory test values.

TLS developed in a total of 4 subjects in pediatric study EFC2975 (1 of 27 subjects [3.7%] in the rasburicase group, 3 of 25 subjects [12.0%] in the allopurinol group) and a total of 7 subjects in adult study EFC4978 (1 of 92 subjects [1.1%] in the rasburicase group, 1 of 92 subjects [1.1%] in the rasburicase/allopurinol group, 5 of 91 subjects [5.5%] in the allopurinol group) and there were no major differences in the incidence of TLS between children and adults.

In Study EFC2975, TLS-associated metabolic abnormalities (the thresholds were pre-defined for serum calcium, bicarbonate, phosphorus, uric acid, potassium, and creatinine) were detected (the table below). Metabolic abnormalities suggestive of TLS tended to be detected more frequently in the rasburicase group than in the allopurinol group at baseline and less frequently

in the rasburicase group than in the allopurinol group after the start of study drug administration, but there were no major differences between the groups.

Also in Study EFC4978, there were no major differences in the development of TLS among the groups (the table below).

Summary of metabolic abnormalities (Study EFC2975)

Event	Protocol-defined threshold	Treatment group	n (%)										
			Baseline	Treatment Day						24-48 hours after the last dose	After the last dose	Overall period	Overall period (excluding baseline)
				1	2	3	4	5	6				
Serum calcium decreased	< 1.75 mmol/L or < 7.0 mg/dL	Rasburicase	0	2 (8.7)	2 (8.0)	2 (7.7)	0	1 (7.7)	0	1 (5.0)	1 (3.8)	6 (22.2)	6 (22.2)
		Allopurinol	0	3 (13.0)	2 (9.1)	6 (25.0)	4 (18.2)	4 (21.1)	1 (10.0)	0	1 (4.5)	6 (24.0)	6 (24.0)
Serum bicarbonate increased	> 30 mEq/L	Rasburicase	3 (11.1)	5 (21.7)	8 (33.3)	5 (19.2)	6 (28.6)	0	0	0	2 (8.0)	12 (44.4)	12 (44.4)
		Allopurinol	2 (8.0)	7 (30.4)	8 (34.8)	6 (25.0)	3 (13.6)	1 (5.3)	1 (10.0)	0	2 (9.1)	12 (48.0)	12 (48.0)
Serum phosphorus increased	> 6.5 mg/dL or > 2.1 mmol/L	Rasburicase	1 (3.8)	2 (8.7)	1 (4.0)	5 (18.5)	0	0	1 (16.7)	0	0	9 (33.3)	9 (33.3)
		Allopurinol	0	0	3 (13.0)	5 (21.7)	4 (19.0)	2 (10.5)	2 (20.0)	0	1 (4.5)	7 (28.0)	7 (28.0)
Serum uric acid increased	> 8 mg/dL or > 475.84 µmol/L	Rasburicase	10 (37.0)	0	1 (3.7)	0	0	0	0	0	0	10 (37.0)	1 (3.7)
		Allopurinol	7 (28.0)	5 (20.0)	0	0	0	0	0	0	0	7 (28.0)	5 (20.0)
Serum potassium increased	> 6.5 mEq/L	Rasburicase	0	0	0	0	0	0	0	0	0	0	0
		Allopurinol	0	0	0	0	0	0	0	0	0	0	0
Serum creatinine increased	> 3 x ULN	Rasburicase	0	0	0	0	0	0	0	0	0	0	0
		Allopurinol	0	0	0	0	0	0	0	0	0	0	0
All events (excluding abnormal serum bicarbonate)		Rasburicase	11 (40.7)	4 (14.8)	3 (11.1)	7 (25.9)	0	1 (4.3)	1 (10.0)	1 (4.0)	1 (3.7)	17 (63.0)	14 (51.9)
		Allopurinol	7 (28.0)	7 (28.0)	4 (16.0)	7 (28.0)	5 (21.7)	5 (22.7)	2 (18.2)	0	2 (8.3)	12 (48.0)	11 (44.0)
All events		Rasburicase	14 (51.9)	8 (29.8)	10 (37.0)	9 (33.3)	6 (22.2)	1 (4.3)	1 (10.0)	1 (4.0)	3 (11.1)	21 (77.8)	20 (74.1)
		Allopurinol	8 (32.0)	11 (44.0)	9 (36.0)	9 (36.0)	8 (34.8)	5 (22.7)	2 (18.2)	0	3 (12.5)	16 (64.0)	15 (60.0)

Summary of TLS-related adverse events and renal adverse events* (Study EFC4978)

	Rasburicase 0.20 mg/kg (N = 92) [n (%)]		Rasburicase/Allopurinol (N = 92) [n (%)]		Allopurinol (N = 91) [n (%)]	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
TLS-related adverse events	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	5 (5.5)	4 (4.4)
TLS	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	5 (5.5)	4 (4.4)
Blood uric acid increased	0	0	0	0	1 (1.1)	1 (1.1)
Renal adverse events	16 (17.4)	4 (4.3)	23 (25.0)	7 (7.6)	17 (18.7)	2 (2.2)
Blood creatine increased†	7 (7.6)	1 (1.1)	9 (9.8)	0	9 (9.9)	0
Proteinuria	6 (6.5)	0	7 (7.6)	0	8 (8.8)	0
Renal failure/renal disorder‡	4 (4.3)	4 (4.3)	8 (8.7)	7 (7.6)	2 (2.2)	2 (2.2)
Blood urea increased	0	0	2 (2.2)	1 (1.1)	0	0
Oliguria	2 (2.2)	1 (1.1)	0	0	0	0
Blood urea nitrogen/creatinine ratio increased	1 (1.1)	0	0	0	0	0

*: The highest-grade event in each subject was counted.
†: Including "blood creatine increased" and "blood creatinine increased"
‡: Including "renal failure acute," "renal failure," "renal impairment," and "renal injury"

PMDA considers as follows:
Based on the pharmacological action of rasburicase, the treatment and prophylaxis of

hyperuricemia associated with tumor lysis can be expected. However, rasburicase has been suggested to have no effects on metabolic abnormalities characteristic of TLS and the difference between rasburicase and allopurinol is not clear in terms of the prevention of TLS.

4.3.B.3) Safety

PMDA concluded that although rasburicase-specific adverse events that deserve attention include hypersensitivity and hemolytic reaction and caution is needed, rasburicase is tolerable when used under the supervision of a physician with knowledge and experience in cancer chemotherapy at a medical institution with facilities for the treatment of emergencies.

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

4.3.B.3).(1) Differences in safety between different doses

PMDA asked the applicant to explain differences in safety between the 0.15 mg/kg and 0.20 mg/kg doses of rasburicase.

The applicant presented the results of pooled analyses of pediatric and adult patients from a total of 12 studies (Japanese clinical studies [ACT5080, ARD5290] and foreign clinical studies [ACT2694, ACT2511, LTS3025, EFC2975, EFC4982, EFC4983, EFC5339, PKM6638, LTS3256, LST3257]) (the tables below) and explained that there were no major differences in the safety of rasburicase between the two doses. From the two compassionate use studies LTS3256 and LST3257, serious adverse events only were counted since they were regarded as reliable safety data.

Although Grade 3/4 adverse events tended to increase in the 0.20 mg/kg group compared to the 0.15 mg/kg group in children, as there were no differences in serious adverse events between the two doses, PMDA largely accepted the applicant's response.

Summary of safety by dose in pediatric patients

	Japan		Overseas		Overall	
	0.15 mg/kg (N = 15) [n (%)]	0.20 mg/kg (N = 15) [n (%)]	0.15 mg/kg (N = 102) [n (%)]	0.20 mg/kg (N = 173) [n (%)]	0.15 mg/kg (N = 117) [n (%)]	0.20 mg/kg (N = 188) [n (%)]
All adverse events	15 (100)	15 (100)	98 (96.1)	171 (98.8)	113 (96.6)	186 (98.9)
Grade 3/4 adverse events	15 (100)	15 (100)	29 (28.4)	107 (61.8)	44 (37.6)	122 (64.9)
Adverse drug reactions	4 (26.7)	2 (13.3)	8 (7.8)	12 (6.9)	12 (10.3)	14 (7.4)
Grade 3/4 adverse drug reactions	2 (13.3)	1 (6.7)	3 (2.9)	4 (2.3)	5 (4.3)	5 (2.7)
Adverse events leading to treatment discontinuation	0	0	1 (1.0)	2 (1.2)	1 (0.9)	2 (1.1)
Deaths*	0	0	1 (1.0)	2 (1.2)	1 (0.9)	2 (1.1)

*: Deaths within 30 days of the last dose

Serious adverse events in pediatric patients

	Japan		Overseas		Overall	
	0.15 mg/kg (N = 15) [n (%)]	0.20 mg/kg (N = 15) [n (%)]	0.15 mg/kg (N = 102) [n (%)]	0.20 mg/kg (N = 1021) [n (%)]	0.15 mg/kg (N = 117) [n (%)]	0.20 mg/kg (N = 1036) [n (%)]
Serious adverse events	1 (6.7)	0	21 (20.6)	249 (24.4)	22 (18.8)	249 (24.0)

Summary of safety by dose in adult patients

	Japan		Overseas		Overall	
	0.15 mg/kg (N = 25) [n (%)]	0.20 mg/kg (N = 25) [n (%)]	0.15 mg/kg (N = 30) [n (%)]	0.20 mg/kg (N = 275) [n (%)]	0.15 mg/kg (N = 55) [n (%)]	0.20 mg/kg (N = 300) [n (%)]
All adverse events	25 (100)	25 (100)	29 (96.7)	264 (96.0)	54 (98.2)	289 (96.3)
Grade 3/4 adverse events	25 (100)	24 (96.0)	24 (80.0)	199 (72.4)	49 (89.1)	223 (74.3)
Adverse drug reactions	10 (40.0)	13 (52.0)	4 (13.3)	20 (7.3)	14 (25.5)	33 (11.0)
Grade 3/4 adverse drug reactions	2 (8.0)	4 (16.0)	1 (3.3)	11 (4.0)	3 (5.5)	15 (5.0)
Adverse events leading to treatment discontinuation	0	1 (4.0)	2 (6.7)	10 (3.6)	2 (3.6)	11 (3.7)
Deaths*	0	0	4 (13.3)	15 (5.5)	4 (7.3)	15 (5.0)

*: Deaths within 30 days of the last dose

Serious adverse events in adult patients

	Japan		Overseas		Overall	
	0.15 mg/kg (N = 25) [n (%)]	0.20 mg/kg (N = 25) [n (%)]	0.15 mg/kg (N = 30) [n (%]	0.20 mg/kg (N = 774) [n (%)]	0.15 mg/kg (N = 55) [n (%)]	0.20 mg/kg (N = 799) [n (%)]
Serious adverse events	1 (4.0)	2 (8.0)	16 (53.3)	173 (22.4)	17 (30.9)	175 (21.9)

4.3.B.3).(2) Differences in safety between rasburicase and allopurinol

Summaries of safety in a foreign phase III study (EFC2975) and a foreign phase III adult study (EFC4978) are as shown in the following tables.

PMDA reviewed the safety profiles in the rasburicase and allopurinol groups [see "4.4 Adverse events observed in clinical studies"] and concluded that there were no major differences.

Summary of safety in Study EFC2975

	Rasburicase 0.20 mg/kg (N = 27) [n (%)]	Allopurinol (N = 25) [n (%)]
Adverse events	26 (96.3)	25 (100)
Grade 3/4 adverse events	15 (55.6)	18 (72.0)
Adverse drug reactions	5 (18.5)	1 (4.0)
Deaths	0	2 (8.0)
Serious adverse events	4 (14.8)	8 (32.0)
Adverse events leading to discontinuation	1 (3.7)	2 (4.0)

Summary of safety in Study EFC4978

	Rasburicase 0.20 mg/kg (N = 92) [n (%)]	Rasburicase 0.20 mg/kg/Allopurinol (N = 92) [n (%)]	Allopurinol (N = 91) [n (%)]
Adverse events	92 (100)	92 (100)	90 (98.9)
Grade 3/4 adverse events	85 (92.4)	86 (93.5)	87 (95.6)
Adverse drug reactions	4 (4.3)	5 (5.4)	1 (1.1)
Grade 3/4 adverse drug reactions	2 (2.2)	3 (3.3)	0
Serious adverse events	36 (39.1)	32 (34.8)	29 (31.9)
Adverse events leading to discontinuation	1 (1.1)	5 (5.4)	2 (2.2)

4.3.B.3).(3) Hypersensitivity

As rasburicase is a protein product manufactured by recombinant technology in the yeast (*S. cerevisiae*) host, there is a concern about the development of antibodies against rasburicase or host cell protein and the associated risk of hypersensitivity. The international standard textbooks (*Harrison's Principles of Internal Medicine* 17th edition [McGraw-Hill Professional, 2008], *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 8th edition [Lippincott Williams & Wilkins, 2008]) also mention hypersensitivity such as bronchospasm, hypoxaemia, or hypotension, as adverse reactions to rasburicase.

Hypersensitivity reactions were reported by 9 of 15 subjects (60.0%) in the 0.15 mg/kg group and 12 of 15 subjects (80.0%) in the 0.20 mg/kg group in Japanese pediatric study ACT5080 and 17 of 25 subjects (68.0%) in the 0.15 mg/kg group and 20 of 25 subjects (80.0%) in the 0.20 mg/kg group in Japanese adult study ARD5290.

In foreign studies, among pediatric patients (ACT2511, ACT2694, EFC2975, LTS3025, EFC5339), hypersensitivity reactions occurred in 49 of 102 subjects (48.0%) in the 0.15 mg/kg group and 112 of 173 subjects (64.7%) in the 0.20 mg/kg group. Among foreign adult patients (ACT2511, ACT2694, LTS3025, EFC4982, EFC4983, EFC5339, PKM6638), hypersensitivity reactions occurred in 19 of 30 subjects (63.3%) in the 0.15 mg/kg group and 149 of 275 subjects (54.2%) in the 0.20 mg/kg group.

(a) In compassionate use studies LTS3256 and LTS3257, serious hypersensitivity reactions were observed in 37 of 848 foreign pediatric patients (4.4%), (b) according to 12 periodic safety update reports (PSUR) (the period covered by the reports: February 23, 2001 to August 31, 2007), as serious adverse events, 14 cases of anaphylactic reaction, 9 cases of bronchospasm, 6 cases of anaphylactic shock, and 2 cases of hypersensitivity were reported and 1 case of fatal bronchospasm was also reported, and (c) non-serious hypersensitivity reactions have occurred frequently. Therefore, PMDA considers that it should be noted that hypersensitivity reactions might occur during the use of rasburicase and appropriate treatment and management are needed.

PMDA asked the applicant to explain the necessity of premedication for rasburicase-associated hypersensitivity.

The applicant explained as follows:
The numbers of cases with hypersensitivity and anaphylactic shock reported as serious adverse events in Japanese and foreign clinical studies (ACT5080, ARD5290, ACT2694, ACT2511, EFC2975, LTS3025, EFC4982, EFC4983, EFC5339, PKM6638, LTS3256, LTS3257) were examined. As a result, such cases were very rare, i.e. 1 case of hypersensitivity and 1 case of anaphylactic shock among 1153 pediatric patients (117 patients in the 0.15 mg/kg group, 1036 patients in the 0.20 mg/kg group) and 1 case of hypersensitivity among 854 adult patients (55 patients in the 0.15 mg/kg group, 799 patients in the 0.20 mg/kg group) and all of these patients recovered following the administration of diphenhydramine, methylprednisolone, or paracetamol and oxygen inhalation etc. In addition, rasburicase is administered to hospitalized patients receiving cancer chemotherapy under close supervision. Therefore, no premedication for hypersensitivity should be required. The European and US labelings also do not advise that premedication for rasburicase-associated hypersensitivity is required.

PMDA accepted the response.

4.3.B.3).(4) Hemolytic reactions
In the application dossier, “hemolytic reactions” were defined as the occurrence of hemolysis, methemoglobinemia, or hemolytic anemia.

The applicant explained about the mechanism of hemolytic reactions to rasburicase as follows:
Rasburicase produces hydrogen peroxide when converting uric acid to allantoin. Hydrogen peroxide is converted to highly reactive hydroxyl radicals in the presence of iron, which cause oxidative injury to lipids (lipid peroxidation), proteins, and nucleic acids and hemolysis is caused by lipid peroxidation of erythrocyte membranes (*Am J Surg* 1991; 161: 488-503). When uricolysis by rasburicase results in an increased hydrogen peroxide concentration exceeding the

capability of the endogenous scavenging mechanisms, hemolysis is likely to develop in patients with a genetic deficiency of enzymes that remove hydrogen peroxide (in humans, G6PD deficiency etc.).

The occurrence of hemolytic reactions in clinical studies was as shown in the following table.

One child in Japanese clinical studies (ACT5080, ARD5290) and 6 children and 2 adults in foreign clinical studies (ACT2511, ACT2694, EFC2975, EFC4982, EFC4983, LTS3025, EFC5339, PKM6638, LTS3256, LTS3257) had hemolytic reactions.

Hemolysis or methemoglobinemia was not reported in Study EFC4978.

Summary of hemolytic reactions

Study	Age (years)	Dose (mg/kg)	Adverse event	Grade	Serious or non-serious	Causality	Date of onset*2	Duration (Days)	Outcome	G6PD deficiency
ACT5080	7	0.20	Hemolysis	3	Non-serious	Yes	Day 2	5	Resolved	No
ACT2511	8	0.15	Hemolysis	3	Serious	likely	Day 2	3	Resolved	Yes
ACT2694	14	0.20	Hemolysis	4	Non-serious	unlikely	Day 6	unknown	Ongoing	unknown
EFC2975	11	0.20	Hemolysis	4	Serious	unknown	Day 5	2	Resolved	No
LTS3257*1	0.4	0.20	Methemoglobinemia	4	Serious	no	Day 15	2	Resolved	not performed
	0.3	0.20	Methemoglobinemia	4	Serious	likely	Day 5	2	Resolved	No
	7	0.20	Hemolytic anemia	3	Serious	likely	Day 3	2	Resolved	Yes
EFC5339	55	0.20	Hemolysis	3	Serious	Yes	Day 2	7	Resolved	Yes
LTS3257*1	45	0.20	Hemolytic anemia	3	Serious	unknown	Day 3	6	Resolved	Yes

*1: Serious adverse events only were collected. *2: Day 1 is defined as the first day of rasburicase administration.

PMDA considers as follows:
Taking also account of the international standard textbooks (*Harrison's Principles of Internal Medicine* 17th edition [McGraw-Hill Professional, 2008], *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 8th edition [Lippincott Williams & Wilkins, 2008]) stating that rasburicase is contraindicated in patients with G6PD deficiency, rasburicase should be contraindicated in patients with G6PD deficiency in Japan, as in foreign countries. Meanwhile, as the prevalence of G6PD deficiency in the Japanese population is about 0.1% and symptomatic cases are even fewer, i.e., very rare (*Internal Medicine* 9th edition [Asakura Publishing Co., Ltd., 2007]), there is little need for mandating screening for G6PD deficiency prior to the use of rasburicase. Therefore, a final conclusion on the need to contraindicate rasburicase in patients with G6PD deficiency in the Japanese package insert will be made, taking account of comments from the Expert Discussion. Hemolytic reactions have been observed also in non-G6PD deficiency cases and according to the PSURs (12 reports; the period covered by the reports, February 23, 2001 to August 31, 2007), 8 cases of serious methemoglobinemia and 1 case of fatal methemoglobinemia have been reported. Thus, it is necessary to be alert to hemolytic reactions during the use of rasburicase and take appropriate action.

4.3.B.4) Anti-rasburicase antibodies

Anti-rasburicase antibody production in Japanese and foreign clinical studies was as follows:
In a Japanese phase I study (TDU4730), 10 of 24 subjects (42%; 3 of 6 subjects in the 0.05 mg/kg group, 3 of 6 subjects in the 0.10 mg/kg group, 2 of 6 subjects in the 0.15 mg/kg group, 2 of 6 subjects in the 0.20 mg/kg group) were tested positive for anti-rasburicase antibodies at 30 days after rasburicase administration. Only 1 subject in the 0.20 mg/kg group was still tested positive at 6 months after administration and there was no positive case at 1 year after

administration. There was no relationship between the dose and the number of subjects with positive antibodies or between the detection of anti-rasburicase antibodies and adverse events.

In Japanese Study ACT5080, 1 patient in the 0.20 mg/kg group who was tested positive for anti-rasburicase antibodies at 4 weeks after rasburicase administration experienced no hypersensitivity-related adverse event during the study period and had a negative follow-up test at 6 months after administration. In Japanese Study ARD5290, among patients tested positive for anti-rasburicase antibodies at 4 weeks after rasburicase administration, 2 of 3 patients in the 0.20 mg/kg group were still tested positive at 6 months after administration. A severe hypersensitivity reaction or an adverse event of special interest was not reported during the observed period.

In a foreign phase I study (TDR2681), 19 of 28 subjects (a single dose, 9 of 16 subjects [56.3%]; multiple doses, 10 of 12 subjects [83.3%]) developed anti-rasburicase antibodies by 6 weeks after rasburicase administration.

Anti-rasburicase antibody production in patients was as shown in the following table.

Summary of anti-rasburicase antibodies in patients

		Dose (mg/kg)	Incidence of anti-rasburicase antibodies [n/N (%) [95% CI]]				
			Baseline	4 weeks after administration	3 months after administration	6 months after administration	1 year after administration
Children	Japan*	0.15	0/15 (0) [0.0, 21.8]	0/14 (0) [0.0, 23.2]	—	—	—
		0.20	0/15 (0) [0.0, 21.8]	1/14 (7.1) [0.2, 33.9]	—	—	—
	Overseas†	0.15	0/97 (0) [0.0, 3.7]	8/76 (10.5) [4.7, 19.7]	—	—	—
		0.20	0/135 (0) [0.0, 2.7]	12/102 (11.8) [6.2, 19.6]	—	—	—
Adults	Japan‡	0.15	0/25 (0) [0.0, 13.7]	2/25 (8.0) [1.0, 26.0]	0/2 (8.0) [0.0, 84.2]	0/0	0/0
		0.20	0/25 (0) [0.0, 13.7]	3/25 (12.0) [2.5, 31.2]	3/3 (100) [29.2, 100.0]	2/3 (66.7) [9.4, 99.2]	0/1 (0) [0.0, 97.5]
	Overseas¶	0.15	0/16 (0) [0.0, 20.6]	1/13 (7.7) [0.2, 36.0]	—	—	—
		0.20	0/109 (0) [0.0, 3.3]	0/1 (0) [0.0, 97.5]	0/92 (0) [0.0, 3.9]	—	—

*: Study ACT5080, †: Studies ACT2511, ACT2694, EFC2975, and LTS3025, ‡: Study ARD5290, ¶: Studies ACT2511, ACT2694, LTS3025, EFC4982, and EFC4983

In Japanese Study ACT5080, anti-SCP antibody was assayed before the administration of rasburicase and 1 patient in the 0.20 mg/kg group had a positive result, but this patient experienced no hypersensitivity-related adverse event. Anti-SCP antibody assay was not performed in other clinical studies.

The applicant explained the immunogenicity of rasburicase as follows:
In a foreign phase IV study evaluating the efficacy and safety of rasburicase in patients with and without previous treatment with a uricolytic agent (EFC5339), anti-rasburicase antibodies (IgG, IgE, neutralizing antibodies) were assayed after rasburicase administration. As a result, the incidences of antibodies as measured by qualitative and quantitative assays were both 0% to 14.3% (1 of 7 patients), which were similar to the results in other Japanese and foreign clinical studies. There were no safety problems considered directly associated with anti-rasburicase antibody production in patients tested positive for any of the above 3 different antibodies or patients with Grade $\geq$ 3 hypersensitivity.

The relationship between neutralizing antibodies that would affect the uricolytic activity of rasburicase and the efficacy of rasburicase was assessed based on pooled data from Studies EFC5339, EFC4978, and PKM6638 (cutoff at 4 years 5 months from the start of the studies). Neutralizing antibodies were assayed in 358 of 394 patients and among the 277 patients receiving rasburicase excluding 81 patients in the allopurinol group in Study EFC4978, 21

patients (7.6%) were positive (9 patients [3.2%] by quantitative assay, 12 patients [4.3%] by qualitative assay). Among the 260 adult patients not previously treated with rasburicase, 21 patients (8.1%) were positive (9 patients [3.5%] by quantitative assay, 12 patients [4.6%] by qualitative assay). Nineteen of the 21 patients with positive neutralizing antibodies (90.5%) were classified as "responders" and the remaining 2 patients were classified as nonresponders because they received antihyperuricemic treatment for longer than scheduled, but their plasma uric acid levels remained low. Therefore, it seems that the development of neutralizing antibodies does not affect the efficacy of rasburicase. Also as to PK, since the clearance in IgG antibody positive cases lied within the range of interindividual variability in negative cases and the time to detection of anti-rasburicase antibodies was mostly ≥ 2 weeks after the initiation of rasburicase [Note by PMDA: See "4.2.B.3) Effects of anti-rasburicase antibodies on PK"], taking account of the duration of treatment (about 5 days), the PK of rasburicase should not be affected by antibody formation.

Based on the above, anti-rasburicase antibody production is unlikely to affect the efficacy, safety, and PK of rasburicase.

PMDA considers as follows:
The applicant's response that as the relationship between anti-rasburicase antibody production and safety has not been identified, antibody production is unlikely to affect the safety of rasburicase is acceptable. However, considering that some of the anti-rasburicase antibodies detected were neutralizing, there is a concern about a decrease of the efficacy of rasburicase in retreated patients with anti-rasburicase antibodies [see "4.3.B.7).(6) Administration of more than one course of rasburicase"]. In addition, the possibility that anti-rasburicase antibodies affect the PK of rasburicase can not be ruled out [see "4.2.B.3) Effects of anti-rasburicase antibodies on PK"].

4.3.B.5) Clinical positioning
In Japan, supportive measures (hydration, urinary alkalinization, the administration of allopurinol) are used for hyperuricemia associated with TLS.

In clinical studies, TLS risk (high or potential risk) was defined based on plasma uric acid level, cancer type (disease stage/disease type), tumor burden, and white blood cell count, etc.

PMDA asked the applicant to explain the choice between conventional supportive measures and rasburicase for hyperuricemia associated with TLS.

The applicant responded as follows:
Supportive measures for hyperuricemia that are currently available in Japan can not always provide adequate control of hyperuricemia and due to its mode of action of directly cleaving uric acid, rasburicase can reduce blood uric acid more rapidly than conventional supportive measures.

At the time of conducting clinical studies, there was no general definition established as a TLS risk classification system. After the filing of this application, guidelines for the management of TLS based on TLS risk classification (hereinafter referred to as the TLS guidelines) (*J Clin Oncol*. 2008; 26: 2767-78) were advocated. Taking also account of the TLS guidelines, (a) for patients presenting with hyperuricemia before the initiation of chemotherapy, the initial management with hydration and rasburicase is recommended and (b) for patients who are non-hyperuricemic before the initiation of chemotherapy, rasburicase is recommended for pediatric and adult patients at high risk for TLS and pediatric patients at intermediate risk for TLS and allopurinol is recommended for adult patients at intermediate risk for TLS and

pediatric and adult patients at low risk for TLS. However, the administration of rasburicase needs to be considered for patients at intermediate or low risk for TLS if (a) they have difficulty in oral intake and are unable to take oral allopurinol, (b) their uric acid levels are not lowered with conventional supportive measures, or (c) they have renal impairment.

PMDA confirmed that the international standard internal medicine textbook (*Harrison's Principles of Internal Medicine* 17th edition. [McGraw-Hill Professional, 2008]) states that rasburicase can be effective in TLS in cases where uric acid levels cannot be lowered sufficiently with the standard preventive approach consisting of allopurinol, aggressive hydration, and urinary alkalinization.

PMDA's view on the clinical positioning of rasburicase is as follows:
Although the submitted data show no clear difference in efficacy between allopurinol and rasburicase, since rasburicase could at least control blood uric acid levels in a similar percentage of patients as allopurinol and the mode of action of rasburicase is different from those of conventional supportive measures, rasburicase is positioned as a drug recommended for patients at high risk for TLS in whom the control of blood uric acid levels with conventional supportive measures is considered inadequate.

However, although (a) bulky disease (including lymphadenopathy), hepatosplenomegaly, elevated white blood cell counts (≥ 50 000/mL), elevated pretreatment LDH (≥ 2-5 times the upper limit of normal), (b) elevated pretreatment uric acid levels, (c) renal impairment, and (d) a history of nephrotoxic medication use (*DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 8th edition [Lippincott Williams & Wilkins, 2008]) etc. have been listed as the risk factors for TLS, as it has been reported that TLS occurs not only in hematological malignancies, but also in a number of other types of cancers including solid tumors and the development of TLS is affected by tumor burden and sensitivity to chemotherapy as well, it is difficult to predict with reliability the development of TLS. While the applicant's explanation about the choice between rasburicase and conventional supportive measures based on the TLS guidelines is understandable, the preferred approach for the management of TLS may be changed according to the evolution of treatment guidelines due to new findings and scientific advances and the revision of the criteria for TLS risk classification, etc.

Therefore, patients considered appropriate to receive rasburicase only need to be selected by physicians who have adequate knowledge and experience in cancer chemotherapy and fully understand the patient populations included in the submitted clinical studies and the efficacy and safety of rasburicase, referring also to the latest information, e.g., TLS treatment guidelines.

It is necessary to appropriately provide information on clinical study data, including data on the avoidance of hyperuricemia-associated renal dysfunction requiring hemodialysis.

4.3.B.6) Indication
The proposed indication was "treatment and prophylaxis of acute hyperuricemia associated with the treatment of hematological malignancies."

Based on the following review in addition to the results of reviews in "4.3.B.2) Efficacy" and "4.3.B.5) Clinical positioning," PMDA concluded as follows:
The appropriate indication for rasburicase should be "prophylaxis of hyperuricemia associated with cancer chemotherapy" and it should be stated in the precautions for indications section of the package insert that "prior to the use of rasburicase, appropriate patients should be selected, considering the risk of developing tumor lysis syndrome." In addition, using an appropriate information leaflet, detailed information considered useful for selecting appropriate patients for

the use of rasburicase should be provided.

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

The content of a review by PMDA is as follows.

4.3.B.6).(1) Intended population

i) The primary disease indication

The applicant explained the reason for proposing the primary disease indication of "hematological malignancies" only as follows:

Although TLS occurs in a variety of malignant tumors, its incidence is higher in hematological malignancies compared to solid tumor malignancies (*Japanese Journal of Clinical Medicine* 1996; 54: 167-71). Thus, the Japanese and foreign clinical studies mainly included patients with hematological malignancies (especially, acute leukemia and malignant lymphoma). As a result, as the efficacy and safety of rasburicase in the management of hyperuricemia in patients with hematological malignancies were confirmed, "hematological malignancies" only have been proposed as the primary disease indication.

However, when PMDA sought the applicant's view on how the efficacy and safety of rasburicase in the management of TLS (hyperuricemia) are related to the primary disease, the applicant responded as follows:

Rasburicase directly acts on uric acid in blood to convert it into the more water-soluble allantoin to be excreted by the kidneys and decreases blood uric acid levels. As this mode of action is not affected by the primary disease or chemotherapy for its treatment, it is not considered that the efficacy and safety of rasburicase in the management of hyperuricemia associated with TLS differ among different primary diseases (the tables below).

Response rate* by disease (< 18 years of age)

	ACT5080 [n/N (%)]		Foreign studies (ACT2511, ACT2694, EFC2975)		EFC2975
	0.15 mg/kg (n = 15)	0.20 mg/kg (n = 15†)	0.15 mg/kg (n = 102‡)	0.20 mg/kg (n = 144**)	Allopurinol (n = 25††)
Leukemia	9/9 (100)	12/12 (100)	85/85 (100)	95/101 (94.1)	8/9 (88.9)
Malignant lymphoma	5/6 (83.3)	2/2 (100)	13/15 (86.7)	27/28 (96.4)	5/5 (100)
Others	—	—	—	—	—

*: Patients were classified as responders if the plasma uric acid endpoint (≤ 6.5 mg/dL in patients aged < 13 years, ≤ 7.5 mg/dL in patients aged ≥ 13 years) was achieved within 48 hours from the initiation of rasburicase and maintained until 24 hours after the last administration of rasburicase and the proportion of responders in the efficacy analysis population excluding unevaluable patients was calculated.

†: 1 unevaluable patient, ‡ : 2 unevaluable patients (both in Study ACT2511), **: 15 unevaluable patients (11 patients in Study ACT2694, 4 patients in Study EFC2975) , ††: 11 unevaluable patients

Response rate* by disease (≥ 18 years of age)

	ARD5290 [n/N (%)]		ACT2511 [n/N (%)]	ACT2694 [n/N (%)]
	0.15 mg/kg (n = 25)	0.20 mg/kg (n = 25)	0.15 mg/kg (n = 17)	0.20 mg/kg (n = 2)
Leukemia	4/4 (100)	4/4 (100)	15/15† (100)	1/1‡ (100)
Malignant lymphoma	21/21 (100)	20/21 (95.2)	1/1 (100)	—
Others	—	—	—	—

*: Patients were classified as responders if the plasma uric acid endpoint (≤ 7.5 mg/dL) was achieved within 48 hours from the initiation of rasburicase and maintained until 24 hours after the last administration of rasburicase and no other antihyperuricemic agent was needed to achieve this endpoint and the proportion of responders in the efficacy analysis population excluding unevaluable patients was calculated.

†: 1 unevaluable patient, ‡: 1 unevaluable patient

Since (a) 16 adult patients in Study LTS3025, 5 pediatric patients in Study LTS3256, and 32 pediatric patients and 4 adult patients in Study LTS3257 had solid tumor malignancies and a publication (*Cancer Chemother Pharmacol* 2003; 51: 187-92) also has reported TLS in patients with solid tumor malignancies, (b) the incidence of TLS differs among different primary

diseases, but the mechanism of development and pathology of TLS are the same regardless of the primary disease, and (c) based on the mode of action of rasburicase, the efficacy of rasburicase is not affected by the primary disease, the inclusion of patients with solid tumor malignancies in the indication for rasburicase has certain clinical significance.

Therefore, the primary disease indication for rasburicase should be "hematological malignancies and solid tumor malignancies."

PMDA asked the applicant to explain the efficacy of rasburicase in patients with solid tumor malignancies.

The applicant responded as follows:
Among the patients with solid tumor malignancies in a foreign phase II study (LTS3025) and compassionate use clinical studies (LTS3256 and LTS3257), 57 patients with blood uric acid data were used to calculate the response rate retrospectively. Patients who were hyperuricemic at baseline were classified as responders if "their blood uric acid levels were normalized" and patients who were non-hyperuricemic at baseline were classified as responders if "normal blood uric acid levels were maintained until the time of assessment after administration." As a result, 43 of 57 patients with solid tumor malignancies (75.4%) were responders (14 patients were unevaluable). The above results indicate that rasburicase is expected to be effective also in patients with solid tumor malignancies. Study EFC5339 included no patients with solid tumor malignancies.

PMDA asked the applicant to explain differences in the safety of rasburicase between patients with solid tumors and those with hematological tumors.

The applicant responded as follows:
In clinical studies including patients with solid tumor malignancies (LTS3025, LTS3256, LTS3257), all of the patients with solid tumor malignancies received 0.20 mg/kg of rasburicase. Thus, the data from these patients were compared to the data from patients with hematological malignancies treated with the same dose of rasburicase. In both children and adults, many of the serious adverse events occurring in patients with solid tumor malignancies and those with hematological malignancies were the events that are commonly reported in association with the primary diseases or chemotherapy. The overall incidence of serious adverse events tended to be higher in pediatric patients with solid tumor malignancies than in those with hematological malignancies (12 of 37 patients [32.4%] and 234 of 992 patients [23.6%], respectively) while it was comparable in adult patients (5 of 20 patients [25.0%] and 166 of 752 patients [22.1%], respectively). In both children and adults, the number of solid tumor cases was small and the number of cases with each event was also limited, but most of the serious adverse events observed in patients with solid tumor malignancies were also observed in patients with hematological malignancies. Thus, there should be no major differences in serious adverse events between patients with solid tumor malignancies and those with hematological malignancies in both children and adults.

PMDA's view on the primary disease indication is as follows:
Patients with hematological malignancies were included in the pivotal efficacy clinical studies, i.e. Japanese phase II studies (ACT5080, ARD5290), foreign phase II studies (ACT2694, ACT2511), and a foreign phase III study (EFC2975) and the use of rasburicase is recommended for this patient population. However, since (a) the development of TLS in patients with solid tumor malignancies (small cell lung cancer, neuroblastoma, etc.) has also been reported (*Clin Oncol* 2006; 18: 773-80) and the TLS guidelines also state that patients with solid tumors sensitive to chemotherapy (drug-sensitive) are at risk of developing TLS, (b) though the

rasburicase efficacy data from patients with solid tumor malignancies are limited, the primary disease is unlikely to affect the blood uric acid lowering effect of rasburicase from a pharmacological standpoint and the effectiveness of rasburicase for TLS in patients with solid tumor malignancies is also expected, and (c) there have been no specific adverse events reported by patients with solid tumor malignancies only and the safety of rasburicase also is not affected by the primary disease, there is no need to limit the primary disease indication to "hematological malignancies."

ii) Age of the intended population

PMDA's view on the age of the intended population is as follows:

(a) There have been no major differences in the PK of rasburicase or plasma uric acid levels over time between children and adults [see "4.2.B.2) PK and PD of rasburicase in children and adults"], (b) a foreign phase III study in children (EFC2975) showed no major differences in the response rate between the rasburicase (21 of 23 patients, 91.3%) and allopurinol (13 of 14 patients, 92.9%) groups and a foreign phase III study in adults (EFC4978), which was submitted as the reference data, demonstrated significant differences in the response rate between the rasburicase (80 of 92 patients, 87.0%) and allopurinol (60 of 91 patients, 65.9%) groups [see "4.3.B.2) Efficacy"], (c) the blood uric acid lowering effect of rasburicase is independent of age also from a pharmacological point of view, and (d) a Japanese phase II study in adult patients (ARD5290) confirmed a certain level of efficacy and safety of rasburicase. Taking account of these findings, there is no need to set the age limits of the intended population.

4.3.B.6).(2) Treatment and prophylaxis of hyperuricemia

The applicant explained the reason for the inclusion of "treatment and prophylaxis" of hyperuricemia in the proposed indication statement of the package insert as follows:

Although the development of TLS can be to some extent predicted from risk factors, as tumor burden and sensitivity to chemotherapy vary from patient to patient, it is difficult to accurately predict the time to the onset of TLS and its severity (*Japanese Journal of Clinical Medicine* 1996; 54: 167-71, *Medical Clinics of Japan* 2000; 26: 660-2). However, when TLS develops, blood uric acid levels are elevated acutely, which may lead to acute renal failure or run a fatal course. Thus, the prevention of TLS is clinically important (*Japanese Journal of Pediatric Medicine* 2000; 32: 917-20, *Japanese Journal of Clinical Medicine* 1996; 54: 167-71). The prevention of TLS is the best approach for patients at risk of developing TLS, i.e. the intended population for rasburicase.

The response rate in patients presenting with hyperuricemia at baseline was high, i.e. 100% (3 of 3 patients) in the 0.15 mg/kg group and 100% (3 of 3 patients) in the 0.20 mg/kg group among adult patients and 87.5% (7 of 8 patients) in the 0.15 mg/kg group and 100% (5 of 5 patients) in the 0.20 mg/kg group among pediatric patients, and plasma uric acid levels rapidly declined within 4 hours from the initiation of rasburicase. Therefore, it was concluded that the efficacy of rasburicase in the treatment of hyperuricemia was demonstrated.

Based on the above, "treatment and prophylaxis" were included in the proposed indication statement.

PMDA considers as follows:

In clinical studies, rasburicase was initiated prior to cancer chemotherapy and the efficacy of rasburicase in the treatment of hyperuricemia associated with cancer chemotherapy has not been evaluated. Thus, "treatment" of hyperuricemia associated with cancer chemotherapy should not be included in the indication statement. Since the submitted data have not confirmed the efficacy of rasburicase in the prevention of TLS or acute renal failure, the terms "tumor lysis syndrome" or "acute renal failure" should not be used and only "hyperuricemia" should be

included in the indication statement. Furthermore, as “hyperuricemia associated with cancer chemotherapy” refers to acute hyperuricemia, the adjective “acute” is unnecessary.

Based on the results of the above reviews (1) and (2), the appropriate indication for rasburicase should be “prophylaxis of hyperuricemia associated with cancer chemotherapy.” Using an information leaflet to promote the proper use of rasburicase, detailed information considered useful for selecting appropriate patients for the use of rasburicase, e.g. the inclusion/exclusion criteria for clinical studies submitted and study results, should be provided.

4.3.B.7) Dosage and administration

The proposed dosage and administration was “The usual dosage for adults and children is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is 5 days as a rule.”

Based on the results of the following review, PMDA concluded that the dosage and administration section should state that “The usual dosage is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is up to 7 days.” and the following statements should be included in the precautions for dosage and administration section of the package insert.

- Clinical symptoms and blood uric acid levels should be monitored and treatment with rasburicase should be limited to the minimum period required for the management of blood uric acid levels.
- The efficacy and safety of dosing beyond 7 days have not been established (no clinical experience).
- The efficacy and safety of retreatment with rasburicase have not been established.
- Chemotherapy should be initiated 4 to 24 hours after the first dose of rasburicase.

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

The content of a review by PMDA is as follows.

4.3.B.7).(1) Dose per administration

The applicant explained the rationale for the proposed dose as follows:

Based on the results of a Japanese phase I study, the doses investigated in foreign clinical studies, and the approved doses overseas, doses of 0.15 mg/kg and 0.20 mg/kg were evaluated for the efficacy and safety of rasburicase in Japanese phase II studies (ACT5290, ACT5080). As a result, adult study ACT5290 showed no major differences in efficacy and safety between the two doses [see “2) Efficacy” and “3) Safety”]. In Study ACT5080 in pediatric patients, there were no major differences in safety between the two doses [see “4.3.B.3) Safety”], while 1 of 15 patients responded inadequately to 0.15 mg/kg of rasburicase [see “4.3.B.2) Efficacy”]. Also in a foreign phase II study (ACT2694), 1 of 12 patients responded inadequately to 0.15 mg/kg of rasburicase and a dose of 0.20 mg/kg was used in all subsequent foreign clinical studies. The intended population for rasburicase, i.e. patients at high risk of developing serious symptoms, e.g. acute renal failure, due to acutely elevated blood uric acid levels as a consequence of chemotherapy need a dose that ensures effectiveness. Therefore, a dose of 0.20 mg/kg that has been suggested to decrease plasma uric acid levels rapidly and reliably is appropriate.

However, as the TLS guidelines based on risk classification (*J Clin Oncol*. 2008; 26: 2767-78) were published after the filing of the application, the applicant explained that the two different doses of 0.15 mg/kg and 0.20 mg/kg need to be used according to the patient’s condition as follows:

The risks and benefits in Japanese and foreign clinical studies were assessed. As a result, the both doses are considered useful. A subgroup analysis of patients presenting with hyperuricemia at baseline showed that the percent reduction in uric acid at 4 hours after the first dose was higher in the 0.20 mg/kg group than in the 0.15 mg/kg group (the table below), suggesting that rasburicase at 0.20 mg/kg decreases uric acid more rapidly. Among Japanese pediatric patients presenting with hyperuricemia at baseline (Study ACT5080), 1 patient in the 0.15 mg/kg group was classified as a nonresponder due to an insufficient reduction in plasma uric acid.

Summary of efficacy results by dose group

			N	Hyperuricemic at baseline (> 7.5 mg/dL in patients aged ≥ 13 years, > 6.5 mg/dL in patients aged < 13 years)		Response rate* (%)	Mean plasma uric acid level at baseline (mg/dL)	Mean plasma uric acid level at 4 hours post-dose (mg/dL)	Percent reduction in uric acid at 4 hours after the first dose (%)
Children	Japanese study (ACT5080)	0.15 mg/kg	15	Yes	8	7/8 (87.5)	10.11	2.75	−77.50
				No	7	7/7 (100)	4.91	0.33	−93.11
		0.20 mg/kg	15	Yes	5	5/5 (100)	9.12	1.08	−90.44
				No	10	9/9 (100)	5.36	0.34	−94.2
	Foreign studies combined (ACT2511, ACT2694, EFC2975)	0.15 mg/kg	102	Yes	14	13/14 (92.9)	10.03	2.57	−77.34
				No	88	85/86 (98.8)	4.06	0.41	−89.81
		0.20 mg/kg	144	Yes	60	43/49 (87.8)	11.61	2.11	−83.84
				No	84	79/80 (98.8)	4.62	0.56	−87.54
Adults	Japanese study (ARD5290)	0.15 mg/kg	25	Yes	3	3/3 (100)	8.80	0.93	−89.40
				No	22	22/22 (100)	4.71	0.25	−95.88
		0.20 mg/kg	25	Yes	3	3/3 (100)	9.53	0.33	−96.74
				No	22	21/22 (95.5)	5.05	0.12	−97.77
	Foreign studies combined (ACT2511, ACT2694)	0.15 mg/kg	17	Yes	2	1/1 (100)	22.36	13.69	−59.32
				No	15	15/15 (100)	4.23	0.65	−80.49
		0.20 mg/kg	2	Yes	1	0/0 (−)	10.70	1.30	−87.85
				No	1	1/1 (100)	3.50	0.50	−85.71

*: The percentage of responders was calculated by dividing by the efficacy analysis population excluding unevaluable patients and unevaluable patients were not included in the denominator. Patients were classified as unevaluable if they could not be classified as either responders or nonresponders because of missing values for plasma uric acid, etc.

In addition to the above, taking into account that rapidly reducing a large amount of uric acid in blood is important for the prognosis of patients, among the intended population, patients who are hyperuricemic before the initiation of chemotherapy and patients who are non-hyperuricemic before the initiation of chemotherapy and at high risk for TLS should receive 0.20 mg/kg and patients who are non-hyperuricemic before the initiation of chemotherapy and at intermediate risk for TLS should receive 0.15 mg/kg.

Accordingly, in addition to a dose of 0.20 mg/kg, a dose of 0.15 mg/kg will also be recommended in the dosage and administration section and it will be advised that (a) a dose of 0.20 mg/kg should be administered to patients presenting with hyperuricemia before the initiation of rasburicase and patients who are considered at high risk for TLS and (b) a dose of 0.15 mg/kg should be administered to patients not presenting with hyperuricemia before the initiation of rasburicase.

PMDA's view on the dose per administration is as follows:
Based on the submitted data, the differences in the efficacy and safety of rasburicase between 0.15 mg/kg and 0.20 mg/kg are not necessarily clear and the applicant's claim about the choice between the two doses is a discussion based on an exploratory investigation and is merely reference information.

On the other hand, a dose of 0.20 mg/kg was used in a foreign phase III study (EFC2975),

which confirmed a significant difference between rasburicase and allopurinol for the primary endpoint of plasma uric acid $AUC_{0\text{-}96}$. Therefore, the appropriate dose of rasburicase should be 0.20 mg/kg.

However, as dose optimization is a post-marketing task, it is necessary to promptly analyze the information obtained from post-marketing surveillance and consider the conduct of clinical development for further dose optimization as appropriate.

4.3.B.7).(2) Duration of treatment

The applicant explained the rationale for the proposed duration of treatment of "5 days as a rule" as follows:

Usually, chemotherapeutic agents are used for about 5 days in patients with hematological malignancies and it has been reported that chemotherapy-induced TLS commonly occurs 48 to 72 hours after the initiation of chemotherapy (*Seminars in Oncology.* 2000;vol.27(No.3): 322-34). The mean duration of treatment with rasburicase was 5 days in foreign clinical studies. The approved duration of treatment is 5 to 7 days in Europe and 5 days in the US [Note by PMDA: the duration of treatment in Europe has been changed to up to 7 days]. Taking account of these points, a duration of treatment of 5 days was considered appropriate also in the Japanese population and chosen for Japanese phase II studies (ARD5290, ACT5080). Since the urinary allantoin levels in Study ARD5290 indicated that a large amount of uric acid had been produced with tumor lysis for as long as 4 to 5 days after the initiation of rasburicase and the plasma half life of rasburicase is approximately 22 hours, rasburicase needs to be administered for at least 5 days. However, as the severity of hyperuricemia varies from patient to patient and rasburicase administration for less than 5 days was able to control blood uric acid levels in some patients overseas, rasburicase administration for less than 5 days is expected to be able to control blood uric acid levels in some patients also in Japan.

Based on the above, the recommended duration of treatment in Japan is 5 days as its efficacy and safety have been confirmed in Japanese clinical studies, but bearing in mind that the duration of treatment may be adjusted at the discretion of a physician, "5 days as a rule" has been proposed. Although there have been no clinical studies that evaluated mainly the efficacy of rasburicase in patients with solid tumor malignancies, as rasburicase was able to control blood uric acid levels in clinical studies involving patients with hematological malignancies, the same duration of treatment as for patients with hematological malignancies is recommended also for patients with solid tumor malignancies.

PMDA asked the applicant to explain the efficacy and safety of dosing beyond 5 days in 97 of 265 patients in foreign clinical studies with a protocol-specified duration of treatment of up to 7 days (ACT2511, ACT2694, EFC2975).

The applicant responded as follows:

Of the 97 patients treated with rasburicase beyond 5 days, 2 patients were nonresponders. As these 2 patients could not receive rasburicase as scheduled after 5 days of treatment with rasburicase, their blood uric acid levels were elevated on Day 6 or Day 7 and these patients were classified as nonresponders. The response rate in pediatric patients was 97.9% (46 of 47 patients) in the 0.15 mg/kg group and 85.7% (36 of 42 patients) in the 0.20 mg/kg group and the response rate in adult patients was 100% (7 of 7 patients) in the 0.15 mg/kg group. Regarding safety, as there were no major differences in the incidence (the table below) or nature of adverse events between patients treated beyond 5 days and those treated for $\leq$ 5 days, there seems no major safety problem with dosing beyond 5 days. As the information identifying the nationality or race of patients was not collected in foreign clinical studies, whether there was a Japanese or East Asian patient treated beyond 5 days is unknown.

Adverse events in patients treated beyond 5 days

	Children				Adults	
	0.15 mg/kg (N = 47) [n (%)]		0.20 mg/kg (N = 43) [n (%)]		0.15 mg/kg (N = 7) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse events	46 (97.9)	10 (21.3)	42 (97.7)	25 (58.1)	7 (100)	6 (85.7)
Serious adverse events	9 (19.1)	6 (12.8)	16 (37.2)	11 (25.6)	3 (42.9)	3 (42.9)

PMDA's view on the duration of treatment is as follows:
Referring to the results from Japanese clinical studies in which rasburicase was to be administered for "5 days" (ACT5080, ARD5290), the applicant recommended a duration of treatment of 5 days as a rule, which is understandable. However, (a) while rasburicase has never been administered beyond 5 days in Japanese patients, the pivotal foreign phase III study (EFC2975) showed no particular safety problems with dosing for up to 7 days and (b) the duration of treatment with rasburicase will be determined according to each patient's clinical symptoms, e.g. blood uric acid levels. Therefore, only the maximum duration of treatment ("up to 7 days") should be specified. In addition, the following statements need to be included in the precautions for dosage and administration section of the package insert: "clinical symptoms and blood uric acid levels should be monitored and treatment with rasburicase should be limited to the minimum period required for the management of blood uric acid levels." and "the efficacy and safety of dosing beyond 7 days have not been established (no clinical experience)." Furthermore, using an information leaflet to promote the proper use, the detailed information on the duration of treatment with rasburicase in clinical studies etc. should be provided.

4.3.B.7).(3) Infusion rate
The infusion times of rasburicase in clinical studies were 30 minutes in a Japanese phase I study, a Japanese phase II study (ARD5290), and foreign phase III studies (EFC2975, EFC4978) and 25 to 35 minutes in a Japanese phase II study (ACT5080).

PMDA asked the applicant to explain whether rasburicase has been infused over less than 30 minutes and the relationship between the infusion rate and safety of rasburicase.

The applicant responded as follows:
In clinical studies that evaluated mainly the efficacy of rasburicase (ACT5080, ARD5290, ACT2694, ACT2511, EFC2975), rasburicase was infused over less than 30 minutes in 81 patients (a total of 123 infusions) and the infusion time was mostly ≥ 25 and < 30 minutes (102 of the 123 infusions). As to efficacy, the 11 patients infused over ≤ 20 minutes (7 patients in the 0.15 mg/kg group, 4 patients in the 0.20 mg/kg group) included 9 responders, 1 nonresponder, and 1 unevaluable patient. The one nonresponder was in the 0.20 mg/kg group and the infusion times on Day 3 and Day 5 were 20 minutes and as the blood uric acid level exceeded the reference range on Day 4 only (6.7 mg/dL), the patient was classified as a nonresponder. As it is predicted that a shorter infusion time will not significantly affect the blood rasburicase concentration at the end of infusion, a shorter infusion time is unlikely to be the cause of nonresponse in this case. Regarding safety, 4 serious adverse events occurred in 3 of the 11 patients (TLS, pneumothorax, pseudomonal sepsis, pneumonia), but a causal relationship to rasburicase was denied for any of the events.

PMDA asked the applicant to explain safety concerns associated with a rapid (bolus) infusion and measures to prevent misuse (a bolus infusion, overdose, etc.).

The applicant responded as follows:
Safety concerns associated with a rapid infusion may include the following possibilities: an

increased susceptibility to hypersensitivity reactions due to the rapid introduction of a foreign protein into the body; and an increased incidence of hemolytic anemia or methemoglobinemia due to hydrogen peroxide produced as a secondary-product of the degradation of a large amount of uric acid within a short period of time following a rapid increase in blood rasburicase concentration. However, the above-mentioned 11 patients infused over ≤ 20 minutes did not experience a serious adverse event of a hypersensitivity reaction such as anaphylaxis, hemolytic anemia, or methemoglobinemia. The infusion rate per body weight (dose per body weight [mg/kg]/infusion time [min]) was faster (> 0.008 mg/kg/min) in 8 patients (the infusion time was 15 minutes at shortest) and 2 of the 8 patients experienced 4 serious adverse events (pseudomonal sepsis, pneumonia, catheter related infection, bacteraemia) after rasburicase was infused faster and a causal relationship to rasburicase was denied for any of the events. Based on the above, although the currently available study data are limited, there seem no major safety concerns associated with the infusion rate as long as the infusion time is between 15 and 30 minutes.

As a measure to avoid a bolus infusion, the proposed brand name will be modified from "Rasuritek for I.V. Injection" to "Rasuritek for I.V. Infusion." In order to prevent misuse including overdose, caution will be provided in the package insert and a healthcare professional-directed information leaflet to promote the proper use of rasburicase will be prepared and distributed.

PMDA accepted the above response and concluded that it should be stated in the dosage and administration section that rasburicase should be administered as an intravenous infusion over at least 30 minutes.

4.3.B.7).(4) Diluent volume for patients aged ≤ 24 months

In Japanese Study ACT5080, the volume of normal saline for dilution was able to be reduced to 10 mL for patients aged ≤ 24 months at the discretion of the investigator or sub-investigator. This study included 2 patients aged ≤ 24 months (1 patient weighing 10.2 kg in the 0.15 mg/kg group, 1 patient weighing 5.7 kg in the 0.20 mg/kg group) and rasburicase was diluted into 10 mL of normal saline for both patients and the final infusion solution concentration was 0.15 mg/mL and 0.11 mg/mL, respectively.

The applicant explained about the concentarion of final infusion solution when the volume of normal saline for dilution is reduced for patients aged ≤ 24 months as follows:

When the dose is 0.20 mg/kg and rasburicase is diluted into 10 mL of normal saline for neonates (body weight, 3 kg) and children aged around 1 year (10 kg) or 50 mL of normal saline for children aged around 12 years (40 kg) and adults (60 kg), the final infusion solution concentration is 0.06 mg/dL, 0.18 mg/dL, 0.14 mg/dL, and 0.21 mg/dL, respectively, showing no major differences, and the concentration of final infusion solution does not become high even for patients aged ≤ 24 months. Analysis of all adverse events and hypersensitivity reactions in pediatric patients aged ≤ 24 months and those aged > 24 months and ≤ 17 years indicates that there are no major differences in safety between the age groups.

Summary of adverse events and hypersensitivity reactions by age group (Studies ACT2511, ACT2694, EFC5339, LTS3025, ACT5080, EFC2975)

Age	≤ 24 months		> 24 months and ≤ 17 years		Total	
Dose group (mg/kg)	0.15 (n = 8)	0.20 (n = 21)	0.15 (n = 109)	0.20 (n = 167)	0.15 (n = 117)	0.20 (n = 188)
No. of patients with an adverse event of hypersensitivity reaction (%)	3 (37.5)	16 (76.2)	55 (50.5)	108 (64.7)	58 (49.6)	124 (66.0)
No. of patients with any adverse event (%)	8 (100)	21 (100)	105 (96.3)	165 (98.8)	113 (96.6)	186 (98.9)
Adverse events by body system						
Gastrointestinal disorders	4 (50.0)	19 (90.5)	99 (90.8)	144 (86.2)	103 (88.0)	163 (86.7)
General disorders and administration site conditions	5 (62.5)	14 (66.7)	59 (54.1)	111 (66.5)	64 (54.7)	125 (66.5)
Respiratory, thoracic and mediastinal disorders	0	8 (38.1)	23 (21.1)	74 (44.3)	23 (19.7)	82 (43.6)
Metabolism and nutrition disorders	2 (25.0)	8 (38.1)	16 (14.7)	69 (41.3)	18 (15.4)	77 (41.0)
Skin and subcutaneous tissue disorders	4 (50.0)	14 (66.7)	35 (32.1)	61 (36.5)	39 (33.3)	75 (39.9)
Musculoskeletal and connective tissue disorders	0	1 (4.8)	43 (39.4)	72 (43.1)	43 (36.8)	73 (38.8)
Infections and infestations	3 (37.5)	12 (57.1)	27 (24.8)	55 (32.9)	30 (25.6)	67 (35.6)
Blood and lymphatic system disorders	0	7 (33.3)	20 (18.3)	59 (35.3)	20 (17.1)	66 (35.1)
Investigations	2 (25.0)	3 (14.3)	25 (22.9)	63 (37.7)	27 (23.1)	66 (35.1)
Nervous system disorders	0	2 (9.5)	47 (43.1)	63 (37.7)	47 (40.2)	65 (34.6)
Vascular disorders	1 (12.5)	5 (23.8)	7 (6.4)	42 (25.1)	8 (6.8)	47 (25.0)
Renal and urinary disorders	0	2 (9.5)	4 (3.7)	33 (19.8)	4 (3.4)	35 (18.6)
Psychiatric disorders	0	2 (9.5)	6 (5.5)	25 (15.0)	6 (5.1)	27 (14.4)
Cardiac disorders	1 (12.5)	5 (23.8)	7 (6.4)	21 (12.6)	8 (6.8)	26 (13.8)
Eye disorders	0	4 (19.0)	2 (1.8)	22 (13.2)	2 (1.7)	26 (13.8)
Injury, poisoning and procedural complications	2 (25.0)	3 (14.3)	6 (5.5)	19 (11.4)	8 (6.8)	22 (11.7)
Hepatobiliary disorders	0	0	6 (5.5)	11 (6.6)	6 (5.1)	11 (5.9)
Endocrine disorders	0	2 (9.5)	2 (1.8)	7 (4.2)	2 (1.7)	9 (4.8)
Ear and labyrinth disorders	0	0	0	7 (4.2)	0	7 (3.7)
Reproductive system and breast disorders	0	1 (4.8)	2 (1.8)	6 (3.6)	2 (1.7)	7 (3.7)
Immune system disorders	0	0	2 (1.8)	4 (2.4)	2 (1.7)	4 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (4.8)	3 (2.8)	3 (1.8)	3 (2.6)	4 (2.1)
Surgical and medical procedures	0	1 (4.8)	0	0	0	1 (0.5)

PMDA concluded as follows:

(a) Generally, compared to adults, children have higher total body water per body weight and a higher percentage of extracellular fluid relative to intracellular fluid, but a lower absolute volume of extracellular fluid and a narrow margin of safety with intravenous hydration. Thus, safety concerns associated with the use of the same preparation procedure as for adults (the volume of the infusion solution) are understandable, (b) the possibility that the concentration of final infusion solution becomes higher in patients aged ≤ 24 months compared to other age groups has not been suggested in the study protocols, and (c) although patients aged ≤ 24 months for whom the diluent volume was reduced to 10 mL in clinical studies are very limited, there have been no safety problems to date. Therefore, the preparation procedure for rasburicase may be described in the precautions for dosage and administration and precautions in use sections of the package insert so that the volume of normal saline for dilution may be reduced to 10 mL for patients aged ≤ 24 months.

4.3.B.7).(5) Time to chemotherapy

The applicant explained the relationship between the initiation of rasburicase and the time to chemotherapy as follows:

Generally, the prevention of TLS is clinically important for patients with hematological malignancies or solid tumor malignancies scheduled to receive chemotherapy. Chemotherapy-induced TLS occurs 2 to 4 days after the initiation of chemotherapy (*Contrib Nephrol* 2005; 147: 61-8, etc.) and rasburicase needs to be administered during the period when TLS is likely to develop. If chemotherapy is initiated within 24 hours after the first dose of rasburicase, the period when TLS is likely to develop will fall within the period of administration of rasburicase. If chemotherapy is initiated before the patient's blood uric acid level is sufficiently lowered, a large amount of uric acid produced by tumor lysis is likely to impose a heavy burden on the kidneys. Therefore, as in clinical studies, it is recommended that chemotherapy should be initiated after confirming that the blood uric acid level at 4 hours after the first dose of rasburicase is low. Accordingly, it will be stated in the precautions for dosage and administration section of the package insert that "chemotherapy should be initiated 4 to 24 hours after the first dose of rasburicase."

PMDA accepted the applicant's explanation.

4.3.B.7).(6) Administration of more than one course of rasburicase

Taking account of anti-rasburicase antibody production following the administration of rasburicase [see "4.3.B.4) Anti-rasburicase antibodies"], PMDA asked the applicant to explain concerns associated with the administration of more than one course of rasburicase (hereinafter referred to as retreatment).

The applicant responded as follows:

According to an integrated report on foreign phase II studies (EFC4983, EFC5339), the incidence and severity of adverse events and serious adverse events were similar between patients previously treated (pre-treated group, 13 adult patients and 6 pediatric patients) and those not previously treated (naïve group, 98 adult patients and 10 pediatric patients) with a uricolytic agent and adverse events including hypersensitivity reactions and hemolytic reactions also showed no tendency to increase in the pre-treated group [see "4.3.B.3) Safety"]. In addition, all patients in Study EFC4983 and about 90% of patients in Study EFC5339 were classified as responders, the response rate was comparable between the pre-treated and naïve groups (the table below), and there was no loss of efficacy of rasburicase in the pre-treated group. However, as the number of retreated cases (19 patients) was limited, it is hard to say that the safety and efficacy of retreatment with rasburicase have been confirmed and retreatment with rasburicase is not recommended.

Efficacy results in patients previously treated or not with a uricolytic agent

	EFC4983		EFC5339					
	Pretreated	Naïve	Children	Pretreated Adults	Total	Children	Naïve Adults	Total
Responders [(n/N (%)]	10/10 (100)	23/23 (100)	5/6 (83.3)	3/3 (100)	8/9 (88.9)	10/10 (100)	67/75 (89.3)	77/85 (90.6)

PMDA asked the applicant to explain the efficacy and safety of retreatment with rasburicase.

The applicant responded as follows:

A total of 83 patients were retreated with rasburicase (excluding patients with other uricolytic agents) in foreign clinical studies (LTS3025, LTS3256, LTS3257). Blood uric acid data were collected for only a portion of the patients (9 patients in Studies LTS3025 and LTS3256), which were used to assess the efficacy of retreatment retrospectively. As a result, all of these patients

were classified as responders. Regarding safety, among the serious adverse events reported (the table below), a causal relationship to rasburicase could not be denied for "hypersensitivity" only (0 patient in the first course of treatment, 1 of 83 patients [1.2%] in the second course of treatment, 2 of 19 patients [10.5%] in the third or subsequent course of treatment) and taking also account of the possibility that anti-rasburicase antibodies develop ≥ 14 days after the first dose of rasburicase, retreatment with rasburicase is not recommended from a safety point of view.

Serious adverse events in retreated patients (Studies LTS3025, LTS3256, LTS3257)

Event	First course (n = 83)		Second course (n = 83)		Third or subsequent course (n = 19)	
	All Grades [n (%)]	Grade 3/4 [n (%)]	All Grades [n (%)]	Grade 3/4 [n (%)]	All Grades [n (%)]	Grade 3/4 [n (%)]
Any serious adverse event	10 (12.0)	10 (12.0)	17 (20.5)	16 (19.3)	5 (26.3)	3 (15.8)
Febrile neutropenia	4 (4.8)	4 (4.8)	0	0	0	0
Respiratory distress	2 (2.4)	2 (2.4)	0	0	0	0
Neutropenia	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	0	0
Neutropenic sepsis	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	0	0
Disease progression	1 (1.2)	1 (1.2)	5 (6.0)	4 (4.8)	2 (10.5)	2 (10.5)
Renal failure	1 (1.2)	1 (1.2)	0	0	1 (5.3)	1 (5.3)
Herpes zoster	1 (1.2)	1 (1.2)	0	0	0	0
Pyrexia	1 (1.2)	0	0	0	0	0
Caecitis	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	0	0
Vomiting	1 (1.2)	1 (1.2)	0	0	0	0
Clostridium difficile colitis	0	0	1 (1.2)	1 (1.2)	0	0
Gastrointestinal haemorrhage	0	0	1 (1.2)	1 (1.2)	0	0
Hypersensitivity	0	0	1 (1.2)	1 (1.2)	2 (10.5)	0
Arthralgia	0	0	1 (1.2)	1 (1.2)	0	0
Acute renal failure	0	0	1 (1.2)	1 (1.2)	0	0
Haemothorax	0	0	1 (1.2)	1 (1.2)	0	0
Thrombocytopenia	0	0	1 (1.2)	1 (1.2)	0	0
Respiratory arrest	0	0	1 (1.2)	1 (1.2)	0	0
Respiratory failure	0	0	2 (2.4)	2 (2.4)	0	0
TLS	0	0	1 (1.2)	1 (1.2)	0	0
Cardiac arrest	0	0	2 (2.4)	2 (2.4)	0	0
Cardiac failure	0	0	0	0	1 (5.3)	1 (5.3)
General physical health deterioration	0	0	0	0	1 (5.3)	1 (5.3)
Multi-organ failure	0	0	1 (1.2)	1 (1.2)	0	0
Intracranial haemorrhage	0	0	1 (1.2)	1 (1.2)	0	0
Disseminated intravascular coagulation	0	0	1 (1.2)	1 (1.2)	0	0
Septic shock	0	0	1 (1.2)	1 (1.2)	0	0
Pneumonia	0	0	1 (1.2)	1 (1.2)	0	0
Anaemia	0	0	0	0	1 (5.3)	1 (5.3)
Ascites	0	0	0	0	1 (5.3)	0
Peripheral oedema	0	0	0	0	1 (5.3)	0
Benign intracranial hypertension	0	0	0	0	1 (5.3)	1 (5.3)

PMDA asked the applicant to explain the efficacy and safety of rasburicase in patients with anti-rasburicase antibodies.

The applicant responded as follows:
Among the patients retreated with rasburicase in Study LTS3257, 42 patients had anti-rasburicase antibody assay results before and after retreatment, of whom 6 patients (15%) were positive before retreatment. Among these 6 patients, 4 patients were assessed for safety of retreatment (though not assessed for the efficacy of retreatment), and 2 of the 4 patients experienced serious allergic reactions. The detected adverse events were assessed as causally related to rasburicase. The details were unknown for the 2 patients other than the 4 patients.

PMDA asked for the applicant's view on how to determine whether rasburicase should be administered to patients with an unknown history of prior treatment with rasburicase due to

transfer from another hospital etc. and how to handle such cases.

The applicant responded as follows:
As rasburicase is used in patients receiving cancer chemotherapy, even if a patient is transferred from another hospital, the information on the treatment that the patient received at the previous medical institution can be obtained during history taking (from the patient or the patient's authorized representative) at the new medical institution and in the case of patients who received chemotherapy, their history of prior treatment with rasburicase can be confirmed by contacting the previous medical institution in most cases. If the use of rasburicase is considered necessary, but a history of prior treatment with rasburicase can not be confirmed, the possiblity of being retreated with rasburicase can not be excluded, but the attending physician will determine whether rasburicase should be used or not, balancing the risks (the development of hypersensitivity reactions) and benefits (a rapid reduction in blood uric acid).

PMDA considers that the use of rasburicase should not be uniformly restricted in patients who have to be retreated with rasburicase or patients with an unknown history of prior treatment with rasburicase due to transfer from another hospital etc. However, at present, (a) patients retreated with rasburicase are limited, (b) some of the anti-rasburicase antibodies detected after rasburicase administration were neutralizing, which raises efficacy concerns, and (c) retreated patients with positive anti-rasburicase antibodies experienced serious adverse events, which raises safety concerns. Thus, PMDA considers that retreatment is not recommended, at least under the circumstances where the presence or absence of antibodies can not be confirmed. Accordingly, it should be cautioned in the precautions for dosage and administration section of the package insert that "the efficacy and safety of retreatment with rasburicase have not been established," and it is necessary to continue to collect information on antibody production etc. in patients retreated with rasburicase after the market launch.

PMDA considers that the above-mentioned patients may need to be tested for anti-rasburicase antibodies from a clinical point of view. PMDA asked the applicant to explain how to respond if testing for anti-rasburicase antibodies is requested in clinical practice.

The applicant responded as follows:
As the relationship between anti-rasburicase antibody production and adverse events such as hypersensitivity reactions has not been identified, anti-rasburicase antibody testing is of little clinical significance and there is no antibody assay development plan in Japan. Although urgent test requests are expected, it takes time to obtain test results, etc. Therefore, medical institutions that request antibody testing will be fully explained about the above situations and told that their requests can not be met.

PMDA considers that the development of anti-rasburicase antibody assay needs to be considered depending on the uses of rasburicase after the market launch, which will be discussed at the Expert Discussion.

4.3.B.7).(7) Use of rasburicase with allopurinol
Concomitant use of allopurinol was prohibited in Japanese phase II studies (ACT5080, ARD5290).

The applicant explained about the use of rasburicase with allopurinol as follows:
Since concurrent administration of rasburicase and allopurinol can not bring out the strengths of each drug in terms of its mode of action etc., there is no possibility that the two drugs are concurrently administered. If allopurinol is not effective, allopurinol is not tolerated, or blood uric acid levels rise unexpectedly and acutely after the initiation of chemotherapy, the blood uric

acid levels will need to be controlled by rasburicase and rasburicase will have to be used following allopurinol. There are several case reports on this usage (*Pharmacothrapy* 2006; 26: 806-12). Furthermore, the possibility that rasburicase is used in combination with allopurinol (e.g. sequential treatment with rasburicase followed by allopurinol as in Study EFC4978) according to the patient's condition at the discretion of the physician in medical practice can not be ruled out.

PMDA understands that there may be cases of unavoidable use of rasburicase in combination with allopurinol, but can not recommend the use of rasburicase with allopurinol due to a lack of safety information. However, as there is a possibility that rasburicase is used with allopurinol, e.g. in the regimen as tested in Study EFC4978, after the market launch, PMDA considers that it is necessary to collect safety information on the use of rasburicase with allopurinol and appropriately provide the information to the medical practice.

4.3.B.7).(8) Use of rasburicase for the treatment of an unexpected acute rise in blood uric acid after the initiation of chemotherapy

PMDA asked the applicant to explain the possibility that rasburicase is not administered prior to chemotherapy, but is administered during chemotherapy for the treatment of an acute rise in blood uric acid.

The applicant responded as follows:

In medical practice, even patients considered not to require the management of blood uric acid levels before the initiation of chemotherapy may experience an unexpected acute rise in blood uric acid after the initiation of chemotherapy. Use of rasburicase in such patients (hereinafter referred to as rescue treatment) is also expected to rapidly reduce blood uric acid levels.
However, since rasburicase has never been used for such treatment purpose in clinical studies or in marketing experience according to overseas post-marketing safety information, the efficacy and safety of rasburicase in this setting are unknown. Therefore, although the use of rasburicase prior to the initiation of chemotherapy is recommended, taking account of the mode of action of rasburicase and its blood uric acid lowering effect demonstrated in clinical studies, rasburicase may be administered with care to patients requiring rescue treatment, balancing the risks and benefits.

PMDA can not recommend the use of rasburicase for rescue purpose due to a lack of information on rasburicase as rescue treatment. However, as the onset of TLS can not always be predicted precisely, PMDA considers that it is necessary to collect information on any patient who received rasburicase as rescue treatment after the market launch and appropriately provide the information to the medical practice.

4.3.B.7).(9) Overdosage

The applicant explained 2 cases of overdosage with rasburicase reported from the foreign marketing experience as follows:

These two cases were both accidental overdosage. One case was a leukemic infant aged 16 days and the infant mistakenly received one dose of rasburicase 1.2 mg, instead of 0.60 mg (0.20 mg/kg), but experienced no adverse drug reactions. The other case was a 69 year-old patient with diffuse large B-cell lymphoma who mistakenly received one dose of 70 mg, instead of 10.5 mg (0.15 mg/kg) and there were multiple reports of non-serious laboratory abnormalities, but no reports of symptoms or signs associated with the overdose.

PMDA considers as follows:

As an overdose of rasburicase can induce hemolytic reaction via increased hydrogen peroxide concentration, its proper use needs to be ensured. Using a healthcare professional-directed

information leaflet to promote the proper use of rasburicase etc., which will be prepared and distributed by the applicant, appropriate caution should be provided.

4.3.B.8) Post-marketing investigations

The applicant explained about the important risks associated with rasburicase as follows:
(a) Rasburicase is associated with the risk of hypersensitivity including anaphylactic shock.
(b) Rasburicase is associated with the risk of methemoglobinemia or hemolytic anemia; patients with G6PD deficiency have a higher incidence of hemolytic anemia.
(c) As there were no retreated patients in Japanese clinical studies and the number of retreated patients was limited even overseas, no sufficient data on rasburicase retreatment are available.

PMDA asked the applicant to present a post-marketing surveillance plan.

The applicant explained as follows:
A drug use-results survey of 3 years duration, including consecutive patients, will be conducted, in which patients will be observed until 1 month after the last administration. The items to be investigated include (a) patient background (G6PD deficiency status for patients with hemolytic anemia or methemoglobinemia only), (b) the treatment for malignancies immediately before and after the use of rasburicase, (c) information on administration of rasburicase and concomitant drugs, and (d) laboratory test values and adverse events. Since the prevalence of G6PD deficiency and the incidences of methemoglobinemia and hemolytic anemia in Japan are very low and the intended population is small, a planned sample size of 200 patients for safety analysis was chosen, also with a view to the feasibility, based on the number of cases of 120 that provides a 95% probability of detecting one case of adverse drug reactions with an incidence of 2.5% (i.e. the incidence of Grade $\geq$ 3 hypersensitivity reactions in Japanese clinical studies).

After completion of the survey period, all medical institutions to which rasburicase has been delivered will be asked if there is a retreated patient and if so, the details on administration of rasburicase and the occurrence of adverse events, especially hypersensitivity reactions, will be investigated retrospectively. If a retreatment case is reported during the survey period, a detailed investigation will be conducted as required. Also when the use of rasburicase in pregnant women/nursing mothers or for hyperuricemia associated with radiation therapy is reported, a detailed investigation will be conducted wherever possible to assess the safety of rasburicase in these cases.

PMDA considers as follows:
As the information on rasburicase in Japanese patients is limited, in addition to the investigations presented by the applicant, it is necessary to (a) collect information on the avoidance of renal impairment requiring hemodialysis, (b) determine if patients with methemoglobinemia or hemolytic anemia have a genetic deficiency etc. of G6PD or glutathione peroxidase, which are endogenous hydrogen peroxide scavenging mechanisms, (c) collect information on patients who received rasburicase as rescue treatment and provide the information appropriately, and (d) assess anti-rasburicase antibody production in patients retreated with rasburicase, via post-marketing surveillance. The information on the use of rasburicase with allopurinol and the doses of rasburicase should also be collected and the necessity of clinical development for further optimized use should be determined.

The surveillance plan including the items to be investigated and sample size will be finalized, taking account of comments from the Expert Discussion.

4.4 Adverse events observed in clinical studies

Deaths reported in Japanese and foreign clinical studies submitted as the safety evaluation data are presented in "4.3 Clinical efficacy and safety." Other main adverse events are shown below.

In Studies TDR2681, ACT2694, ACT2511, EFC2975, LTS3025, LTS3256, and LTS3257 in which causality of adverse events to study drug was assessed as "likely," "unlikely," "no," or "unknown," adverse events assessed as "likely," "unlikely," or "unknown" were counted as those for which a causal relationship to study drug could not be denied.

4.4.1) Japanese phase I study (Study TDU4730)

Adverse events occurred in 0 of 6 subjects (0%) in the rasburicase 0.05 mg/kg group, 3 of 6 subjects (50.0%) in the rasburicase 0.10 mg/kg group, 3 of 6 subjects (50.0%) in the rasburicase 0.15 mg/kg group, 1 of 6 subjects (16.7%) in the rasburicase 0.20 mg/kg group, and 1 of 8 subjects (12.5%) in the placebo group. Of which, headache (2 subjects in the rasburicase 0.10 mg/kg group [33.3%]) was reported as an adverse event occurring in at least 2 subjects.

There were no serious adverse events or adverse events leading to study drug discontinuation.

4.4.2) Japanese phase II study (Study ACT5080)

Adverse events occurred in 15 of 15 subjects (100%) in the rasburicase 0.15 mg/kg group and 15 of 15 subjects (100%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.15 mg/kg group (N = 15) [n (%)]		0.20 mg/kg group (N = 15) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	15 (100)	15 (100)	15 (100)	15 (100)
ALT increased	14 (93.3)	10 (66.7)	14 (93.3)	11 (73.3)
Alopecia	13 (86.7)	0	14 (93.3)	0
Lymphocyte count decreased	13 (86.7)	12 (80.0)	13 (86.7)	12 (80.0)
White blood cell count decreased	14 (93.3)	13 (86.7)	13 (86.7)	13 (86.7)
AST increased	14 (93.3)	5 (33.3)	12 (80.0)	7 (46.7)
Neutrophil count decreased	14 (93.3)	14 (93.3)	12 (80.0)	11 (73.3)
Nausea	11 (73.3)	0	11 (73.3)	0
γ-GTP increased	12 (80.0)	2 (13.3)	10 (66.7)	1 (6.7)
Blood bilirubin increased	7 (46.7)	1 (6.7)	10 (66.7)	3 (20.0)
Vomiting	10 (66.7)	0	10 (66.7)	0
Blood albumin decreased	6 (40.0)	0	9 (60.0)	0
Constipation	8 (53.3)	0	8 (53.3)	0
Antithrombin III decreased	5 (33.3)	0	7 (46.7)	1 (6.7)
Blood sodium decreased	4 (26.7)	1 (6.7)	7 (46.7)	0
Blood urea increased	3 (20.0)	0	7 (46.7)	0
Anorexia	5 (33.3)	2 (13.3)	7 (46.7)	2 (13.3)
Blood LDH increased	7 (46.7)	2 (13.3)	6 (40.0)	1 (6.7)
Pyrexia	6 (40.0)	0	6 (40.0)	0
Abdominal pain	4 (26.7)	1 (6.7)	6 (40.0)	0
Platelet count decreased	10 (66.7)	7 (46.7)	5 (33.3)	3 (20.0)
Stomatitis	6 (40.0)	1 (6.7)	5 (33.3)	0
Headache	3 (20.0)	0	5 (33.3)	0
Haemoglobin decreased	5 (33.3)	3 (20.0)	4 (26.7)	4 (26.7)
Diarrhoea	8 (53.3)	1 (6.7)	4 (26.7)	1 (6.7)
Infection	1 (6.7)	1 (6.7)	4 (26.7)	2 (13.3)
Blood potassium decreased	1 (6.7)	1 (6.7)	4 (26.7)	0

Blood fibrinogen decreased	3 (20.0)	3 (20.0)	4 (26.7)	3 (20.0)
Back pain	4 (26.7)	0	4 (26.7)	0
Cushingoid	1 (6.7)	0	3 (20.0)	0
Neutrophil count increased	0	0	3 (20.0)	0
Puncture site pain	1 (6.7)	0	3 (20.0)	0
Protein total decreased	1 (6.7)	0	3 (20.0)	0
Injection site extravasation	0	0	3 (20.0)	0
Disseminated intravascular coagulation	2 (13.3)	2 (13.3)	3 (20.0)	1 (6.7)
Epistaxis	5 (33.3)	0	3 (20.0)	1 (6.7)
Anaemia	7 (46.7)	6 (40.0)	3 (20.0)	2 (13.3)
Urticaria	3 (20.0)	0	3 (20.0)	0
Blood calcium decreased	3 (20.0)	0	2 (13.3)	0
Malaise	3 (20.0)	0	2 (13.3)	0
Hyponatraemia	4 (26.7)	1 (6.7)	2 (13.3)	1 (6.7)
Febrile neutropenia	4 (26.7)	4 (26.7)	2 (13.3)	2 (13.3)
Blood potassium increased	3 (20.0)	0	1 (6.7)	0
Blood phosphorus increased	3 (20.0)	0	1 (6.7)	0
Hyperbilirubinaemia	3 (20.0)	2 (13.3)	1 (6.7)	1 (6.7)
Weight decreased	5 (33.3)	1 (6.7)	1 (6.7)	0
Hypoalbuminaemia	4 (26.7)	0	1 (6.7)	0
Lymphocyte count increased	3 (20.0)	0	0	0

Serious adverse events occurred in 1 of 15 subjects (6.7%) in the 0.15 mg/kg group, which included brain herniation, cerebral haemorrhage, and brain oedema. A causal relationship to study drug was denied for any of these events.

There were no adverse events leading to study drug discontinuation.

Adverse events occurring between the first dose of rasburicase and the initiation of chemotherapy were reported by 4 of 15 subjects (26.7%) in the 0.15 mg/kg group and 6 of 15 subjects (40.0%) in the 0.20 mg/kg group. Of which, neutrophil count decreased (2 subjects in the 0.20 mg/kg group [13.3%]) was reported as an adverse event occurring in at least 2 subjects.

4.4.3) Japanese phase II study (Study ARD5290)

Adverse events occurred in 25 of 25 subjects (100%) in the rasburicase 0.15 mg/kg group and 25 of 25 subjects (100%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.15 mg/kg group (N = 25) [n (%)]		0.20 mg/kg group (N = 25) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	25 (100)	25 (100)	25 (100)	24 (96.0)
White blood cell count decreased	24 (96.0)	22 (88.0)	22 (88.0)	21 (84.0)
Neutrophil count decreased	22 (88.0)	22 (88.0)	19 (76.0)	19 (76.0)
Lymphocyte count decreased	16 (64.0)	15 (60.0)	18 (72.0)	15 (60.0)
Alopecia	20 (80.0)	0	18 (72.0)	0
Nausea	12 (48.0)	0	15 (60.0)	1 (4.0)
AST increased	6 (24.0)	0	11 (44.0)	1 (4.0)
Constipation	10 (40.0)	4 (16.0)	11 (44.0)	3 (12.0)
Platelet count decreased	8 (32.0)	4 (16.0)	9 (36.0)	3 (12.0)
Vomiting	6 (24.0)	0	9 (36.0)	0
ALT increased	7 (28.0)	1 (4.0)	8 (32.0)	1 (4.0)
Malaise	7 (28.0)	0	8 (32.0)	0
Stomatitis	3 (12.0)	0	8 (32.0)	1 (4.0)

Anorexia	7 (28.0)	1 (4.0)	8 (32.0)	1 (4.0)
Haemoglobin decreased	11 (44.0)	4 (16.0)	6 (24.0)	0
Pyrexia	4 (16.0)	0	6 (24.0)	1 (4.0)
Blood ALP increased	4 (16.0)	0	5 (20.0)	0
Blood LDH increased	5 (20.0)	0	5 (20.0)	1 (4.0)
Hyperglycaemia	6 (24.0)	2 (8.0)	5 (20.0)	1 (4.0)
Anaemia	4 (16.0)	2 (8.0)	5 (20.0)	3 (12.0)
Diarrhoea	8 (32.0)	0	4 (16.0)	0
Oedema	5 (20.0)	0	4 (16.0)	0
Blood bilirubin increased	7 (28.0)	0	3 (12.0)	0
Hypokalaemia	5 (20.0)	1 (4.0)	3 (12.0)	1 (4.0)
Rash	5 (20.0)	1 (4.0)	3 (12.0)	0
Headache	5 (20.0)	0	2 (8.0)	0
Insomnia	5 (20.0)	0	2 (8.0)	0

Serious adverse events were reported by 1 of 25 subjects (4.0%) in the 0.15 mg/kg group (unstable angina) and by 2 of 25 subjects (8.0%) in the 0.20 mg/kg group (hepatic enzyme increased and sepsis/septic shock, 1 subject each [4.0%]). Of which, a causal relationship to study drug could not be denied for hepatic enzyme increased in the 0.20 mg/kg group.

Adverse events leading to study drug discontinuation were observed in 1 of 25 subjects (4.0%) in the 0.20 mg/kg group, which were hepatic enzyme increased and blood LDH increased.

Adverse events occurring between the first dose of rasburicase and the initiation of chemotherapy were reported by 2 of 25 subjects (8.0%) in the 0.15 mg/kg group and 6 of 25 subjects (24.0%) in the 0.20 mg/kg group. Of which, those reported by at least 2 subjects were hypersensitivity and rash in the 0.20 mg/kg group (2 subjects each [8.0%]).

4.4.4) Foreign phase I study (Study TDR2681)

Following a single dose of rasburicase (0.05 mg/kg group, 0.10 mg/kg group, 0.15 mg/kg group, 0.20 mg/kg group), no adverse events were reported. Following multiple doses of rasburicase, adverse events occurred in 1 of 4 subjects (25.0%) in the 0.10 mg/kg group, 1 of 4 subjects (25.0%) in the 0.15 mg/kg group, and 0 of 4 subjects (0%) in the 0.20 mg/kg group.

There were no serious adverse events or adverse events leading to study drug discontinuation.

4.4.5) Foreign phase II study (Study ACT2694)

Adverse events occurred in 11 of 12 subjects (91.7%) in the rasburicase 0.15 mg/kg group and 119 of 119 subjects (100%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.15 mg/kg group (N = 12) [n (%)]		0.20 mg/kg group (N = 119) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	11 (91.7)	8 (66.7)	119 (100)	74 (62.2)
Vomiting	8 (66.7)	0	72 (60.5)	3 (2.5)
Pyrexia	6 (50.0)	2 (16.7)	52 (43.7)	8 (6.7)
Nausea	5 (41.7)	0	44 (37.0)	3 (2.5)
Diarrhoea	2 (16.7)	0	40 (33.6)	1 (0.8)
Headache	6 (50.0)	0	26 (21.8)	0
Mucosal inflammation	3 (25.0)	1 (8.3)	26 (21.8)	11 (9.2)
Abdominal pain	2 (16.7)	0	26 (21.8)	3 (2.5)
Constipation	2 (16.7)	0	25 (21.0)	1 (0.8)

Rash	3	(25.0)	1	(8.3)	16	(13.4)	1	(0.8)
Alopecia	4	(33.3)	0		7	(5.9)	0	
Weight decreased	3	(25.0)	0		3	(2.5)	2	(1.7)
Oral pain	3	(25.0)	0		0		0	

Serious adverse events (if the same event occurred more than once in the same patient, only the first episode was counted) were reported by 5 of 12 subjects (41.7%) in the 0.15 mg/kg group, which included pyrexia and bacterial sepsis (2 subjects each [16.7%]) and sepsis, abdominal pain, and diabetes mellitus (1 subject each [8.3%]), and by 53 of 119 subjects (44.5%) in the 0.20 mg/kg group, which included pyrexia (23 subjects [19.3%]), mucosal inflammation (7 subjects [5.9%]), neutropenia (6 subjects [5.0%]), sepsis (6 subjects [5.0%]), and bacteraemia (3 subjects [2.5%]) etc. Of which, a causal relationship to study drug could not be denied for pyrexia and diabetes mellitus (1 subject each [8.3%]) in the 0.15 mg/kg group and pyrexia (8 subjects [6.7%]), neutropenia (5 subjects [4.2%]), and bacteraemia, mucosal inflammation, and sepsis (2 subjects each [1.7%]) etc. in the 0.20 mg/kg group.

Adverse events leading to study drug discontinuation were observed in 1 of 119 subjects (0.8%) in the 0.20 mg/kg group, which were dyspnoea at rest and bronchospasm.

4.4.6) Foreign phase II study (Study ACT2511)

Adverse events occurred in 103 of 107 subjects (96.3%) in the rasburicase 0.15 mg/kg group. Adverse events with an incidence of 20% or greater were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.15 mg/kg group (N = 107) [n (%)]			
	All Grades		Grade 3/4	
Any event	103	(96.3)	34	(31.8)
Vomiting	45	(42.1)	0	
Pyrexia	41	(38.3)	8	(7.5)
Abdominal pain	37	(34.6)	4	(3.7)
Headache	33	(30.8)	1	(0.9)
Constipation	26	(24.3)	1	(0.9)

Serious adverse events were reported by 25 of 107 subjects (23.4%), which included pyrexia (9 subjects [8.4%]), acute renal failure (3 subjects [2.8%]), neutropenia (3 subjects [2.8%]), tumor lysis syndrome (2 subjects [1.9%]), and tachyarrhythmia (2 subjects [1.9%]) etc. Of which, a causal relationship to study drug could not be denied for acute renal failure (2 subjects [1.9%]) and acute pulmonary oedema, dyspnoea, nephritis, tachyarrhythmia, and haemolysis (1 subject each [0.9%]).

Adverse events leading to study drug discontinuation were observed in 2 of 107 subjects (1.9%), which included allergic dermatitis and acute renal failure (1 subject each [0.9%]).

4.4.7) Foreign phase III study (Study EFC2975)

Adverse events occurred in 26 of 27 subjects (96.3%) in the rasburicase 0.20 mg/kg group and 25 of 25 subjects (100%) in the allopurinol group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	Rasburicase group (N = 27) [n (%)]		Allopurinol group (N = 25) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	26 (96.3)	15 (55.6)	25 (100.0)	18 (72.0)
Vomiting	15 (55.6)	1 (3.7)	9 (36.0)	1 (4.0)

Pyrexia	11 (40.7)	0	8 (32.0)	1 (4.0)
Nausea	9 (33.3)	1 (3.7)	6 (24.0)	2 (8.0)
Diarrhoea	8 (29.6)	0	4 (16.0)	1 (4.0)
Back pain	8 (29.6)	0	8 (32.0)	0
Headache	7 (25.9)	0	3 (12.0)	0
Irritability	5 (18.5)	0	5 (20.0)	0
Mucosal inflammation	3 (11.1)	0	8 (32.0)	3 (12.0)
Epistaxis	3 (11.1)	0	6 (24.0)	0

Serious adverse events were reported by 4 of 27 subjects (14.8%) in the rasburicase group, which included vomiting (2 subjects [7.4%]) and diarrhoea, stomatitis, pyrexia, haemolysis, and convulsion (1 subject each [3.7%]), and by 8 of 25 subjects (32.0%) in the allopurinol group, which included pyrexia (2 subjects [8.0%]) and vomiting, pseudomonal sepsis, coagulopathy, mouth haemorrhage, laryngospasm, neutropenia, hyperglycaemia, meningitis, dehydration, hypotension, intracranial haemorrhage, brain herniation, cerebral haemorrhage, brain oedema, and sepsis (1 subject each [4.0%]). Of which, a causal relationship to study drug could not be denied for haemolysis, vomiting, and convulsion (1 subject each [3.7%]) in the rasburicase group and vomiting, dehydration, and hypotension (1 subject each [3.7%]) in the allopurinol group.

An adverse event leading to study drug discontinuation was reported by 1 of 27 subjects (3.7%) in the rasburicase group, which was haemolysis.

4.4.8) Foreign phase II study (Study EFC4982)

Adverse events occurred in 100 of 100 subjects (100%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.20 mg/kg group (N = 100) [n (%)]	
	All Grades	Grade 3/4
Any event	100 (100)	88 (88.0)
Haemoglobin	94 (94.0)	37 (37.0)
Blood LDH	86 (86.0)	9 (9.0)
Blood phosphorus	76 (76.0)	16 (16.0)
Neutrophil count	65 (65.0)	53 (53.0)
Platelet count	52 (52.0)	17 (17.0)
Blood potassium	52 (52.0)	11 (11.0)
Nausea	47 (47.0)	3 (3.0)
Neutropenia	42 (42.0)	42 (42.0)
Headache	40 (40.0)	2 (2.0)
Pyrexia	40 (40.0)	5 (5.0)
Neutropenic infection	39 (39.0)	29 (29.0)
Vomiting	33 (33.0)	4 (4.0)
Anaemia	29 (29.0)	29 (29.0)
White blood cell count	27 (27.0)	20 (20.0)
Alopecia	25 (25.0)	2 (2.0)
Asthenia	24 (24.0)	9 (9.0)
Diarrhoea	20 (20.0)	4 (4.0)
Blood calcium	20 (20.0)	1 (1.0)
Cardiovascular disorder	20 (20.0)	10 (10.0)

Serious adverse events were reported by 42 of 100 subjects (42.0%), which included febrile bone marrow aplasia (14 subjects [14.0%]), febrile neutropenia (11 subjects [11.0%]), anemia

(10 subjects [10.0%]), asthenia (6 subjects [6.0%]), and pyrexia (5 subjects [5.0%]) etc. Of which, a causal relationship to study drug could not be denied for hepatic function abnormal, hepatic enzyme increased, blood LDH increased, atrial fibrillation, and secondary hypertension (1 subject each [1.0%]).

Adverse events leading to study drug discontinuation were observed in 4 of 100 subjects (4.0%), which included hepatic enzyme increased (2 subjects [2.0%]) and AST increased, gastrointestinal haemorrhage, lower gastrointestinal haemorrhage, hepatic function abnormal, liver function test abnormal, and blood LDH increased (1 subject each [1.0%]).

4.4.9) Foreign phase II study (Study EFC4983)

Adverse events occurred in 10 of 10 subjects (100%) in the pre-treated group and 20 of 23 subjects (87.0%) in the naïve group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	Pre-treated group (N = 10) [n (%)]		Naïve group (N = 23) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	10 (100)	8 (80.0)	20 (87.0)	18 (78.3)
Thrombocytopenia	4 (40.0)	4 (40.0)	9 (39.1)	8 (34.8)
Hyperphosphataemia	3 (30.0)	0	8 (34.8)	1 (4.3)
Blood LDH increased	1 (10.0)	1 (10.0)	7 (30.4)	3 (13.0)
Anaemia	7 (70.0)	6 (60.0)	7 (30.4)	4 (17.4)
Blood ALP increased	0	0	5 (21.7)	0
Leukopenia	2 (20.0)	1 (10.0)	5 (21.7)	5 (21.7)
Hyponatraemia	2 (20.0)	1 (10.0)	4 (17.4)	2 (8.7)
Azotaemia	2 (20.0)	0	3 (13.0)	0
Hypokalaemia	2 (20.0)	2 (20.0)	3 (13.0)	0
Hypocalcaemia	4 (40.0)	0	3 (13.0)	0
Febrile neutropenia	2 (20.0)	2 (20.0)	3 (13.0)	3 (13.0)
Asthenia	2 (20.0)	0	3 (13.0)	1 (4.3)
AST increased	2 (20.0)	0	2 (8.7)	0
Hyperglycaemia	3 (30.0)	0	2 (8.7)	1 (4.3)
Constipation	2 (20.0)	0	2 (8.7)	1 (4.3)
Blood creatinine increased	2 (20.0)	0	1 (4.3)	0
Dyspnoea	2 (20.0)	1 (10.0)	1 (4.3)	1 (4.3)
Hypoproteinaemia	2 (20.0)	0	1 (4.3)	0
Mucosal inflammation	2 (20.0)	2 (20.0)	0	0

Serious adverse events were reported by 4 of 10 subjects (40.0%) in the pre-treated group, which included thrombocytopenia (2 subjects [20.0%]) etc., and by 8 of 23 subjects (34.8%) in the naïve group, which included thrombocytopenia (2 subjects [8.7%]), neutropenic infection (2 subjects [8.7%]), and febrile neutropenia (2 subjects [8.7%]) etc. A causal relationship to study drug was denied for any of these events.

There were no adverse events leading to study drug discontinuation in the naïve group. One subject in the pre-treated group was discontinued from the study due to an overdose of rasburicase, but no adverse events associated with the overdose were reported.

4.4.10) Foreign phase IV study (Study EFC5339)

Adverse events occurred in 9 of 9 subjects (100%) in the pre-treated group and 85 of 85 subjects (100%) in the naïve group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	Pre-treated group (N = 9) [n (%)]		Naïve group (N = 85) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	9 (100)	9 (100)	85 (100)	81 (95.3)
Nausea	2 (22.2)	0	51 (60.0)	0
Thrombocytopenia	8 (88.9)	7 (77.8)	51 (60.0)	51 (60.0)
Anaemia	7 (77.8)	6 (66.7)	51 (60.0)	42 (49.4)
Neutropenia	6 (66.7)	5 (55.6)	48 (56.5)	46 (54.1)
Diarrhoea	4 (44.4)	0	42 (49.4)	1 (1.2)
Hyperglycaemia	4 (44.4)	2 (22.2)	38 (44.7)	7 (8.2)
Hypokalaemia	6 (66.7)	4 (44.4)	37 (43.5)	15 (17.6)
Fatigue	2 (22.2)	0	36 (42.4)	4 (4.7)
Pyrexia	3 (33.3)	0	35 (41.2)	3 (3.5)
Vomiting	2 (22.2)	0	35 (41.2)	1 (1.2)
Hypocalcaemia	3 (33.3)	0	33 (38.8)	9 (10.6)
Peripheral oedema	0	0	32 (37.6)	3 (3.5)
Mucosal inflammation	1 (11.1)	0	30 (35.3)	0
Constipation	2 (22.2)	0	29 (34.1)	0
Hypoalbuminaemia	0	0	27 (31.8)	4 (4.7)
Tachycardia	3 (33.3)	0	26 (30.6)	0
Headache	2 (22.2)	1 (11.1)	24 (28.2)	0
Rash	2 (22.2)	0	23 (27.1)	2 (2.4)
AST increased	4 (44.4)	0	22 (25.9)	6 (7.1)
ALT increased	3 (33.3)	1 (11.1)	22 (25.9)	5 (5.9)
Hypotension	2 (22.2)	0	21 (24.7)	4 (4.7)
Catheter site pain	0	0	20 (23.5)	0
Hyponatraemia	2 (22.2)	1 (11.1)	20 (23.5)	2 (2.4)
Hypophosphataemia	2 (22.2)	1 (11.1)	20 (23.5)	8 (9.4)
Insomnia	0	0	20 (23.5)	0
Chills	0	0	19 (22.4)	0
Anorexia	3 (33.3)	1 (11.1)	19 (22.4)	0
Hypomagnesaemia	1 (11.1)	0	18 (21.2)	1 (1.2)
Sepsis	0	0	18 (21.2)	16 (18.8)
Alopecia	0	0	17 (20.0)	1 (1.2)
Febrile neutropenia	2 (22.2)	2 (22.2)	17 (20.0)	12 (14.1)
Abdominal pain	3 (33.3)	0	17 (20.0)	2 (2.4)
Anxiety	3 (33.3)	0	16 (18.8)	0
Pain in extremity	2 (22.2)	1 (11.1)	9 (10.6)	1 (1.2)

Serious adverse events occurred in 6 of 10 subjects (60.0%) in the pre-treated group. Serious adverse events were reported by 33 of 85 subjects (38.8%) in the naïve group, which included neutropenic infection (6 subjects [7.1%]), febrile neutropenia (6 subjects [7.1%]), left ventricular dysfunction (3 subjects [3.5%]), blood bilirubin increased (2 subjects [2.4%]), neutropenic sepsis (2 subjects [2.4%]), and sepsis (2 subjects [2.4%]) etc. Of which, a causal relationship to study drug could not be denied for AST increased, tumor lysis syndrome, haemolysis, and convulsion (1 subject each [1.2%]) in the naïve group.

Adverse events leading to study drug discontinuation were observed in 5 of 85 subjects (5.9%) in the naïve group, which included AST increased, panic attack, bone pain, bradycardia, and convulsion (1 subject each [1.2%]).

Adverse events leading to study drug interruption were observed in 1 of 85 subjects (1.2%) in the naïve group, which included blood bilirubin increased and haemolysis (1 subject [1.2%]).

4.4.11) Foreign PK study (Study PKM6638)

Adverse events occurred in 13 of 13 subjects (100%) in the rasburicase 0.15 mg/kg group and 12 of 12 subjects (100%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater in either treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.15 mg/kg group (N = 13) [n (%)]		0.20 mg/kg group (N = 12) [n (%)]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	13 (100)	11 (84.6)	12 (100)	7 (58.3)
Nausea	5 (38.5)	0	6 (50.0)	0
Febrile neutropenia	5 (38.5)	4 (30.8)	6 (50.0)	6 (50.0)
Constipation	6 (46.2)	0	5 (41.7)	0
Neutropenia	2 (15.4)	2 (15.4)	4 (33.3)	4 (33.3)
Diarrhoea	4 (30.8)	0	3 (25.0)	0
Headache	2 (15.4)	0	3 (25.0)	0
Pyrexia	0	0	3 (25.0)	0
Vomiting	3 (23.1)	0	3 (25.0)	0
Thrombocytopenia	3 (23.1)	3 (23.1)	2 (16.7)	2 (16.7)
Rash	3 (23.1)	0	2 (16.7)	0
Dyspnoea	3 (23.1)	1 (7.7)	0	0
Anaemia	4 (30.8)	3 (23.1)	0	0

Serious adverse events were reported by 7 of 13 subjects (53.8%) in the 0.15 mg/kg group, which included febrile neutropenia (3 subjects [23.1%]) and diverticulitis, respiratory failure, and lung infiltration (1 subject each [7.7%]), and by 1 of 12 subjects (8.3%) in the 0.20 mg/kg group, which included febrile neutropenia. A causal relationship to study drug was denied for any of these events.

An adverse event leading to study drug discontinuation was observed in 1 of 13 subjects (7.7%) in the 0.15 mg/kg group, which was lung infiltration.

4.4.12) Foreign safety study (Study LTS3025)

Adverse events occurred in 73 of 82 subjects (89.0%) in the rasburicase 0.20 mg/kg group. Adverse events with an incidence of 20% or greater were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	0.20 mg/kg group (N = 82) [n (%)]	
	All Grades	Grade 3/4
Any event	73 (89.0)	23 (28.0)
Nausea	33 (40.2)	2 (2.4)
Vomiting	23 (28.0)	1 (1.2)
Pyrexia	17 (20.7)	2 (2.4)

Serious adverse events were reported by 16 of 82 subjects (19.5%), which included pyrexia (3 subjects [3.7%]), dyspnoea (2 subjects [2.4%]), neutropenia (2 subjects [2.4%]), and hypotension (2 subjects [2.4%]) etc. Of which, a causal relationship to study drug could not be denied for dyspnoea (2 subjects [2.4%]) and hot flush, cyanosis, chills, diarrhoea, cough, acute respiratory distress syndrome, chest pain, atrial fibrillation, headache, rhinorrhoea, and tachycardia (1 subject [1.2%]).

Adverse events leading to study drug discontinuation were observed in 1 of 82 subjects (1.2%),

which included hot flush, chills, cough, chest pain, dyspnoea, headache, and rhinorrhoea.

4.4.13) Foreign safety study (Study LTS3256)
Serious adverse events occurred in 59 of 278 subjects (21.2%) in the rasburicase 0.20 mg/kg group, which included neutropenic sepsis (16 subjects [5.8%]), febrile neutropenia (11 subjects [4.0%]), disease progression (5 subjects [1.8%]), and septic shock (5 subjects [1.8%]) etc. Of which, a causal relationship to study drug could not be denied for neutropenic sepsis (5 subjects [1.8%]), febrile neutropenia (3 subjects [1.1%]), and septic shock (2 subjects [0.7%]).

4.4.14) Foreign safety study (Study LTS3257)
Serious adverse events occurred in 206 of 1069 subjects (19.3%) in the rasburicase 0.20 mg/kg group, which included febrile neutropenia (43 subjects [4.0%]), disease progression (36 subjects [3.4%]), pyrexia (20 subjects [1.9%]), and neutropenia (17 subjects [1.6%]) etc. Of which, a causal relationship to study drug could not be denied for febrile neutropenia (11 subjects [1.0%]), disease progression (5 subjects [0.5%]), neutropenic sepsis and cardiac arrest (4 subjects each [0.4%]), anemia and convulsion (3 subjects each [0.3%]), and thrombocytopenia, respiratory arrest, neutropenia, tumor lysis syndrome, pyrexia, and hemolytic anemia (2 subjects each [0.2%]) etc.

4.4.15) Foreign phase III study (Study EFC4978)
Adverse events occurred in 92 of 92 subjects (100%) in the rasburicase 0.20 mg/kg group, 92 of 92 subjects (100%) in the rasburicase/allopurinol group, and 90 of 91 subjects (98.9%) in the allopurinol group. Adverse events with an incidence of 20% or greater in any treatment group were as shown in the following table.

Adverse events with an incidence of 20% or greater

Adverse event	Rasburicase (N = 92) [n (%)]				Rasburicase/Allopurinol (N = 92) [n (%)]				Allopurinol (N = 91) [n (%)]			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
Any event	92	(100)	85	(92.4)	92	(100)	86	(93.5)	90	(98.9)	87	(95.6)
Nausea	53	(57.6)	1	(1.1)	56	(60.9)	1	(1.1)	50	(54.9)	2	(2.2)
Diarrhoea	52	(56.5)	0		52	(56.5)	4	(4.3)	51	(56.0)	3	(3.3)
Thrombocytopenia	52	(56.5)	50	(54.3)	49	(53.3)	48	(52.2)	48	(52.7)	45	(49.5)
Neutropenia	50	(54.3)	50	(54.3)	45	(48.9)	41	(44.6)	45	(49.5)	43	(47.3)
Pyrexia	46	(50.0)	5	(5.4)	56	(60.9)	3	(3.3)	51	(56.0)	2	(2.2)
Peripheral oedema	46	(50.0)	2	(2.2)	40	(43.5)	3	(3.3)	39	(42.9)	6	(6.6)
Hypokalaemia	35	(38.0)	8	(8.7)	32	(34.8)	9	(9.8)	36	(39.6)	9	(9.9)
Vomiting	35	(38.0)	1	(1.1)	34	(37.0)	0		28	(30.8)	1	(1.1)
Hypocalcaemia	31	(33.7)	9	(9.8)	41	(44.6)	10	(10.9)	44	(48.4)	14	(15.4)
Anaemia	31	(33.7)	25	(27.2)	31	(33.7)	19	(20.7)	43	(47.3)	31	(34.1)
Hyperglycaemia	27	(29.3)	8	(8.7)	34	(37.0)	13	(14.1)	35	(38.5)	10	(11.0)
Hypotension	27	(29.3)	4	(4.3)	24	(26.1)	4	(4.3)	23	(25.3)	5	(5.5)
Chills	26	(28.3)	0		33	(35.9)	0		33	(36.3)	1	(1.1)
Rash	26	(28.3)	1	(1.1)	31	(33.7)	1	(1.1)	30	(33.0)	1	(1.1)
Hypoalbuminaemia	25	(27.2)	6	(6.5)	24	(26.1)	1	(1.1)	27	(29.7)	2	(2.2)
Hyponatraemia	25	(27.2)	5	(5.4)	22	(23.9)	5	(5.4)	23	(25.3)	4	(4.4)
Headache	25	(27.2)	1	(1.1)	31	(33.7)	0		33	(36.3)	1	(1.1)
Constipation	25	(27.2)	1	(1.1)	26	(28.3)	0		31	(34.1)	0	
Mucosal inflammation	23	(25.0)	3	(3.3)	25	(27.2)	2	(2.2)	24	(26.4)	0	
Febrile neutropenia	23	(25.0)	17	(18.5)	24	(26.1)	19	(20.7)	26	(28.6)	23	(25.3)
Anxiety	22	(23.9)	3	(3.3)	16	(17.4)	0		16	(17.6)	0	
Dyspnoea	20	(21.7)	3	(3.3)	18	(19.6)	1	(1.1)	18	(19.8)	6	(6.6)
Anorexia	20	(21.7)	2	(2.2)	23	(25.0)	4	(4.3)	25	(27.5)	2	(2.2)
Tachycardia	20	(21.7)	1	(1.1)	23	(25.0)	0		22	(24.2)	1	(1.1)

Abdominal pain	20	(21.7)	3	(3.3)	31	(33.7)	4	(4.3)	23	(25.3)	2	(2.2)
Fatigue	19	(20.7)	1	(1.1)	28	(30.4)	4	(4.3)	34	(37.4)	2	(2.2)
Insomnia	17	(18.5)	0		27	(29.3)	0		34	(37.4)	0	
Hypophosphataemia	16	(17.4)	4	(4.3)	21	(22.8)	6	(6.5)	15	(16.5)	6	(6.6)
Epistaxis	16	(17.4)	1	(1.1)	15	(16.3)	2	(2.2)	20	(22.0)	0	
AST increased	15	(16.3)	0		22	(23.9)	3	(3.3)	20	(22.0)	4	(4.4)
Dizziness	14	(15.2)	0		17	(18.5)	0		19	(20.9)	0	
Pharyngolaryngeal pain	13	(14.1)	1	(1.1)	19	(20.7)	0		9	(9.9)	0	
Asthenia	12	(13.0)	1	(1.1)	12	(13.0)	0		19	(20.9)	2	(2.2)
ALT increased	10	(10.9)	3	(3.3)	25	(27.2)	4	(4.3)	16	(17.6)	2	(2.2)

Serious adverse events occurred in 36 of 92 subjects (39.1%) in the rasburicase group, which included neutropenic infection and neutropenic sepsis (5 subjects each [5.4%]), febrile neutropenia (4 subjects [4.3%]), thrombocytopenia, respiratory distress, respiratory failure, atrial fibrillation, multi-organ failure, pyrexia, and abdominal pain (2 subjects each [2.2%]) etc. Serious adverse events occurred in 32 of 92 subjects (34.8%) in the rasburicase/allopurinol group, which included neutropenic infection (4 subjects [4.3%]), febrile neutropenia, respiratory failure, and pulmonary haemorrhage (3 subjects each [3.3%]), and multi-organ failure (2 subjects [2.2%]) etc. Serious adverse events occurred in 29 of 91 subjects (31.9%) in the allopurinol group, which included neutropenic infection (8 subjects [8.8%]), febrile neutropenia (5 subjects [5.5%]), neutropenic sepsis and tumor lysis syndrome (3 subjects [3.3%]), and multi-organ failure (2 subjects [2.2%]) etc. Of which, a causal relationship to study drug could not be denied for hypersensitivity (1 subject [1.1%]) in the rasburicase group and liver function test abnormal and drug hypersensitivity (1 subject each [1.1%]) in the rasburicase/allopurinol group.

Adverse events leading to study drug discontinuation were observed in 1 of 92 subjects (1.1%) in the rasburicase group, which were neutropenic sepsis and hyperbilirubinaemia. Adverse events leading to study drug discontinuation were observed in 5 of 92 subjects (5.4%) in the rasburicase/allopurinol group, which included respiratory failure, confusional state, pulmonary haemorrhage, tachycardia, and drug hypersensitivity (1 subject each [1.1%]). Adverse events leading to study drug discontinuation were observed in 2 of 91 subjects (2.2%) in the allopurinol group, which included tumor lysis syndrome (2 subjects [2.2%]) and multi-organ failure (1 subject [1.1%]).

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-1, 5.3.5.2-2). As a result, the following findings were noted at some clinical trial sites: (1) the operation of the Institutional Review Board (IRB) was not in accordance with the standard operating procedures (examination and deliberation of the appropriateness of continuing the clinical trial in response

to the reports of adverse drug reactions that are both serious and unexpected informed by the sponsor; examination and deliberation of the appropriateness of protocol amendments and associated revisions to the informed consent document since the protocol amendments may affect the subject's willingness to continue participation in the trial; and participation of the investigator etc. in the deliberation/vote of the IRB, etc.); (2) a part of the documents (a document to confirm the investigator's agreement to the protocol) were not retained; and (3) the investigator failed to obtain new written consent from subjects who were already participating in the clinical trial, using the above-mentioned revised informed consent document, etc. Such findings suggested that the above faults in the operation of the IRB had not been appropriately monitored by the sponsor in accordance with the standard operating procedures, but PMDA concluded that there should be no major problems with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that rasburicase is approvable as its efficacy and safety have been demonstrated. The following issues will mainly be discussed at the Expert Discussion and a final conclusion on the indication and dosage and administration will be made, taking account of comments from the Expert Discussion.

- Efficacy of rasburicase
- Safety of rasburicase
- Clinical positioning of rasburicase
- Indication
- Dosage and administration
- Post-marketing investigations

Review Report (2)

August 19, 2009

I. Product Submitted for Registration

[Brand name]	Rasuritek 1.5 mg for I.V. Infusion
	Rasuritek 7.5 mg for I.V. Infusion
[Non-proprietary name]	Rasburicase (Genetical Recombination)
[Applicant]	Sanofi-aventis K.K.
[Date of application]	February 26, 2008

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' comments based on the Review Report (1). Discussions with the expert advisors are summarized below.

The relevant expert advisors have declared that they do not fall under the Item 4 (excluding (2)) or 5 (1) of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008), regarding the product submitted for registration.

1) Data for review

The applicant explained that a clinical data package for registration of rasburicase was constructed by positioning a Japanese phase II study (ACT5080) as a bridging study and foreign phase II studies (ACT2694, ACT2511) as the studies to be bridged to allow extrapolation of foreign clinical data, i.e. a foreign phase III study (EFC2975) etc. However, as there were a number of differences between the above Japanese and foreign phase II studies regarding the daily dosing frequency, duration of treatment, and inclusion/exclusion criteria etc., the applicant identified only a portion of subjects enrolled into the studies to be bridged and assessed the similarity of clinical study data between Japan and overseas.

PMDA considers that it is not appropriate to identify only those who met the conditions of the bridging study among subjects enrolled into the studies to be bridged and discuss the similarity of clinical study data between Japan and overseas. However, based on the submitted clinical study data etc., rasburicase was characterized as insensitive to ethnic factors. Thus, PMDA determined that foreign clinical data can be utilized in support of registration and conducted a regulatory review based on the submitted Japanese and foreign clinical data.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. As considerations for this bridging strategy, the following comments were raised from the expert advisors:

- While a fixed dosage regimen was used in the Japanese phase II study that was designed to serve as the bridging study, the dosage regimen in the foreign phase II studies to be bridged was able to be adjusted according to individual patients' conditions. Therefore, generally, bias introduced by identifying only those treated with the same dosage regimen as in the Japanese phase II study among subjects enrolled into the foreign phase II studies is unavoidable and there is a possibility that the dose responses obtained from the two studies and the bridging study can not be compared and assessed precisely. However, rasburicase at the doses tested has been found to be able to control blood uric acid levels,

and such results allow the acceptance of the conclusion that foreign clinical data can be utilized.

2) Efficacy

PMDA considered that the efficacy endpoint of achieving a sufficient reduction in blood uric acid is appropriate as cancer chemotherapy can be completed following appropriate management of hyperuricemia associated with cancer chemotherapy and evaluated the efficacy of rasburicase based on this endpoint. As a result, based on the plasma uric acid $AUC_{0\text{-}96}$ in a foreign phase III study (EFC2975) and plasma uric acid response rates in Japanese and foreign phase II studies (ACT5080, ARD5290, ACT2694, ACT2511), PMDA concluded that the efficacy of rasburicase was demonstrated.

As the true clinical purpose of the control of blood uric acid levels in patients receiving cancer chemotherapy is to prevent acute renal failure associated with tumor lysis syndrome (TLS), the incidence of renal impairment etc. was also assessed. As a result, PMDA concluded that although rasburicase is also expected to prevent TLS-associated renal impairment such as acute renal failure and help avoid dialysis through its blood uric acid lowering effect, the difference from allopurinol is not clear.

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

- Conventional supportive measures can not always provide adequate control of hyperuricemia and rasburicase has a novel mode of action and can be administered intravenously unlike allopurinol. Thus, rasburicase is considered useful as a new therapeutic option.
- Given that rasburicase is not different from conventional supportive measures in preventing renal impairment and has also no apparent advantages in terms of safety and convenience, rasburicase can not be considered a markedly more innovative drug compared to conventional supportive measures just because it has a novel mode of action. Thus, it is necessary to provide appropriate information to prevent overestimation or exaggerated expectations of rasburicase.
- The incidence etc. of TLS-associated acute renal failure requiring hemodialysis is a consequence of a complex of factors such as abnormalities in levels of electrolyte other than uric acid and in metabolism that are associated with the primary disease or treatment, and disseminated intravascular coagulation (DIC) associated with the primary disease. Therefore, the incidence etc. of TLS-associated acute renal failure requiring hemodialysis is not appropriate as the primary endpoint for assessing the efficacy of rasburicase that is expected to have an effect on uric acid levels only.
- As rasburicase, which is a foreign protein, is associated with serious risks such as anaphylactic shock, the prevention of TLS-associated acute renal failure requiring hemodialysis, etc. should be used as the true endpoint in order to assess the risks and benefits of rasburicase and conventional therapies. However, TLS-associated acute renal failure requiring hemodialysis develops rarely in patients receiving cancer chemotherapy and considering the feasibility of a clinical trial to confirm the efficacy of the drug using the true endpoint, evaluation of a surrogate endpoint is unavoidable.

In view of the comments from the Expert Discussion, PMDA considers as follows:

Since rasburicase has been developed for the purpose of treatment and prophylaxis of acute hyperuricemia associated with tumor lysis among TLS symptoms and is expected to have an effect on uric acid levels only, it is possible to evaluate the control of blood uric acid levels as a measure of the efficacy of rasburicase and based on the submitted clinical study data, the

efficacy of rasburicase has been demonstrated. However, at present, there is no definite information on the effects of rasburicase on acute renal failure resulting from TLS. Therefore, it is necessary to provide the following information: the difference between rasburicase and allopurinol, a conventional therapy, is not clear in terms of the prevention of TLS and the prevention of TLS-associated renal impairment such as acute renal failure and the avoidance of dialysis.

PMDA instructed the applicant to appropriately provide the above information, using materials etc. and the applicant accepted it.

3) Safety

PMDA concluded that although rasburicase-specific adverse events that deserve attention include hypersensitivity and hemolytic reactions (hemolysis, methemoglobinemia, hemolytic anemia) and these events require caution, rasburicase is tolerable when used under the supervision of a physician with knowledge and experience in cancer chemotherapy at a medical institution with facilities for the treatment of emergencies. PMDA considered as follows: taking account of the mechanism of the development of hemolytic reactions associated with rasburicase, it is necessary to adequately caution against the use of rasburicase in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and rasburicase needs to be contraindicated in these patients in Japan, as in foreign countries. Meanwhile, as the prevalence of G6PD deficiency in the Japanese population is very low at about 0.1% and symptomatic cases are even fewer and very rare (*Internal Medicine* 9th edition [Asakura Publishing Co., Ltd., 2007]), there is little need for mandating screening for G6PD deficiency to make a definitive diagnosis prior to the use of rasburicase.

The following comments on the above conclusion of PMDA were raised from the expert advisors at the Expert Discussion:

- Hypersensitivity was reported commonly in Japanese studies (ACT5080, ARD5290). In Japanese and foreign clinical studies, 1 of 1153 subjects developed a serious adverse event of anaphylactic shock. Taking into account that anaphylaxis can be a direct cause of death, the incidence is by no means low. Thus, anaphylaxis must be taken seriously and overseas post-marketing information needs to be analyzed in more details.
- According to the results from clinical studies and safety pharmacology studies, caution about the risk of cardiac events is required when using rasburicase.
- As methemoglobinemia is a rare condition, it is necessary to appropriately provide information on clinical symptoms and laboratory findings of methemoglobinemia and its treatment etc. to the medical practice.
- Rasburicase should be contraindicated in patients with G6PD deficiency as in foreign countries.
- It is not practicable to screen patients for G6PD deficiency to make a definitive diagnosis prior to the initiation of rasburicase. As the incidences of hypersensitivity and hemolytic reactions are low, as long as adequate caution is provided and rasburicase is used only at medical institutions capable of dealing with these events, there is little need to contraindicate rasburicase in patients with G6PD deficiency.
- Although rasburicase should be contraindicated in patients previously diagnosed with G6PD deficiency, as there are patients with no previous history of hemolysis and no definitive diagnosis of G6PD deficiency, a practicable approach is to take a careful history regarding the presence or absence of hemolysis and hemoglobinuria and previous illnesses prior to the use of rasburicase and then make a definitive diagnosis if G6PD deficiency is suspected (a relevant caution statement should be included in the package insert).

Taking account of the comments from the Expert Discussion, PMDA conducted the following reviews.

3).(1) Hypersensitivity
PMDA asked for the applicant's view on measures to call attention to anaphylactic reactions in Japan, based on overseas post-marketing information on anaphylactic reactions.

The applicant responded as follows:
In foreign marketing experience (February 23, 2001 to July 31, 2009), 23 cases of anaphylactic events (9 cases of anaphylactic shock, 14 cases of anaphylactic reaction) were reported, which all resolved. As rasburicase is administered to hospitalized patients receiving cancer chemotherapy under close supervision, early detection and appropriate measures should be possible. It will be cautioned in the warnings section etc. of the package insert that after rasburicase administration, patients should be closely monitored and if serious hypersensitivity including anaphylactic shock occurs, appropriate measures should be taken.

PMDA accepted the response.

3).(2) G6PD deficiency
PMDA asked the applicant to explain whether patients are screened for G6PD deficiency prior to the use of rasburicase overseas and the possibility of mandating screening for G6PD deficiency in Japan.

The applicant responded as follows:
In both the US and Europe, rasburicase has been contraindicated in patients with G6PD deficiency because patients with abnormal G6PD are considered at increased risk for hemolytic anemia etc. due to the mode of action of rasburicase. However, since (a) the prevalence of G6PD deficiency is generally low in a majority of ethnic groups and even in patients of African or Mediterranean ancestry at higher risk for G6PD deficiency, G6PD deficiency can usually be predicted by taking their medical or family history etc. in most cases, (b) considering the treatment of the primary disease of candidate patients, there may not be enough time to screen for G6PD deficiency prior to the initiation of rasburicase, and (c) even if hemolytic anemia etc. occur, it can be managed in most cases, screening for G6PD deficiency prior to the use of rasburicase is not mandated in foreign medical practice.

In Japan, usually, the screening test for G6PD deficiency can not be performed as part of routine tests at medical institutions and will be performed at outside laboratories. Taking also account of the time required to perform the test, there will not be enough time to screen for G6PD deficiency prior to the use of rasburicase as in foreign countries. Besides G6PD deficiency, abnormalities of glutathione reductase, glutathione peroxidase, glutamylcysteine synthetase, and glutathione synthetase are also considered to be involved in hemolysis following the administration of rasburicase, but these enzymes can not be measured in routine practice in Japan.

Based on the above, as a caution against the use of rasburicase in a high-risk population for hemolytic anemia associated with rasburicase, rasburicase needs to be contraindicated in patients with abnormal G6PD as in foreign countries. Meanwhile, as rasburicase will be used at medical institutions capable of managing hemolytic anemia etc., screening for G6PD deficiency prior to the use of rasburicase is not considered essential.

PMDA's view on a caution against the use of rasburicase in patients deficient in G6PD etc. is as

follows:
Due to the mode of action of rasburicase, patients deficient in the enzymes that are involved in the endogenous hydrogen peroxide scavenging mechanism, e.g. G6PD are at increased risk for hemolytic anemia etc. Thus, rasburicase should be contraindicated in patients with known deficiency of these enzymes. On the other hand, taking into account that events such as hemolytic anemia associated with rasburicase have been observed also in non-G6PD-deficient patients and the screening test is not performed in routine practice, it is necessary to provide an adequate caution about hemolytic anemia etc. and in patients with unknown deficiency of these enzymes, rasburicase needs to be used with care at medical institutions capable of dealing with these events under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy, after carefully taking medical and family histories etc. and balancing the risks and benefits. Therefore, as long as rasburicase is used at a medical institution capable of dealing with these events under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy, at present, there is little need to mandate screening of all patients with unknown G6PD etc. deficiency prior to the use of rasburicase, as in foreign countries.

Based on the above, PMDA concluded that the following caution statements about patients with G6PD deficiency should be included in the package insert and instructed the applicant accordingly.

Contraindications:
Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or other erythroenzymopathies known to cause hemolytic anemia [Hemolytic anemia may develop.]

Warnings:
Rasburicase administered to a patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency caused severe hemolytic anemia in a foreign clinical study. A careful history including family history should be taken to detect G6PD deficiency or other erythroenzymopathies.

PMDA also instructed the applicant to provide detailed information on the symptoms of hemolytic anemia and methemoglobinemia, using materials etc. and the applicant accepted it.

3).(3) Cardiac events
PMDA asked for the applicant's view on whether to caution about cardiac events.

The applicant responded as follows:
In order to assess the effects of rasburicase on cardiac function, Grade 3 or 4 cardiac adverse events and serious cardiac adverse events were analyzed. As a result, the incidences of these events were low (the table below) and there was also no consistent trend in the events reported.

Incidences of Grade 3 or 4 cardiac adverse events and serious cardiac adverse events

	Children [n/N (%)]		Adults [n/N (%)]	
	0.15 mg/kg	0.20 mg/kg	0.15 mg/kg	0.20 mg/kg
Grade 3 or 4 cardiac adverse events	0/177* (0)	12/188* (6.4)	4/55‡ (7.3)	26/300‡ (8.7)
Serious cardiac adverse events	0/177† (0)	6/1036† (0.6)	3/55** (5.5)	26/799** (3.3)

*: ACT5080, ACT2511, ACT2694, EFC2975, LTS3025, EFC5339
†: ACT5080, ACT2511, ACT2694, EFC2975, LTS3025, EFC5339, LTS3256, LTS3257
‡: ARD5290, ACT2511, ACT2694, LTS3025, EFC4982, EFC4983, EFC5339, PKM6638
**: ARD5290, ACT2511, ACT2694, LTS3025, EFC4982, EFC4983, EFC5339, PKM6638, LTS3256, LTS3257

Increased heart rate and decreased stroke volume noted in a safety pharmacology study in dogs

were considered related to a halothane anesthetic. Cardiac adverse events assessed as causally related to rasburicase in clinical studies were atrial fibrillation in 1 subject and secondary hypertension in 1 subject (both subjects were adults in the 0.20 mg/kg group). Considering that rasburicase is used in patients receiving cancer chemotherapy, cardiac adverse events are unlikely to be attributable to rasburicase. Therefore, at present, there is no need to caution about the effects of rasburicase on cardiac function.

PMDA considers as follows:
The applicant discussed that the events observed in a safety pharmacology study in dogs were related to a halothane anesthetic and explained that cardiac adverse events are unlikely to be attributable to rasburicase despite that the cardiac events reported during clinical use have been assessed as causally related to rasburicase. The basis for these discussion and explanation is unknown. However, as rasburicase is used in patients receiving cancer chemotherapy, it is administered in an inpatient setting under close supervision and cardiac adverse events associated with rasburicase will be listed in the package insert based on clinical study data to provide information. Thus, at present, a further caution is unnecessary. After the market launch, the occurrence of cardiac events should be watched for and the necessity of providing a further caution should be reviewed.

4) Clinical positioning
PMDA's view on the clinical positioning of rasburicase was as follows [see Review Report (1) "4.3.B.5) Clinical positioning"]:
Although the submitted data show no clear difference in efficacy between allopurinol and rasburicase, since rasburicase was effective in a similar percentage of patients as allopurinol regarding at least the initial management of plasma uric acid levels and the mode of action of rasburicase is different from those of conventional supportive measures, rasburicase is positioned as a drug recommended for patients expected to be at high risk for TLS in whom the control of blood uric acid levels with conventional supportive measures is considered inadequate.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA's view on the selection of patients for the use of rasburicase was as follows [see Review Report (1) "4.3.B.5) Clinical positioning"]:
As described in the above, rasburicase should be administered to patients at high risk for TLS. However, as the risk of developing TLS is affected by tumor burden and sensitivity to chemotherapy as well, it is difficult to predict with reliability the development of TLS. While the applicant's explanation that patients who should use rasburicase should be selected based on the publication (*J Clin Oncol* 2008; 26: 2767-78) is understood, the preferred approach for the management of TLS may be changed according to the evolution of treatment guidelines and the revision of the criteria for TLS risk classification, etc. Therefore, patients considered appropriate to receive rasburicase only need to be selected by physicians with adequate knowledge and experience in cancer chemotherapy, after fully understanding the patient populations included in the submitted clinical studies and the efficacy and safety of rasburicase, referring also to the latest information, e.g. treatment guidelines.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

5) Indication
As a result of its review in the Review Report (1) "4.3.B.6)(1) Intended population," PMDA concluded that there is no need to restrict the use of rasburicase according to the primary disease or age. In clinical studies submitted, rasburicase was initiated prior to cancer chemotherapy and

the efficacy of rasburicase in the “prophylaxis” of hyperuricemia associated with cancer chemotherapy has been evaluated, but the “treatment efficacy” of rasburicase as symptomatic rescue treatment in patients who developed hyperuricemia unexpectedly after the initiation of cancer chemotherapy has not been investigated. Thus, PMDA considered that rasburicase should not be indicated for the “treatment” of hyperuricemia associated with cancer chemotherapy.

Based on the above, PMDA concluded that the appropriate indication for rasburicase should be “the prophylaxis of hyperuricemia associated with cancer chemotherapy” and it should be stated in the precautions for indications section of the package insert that “prior to the use of rasburicase, appropriate patients should be selected, considering the risk of developing tumor lysis syndrome.” In addition, PMDA considered that using an information leaflet to promote the proper use of rasburicase, detailed information considered useful for selecting appropriate patients for the use of rasburicase, e.g. the inclusion/exclusion criteria for the clinical studies submitted and study results, should be provided.

The following comments on the above conclusion of PMDA were raised from the expert advisors at the Expert Discussion:

- It is not uncommon to see patients with already high levels of uric acid before the initiation of cancer chemotherapy. The wording of the indication, “prophylaxis” does not define who should receive rasburicase.
- The TLS guidelines (*J Clin Oncol*. 2008; 26: 2767-78) state that the administration of rasburicase needs to be considered if uric acid levels are not controlled with allopurinol. In addition, based on its pharmacological action, the treatment efficacy of rasburicase is also expected. Therefore, the use of rasburicase should not be restricted to “prophylaxis” and rasburicase may be indicated for “treatment” as well.
- Rasburicase may also be indicated for patients with solid tumor malignancies. However, since rasburicase is a drug recommended for patients at high risk for TLS in whom the control of blood uric acid levels with conventional supportive measures is considered inadequate, if the term “prophylaxis” is used in the indication section of the package insert, there will be a concern that rasburicase might be administered also to patients at low risk for TLS who do not need rasburicase, e.g. many of patients with solid tumor malignancies. As long as the timing of cancer chemotherapy relative to rasburicase initiation is specified in the package insert, even if the indication section reads “hyperuricemia associated with cancer chemotherapy” without using the terms “treatment” or “prophylaxis,” the usage of rasburicase will not be misunderstood in medical practice.
- It should be stated in the precautions for indications section of the package insert that “the use of rasburicase should be considered if the control of blood uric acid levels with conventional supportive measures is considered inadequate.”
- Rasburicase should be used for the prevention and treatment of TLS when adequate hydration and management of metabolic acidosis and renal failure produce little effect and uric acid levels are high. Casual use of rasburicase as a result of underestimating the risk of xenogeneic immunoreaction, e.g. anaphylactic reaction, would be a problem.

Taking account of the comments from the Expert Discussion, PMDA concluded as follows:
As long as it is appropriately cautioned that the efficacy of rasburicase in the treatment of hyperuricemia occurring after the initiation of cancer chemotherapy has not been evaluated and the information on the patient populations included in clinical studies and the timing of cancer chemotherapy relative to rasburicase initiation [see “6) Dosage and administration”] is provided, rasburicase can be properly used based on clinical study results even without using the term

"prophylaxis" in the indication section of the package insert. Therefore, the appropriate indication should be "hyperuricemia associated with cancer chemotherapy" and the following caution statements should be included in the precautions for indications section of the package insert.

- Prior to the use of rasburicase, appropriate patients should be selected, considering the risk of developing tumor lysis syndrome and rasburicase should be used only when the control of blood uric acid levels with conventional supportive measures is considered inadequate.
- The efficacy and safety of rasburicase in the treatment of hyperuricemia occurring after cancer chemotherapy have not been established (no clinical experience).

PMDA instructed the applicant to include the above statements in the indication and precautions for indications sections of the package insert and the applicant accepted it. PMDA also instructed the applicant to provide detailed information considered useful for selecting appropriate patients for the use of rasburicase, e.g. the inclusion/exclusion criteria for the clinical studies submitted and study results, to healthcare providers, using an information leaflet to promote the proper use of rasburicase, and the applicant accepted it.

6) Dosage and administration

Based on its review in the Review Report (1), PMDA concluded that the appropriate dosage and administration statement should be "The usual dosage is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is up to 7 days." and the following statements should be included in the precautions for dosage and administration section of the package insert.

- Clinical symptoms and blood uric acid levels should be monitored and treatment with rasburicase should be limited to the minimum period required for the management of blood uric acid levels.
- The efficacy and safety of dosing beyond 7 days have not been established (no clinical experience).
- The efficacy and safety of retreatment with rasburicase have not been established.
- Chemotherapy should be initiated 4 to 24 hours after the first dose of rasburicase.

The above conclusion of PMDA was largely supported by the expert advisors at the Expert Discussion. However, the following comments on the recommended duration of treatment were raised from the expert advisors:

- The duration of treatment of 5 days is not explicitly recommended in the dosage and administration section of the package insert, which is understandable. However, the durations of treatment investigated in clinical studies should be clearly stated in the clinical studies section etc. of the package insert.
- In patients with anti-rasburicase antibodies before treatment, antibody production may be increased within a short period of time and anaphylactic reactions may occur. Thus, there is no need to prolong the duration of treatment to 7 days.
- Rasburicase causes degradation of uric acid within blood samples left at room temperature, resulting in spuriously low uric acid levels, which might lead to premature termination of treatment. Therefore, the sample handling procedure etc. should appropriately be described in the package insert etc. to provide caution adequately.

Taking account of the comments from the Expert Discussion, PMDA concluded that the following statements should be included in the dosage and administration and precautions for dosage and administration sections of the package insert:

Dosage and administration:
The usual dosage is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion over at least 30 minutes. The duration of treatment is up to 7 days.

Precautions for dosage and administration:

- Rasburicase should be initiated 4 to 24 hours prior to the initiation of cancer chemotherapy.
- The efficacy and safety of dosing beyond 7 days have not been established (no clinical experience).
- Clinical symptoms and blood uric acid levels should be monitored and treatment with rasburicase should be limited to the minimum period required for the management of blood uric acid levels.
- The efficacy and safety of retreatment after the first course of rasburicase (up to 7 days of treatment) have not been established (insufficient clinical data).

PMDA instructed the applicant to (a) provide information on the dosage regimens used in Japanese and foreign clinical studies (the duration of treatment, the daily dosing frequency, etc.) through the clinical studies section of the package insert and an information leaflet to promote the proper use of rasburicase etc. and (b) ensure that healthcare professionals are informed of the blood sample handling procedure for blood uric acid monitoring, using an information leaflet to promote the proper use of rasburicase etc. as well as the package insert. The applicant accepted it.

7) Post-marketing investigations
The applicant plans to conduct a post-marketing drug use-results survey including consecutive patients (target number of cases of 200; observation period, until 1 month after the last administration; planned duration of survey, 3 years) to collect safety information under routine use of rasburicase. The items to be investigated include (a) patient background (G6PD deficiency status is also to be tested for patients who develop hemolytic anemia or methemoglobinemia only), (b) the treatment for malignancies immediately after the use of rasburicase, (c) the treatment for malignancies immediately before the use of rasburicase if rasburicase is administered for hyperuricemia occurring after cancer chemotherapy, (d) information on administration of rasburicase and concomitant drugs, and (e) laboratory test values and adverse events. The applicant explained that a detailed investigation will be conducted on retreatment with rasburicase, the use of rasburicase in pregnant women/nursing mothers, or the use of rasburicase for hyperuricemia associated with radiation therapy, if such cases are reported.

PMDA considered that the following information should also be collected via post-marketing surveillance and the obtained results need to be discussed.

- Information on the avoidance of renal impairment requiring hemodialysis after rasburicase administration
- Whether patients with hemolytic anemia or methemoglobinemia have a deficiency of not only G6PD, but also of glutathione peroxidase, another scavenging mechanism of endogenous hydrogen peroxide
- Detailed information on patients treated with rasburicase for hyperuricemia occurring after cancer chemotherapy, in addition to the information on the treatment for malignancies immediately before the use of rasburicase
- Anti-rasburicase antibody production in patients retreated with rasburicase

PMDA also considered that based on the obtained information on the use of rasburicase with

allopurinol and the doses of rasburicase, clinical development for further optimization of the dosage regimen needs to be considered.

Furthermore, PMDA considered as follows:
Although retreatment with rasburicase is not recommended, there will be patients who have to be retreated with rasburicase or patients with an unknown history of prior treatment with rasburicase due to transfer from another hospital etc. Since some of the anti-rasburicase antibodies detected after rasburicase administration were neutralizing, and the patients who were positive for anti-rasburicase antibodies and received rasburicase experienced serious adverse events, when retreatment with rasburicase is considered for the patients described above, anti-rasburicase antibody testing needs to be performed. After the market launch, anti-rasburicase antibody test requests from healthcare providers should also be investigated and the development of antibody assay etc. needs to be considered as appropriate.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. Besides the above items to be investigated, comments were raised from the expert advisors on other items to be investigated, the significance of investigations, and cautions in investigations etc. as follows:

- Allergic reactions such as urticaria, pyrexia, and asthma, including anaphylaxis, should be investigated in details and patients should be tested for antibodies before and after treatment.
- How G6PD and glutathione peroxidase test results will be utilized in medical practice is unclear and the significance of testing is not high.
- It will be unavoidable from a practical standpoint that G6PD deficiency will be tested only in patients with hemolytic anemia or methemoglobinemia. Meanwhile, interpretation of the test results will be difficult without any available definitive information on the prevalence of G6PD deficiency in Japan.
- The applicant explained that the relationship between anti-rasburicase antibody production and occurreance of adverse events such as hypersensitivity reactions has not been identified. However, serious allergic reactions (causally related to rasburicase) have occurred in 2 of the 4 patients with available data (among 6 patients with positive anti-rasburicase antibodies before retreatment). Thus, the applicant’s claim is inappropriate.
- If anti-rasburicase antibody assay is developed, assay sensitivity and specificity should also be determined.
- In view of the risk of developing TLS, rasburicase is expected to be used primarily in patients receiving initial chemotherapy. Patients with recurrence/relapse are not usually anticipated to be at high risk for TLS as they have been closely followed up in an inpatient or outpatient setting. Therefore, there will be few occasions to consider retreatment with rasburicase.

Taking account of the comments from the Expert Discussion, PMDA conducted the following review:

Patients with hemolytic anemia or methemoglobinemia only will be tested for G6PD deficiency via post-marketing surveillance. PMDA asked the applicant to explain in details how the test results will be interpreted and the information will be provided to the medical practice.

The applicant responded as follows:
Detailed information regarding a medical history (hemolytic anemia, jaundice, etc.), a family history, and premonitory or initial symptoms of the event of patients with hemolytic anemia or

methemoglobinemia will be obtained wherever possible via drug use-results survey. The results of G6PD deficiency test will also be collected only if the test is performed at the discretion of the attending physician. However, as this test is not performed in routine practice, most of the patient background information obtained via drug use-results survey will be based on history taking etc. Thus, such information excluding the information on G6PD deficiency test will mainly be provided to healthcare providers.

Currently in Japan, it is difficult to perform a test for deficiency of endogenous hydrogen peroxide scavenging mechanisms other than G6PD. Moreover, many of patients with hematological malignancies, i.e. the main patient population for rasburicase, receive blood transfusion. In order to accurately assess whether such patients themselves are deficient in G6PD etc., samples need to be taken several months after blood transfusion. Taking account of the above situations, it is not necessarily useful to perform a test for deficiency of G6PD etc. for patients with hemolytic anemia or methemoglobinemia. Thus, there is no plan to conduct a clinical study intended to investigate the deficiency of G6PD etc. However, the necessity of further information collection and investigation etc. will be reviewed if hemolytic anemia is reported commonly in non-G6PD-deficient Japanese patients, or in other similar situations.

PMDA's view on the conduct of a test for deficiency of G6PD etc. in patients with hemolytic anemia or methemoglobinemia after the market launch is as follows:
Since the prevalence of G6PD deficiency in Japan is not necessarily accurately known and hemolytic anemia has been reported also in non-G6PD-deficient patients, an investigation of abnormalities of enzymes involved in the removal of hydrogen peroxide, including G6PD, has a certain significance. On the other hand, (a) testing for G6PD etc. deficiency is not prevalent in Japan and not performed in routine practice, (b) at present, there is little need to mandate screening of all patients prior to the use of rasburicase [see "3) Safety"], and (c) since retreatment with rasburicase will be needed in a limited number of patients as long as appropriate patients are selected based on the risk of developing TLS, the test will not necessarily be performed in patients who develop hemolytic anemia etc. after rasburicase administration only to investigate the cause. Taking account of these points, it is unavoidable to collect information on G6PD etc. deficiency status of patients with hemolytic anemia or methemoglobinemia only if the test results are available under routine uses, for reviewing the necessity of a further investigation, etc.

Taking account of the above discussion, PMDA instructed the applicant to plan to also collect the information on the avoidance of renal impairment requiring hemodialysis and patients who received rasburicase as rescue treatment via drug use-results survey.

The applicant responded that they will take the following actions:
For a drug use-results survey, a case report form to collect the following information on renal function will be developed and the information on the avoidance of renal impairment will be obtained.

- Presence or absence of prior or concurrent renal disease (renal impairment, renal failure, abnormal renal function test [serum creatinine], oliguria, dialysis, etc.)
- Presence or absence of prior or concurrent abnormal electrolytes (hyperphosphatemia, hypocalcemia, hyperkalemia, etc.)
- Laboratory values: serum creatinine, Na, K, Ca, P, etc. before and after rasburicase administration
- Adverse events: name of adverse event, date of onset, serious or non-serious, actions taken (dialysis, etc.), outcome, causality, possible other causes (concomitant medications, concomitant illnesses, etc.)

Patients who received rasburicase as rescue treatment can be identified by adding “rescue treatment of hyperuricemia associated with cancer chemotherapy” to the indication column in the case report form.

PMDA’s view on anti-rasburicase antibody test is as follows:
Although administration of more than one course of rasburicase is not recommended, if more than one course of rasburicase is administered due to clinical necessity, information should be collected and the development of anti-rasburicase antibody assay needs to be considered depending on the uses of rasburicase after the market launch or other needs.

The applicant responded as follows:
Based on factors including the uses of rasburicase and changes in test requests from healthcare providers after the market launch, if a serious safety concern considered associated with antibody production arises (e.g. a marked increase in reports of anaphylactic shock), the development of anti-rasburicase antibody assay will be considered.

PMDA accepted it.

III. Overall Evaluation
Rasburicase is a recombinant urate-oxidase enzyme, which converts uric acid to more water-soluble allantoin. PMDA recognizes that the efficacy of rasburicase in the prevention of TLS/renal impairment is not clear and the difference in efficacy between rasburicase and allopurinol also is not clear. However, rasburicase was effective in a similar percentage of patients as allopurinol regarding at least the initial management of blood uric acid levels, and the blood uric acid lowering effect of rasburicase has been demonstrated. While supportive measures for hyperuricemia (allopurinol, urinary alkalinization, hydration, etc.) are available, the mode of action of rasburicase is different from those of conventional supportive measures. Based on the above, the use of rasburicase is recommended only for patients expected to be at high risk for TLS in whom conventional supportive measures are considered inadequate in controlling blood uric acid levels.

PMDA reviewed the submitted application data and concluded that the product may be approved for the following indication and dosage and administration, provided that appropriate cautions will be included in the package insert and information concerning the proper use of rasburicase will be provided appropriately after the market launch, and the compliance with the proper use of rasburicase will be ensured under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies.

As the application falls under the category of drugs with new active ingredients, the appropriate re-examination period is 8 years. The drug substance and the drug product are both classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Indication]
Hyperuricemia associated with cancer chemotherapy

[Dosage and administration]
The usual dosage is 0.2 mg/kg of rasburicase administered as a single daily intravenous infusion

over at least 30 minutes. The duration of treatment is up to 7 days.

[Warnings]

1. Rasuritek may cause severe hypersensitivity including anaphylactic shock. Patients should be closely monitored also after the end of administration. If symptoms occur, the drug should be discontinued immediately and appropriate therapeutic measures taken.
2. Hemolytic anemia or methemoglobinemia may occur. If symptoms occur, the drug should be discontinued immediately and appropriate therapeutic measures taken.
3. Rasuritek administered to a patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency caused severe hemolytic anemia in a foreign clinical study. A careful history including family history should be taken to detect G6PD deficiency or other erythroenzymopathies.

[Contraindications]

1. Patients with a history of hypersensitivity to Rasuritek or any of the excipients
2. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or other erythroenzymopathies known to cause hemolytic anemia [Hemolytic anemia may develop.]

[Precautions for indications]

1. Prior to the use of Rasuritek, appropriate patients should be selected, considering the risk of developing tumor lysis syndrome and Rasuritek should be used only when the control of blood uric acid levels with conventional supportive measures is considered inadequate.
2. The efficacy and safety of Rasuritek in the treatment of hyperuricemia occurring after cancer chemotherapy have not been established (no clinical experience).

[Precautions for dosage and administration]

1. Rasuritek should be initiated 4 to 24 hours prior to the initiation of cancer chemotherapy.
2. The efficacy and safety of dosing beyond 7 days have not been established (no clinical experience).
3. Clinical symptoms and blood uric acid levels should be monitored and treatment with Rasuritek should be limited to the minimum period required for the management of blood uric acid levels.
4. The efficacy and safety of retreatment after the first course of Rasuritek (up to 7 days of treatment) have not been established (insufficient clinical data).
5. Infusion solution preparation procedure: Reconstitute one vial of Rasuritek with one ampule of the provided reconstitution diluent and dilute the required volume of the reconstituted solution into 50 mL of normal saline. The volume of normal saline for dilution may be reduced to 10 mL for patients aged $\leq$ 24 months. During reconstitution, swirl very gently to avoid foaming. Mix the reconstituted solution into normal saline promptly after reconstitution.