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| PRODUCT: MK-1986 | PROTOCOL/AMENDMENT VERSION NO.: 1986-045-00-V3 |
| REVOPS ID NO: NIS106694<br>EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08063.002 | NIR DRC APPROVAL DATE: NOVEMBER 25, 2025 |

# A POST-MARKETING DATABASE SURVEILLANCE TO INVESTIGATE THE RISK OF DIAGNOSED MYELOSUPPRESSION EVENTS IN MRSA PATIENTS TREATED WITH TEDIZOLID OR LINEZOLID IN JAPAN

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## PASS INFORMATION

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|---|---|
| **Title** | A post-marketing database surveillance to investigate the risk of diagnosed myelosuppression events in MRSA patients treated with tedizolid or linezolid in Japan |
| **Protocol Version identifier** | 00-v3 |
| **Date of last version of protocol** | December 1, 2025 |
| **HMA-EMA Catalogues of RWD No:** | To be registered |
| **Active substance** | J01XX11, Tedizolid Phosphate |
| **Medicinal product(s):** | SIVEXTRO® Tablets 200mg, SIVEXTRO® for iv infusion 200mg |
| **Joint PASS** | No |
| **Research question and objectives** | To investigate myelosuppression related to the identified risks for tedizolid compared to linezolid from 21-Aug-2018 to 31-Mar-2025. |
| **Country(-ies) of study** | Japan |
| **Author** | PPD<br>Sr. Spclst, Drug Safety, Program Operation 1<br>PPD<br>Associate Principal Scientist, Epidemiology<br>Biostatistics and Research Decision Sciences (BARDS) |
| **Marketing authorisation holder(s) including MAH Contact Person** | MSD K.K.<br>PPD<br>Sr. Spclst, Drug Safety, Program Operation 1 |

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| **Merck Final Repository (REDS) Date** | |
| **Date of Health Authority Approval of Protocol** | December 9, 2025 |

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical Classification System |
| CI | Confidence Interval |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DPC | Diagnosis Procedure Combination |
| DSUR | Development Safety Update Reports |
| GPP | Good Pharmacoepidemiology Practice |
| GPSP | Good Post-marketing Study Practice |
| Health Outcomes | Clinical events or outcomes which may be represented as diagnoses, treatment or procedures (examples include syncope, disease progression or hypoglycemia collected as study endpoints) |
| ICD-10 | International statistical Classification of Diseases and related health problems 10th revision |
| IPTW | Inverse Probability of Treatment Weighting |
| IQR | InterQuartile Range |
| JLAC10 | Japanese Laboratory Code Version 10 |
| JMDC | JMDC Claims Database |
| JPC | Japan Package Circular |
| MDV | Medical Data Vision |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| OR | Odds Ratio |

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|---|---|
| MID-NET | Medical Information Database NETwork |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PS | Propensity Score |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SMQ | Standardized MedDRA Queries |
| SOP | Standard Operating Procedures |
| SQI | Significant Quality Issue |
| SS-MIX2 | Standardized Structured Medical record Information eXchange 2 |

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# 1 RESPONSIBLE PARTIES

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|---|---|
| Principal investigators | PPD<br>PPD |
| Coordinating investigator for each country in which the study is to be performed | N.A. |
| Sponsor contacts | Kitanomaru Square, 1-13-12, Kudan-kita, Chiyoda-ku,<br>Tokyo 102-8667 |
| Other contacts | N.A. |
| Supplier/Collaborator | CCI |
| Investigators | N.A. |
| Shared responsibilities | N.A. |

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## 2 ABSTRACT

| | |
|---|---|
| Title | A post-marketing database surveillance to investigate the risk of diagnosed myelosuppression events in MRSA patients treated with tedizolid or linezolid in Japan |
| Protocol Number / Version | 1986-045-00-v3 |
| Date | December 1, 2025 |
| Author | PPD<br><br>Sr. Spclst, Drug Safety, Safety Program Operation 1<br><br>PPD<br><br>Associate Principal Scientist, Epidemiology<br><br>Biostatistics and Research Decision Sciences (BARDS) |
| Rationale & Background | To determine whether the risk of diagnosed myelosuppression is higher with the use of tedizolid compared to the use of the control drug linezolid quantitatively among patients prescribed anti-MRSA drugs between August 2018 (the month this drug was launched) and March 2025. |
| Research Question(s) & Objective(s) | Research question<br><br>To investigate diagnosed myelosuppression related to the identified risks for tedizolid compared to linezolid from 21-Aug-2018 to 31-Mar-2025.<br><br>Primary objective:<br><br>To compare the risk of diagnosed myelosuppression between patients taking tedizolid and those taking linezolid. |
| Study Design | Cohort, active comparator, new user design |

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|---|---|
| Population | The study population is MRSA patients who are treated with tedizolid or linezolid between 21-Aug-2018 and 31-Mar-2025. |
| Variables | Outcomes:<br><br>Meeting or exceeding Grade 2 or higher by CTCAE criteria for any of the following items.<br><br>▪ Decreased white blood cells, decreased platelets, decreased neutrophils, anemia (decreased hemoglobin).<br><br>The specific cut-off points are as follows.<br><br>Decreased white blood cells: < 3,000/$mm^3$<br><br>Decreased platelets: < 75,000/$mm^3$<br><br>Decreased neutrophils: < 1,500/$mm^3$<br><br>Anemia (decreased hemoglobin): < 10.0 g/dL<br><br>Covariates:<br><br>Age, sex, comorbidities |
| Data Sources | MID-NET |
| Study Size | All patients who meet the inclusion/exclusion criteria with MRSA treated with tedizolid or linezolid in MID-NET database will be included.<br><br>During the cohort entry period (21-Aug-2018 to 31-Mar-2025), it is estimated that 100-200 patients will be prescribed tedizolid. |
| Data Analysis | Incidence rates of myelosuppression and binomial confidence intervals will be calculated descriptively for tedizolid and linezolid groups separately. The number and percentage of myelosuppression will be calculated based on myelosuppression test items and |

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| | grades. For all patients, the exposure time starts the day after the initiation of treatment date.<br><br>If there are 10 or more events observed for each treatment group, crude odds ratios and 95% CI will be estimated using logistic regression models, to compare the risk of myelosuppression between the tedizolid group and linezolid group.<br><br>Inverse probability of treatment weighting (IPTW) approach will be used to adjust for potential confounding between the tedizolid and linezolid groups. PS will be generated using probability estimates from a logistic regression model in which treatment with tedizolid or linezolid will be the binary dependent variable and patient characteristics (see Section 7.3.3) will be used as predictors of being treated with tedizolid or linezolid, if 10 patients exposed to tedizolid are observed per predictor. The IPTW approach uses weights derived from the PS to create a pseudo-population such that the distribution of baseline covariates in the population is independent of treatment assignment. For each patient, the weight will be assigned as the inverse of the propensity score for the tedizolid group and as the inverse of 1 minus the propensity score for the linezolid group will be calculated. The balance of baseline covariates will be assessed by using standardized mean differences; covariates will be well-balanced if the standardized mean difference is <0.1. The distribution and variance for continuous variables will also be assessed between the treatment groups. Once balance of the covariates is achieved across the two treatment groups, the average difference in the risk of myelosuppression between the two treatment groups will be estimated using logistic regression models accounting for variance estimation (e.g., robust variance estimator).<br><br>Basic statistics on the surveillance population will be presented as n (%), mean ± standard deviation (SD), or median (interquartile range [IQR]), as appropriate. |

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| Milestones | |
|---|---|
| Start of data collection: | January 16, 2026 |
| End of data collection: | Feb-2026 (estimated) |
| Final report of study results: | May-2026 |

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## 3 AMENDMENTS AND UPDATES

| Amendment or Update no | Date | Section of Study Protocol | Amendment or Update | Reason | NIR DRC Approval Date | NIR DRC Version No |
|---|---|---|---|---|---|---|
| 1 | November 4, 2025 | Section 2 ABSTRACT: modified date of protocol finalization, modified author affiliation, modified end date of study period, changed from "incidence rates" to "risk".<br><br>Section 4 MILESTONES: edited the year for data analysis to start.<br><br>Section 5 RATIONALE AND BACKGROUND: changed the end of study period.<br><br>Section 6.1 Research Question: changed the end of study period.<br><br>Section 6.2 Research Objectives: changed from | Update | Updated based on the results of the epidemiological consultation with the PMDA. | October 21, 2025 | v2 |

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| | | "incidence rates" to "risk".<br><br>Section 7.1 Study Design: added "Incidence rates of diagnosed myelosuppression and binomial confidence intervals will be calculated descriptively for tedizolid and linezolid groups separately. If sample size is sufficient (10 or more events observed for each treatment group),"; added rationale for new user design.<br><br>Section 7.2.2 Inclusion criteria: modified code list for confirmed or suspected diagnosis of MRSA in a sensitivity analysis; added a sensitivity analysis for confirmed or suspected/probable diagnosis of MRSA; changed the lookback period.<br><br>Section 7.2.3 Exclusion criteria: added an exclusion | | | | |

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| | | criterion for patients who have prescription records for tedizolid or linezolid only on the index date; added an exclusion criterion to exclude patients with hematological diseases.<br><br>Section 7.2.4 Participant follow-up: clarified the definition of follow-up period.<br><br>Section 7.2.5 Longitudinality: clarified gap and grace periods; removed the mention of minimum follow-up period of one month.<br><br>Section 7.3.3 Covariates: modified covariates.<br><br>Section 7.8.3 Sensitivity analyses: removed an analysis on using worst value to assess myelosuppression; modified lookback period, modified | | | | |

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| | | code list for confirmed or suspected diagnosis of MRSA; added an analysis on confirmed or suspected/probable diagnosis of MRSA.<br><br>All relevant sections: modified terminology related to "periods", such that study period is 21-Aug-2017 to 31-Mar-2025, and cohort entry period is 21-Aug-2018 to 31-Mar-2025. | | | | |
| 2 | December 1, 2025 | 7.3.3 Covariates / Table 4: Covariates list<br><br>In the Sensitivity analyses, the look back period will change. Accordingly, the covariate ascertainment window must also change. Therefore, revise "60 days prior to the index date [-1, -60]" to "Look back period." | Update | Revisions to align different sections of the protocols, following PMDA's directives | November 25, 2025 | v3 |

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| 3 | December 17 2025 | PASS INFORMATION Date of Health Authority Approval of Protocol<br><br>"To be added" to "December 9, 2025" | Update | Minor update triggered by PMDA approval | November 25, 2025 | v3 |

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# 4 MILESTONES

| **Milestone** | **Planned Date** |
|---|---|
| Tedizolid Approval date | 23-Mar-2018 |
| Tedizolid Launch date | 21-Aug-2018 |
| Registration in the HMA-EMA RWD Catalogue | To be registered |
| Start of data collection | January 16, 2026 |
| End of data collection | Feb-2026 (estimated) |
| MID-NET utilization approval and contract | Aug-2025 |
| Epidemiological consultation by PMDA | Oct-2025 |
| MID-NET data analysis | Feb-2026 (estimated) |
| Final report of study results | May-2026 |
| Submission of research results | May-2026 |

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# 5 RATIONALE AND BACKGROUND

In a 21-day repeated-dose study in healthy patients, effects on hematological parameters over time and with increasing doses were observed when the dosing period exceeded 6 days. The incidence of adverse events related to hematologic and lymphatic disorders and laboratory tests in the 1,050 patients included in the safety analysis of international Phase II/III clinical trials (Studies TR701-104, 112, 113, and 126) were anemia in 0.6% (6/1,050 patients), leukopenia in 0.1% (1/1,050 patients), decreased white blood cell count in 0.1% (1/1,050), and decreased platelet count in 0% (0/1,050). There were no serious cases. In the international Phase III clinical trials (Studies TR701-112 and 113), clinical changes in neutrophils and hemoglobin were similar in the active drug and control linezolid groups, but fewer patients had abnormal platelet counts in the active drug group than in the linezolid group. In a Japanese Phase III clinical study (Study 16099), one case of anemia (1/83, 1.2%) and one case of decreased platelet count (1/83, 1.2%) were reported as adverse events related to myelosuppression. Anemia in one case was causally related to the drug. There were no serious cases. The incidence of adverse events was lower in the actual drug group than in the control linezolid group, particularly the proportion of patients with decreased platelet counts. As of June 20, 2017, after tedizolid has been marketed, a review of cases with adverse reactions reported as "SMQ: Haematopoietic cytopenias affecting more than one type of blood cell; SMQ: Haematopoietic erythropenia; SMQ: Haematopoietic leukopenia; SMQ: Haematopoietic thrombocytopenia" revealed that there were 9 cases (including 7 serious cases) suggestive of myelotoxicity, including 6 cases of decreased platelet count, 1 case of hemoglobin decreased, 3 cases of anemia, and 1 case of lymphocytopenia. In all cases, the involvement of tedizolid phosphate was not considered clear due to confounding factors such as the patient's underlying disease, other suspect drugs, or lack of detailed information. The "Serious Adverse Reactions" section of the electronic supplement for the analog linezolid alerts that adverse reactions related to myelosuppression occur at a frequency of approximately 1-10%, and that decreased platelet count tends to occur more frequently when administered for more than 14 days.

Myelosuppression is a risk identified in the Japan risk management plan.

To determine whether the risk of diagnosed myelosuppression is higher with the use of tedizolid compared to the use of the control drug linezolid quantitatively among patients prescribed anti-MRSA drugs between August 2018 (the month this drug was launched) and March 2025.

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# 6 RESEARCH QUESTION AND OBJECTIVES

## 6.1 Research Question

To investigate the diagnosis of myelosuppression related to the identified risks for tedizolid compared to linezolid from 21-Aug-2018 to 31-Mar-2025.

## 6.2 Research Objectives

### 6.2.1 Primary Objectives

To compare the risk of diagnosed myelosuppression between those taking tedizolid and those taking the linezolid.

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# 7 RESEARCH METHODS

## 7.1 Study Design

This is an observational cohort study with active comparator new user design, using MID-NET. The study will be conducted using only structured secondary data. Patients with recorded diagnosis of MRSA and one of the common indications between tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) (see Appendix A) followed by a prescription of tedizolid or linezolid, after the marketing of tedizolid on 21-Aug-2018, will be included in the study (3-5). Incidence rates of diagnosed myelosuppression and binomial confidence intervals will be calculated descriptively for tedizolid and linezolid groups separately. If sample size is sufficient (10 or more events observed for each treatment group), the odds of diagnosed myelosuppression between those taking tedizolid and those taking linezolid will be compared, and the odds ratio will be estimated. Active comparator new user designs are useful for mitigating bias in observational studies, given all other design features are reasonable (6).

In this study, a new user design will be adopted for the following reasons.

- By including only cases without prior use of tedizolid or linezolid, the impact of selection bias and confounding can be reduced in this study using secondary data.

- If cases with a history of tedizolid or linezolid use are included in this study, the study population may consist of individuals for whom tedizolid or linezolid was previously discontinued due to adverse reactions attributable to tedizolid or linezolid, and then re-prescribed. In such a population, the risk of outcomes attributable to tedizolid or linezolid is relatively higher compared with other populations.

In addition, sensitivity analysis will be conducted in which cases with prescriptions of anti-MRSA drugs other than tedizolid or linezolid prior to the prescription of tedizolid or linezolid are excluded (see Section 7.8.3 (1)).

## 7.2 Setting

### 7.2.1 Database

This surveillance will be analyzed using a database provided by MID-NET. MID-NET is a medical information platform developed by the Pharmaceuticals and Medical Devices Agency (PMDA). Establishment of the MID-NET medical data platform provided a reliable and valuable resource for drug safety assessments in Japan. This platform is designed and developed by the Ministry of Health, Labour and Welfare and includes the prescription drugs from the Medical Devices Agency as well as 31 hospitals from 9 healthcare organizations across Japan and approximately 8.3 million patient's data are available. MID-NET is a distributed and closed platform system that connects all collaborative organizations through a

central data center. MID-NET has three types of datasets: SS-MIX2 data such as electronic medical records, Administrative claims data, and DPC data. These datasets can be linked at the patient level. Several coding standards are used to standardize the data stored in MID-NET to allow the integration of information originating from different hospitals. A rigorous and consistent quality management system was implemented to ensure that MID-NET data are of high quality and meet Good Post-marketing Study Practice (GPSP). A major advantage of MID-NET is that approximately 260 standardized clinical laboratory test values are available for analysis (1, 2).

The advantages of MID-NET are as follows:

1. Standardized clinical laboratory data are available.

2. MID-NET captures data for both non-elderly and elderly patients, especially compared to the JMDC Claims Database (JMDC), which basically captures only data for non-elderly patients.

3. Compared to other databases (JMDC: about every 5 months, Medical Data Vision (MDV): every 2 months), the data is updated almost in real time (Every 1 week to 1 month).

By considering these advantages, this surveillance will be conducted by using MID-NET to investigate myelosuppression and compliance with laboratory tests.

To utilize MID-NET, we will send a data extraction script set from the MID-NET data center to the over 30 participating institutions. Each institution accepts the script set and sends the anonymized output raw data set back to the central data center, which will then combine the data so it can be analyzed by MSD. The script is based on the combination of SS-MIX2, Administrative claims and DPC data. The script is composed of two settings, “Setting extraction” and “Setting output”.

**Setting extraction conditions:**

The extraction condition matches any one of the following conditions from the SS-MIX2, Administrative claims or DPC data.

- SS-MIX2
  The prescription / injection data including prescription dispensing order records and administration records for both inpatient and outpatient, YJ code matches one of tedizolid (ATC code: J01XX11) or linezolid (ATC code: J01XX08), AND
  Disease name order, International Classification of Diseases 10 (ICD-10) code matches MRSA and one of the common indications between tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) . The disease code list is provided as an Appendix A.

- Administrative claims
  Drug information data, including prescription dispensing records and medication administration records for both inpatient and outpatient, receipt code matches one of tedizolid (ATC code: J01XX11) or linezolid (ATC code: J01XX08), AND
  Disease name order, diagnosis code matches MRSA and one of the common indications between tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) . The disease code list is provided as an Appendix A.

- DPC
  Drug information data including prescription dispensing order records and administration records for inpatient, receipt code matches one of tedizolid (ATC code: J01XX11) or linezolid (ATC code: J01XX08), AND
  Disease name order, diagnosis code match MRSA and one of the common indications between tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) . The disease code list is provided as an Appendix A.

**Setting output conditions:**

Table 1 shows the settings of the data tables belonging to each data type.

**Table 1: Data tables**

| Study period | Data types | Table name |
|---|---|---|
| 21-Aug-2017<br>to<br>31-Mar-2025 | SS-MIX2 | Visit information (The date of death recorded in SS-MIX2 as "date of death" or "death" in the hospital visit information summary) |
| | | Diagnostic information (illness order) |
| | | Diagnostic information (discharge summary) |
| | | Prescription / injection order |
| | | Prescription / injection |
| | | Specimen test information |
| | DPC | DPC patient information, including demographics |
| | | DPC admission and discharge information (recorded in the DPC file as "death" in the discharge summary) |
| | | DPC diagnostic information |
| | | DPC drug information |
| | | DPC medical practice information |
| | Administrative claims | Receipt diagnostic information |
| | | Receipt drug information |
| | | Receipt medical care information |

### 7.2.2 Inclusion criteria

The patients are included if they meet all the following criteria:

1. Patients with a new prescription date (index date) for tedizolid (ATC code: J01XX11) or linezolid (ATC code: J01XX08) during the cohort entry period (21-Aug-2018 to 31-Mar-2025).

   A new prescription for tedizolid or linezolid is defined based on Tables 2 and 3. Includes all patients who have been prescribed the above medications, regardless of whether they are outpatients, inpatients, or emergency cases.
2. Primary analysis: Patients with confirmed diagnosis of MRSA (ICD-10: A49.0 and disease name notation: MRSA infection) and confirmed diagnosis of indications for both tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) in the same month or previous month of the index date. The disease code list is provided as Appendix A.

   Sensitivity analysis-1 (see Section 7.8.3 (4)): Patients with confirmed or suspected diagnosis of MRSA (ICD-10: A49.0 and disease name notation: MRSA infection) and confirmed diagnosis of indications for both tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) in the same month or previous month of the index date. The disease code list is provided as Appendix A.

   Sensitivity analysis-2 (see Section 7.8.3 (5)): Patients with confirmed or suspected / probable diagnosis of MRSA (ICD-10: A49.0 and disease name notation: MRSA infection, Staphylococcal infection, MRCNS infection, MSSA infection, MRSE infection, and Vancomycin-resistant Staphylococcus aureus infection) and confirmed diagnosis of indications for both tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) in the same month or previous month of the index date. The disease code list is provided as Appendix A.

   Index date is the first prescription date of tedizolid or linezolid observed in the cohort entry period (21-Aug-2018 to 31-Mar-2025). That is defined by using the prescription order in the SS-MIX2 data of the MID-NET dataset. New tedizolid prescription patients will be tedizolid group and new linezolid prescription patients will be linezolid group.

   Diagnosis of MRSA and indications for tedizolid or linezolid are defined by using the disease name order in the SS-MIX2 data or DPC data or Administrative claims data of the MID-NET dataset.

All age and sex will be included.

**Table 2: The estimated treatment patterns in the tedizolid group**

| Pre-treatment* | At index date | Inclusion/Exclusion |
|---|---|---|
| - | Tedizolid (J01XX11) | Inclusion |
| Linezolid (J01XX08) | Tedizolid (J01XX11) | Exclusion |
| Arbekacin (J01GB12) | Tedizolid (J01XX11) | Inclusion |
| Teicoplanin (J01XA02) | Tedizolid (J01XX11) | Inclusion |
| Daptomycin (J01XX09) | Tedizolid (J01XX11) | Inclusion |
| Vancomycin (J01XA01) | Tedizolid (J01XX11) | Inclusion |

* < 60 days before the index date [-60, -1]

**Table 3: The estimated treatment patterns in the linezolid group**

| Pre-treatment* | At index date | Inclusion/Exclusion |
|---|---|---|
| - | Linezolid (J01XX08) | Inclusion |
| Tedizolid (J01XX11) | Linezolid (J01XX08) | Exclusion |
| Arbekacin (J01GB12) | Linezolid (J01XX08) | Inclusion |
| Teicoplanin (J01XA02) | Linezolid (J01XX08) | Inclusion |
| Daptomycin (J01XX09) | Linezolid (J01XX08) | Inclusion |
| Vancomycin (J01XA01) | Linezolid (J01XX08) | Inclusion |

* < 60 days before the index date [-60, -1]

### 7.2.3 Exclusion criteria

Those with any of the following criteria will be excluded:

1. Patients who do not have 60 days lookback period prior to the index date.

   To increase the number of patients included in the study, the lookback period was kept as short as possible. Based on the results of the feasibility study, changing the lookback period from 90 days to 30 days was estimated to increase the number of patients by approximately 10% (72.7% to 81.8% for tedizolid and 72.9% to 85.0% for linezolid, respectively). The analysis with a lookback period of 30 days will be performed as a sensitivity analysis (see Section 7.8.3 (2)).
2. Patients who have prescriptions for both tedizolid and linezolid on the same index date.

   This exclusion criterion will exclude the patients who cannot be assigned to either of the exposure groups.
3. Patients who have one or more events of myelosuppression (grade 2 or higher by CTCAE Version 5.0 criteria for any of the decreased white blood cells, decreased platelets, decreased neutrophils, anemia (decreased hemoglobin): see Section 7.3.2 for details) within 14 days prior to the index date.
4. Patients who have prescription records for tedizolid or linezolid only on the index date.
5. Patients who have a diagnosis of hematological diseases (such as myelodysplastic syndrome, aplastic anemia, and immune thrombocytopenia) defined by ICD-10 code within lookback period. The disease code list is provided as Appendix A.

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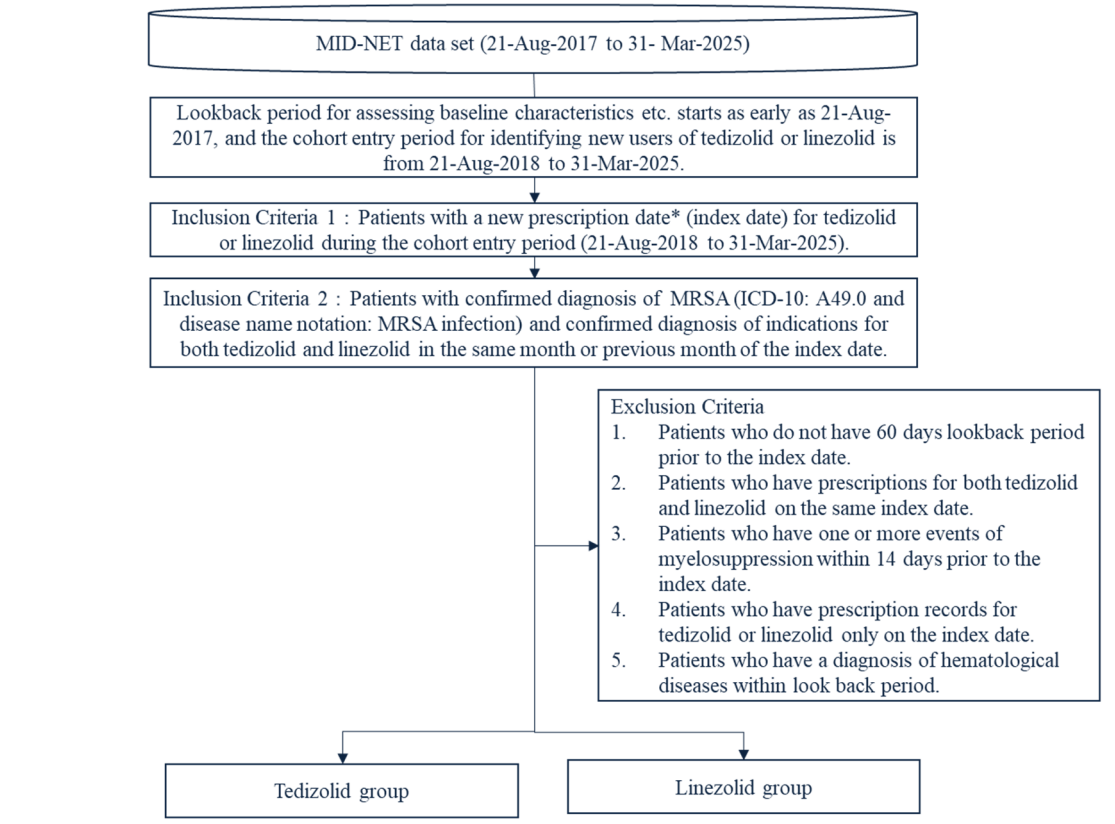
**Figure 1: Flow diagram**




*New prescription date is the first prescription date of tedizolid or linezolid observed during the cohort entry period (21-Aug-2018 to 31-Mar-2025).

### 7.2.4 Participant follow-up

The follow-up will begin on the day after the index date.

The follow-up end date will be defined as the date of treatment period end, date of death, the end of the study period, start date of other treatment drug, or date of outcome onset whichever comes first. The date of death means recorded in SS-MIX2 as “date of death” or “death” in the hospital visit information summary or recorded in the DPC file as “death” in the discharge summary. If discrepancies in the date of death are found between SS-MIX2 and DPC, preference is given to the DPC data. If the date of death is missing in the DPC data, the missing information will be supplemented using the SS-MIX2 data, if available.

Switching of the medication from one treatment group to another (from tedizolid to linezolid group or vice versa) or an addition of the other medication will also be considered as a termination of the initial treatment, and patients will be censored on the day of termination of the initial treatment, which will be operationally defined as the start of another treatment per the database. Note, the additional date (date when another medication is added) and the switching date (overlapping treatment date) are included in the follow-up period.

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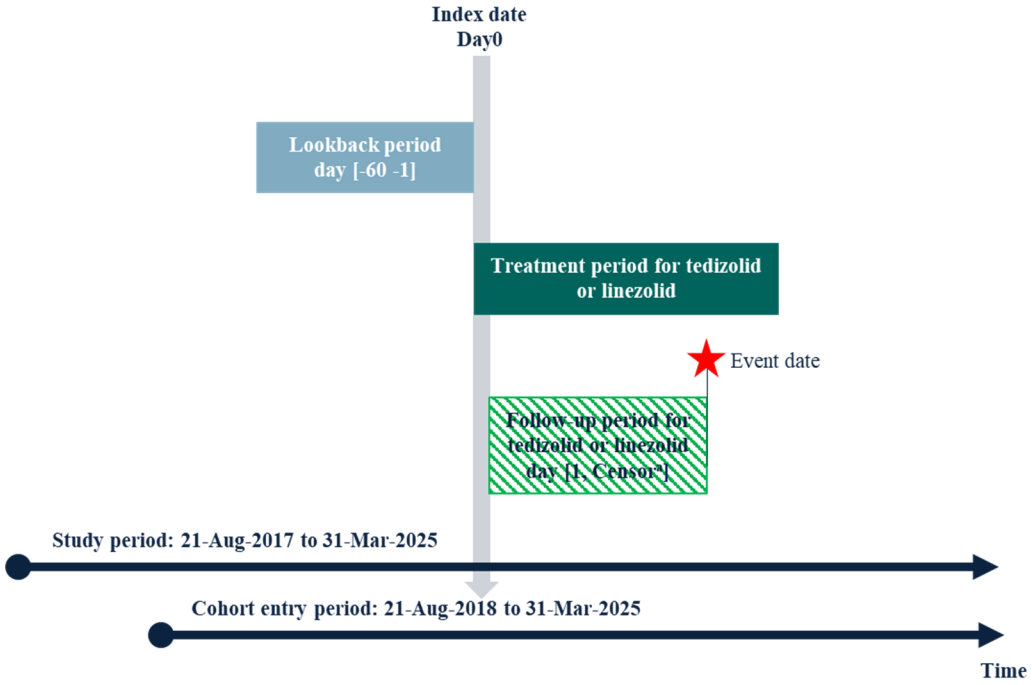
Note, the previous feasibility study shows the median time to discontinuation of initial treatment as [redacted] days.

**Figure 2: Follow-up Schema**




a. the treatment period end, date of death, the end of study period, start date of other treatment drug, date of outcome onset, whichever comes first.

### 7.2.5 Longitudinality

This is a longitudinal surveillance. Factors to be considered in describing the clinical course of each patient are as follows:

1. All patients must have 60 days history before the index date (Lookback period).
2. The treatment period (continuous prescription period) for the tedizolid and linezolid groups is defined as from the index date to the end date of the last prescription period + grace period - 1.

   A prescription period will be defined as prescription date + number of day's supply - 1.

   The gap period is defined as the period from the end of the prescription period to the start of the next prescription period.

   If the gap period is <14 days, the prescription periods are considered to be continued, and the prescription periods are consolidated. If the gap period is ≥14 days, the prescription periods are not consolidated, and the prescription periods after the gap period are not included in the analysis.

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The gap periods for primary analysis are set at 14 days for tedizolid and linezolid based on the results of the feasibility study. It showed that the median gap period in the 1st use was [redacted] days for tedizolid group and [redacted] days for linezolid group, However, an analysis with a gap period of 7 days was also conducted as a sensitivity analysis (see Section 7.8.3 (3)). In addition, the feasibility study showed that the percentage of injections used was quite high (55/62 (88.7%) for tedizolid group and 476/574 (82.9%) for linezolid group). Since most of the medication was injectable, the possibility of residual medication was considered to be low, and unnecessary to set a gap period longer than 14 days. Also, it was considered unnecessary to set different treatment periods for injectable and oral agents.

The grace period is defined as the duration during which the effects of the drug may still be present, considering residual medication. It is considered the period that is added to the end date of the last prescription period. In this study, the grace period is set to be the same length as the gap period.

## 7.3 Variables

### 7.3.1 Exposure

The group of patients who are newly prescribed/exposed to tedizolid during the cohort entry period (21-Aug-2018 to 31-Mar-2025) will be considered as the tedizolid group. The start date of the cohort entry period coincides with the date tedizolid was placed on the market, so the index date corresponds to the new incident use of tedizolid in the database. The group of patients who newly start linezolid during the cohort entry period (21-Aug-2018 to 31-Mar-2025) will be considered as the linezolid group.

Patients will be considered as being exposed to the medication if there is a record for drug supply, i.e., prescription or dispensation record. Each prescription or dispensation will initiate a new prescription period that ends after the drug supply runs out. Also, a gap day between two prescription / dispensation records will be considered as a continuous prescription period if it is below the gap period.

### 7.3.2 Outcomes

The outcome of interest in the study is myelosuppression. Myelosuppression is defined as following.

Meeting or exceeding Grade 2 or higher by CTCAE Version 5.0 criteria for any of the following items (7).

Decreased white blood cells, decreased platelets, decreased neutrophils, anemia (decreased hemoglobin).

The specific cut-off points are as follows (7).

Decreased white blood cells: < 3,000/mm3

Decreased platelets: < 75,000/mm3

Decreased neutrophils: < 1,500/mm3

Anemia (decreased hemoglobin): < 10.0 g/dL

The date of outcome onset is the date of the first test when one of the above test items.

As described in Section 5, no severe cases of myelosuppression associated with tedizolid were observed in clinical trials. The results of the feasibility study during the lookback period 30 days indicate that if CTCAE grade 1 is included into the definition, most cases will exhibit myelosuppression (Tedizolid group: 43/49 (88%), linezolid group: 384/467 (82%)). Based on the results, when grade 1 or higher was used as the cut-off point, most cases will be excluded. Also, there is literature that evaluates myelosuppression using the same definition (cut-off point is grade 2 or higher) (8). This paper evaluates the incidence of myelosuppression in cancer patients who underwent radiation therapy. Although the design of this study differs from the paper, the definition of myelosuppression as CTCAE grade 2 or higher was considered to have some potential validity. From the above, the cut-off point was set at grade 2 or higher (see above for specific cut-off points). However, since the possibility of severe bone myelosuppression cannot be ruled out in clinical practice, a sensitivity analysis (see Section 7.8.3 (6)) will also be conducted using grade 3 or higher as cut-off points.

The values of CTCAE grade 2 and 3 for each test item are as follows.

Decreased white blood cells: Grade2: < 3,000-2,000 /$mm^3$, Grade3: < 2,000-1,000 /$mm^3$

Decreased platelets: Grade2: < 75,000-50,000 /$mm^3$, Grade3: < 50,000-25,000 /$mm^3$

Decreased neutrophils: Grade2: < 1,500-1,000 /$mm^3$, Grade3: < 1,000-500 /$mm^3$

Anemia (decreased hemoglobin): Grade2: < 10.0-8.0 g/dL, Grade3: < 8.0 g/dL

[Data components used for capturing the outcome]
– The test values will be captured using the laboratory test results table: JLAC10 code
The code list for outcome definition is in Appendix A.

### 7.3.3 Covariates

The following variables for characterizing the study population will be collected and summarized:

- Demographics (age, sex)

- Year of prescription starts
- Severity of MRSA (pneumonia, sepsis, renal failure, dialysis, other anti-MRSA treatment)
- Comorbidities (cancer, heart-related disease, liver-related disease, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease)
- Treatment history (drugs that cause myelosuppression)

Among the above variables, those expected to be confounders at this stage are listed in Table 4, which will be considered for covariate adjustment in the analysis.

**Table 4: Covariates list**

| Name of the covariate | Decision category | Measurement origin date and period |
|---|---|---|
| **Patient characteristics at the start of follow-up** | | |
| Age | Continuous variable | Index date [0,0] |
| Sex | Male/Female | |
| **Severity of MRSA** | | |
| Sepsis | Yes/No | Lookback period |
| Renal failure | Yes/No | |
| **Comorbidities** | | |
| Cancer | Yes/No | Lookback period |
| Heart-related disease | Yes/No | |
| Liver-related disease | Yes/No | |
| **Treatment history (Drugs that cause myelosuppression)** | | |
| Immunosuppressants | Yes/No | Lookback period |
| Antitumor agents | Yes/No | |
| Antirheumatic agents | Yes/No | |
| Steroids | Yes/No | |

## 7.4 Data Sources

See Section 7.2.1.

### 7.4.1 Study Procedures

#### 7.4.1.1 Forecasted schedule

See Section 4.

#### 7.4.1.2 Schedule and rationale for the progress of the surveillance and the milestones for evaluating the obtained results or reporting to PMDA

If necessary, consider further activities and measures based on the results of this surveillance.

#### 7.4.1.3 Additional measures that may be implemented based on the results of the drug safety monitoring activities and criteria for starting them

If necessary, consider further activities and measures based on the results of this surveillance.

#### 7.4.1.4 Responsible person

| Title | Department | Name |
|---|---|---|
| Safety management supervisor | Pharmacovigilance | PPD |

#### 7.4.1.5 Organizational structure

The organization is shown in Appendix B.

#### 7.4.1.6 Organizational structure

Database vendor: Pharmaceuticals and Medical Devices Agency (PMDA)

Address: Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki Chiyoda-ku, Tokyo

Business scope: dataset creation from the 31 collaborating hospitals

Data analysis

Supplier: CCI

Address: Acropolis TOKYO, 6-29 Shinogawamachi, Shinjuku-ku, Tokyo, 162-0814, Japan

Business scope: Dataset analysis

#### 7.4.1.7 Record keeping

Appropriate documents shall be saved in accordance with the MSD GPSP SOP and various guidance related to MID-NET.

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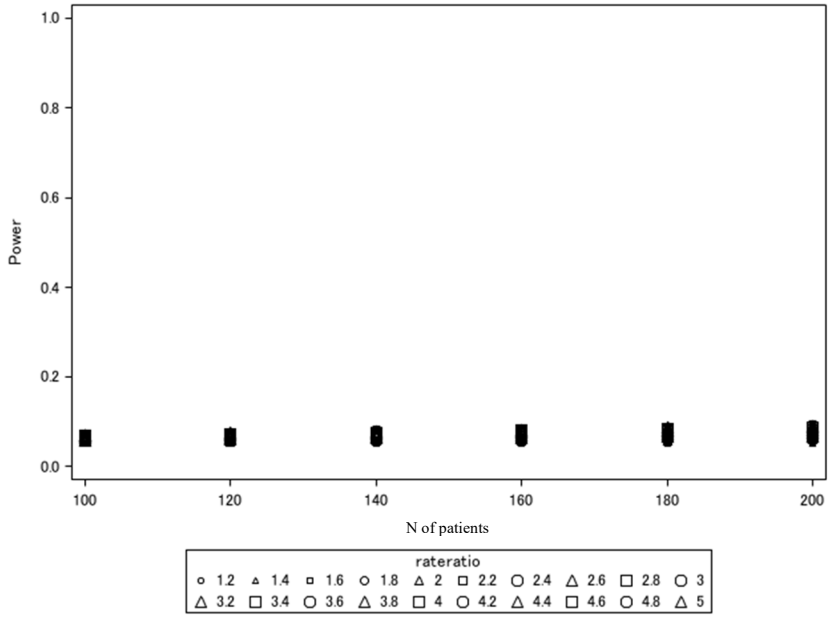
## 7.5 Study Size

In a Phase III clinical study in Japan (Study 16099), one case of an adverse event related to myelosuppression that was causally related to the drug was reported: anemia (1/83 patients, 1.2%).
Based on this consideration, the incidence of an event in the tedizolid was assumed to be 1.2%.
Based on the results of the feasibility study, the median continued prescription period for tedizolid was CCI days, with a 75% tile of CCI days. From the above, a follow-up period of about 30 days was assumed.
According to the results of the MID-NET survey, there were CCI cases of patients prescribed tedizolid with confirmed diagnosis of MRSA during the period from May 2018 to March 2025. Considering the loss of cases due to exclusion criteria, it is estimated 100-200 patients will be included in the study.
Under this assumption, the power is shown below (Fig. 3) when the risk ratio (rate ratio) is set between 1.2 and 5.0 and the sample size of the tedizolid group is varied in 20 increments from 100 to 200 of the predicted accumulation. Note that sample size of the control group (linezolid) was assumed to be approximately 10 times that of the tedizolid group. A generalized linear model assuming Poisson distribution was used to detect group differences.

**Figure 3: Power at each sample size assuming an event incidence rate of 1.2% and a risk ratio of 1.2-5 in the tedizolid group**




For each condition, there was no sample size required for Power to be greater than 80%.

## 7.6 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data *not* obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. The investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

**Data Management Software and Hardware:**

Data management and analyses will be performed using SAS 9.4.

**Description of Data Preparation and Methods for Data Retrieval and Collection:**

This surveillance will utilize post-marketing database studies that must comply with the quality standards stipulated in the ministerial ordinance for good post-marketing study practices (GPSP) and their related guidelines.

Data management for this surveillance will be conducted using standard MID-NET processes. The processes will take into consideration any data governance imposed on the data source. MSD and CCI will adhere to all local and regional laws on data protection and privacy.

## 7.7 Programming Quality

This study will incorporate the following quality checks for data analysis and reporting programming:

- Creating a program requirements and specification document (PRS)
- Developing and testing of statistical programs which includes ensuring the programs run successfully and all output are reviewed to ensure they meet the criteria included in the (PRS). This includes validating that all inputs (metadata or parameter values) are correctly specified in the programs and are consistent with the PRS.
- Independent Review and Testing, conducted by a second programmer to ensure that the input and outputs of the programs created by the first programmer meet the documented PRS. This includes the following 2 activities:

- Review of code to ensure the program aligns with the PRS
- Execution of code and review of results for some or all scenarios

And may include the following activity:

- Parallel programming of a small piece of critical code

- Independent Double Programming, conducted by second programmer. After programming is completed, the programs and results of the second programmer and compared to those of first programmer to ensure consistency. If discrepancies are found, the programmers will repeat steps until consistency is achieved.

- Review of outputs/results to ensure accuracy and format of each deliverable.

## 7.8 Data Analysis

### 7.8.1 Patient characteristics

Basic statistics on the surveillance populations will be presented as n (%), mean ± SD, or median (interquartile range [IQR]), as appropriate.

### 7.8.2 Primary objective

Incidence rates of myelosuppression and binomial confidence intervals will be calculated descriptively for tedizolid and linezolid groups separately. The number and percentage of patients with myelosuppression will be calculated based on myelosuppression test items and grades. For all patients, the exposure time starts the day after the initiation of treatment date.

If there are 10 or more events observed for each treatment group, crude odds ratios and 95% CI will be estimated to be using logistic regression models, to compare the risk of myelosuppression between the tedizolid group and linezolid group (9).

Inverse probability of treatment weighting (IPTW) approach will be used to adjust for potential confounding between the tedizolid and linezolid groups (10,11). PS will be generated using probability estimates from a logistic regression model in which treatment with tedizolid or linezolid will be the binary dependent variable and patient characteristics (see Section 7.3.3) will be used as predictors of being treated with tedizolid or linezolid, if 10 patients exposed to tedizolid are observed per predictor. The IPTW approach uses weights derived from the PS to create a pseudo-population such that the distribution of baseline covariates in the population is independent of treatment assignment. For each patient, the weight will be assigned as the inverse of the propensity score for the tedizolid group and as the inverse of 1 minus the propensity score for the linezolid group will be calculated. The balance of baseline covariates will be assessed by using standardized mean differences; covariates will be well-balanced if the standardized mean difference is <0.1 (12,13). The

distribution and variance for continuous variables will also be assessed between the treatment groups (13). Once balance of the covariates is achieved across the two treatment groups, the average difference in the risk of myelosuppression between the two treatment groups will be estimated using logistic regression models accounting for variance estimation (e.g., robust variance estimator) (14).

### 7.8.3 Sensitivity analyses

The following sensitivity analyses are planned:

1) The analysis will be conducted that does not allow for a history of administration of anti-MRSA drugs other than tedizolid and linezolid within lookback period.
2) The analysis will be conducted with the lookback period changed to 30 days.
3) The analysis will be conducted with the gap period changed to 7 days.
4) The analysis will be conducted with the following changes to the inclusion criteria 2.

   Patients with confirmed or suspected diagnosis of MRSA (ICD-10: A49.0 and disease name notation: MRSA infection) and confirmed diagnosis of indications for both tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) in the same month or previous month of the index date. The disease code list is provided as Appendix A.
5) The analysis will be conducted with the following changes to the inclusion criteria 2.

   Patients with confirmed or suspected / probable diagnosis of MRSA (ICD-10: A49.0 and disease name notation: MRSA infection, Staphylococcal infection, MRCNS infection, MSSA infection, MRSE infection, and Vancomycin-resistant Staphylococcus aureus infection) and confirmed diagnosis of indications for both tedizolid and linezolid (1: Deep Skin Infections, Chronic Abscesses, 2: Secondary infection of trauma, burns, and surgical wounds) in the same month or previous month of the index date. The disease code list is provided as Appendix A.
6) The analysis will be conducted using grade 3 or higher as cut-off points for myelosuppression.

   The specific cut-off points are as follows.

   Decreased white blood cells: < 2,000/mm3

   Decreased platelets: < 50,000/mm3

   Decreased neutrophils: < 1,000/mm3

   Anemia (decreased hemoglobin): < 8.0 g/dL
7) The analysis will be conducted that the period for excluding a history of myelosuppression is changed from within 14 days of the index date to within 30 days of the index date.

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### 7.8.4 Missing value

Missingness in the baseline covariates will be presented in tables. As most of the baseline covariates are defined as being present when there are corresponding diagnoses / prescriptions on record, there will be no missingness for these variables (those lacking the records will be considered as not having the condition). Missingness in other variables (e.g., age, sex) is possible, and will be handled appropriately depending on their size and suspected cause. Special consideration for outliers are not planned.

## 7.9 Quality Control

All parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practices (GVP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP and GVP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are estimated to appropriately implement the action plan in a timely manner.

## 7.10 Limitations of the Research Methods

The number of patients treated with tedizolid or linezolid are likely to be very small because of the low use of these medications, even before applying the inclusion and exclusion criteria (which requires a MRSA diagnosis and specific prior therapies). In addition, the treatment period for these cohorts will be relatively short. Given very small numbers (patients / patient years), a high-risk population, previous treatment with other MRSA drugs that could be associated with myelosuppression that are diagnosed at a later time, and many concomitant medications that can also be associated with the myelosuppression, it is possible that rates may be higher than observed in clinical trials or that there will appear to be imbalances between the two cohorts (who are actually taking bioequivalent medications), etc. Therefore, assessment of OR is likely to be inconclusive and care must be taken in interpretation of the data and generalizability of the surveillance results. Also, if there are no events in either the tedizolid or linezolid group, the OR cannot be calculated. Crude OR should not be calculated with less than 10 events.

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When estimating the marginal effect of rare exposure, results using PS methods could be biased (15). Logistic regression models generating PS with small number of patients in tedizolid group might suffer from convergence problems and unstable parameter/coefficient estimates, as limited data provide insufficient information for reliable model fitting (16). Additionally, when a treatment group is rare, this group of patients are likely to receive very large weights, and thus have a disproportionate influence on the analysis, which is suspected to be the case with tedizolid based on the feasibility assessment. As these patients represent only a small proportion of the target study population, their disproportionate influence on the analysis may affect the precision of the average marginal effect estimate (17).

The sensitivity analysis which further restricts the population is even more likely to be inconclusive. More details on the specific limitations which may affect the surveillance results and their interpretation are described below.

- MID-NET contains data mostly from secondary care hospitals. Hence, data from primary care settings is limited, which may cause selection biases and limit generalizability of the results to the general MRSA population.
- Another major limitation of MID-NET is that patients cannot be followed up if they receive care at other healthcare facilities that do not contribute to MID-NET due to lack of patient-level data linkages among hospitals. Event incidences (e.g., diagnoses, laboratory tests, death, etc.) that occur outside the 31 hospitals are not captured in MID-NET, even during the follow-up period.
- The frequency of some laboratory tests may be low and/or the proportion of abnormal values may be overestimated because normal routine lab tests from the community are not captured.
- Representativeness – MID-NET in this activity comprises only 31 hospitals. When the 31 hospitals have specific clinical practices or include specific patients, e.g. more secondary prevention patients, the surveillance population or the results may not represent the general MRSA patient population or practices in Japan. MID-NET is made up of major hospital groups (Kitasato University and Tokushukai Hospital) and university hospitals. The patients prescribed tedizolid per the label may not be representative of all patients who take tedizolid (e.g., we know that some patients will not have a MRSA diagnosis, or may switch from a drug where switching is not specified in the JPC.
- Validity of outcome definitions – there is not a consensus on the best algorithms for defining the myelosuppression overall or specifically in Japanese databases. The algorithms that do exist may not have optimal sensitivity, specificity, and positive predictive value.
- Age, some comorbidities, some prior/concomitant drugs, etc. could affect risk of myelosuppression which is why we will examine demographic and clinical characteristics of the 2 groups as well as characteristics of drug utilization (e.g., duration of treatment, duration of follow-up, reasons for censoring). If there are

differences in compliance / censoring, this could also affect the rates of myelosuppression and limit interpretation of the results. Therefore, a nominal elevation of OR may be seen due to imbalance of these factors, which needs to be taken into account in interpretation of the results and potentially limits generalizability.

- Residual confounding may persist despite efforts to adjust for measured covariates. Small sample size might also limit our ability to sufficiently control for confounding. We will discuss this limitation and the potential direction and magnitude of residual confounding in the final study report. Selection bias - tedizolid is a newly approved drug and could alert the prescribing physicians to monitor the patient more closely, resulting in enhanced capture of adverse events compared to the linezolid. This may lead to an overestimation of the risk for tedizolid.
- The disease diagnoses used to define covariates may be recorded for the purposes of claims, and coded diagnoses can be inaccurate and may lead to residual confounding.
- The database will only provide data on the prescription (and some dispensation data) for the medications. The actual use of the medication is not guaranteed and misclassification bias is possible. However, we don't expect this misclassification to be different in nature between the two exposure drugs and likely to be non-differential.

## 7.11 Other Aspects

N.A.

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# 8 PROTECTION OF HUMAN SUBJECTS

## 8.1 Informed Consent

This study will not require participant informed consent.

This study will not require participant IRB/EC review.

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Whenever feasible, study files should be coded and stripped of personal identifiers, and code keys should be stored separately from study files.

MID-NET is operated and managed under the Act on Pharmaceuticals and Medical Devices Agency, Independent Administrative Agency (Act No. 192, 2002), and is exempt from requirements to obtain informed consent from patients in accordance with the Act on the Protection of Personal Information (Act No. 57, 2003), and the PMDA discloses information on the utilization of MID-NET data and provides opportunities for patients to deny the provision of their hospital data to MID-NET.

### 8.1.1 Consent and Collection of Specimens for Future Biomedical Research

N.A.

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# 9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

### Adverse Event and Product Quality Complaint Reporting

This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events or product quality complaints to regulatory agencies is planned for this database study because there is no access to individual patient/subject records and it is not possible to assess the causality of individual cases. The investigator should refer to their institution's policy or local laws and regulations regarding reporting of any suspected adverse reactions and product quality complaints.

Any health outcomes (if collected per Section 7.3.2), including any that qualify as adverse events, will be summarized as part of any interim analysis (including safety analysis, if required) and in the final study report, which will be provided to regulatory agencies by the Sponsor as required. Any relevant safety information will be summarized and the Sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

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# 10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal, abstract/presentation at a scientific conference or symposium, or results posted on the HMA-EMA Catalogue of real-world studies. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally.

# 11 REFERENCES


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# 12 ANNEXES

## Annex 1 ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15 OCT 2018

Doc.Ref. EMA/540136/2009

### ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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| **Study title: A post-marketing database surveillance to investigate the risk of diagnosed myelosuppression events in MRSA patients treated with tedizolid or linezolid in Japan** |

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| **EU PAS Register® number:** |

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**Study reference number (if applicable):**

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 4 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 4 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim report(s) | ☐ | ☐ | ☒ | |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 4 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 4 |

Comments:

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| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 5 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 6.2 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 7 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

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| 2.1.4: The purpose of the study is to assess risk and provides estimates with associated confidence limits . |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

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| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 7.1 |
| 3.2 | Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 7.2 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 7 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | 7 |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☐ | ☐ | ☒ | |

Comments:

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| 3.5 This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events to regulatory agencies is planned. |

| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 7 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 7 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 7 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 7 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 7 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 7 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 7 |

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Comments:

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| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 7.3.1<br>7.2.5 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☒ | ☐ | |
| 5.3 Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 7.3.1<br>7.2.5 |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 7.3.1<br>7.2.5 |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☒ | ☐ | |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 7.3.1 |

Comments:

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| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 7.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 7.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☐ | ☒ | ☐ | |

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| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☒ | ☐ | |

Comments:

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| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | 7.3.3 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 7.1 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 7.3.2 |

Comments:

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| **Section 8: Effect measure modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☒ | ☐ | |

Comments:

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| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 7.3.1 |

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| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 7.3.2 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 7.3.3 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 7.3.1 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 7.3.2 |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 7.3.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 7.3.1 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 7.3.2 |
| 9.3.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 7.3.3 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 7.4 |

Comments:

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 7.8 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 7.8 |

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 7.8 |
| 10.4 Are stratified analyses included? | ☐ | ☒ | ☐ | |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 7.8 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☒ | ☐ | ☐ | 7.8 |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 7.8 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 7.8 |

Comments:

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| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☐ | ☐ | ☒ | |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 7.10 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 7.10 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☒ | ☐ | ☐ | 7.10 |

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☒ | ☐ | ☐ | 7.10 |

Comments:

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| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☐ | ☒ | ☐ | |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☒ | ☐ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 7.6 |

Comments:

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| Any ethical or IRB review and data protection requirements needed for this retrospective analysis of a secondary data source will be determined and implemented prior to the initiation of the study. |

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 3 |

Comments:

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| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 10 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 10 |

Comments:

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Name of the main author of the protocol: _____

Date: 01/December/2025

Signature: _____

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|---|---|
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## Annex 2 Administrative and Regulatory Details

### *Confidentiality:*

### *Confidentiality of Data*

The investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence. If applicable such information will be divulged to Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

### *Confidentiality of Subject Records*

The investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

The investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

### *Confidentiality of Investigator Information*

The investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. The

investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

***Administrative:***

***Compliance with Financial Disclosure Requirements***

*Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.*

*The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.*

***Compliance with Law, Audit and Debarment***

*The investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.*

*The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.*

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*The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.*

*The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.*

*Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.*

*The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.*

*The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.*

*Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.*

*In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.*

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| PRODUCT: MK-1986 | PROTOCOL/AMENDMENT VERSION NO.: 1986-045-00-V3 |
| REVOPS ID NO: NIS106694<br>EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08063.002 | NIR DRC APPROVAL DATE: NOVEMBER 25, 2025 |

*According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.*

***Compliance with Study Registration and Results Posting Requirements***

*Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), as well as the European Medicines Agency GVP Module VIII, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to one or more study registries such as the HMA-EMA Catalogue of RWD Studies. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements for all post-marketing safety and efficacy studies. Information posted will allow subjects to identify potentially appropriate primary data collection studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.*

*The investigator acknowledges that the statutory obligations under FDAMA/FDAAA and EMA GVP Module VIII are that of the Sponsor and agrees not to submit any information about this study or its results to a study registry without consulting with the Sponsor.*

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| PRODUCT: MK-1986 | PROTOCOL/AMENDMENT VERSION NO.: 1986-045-00-V3 |
| REVOPS ID NO: NIS106694<br>EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08063.002 | NIR DRC APPROVAL DATE: NOVEMBER 25, 2025 |

## Annex 3: Global Qualified Person for Pharmacovigilance (GQPPV), EU/UK QPPV

PPD
**Global Qualified Person for Pharmacovigilance (GQPPV) EU/UK QPPV**
**Tel: +PPD,**
**Fax: +PPD**
**Email: PPD**

**MSD Europe Belgium SRL**
**Boulevard du Souverain, 25**
**1170 Watermael-Boitsfort**
**Bruxelles, Belgique**

**Deputy QPPV:**
PPD
Tel: +PPD
Facsimile No: +PPD
Email: PPD

**GQPPV Office Physician:**
PPD
Tel: +PPD ; Fax: +PPD
Email: PPD

Emergency/Out of Hours: As above or via +44 (0)208 154 8000

Dear Sir/Madam,

**Re: Global, EU/UK QPPV Signature Page for PASS**
**INN:**
**Product: MK-1986**
**Protocol No: 1986-045-00-V3**
**Epidemiology No: EP08063.002**
**Protocol Date: December 1, 2025**
**MAH: MSD KK**

In line with the Guideline on Good Pharmacovigilance Practice (GVP), Module VIII - Post-Authorization Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the Global Qualified Person for the Pharmacovigilance (GQPPV), EU/UK QPPV.

Yours faithfully

PPD
PPD
**Global Qualified Person for Pharmacovigilance (GQPPV)**
**EU/UK QPPV**

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| PRODUCT: MK-1986 | PROTOCOL/AMENDMENT VERSION NO.: 1986-045-00-V3 |
| REVOPS ID NO: NIS106694<br>EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08063.002 | NIR DRC APPROVAL DATE: NOVEMBER 25, 2025 |

# 13 SIGNATURES

## 13.1 Sponsor's Representative

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|---|---|
| PRINTED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |

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|---|---|
| PRODUCT: MK-1986 | PROTOCOL/AMENDMENT VERSION NO.: 1986-045-00-V3 |
| REVOPS ID NO: NIS106694<br>EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08063.002 | NIR DRC APPROVAL DATE: NOVEMBER 25, 2025 |

# 14 APPENDICES

Appendix A: Code list

Appendix B: Organization to conduct the surveillance (specific material for PMDA)