Amendment 3

Protocol Title: A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism

Amgen Protocol Number AMG 416 20120360

Amendment Date: 17 October 2014

Rationale:

This document summarizes the changes to Protocol 20120360 in Amendment 3. This amendment adds a secondary endpoint based on efficacy and re-prioritizes the order of sequential statistical testing of secondary endpoints, based on the results of recently-concluded, phase 3, placebo-controlled studies 20120229 and 20120230, for which an indirect comparison was made to concluded phase 3, placebo-controlled studies of cinacalcet.
Description of Changes:

Section: Title Page

Add:

**Amendment 3 Date:** 17 October 2014

Section: Investigator’s Agreement

Replace:

30 August 2013

With:

17 October 2013

Section: Protocol Synopsis (Secondary Objectives)

Replace:

mean days of vomiting or nausea per week

With:

mean **number of** days of vomiting or nausea per week

Add:

**proportion of subjects with > 30% decrease in serum PTH from baseline**

Section: Protocol Synopsis (Hypothesis)

Replace:

mean days of vomiting or nausea per week

With:

mean **number of** days of vomiting or nausea per week

Add:

**by the proportion of subjects with > 30% decrease in serum PTH from baseline**
Section: Protocol Synopsis (Primary Endpoint)

Add:

(non-inferiority)

Section: Protocol Synopsis (Key Secondary Endpoint)

Replace:

- mean number of days of vomiting or nausea per week in the first 8 weeks
- achievement of a > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP

With:

- achievement of a > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
- achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
- mean number of days of vomiting or nausea per week in the first 8 weeks

Section: Protocol Synopsis (Statistical Considerations)

2nd paragraph
Replace:

If this criterion is met, the 2 key secondary endpoints will be tested sequentially

With:

If this criterion is met, the 3 key secondary endpoints will be tested sequentially

2nd paragraph
Replace:

If both of the key secondary endpoints meet statistical significance,

With:

If all 3 of the key secondary endpoints meet statistical significance

Section: Study Glossary

Add:

CMH Cochran-Mantel-Haenszel
Section 1.2: Secondary

Replace:

mean days of vomiting or nausea per week

With:

mean number of days of vomiting or nausea per week

Add:

proportion of subjects with > 30% decrease in serum PTH from baseline

Section 2.4: Clinical Hypothesis

2nd paragraph

Replace:

Treatment with AMG 416 is superior to treatment with cinacalcet as measured by the mean days of vomiting or nausea per week in the first 8 weeks, and by the proportion of subjects with > 50% decrease in pre-dialysis serum PTH from baseline.

With:

Treatment with AMG 416 is superior to treatment with cinacalcet as measured by the proportion of subjects with > 50% decrease in pre-dialysis serum PTH from baseline, by the proportion of subjects with > 30% decrease in pre-dialysis serum PTH from baseline, and by the mean number of days of vomiting or nausea per week in the first 8 weeks.

Section 10.1.1: Study Endpoints

Replace:

Primary Endpoint

Achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH level during the efficacy assessment phase (EAP).

With:

Achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH level during the efficacy assessment phase (EAP) (**non-inferiority**).
Replace:

**Key Secondary Endpoints**

- mean number of days of vomiting or nausea per week in the first 8 weeks
- achievement of a > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP

With:

**Key Secondary Endpoints**

- achievement of a > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
- achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
- mean number of days of vomiting or nausea per week in the first 8 weeks

**Section 10.2: Sample Size Considerations**

4th paragraph

Add:

**For the test of superiority based on the key secondary endpoint of achievement of >30% reduction from baseline in mean pre-dialysis PTH during the EAP, 300 subjects per treatment group will provide more than 90% power to detect a statistically significant difference between the treatment groups at the 5% significance level (two-sided), assuming a 68% and 57% response rate in subjects randomized to AMG 416 and cinacalcet, respectively.**

4th paragraph

Replace:

The assumption of a 45% response rate at 6 months in the cinacalcet group is based on results generated from the Amgen EVOLVE trial in the subset of subjects who had a baseline PTH > 500 pg/mL, and the assumption of a 60% response rate in the AMG 416 group is based on data observed in subjects with baseline PTH > 500 pg/mL in the AMG 416 open-label phase 2 study.
With:

The assumption of a 45% and 57% response rate at 6 months in the cinacalcet group for >50% and >30% reduction, respectively, in mean pre-dialysis PTH during the EAP is based on results generated from the Amgen EVOLVE trial in the subset of subjects who had a baseline PTH > 500 pg/mL, and the assumption of a 60% and 68% response rate in the AMG 416 group for >50% and >30% reduction in mean pre-dialysis PTH during the EAP is based on data observed in subjects with baseline PTH > 500 pg/mL in the AMG 416 open-label phase 2 study.

Section: 10.5.1 General Considerations

1st paragraph

Replace:

If this criterion is met, the 2 key secondary endpoints will be tested sequentially.

With:

If this criterion is met, the 3 key secondary endpoints will be tested sequentially.

1st paragraph

Replace:

If both key secondary endpoints meet statistical significance,

With:

If all 3 key secondary endpoints are statistically significance,

Section: 10.5.3 Key Secondary Efficacy Endpoints

Replace:

two key secondary efficacy endpoints

With:

3 key secondary efficacy endpoints
Replace:

- mean number of days of vomiting or nausea per week in the first 8 weeks
- achievement of > 50% reduction in mean pre-dialysis serum PTH from baseline during the EAP

With:

- achievement of > 50% reduction in mean pre-dialysis serum PTH from baseline during the EAP (superiority)
- achievement of > 30% reduction in mean pre-dialysis serum PTH from baseline during the EAP (superiority)
- mean number of days of vomiting or nausea per week in the first 8 weeks

Replace:

The endpoint of achievement of > 50% reduction in mean pre-dialysis serum PTH from baseline during the EAP will be analyzed using the CMH test stratified by the randomization stratification factors.

With:

The endpoint of achievement of > 50% and > 30% reduction in mean pre-dialysis serum PTH from baseline during the EAP will be analyzed using the CMH test stratified by the randomization stratification factors.

Add:

In these analyses, subjects will be considered as not achieving the endpoint if they do not have PTH data during the EAP (ie, nonresponder imputation).

Section: 10.5.4 Other Secondary Efficacy Endpoints

Replace:

The following secondary endpoints will be evaluated if both of the above key secondary endpoints are considered statistically significant

With:

The following secondary endpoints will be evaluated if all of the above key secondary endpoints are considered statistically significant