



**WT2725 DOSING EMULSION
STUDY NO. D8350004
PROTOCOL AMENDMENT HISTORY**

**INITIAL PHASE 1 STUDY OF WT2725 DOSING EMULSION IN
PATIENTS WITH ADVANCED MALIGNANCIES**

IND No. 15,065

NCT01621542

31 Aug 2016

Original Protocol Version 1.0 (2 Mar 2012)

Non-substantial Amendment No. 1 (04 May 2012)

Amendment No. 1, Protocol Version 2.0 (06 July 2012)

Amendment No. 2, Protocol Version 3.0 (13 July 2012)

Amendment No. 3, Protocol Version 4.0 (27 Mar 2013)

Non-substantial Amendment No. 2 (12 Apr 2013)

Amendment No. 4, Protocol Version 5.0 (31 May 2013)

Amendment No. 5, Protocol Version 6.0 (13 Dec 2013)

Non-substantial Amendment No. 3 (18 Feb 2014)

Non-substantial Amendment No. 4 (09 Sep 2014)

Amendment No. 6, Protocol Version 7.0 (03 Dec 2014)

Non-substantial Amendment No. 5 (12 Jan 2015)

Non-substantial Amendment No. 6 (11 Mar 2015)

Non-substantial Amendment No. 7 (24 Apr 2015)

Non-substantial Amendment No. 8 (31 Aug 2016)

1. SUMMARY AND AMENDMENT HISTORY

The original protocol (Version 1.0), dated 02 Mar 2012, was amended 6 times. There were also 8 non-substantial amendments (administrative letters). Brief summaries of the changes are outlined in the sections below.

2. NON-SUBSTANTIAL AMENDMENT NO. 1 (04 MAY 2012)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative clarifications to Protocol D8350004 (Version 1.0, 02 Mar 2012):

Baseline biomarker samples need only be collected in patients that have met all eligibility criteria and are ready to begin study treatment, thus:

1. Collect one blood sample for each cytotoxic T lymphocyte induction activity (CTL), anti-WT1 antibodies, and retrospective biomarker analyses predose on Day 1 only, and do not collect these samples earlier during screening.
2. The existence of tumor tissue samples for immunohistochemistry (IHC) should be confirmed during the screening period, however, provide these to the sponsor only for patients who receive study drug. Additionally, for patients who require a tumor biopsy at screening in order to provide this tissue sample do not have the biopsy performed until eligibility for the study has been confirmed.

3. AMENDMENT NO. 1, PROTOCOL VERSION 2.0 (06 JUL 2012)

The protocol was amended to incorporate the following changes.

In order to enroll a more homogenous population allowing for a more precise assessment of outcomes while exposing fewer patients overall, the following changes are being made to the protocol:

- Restrict the types of malignancies that qualify patients for enrollment into the study to glioblastoma, ovarian, acute myeloid leukemia (not including acute promyelocytic leukemia), and non-small cell lung cancer and require at least 6 evaluable patients with each to be enrolled.
- Limit the current evaluation to a single route of administration, subcutaneous.
- Allow dose level increases for patients who have not experienced a DLT, \geq Grade 2 study drug-related injection-site reaction, or required a dose reduction and completed the consolidation phase of treatment on the dose level of their assigned cohort (ie, without requiring prior dose reduction).

The following additional changes/clarifications are being made to the protocol:

- Grade 3 adverse events of nausea, vomiting, and fatigue that are common and manageable in cancer patients will not be considered DLT if they can be ameliorated to < Grade 3 with standard supportive care management. As is common in oncology studies these should not limit the dose if they are responsive to standard supportive measures that lessen the severity.
- Reduce expected number of patients to be enrolled.
- Expand response criteria with International Working Group response criteria for acute myeloid leukemia and applicable tumor markers.
- Add 3 blood draws to collect samples for isolation of peripheral blood mononuclear cells. Include exploratory endpoint related to peripheral blood mononuclear cells evaluation.
- Add analysis of adverse events by last dose level administered before occurrence of event.
- Modified exclusion for previous chemotherapy administration.
- Change start of reporting of adverse events, serious adverse events, and pregnancies
- Clarify that no more than 4 doses of study drug will be administered during the DLT Evaluation Period (Days 1 - 29).
- Clarify meaning of “staff member” in exclusion criteria number 15.
- Provide estimated period of time to enroll each cohort of subjects.
- Update contact information for medical monitor and serious adverse event reporting.
- Revise list of reasons for study drug discontinuation/study participation termination.
- Revise definitions for reporting adverse events:
 - add “unlikely” to the reasons for causal relationship of adverse events (AE) to study medication and specify that “unlikely” relationship will be grouped with not related events per National Cancer Institute guidelines.
 - remove “frequency of AE” from parameters reported
- Include assigned IND number.
- Incorporate changes to the protocol made with Non-substantial Amendment 1.0 dated 4 May 2012:
 - Clarify that baseline biomarker samples need only be collected in patients that have met all eligibility criteria and are ready to begin study treatment. Biomarker sample collection is therefore reduced to one blood sample for each cytotoxic T lymphocyte induction activity (CTL), anti-WT1 antibodies, and retrospective biomarker analysis predose on Day 1 only, with no sampling during screening.
 - Clarify when and for whom tumor tissue samples will be collected. The existence of tumor tissue samples for immunohistochemistry (IHC) should be confirmed during the screening period, however, these will be provided to the

sponsor only for patients who receive study drug. Additionally, for patients who require a tumor biopsy at screening in order to provide this tissue sample the biopsy will not be performed until eligibility for the study has been confirmed.

4. AMENDMENT NO. 2, PROTOCOL VERSION 3.0 (13 JUL 2012)

The following changes were made to the protocol in order to adhere to the sponsor's internal standards:

- Revise definitions for reporting adverse events:
 - remove “unlikely” from the reasons for causal relationship of adverse events to study medication and adjust adverse event statistical analysis accordingly
- Change start time for collection of adverse events, serious adverse events, and pregnancies to the time of informed consent

5. AMENDMENT NO. 3, PROTOCOL VERSION 4.0 (27 MAR 2013)

The following changes were made to the protocol:

- In order to more completely assess disease progression and patient survival, these parameters will continue to be assessed every 3 months following the end of study visit.
- As patients with Grade 2 hematology values may be enrolled in the study and hematologic toxicity has not been observed with WT2725 during this study, the dose-limiting toxicity definition related to hematology parameters has been revised to include at least a 2 grade shift.
- It is not currently known whether administering and evaluating a DTH skin test immediately associated with vaccination or remote from vaccination correlates best with other outcomes. In order to assess and compare both methods, additional DTH skin tests were added at Days 1, 29, and 85, which resulted in adding visits at Days 31 and 87 to evaluate the DTH skin tests. In order to limit the visit schedule burden on patients, Day 2 assessments were moved to Day 3 to coincide with DTH skin test evaluation from Day 1.
- In order to increase the precision of the baseline CTL value upon which changes at subsequent time points are determined, an additional baseline CTL blood sample was included during screening.
- Results of an additional historical tumor assessment prior to baseline, if available, are requested in order to provide more information on tumor progression rate.

- In order to limit testing to patients with a reasonable possibility of a positive result, clarification was provided regarding when hepatitis B and C, human immunodeficiency virus (HIV) 1, and HIV 2 testing are required at screening.
- In order to be consistent with tumor marker response criteria, the window for collection of tumor markers during screening was shortened to 14 days prior to first dose.
- As hematologic toxicity with WT2725 has not been demonstrated in this study, the inclusion criteria for bone marrow and immune reserve was revised by lowering required absolute neutrophil count from $\geq 1500/\mu\text{l}$ to $\geq 1000/\mu\text{l}$, platelets from $\geq 10.0 \times 10^4/\mu\text{l}$ to $\geq 5.0 \times 10^4/\mu\text{l}$ after stem cell transplant, and absolute lymphocyte count (ALC) from $\geq 1000/\mu\text{l}$ to $\geq 500/\mu\text{l}$ after stem cell transplant in order to allow enrollment of a greater and more relevant patient population.
- Revised definition of progressive disease (PD) criteria and the definition of treatment failure in acute myeloid leukemia (AML) to be more consistent with the intent of the protocol.
- As tumor marker assessment for patients with AML and ovarian cancer provide useful response data and assays for both are now available through study laboratories, tumor marker assessment for these patients were required.
- In order to align the protocol with corticosteroid doses used in clinical practice for patients with glioblastoma multiforme, the exclusion criteria were revised with a small increase in the corticosteroid equivalent in terms of dexamethasone dose and another corticosteroid equivalent was provided.
- Excluded from further DTH testing, patients with DTH reactivity resulting in erythema with induration greater than 2 cm or that leads to ulceration of the skin test site as not tolerable.
- Removed IHC requirement for AML patients with assessment of RT-PCR for WT1 transcript.
- Shortened to 30 days the interval prior to screening that prior therapy and concomitant medication information need to be provided.
- Provided operational clarifications for the following:
 - Clarified that AML patients need not have tumor tissue samples at screening and should instead provide a bone marrow aspirate, bone marrow biopsy, and/or PCR for WT1 transcript performed before the first dose of study drug.
 - Clarified that the minimum interval for administration of molecular-targeted agents not associated with myelosuppression or immunosuppression is 21 days or 5-half-lives if that is less than 21 days.
 - Clarified that the windows for subsequent dosing are included to allow patients to recover from intercurrent medical conditions.
 - Clarified description for end of dose escalation.

- Clarified that patients with progressive disease (PD) based on tumor assessments that are experiencing clinical benefit in the investigator’s opinion may continue on study to undergo repeat tumor assessments to achieve subsequent stabilization or improvement for consistency with the Immune-related Response Criteria (irRC).
- Added window for 6 and 24 hour post-dose collection of blood samples for retrospective biomarker samples.
- Added footnote to Schedules of Assessments to indicate location in protocol of required clinical laboratory tests.

6. NON-SUBSTANTIAL AMENDMENT NO. 2 (12 APR 2013)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Protocol D8350004 (Version 4.0, 27 Mar 2013):

1. Appointment of a new Medical Monitor to replace [REDACTED] There is no change to the related contact information for the Medical Support Center, as noted below.

Medical Monitor	[REDACTED] Medical Director, Oncology – Medical Affairs PRA International	[REDACTED]
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7. AMENDMENT NO. 4, PROTOCOL VERSION 5.0 (31 MAY 2013)

The following changes were made to the protocol:

- Addition of the recommended Phase 2 dose (RP2D) identified from this study to the dose rationale section.
- Addition of a summary of adverse reactions observed during the dose escalation part of this study to the risk/benefit section.
- Addition of up to 3 cohorts of patients treated at the RP2D in order to further characterize the safety and efficacy of WT2725 Dosing Emulsion in subsets of patients. Each of these cohorts will enroll 10 patients of a selected tumor type.
- Increase in the number of proposed investigational sites and overall patient enrollment in order to accommodate the increased patient recruitment and selected tumor types for the RP2D cohorts.

- Removal of hematology eligibility criteria for acute myeloid leukemia (AML) patients enrolling after the completion of dose escalation, as WT2725 Dosing Emulsion has not been shown to adversely affect these parameters and patients with AML are expected to have baseline leukemia-related cytopenias.
- Clarification of tumor tissue sampling required for patients with AML at screening and during the study.
- Clarification of doses of systemic corticosteroids not permitted during the study.
- Incorporate change to the protocol made with Administrative Letter 1 dated 12 April 2013:
 - Appointment of new Medical Monitor [REDACTED] MD.

8. AMENDMENT NO. 5, PROTOCOL VERSION 6.0 (13 DEC 2013)

The following changes were made to the protocol:

- Simplified acceptable timing for baseline tumor assessments.
- Provided additional confirmation requirements for progressive disease in glioblastoma and ovarian cancer.
- Increased frequency of tumor marker assessments drawn from peripheral blood samples from every 8 weeks to every 4 weeks after first dose in order to increase accuracy of the results relative to time course and intertest variability. These additional samples will likely be drawn at the same time as samples for other clinical laboratories.
- Provided consistency throughout the protocol that AML subjects do not need to meet hematologic criteria after completion of the dose escalation phase of the study, which is already complete.
- Reduce elapsed time between recent infection treatment and first dose of study drug from 14 days to 4 days to reduce unnecessary wait time between completion of infection treatment and start of study treatment.
- Replaced Medical Monitor [REDACTED] MD with [REDACTED] MD. Contact information remained the same.
- Updated title of responsible physician.

9. NON-SUBSTANTIAL AMENDMENT NO. 3 (18 FEB 2014)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Protocol D8350004 (Version 6.0, 13 Dec 2013):

Effective 24 Feb 2014, Sunovion Pharmaceuticals Pharmacovigilance and Risk Management as identified in the protocol will no longer be the contact for reporting of SAEs, pregnancies, and any other immediately reportable events. From 24 Feb 2014 these events should be reported to:

PPD Pharmacovigilance (PVG)

Phone hotline: (919) 456-6001

Fax: (919) 654-0211

Email: SunovionSafety@druginfo.com

10. NON-SUBSTANTIAL AMENDMENT NO. 4 (09 SEP 2014)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Protocol D8350004 (Version 6.0, 13 December 2013):

The responsible physician for the study has changed from [REDACTED] MD, [REDACTED] to [REDACTED] MD | [REDACTED]

11. AMENDMENT NO. 6, PROTOCOL VERSION 7.0 (03 DEC 2014)

The following changes were made to the protocol:

- Initial dose escalation in this study was completed, with the highest planned dose of 9.0 mg being administered without dose-limiting toxicity. This dose was anticipated to be a recommended phase 2 dose (RP2D), and additional patients were enrolled and initiated treatment at this dose. With the expanded cohorts of patients treated at 9.0 mg, no important unanticipated risks, potential risks, or safety signals have been observed; the 9.0 mg dose is not considered the maximum tolerated dose (MTD). Based on the potential of WT2725 Dosing Emulsion to be of benefit to patients and the lack of tolerability issues observed for the expansion cohorts at the RP2D of 9.0 mg a second part has been added to the study which includes 2 additional dose escalation cohorts (18.0 and 27.0 mg). These cohorts are restricted to patients with glioblastoma and acute myeloid leukemia (AML) in order to accumulate more data with these malignancy types. In order to obtain adequate data for assessment of these dose levels, pending successful DLT evaluation, enrollment in each of these 2 cohorts is open to 10 patients with at least 4 patients of each of these malignancy types in each cohort. If the MTD is reached in Part 2 before the total of 20 patients are enrolled, remaining patients will be enrolled at the prior dose level. In the event that a dose level is excluded from further study due to dose limiting toxicity all patients may continue the study at the most recently completed study

without DLT, eg, if the 27.0 mg dose is excluded due to DLT all patients may continue at 18.0 mg. Additionally, Part 2 of the study will evaluate an extended Induction Phase, ie, 8 weeks instead of 4 weeks, and an extended Consolidation Phase, ie 12 weeks instead of 6 weeks.

- The following changes to the study design were implemented for Part 2:
 - In order to prevent abrupt cessation of prior therapy that may be making an effective contribution to the management of disease, patients who have been established on treatment with hydroxyurea may continue up to one cycle of hydroxyurea following entry into this study.
 - As WT2725 Dosing Emulsion has not been shown to adversely affect hematology parameters and patients with AML are expected to have baseline leukemia-related cytopenias and often receive prophylactic antibiotics:
 - Reduced absolute lymphocyte count (ALC) necessary for enrollment to $\geq 900/\mu\text{l}$ from $\geq 1000/\mu\text{l}$ for non-AML patients.
 - Removed hematological eligibility criteria for AML patients.
 - Loosened eligibility criteria for patients with infection to allow patients to enroll who have an infection without body temperature $> 38.3^{\circ}\text{C}$ within 48 hours prior to planned first dose of study drug.
 - In order to obtain adequate response data, added to eligibility criteria that patients with AML must be willing to undergo bone marrow aspiration/biopsy during treatment if there are no other indicators of measureable disease.
 - Increased potential number of clinical sites to accommodate enrollment in Part 2 of the study.
 - Clarified that screening period is 21 days in length.
- Changes for Parts 1 and 2 of the study include:
 - Indicated that tumor markers drawn from peripheral blood samples may be performed more frequently than every 4 weeks.
 - Updated summary of known potential risks and benefits based on review of preliminary data from this study.
 - Modifications to the International Working Group response criteria in acute myeloid leukemia (IWG) were made to accommodate the previously treated patients enrolled in this study.
 - Revised description of study drug to accommodate for new doses and deleted additional details, which are fully described in the pharmacy manual.
 - Included change in reporting contact for serious adverse events and pregnancies from Administrative Letter 3.
 - Included change in sponsor's responsible physician from Administrative Letter 4.
 - Updated List of Abbreviations for new terms.

- Updated confidentiality statement in line with corporate guidelines.

12. NON-SUBSTANTIAL AMENDMENT NO. 5 (12 JAN 2015)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following typographical error to Protocol D8350004 (Version 7.0, 3 Dec 2014):

1. Patient Inclusion Criteria - Part 2, #10

The ANC \geq 100/ μ l (\geq 500/ μ l after stem cell transplant) requirement is incorrect.

An ANC \geq 1000/ μ l (\geq 500/ μ l after stem cell transplant) is required.

There are no other changes to this inclusion criterion.

13. NON-SUBSTANTIAL AMENDMENT NO. 6 (11 MAR 2015)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative changes to Protocol D8350004 (Version 7.0, 3 Dec 2014):

1. As a result of new study drug supply, there is a change in the volume of WT2725 Injection or diluted WT2725 Injection (from 0.3 mL to 0.4 mL) to be mixed with W/O pre-Emulsion (from 0.7 mL to 0.93 mL) in order to make the dosing emulsion. There is no change in the ratio of WT2725 Injection or diluted WT2725 Injection to W/O pre-Emulsion. Complete revised instructions will be provided in the updated Pharmacy Manual.
2. In order to accommodate the higher doses introduced by Amendment 6 (18 and 27 mg), 2 mL syringes will also be acceptable (in addition to 1 mL syringes) for use in administering WT2725 Dosing Emulsion. Appropriate 2 mL syringes will be supplied.
3. The modified International Working Group (IWG) response criteria are being updated to remove the category of Morphologic leukemia free state (MLFS) which is considered redundant with the updated definition of CRi that was included in Amendment 6 (Protocol Version 7.0).

14. NON-SUBSTANTIAL AMENDMENT NO. 7 (24 APR 2015)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Protocol D8350004 (Version 7.0, 3 Dec 2014):

1. The following change is being made to the study procedures to reduce potentially unnecessary invasive procedures. For patients with acute myeloid leukemia who have evidence of disease in peripheral blood it is assumed that disease is present in the bone marrow therefore performance of bone marrow aspiration and/or bone marrow biopsy are optional at baseline. If there is no evidence of disease in peripheral blood then bone marrow aspiration and/or bone marrow biopsy is required at baseline.

15. NON-SUBSTANTIAL AMENDMENT NO. 8 (31 AUG 2016)

The purpose of this non-substantial amendment (administrative letter) was to notify the Investigators of the following administrative change to Protocol D8350004 (Version 7.0, 3 Dec 2014):

1. The responsible physician for the study has changed to [REDACTED] MD, [REDACTED]
[REDACTED] from
[REDACTED] MD [REDACTED]