# Amendment 1 Summary of Changes

## Protocol ALN-CC5-001 dated 08 December 2014

## A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

### Rationale for amendment 1

The primary purpose for this protocol amendment [redacted] pertaining to study drug administration and follow-up of subjects who withdraw from the study; the addition of pregnancy and breastfeeding as exclusion criteria; and the plan for the unblinding coding system in the event that rapid unblinding becomes necessary.

The above issues are addressed as follows in this Amendment #1:

The protocol has been updated to indicate that patients who are withdrawn from the study because individual stopping criteria have been met, or the subject/patient requires the use of a prohibited medication, which in the opinion of the Sponsor or Investigator, may jeopardize the study results or represent a risk to the participant, will receive no further study medication but will continue to be followed for safety.

The protocol wording has been clarified to ensure it is clear that any woman with a positive pregnancy test during the study will not receive further study drug and will continue to be followed for safety. Additionally, pregnancy and breastfeeding have been added as exclusion criteria.

The protocol has been updated according to International Conference on Harmonisation regulations which state that the coding system in the blinded part of the study will include a mechanism permitting rapid unblinding and that the investigator will not be required to discuss unblinding with the sponsor if emergent unblinding is necessary.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

## Table 1: Amendment 1 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in amendment X are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

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| ***Purpose:*** | ***Include pregnancy and breastfeeding as an exclusion criterion*** |
| Primary change: | Section 5.2.1, Exclusion Criteria for all Subjects in Part A and Part B |
| **Added text:** | **31. Woman who are pregnant or breastfeeding** |
| Section(s) also containing this change: | • SYNOPSIS<br>• Section 5.2.2, Exclusion Criteria for All Patients in Part C (criterion 16)<br>• Section 10.1.7.6, Pregnancy Screening |
| ***Purpose:*** | ***Add specification that subjects/patients meeting withdrawal criteria will not receive further study drug and will continue to be followed for safety*** |
| Primary change: | Section 5.3.1 Reason for Withdrawal |
| **Added text:** | **Where a subject/patient meets withdrawal criteria for the study, no further study drug will be administered and, wherever possible, such study participants will continue to be followed for safety (see Section 5.3.2).** |
| ***Purpose:*** | ***Specify the reasons for withdrawal when no further study drug will be administered*** |
| Primary change: | Section 5.3.2, Handling of Withdrawals |
| ***Formerly read:*** | In the event that a subject/patient withdraws or is withdrawn from the study, the Investigator will inform the Medical Monitor and Sponsor immediately. If there is a medical reason for withdrawal, the subject/patient will remain under the supervision of the Investigator for protocol specified safety follow-up procedures. The SRC will be notified. |
| ***Now reads:*** | In the event that a subject/patient withdraws or is withdrawn from the study, the Investigator will inform the Medical Monitor and Sponsor immediately. If **a subject/patient is withdrawn because individual stopping criteria have been met, the subject/patient requires the use of a prohibited medication, which in the opinion of the Sponsor or Investigator, may jeopardize the study results or represent a risk to the participant, or** there is **another** medical reason for withdrawal, **no further study drug will be administered and** the subject/patient will remain under the supervision of the Investigator for protocol specified safety follow-up procedures. The SRC will be notified. |

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| ***Purpose:*** | ***Include a mechanism permitting rapid unblinding by the Investigator in emergency situations if it is in the best interest of the subject and allowing unrestricted and immediate access to break the treatment code for the Investigator*** |
| Primary change: | Section 6.6.1, Breaking the blind |
| **Formerly read:** | In case of emergency, the clinical study site pharmacist will access the randomization list, which contains the study drug assignment for ~~the~~ subject.<br>If a subject becomes pregnant or seriously ill during the study or follow-up period, the blind should be broken only if knowledge of the treatment administered will affect treatment options available for the subject. ~~B~~before breaking the blind, the Investigator, or designee, should attempt to contact the Medical Monitor and the Sponsor ~~as soon as possible. If the blind should be broken, individuals from the Sponsor, who are not related to the conduct of the study, will assist with the unblinding of the subject.~~ If there is a requirement to unblind subjects at the cohort level, only the subjects in that cohort will be unblinded.<br>A record of when the blind was broken, who broke the blind, and why it was broken, will be maintained in the TMF. Should unblinding occur, it will not have an impact on the planned study analyses. |
| **Now reads:** | In case of emergency, the clinical study site pharmacist will **have** access **to** the randomization list, which contains the study drug assignment for subjects.<br>**The coding system in the blinded part of the study includes a mechanism permitting rapid unblinding. If the blind is prematurely broken, the investigator will promptly document and explain any unblinding to the sponsor. In emergency situations, the investigator may need to break the treatment code immediately, or as quickly as possible, if it is in the best interest of the subject; thus, the investigator will have unrestricted and immediate access to break the treatment code via the randomization list held by the site pharmacist.**<br>If a subject becomes pregnant or seriously ill during the study or follow-up period, the blind should be broken only if knowledge of the treatment administered will affect treatment options available for the subject. **If possible, b**efore breaking the blind, the Investigator, or designee, should attempt to contact the Medical Monitor and the Sponsor. If there is a requirement to unblind subjects at the cohort level, only the subjects in that cohort will be unblinded.<br>A record of when the blind was broken, who broke the blind, and why it was broken, will **also** be maintained in the TMF. Should unblinding occur, it will not have an impact on the planned study analyses. |

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| ***Purpose:*** | ***Update to include continued safety follow-up for subjects/patients who become pregnant during this study*** |
| Primary change: | Section 10.6.1, Pregnancy Reporting |
| **Formerly read:** | A subject/patient who becomes pregnant during this study must be instructed to stop all study drug administration. The Investigator or Sub-investigator must report a subject/patient or partner pregnancy to the Sponsor or its agency within 24 hours of being notified of the pregnancy. Details of the pregnancy will be reported on a Pregnancy Report Form. The subject/patient/partner shall receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. ~~M~~onitoring of the subject/patient/partner will continue until the conclusion of the pregnancy, and the outcome of the pregnancy will be reported to the Sponsor. |
| **Now reads:** | A subject/patient who becomes pregnant during this study must be instructed to stop all study drug administration **and will continue to be followed for safety**. The Investigator or Sub-investigator must report a subject/patient or partner pregnancy to the Sponsor or its agency within 24 hours of being notified of the pregnancy. Details of the pregnancy will be reported on a Pregnancy Report Form. The subject/patient/partner shall receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. **Safety m**onitoring of the subject/patient/partner will continue until the conclusion of the pregnancy, and the outcome of the pregnancy will be reported to the Sponsor.<br>**If, in the opinion of the Investigator, knowledge of the study drug assignment is required to monitor the pregnancy for safety, then unblinding procedures detailed in Section 6.6.1 will be followed.** |
| Section(s) also containing this change: | • Section 10.1.7.6, Pregnancy Screening |

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| ***Purpose: Correct typographical errors, punctuation, grammar, and formatting*** |
| These changes are not listed individually. |

# Amendment 2 Summary of Changes

## Protocol ALN-CC5-001 dated 16 June 2015

## A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

### Rationale for amendment 2

Part A

[redacted].

Part B and Part C

Biweekly and monthly dosing regimens may be explored based on nonclinical data; corresponding pharmacokinetic sampling schedules have been developed in support of these dosing regimens.

Overall

Administrative changes between protocol amendments 1 and 2 have been incorporated.

Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

**Table 1: Amendment 2 Detailed Summary of Changes**

The primary section(s) of the protocol affected by the changes in amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

***Purpose:*** *Clarified the timing of vital sign and ECG measurements*

The primary change occurs in Tables 1, 2, and 3 – Schedule of Assessments for Parts A, B, and C.

Added text: **Vital sign assessments should be performed 30 minutes and 4 hours postdose on Day 0. The Day 0 ECG should be performed after dosing (+4 hours). After Day 0, the ECG should be performed up to 12 hours after administration of subsequent doses of study drug.**

***Purpose:*** *Added an exploratory objective,* [redacted]

The primary change occurs in Section 2.3, Exploratory Objectives

Section that also contains this change is:

- Synopsis
- Tables 1, 2, and 3 – Schedule of Assessments for Parts A, B, and C
- Section 9.2, Exploratory [redacted]
- 11.3.5, Exploratory Analysis

***Purpose:*** *Updated the number and location of clinical trial sites*

The primary change occurs in Section 3.1, Overall Study Design

Formerly read: ~~The~~ study will be conducted at up to ~~4~~ clinical study centers ~~in the UK~~ and in the following ~~3~~ parts

Now reads: **This multinational** study will be conducted at up to **6** clinical study centers in the following parts

Section that also contains this change is:

- Synopsis

***Purpose:*** *Clarified the anticipated duration of the study to be from screening through last subject/patient, last visit*

The primary change occurs in Section 3.1, Overall Study Design

Formerly read: It is anticipated that this study will last for ~~up to~~ 1 year from screening through the last subject/patient, last visit.

Now reads: It is anticipated that this study will last for **approximately** 1 year from screening through the last subject/patient, last visit.

Section that also contains this change is:

- Synopsis

***Purpose:*** *Increased number of patient in Part C and clarified that approximately 8 of these patients should be on a stable dose of eculizumab*

The primary change occurs in Section 3.2, Number of Subjects and Patients

Formerly read: Part C: Up to 8 patients ~~with PNH who are either naïve to eculizumab treatment or~~ on stable dose~~s~~ of eculizumab (as assessed by the Investigator)

Now reads: Part C: Up to **16 patients with PNH (approximately** 8 patients on **a** stable dose of eculizumab (as assessed by the Investigator)

Section that also contains this change is:

- Synopsis
- Section 3.1, Overall Study Design

***Purpose:*** *Increased dosing period to approximately 13 weeks and added the possible investigation of biweekly and monthly dosing regimens and PK schedules, if recommended by the SRC*

The primary change occurs in Section 3.1.2, Multiple-ascending Dose Phase (Part B)

Formerly read: Subjects will be re-admitted to the clinical study site for administration of each of the ~~4~~ remaining weekly doses of study drug.

Now reads: Subjects will be re-admitted to the clinical study site for administration of each of the remaining weekly doses of study drug **over an approximately 13 week treatment period. If recommended by the SRC, biweekly and monthly dosing regimens and corresponding PK schedules may be investigated (Appendix 18.1).**

Section that also contains this change is:

- Synopsis

- Table 11: Pharmacokinetic Time Points for the Multiple-ascending Dose Phase – Weekly, Biweekly, and Monthly Dosing Schedules (Part B)
- Appendix 18.2, Schedules of Assessments for Dosing Regimens for Multiple-ascending Dose (Part B) Cohorts

***Purpose:*** *Clarified that Part C of the study may investigate weekly, biweekly, or monthly dosing regimens*

The primary change occurs in Section 3.1.3, Multiple Dose Phase (Part C)

Added text: **Weekly, biweekly, or monthly dosing regimens may be investigated.**

Section that also contains this change is:

- Synopsis
- Table 12: Pharmacokinetic Time Points for the Multiple Dose Phase (Part C)

***Purpose:*** *Updated the inclusion criteria for acceptable methods of contraception for female subjects of childbearing potential (Parts A, B, and C)*

The primary change occurs in Section 5.1.1, Inclusion Criteria for all Subjects in Part A and Part B, and Section 5.1.2, Inclusion Criteria for all Patients in Part C

Added text: **The subject's male partner has undergone documented vasectomy with documentation of azoospermia (male sterilization) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).**

Added text: True abstinence: when this is in line with the preferred and usual lifestyle of the subject**, including female subjects with same sex partners**. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

Section that also contains this change is:

- Synopsis

***Purpose:*** *Updated the inclusion criteria for acceptable methods of contraception for male subjects if the male subject's partner could become pregnant (Parts A, B, and C)*

The primary change occurs in Section 5.1.1, Inclusion Criteria for all Subjects in Part A and Part B, and Section 5.1.2, Inclusion Criteria for all Patients in Part C

Added text: True abstinence: when this is in line with the preferred and usual lifestyle of the subject**, including male subjects with same sex partners**. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

Section that also contains this change is:

- Synopsis

***Purpose:*** *Clarified exclusion criteria for HIV infection, HCV infection, or chronic HBV infection*

The primary change occurs in Section 5.2.2, Exclusion Criteria for All Patients in Part C

Added text: **Known** clinical laboratory evidence or clinical diagnosis of HIV infection, HCV infection, or chronic HBV infection (as shown by HBsAg positivity).

Section that also contains this change is:

- Synopsis

***Purpose:*** *Increased number of patients in the study due to the increase in the number of patients in Part C*

The primary change occurs in Section 11.1, Sample Size and Randomization

Formerly read: Up to ~~68~~ participants (60 subjects and ~~8~~ patients) are expected be enrolled in the study (including optional cohorts).

Now reads: Up to **76** participants (60 subjects and **16** patients) are expected be enrolled in the study (including optional cohorts).

Section that also contains this change is:

- Synopsis
- Section 3.2, Number of Subjects and Patients

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| ***Purpose:*** | *Corrected the blood volume for Part B and Part C* |
| The primary change occurs in Section 10.1.6, Maximum Blood Volume | |
| Formerly read: | Part A: up to ~~400~~ mL over the course of 70 days<br>Part B: up to ~~500~~ mL over the course of 140 days<br>Part C: up to ~~500~~ mL over the course of 140 days |
| Now reads: | Part A: up to **500** mL over the course of 70 days<br>Part B: up to **600** mL over the course of 140 days<br>Part C: up to **800** mL over the course of 140 days |
| ***Purpose:*** | *Clarified the timing of vaccinations* |
| The primary change occurs in Section 10.1.8, Part A and Part B Vaccination Specifications | |
| Added text: | Subjects who were not previously vaccinated will be vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine**. Vaccinations should be administered within the 90 day screening period** according to the following plan **(Note: Vaccination day is not the same as Study Day)**: |
| ***Purpose:*** | *Removed 15-minute PK timepoint* |
| The primary change occurs in Tables 10, 11 and 12, Pharmacokinetic Time Points for Parts A, B, and C, respectively | |
| ***Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting*** | |
| These changes are not listed individually. | |

# ALN-CC5-001

## Summary of Changes

## Protocol Amendment 3, dated 13 November 2015

## A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

### Rationale for the amendment

The primary purpose of this amendment is to extend study drug dosing through 39 weeks in the multiple-dose phase in patients with paroxysmal nocturnal hemoglobinuria (PNH; Part C). An extension of the dosing is supported by [redacted] Schedules of Assessments were added and pharmacokinetic time points were updated to align with the new dosing regimens.

[redacted]

In Part C, a maximum of 3 cohorts comprised of at least 4 patients each will be enrolled to permit an assessment of the effect of cohort-based dose modifications in this patient population during longer-term dosing. During the dosing period, the SRC will meet at regular intervals to review ongoing safety, tolerability, and available PD data from Part B and Part C, including degree of complement inhibition and clinically meaningful suppression of intravascular hemolysis as evaluated by LDH levels (Part C only). Based on these reviews, the SRC will recommend cohort initiation and the dose and dosing regimen to be administered to patients in the cohort or all patients in Part C. To further reduce patient burden in Part C, ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider. Since safety information is analyzed locally at the clinical study center, patient safety will be

maintained. To implement a more feasible study design in this amendment, after completing the 13 week dosing period, patients in Cohort 1 may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC.

Additionally, in Part A and B, unblinding will occur at the cohort level. In Part B and C of the study, editorial and minor administrative errors identified since protocol amendment 2, dated 16 June 2015, were corrected and editorial changes were made to improve protocol clarity and to align with the adaptive design features of the study. Study assessments and visits were harmonized with the new dosing regimens that may be investigated and antidrug antibody assessments added. Intermediate overnight visits to the clinical study center were removed to reduce the burden of visits to the clinical study center on patients. The Schedule of Assessments from Part B (5 weekly doses), which was inadvertently removed in protocol amendment 2, was incorporated back into the protocol.

A detailed summary of the changes is provided in Table 1. Minor administrative updated and corrections to typographical errors, abbreviations, and formatting are not detailed.

**Table 1: Amendment 3 Detailed Summary of Changes**

The primary section(s) of the protocol affected by the changes in the amendment are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

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| *Purpose:* | [redacted] |
| **Primary change:** | **Section 2.3, Exploratory Objectives** |
| **Now reads:** | [redacted] |
| Other sections affected by this change: | • Protocol Synopsis<br>• Section 9.3.4, [redacted]<br>• Section 11.3.5, Exploratory Analysis<br>• All Schedule of Assessment Tables for Part C (Table 3, Table 20, Table 21, and Table 22) |

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| *Purpose:* | *Evaluate less frequent dosing regimens and lower doses in Part B and update and add Schedules of Assessments and PK time point tables to align with new dosing regimens* |
| **Primary change:** | **Section 3.1.2, Multiple-ascending Dose Phase (Part B)** |
| **Now reads:** | Part B of the study will be performed in a randomized (3:1), placebo-controlled, double-blind design to assess MAD of ALN-CC5 in healthy subjects (Figure 2).<br>Subjects will be screened from -90 to -2 days before dose administration. Eligible subjects will be admitted to the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Subjects will be randomized on Day 0 and will receive an initial dose of study drug. Subjects will be discharged from the clinical study site following the completion of the 24 ~~hours~~hour postdose follow-up assessments. ~~Subjects will be re-admitted to the clinical study site for administration of each of the remaining weekly doses of study drug over an approximately 13 week treatment period. If recommended by the SRC, biweekly and monthly dosing regimens and corresponding PK schedules may be investigated (Appendix 18.2). Following completion of the 24 hours postdose follow-up assessments, subjects will be discharged from the clinical study site.~~Subjects will return to the clinical study site ~~on an outpatient basis~~ at the time points in the Schedule of Assessments (Table 2**, Table 15, Table 16, Table 17, Table 18, and Table 19**) ~~for~~**and PK table (Table 11 and Table 12) for study drug administration and** safety, tolerability, PK, and PD monitoring ~~through SC doses administered over an approximately 13 week treatment period~~**over the treatment period and for postdose follow-up.** For subjects with serum complement activity below normal range at the last postdose follow-up visit ~~(Day 140)~~, monitoring visits will occur ~~every 28±7 days~~ until serum complement activity is within the normal reference range **for all subjects in that cohort** as assessed by CAP ELISA.– [redacted] |

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| Other section affected by this change: | • Protocol Synopsis<br>• Figure 2, Multiple-ascending Dose Phase – Weekly Dosing (Part B) Flow Diagram<br>• Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses<br>• Table 11: Pharmacokinetic Time Points for Multiple-ascending Dose Cohorts (Part B) – Weekly Dosing<br>• Table 12: Pharmacokinetic Time Points for the Multiple-ascending Dose Phase (Part B) – Other Dosing Schedules<br>• Table 15: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 13 Weekly Doses<br>• Table 16: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Once Every 2 Weeks Dosing<br>• Table 17: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Monthly Dosing<br>• Table 18: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing<br>• Table 19: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Monthly Dosing |
| *Purpose:* | *Evaluate less frequent dosing regimens in Part C, update and add Schedules of Assessments and PK time point tables to align with new dosing regimens, and permit ALN-CC5 administration at home between visits to the clinical study center by a home healthcare provider* |
| **Primary change:** | **Section 3.1.3, Multiple Dose Phase (Part C)** |
| **Now reads:** | Part C of the study will be conducted in patients with PNH in an open-label design to assess multiple doses of ALN-CC5. The start of Part C and the study drug dose will depend on SRC review of safety, tolerability, and available PD data from Part A and Part B (Figure 3). **A maximum of 3 cohorts, comprised of at least 4 patients each, will be enrolled in Part C. Overall, patients in Part C will undergo a maximum of 39 weeks of ALN CC5 dosing.**<br>Patients will be screened from -90 to -2 days before dose administration. Patients will have a consultation at the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Patients will be admitted and dosed on Day 0. Patients will be discharged from the clinical study site following the completion of the 24 ~~hours~~**hour** postdose follow-up assessments. Patients will return to the clinical study site at the time points in the Schedule of Assessments (Table 3**, Table 20, Table 21, and Table 22**) ~~on an outpatient basis for each of the remaining doses of~~**and PK table (Table 13 and Table 14) for** study drug **administration** and for safety, tolerability, PK, and PD monitoring ~~at specified time points~~ over ~~an approximately 13 week~~**the** treatment period ~~through the last~~**and for** postdose follow-up ~~visit (Day 140). Weekly, biweekly~~**.** For patients with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur ~~every 28±7 days~~ until serum complement activity is within the |

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| | normal reference range as assessed by CAP ELISA.<br>**In Part C, ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5. Patients will return to the clinical study center every other month for assessments; however, in between, visits can be completed by a home healthcare provider.**<br>After the last dose of study drug, eligible patients may transition to ~~a Phase 2~~**an** open-label extension study immediately after administration of the last dose of study drug or obtain standard of care treatment. |
| Other section affected by this change: | • Protocol Synopsis<br>• Section 7.5, Study Drug Administration<br>• Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)<br>• Table 13: Pharmacokinetic Time Points for the Multiple Dose Phase (Part C) – 13 Weekly Doses (Cohort 1)<br>• Table 14: Pharmacokinetic Time Points for the Multiple Dose Phase (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing or Followed by Monthly Dosing (Cohort 2 and Cohort 3)<br>• Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)<br>• Table 21: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Monthly Dosing (Cohort 2 and Cohort 3)<br>• Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up) |
| *Purpose:* | *Updated the treatment and study duration* |
| **Primary change:** | **Section 3.1.5, Treatment and Study Duration** |
| **Now reads:** | **A single SC dose of study drug will be administered in Part A. In Part B and Part C, respectively, study drug will be administered over a maximum of a 13 or a 39 week period. It is anticipated that this study will last for a maximum of 2 years from screening through the last subject/patient, last visit. End of study is defined as last subject/patient, last visit. It is anticipated that the duration of study participation for a subject/patient will be 454 days (65 weeks).** |
| Other sections affected by this change: | • Protocol Synopsis<br>• Section 10.1.6, Maximum Blood Volume |

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| *Purpose:* | *Extend study drug dosing through 39 weeks in the multiple-dose phase in patients with PNH in Part C, enroll a maximum of 3 cohorts comprised of at least 4 patients and permit SRC recommended cohort initiation and dose modifications, and permit patients in Cohort 1 to transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed* |
| **Primary change:** | **Section 4.3, Study Drug Dosing and Regimen Modifications in Part C** |
| **Now reads:** | **Part C will be initiated if the SRC, based on their expert clinical experience in treating PNH patients, determines that the safety, tolerability, and available PD (C5 levels and complement activity) data derived from Part A and Part B is clinically meaningful and the risk-benefit assessment is favorable.**<br>**Figure 4 illustrates the cohort enrollment and dose and dosing regimen modification plan for Part C. A maximum of 3 cohorts, comprised of at least 4 patients each, will be enrolled. The SRC will meet at regular intervals (approximately every 8 weeks) to review ongoing safety, tolerability, and available PD data from Part B and Part C to recommend cohort initiation and to determine the dose and dosing regimen to be administered to all patients in a cohort or all patients in Part C. During the dosing period, the SRC may also recommend the ALN-CC5 dose and regimen be modified for all patients, based on the degree of complement inhibition and clinically meaningful suppression of intravascular hemolysis as evaluated by LDH (Part C only). Part C does not include sentinel dosing.**<br>**Dosing in Cohort 1 may initiate after SRC review of data from Part A and Part B at a dose no greater than the highest safe and tolerated dose explored in Part B. Initially, 13 weekly doses of ALN-CC5 will be administered. After completing the 13 week dosing period, patients in Cohort 1 may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC.**<br>**Dosing in Cohort 2 may initiate after SRC review of data from subjects in Part B, Cohorts 4, 5, and 6, who completed ≥10 weeks of dosing. Additionally, dosing in Cohort 2 may initiate after SRC confirmation that clinically meaningful suppression of intravascular hemolysis (evaluated by LDH levels) has occurred in at least 4 patients in Part C, Cohort 1, who completed ≥8 weeks of dosing. Initially, ALN-CC5 will be administered once weekly for 5 doses.**<br>**Dosing in Cohort 3 may initiate to further explore dose and dosing regimens after ≥4 patients in Part C, Cohort 2 complete ≥13 weeks of dosing data have been evaluated by the SRC. Initially, ALN-CC5 will also be administered once weekly for 5 doses.**<br>**After an initial dosing period (5 or 13 weekly doses), the SRC may recommend a dose or dosing regimen modification. The regimen can be modified in Cohorts 1, 2, and 3 to once every 2 weeks or once monthly dosing, or weekly dosing continued. The SRC may also determine that de-escalation to a lower dose and regimen or re-escalation to a higher dose and regimen is appropriate. Overall, patients in Part C will undergo a maximum of 39 weeks of ALN CC5 dosing.** |

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| | **Patients with confirmed PNH and on stable doses of eculizumab (as assessed by the Investigator) will continue receiving treatment concomitantly with ALN-CC5 at a dose and regimen determined by the SRC. These patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition (as determined by the SRC during review of data from Part A and Part B). Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration at a dose and regimen determined by the SRC.** |
| Other sections affected by this change: | • Figure 4, Study Drug Dosing in the Multiple-dose Phase (Part C)<br>• Section 11.3, Statistical Methodology<br>• All Schedules of Assessment and PK Time Point tables for Part C (Table 3, Table 13, Table 14, Table 20, Table 21, and Table 22) |
| *Purpose:* | *In Part A and B, unblinding will occur at the cohort level* |
| **Primary change:** | **Section 6.6, Randomization and Blinding** |
| **Now reads:** | Part A and Part B will be conducted in a randomized 3:1 (ALN CC5:placebo), double-blinded, placebo-controlled manner.<br>The study subjects, Investigators, Medical Monitors, and members of the study team at the Sponsor and at the Contract Research Organization(s) (CROs), clinical study site personnel, and members of the SRC will remain blinded to the treatment assignment ~~at least throughout the decision-making time points and until end of study for each subject~~**until all subjects** in a cohort ~~(see Table 6)~~**complete PD follow-up**. |
| Other sections affected by this change: | • Protocol Synopsis |
| *Purpose:* | *Specify immunogenicity assessment criteria* |
| **Primary change:** | **Section 10.1.7.3,** [redacted] |
| **Now reads:** | [redacted]<br>**Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.** |
| Other sections affected by this change: | • Protocol Synopsis<br>• All Schedule of Assessment tables |

| | |
|---|---|
| *Purpose:* | *Extended minimum time permitted for concomitant antibiotic treatment through PD follow-up period in Part A and B* |
| **Primary change:** | **Section 10.1.9, Prophylactic Antibiotic Administration and Compliance Check** |
| **Now reads:** | Ciprofloxacin will be administered in accordance with the manufacturer's instructions. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments.<br>Subjects participating in Part A and Part B will be treated with prophylactic ciprofloxacin (according to standard practice at the clinical study sites) from start of dosing with **study drug (**ALN-CC5 ~~and at least until Day 21 (SAD part) and Day 35 (MAD part)~~ or **placebo)** until serum complement activity**, as assessed by CAP ELISA, for all subjects in the cohort** returns to within the normal reference range~~ as assessed by CAP ELISA~~.<br>Patients in Part C will receive antibiotics at the discretion of the investigator.<br>~~Full details~~**Details** of antibiotic compliance methodology will be described in the Study **Operations** Manual~~/Procedures~~. |
| Other sections affected by this change: | • Protocol Synopsis<br>• All Schedule of Assessment tables for Parts A and B |

# ALN-CC5-001 Protocol Amendment 4

## Summary of Changes dated 16 August 2016

## A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

### Rationale for Protocol Amendment

Protocol ALN-CC5-001 is an ongoing study. Although subjects and patients are no longer being enrolled or treated in this study, subjects and patients continue to be followed in accordance with the protocol. The primary purpose of this amendment is to update the timing of treatment unblinding for healthy subjects in Parts A and B to avoid unnecessarily prolonged prophylaxis antibiotic treatment in normal healthy volunteers who have been assigned placebo, and in ALN-CC5 exposed subjects who have recovered to complement activity within the reference range. This change in the unblinding procedure is based on the observed pharmacodynamic duration of ALN-CC5 plus the unblinding of treatment at the cohort level, which have necessitated all healthy subjects in a cohort to continue daily antibiotics and clinic visits every 28 days regardless of treatment assignment (ALN-CC5 or placebo) and the level of complement activity (as assessed by complement alternative pathway [CAP] enzyme-linked immunosorbent assay [ELISA]). Currently, the protocol requires that all subjects in a cohort complete pharmacodynamic (PD) follow-up in the study before the unblinding of that cohort. With this amendment to the protocol, unblinding of investigators and individual subjects to treatment assignment will occur at a minimum of 9 months after a subject receives his or her last dose of study drug. If an individual subject's complement functional activity as measured by CAP ELISA is within the reference range, prophylactic antibiotics will be stopped after unblinding and that subject will have completed the study. If an individual subject who received ALN-CC5 has a CAP ELISA result that has not returned to within the reference range after unblinding, then prophylactic antibiotics will continue and the subject will be required to attend follow-up visits until the CAP ELISA result returns to within the reference range. Unblinding the treatment assignment of individual subjects in this manner will maintain the safety of subjects, as it will allow for subjects to discontinue daily prophylactic antibiotic use and follow-up clinic visits.

In addition, clarifications are being implemented in this amendment as outlined below:

- Increased the anticipated time for screening through the last subject/patient from a maximum of 2 years to a maximum of 3 years and increased the anticipated duration of study participation for a subject/patient to 665 days (1 year and 10 months) due to the observed PD duration of ALN-CC5.
- Removed hepatitis B core antibodies from the viral serology section of the protocol, as this was only in a single location in the protocol and was included in error.
- Corrected the start of AE collection for Part B to begin after the first dose of ALN-CC5 to align with Section 10.4 of the protocol.

- Increased the estimated total protocol-specified blood volume for Part C from 800 mL to 900 mL over the duration of the study. This is a result of the estimated blood volume required for the lactate dehydrogenase analysis being determined to be more than originally estimated.
- Aligned the hemoglobinuria evaluation to Day -1 and Day 1 (not Day 0) and the coagulation sampling to every 2 weeks followed by once monthly starting at Day 84.
- Removed a reference to Cohort 1in the footnotes in Table 3 and Table 22 for alignment with Section 4.3 of the protocol.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

**Table 1: Protocol Amendment 4 Detailed Summary of Changes**

The primary section(s) of the protocol affected by the changes in Protocol Amendment 4 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

*Purpose: Updated the timing of treatment unblinding and follow-up period for healthy subjects in Parts A and B*

The primary change occurs in Section 6.6, Randomization and Blinding

Now reads: The study subjects, Investigators, Medical Monitors, and members of the study team at the Sponsor and at the Contract Research Organization(s) (CROs), clinical study site personnel, and members of the SRC will remain blinded to the treatment assignment ~~until all subjects in a cohort complete PD follow up~~**for a minimum of 9 months after a subject receives his or her last dose of study drug. If an individual subject's complement functional activity as measured by CAP ELISA is within the reference range, prophylactic antibiotics will be stopped after unblinding and that subject will have completed the study. If an individual subject who received ALN-CC5 has a CAP ELISA result that has not returned to within the reference range after unblinding, then prophylactic antibiotics will continue and the subject will be required to attend follow-up visits until the CAP ELISA result returns to within the reference range.**

Section(s) also containing this change:

- Synopsis
- Table 1: Schedule of Assessments for Single-ascending Dose Cohorts (Part A)
- Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses
- Section 3.1.1, Single-ascending Dose Phase (Part A)
- Section 3.1.2, Multiple-ascending Dose Phase (Part B)
- Section 10.1.9, Prophylactic Antibiotic Administration and Compliance Check
- Table 15: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 13 Weekly Doses
- Table 16: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Once Every 2 Weeks Dosing
- Table 17: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Monthly Dosing
- Table 18: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing
- Table 19: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Monthly Dosing

*Purpose: Increased the anticipated time for screening through the last subject/patient and for the duration of study participation for a subject/patient*

The primary change occurs in Section 3.1.5, Treatment and Study Duration

Now reads: A single SC dose of study drug will be administered in Part A. In Part B and Part C, respectively, study drug will be administered over a maximum of a 13 or a 39 week period. It is anticipated that this study will last for a maximum of ~~2 years~~ **3 years** from screening through the last subject/patient, last visit. End of study is defined as last subject/patient, last visit. It is anticipated that the duration of study participation for a subject/patient will be **665 days (1 year and 10 months)**~~454 days (65 weeks)~~.

Section(s) also containing this change:

- Synopsis

*Purpose: Aligned the start time of AE collection time for Part B with Section 10.4 of the protocol*

The primary change occurs in Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses

Now reads: *Under the Review/record AEs assessment, removed 'X' at Screening and inserted 'X' starting at Day 0*

*Purpose: Increased the blood volume for Part C from 800 mL to 900 mL*

The primary change occurs in Section 10.1.6, Maximum Blood Volume

Now reads: The maximum total blood volume that will be collected from subjects and patients participating in this study will be documented in the Study Manual/Procedures. Maximum total blood volume according to study part is as follows:

- Part A: up to 500 mL over the course of 70 days
- Part B: up to 600 mL over the course of 140 days
- Part C: up to ~~800 mL~~ **900 mL** over the course of approximately 1 year

*Purpose: Removed hepatitis B core antibodies from the viral serology section of the protocol for alignment within the protocol*

The primary change occurs in Section 10.1.7.4, Viral Serology

Now reads: Serology will be performed at the time points in the Schedule of Assessments. During screening, subjects and patients will be tested for HIV I and II antibody, HBsAg, ~~hepatitis B core antibodies,~~ and anti HCV. Results of the assessments will not be entered into the study database. If a subject/patient is confirmed positive for any of these tests, the subject/patient will be referred for further examination, counseling, or treatment and is not eligible for the study.

*Purpose: Aligned the hemoglobinuria evaluation to Day -1 and Day 1 (not Day 0)*

The primary change occurs in Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)

Now reads: Under the Hemoglobinuria evaluation, added an 'X' at Day -1 and Day 1 and removed 'X' at Day 0

*Purpose: Aligned the coagulation sampling to every 2 weeks followed by once monthly starting at Day 84*

The primary change occurs in Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)

Added text: Under the Biochemistry, hematology, and coagulation assessment, added a cross-reference the appropriate footnote

Section(s) also containing this change:

- Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)
- Table 21: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Monthly Dosing (Cohort 2 and Cohort 3)

*Purpose: Removed reference to Cohort 1 for alignment within the protocol*

The primary change occurs in Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)

Now reads: After completing the 13 week dosing period, patients ~~in Cohort 1~~ may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC

Section(s) also containing this change:

- Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up)

*Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting*

These changes are not listed individually.

# ALN-CC5-001 Protocol Amendment 5

## Summary of Changes dated 12 June 2017

## A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

### Rationale for Protocol Amendment

The protocol is being amended primarily to revise the study follow-up period, with the objective of reducing the risks associated with long-term antibiotic exposure, while ensuring subject and patient safety. Per the current protocol, study participants administered ALN-CC5 receive prophylactic ciprofloxacin to minimize susceptibility to meningococcal infections during the follow-up period until their serum complement activity is within the normal reference range. To date, several study participants with near-normal complement activity have been required to receive long-term prophylactic ciprofloxacin.

To potentially balance the health risks of slightly reduced complement activity with the risks of long-term ciprofloxacin use, this protocol amendment will require that participants continue in follow-up until serum complement activity is within the normal reference range OR until the Safety Review Committee makes a recommendation on a case-by-case basis to discontinue follow-up and prophylactic ciprofloxacin treatment, whichever is sooner. The decision cannot be made until after completion of the last postdose follow-up visit.

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting, including administrative changes noted in Protocol Administrative Change #3 (dated 28 October 2016) are not detailed.

## Table 1: Protocol Amendment 5 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in the protocol amendment are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

*Purpose: Added an alternative threshold for discontinuation from study follow-up*

The primary change occurs in Section 3.1.1 Single Ascending Dose Phase (Part A)

Now reads: For subjects with serum complement activity below normal range at the last postdose follow up visit (Day 70), monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA **or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3.). The decision cannot be made until after completion of the last postdose follow-up visit.**

Section(s) also containing a similar change:

- Synopsis
- Table 1: Schedule of Assessments for Single-ascending Dose Cohorts (Part A)
- Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses
- Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)
- Table 15: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 13 Weekly Doses
- Table 16: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Once Every 2 Weeks Dosing
- Table 17: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Monthly Dosing
- Table 18: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing
- Table 19: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Monthly Dosing
- Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up)
- Section 1.9.3, Risk Mitigation Strategy
- Section 3.1.2, Multiple Ascending Dose Phase (Part B)
- Section 3.1.3, Multiple Dose Phase (Part C)
- Section 6.6, Randomization and Blinding
- Section 10.1.9, Prophylactic Antibiotic Administration and Compliance Check

*Purpose: To indicate that another purpose of the Safety Review Committee (SRC) Meetings is to determine whether a study participant may be discontinued from study follow-up*

The primary change occurs in Section 3.5.3 Timing and Purpose of Review Meetings

Added text: **To balance the health risks of slightly reduced complement activity with the risks of long-term ciprofloxacin use, the SRC will**

**also determine whether study follow-up and prophylactic ciprofloxacin treatment will be discontinued in subjects or patients with complement activity below the normal range. The decision cannot be made until after completion of the last postdose follow-up visit.**

*Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting[, including administrative changes, if appropriate]*

These changes are not listed individually.