POST AUTHORIZATION SAFETY STUDY PROTOCOL

Eribulin mesilate

Incidence and Resolution of Eribulin-induced peripheral Neuropathy (**IRENE**)

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PASS Information

Title	Incidence and Resolution of Eribulin-induced peripheral Neuropathy (**IRENE**)
Protocol version identifier	1.0
Date of last version of protocol	05 May 2016
EU PAS register number	Not applicable at date of protocol version 1.0
Active substance	Eribulin mesilate, E7389
Medicinal product	Halaven®
Product reference	***EU/1/11/678/001-004***
Procedure number	***N/A***
Marketing authorization holder	Eisai Europe Ltd.
Joint PASS	No
Research question and objectives	**Primary Objective** • To characterize and determine the incidence of eribulin-induced peripheral neuropathy (PN), and frequency and time to resolution of eribulin-induced PN in patients treated with eribulin in a real life setting for locally advanced or metastatic breast cancer (MBC), following one or two prior chemotherapeutic regimens for advanced disease. **Secondary Objective(s)** To assess the impact of eribulin treatment on Health-related quality of life (HRQoL) using Patient Neurotoxicity Questionnaire (PNQ) and EuroQOL- 5 Dimensions 3 Levels Questionnaire (EQ-5D-3L in subjects with locally advanced or MBC in a real life setting. • To assess the impact of eribulin-induced PN on HRQoL using the PNQ and EQ-5D-3L questionnaires in a real life setting. • To evaluate the effectiveness of eribulin in a real life setting for locally advanced or MBC as measured by time to disease progression. • To evaluate the safety and tolerability of eribulin in a real life setting for locally advanced or MBC.
Country of study	**Germany**
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2 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz (German Medicinal Products Act)
AMS	Advanced Medical Services (CRO)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
CDMS	Clinical Data Management System
CHMP	European Medicines Agency's Committee for Medicinal Products for Human Use
CIPN	Chemotherapy-induced peripheral neuropathy
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	for example
EMA	European Medicines Agency
ENCePP	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-3L	EuroQOL- 5 Dimensions 3 Levels Questionnaire
FPI	First Patient In (=date of first signed informed consent)
GCP	Good Clinical Practice
GKV	Spitzenverband Bund der Krankenkassen (Confederation of Statutory Health Insurance Providers)
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HRQoL	Health Related Quality of Life
IEC	Independent Ethics Committee
Incl.	including
KBV	Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians)
LPI	Last Patient In
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MBC	Metastatic Breast Cancer
MTA	Microtubule-targeting agent
PASS	Post Authorization Safety Study
Pat. ID	Patient Identification Number
PKV	Verband der Privaten Krankenversicherung e.V. (Association of Private Health Insurers)
PN	Peripheral Neuropathy
PNQ	Patient Neurotoxicity Questionnaire
PRAC	Pharmacovigilance Risk Assessment Committee
QOL	Quality of Life questionnaire
QPPV	Qualified Person for Pharmacovigilance

SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SMQ	standard MedDRA Query
SOP	Standard Operating Procedure
SSL	Secure Sockets Layer

3 Responsible Persons and Institutions

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4 Abstract

Title	Incidence and Resolution of Eribulin-induced peripheral Neuropathy (**IRENE**)
Protocol No.	E7389-M044-504
Active substance	Eribulin mesilate; E7389
Medicinal product	Halaven®
Study design	Observational, post authorization, single-arm, prospective multicenter cohort study
Population	Female patients ≥18 years with locally advanced or metastatic breast cancer (MBC).
Rationale and background	Approximately 36% of eribulin-treated patients with locally advanced or MBC experience peripheral neuropathy (PN). Chemotherapy-induced PN is generally considered to be an important dose-limiting side effect, but there is a lack of information concerning its long-term persistence and its resolution. This study aims to assess the incidence, frequency and the time to resolution of eribulin-induced PN in patients with locally advanced or MBC.
Research question and objectives	**Primary Objective** • To characterize and determine the incidence of eribulin-induced PN, and frequency and time to resolution of eribulin-induced PN in patients treated with eribulin in a real life setting for locally advanced or MBC following one or two prior chemotherapeutic regimens for advanced disease. **Secondary Objective(s)** • To assess the impact of eribulin treatment on Health-related quality of life (HRQoL)using PNQ and EQ-5D-3L questionnaires in subjects with locally advanced or MBC in a real life setting. • To assess the impact of eribulin-induced PN on HRQoL using PNQ and EQ-5D-3L questionnaires in a real life setting. • To evaluate the effectiveness of eribulin in a real life setting for locally advanced or MBC as measured by time to disease progression. • To evaluate the safety and tolerability of eribulin in a real life setting for locally advanced or MBC.
Participating countries	Germany
Number of study sites	Approximately 60
Number of patients	Approximately 400

Inclusion criteria	• Locally advanced or metastatic breast cancer eligible for treatment with eribulin according to Fachinformation (German equivalent of Summary of Product Characteristics). • Maximum of two prior chemotherapeutic regimens for advanced disease. • Age ≥18 years at the time of Informed Consent. • Ability to understand and willingness to respond to questions related to their health. • Decision for the patient to start treatment with eribulin has been made prior to inclusion in this study. • Signed written Informed Consent.
Exclusion criteria	• Previous treatment with eribulin in any line of treatment. • Contraindication according to the Fachinformation of eribulin. • Pregnancy or lactation. • Participation in an interventional clinical trial at the same time.
Treatment	All patients will be treated with eribulin according to Fachinformation and managed according to clinical practice.
Study duration per patient	The estimated observation period for each patient is anticipated to be approximately 15 months. However, in case of PN, the patients will be documented until death or resolution of PN, or return to baseline level, whichever comes first.
Planned Study Period	FPI is planned for in July 2016. LPI is planned for July 2019. The end of the study will be determined based on the time of follow-up of PN patients, but is estimated to be Sep 2021. A study report is planned to be submitted to the EMA by Dec 2019. The sponsor may choose to terminate the study at any point if it is deemed that sufficient data to characterize and determine the incidence and resolution of eribulin-induced PN has been collected. For this, periodic monitoring and analysis of the progress of the study will be conducted after each 100 patients are enrolled.

Study endpoints	**Primary Endpoint(s)** • The number and proportion of patients experiencing eribulin-induced PN. • Severity of eribulin-induced PN as determined by CTCAE grade version 4.0. • Frequency of dose modifications or discontinuation of eribulin treatment due to eribulin-induced PN. • Time to eribulin treatment discontinuation due to eribulin-induced PN. • Frequency of resolution of eribulin-induced PN defined as the number and proportion of resolved cases (defined as ended or returned to baseline as determined by CTCAE grade version 4.0) amongst the patients who experience eribulin-induced PN. • Time to resolution of eribulin-induced PN will be defined as the time from onset (or worsening from baseline) to the date of resolution (defined as stop of PN or return to baseline) as determined by CTCAE grade version 4.0. • Therapeutic interventions (e.g. analgesics) being used to treat eribulin-induced PN. **Secondary Endpoint(s)** • Health-related quality of life scores measured using the PNQ and EQ-5D-3L questionnaires. • Time to disease progression is defined as the time from the start of eribulin treatment to Investigator assessment of disease progression (clinical or radiological). • The number and proportion of patients experiencing non-serious and serious AEs.
Study procedure	Treatments, assessments (e.g. safety) and examinations (e.g. laboratory evaluations, physical examinations) will be performed according to the Fachinformation and the routine clinical practice at each site. In addition, all patients will be asked to complete Health-related quality of life questionnaires (PNQ and EQ-5D-3L) at baseline before first administration of eribulin, on the first day of each treatment cycle and at the off treatment visit. Patients with eribulin-induced PN are followed up monthly and are asked to continue to complete the PNQ if possible. The decision to treat the patient with eribulin is made independently of study participation, thus before the patient is informed about the study and asked about participation.

Data Source	The main data source is the patient's medical record from which data is transferred into the paper or electronic CRF. Paper patient questionnaires serve as a second type of data source.
Assessments	**Effectiveness Assessments** Disease assessment will be recorded according to the clinical practice of each Investigator. **Safety Assessments** Safety assessments will consist of recording of all PN cases and other non-serious Adverse Events (AEs) and all Serious Adverse Events (SAEs). **Other Assessments** Patients will be asked to complete Quality of Life assessments using the Patient Neurotoxicity Questionnaire (PNQ) and EuroQOL-5 Dimensions 3 Levels (EQ-5D-3L) questionnaires at Baseline (prior to the administration of eribulin), on Day 1 of every treatment cycle (starting on Day 1 of Cycle 2), and at the off treatment visit.. In case of eribulin-induced PN patients are asked to continue to complete the PNQ monthly. during the follow-up period.
Statistical analysis	**Analysis Sets** For the analyses of safety and effectiveness parameters the Safety Analysis Set will be used, which is defined as the group of patients who received at least one dose of eribulin. This set will be the analysis set for all effectiveness and safety evaluations. **Effectiveness Analyses** Time to disease progression will be summarized and plotted using the Kaplan-Meier method. Median, and first and third quartiles from Kaplan-Meier estimation for time to disease progression will be provided with 95% confidence intervals (CIs). **Safety Analyses** The incidence of eribulin-induced PN as well asnon-serious AEs and serious AEs will be summarized for the Safety Analysis Set. Separate summaries will be presented by seriousness and severity of eribulin-induced PN. Severity of eribulin-induced PN will be classified using CTCAE (version 4.0) criteria. Prior and concomitant medications, medical/surgical history and patient demographics will be summarized and listed. Time to PN resolution will be summarized and analyzed for patients with eribulininduced PN only. **Other Analyses** Health related quality of life questionnaire scores, obtained through the PNQ and EQ-5D-3L questionnaires will be summarized over time. A more detailed specification of the planned analysis will be given in a statistical analysis plan (SAP) which will be finalized before the analysis of the data.
Interim Analysis	After each 100 subjects enrolled the sponsor will analyze the study progress. In particular, the incidence rate of PN will be assessed in order to review the reliability of the assumptions made. An interim study report will be submitted to the EMA by Dec 2019.

Flowchart

Period	Baseline	Treatment			Off-Treatment	Follow-up[f]
		Cycle 1- Last		End of Treatment		
Day	Prior to first infusion	1	8		Approx. 30 days after last dose	Monthly
Documentation						
Informed Consent	X					
Inclusion/Exclusion	X					
Demography	X					
Current disease status	X					
Medical/Surgical History	X					
Previous chemotherapies	X					
Previous neurotoxic therapies[a]	X					
PN predispositions	X					
Pre-existing PN (incl. CTCAE grade)	X					
Information of neurological assessment and consulting	X					
Non-serious AEs[b]	X	X				X
Serious AEs[b]	X	X				X
Details on eribulin-induced PN cases (incl. CTCAE grade)		X				X
Eribulin Administration (according to Fachinformation)		X	X			
Concomitant medication/ therapy[c]	X					
PN related therapies[d]	X					X
Subsequent anti-cancer therapy				X	X	X
Occurrence of eribulin-induced PN		X			X	
Disease progression		X		X	X	
EQ-5D-3L	X	X[e]			X	
PNQ	X	X[e]			X	X
Reason for termination of eribulin				X		

a. Neurotoxic therapies are defined in section 9.3

b. Serious and non-serious Adverse Events must be recorded from the time of Informed Consent up until 30 days after the last eribulin administration. Eribulin-induced PN events during the study will be recorded until the end of the follow-up period.
c. Concomitant medications and therapies are recorded up to 30 days after last dose.
d. PN related concomitant medication and therapy of patients with eribulin-induced PN during the study will be recorded until the end of the follow-up period.
e. The questionnaires should be completed prior to infusion on Day 1(the questionnaire is not filled out on first day of cycle 1 if completed at Baseline) and at the Off Treatment visit. These are completed by site personal on-site or by phone.
f. The follow-up period will be conducted only for patients with eribulin-induced PN. Follow-up is done until resolution to baseline or death, independent of treatment with any new anti-cancer therapy. The follow-up is done monthly via phone call or physical examination and includes completion of PNQ if possible.

The timepoints for visits are not defined, but will take place as in routine clinical care.
The CRF/eCRF forms attempt to approximate the normal course of treatment as closely as possible to facilitate documentation. They are not intended to dictate a treatment schedule.

5 Amendments and Updates

Not applicable.

6 Milestones

Milestone	Planned date
Start of data collection (First Patient In = date of first signed Informed Consent)	July 2016
End of patient recruitment*	July 2019
End of regular data collection (Last patient completed Off-Treatment documentation)	Oct 2020
Interim report	December 2019
Study Progress Report	Not applicable
End of overall data collection (Last PN patient completed follow-up period and complete analysis dataset is available)	Nov 2021
Final report of study results	Mar 2022

*If the incidence of peripheral neuropathy is lower than expected based on historic data the recruitment period may be extended.

The sponsor may choose to terminate the study at any point if it is deemed that sufficient data to characterize and determine the incidence and resolution of eribulin-induced PN has been collected.

7 Rationale and Background

Halaven® (eribulin mesilate) is a non-taxane inhibitor of microtubule dynamics belonging to the halichondrin class of antineoplastic agents. Eribulin is a synthetic analogue of the natural marine halichondrin B found in the sponge genus Halichondria. It inhibits the mitotic spindle formation by irreversibly binding to microtubules and thereby inhibiting the microtubule growth phase preventing cell proliferation and increasing apoptosis.

Eribulin achieved a marketing authorization in Europe in 2011. It has been approved in more than 50 countries for patients with locally advanced or MBC who have previously received at least 1 chemotherapeutic regimen for advanced disease (Kaufmann et al, 2015).

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect and a dose-limiting factor of many antineoplastic drugs. CIPN is a toxic neuropathy resulting from the direct damage of the peripheral nervous system by chemotherapeutic drugs (Kaley, DeAngelis, 2009). The underlying mechanisms are not clearly understood. Basically two different mechanisms can be distinguished: demyelination and axonal damage (Bartsch et al, 2010). Chemotherapeutic drugs target the neuronal cell body, the axonal transport system,

the myelin sheath, and glial support structures of peripheral nerves leading to neurotoxic effects.

CIPN typically shows a distal symmetric "stocking and glove" distribution in the feet and hands (Boland et al, 2010). Most common are sensory neuropathies with symptoms in the long distal nerves like tingling, numbness, paresthesia or neuropathic pain (Grisold et al, 2012). Besides sensory nerves, motor nerves may also be affected by CIPN leading e.g. to weakness, muscle cramps, muscle fatigue and ataxia. Autonomic nerves are less commonly affected by CIPN (Bartsch et al, 2010).

In a meta-analysis analyzing data of 4179 cancer patients the prevalence of CIPN was assessed to be 68.1% immediately after chemotherapy and 60% when measured after 3 months (Seretny et al, 2014).

The development of CIPN is usually dose dependent, but there are some drugs having immediate neurotoxic effects (Grisold et al, 2012). Microtubule-targeting agents (MTA) including vinca alkaloids, taxanes (Carlson and Ocean, 2011) and eribulin (Cortes et al, 2012) are some of the most common classes of chemotherapeutic drugs for the treatment of breast cancer. As the microtubule function is critical to normal neuronal function, MTA therapy is commonly associated with some form of neuropathy leading to CIPN (Vahdat et al, 2013).

CIPN can begin weeks to months after initial treatment and reach a peak at, or after the end of treatment. In some cases, the pain and paresthesia completely resolve after treatment is stopped. However, in most cases CIPN is only partially reversible and can be permanent (Pachmann et al, 2011).

In a summary of clinical safety of eribulin submitted to European Medicines Agency (EMA) in 2014, the incidence of treatment-emergent PN was assessed in all eribulin-treated patients enrolled in phase II/III breast cancer studies (n=1503). Of the total 1503 eribulin-treated patients, 35.6% experienced PN based on the broad standard MedDRA Query (SMQ) for neuropathy. The median PN was 85.5 days which is after 4 eribulin treatment cycles. Up to 7.7% of the patients experienced grade 3 and 4 CTCAE PN (Common Terminology Criteria for Adverse Events).

195 patients (13.0% of all patients) of the phase II/III breast cancer population, had unresolved PN 30 days after the last dose. Grade 3-4 PN resolved to grade 1, 0 or baseline in 49.1% of the patients in a median time of 8.1 weeks. PN is the most common adverse event leading to discontinuation of eribulin treatment (3.3%) (Assessment Report Halaven-Variation, 2014).

Chemotherapy-induced PN is identified as an important dose-limiting side effect, but there is a lack of information concerning its long-term persistence and its resolution.

Since there are no new ongoing clinical studies to address the issue of the frequency of resolution of PN and the time to resolution of PN, this observational study is designed to provide this information.

8 Research Question and Objectives

This study is designed to assess the frequency and the time to resolution of eribulin-induced PN in patients with locally advanced or metastatic breast cancer. In this study eribulin-induced PN is defined as new onset of PN, or worsening of pre-existing PN during the study as assessed by clinical exam, occurring any time after the first dose of eribulin until 30 days after the last dose of eribulin.

Patients who have not developed eribulin-induced PN at the time of the last dose of eribulin and who initiate a new anti-cancer therapy with a know neurotoxic potential within 30 days after the last dose of eribulin and experience a new onset of PN or deterioration of pre-exisitng PN will not be considered as eribulin-induced PN

The primary objective of this study is to characterize and determine the incidence frequency and time to resolution of eribulin-induced PN in patients treated with eribulin in a real life setting for locally advanced or MBC, following one or two prior chemotherapeutic regimens for advanced disease.

Secondary objectives are to assess the impact of eribulin-induced PN on Health-related quality of life questionnaires (PNQ [v. xxx] and EQ-5D-3L [version Germany 1995]) and to assess the impact of eribulin-induced PN on PNQ and EQ-5D-3L in a real life setting. To evaluate the effectiveness of eribulin in a real life setting for locally advanced or MBC as measured by time to disease progression and to evaluate the safety and tolerability of eribulin in a real life setting for locally advanced or MBC.

Primary endpoints of this study are:

- Number and proportion of patients experiencing eribulin-induced PN (regardless of seriousness).
- Severity of eribulin-induced PN as determined by CTCAE grade (version 4.0).
- Frequency of dose modifications or discontinuation of eribulin treatment due to eribulin-induced PN.
- Time to eribulin treatment discontinuation due to eribulin-induced PN.
- Frequency of resolution of eribulin-induced PN defined as the number and proportion of resolved cases (defined as ended or returned to baseline as determined by CTCAE grade version 4.0) amongst the patients who experience eribulin-induced peripheral neuropathy.
- Time to resolution of eribulin-induced PN will be defined as the time from onset (or worsening from baseline) to the date of resolution (defined as stop of PN or return to baseline) as determined by CTCAE grade version 4.0.
- Therapeutic interventions (e.g. analgesics) being used to treat eribulin-induced PN.

Secondary Endpoints of this study are:

- Health-related quality of life scores measured using the PNQ and EQ-5D-3L questionnaires.

- Time to disease progression is defined as the time from the start of eribulin treatment to Investigator assessment of disease progression (clinical or radiological).
- The number and proportion of patients experiencing non-serious and serious ADRs

9 Research Methods

9.1 Study Design

This study is a non-interventional Post Authorization Safety Study (PASS). It is designed as an observational, single-arm, prospective cohort study. Due to the nature of an observational study, patients with locally advanced or MBC will be treated according to the routine clinical practice at each site. In all cases, the decision to treat patients with eribulin will be performed prior to the decision to include the patient in the study. Eribulin will be administered according to Fachinformation (German equivalent of Summary of Product Characteristics).

9.2 Study Setting

9.2.1 Planned Number of Study Sites

Approximately 60 study sites in Germany will be involved in the study.

9.2.2 Patient Population

An enrolment of about 400 patients with locally advanced or MBC is planned for the study.

Subjects with new onset of peripheral neuropathy during the study, or worsening of pre-existing peripheral neuropathy on study, should be followed by investigator until resolution to baseline or death, independently of whether they are receiving a new anti-cancer therapy or not.

The estimated observation period for each patient is anticipated to be approximately 15 months. However, in case of PN, the patients will be documented until death or resolution of PN, or return to baseline level, whichever comes first.

Inclusion Criteria

The patients will only be included in the study if they meet all of the following criteria:

- Locally advanced or MBC eligible for treatment with eribulin according to Fachinformation.
- Maximum of two prior chemotherapeutic regimens for advanced disease.
- Age ≥18 years at the time of Informed Consent.
- Ability to understand and willingness to respond to questions related to their health.
- Decision for the patient to start treatment with eribulin has been made prior to inclusion in this study.
- Signed written Informed Consent.

Exclusion Criteria

The patients will only be included in the study if they do not meet any of the following criteria:

- Previous treatment with eribulin in any line of treatment.
- Contraindication according to the Fachinformation of eribulin.
- Pregnancy or lactation.
- Participation in an interventional clinical trial at the same time.

9.2.3 Documentation Schedule

The time point of documentation is not defined, but will take place during a routine visit according to routine clinical care based on medical necessity. The documentation described here does not influence the individual treatment course.

Baseline data prior to start of eribulin treatment will be documented. During the treatment with eribulin there are two regular visits at day 1 and 8 of each treatment cycle. An Off-Treatment Documentation will be performed approximately 30 days after the last eribulin dose according to the treating physician's routine. The maximum estimated observation period for each patient is anticipated to be approximately 15 months. The maximum number of eribulin treatment cycles which will be documented within this study is 25. In case of PN, the patients will be documented until death or resolution of PN, or return to baseline level, whichever comes first.

The Follow-Up period will be conducted only for patients with eribulin-induced PN during the study (including 30 days after the final eribulin dose). These patients will be followed monthly, if possible, until resolution of PN to baseline or death, independently if they are receiving a new anti-cancer therapy. The follow-up is done via phone call or physical examination by the physician. Patients will be considered lost to follow-up when site took 3 unsuccessful attempts to contact the patient.

Baseline Documentation

- Check of inclusion and exclusion criteria.
- Patient information and written Informed Consent.
- Demographic data.
- Diagnosis and current disease status.
- Relevant medical/ surgical history including concomitant diseases.
- Previous chemotherapies (max. 2 chemotherapeutic regimen for advanced disease).
- Previous/ongoing neurotoxic therapies in detail.
- Existing PN predispositions.
- Any pre-existing (resolved or ongoing) PN including CTCAE classification and documentation of any obtained neurological consultation and procedures.
- Patient will be asked to complete PNQ and EQ-5D-3L (prior to first eribulin dose).

Treatment Period

During the treatment period the following data collection will be performed at each eribulin treatment cycle:

Day 1

- Eribulin administration.
- Occurrence of new PN or worsening of pre-existing PN since last documentation.
- If new PN: CTCAE classification and documentation of any obtained neurological consultation and procedures
- If existing PN: current CTCAE grade (except 1. Cycle).
- Patient will be asked to complete PNQ and EQ-5D-3L. (except 1. Cycle).
- Disease progression.

Day 8

- Eribulin administration.

End of Treatment

- Reason for termination of eribulin.
- Disease progression.
- Subsequent anti-cancer therapy.

Continuous Documentation during treatment period

- Changes in concomitant medication and therapy since Baseline.
- Reporting of non-serious AEs and serious AEs which occurred since Informed Consent.

Off-Treatment Documentation

- Occurrence of new PN or worsening of pre-existing PN since last documentation.
- If new PN: CTCAE classification and documentation of any obtained neurological consultation and procedures
- If existing PN: current CTCAE grade
- Patient will be asked to complete PNQ and EQ-5D-3L.
- Disease progression.
- Changes in concomitant medication and therapy.
- Subsequent anti-cancer therapy.
- Non-serious AEs and serious AEs.

Follow-Up Period

- Collection of PNQ.
- Current CTCAE grade of PN
- Changes in concomitant medication and therapy related to PN.
- New or changed anti-cancer therapy.
- Eribulin-induced PN AEs and serious AEs

End of study

- Date of study stop
- Reason for study stop

9.2.4 Active Substance

Commercial available eribulin.

9.2.5 Concomitant Medications and Therapies

The Investigator will record concomitant medication and therapy used by the patient during the study from the date of signature of Informed Consent until 30 days after the final eribulin dose in the appropriate section of the CRF/eCRF. Concomitant medication and therapy of patients with eribulin-induced PN during the study will be recorded until the end of the follow-up period.

Any new anti-cancer therapy will be recorded at the end of eribulin treatment, at the off-treatment documentation and for PN patients also during the follow-up period.

Alternative substances such as herbals or homeopathic medication should also be documented, especially if a neurotoxic impact cannot be excluded.

9.2.6 Patient Completion and Withdrawal

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and without giving a reason. Any withdrawal must be fully documented in the CRF/ eCRF and source documents.

Discontinuation from the study for any other reasons (e.g. death) also has to be documented in the CRF/eCRF.

Patients who terminate the study prematurely for whatever reason will not be replaced.

9.3 Variables

9.3.1 Definition of Peripheral Neuropathy (PN)

Investigator will assess new and pre-existing PN based on the CTCAE grading.

Standard MedDRA Queries will be used to capture PN not diagnosed as PN.

9.3.2 Definition of PN Predisposition

Following conditions will be assessed as PN predispositions:

- Diabetes mellitus type I/II
- Herpes zoster
- Inflammatory diseases e.g. vasculitis, rheumatoid arthritis, systemic lupus erythematosus.
- Hypothyroidism
- Renal impairment
- Alcohol abuse
- Infection associated with neuropathy e.g. tuberculosis, HIV, leprosy, Lyme disease

The assessment of other PN dispositions is at the discretion of the investigator.

9.3.3 Definition of neurotoxic treatments

Following treatments will be assessed as neurotoxic treatments:

- Taxanes
- Platinum derivatives
- Vinca alkaloids
- INH (isoniazid)

The assessment of other treatments with neurotoxic potential is at the discretion of the investigator.

9.3.4 Substances masking the onset and intensity of PN

- Neurotropic vitamins (B1, B6, and B12)
- Alpha lipoic acid

The assessment of other substances masking the onset and intensity of PN is at the discretion of the investigator.

9.3.5 Exposure

Eribulin exposure will be assessed by the Investigator by documenting the amount of eribulin administration at each treatment day in each eribulin treatment cycle. The exposure will be assessed starting the first day of eribulin administration until the final dose of eribulin. The eribulin dose may be adjusted by the Investigator according to routine clinical practice.

9.3.6 Definition of disease progression

The Investigator will assess the disease progress according to the clinical routine either by:

- Radiography
- Clinical Examination

9.3.7 Coding of Concomitant medication

The Investigator will document concomitant medication.

Concomitant medication is coded according to WHO Drug Dictionary Enhanced with Herbal Version.

9.3.8 Confounders

- Spinal diseases (e.g. Morbus Bechterew, Morbus Scheuermann, scoliosis)
- PN predispositions
- Neurotoxic treatments
- Substances masking the onset and intensity of PN

9.4 Data Source

As this is a non-interventional study, the main data source is the patient's medical record from which data is transferred into the paper or electronic CRF. Paper patient questionnaires serve as a second type of data source.

Each paper and electronic CRF and its respective patient questionnaires will have a unique consecutive number within the study (Patient ID).

The site has to maintain a Patient Identification List (to be kept at site) linking the patient to the Patient ID within the study.

9.5 Study Size

Since this is an exploratory study and no formal hypothesis-testing will be carried out, there will be no formal sample size calculation. Sample size considerations mainly depend on the desired precision of the estimate for the PN-incidence-rate.

Assuming a 35% incidence rate of all-grade PN, enrolment of 400 patients will have approximately 140 patients (with 95% CI of incidence rate [30%, 40%] and patients [121, 159]) to develop PN. Besides, assuming thirty-three per cent of recovery rate, 140 patients of PN will have approximately 47 patients (with 95% CI of recovery rate [25%, 41%] and patients [35, 58]) to resolve. These sample sizes would be sufficient to assess the frequency and time to resolution of PN.

9.6 Data Management

All relevant data for this study will be entered into the paper CRFs supplied by the Sponsor or captured electronically in a project specific programmed Electronic Data Capture (EDC) application, also referred to as electronic CRF (eCRF). Sites may choose their preferred way of documentation, whereas patient questionnaires are always completed by the patient on paper.

The patient questionnaires will be collected at the site, thoroughly checked by the physician for any potential adverse events and sent to ***AMS*** Advanced Medical Services GmbH, the clinical research organization (CRO).

Completed eCRF/CRFs should be (electronically) signed on all required pages by the Investigator after completion. Completed paper CRF pages will be sent to ***AMS*** GmbH for further processing.

Personal data of patients are gathered, stored and processed exclusively in a pseudonymous form according to national data protection laws.

All study data incl. adverse events are entered into the Clinical Data Management System (CDMS, Clincase, Quadratek Data Solutions Ltd.), either directly by sites or by ***AMS*** GmbH performing single data entry of paper CRFs, paper adverse event reports and all paper patient questionnaires. Clincase is fully 21 CFR part 11 compliant. The system is accessed via a secure website (SSL encryption) by registered user's utilization of unique user name and password. Depending on their role within the study, individual users are assigned a defined level of access. The access rights to the CDMS system are controlled by authorized ***AMS*** staff. The server is backed up once daily.

9.7 Data analysis

9.7.1 Statistical Analysis

Since this study is an observational study, epidemiological methods will be employed for data analyses. Descriptive analyses will be performed of all collected data. No formal statistical hypothesis will be formulated and no statistical tests will be carried out.

For quantitative variables, descriptive statistics will include the number of patients (n), the number of patients with missing values (Nmiss), mean, standard deviation, median, 25%, 75% and 90% and 95% quantiles, Minimum and maximum.

Categorical data will be summarized descriptively by absolute and relative frequencies: n and (%). The denominator for all percentages will be the total number of patients, within the respective group, unless otherwise indicated. Percentages will be presented to one decimal place and will not be displayed for zero frequencies. A row denoted "Missing" will be included in all tabulations to clearly indicate the completeness of the collected data.

The main outcomes of the study are:

Eribulin-induced PN:
Eribulin-induced PN is defined as new onset PN or worsening of pre-existing PN during the study, occurring any time after the first dose of eribulin until 30 days after last dose of eribulin. Patients who have not developed eribulin-induced PN at the time of the last dose of eribulin and who initiate a new anti-cancer therapy with a know neurotoxic potential within 30 days after the last dose of eribulin and experience a new onset of PN or deterioration of pre-exisitng PN will not be considered as eribulin-induced PN

Incidences of eribulin-induced PN will be summarized overall and by CTCAE grade. Calculation of incidences will be based on the total number of patients exposed to eribulin. A patient who experiences more than one episode of PN will be counted only once. Incidence rates will be presented with approximate confidence intervals.

In addition PN will be summarized also by severity, outcome, and duration. For the summary of PN by severity (CTCAE grade version 4.0) each patient is counted with the most severe event.

Time to eribulin treatment discontinuation due to eribulin-induced PN will be analyzed using Kaplan-Meier methodology.

The frequency and time to PN resolution will be summarized and analyzed only for patients with eribulin-induced PN.

AEs
Incidences of AEs and serious AEs will be summarized by MedDRA preferred term (PT) and system organ class (SOC). Calculation of incidences will be based on the total number of patients exposed to eribulin. A patient who experiences more than one AE will be counted only once, if these AEs belong to the same category (e.g., same system organ class or MedDRA preferred term).

In addition AEs (SOC and PTs) will be summarized also by outcome, time to onset and duration.

Time to disease progression

Time to disease progression will be analyzed and plotted using Kaplan-Meier methodology. The median (and other quartiles) of time to disease progression will be reported along with their 95% confidence interval.

Subgroup analyses

Subgroup analyses with respect to age (specialist versus general practitioner) are anticipated. Further subgroup analyses may be specified in the SAP.

Unless otherwise stated, no data imputation will be performed.

Statistical software SAS® (Version 9. 3 or above) will be used for statistical data analysis.

9.8 Quality control

The study will be conducted and reported in accordance with applicable Standard Operating Procedures (SOPs) and the Guideline on Good Pharmacovigilance Practices (GVP) Module III.

Data management and quality assurance for the study are in accordance with the document „Gemeinsame Bekanntmachung des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Anzeige von Anwendungsbeobachtungen nach §67 Absatz 6 Arzneimittelgesetz und zur Anzeige von nichtinterventionellen Unbedenklichkeitsprüfungen nach §63f und g Arzneimittelgesetz" in the draft version of October 20th, 2014.

Monitors of the appointed CRO ***AMS*** GmbH will perform on-site initiation visits (including eCRF training). The site staff will be trained with special emphasis on collecting and reporting of adverse events and PN in particular.

During the course of the study ***AMS*** GmbH will perform remote monitoring in each study site 2 to 3 months after recruitment of the first patient. This will be complemented with yearly on-site monitoring visits for three years.

It is planned to perform a source data validation (SDV) in 10% of recruited patients (randomly chosen and equally distributed over participating sites) but at least 30 patients in total.

To ensure legibility of paper documentation, ballpoint pens should be used to fill out (no pencils, felt tip or fountain pens). An erroneous record shall be struck through so that the original record remains legible. The correction should be indicated with a date and initials. Completeness and accuracy of the documented data is confirmed by the (electronic) signature of the responsible physician or his/her delegate.

Data are automatically checked for plausibility and completeness by programmed edit checks during the electronic data entry (by the site or by ***AMS*** GmbH) in the CDMS system. Other discrepancies, particularly in the documentation of adverse events, are clarified by addressing manual queries to the site. ***AMS*** GmbH will check paper CRFs and eCRFs for

hidden undocumented/unreported adverse events. In such cases, the site is contacted for clarification and is urged to correctly document/report the event, if appropriate.

There will be a regular reconciliation between the adverse events documented in the study database and in the safety database.

For quality control purposes, the data entered by ***AMS*** GmbH is reviewed by checking 100% of the data of a random selection of $\sqrt{n} + 1$ patient datasets that were documented on paper.

Due to the non-interventional character of the study, missing values and/or implausibility may persist and will be accepted.

Participating sites are responsible for archiving the Patient Identification List and the study documents for at least 10 years after end of study or in accordance with local legislation.

9.8.1 Quality Assurance

For quality assurance reasons the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or Independent Ethics Committees (IECs) may conduct quality assurance audits at any time during or following the study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

Audits shall ensure that the study is planned, conducted, evaluated and reported in concordance with this protocol, and the applicable Standard Operating Procedures (SOPs), and all applicable international guidelines and local drug laws, and that the documentation of the study is available, complete, organized and valid.

9.9 Limitations of the research methods

The study will be non-comparative. The lack of an internal reference therapy is a weakness of this study and should be kept in mind when interpreting the data. Putting the results on safety and effectiveness into context will be challenging.

In non-interventional studies, the amount of data cleaning is limited. Therefore, missing values and/or implausible values are to be expected. The SAP will provide a detailed description on how to handle those values. In general, no substitution of missing values is planned.

10 Protection of human subjects

10.1 Ethical, Legal and Administrative Aspects

This study is a Post Authorization Safety Study (PASS) according to German Drug Law (AMG) §4 (34) and conducted voluntarily in accordance with Article 107m of Directive 2001/83/EC.

Independent Ethics Committee

Prior to study start, the observational study protocol along with the patient questionnaires, the patient information and Informed Consent form is presented to a competent ethics committee for assessment. Each participating physician may also seek advice from her/his competent ethics committee in line with professional legal obligations. The study protocol, the patient questionnaires, the patient information and Informed Consent form and the first ethics committee assessment may be disclosed for this purpose.

Notifications / Registration

This PASS will be notified pursuant to AMG § 63f to the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte), the National Association of Statutory Health Insurance Physicians (KBV, Kassenärztliche Bundesvereinigung), the Confederation of Statutory Health Insurance Providers (GKV, Spitzenverband der Krankenversicherungen) and the Association of Private Health Insurers (PKV, Verband der privaten Krankenversicherungen) by the sponsor. The names, addresses and unique lifetime IDs of participating physicians will be submitted to KBV, PKV and GKV. Fees paid to the sites as well as the number of enrolled patients will be reported (quarterly and annually) to KBV, PKV and GKV. Moreover, after completion of the study, a final list indicating the number of enrolled patients and the sum of fees paid per site will be provided to KBV, PKV and GKV.

This study will be listed in the electronic register of studies of The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

The study protocol as well as the final study report will be published in BfArM's internet portal.

10.2 Patients' Information and Informed Consent

Patients will be informed in detail by the Investigator or delegate about all pertinent aspects of the study. The decision for the patient to start treatment with eribulin will have been made prior to inclusion in this study. It is the responsibility of the Investigator to ensure that no patient data is documented in eCRF/CRF before having obtained written Informed Consent.

The Investigator or a delegate will inform the patients that they are completely free to refuse to enter the study or to withdraw from it at any time. All patients should be given sufficient time to request further details about the study before signing the Informed Consent form. Patients will personally sign and date the Informed Consent form. The Informed Consent will be documented in the source data.

One copy of the consent form signed and dated by the patient and by the physician who informed the patient will be kept at the study site; a second copy will be handed over to the patient. Each patient must receive a patient information sheet written in local language.

In case of new relevant information, all concerned patients should be informed and re-consented in a timely manner, if applicable.

10.3 Confidentiality of Study Documents and Patient Records

The Investigator must verify that each patient has consented, in writing, to direct access to her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

With their consent the patients also gives their agreement to the documentation of clinical data in the bounds of the non-interventional study, to their transmission for review to the Sponsor, to the responsible regulatory authorities and, in case of person related data, to their perusal by representatives of the Sponsor or of the authorities.

Neither the names of the patients nor any other records identifying the patients will be made publicly available by the Investigator or by the Sponsor.

The Investigator must ensure that each patient's pseudonymity will be strictly maintained. On CRFs/eCRFs or other documents submitted to the Sponsor, patients must not be identified by their name, but by a unique identification code (Pat. ID). If patient names are included on copies of documents submitted to the Sponsor, the names must be obliterated and the assigned Pat. ID must be added to the documents instead.

The Investigator will keep a separate Patient Identification List of these codes, along with the full names and dates of birth of the patients. Documents which contain the names associated with these codes are not for submission to the Sponsor. They will, together with completed consent forms, be maintained by the Investigator in strict confidence.

10.4 Proprietary Rights on Study Data and Publication of Results

By conducting this study, the Investigator affirms to the Sponsor that he/she will maintain, in strict confidence, information provided to him/her by the Sponsor, including data generated from this study, except as exempted for regulatory purposes.

Data and results of this study are the sole property of the Sponsor and may be used world-wide for product documentation and publications.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any personnel involved in this study will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

11 Management and Reporting of Adverse Events / Adverse Drug Reactions

Assessment of all adverse events experienced by the patient will be performed throughout the course of the study from the time of patient's signature of Informed Consent.

Study site personnel will record and report **all Adverse Events (AEs) and all serious Adverse Events (SAEs),** whether observed by the Investigator or reported by the patient (see section 11.2.1 Monitoring of Adverse Events).

Any new onset of PN or worsening of pre-existing PN is recorded and reported as AE/SAE, following the usual processes described below.

11.1 Definitions and Guidelines

11.1.1 Adverse Event (AE) and Adverse Drug Reaction (ADR)

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with the medicinal product.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse drug reaction (ADR) is any untoward and unintended response to a medicinal product related to any dose administered. A causal relationship between the medicinal product and the adverse response is at least a reasonable probability. All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship (see section 11.1.3).

For the purpose of this protocol the term „AE/ADR" will also include:

- **Significant abnormalities in clinical laboratory values:** If routine laboratory values are abnormal, they may be considered an AE/ADR if the identified laboratory abnormality leads to any change in care by the clinician. Examples of laboratory abnormalities which should be considered as AEs/ADRs include those which result in withdrawal of treatment, withholding treatment pending some investigational outcome, reduction of dose of the treatment or additional concomitant treatment. It is up to the clinician to determine whether an abnormal laboratory value constitutes an AE/ADR. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE/ADR.
- **Events of Special Interest:** events which might not be an AE/ADR but are still collected and entered into the safety database. These events include but are not limited to:
    - Medication errors
    - Off-label use
    - Lack of therapeutic efficacy
    - Overdose
    - Abuse
    - Misuse
    - Occupational exposure
    - Suspected adverse reactions related to quality defect or falsified medicinal products
    - Interactions with other drugs/devices/food/alcohol

- Breast feeding

An Event of Special Interest may or may not include an AE/ADR or SAE/SADR.

- **Infectious Agent Report:** A report involving the suspected transmission of an infectious agent via an Eisai product. Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

All other medical conditions which are present at baseline should NOT be considered as AEs unless a worsening in severity or frequency occurs during the study.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

11.1.2 Serious Adverse Event (SAE) and Serious Adverse Drug Reaction (SADR)

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability/incapacity**
- **Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)**

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

11.1.3 Classification of Causality

Every effort must be made by the investigator to categorize each AE according to its relationship to the study treatment, by considering the following items:

- Temporal relationship of the onset of the AE to the initiation of the treatment.
- Discontinuation or reintroduction of treatment affecting the course of the AE.
- Known association of the AE with the treatment.
- Risk factors present in the study patient known to increase the occurrence of the AE.
- Non-treatment related factors known to be associated with the occurrence of the AE.

Not related
A causal relationship between the treatment and the AE is not a reasonable possibility.

Related
A causal relationship between the treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable".

11.2 Monitoring, Recording and Reporting of Adverse Events

11.2.1 Monitoring of Adverse Events

It is the Investigators responsibility to monitor Adverse Events. Data on AEs will be obtained at regular site visits, based on the constant survey of the patient's health status by the Investigator and on information spontaneously provided by the patient and/or through questioning of the patient. AE data may also be obtained from patient questionnaires, but information thus collected must be reviewed and assessed medically by the Investigator before it is transcribed and processed.

If a patient is seen by a physician not involved in the study in relation to an AE, the Investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to appropriate reporting of the event.

11.2.2 Recording Adverse Events

Within this study all types of adverse events are recorded using the EISAI ADVERSE EVENT REPORT FORM.

The Investigator should use the definitions provided in the above sections and should observe the following guidelines:

- Whenever possible, recognized medical terms should be used to describe an event rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.

- Events should be described using a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis.')
- However, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual event.
- Provisional diagnosis (e.g. "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis if finally available.

Events occurring secondary to other events (e.g. sequelae or complications) should be identified by the primary cause. A primary event, if clearly identifiable, generally represents the most accurate clinical term to record. The Investigator should be invited to provide his/her opinion of which is the primary event, or "Reporter's highlighted term".

Complete and accurate data on all events experienced for the duration of the recording period, as defined in section 11.2.3, will be reported on an ongoing basis.

It is important that each report includes a description of the event, whether it is considered serious (and if so the criterion satisfied), its duration (onset and resolution dates), , its relationship to eribulin, any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of eribulin) and its outcome.

11.2.3 Recording Period

AEs and SAEs must be recorded on an on-going basis from the day of written Informed Consent until **30 days** after the last eribulin administration. Eribulin-induced PN events during the study will be recorded until the **end of the follow-up period.**

In case of on-going AEs and SAEs at Off-Treatment documentation, the events should be followed up with reasonable effort until they have been resolved or if resolution is unlikely, to stabilization. The length of follow-up of ongoing AEs/SAEs depends on the severity and the progression of the event. If a patient is lost-to follow-up, on-going AEs/SAEs cannot be followed-up.

11.2.4 Reporting Procedures

Reporting of SAEs, AEs, Events of Special Interest and Infectious Agent reports

If any SAE (see section 11.1.2), AE (see section 11.1.1), Event of Special Interest or Infectious Agent report occurs during the course of the study, as soon as possible after becoming aware of the event, **but not later than 24 hours** the Investigator has to fill the EISAI ADVERSE EVENT REPORT FORM as completely as possible including the assessment of causality and send the form either directly online via the eCRF system or by email or fax to:

AMS GmbH
E-mail: safety.irene@ams-europe.com
Fax: +49 (0)621 700 95 950

For any new SAE, AE, Event of Special Interest or Infectious Agent report, the following minimum information is required as initial notification:

- Clear identification of the Investigator/Reporter with full contact information
- Patient identification details (e.g. study number, site number, patient identification number, year of birth, sex),
- Suspect medicinal product
- Diagnosis of the adverse event (or a brief description of signs/symptoms/clinical course if the diagnosis is not available)

Initial reports may be followed by detailed descriptions which may include copies of hospital case reports, autopsy reports and other documents when requested and applicable. Any follow-up information received should be forwarded within one business day of its receipt to the same recipient as above. If the follow-up information changes the clinician's assessment of causality, this should also be noted on the follow-up EISAI ADVERSE EVENT REPORT FORM.

11.3 Reporting of Pregnancy

All pregnancies occurring from the date of Informed Consent signature until at least 30 days after the last eribulin administration must be recorded in the Pregnancy Report Form.

As soon as possible after becoming aware of the pregnancy, **but not later than 24 hours**, the Investigator has to fill the first sections of the Pregnancy Report Form and send it by email or fax to:

Eisai Arzneimittelsicherheit
E-mail: arzneimittelsicherheit@eisai.net
Fax: +49 (0)69 66585-45

If the pregnancy is associated with an AE, such as miscarriage, or abnormal birth, then please complete an "EISAI ADVERSE EVENT REPORT FORM" form (see section 11.2.4).

Investigators must actively follow-up and report the outcome of all pregnancies to the Sponsor by completing the Pregnancy Outcome Form and forwarding to the Sponsor. Timelines vary according to the nature of the pregnancy outcome.

11.4 Reporting to competent authorities

Adverse drug reactions and serious adverse events will be reported by the Sponsor to the competent authorities in compliance with local and regional law and established guidance by Eisai, or a third party acting on behalf of Eisai. The format of these reports will be dictated by the local and regional requirements.

12 Plans for disseminating and communicating study results

A summary of the results is planned to be submitted as interim report to EMA end of 2019. A final study report will be submitted to the competent authorities (BfArM and EMA) approximately 3 months after the last patient finished the follow-up period.

The sponsor reserves the right to publish the study results e.g. publication and/or presentation at scientific congresses.

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Annex 1- Patient Neurotoxicity Questionnaire (PNQ)

Patient Neurotoxicity Questionnaire (PNQ)®
Taxanes, Cisplatin and Carboplatin

Item 1.

☐ A	☐ B	☐ C	☐ D*	☐ E*
I have no numbness, pain or tingling in my hands or feet.	I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living.	I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities of daily living.

Item 2.

☐ A	☐ B	☐ C	☐ D*	☐ E*
I have no weakness in my arms or legs	I have a mild weakness in my arms or legs. This does not interfere with my activities of daily living.	I have moderate weakness in my arms or legs. This does not interfere of my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.	I have severe weakness in my arms or legs. It completely prevents me from doing most activities of daily living.

* Please indicate by placing an X in the box or writing in the space provided which activity or activities have been interfered with as a result of therapy.

My ability to:

☐ Button clothes	☐ Open doors	☐ Fasten buckles	☐ Write	☐ Sew
☐ Use a knife	☐ Put in or remove contact lenses	☐ Sleep	☐ Walk	☐ Work
☐ Use a fork	☐ Dial or use telephone	☐ Climb stairs	☐ Put on jewelry	☐ Tie shoes
☐ Use a spoon	☐ Operation of remote control	☐ Type on a keyboard	☐ Knit	☐ Drive
	☐ Other eating utensils, etc	☐ Perform activities of importance to me, specify:		