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RESEARCH**

APPLICATION NUMBER:

202799Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202799/Peginesatide (Omontys)

PMR Description:

RCT “peri-dialysis”

Conduct a prospective randomized, controlled trial (RCT) of Omontys versus a U.S. marketed ESA in anemic patients with chronic kidney disease (CKD) who are in the time interval around the initiation of dialysis (defined as incident dialysis patients for this purpose) and at least a reasonable proportion (to be decided during the protocol development) who have not received an ESA previously. Continue the trial through the stabilization period on dialysis and the maintenance period on dialysis sufficient to assess the comparative safety (and efficacy) of Omontys using a primary outcome of Major Adverse Cardiovascular Events (MACE) with supporting safety evidence including SAEs, AEs leading to discontinuation, and study/drug discontinuations. Use a blinded independent panel to adjudicate potential MACE events. Stratify randomization for important adverse cardiovascular risk factors. Justify the sample size and risk ratio chosen to evaluate the MACE endpoint. Justify the choice of active control comparator and dosing plan for both treatment arms. Assess transfusion use and identify the reasons that transfusions are given (e.g., active bleeding, pre-op for a procedure, and symptoms). Submit the protocol for FDA review and FDA concurrence before beginning enrollment. Submit a labeling supplement with the final clinical study report and complete raw datasets for this PMR trial.

PMR Schedule Milestones:

Preliminary protocol submission:

09/2012

Final Protocol Submission:

03/2013

Trial Completion:

08/2018

Final Report Submission:

08/2019

Other: _____

N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor has conducted two trials in patients with CKD not on dialysis (NOD) in which the safety of peginesatide appears numerically worse than that of the active control comparator, Darbepoetin. While two trials of a total of approximately 1000 patients with CKD on dialysis and on a stabilized ESA therapy show similar safety to that of an Epoetin comparator regimen, there remains some residual uncertainty of the true safety of peginesatide, and the safety outcomes are not likely to be able to be assessed further in the indicated population (CKD on dialysis), considering that the drug is to be approved for this on-dialysis indication. Thus, the need to study the safety of the drug in the CKD NOD population that is soon expected to begin dialysis and is in need of initiating ESA therapy. Additional safety information is needed in the pre-dialysis, peri-dialysis, and longer term exposure on dialysis populations/

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

While the benefit-risk profile of peginesatide appears favorable in the CKD on dialysis population as studied in the trials, the safety of Peginesatide in patients with CKD not on dialysis is uncertain and may influence future decisions for all ESA-acting drugs. However, some patients with CKD NOD may benefit from the availability of this drug (e.g. those with PRCA or hypersensitivity reactions to currently approved ESAs).
This trial is necessary to provide a better overall safety description.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a prospective randomized, controlled trial (RCT) of Omontys versus a U.S. marketed ESA in anemic patients with chronic kidney disease (CKD) who are in the time interval around the initiation of dialysis (defined as incident dialysis patients for this purpose) and at least a reasonable proportion (to be decided during the protocol development) who have not received an ESA previously. Continue the trial through the stabilization period on dialysis and the maintenance period on dialysis sufficient to assess the comparative safety (and efficacy) of Omontys using a primary outcome of Major Adverse Cardiovascular Events (MACE) with supporting safety evidence including SAEs, AEs leading to discontinuation, and study/drug discontinuations. Use a blinded independent panel to adjudicate potential MACE events. Stratify randomization for important adverse cardiovascular risk factors. Justify the sample size and risk ratio chosen to evaluate the MACE endpoint. Justify the choice of active control comparator and dosing plan for both treatment arms. Assess transfusion use and identify the reasons that transfusions are given (e.g., active bleeding, pre-op for a procedure, and symptoms).

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

EBLA ALI IBRAHIM
03/28/2012

ROBERT C KANE
03/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 202799
Product Name: Peginesatide (Omontys)

PMR/PMC Description: Phase 3 open-label follow-up extension study to evaluate the safety, tolerability and efficacy of peginesatide for the maintenance treatment of anemia due to CKD in pediatric subjects on dialysis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 12/2017
Trial Completion: 06/2026
Final Report Submission: 01/2027
Other: None

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 Other

Conduct a Phase 3 open-label, single arm, follow-up study to evaluate the safety, tolerability and efficacy of peginesatide for the maintenance treatment of anemia in children with CKD on hemodialysis. Patients who complete the initial Phase 3 study (see PMC #3) should be enrolled in this study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has conducted two trials of peginesatide versus an Epoetin comparator regimen (epoetin alfa or beta) in a total of 1066 adult patients with CKD on dialysis (OD) whose hemoglobin levels were stabilized on ESA therapy prior to initiating peginesatide or study comparator. The results of the studies demonstrated similar safety and efficacy of peginesatide to that of the Epoetin comparator regimen. The goal of this study is to provide additional safety and clinical outcome follow-up information on the pediatric population studied.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - X Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - X Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

EBLA ALI IBRAHIM
03/28/2012

ANDREW DMYTRIJUK
03/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 202799
Product Name: Peginesatide (Omontys)

PMR/PMC Description: Phase 3 randomized, active-controlled, open-label, multicenter study to evaluate the efficacy and safety of peginesatide for the maintenance treatment of anemia due to chronic kidney disease (CKD) in pediatric patients on dialysis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/2017
Trial Completion: 06/2025
Final Report Submission: 01/2026
Other: None

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Conduct a Phase 3, randomized, active-controlled, open-label, multicenter, parallel group study to evaluate the efficacy and safety of peginesatide for the treatment of anemia due to chronic kidney disease (CKD) in pediatric patients from 1 year to < 18 years of age who are currently receiving ESA treatment and are on dialysis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has conducted two trials of peginesatide versus an Epoetin comparator regimen (epoetin alfa or beta) in a total of 1066 adult patients with CKD on dialysis (OD) whose hemoglobin levels were stabilized on ESA therapy prior to initiating peginesatide or study comparator. The results of the studies demonstrated similar safety and efficacy of peginesatide to that of the Epoetin comparator regimen. The goal of this study is to evaluate efficacy of peginesatide and provide some comparative safety information in this pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

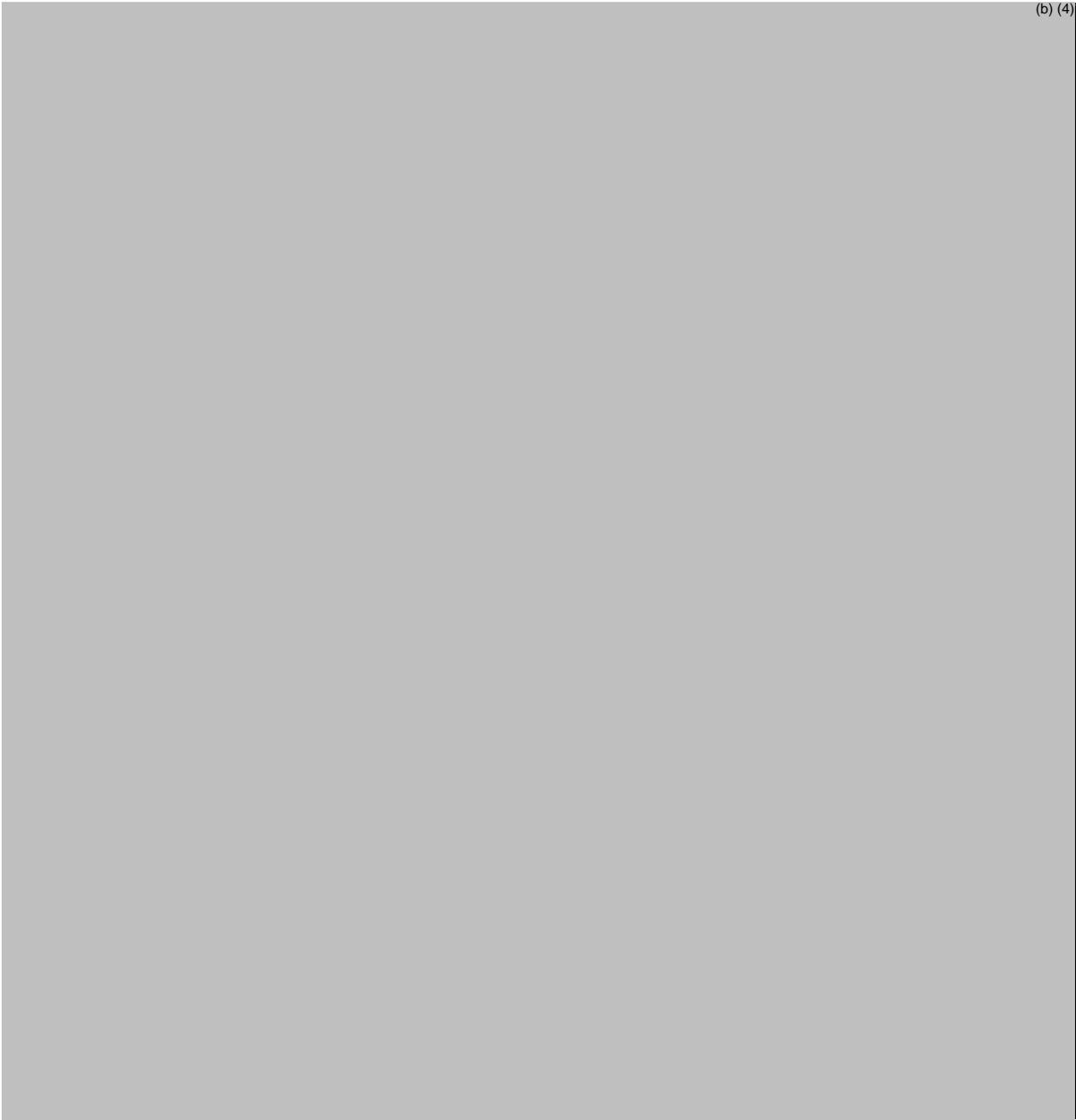
- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.



Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

X Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

EBLA ALI IBRAHIM
03/28/2012

ANDREW DMYTRIJUK
03/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 202799
Product Name: Peginesatide (Omontys)

PMR/PMC Description: Phase 2 open-label follow-up study to evaluate the safety, tolerability and efficacy of peginesatide for the maintenance treatment of anemia due to chronic kidney disease (CKD) in pediatric patients who are on hemodialysis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 09/2013
Trial Completion: 10/2016
Final Report Submission: 05/2017
Other: None

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 Other

Conduct a Phase 2 open-label, single arm, follow-up study to evaluate the safety, tolerability and efficacy of peginesatide for the maintenance treatment of anemia due to CKD in children with CKD on hemodialysis. Patients who complete the initial pharmacokinetic study (see PMC #1) should be enrolled in this study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has conducted two trials of peginesatide versus an Epoetin comparator regimen (epoetin alfa or beta) in a total of 1066 adult patients with CKD on dialysis (OD) whose hemoglobin levels were stabilized on ESA therapy prior to initiating peginesatide or study comparator. The results of the studies demonstrated similar safety and efficacy of peginesatide to that of the Epoetin comparator regimen. The goal of this study is to provide additional safety and clinical outcome follow-up information on the pediatric population studied.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - X Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - X Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

EBLA ALI IBRAHIM
03/28/2012

ANDREW DMYTRIJUK
03/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 202799
Product Name: Peginesatide (Omontys)

PMR/PMC Description: Safety, Efficacy and Pharmacokinetics of Peginesatide In Pediatric Patients with Anemia Due to Chronic Kidney Disease (CKD) Who Are on Hemodialysis.

PMR/PMC Schedule Milestones: Final Protocol Submission: 03/2013
Trial Completion: 05/2016
Final Report Submission: 12/2016
Other: None

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
 Life-threatening condition
 Long-term data needed
 Only feasible to conduct post-approval
 Prior clinical experience indicates safety
 Small subpopulation affected
 Theoretical concern
 Other

Conduct an open-label study to evaluate the safety, efficacy, and pharmacokinetics of peginesatide for the maintenance treatment of anemia due to chronic kidney disease (CKD) in pediatric patients who are on hemodialysis and who are already receiving erythropoiesis-stimulating agent (ESA) therapy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has conducted two trials of peginesatide versus an Epoetin comparator regimen (epoetin alfa or beta) in a total of 1066 adult patients with CKD on dialysis (OD) whose hemoglobin levels were stabilized on ESA therapy prior to initiating peginesatide or study comparator. The results of the studies demonstrated similar safety and efficacy of peginesatide to that of the Epoetin comparator regimen. This study should provide information on safety, effectiveness and dosing in pediatric population being studied.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- X Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

X Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202799/Peginesatide (Omontys)

PMR Description: Post marketing comparative observational safety study of dialysis patients (both incident and prevalent) receiving Omontys versus a U.S. marketed ESA to assess safety of long term use. Provide the protocol and analysis plan for FDA review and concurrence prior to commencing the study. The between-group comparison must balance by site and by patient characteristics that are important for cardiovascular, stroke and mortality outcome. Pre-specify the study questions, the testable hypothesis and analysis plan.

PMR Schedule Milestones:	Preliminary Protocol Submission no later than:	<u>08/2012</u>
	Final Protocol Submission:	<u>02/2013</u>
	Study Completion:	<u>07/2016</u>
	Final Report Submission:	<u>03/2018</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

While the benefit-risk profile of peginesatide appears favorable in the CKD on dialysis population as studied in the trials, the safety of Peginesatide in patients with CKD not on dialysis is uncertain and may influence future decisions for all ESA-acting drugs. However, some patients with CKD NOD may benefit from the availability of this drug (e.g. those with PRCA or hypersensitivity reactions to currently approved ESAs).

This monitoring plan is necessary to provide a better overall safety description.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

See above.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

EBLA ALI IBRAHIM
03/28/2012

ROBERT C KANE
03/28/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: February 28, 2012
To: Ebla Ali Ibrahim, Regulatory Health Project Manager, DHP
From: Adora Ndu, Regulatory Review Officer, DDTCP
Subject: NDA 202799
DDTCP comments for Omontys (peginesatide) injection
Medication Guide, Instructions for Use (2)

On July 21 2011, DDTCP received a consult request from DHP to review the proposed Medication Guide, Instructions for Use for the pre-filled syringe, and Instructions for Use for vials for Omontys (peginesatide) injection.

DDTCP has reviewed the proposed labeling using the following versions of the proposed labels received on February 27, 2012:

- Clean copy peginesatide DMPP MG Review.doc
- Clean copy IFU (Pre-filled syringe) DMPP.doc
- Clean copy OMONTYS IFU (vial).doc

After review of the proposed labeling, DDTCP offers the following comments. If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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/s/

ADORA NDU
03/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Office of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 24, 2012

To: Ann Farrell, MD, Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Medication Guide and
Instructions for Use)

Drug Name (established name): OMONTYS (peginesatide acetate)

Dosage Form: injection for intravenous or subcutaneous use

Application Type/Number: NDA 202799

Applicant: Affymax Inc.

1 INTRODUCTION

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Omontys (peginesatide acetate) injection for intravenous or subcutaneous use.

On May 21, 2011, Affymax Inc., submitted original New Drug Application (NDA) 202799 for Omontys (peginesatide acetate) injection for intravenous or subcutaneous use for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

2 MATERIAL REVIEWED

- Draft Omontys (peginesatide acetate) injection for intravenous or subcutaneous use Medication Guide (MG) and Instructions for Use (IFU) received May 23, 2011, and revised by the review division and received by DMPP on February 6, 2012.
- Draft Omontys (peginesatide acetate) injection for intravenous or subcutaneous use Prescribing Information (PI) received May 23, 2012, and revised by the review division and received by DMPP on February 15, 2012.
- Approved Epogen (epoetin alfa) injection for intravenous or subcutaneous use Medication Guide (MG) and Instructions for Use (IFU) dated June 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFUs document using the Verdana font, size 11.

In our review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the prescribing information (PI)

- ensured that the MG and IFUs are consistent with the approved comparator label where applicable
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured the MG and IFUs are consistent with the approved comparator labeling where applicable.
- ensured that the MG, meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG and IFUs are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
02/24/2012

BARBARA A FULLER
02/24/2012

LASHAWN M GRIFFITHS
02/24/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: 1/31/2012

To: Ebla Ali Ibrahim, Regulatory Project Manager
Trinh Scott, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 202799,
Peginesatide

In response to your labeling consult request on July 21, 2011, we have reviewed the draft Package Insert for Peginesatide and offer the following comments. Note that these comments are based upon the January 25, 2012 version of the label.

Section	Statement	Comment
<div style="background-color: #cccccc; width: 100%; height: 100%;"></div>	<div style="background-color: #cccccc; width: 100%; height: 100%;"></div>	<p>We recommend (b) (4)</p> <div style="background-color: #cccccc; width: 100%; height: 100%;"></div> <p>This information seems out of place and should be moved to where clinical data is shared.</p>
<div style="background-color: #cccccc; width: 100%; height: 100%;"></div>	<div style="background-color: #cccccc; width: 100%; height: 100%;"></div>	<div style="background-color: #cccccc; width: 100%; height: 100%;"></div>

<p>(b) (4)</p>		
<p>(b) (4)</p>		<p>This text is inconsistent with other sections of the PI. (b) (4)</p>
<p>(b) (4)</p>		<p>We recommend revising this section by adding in the word “endogenous” to describe erythropoietin. This will prevent any false interpretations or implied superiority to other ESA products.</p> <p>(b) (4)</p>

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/s/

JAMES S DVORSKY
01/31/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 23, 2011

Reviewer(s): Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, Pharm.D., BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Omontys (Peginesatide) Injection
Pre-filled Syringe: 1 mg/0.5 mL, 2 mg/0.5 mL,
3 mg/0.5 mL, 4 mg/0.5 mL, 6 mg/0.5 mL

Single-Dose Vial: 2 mg/0.5 mL, 3 mg/0.5 mL,
4 mg/0.5 mL, 5 mg/0.5 mL, 6 mg/0.5 mL

Multi-Use Vials: 10 mg/mL and 20 mg/2 mL (10 mg/mL)

Application Type/Number: NDA 202799

Applicant/sponsor: Takeda Pharmaceuticals North America, Inc.

OSE RCM #: 2011-2388

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1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's (DMEPA) evaluation of the proposed packaging, labels, and labeling of Omontys (Peginesatide) Injection for vulnerabilities that may lead to medication errors. This review responds to a June 24, 2011 request from the Division of Hematology Products for DMEPA.

1.1 PRODUCT INFORMATION

Omontys (Peginesatide) Injection is an erythropoiesis-stimulating agent (ESA) that is indicated for the treatment of anemia associated with chronic renal failure in adult patients on dialysis. Omontys will not be indicated for the treatment of anemia in chronic kidney failure patients not on dialysis or for treatment of anemia due to cancer chemotherapy. Omontys will be supplied in single-dose vials, multi-dose vials, and prefilled syringes containing the following strengths:

- Single-Dose Vials: 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL.
- Multi-Dose Vials: 10 mg/mL and 20 mg/2 mL (10 mg/mL)
- Pre-filled Syringes: 1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL. The Applicant proposes to use a (b) (4)

Omontys is dosed at 0.04 mg/kg to 0.08 mg/kg subcutaneously or intravenously once a month for treatment-naïve patients and between 2 mg and 20 mg subcutaneously or intravenously once a month for patients previously treated with Epoetin Alfa or Darbepoetin Alfa. Omontys vials or prefilled syringes should be stored between 2°C and 8°C (36°F to 46°F) and protected from light.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Labels submitted on May 27, 2011
- Carton Labeling submitted on May 27, 2011
- Insert Labeling and Instructions for Use submitted on May 27, 2011

Additionally, since Omontys is an erythropoiesis-stimulating agent (ESA) similar to currently marketed ESAs, Epogen (Epoetin Alfa) and Aranesp (Darbepoetin Alfa), we reviewed a recent AERS search conducted on August 1, 2011, in OSE Review #2011-2577 to identify relevant medication errors involving Epogen and Aranesp because these errors may be indicative of the errors that may occur with Omontys.

The OSE Review #2011-2577 AERS search used the following search terms: active ingredients "epoetin alfa" and "darbepoetin alfa", trade name "Epogen", "Procrit", and "Aranesp" and verbatim terms "Epog%", "Procrit%", and "Aranes%". The reaction terms used were the MedDRA High Level Group

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame of the search was limited to August 1, 2008 until August 1, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label, labeling, or packaging of the product, the case was considered pertinent to this review.

Reports excluded from the case series include cases that did not describe a medication error (i.e., adverse events unrelated to a medication error, medication error due to another concomitant drug product). Additionally, medication error cases not applicable to this review (i.e., wrong strength, wrong drug, product quality issue, or wrong frequency of administration) were placed in Appendix D. See Appendices E and F for ISR #s and detailed narratives of all cases.

Following exclusions, OSE Review #2011-2577 evaluated a total of 21 cases relevant to this review. Nineteen cases from the Epogen/Procrit AERS search and two cases from the Aranesp search were identified. The twenty one cases were further categorized into the following medication error types:

- Wrong Route (n=19)

Eighteen (n=18) Epogen/Procrit and one (n=1) Aranesp case described wrong route of administration errors. All 19 cases described intramuscular administration rather than subcutaneous or intravenous. One case reported the container closure system involved (vial). The outcomes that were reported involved irritation at the site of administration.

- Wrong Technique (n=1)

One case (n=1) of Epogen/Procrit wrong technique involved the shaking of the vial prior to administration. No outcome was reported.

- Device Malfunction (n=1)

One case involving Aranesp (n=1) described device malfunction. The needle on the Aranesp prefilled syringe was completely detached and floating in the syringe. No outcome was reported.

3 MEDICATION ERROR EVALUATION AND DISCUSSION OF DEFICIENCIES IDENTIFIED

The Applicant plans to market three packaging configurations for the proposed Peginesatide Injection. The configurations proposed are single-dose vials, multi-dose vials, and single-dose prefilled syringes. Single-dose vials and single-dose prefilled syringes can be used in healthcare clinics and by patients at home. Multi-use vials can be used only in healthcare clinics.

The proposed strengths are appropriate for the intended dosing provided in the *Dosage and Administration* Section of the prescribing information labeling.

However, we identified the following areas of vulnerability with the proposed container closure systems, labels, and labeling.

3.1 SINGLE-USE PREFILLED SYRINGE

The Applicant indicates that the syringes for this product will a

(b) (4)

DMEPA is

aware that this type of pre-filled syringe (b) (4) has mechanical problems causing syringe leakage, needle separation, and needle breakage with multiple marketed products (b) (4). Syringe leakage and needle separation have caused medication errors such as underdose, overdose, and dose omissions. (b) (4)

As a result, since other packaging configurations for this product are available such as single dose and multi-dose vials, we do not recommend the approval of pre-filled syringe that uses (b) (4) until the Applicant conducts thorough extensive mechanical testing and human factors studies.

DMEPA notified the Division and ONDQA of these issues and requested CDRH consult via email on August 31, 2011.

3.2 PRESCRIBING INFORMATION LABELING

The prescribing information labeling uses dangerous abbreviations (i.e., IV and SC), symbols (i.e., '<' and '≥'), and trailing zeros to express strength (i.e., 10 mg/1.0 mL and 20 mg/2.0 mL). These dangerous abbreviations, symbols, and dose designations appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations² because all of them have been misinterpreted. As a part of the campaign to reduce medication errors related to error prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that includes the use of error-prone abbreviations, symbols, and dose designations. Thus, these abbreviations, symbols, and dose designations should be revised.

Additionally, Section 2.3, *Monitoring and Dose Adjustment*, is poorly organized, cumbersome, and hard to follow because information regarding monitoring, dose adjustments, and dose omission is clustered together and lacks specific sequence. This may lead to confusion and medication errors. Thus, this section requires revising for clarity.

3.3 INSTRUCTIONS FOR USE

The clarity and prominence of important information presented in the Instructions for Use (IFU) labeling can be improved. Several figures that should aid patient comprehension of the IFU better are unclear, confusing, and lack details (e.g., Figure 1, Figure 5, and Figure 11 for Prefilled Syringe IFU). Additionally, some sections do not contain any illustrations to help with IFU comprehension (e.g., how to remove a needle from the venous port). Furthermore, some of the important information such as storage environment is omitted. As a result, lack of clarity and prominence of the information may lead to confusion and medication errors. Thus, the Instructions for Use should be revised to provide better clarity and prominence of the information.

3.4 MULTIPLE DOSE VIAL LABELS AND CARTON LABELING

Both multi-use vial labels and carton labeling containing 10 mg/mL and 20 mg/mL contain (b) (4)

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² Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

3.5 VIAL AND PRE-FILLED SYRINGE LABELS

The vial labels can be improved to help differentiate among different strengths. The colored blocks containing the strength of the product are placed on the side panel of the labels. However, if the product is placed on the shelf facing forward, the side panel with the different-colored blocks and strength will not be seen. Thus, selection of the wrong strength may occur. Thus, the labels should be revised to relocate the colored block with the strength to the principle display panel to ensure sufficient differentiation among the different available strength.

Additionally, the route of administration is not present on the label. This is an important and required piece of information. However, less important information such as manufacturer's information is placed on the principle display panel. DMEPA identified several medication errors involving wrong route of administration with similar products, Aranesp and Epogen. Thus, placing the correct route of administration on the labels is important to avoid this type of error.

Furthermore, since the single-dose vials and pre-filled syringes do not contain preservatives and should not be re-used and multi-dose vials contain preservatives and can be used several times, it is important to emphasize this difference on the labels in order to avoid administration of a preservative-free product several times and compromise the sterility of the product.

3.6 CARTON LABELING INCLUDING PRE-FILLED SYRINGE TRAY LABELING

All carton labeling employs a two-colored triangle containing the strength of the product. Although the upper, smaller portion of the triangle contains different colors, the lower, bigger portion of the triangle is a red-brown color used on all strengths of the product. Thus, all of the Peginesatide Injection's carton and tray labeling look similar. The insufficient difference in the background color used to distinguish between different strengths may lead to selection errors and administration of the wrong strength. Thus, the carton and tray labeling require revisions to highlight different strengths of the product.

3.7 SINGLE USE VIALS AND PREFILLED SYRINGE

The single-use vials and prefilled syringe state "single dose"; thus, implying that the entire contents of the vial or the syringe should be administered at one time. However, since the package insert labeling expresses Omontys's dose as initial therapy in milligrams per kilogram (i.e., 0.04 mg/kg to 0.08 mg/kg), the dose may not necessarily be rounded up or down to the entire vial. Thus, part of the vial contents may be administered. As a result, the vial and syringe should contain a statement "single-use" instead of "single dose" to emphasize that the vial or syringe should not be used more than one time.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels, labeling, and packaging introduce vulnerability that can lead to medication errors. The identified deficiencies should be revised prior to approval. Section 4.1 *Comments to the Division* contains our recommendations related to the device (i.e., prefilled syringes), prescribing

information labeling, and Instructions for Use (IFU). Section 4.2 *Comments to the Applicant* contains our recommendations related to the vial and pre-filled syringe labels, as well as carton and tray labeling.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

4.1 COMMENTS TO THE DIVISION

A. General

1. The Applicant indicates that the syringe for this product will be a (b) (4). DMEPA is aware that this type of pre-filled syringe (b) (4) has mechanical problems causing syringe leakage, needle separation, and needle breakage with multiple marketed products (b) (4). Syringe leakage and needle separation have caused medication errors such as underdose, overdose, and dose omissions. (b) (4). As a result, since other packaging configurations for this product are available such as single dose and multi-dose vials, we do not recommend the approval of pre-filled syringe that uses (b) (4) until the Applicant conducts thorough extensive mechanical testing and human factors studies.

DMEPA notified the Division and ONDQA of these issues and requested CDRH consult via email on August 31, 2011.

2. As a part of the campaign to reduce medication errors related to error prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that includes the use of error-prone abbreviations, symbols, and dose designations. Thus, we recommend the following revisions be implemented in support of this campaign.
 - Revise all instances of the abbreviation ‘IV’ to read ‘intravenously’. The abbreviation ‘IV’ is a dangerous abbreviation that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations³ because the abbreviation has been confused with the abbreviations ‘IM’ (intramuscular), ‘IU’ (international units), and ‘IN’(intranasal).
 - Revise all instances of the abbreviation ‘SC’ to read ‘subcutaneously’. This abbreviation is a dangerous abbreviation that appears on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because this abbreviation has been confused with the abbreviation ‘SL’ (sublingually).
 - Revise all instances of the symbol ‘<’ and ‘≥’ to read “less than” and “equal or greater than.” The symbols ‘<’ and ‘>’ are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended.

*** This document contains proprietary information that should not be released to the public

³ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

- Delete trailing zeros throughout the package insert. Trailing zeros have led to misinterpretations of numbers. For example, 10 mg/1.0 mL or 20 mg/2.0 mL may be misinterpreted as 10 mg/10 mL or 20 mg/20 mL. Thus, we request you revise 10 mg/1.0 mL and 20 mg/2.0 mL to read as 10 mg/mL and 20 mg/2 mL.

B. Prescribing Information Labeling

1. *Dosage and Administration* Section, *Highlights of Prescribing Information* and *Full Prescribing Information*

- Please specify whether dosing is based on actual body weight or ideal body weight.
- To improve clarity of the sentence, include the units of measure after every number in *Dosage and Administration* Section. Thus, revise the phrases “0.04 to 0.08 mg/kg” and “10 to 12 g/dL” to state “0.04 mg/kg to...” and “10 g/dL to 12 g/dL”.
- We recommend deleting the words (b) (4) from expression of the weight as this phrase is redundant and occupies space. Thus, revise the phrase (b) (4) to read “0.04 mg/kg to 0.08 mg/kg”.

2. Section 2.3, *Monitoring and Dose Adjustment*

The presentation of the information throughout this Section is disorganized and hard to follow because information regarding monitoring, dose adjustments, and dose omission is clustered together, lacks sequence, and is presented in paragraph format rather than bullet point format. Thus, we request this section be revised to include underlined separate subheadings for monitoring, dose adjustment, and missed dose. Additionally, complicated dose adjustment information should be simplified by using bullet points, tables, or some other means. We recommend the following:

Monitoring

When Omontys therapy is initiated or the dose adjusted, the hemoglobin should be monitored every 2 weeks until stabilized, and at least monthly thereafter to achieve and maintain hemoglobin levels within the range of 10 g/dL to 12 g/dL. A significant change in hemoglobin may not be observed for several weeks after the dose is adjusted.

Other ESAs should not be administered while a patient is receiving Omontys. If another ESA is administered during Omontys therapy, consideration should be given to the hemoglobin and expected duration of pharmacodynamic effect of the non- Omontys ESA with regards to the timing of the next Omontys dose.

Dose Adjustment

- *If hemoglobin is not within the recommended range of 10 g/dL to 12 g/dL, the dose may be increased or decreased by approximately 25%, as needed. If needed, dose adjustments should be made only once a month.*
- *During Omontys therapy, if the increase in hemoglobin is greater than 1 g/dL in the 2 weeks prior to the next dose or greater than 2 g/dL in 4 weeks, the next monthly dose of Omontys should be reduced by approximately 25%.*
- *If the hemoglobin is increasing and approaching 12 g/dL or exceeds 12 g/dL, the dose should be reduced by approximately 25% and/or withheld until the hemoglobin begins to decrease. After a dose has been withheld and once the hemoglobin begins to decrease, Omontys may be restarted at a dose approximately 25% below the previously administered dose.*

For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate Omontys dose titrations over a 12-week period:

- Do not administer higher or more frequent Omontys doses. Use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent red blood cell (RBC) transfusions.
- Evaluate and treat for other causes of anemia.
- Thereafter, continue to monitor the hemoglobin level and if responsiveness improves, make [TRADE NAME] dose adjustments as described in this section. If responsiveness does not improve and the patient needs recurrent RBC transfusions, discontinue [TRADE NAME] and evaluate potential causes [see Warnings and Precautions (5.5, 5.6, 5.9)].

For patients on Omontys as initial therapy:

- If the increase in hemoglobin is less than 1 g/dL over the initial 4 weeks of treatment and iron stores are adequate or if the hemoglobin is less than 10 g/dL, the dose of Omontys may be increased by approximately 25% [see Warnings and Precautions (5.9)].
- If the hemoglobin is less than 10 g/dL but the increase in hemoglobin is greater than 1 g/dL in 2 weeks prior to the next dose or greater than 2 g/dL in 4 weeks, consideration should be given to reducing the next dose by approximately 25%.

Missed Dose

If a dose of [TRADE NAME] is missed, administer the missed dose as soon as possible and restart [TRADE NAME] at the prescribed once monthly dosing frequency.

[REDACTED] (b) (4)

[REDACTED] . Thus, revising this statement to make a positive one may help minimize the wrong technique errors.

C. Instructions for Use (IFU) for Single-Use Vial

1. [REDACTED] (b) (4)

We recommended adding a statement regarding storage of the product because this is an important piece of information for the correct use of the product. Thus, revise as follows:

6. Store Omontys in the refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.

2. [REDACTED] (b) (4)

Revise step 4 to include the statement after the first sentence that reads “Throw vial away after one use even if there is medicine left in the vial.” We recommend addition of this statement to emphasize that this is a single use vial.

3. *Preparing the Dose of Omontys* Section

- Revise step 1 to add a statement after the first sentence that reads “Leave the rubber stopper on the vial”. We recommend an addition of this statement to ensure that patients do not open and discard the rubber stopper.
- Revise step 8 to add that the dose should be measured in milliliters to ensure patients inject the correct dose. Thus, revise the last statement to read “Slowly pull back the plunger to fill

the syringe with Omontys liquid to the line on the syringe that matches the dose in milliliters (mL) your healthcare provider has given you.

4. *Selecting and Preparing the Injection Site, Subcutaneous Route Section*

- a. Revise Figure 13 to improve the visibility of the injection site intended for outer area of the upper arms. Currently, the image of the intended injection site of for outer area of the upper arms is not prominent, which may lead to wrong route of administration errors.
- b. Revise Step 7 to include the first statement that reads [REDACTED] ^{(b) (4)}
[REDACTED] We recommend inclusion of this statement to help avoid needle sticks after administration of the injection by the patient or caregiver.

5. *Selecting and Preparing the Injection Site, Intravenous Route Section*

We recommend bolding the statement “If you are peritoneal dialysis patient, do NOT administer Omontys through peritoneal dialysis catheter”. This information is important to help avoid wrong route errors.

D. Instructions for Use (IFU) for Prefilled Syringe

1. See Sections C.1 and C.5 and revise this IFU accordingly.

2. *Setting Up for an Injection Section*

The image of the pre-filled syringe in Figure 1 is unclear and confusing, because it is small and it is difficult to see which part of the syringe is labeled as “Needle Guard”. Additionally, the barrel of the syringe is not labeled, even though the IFU refers to the barrel of the syringe in Step 1.a of the *Preparing the Dose of Omontys* Section. Thus, we recommend revising the image of the pre-filled syringe to provide a more prominent, clear image with clear labels of the needle guard and syringe barrel.

3. *Selecting and Preparing the Injection Site, Subcutaneous Route Section*

- a. Revise Figure 5 to improve the visibility of the injection site intended for outer area of the upper arms. Currently, the image of the intended injection site of for outer area of the upper arms is not prominent, which may lead to wrong route of administration errors.
- b. The image in Figure 11 does not match the description in Step 6 because according to this step the plunger should be already released when the entire needle is guarded. Thus, we recommend revising Figure 11 to include two images: 1) the removal of the needle from the skin and the plunger is still pressed and 2) the plunger is released and the needle is guarded by the needle guard.

4. *Selecting and preparing the Injection Site, Intravenous Route Section.*

Step 3 does not contain any images to illustrate the process of removing needle from the venous port and releasing the plunger. Thus, to improve comprehension of this step, we recommend an addition of two images: 1) the removal of the syringe from the venous port without releasing the plunger and 2) the plunger is released and the needle is guarded by the needle guard.

4.1 COMMENTS TO THE APPLICANT

A. (b) (4) Vial Labels (10 mg/mL and 20 mg/2 mL)

1. (b) (4)
In this case the 10 mg vial may be read as 20 mg vial and vice versa; thus, leading to overdoses and underdoses. Revise accordingly.
2. (b) (4)
This information is included in the total drug content statement.
3. Relocate or also include the strength with the background colored block to the principle display panel. If placed on the shelf with the principle display panel facing forward, the side panel with the strength and different background colored blocks will not be seen because this information can only be seen from a side.
4. Add the route of administration “For Intravenous or Subcutaneous Use Only” to the principle display panel to help prevent wrong route of administration errors. DMEPA identified multiple wrong route of administration error cases involving similar products in the same class. Patients and healthcare practitioners administered the products intramuscularly instead of intravenously or subcutaneously.
5. Relocate the manufacturer’s information to the side panel, so that the most important information is prominent on the principle display panel (e.g., proprietary and established names, dosage form, product strength, and route of administration).

B. Single-Use Vials Labels (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5mL, 6 mg/mL)

1. See comments A.3 through A.5 and revise single-use vials labels accordingly.
2. (b) (4) located on the principle display panel as this statement is confusing and occupies space.
3. Revise the statement (b) (4) to state “Single Use Vial Only. Discard Unused Portion”. We recommend this revision to emphasize that this vial is for single use only because the statement “single dose” implies that the entire vial is administered every time. However, since package insert labeling expresses the dose in mg/kg (i.e., 0.04 mg/kg to 0.08 mg/kg), the dose may not be rounded up or down to equal the contents of the entire vial.

C. (b) (4) Vial Carton Labeling (10 mg/mL and 20 mg/2 mL)

1. See comments A.1 and A.2 above and revise multi-use vial carton labeling accordingly.
2. Different strengths of the product appear similar due to insufficient difference in the background color. Prominent red-brown color blocks appear on each carton making all the cartons look similar to each other. The upper, differently-colored, triangle blocks containing the products’ strength are smaller than the red-brown color blocks. This decreases the differentiation between the strengths. Thus, use only the differently-colored upper blocks for the entire background color block.

3. Delete, move, or minimize the three colored line graphic above the proprietary name “Omontys” as this graphic reduce the readability of the proprietary name.
 4. Revise the statement “For IV or SC Use Only” to read for “For Intravenous or Subcutaneous Use Only”. Additionally, increase the prominence of this statement by increasing font size. Abbreviations ‘IV’ and ‘SC’ appear on ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations⁴ because abbreviation ‘IV’ has been confused with the abbreviations ‘IM’ (intramuscular), ‘IU’ (international units), and ‘IN’(intranasal) and abbreviation ‘SC’ has been confused with the abbreviation ‘SL’ (sublingual). Additionally, we identified medication error cases involving Epogen and Aranesp that reported administration of these products intramuscularly instead of intravenously or subcutaneously.
 5. Revise medication guide statement to be consistent with other medication guide statements for other product. For example, you medication guide statement can read as follows “ATTENTION PHARMACIST: Dispense enclosed Medication Guide to each patient”.
- D. Single-Use Vial Carton Labeling (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5mL, 6 mg/0.5mL)**
1. See comments B.2 and B.3 and revise single-use vial carton labeling accordingly.
 2. See comments C.2 through C.5 and revise single-use vial carton labeling accordingly.
- E. Single-Use Prefilled Syringe (1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, 6 mg/0.5 mL)**
1. Relocate the colored blocked to appear around the horizontally placed strength. Additionally, delete the vertically placed strength. We recommend this revision to help differentiate among the different strengths and to increase the readability of the strength.
 2. (b) (4) from the principle display panel as this statement is confusing and occupies space.
 3. Revise the statement (b) (4) to read “Single Use Pre-Filled Syringe. Discard After One Use” to emphasize that the syringe should not be re-used.
 4. Add the route of administration “For Intravenous or Subcutaneous Use Only” if space permits.
- F. Single-Use Prefilled Syringe Tray Labeling and Carton Labeling (1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5mg/0.5 mL, 6 mg/0.5 mL)**
1. See comments C.3 through C.5 and revise single-use prefilled syringe tray labeling and carton labeling accordingly.
 2. See comment E.3 and revise single-use prefilled syringe tray labeling and carton labeling accordingly.
 3. Although different product strengths appear sufficiently differentiated, we ask you use only the differently-colored upper blocks for the entire background color block to be consistent with carton labeling for single dose and multi dose vials.

⁴ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

5 REFERENCES

1. *McMillan, Teresa. OSE Review #2011-2577 Aranesp, Epogen, Procrit Label and Labeling Review, August 26, 2011.*

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix D: Cases from OSE Review #2011-2577 that do not inform Omontys label, labeling, and packaging review (OSE Review (2011-2388))

- Wrong Strength

The Epogen/Procrit (n=1) AERS search identified one case reported in 2009 of wrong strength that involved an error associated with overlapping numerals in strength (i.e. 4,000 units vs. 40,000 units). No outcome or root cause was reported.

The Aranesp AERS search identified three cases (n=3) reported in 2010 and 2011 of wrong strength. Two of the three cases involved an error associated with overlapping numerals in strength (i.e. 30 mcg vs. 300 mcg, 10 mcg vs. 100 mcg). In the case of the Aranesp 30 mcg vs. 300 mcg the reporter states that the error occurred due to “bad information transmission and an error of prescription reading”. The incorrect dose was administered and the patient was hospitalized, but no outcome was reported. In the case of the Aranesp 10 mcg vs. 100 mcg, the reporter states the drug administration error occurred as a result of a dispensing error. The patient did not experience any adverse effects due to the error. The remaining case involved a hospitalized patient receiving Aranesp 100 mcg instead of Aranesp 40 mcg. No adverse events were reported and the root cause of the error was not identified.

- Wrong Drug

Two cases (n=2) described wrong drug error. Aranesp was administered in error in both cases. One case reported that a patient received Aranesp 200 mcg accidentally instead of Procrit 10,000 units. The other case reported that the patient received Aranesp 30 mcg instead of Neupogen (no strength indicated). No outcome or root cause of the errors was reported.

- Product Quality Issues/Wrong Dose

The two cases (n=2) reported underdoses of Epogen/Procrit due to a product quality issue of the product vials containing less than the expected amount. No outcomes were reported.

- Wrong Frequency

One case (n=1) involving Aranesp reported the wrong frequency of administration. The patient was prescribed Aranesp 500 mcg once every three weeks and was administered Aranesp 500 mcg once weekly for three weeks. The physician reported the occurrence as a “dose mistake” and stated there was no adverse event.

Appendix E: ISR #s for Epogen/Procrit and the narratives for the 22 relevant cases

ISRNUM	Narratives
5885937	
6279303	Patient with an unspecified history initiated an unspecified Procrit therapy. For an unknown duration of time, the patient experienced an incorrect route of administration reported as 'inject Procrit intramuscularly.' Patient was instructed on subcutaneous injections. The event was resolved. Disposition of Procrit was not provided.
6279336	Patient with an unspecified malignancy on chemotherapy initiated Procrit (dose, route and frequency not provided). On an unknown date later, the patient experienced an incorrect route of drug administration described as 'gave Procrit shot as intramuscular instead of subcutaneously in error.' Treatment details were not provided. The event was reported as ongoing. Disposition of Procrit was not provided.
6279340	Patient with chronic kidney disease initiated Procrit 10000 units subcutaneously once weekly. The following month, on 04/Dec/2008, the patient experienced an incorrect route of drug administration reported as 'Procrit injection given intramuscularly.' Treatment details were not provided. 'No untoward complaints' were reported from the patient. The event was reported as 'not resolved.' Disposition of Procrit was not provided.
6811221	
6811341	
7361845	
7343226	This spontaneous report received from a consumer refers to a 56 year old male patient on Epogen for medication induced anemia. No medical history was reported. Concomitant medications reported included Pegasys (peginterferon alfa-2A). The patient began unspecified Epogen therapy on 13/Aug/2010; baseline hemoglobin (Hgb) was not provided. Approximately six months later, on 15/Feb/2011 the patient experienced a circumstance capable leading to medication error described as the patient received vials containing less than 1ml of product. Reporter stated the vials were a 3/4 full. The patient intended to use the vials as his physician said him to not miss a dose. Additionally, the patient experienced drug ineffective described as his red blood cells were still low; value was not provided. No treatment information was reported. The outcome of the events circumstance capable leading to medication error and drug ineffective was reported as unknown. Additional information was not provided.
7591787	
6037718	
6279090	.
6279318	Patient with an unspecified history initiated Procrit (dose, route, and frequency not provided) for an unspecified indication. On an unknown date later, the patient experienced an incorrect route of drug administration described as 'patient inadvertently administered Procrit intramuscularly instead of subcutaneously.' Treatment and outcome details were not provided. Disposition of Procrit was not provided.
6279338	
6279931	
6796321	
6535282	
6811283	Patient with unknown indication started unspecified Procrit therapy. At an unknown time, the patient experienced incorrect route of drug administration reported as "possibly administered Procrit intramuscularly." Treatment and outcome details were not provided. Disposition of Procrit was not provided.
6811364	Patient with anemia receiving Pegasys (peginterferon alfa 2-A) for hepatitis C was administered an initial dose of Procrit at 20000 units via inappropriate route described as "given intramuscularly" per pharmacy prescription label instructions that state "to give Procrit IM (intramuscularly) or IV (intravenously)." Treatment details were not provided. No untoward adverse events were reported. Procrit therapy was continued.

7023647	
7154477	
7366252	
7051561	
7077292	
7176360	
7637671	
7618880	
6279965	Patient with an unspecified history initiated Procrit (dose, route, and frequency not provided) for an unspecified indication. On an unknown date later, the patient experienced an incorrect route of drug administration described as 'Procrit given intramuscularly and there were no adverse reactions as of yet.' Treatment and outcome details were not provided. Disposition of Procrit was not provided.
6811227	Patient started Procrit therapy for an unspecified indication; date, dose, route and frequency were not provided. It was reported that the patient "was given Procrit injection intramuscularly instead of subcutaneously." Treatment details were not provided. The event was ongoing. Procrit therapy was continued.
6811313	
6811349	
6811397	Elderly obese patient with unspecified medical history started Procrit 40000 units subcutaneously (SC) monthly for an unknown indication. Reportedly at doctor's office over an unspecified period of time the patient received Procrit injections "being administered intramuscularly." No untoward events were reported by the patient. On an unknown date later, Procrit was temporarily discontinued for an unspecified reason. After an unknown time, under the care of a different physician the patient restarted Procrit therapy (dose, frequency and Hgb were not provided) and the injections were administered SC. Procrit therapy was continued.
7111709	
7064618	
7637670	
6279942	
6279962	Patient with unspecified anemia was to receive Procrit 20000 units (U) subcutaneously one time. Instead, the patient received 20000 U intramuscularly. No untoward effects reported. Treatment and outcome details were not provided.
6811174	Patient started Procrit 10000 units every three weeks for an unspecified indication and was administered an initial dose "intramuscular instead of subcutaneously." Treatment and outcome details were not provided. It was reported that the patient "not complaining of any symptoms." Disposition of Procrit was not provided.
6811184	
6934516	
7045664	
7141983	
7602564	
7179212	
6279277	Female patient with history of stage III breast cancer, unilateral mastectomy, chemotherapy induced anemia, radiation therapy, remission and anemia began Procrit therapy. Following initial chemotherapy (date not provided) the patient remained anemic, therefore continued Procrit therapy (unspecified dose/regimen), hemoglobin was 'typically' 11.0 during remission (2-3 years), but was 'lower' when receiving initial chemotherapy. At an unknown time following remission, the patient developed metastases to lungs, bone, brain (> 30 lesions) and the spinal cord. In Apr/2008 the patient was receiving Procrit 40,000 IU subcutaneously weekly and concomitant chemotherapy. Hemoglobin of 9.5. Additionally, the patient reported that Procrit was being administered by a friend who was shaking the vial prior to administration. Additional information was not provided.
6279335	Patient with unspecified anemia initiated Procrit 4000 units (U) subcutaneously twice weekly.

	Approximately three weeks later, the patient received 40000 U instead of 4000 U. Treatment details were not provided. The event was reported as ongoing. No additional information available. Disposition of Procrit was not provided.
6811142	
6811317	
6811362	Patient with myelodysplastic syndrome and a history of prostate cancer, hypertension, and diabetes mellitus started Procrit 60000 units (U) once weekly; route and baseline hemoglobin were not provided. Pharmacist reported approximately one year and three months post initiation, a nurse gave two injections of Procrit; "one 20000 U intramuscularly (IM) from a multidose dose vial, and one 40000 U IM from a single dose vial." Treatment details were not provided, and the event was ongoing. Additional information was not provided. Procrit therapy was continued. ADDITIONAL INFORMATION RECEIVED ON 25/Jan/2010: Additional details on the patient's medical history included type 2 diabetes mellitus. It was reported that the patient received "Procrit injections intramuscularly instead of subcutaneously." Treatment details were not provided. The pharmacist stated the event was resolved and was not related to Procrit therapy.
6811422	
6803316	
7637668	
7637685	
5973127	Patient with chronic renal failure and a history of stroke and diabetes receiving warfarin sodium, received an initial dose of Procrit 10,000 units subcutaneously; baseline Hemoglobin was not provided. The patient subsequently developed injection site swelling and redness. Hours later, the patient was hospitalized for a hemorrhage on the right side of the brain. Treatment details were not provided. The next day, the patient died. ADDITIONAL INFORMATION RECEIVED ON 21/Nov/2008: On (b) (6) the patient had a blood pressure of 148/98. Concomitant medications included carvedilol, furosemide, ramipril, metformin, levemir, verapamil, calcitriol, iron, ezetimibe/simvastatin, and fludrocortisone. On (b) (6) the patient received Procrit injection from a home health nurse and according to the hospital later that day it was reported that 'it looks like the needle hit a vein and was accidentally given intravenously, instead of subcutaneously in the stomach area.' Four hours later the patient vomited blood and developed a headache. Two hours later, the patient went to the emergency department where the 'doctors said she had a quick rise in blood pressure.' The hypertension led to an intracerebral bleed ('one of her brain veins popped and there was a hemorrhage'), which eventually led to cardiopulmonary arrest and life support. On (b) (6) the patient was removed from life support and died.
5875424	
5868396	
6279298	
6283273	Patient initiated Procrit 40000 units subcutaneously (SC) (frequency not provided) for perisurgical red blood cell stimulation associated with an unspecified surgery. On an unknown date, the patient experienced an incorrect route of drug administration reported as 'patient inadvertently administered Procrit intramuscularly instead of SC.' Treatment and outcome details were not provided. Disposition of Procrit was not provided.
6665599	
6811340	
6811398	
6811418	
6811424	Patient with chronic kidney disease started Procrit 8000 units three times weekly; date started and route were not provided. After an unspecified period of exposure, the patient experienced skin thinness, skin tear and drug administered via inappropriate route reported as "recently and in the past patient received Procrit intramuscularly (IM) because he has very thin skin that tears and it's very hard to give subcutaneously." Treatment details were not provided. The events were ongoing. At an unknown time post receiving the first Procrit dose, the patient started dialysis and subsequently "came back off of it." Procrit therapy was continued.

7110904	
7152370	
5866658	
6279194	
6279220	
6279291	
6575034	.
6811146	
6811182	Patient with chronic kidney disease started Procrit 20000 units (U) every two weeks (Q2W); route unknown. Approximately four months later, in Mar/2009, the patient developed an unspecified infection. Treatment included azithromycin. Outcome details were not provided. About one month later, in May/2009, Procrit therapy was increased to 22000 U Q2W (route was not provided) for an unspecified reason. The following month, on 30/Jun/2009, the patient experienced incorrect route of drug administration reported as "received Procrit intramuscularly." Treatment details were not provided. The event resolved. Disposition of Procrit was not provided.
6811273	Patient with an unknown indication receiving unspecified Procrit therapy experienced incorrect route of drug administration reported as "was administered Procrit intramuscularly instead of subcutaneously." Treatment details were not provided. No untoward "effects" were noted at the time of the report. Procrit therapy was continued.
6811346	
7402852	
7027399	
7031667	
7367549	This spontaneous report received from a nurse refers to a patient on Procrit for anemia. At the time of the event the patient had medical history including unspecified anemia, pulmonary fibrosis and Alzheimer's disease. No concomitant medications were reported. The patient began Procrit 10000 units, three times weekly on an unknown date. Baseline hemoglobin (Hgb) was not provided. On 14/Mar/2011, the patient's Hgb was of 9.6 (unit not provided). Approximately two days later, on 16/Mar/2011 the patient experienced a medication error described as the patient received Aranesp 200 mcg accidentally. The reporting nurse stated that the patient had normal kidney function and was being cared in a nursing home. No treatment information was reported. The outcome of the event medication error was reported as unknown. The nurse also commented that the physician was considering transferring patient to the hospital or referring to a cardiologist.
7630865	
6206475	
6279334	
6545282	
6811264	Patient hospitalized with pneumonia not on Epogen was mistakenly administered Epogen 28000 units from multi-dose vial formulation via inhalation instead of administration of inhalation of normal saline solution for sputum induction. Treatment details were not provided. It was reported that "no issues were noted throughout the day," and the patient was discharged. Outcome details were not provided.
6811421	
7043805	
7548189	
7380346	

Appendix F: ISR #s for Aranesp and the narratives for the 8 relevant cases

ISRNUM	Narratives
7244432	
5942352	
6481011	A 57 year old female patient with ovarian cancer, hypertension, and diabetes, receiving unspecified chemotherapy with Aranesp support experienced an overdose of Aranesp within three weeks of commencing the drug. Aranesp was prescribed at 500mcg once every three weeks, and was administered at 500mcg once weekly for three weeks in error. Haemoglobin on the day of initial Aranesp administration was reported as 10.3g/dL, and 20 days later was 12.2g/dL. No further information was supplied. The reporting physician stated that there was a reasonable possibility that the overdose may have been caused by Aranesp. Additional information received on 28/Oct/2009: The reporting physician noted he did not have any additional information (including no adverse clinical symptoms) to report since the last Aranesp injection. Additional information received on 04/Dec/2009: The reporting physician subsequently reported that there was no adverse event but did state that there was a "dose mistake". Haemoglobin was reported to have increased to 15g. No further information was provided.
6781426	
6976349	
7504777	
7585903	
6796321	
6822896	This case is considered medically important. Patient with a history of renal failure started Aranesp; start date, dose, route, frequency and baseline hemoglobin were not provided. After an unspecified time of exposure, the patient experienced an overdose described as "received ten times the dose he should have." Treatment and outcome details were not provided. Disposition of Aranesp was not provided. Additional information was not provided. ADDITIONAL INFORMATION RECEIVED ON 01/Jul/2010: It was reported that Aranesp therapy was prescribed at 30 mcg [date, route, frequency and baseline hemoglobin (Hgb) were not provided]. After an unspecified time later, the patient experienced accidental overdose reported as "but injection was made with Aranesp 300 mcg by a nurse in a hospital unit." The reporter commented that there was a bad information transmission and an error of prescription reading. Treatment and outcome details were not provided. At an unknown time later, the patient was discharged from the hospital with Hgb of 9.5 g/dL. It was also noted that the hemogram was planned to be monitored every week, and no more information will be available to the reporter.
7366252	
7597081	
7568487	
7618880	
6274290	
6924600	
6987589	

7334824	
7033870	
7126876	
5978842	
6781401	
6832926	<p>This case was considered medically important. An elderly female patient with unknown medical history began Aranesp 10 mg in an unknown indication. At an unspecified time, the patient erroneously received 100 mg instead of a dose of 10 mg. Treatment and outcome details were not provided. The status of Aranesp was not provided.</p> <p>ADDITIONAL INFORMATION RECEIVED ON 05/JUL/2010: The drug administration error occurred due to a dispensing error approximately three months after the patient started Aranesp 10 mcg weekly. Treatment included stopping Aranesp for two weeks. The patient did not experience any adverse effect due to the drug administration error. Additional treatment and outcome details were not provided. No additional information was provided.</p>
7019234	
6062903	
6316024	
6522867	
6389541	
6671608	
6828154	
6155725	
6448027	
6511845	
6946181	
7056667	
7682798	
6237499	
6217827	
6274487	
6358388	
6698484	
7402852	
7337357	<p>This Spontaneous report received from a Pharmacist refers to a 87 Years old Male patient on Aranesp for Chronic renal insufficiency. The patient began Aranesp 40mcg twice a week. Baseline hemoglobin was not provided. On an unknown date, the patient was readmitted to hospital (details were not provided). During hospitalization the patient was inadvertently given a 100mcg dose instead of 40mcg. Treatment and outcome details were not provided. Disposition of Aranesp was not provided. Additional information was not</p>

	<p>provided. ADDITIONAL INFORMATION RECEIVED ON 14/Dec/2010: Clinical pharmacist reported that the patient was not readmitted to the hospital due to Aranesp. The reporter further stated that it appeared that there were no adverse effects in the patient - the patient has been discharged from hospital. Additional information was not provided.</p> <p>ADDITIONAL INFORMATION RECEIVED ON 23/Dec/2010: It was reported that one week after discharge, the patient received Aranesp 40 mcg. No adverse were seen on blood tests. Additional information was not provided.</p> <p>ADDITIONAL INFORMATION RECEIVED ON 25/Feb/2011: The reporter noted that the patient received Aranesp 200ug weekly. The events medication error, hospitalization and accidental overdose were assessed as serious by the reporter. The outcome of the events was reported as unknown. The reporter stated that there was a reasonable possibility that the events were related to Aranesp therapy. Additional information was not provided. Information received from a Regulatory Authority, therefore this case was closed to follow up.</p>
7052647	
7084607	
7367549	<p>This spontaneous report received from a nurse refers to a patient on Procrit for anemia. At the time of the event the patient had medical history including unspecified anemia, pulmonary fibrosis and Alzheimer's disease. No concomitant medications were reported. The patient began Procrit 10000 units, three times weekly on an unknown date. Baseline hemoglobin (Hgb) was not provided. On 14/Mar/2011, the patient's Hgb was of 9.6 (unit not provided). Approximately two days later, on 16/Mar/2011 the patient experienced a medication error described as the patient received Aranesp 200 mcg accidentally. The reporting nurse stated that the patient had normal kidney function and was being cared in a nursing home. No treatment information was reported. The outcome of the event medication error was reported as unknown. The nurse also commented that the physician was considering transferring patient to the hospital or referring to a cardiologist.</p>
7504765	
7513173	
6432403	
6781410	<p>Patient with unknown history started Aranesp therapy with pre-filled syringe (PFS) at frequency ranged "from once weekly to once monthly" for an unknown indication; date started, dose, and baseline hemoglobin were not provided. Approximately one year later, the patient attempted to administer Aranesp with PFS, pulled needle cover off of PFS and didn't pay attention or notice if there was a needle there at the time. The patient pushed the plunger of the syringe to administer the injection, but "the medication just leaked out." Then the patient looked at the syringe and noticed that the needle was completely detached and floating inside the barrel of the syringe. Reportedly the patient "did not feel the needle when she tried to administer the medication." Treatment and outcome details were not provided. Approximately one week later, the patient experienced tiredness. Treatment and outcome details were not provided. Aranesp therapy was continued.</p>
7563128	<p>This spontaneous report received from a nurse refers to a male patient on Aranesp for chronic kidney disease. At the time of the event the patient had medical history including peritoneal dialysis and diabetic neuropathy. On an unknown date, the patient began Aranesp SureClick 20 ug; route and frequency were not provided. Baseline hemoglobin (Hgb) was not provided. It was reported that the patient was trained to use SureClick on his leg and held it at 90 degree angle but did not received training on using Prefilled Syringes with automatic needle guard (ANG). After an unspecified period of exposure, Aranesp was changed to 30ug for unspecified reasons. Hgb was not provided. In Jan/2011, the patient was changed to prefilled syringe with ANG Aranesp 30ug. After the second or third injection, on (b) (6) the patient experienced swelling at injection site left thigh that was so painful that was unable to move his leg. Subsequently, the patient</p>

	<p>was hospitalized (details were not provided). Hgb was not provided. A scan was performed and revealed that a deep vein was pierced, a significant fluid oedema in the subcutaneous tissues and an echolucent area with low volum tracking from a deep vein to the skin surface. Treatment included flucloxacillin sodium. The patient was discharged on (b) (6). Hgb was not provided. The patient was changed back to Aranesp SureClick at a dose of 60ug every other week. Hgb was not provided. The outcome of the events was reported as recovering. The nurse stated that there was a reasonable possibility that the event injection site swelling may have been related to Aranesp therapy.</p> <p>ADDITIONAL INFORMATION RECEIVED FROM A HEALTH AUTHORITY ON 29/Mar/2011: The patients concomitant medications included amlodipine, gliclazide, lanthanum carbonate, and valsartan. The patient received Aranesp 30 mcg, subcutaneously on 17/Jan/2011. Approximately (b) (6) the patient experienced oedema peripheral described as a 3 x 3 cm swelling in left thigh. An ultrasound scan showed significant fluid oedema, possible infection and low volume blood flow tracking from a deep vein caused by subcutaneous injection of Aranesp. Treatment included unspecified antibiotics. Aranesp therapy was withdrawn. The outcome of the event peripheral oedema was reported as resolving. It was reported that there was a reasonable possibility that the event peripheral oedema may have been caused by Aranesp injection.</p> <p>ADDITIONAL INFORMATION RECEIVED ON 14/Jun/2011: The information for this case was received from Health Regulatory Authority. The patient following Aranesp injection developed a 3x3cm swelling in the lower medial aspect of his left thigh. Ultrasound scan showed significant fluid oedema, possible infection and low volume blood flow tracking from deep vein caused by subcutaneous injection of Aranesp. The reporter stated that it was medically significant as requiring antibiotics and ultrasound scan. The patient was admitted under the medics at a hospital for a day. Ultrasound scan appearance was suggestive of a haematoma. There was no definite sign of infection although the inflammatory markers were raised (but the patients white blood cell count was not raised). The inflammatory markers were probably raised because of swelling. The swelling subsided in a fortnight. Currently, the patient was well. The reporter suspected that when the patient self-injected with the pre-filled Aranesp syringe the patient might have accidentally punctured a vein due to the length of the needle (approximately 1.5cm). Case reported by Regulatory Authority, therefore this case was closed to follow-up.</p>
6698484	<p>This case is considered medically important. Patient with breast cancer treated with chemotherapy (not provided) started Neupogen for neutropenia; date started, dose and frequency were not provided. After an unspecified time, the patient experienced a wrong drug administration reported as error administration of Aranesp 30ug to patient instead of Neupogen. Treatment and outcome details were not provided. The reporter stated that the patient had also anemia due to chemotherapy. Disposition of Neupogen was not provided. The physician considered the event as a significant hazard. Additional information was not provided.</p>

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/s/

YELENA L MASLOV
12/23/2011

IRENE Z CHAN
12/23/2011

CAROL A HOLQUIST
12/23/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: December 15, 2011

TO: Trinh Scott, Regulatory Project Manager
Andrew Dmytrijuk, M.D., Medical Officer
Kathy Robie-Suh, M.D., Ph.D., Team Leader
Division of Hematology Products (DHP)

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

SUBJECT: Evaluation of Clinical Inspections

NDA: 202799

APPLICANT: Affymax, Inc.

DRUG: peginesatide (AF37702)
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Treatment of anemia associated with chronic renal failure in patients on dialysis

CONSULTATION REQUEST DATE: August 1, 2011 (signed)
DIVISION ACTION GOAL DATE: February 14, 2012
PDUFA DATE: March 27, 2012

I. BACKGROUND:

AF3702 injection, a synthetic dimeric peptide linked to polyethylene glycol, is an erythropoiesis stimulating agent (ESA) for the treatment of anemia due to chronic renal failure. AF37702 binds and activates the erythropoietin receptor and stimulate erythropoiesis in human red cell precursors in vitro.

Two adequate and well-controlled studies were submitted in support of this NDA submission. The drug is an NME. For each study protocol, two domestic clinical sites were audited because these were high enrollment centers. Two Russian foreign sites, representing an additional supportive study, were selected because these were pertinent to labeling, where adult patients on dialysis were naïve to ESA therapy.

Study AFX01-12 was a **Phase 3**, randomized, active-controlled, open-label, multicenter study of the safety and efficacy of AF37702 injection for the maintenance treatment of anemia due to chronic renal failure in hemodialysis patients. The primary efficacy endpoint was the mean change in hemoglobin between baseline and the evaluation period (mean hemoglobin from Weeks 29 through 36).

Study AFX01-14 was a **Phase 3**, randomized, active-controlled, open-label, multicenter study of the safety and efficacy of AF37702 Injection for the maintenance treatment of anemia due to chronic renal failure in hemodialysis patients previously treated with Epoetin. The primary efficacy endpoint of this study was the mean change hemoglobin between baseline and the evaluation period (mean hemoglobin from Weeks 29 through 36).

Study AFX01-15 was a **Phase 2** multicenter randomized, parallel design, active-controlled, open-label, study of AF37702 Injection to examine the correction of anemia due to chronic renal failure in patients on dialysis, who had not received an ESA in the previous 12 weeks prior to randomization or who had known intolerance to ESAs. Thus, these subjects were presumed to be ESA-naïve. Only Epoetin alfa (Eprex®), however, was used as the active concurrent control in the study. The primary efficacy endpoint of this study was a change in hemoglobin from baseline to a defined evaluation period (mean hemoglobin from weeks 21 through 28).

II. RESULTS (by protocol/site):

Name of CI City, State	Protocol/Study Site/# of Subjects	Insp. Date	Final Classification*
Brigitte Schiller-Moran, M.D. San Jose, CA	Protocol #AFX01-12 Site #1005	September 14 to 19, 2011	NAI
Edouard Martin, M.D. Lauderdale Lakes, FL	Protocol #AFX01-14 Site #1041	September 12 to 16, 2011	NAI
Andrey Gurevich, M.D. St. Petersburg, RUSSIA	Protocol #AFX01-15 Site #4002	December 1 to December 6, 2011	Preliminary: VAI
Konstantin Gurevich, M.D. St. Petersburg, RUSSIA	Protocol #AFX01-15 Site #4003	November 28 to 30, 2011	Preliminary: VAI
Affymax, Inc.	Sponsor	October 7 to 14, 2011	NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Brigitte Schiller-Moran, M.D., M.D. /Study Protocol #AFX01-12/Site #1005

Satellite Healthcare, Inc.

300 Santana Row, San Jose, CA 95128

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 14 and September 19, 2011.

A total of 40 subjects were screened, 33 were randomized and 23 completed the study. There was no under-reporting of serious adverse events. An audit of 15 randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

Data submitted by this clinical site appear acceptable for this specific indication.

2. Edouard Martin, M.D., /Study Protocol AFX01-14/Site #1041

South Florida Research Institute
2951 Northwest 49th Ave, Suite 101, Lauderdale Lakes, FL 33313

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from September 12 and September 16, 2011.

A total of 75 subjects were screened, 52 subjects were randomized, and 34 subjects completed the study. There was no under-reporting of serious adverse events noted. An audit of 18 of randomized subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for subjects that were randomized, were verified against the case report forms and NDA subject line listings.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

3. Andrey Gurevich, M.D. /Study Protocol AFX01-15 Site #4002

St. Petersburg Medical Academy for Postgraduate Studies, Nephrology Center 41 Kirochnaya Str., 19105 St. Petersburg, Russia

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from December 1 to December 6, 2011, 2011. A total of 17 subjects were screened, 15 were randomized and 14 completed the study. An audit of 15 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were verified against the case report forms and NDA subject line listings and no discrepancies were noted. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (ORA List of Inspectional Observations) was, however, issued at the end of the inspection for lack of an adequate electronic trail for source data documentation of dose preparation and administration for 4 of 15 subjects.

Medical Officer's Comments:

A minor regulatory deficiency was identified. There was an apparent lack of a sufficient electronic trail for recording source data for dose preparation and administration, on 4 of 15 randomized patients, when there was an administrative transition to an electronic format for these 4 patients. On December 9, 2011, this was communicated with DHP, who considered the observation as not critical or not significant. Further, DHP indicated that AFX01-15 is only a supportive study, and not considered by the review division as an adequate and well-controlled investigation. OSI does not consider this observation as significant.

d. Data acceptability/reliability for consideration in the NDA review decision.

Data submitted by this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

4. Konstantin Gurevich, M.D. /Study Protocol AFX01-15 Site #4003

St. Elizabeth City Hospital, Department of Hemodialysis
14 Vavilovkyh Str., 195257 St. Petersburg, Russia

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 28-30, 2011. A total of 10 subjects were screened, 6 were randomized and 6 completed the study. An audit of 6 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for randomized subjects whose records were verified against the case report forms and NDA subject line listings and no discrepancies were noted. There was no under-reporting of serious adverse events.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A one-item Form FDA 483 (ORA List of Inspectional Observations) was, however, issued at the end of the inspection related to inadequate and inaccurate record keeping. Specific examples that are not critical findings include: (a) for Subject 4003-046, source data, which was nurse's entry in the Dialysis Card, recorded a dose and units administered on August 19, 2008 of 2.0 mL while the Case Report Form reported 2.4 mg, and (b) for Subject 4003-067, source data, which was nurse's entry in the Dialysis Card, recorded a dose administered on October 21, 2008 of 6.0 mg while the Case Report Form reported 6.3 mg.

Medical Officer's Comments:

While these were regulatory deficiencies, OSI does not consider the above observations as significant as they are isolated in nature. On December 9, 2011, this was communicated with DHP, who considered these record keeping inconsistencies as not critical at all. Further, DHP indicated that AFX01-15 is only a supportive study, and not considered by the review division as an adequate and well-controlled investigation.

d. Data acceptability/reliability for consideration in the NDA review decision.

The regulatory deficiency noted above, related to incomplete or inaccurate record keeping is considered sporadic or minor in nature and to not significantly impact overall study data reliability. Data submitted by this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR INSPECTION

Affymax, Inc.

4001 Miranda Ave.
Palo Alto, CA 94304

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from October 7 to 14, 2011, 2011.

The inspection verified study Protocol #AFX01-12, Protocol #AFX01-14 and Protocol #AFX01-15. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, communication with the Sponsor and drug accountability, staff training and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events. No discrepancies were noted. This sponsor appeared to have executed sponsor responsibilities adequately. No Form FDA 483 was issued at the end of the Sponsor inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data in support of efficacy and safety from this Sponsor oversight appear acceptable for this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two U.S. and two foreign clinical investigator sites, plus Sponsor (Affymax, Inc.), were inspected in support of this application. Based on review of inspectional findings for four clinical investigators, the study data collected appear generally reliable in support of the requested indication.

While Form FDA 483s were issued to Dr. Konstantin Gurevich's and Dr. Andrey Gurevich's sites for preliminary observations related to incomplete or inaccurate record keeping, these are considered sporadic or minor in nature and not significant to impact data reliability. The data are considered reliable in support of the study.

Note: Observations noted above, for the foreign clinical sites are based on the preliminary communications from the field investigator; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
12/16/2011

SUSAN LEIBENHAUT
12/16/2011

TEJASHRI S PUROHIT-SHETH
12/16/2011

Executive CAC

Date of Meeting: November 15, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Dan Mellon, Ph.D., DAAAP, Alternate Member
Haleh Saber, Ph.D., DHOT, Team Leader
Kimberly Ringgold, Ph.D., DHOT, Presenting Reviewer

Author of Minutes: Kimberly Ringgold, Ph.D., DHOT

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 202799

Drug Name: Peginesatide, AF37702 (proposed trade name Omontys)

Sponsor: Affymax

Background

Peginesatide (AF37702) is intended for the treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis. Peginesatide is a synthetic, PEGylated dimeric peptide and belongs to a class of erythropoiesis stimulating agents (ESA). The amino acid sequence of AF37702 is not related to that of erythropoietin (EPO); however, it is proposed to stimulate the erythropoietin receptor. Peginesatide was negative in a standard battery of genotoxicity assays. The sponsor has conducted a standard 2-year rat study and a Tg.rasH2 mouse transgenic study to evaluate the carcinogenic potential of AF37702. Both studies were conducted according to ECAC recommendations.

Rat Carcinogenicity Study

AF37702 was administered to Sprague-Dawley rats (53/sex/group) at doses of 0 (saline & vehicle controls), 0.01, 0.1, 0.25 mg/kg AF37702 given intravenously every 3 weeks for 97-101 weeks. The vehicle was 20mM phosphate and 0.003% Tween 20 in 4.7% sorbitol, pH range 5.9-6.0. Additional animals in satellite (toxicokinetic) groups were administered a vehicle or the drug. Terminal sacrifice was at week 97 for males and 101 for females. The survival of high dose males was significantly lower than that of controls. No difference in survival was observed in drug-treated females compared to controls. Non-neoplastic findings were consistent with the pharmacology of AF37702, which included increased RBCs and indices (HGB, HCT), enlarged spleen, increased hematopoiesis in spleen, and hyperplasia in bone marrow. The incidences of lymphomas were slightly numerically increased in dosed males and females. However, these

incidences were not statistically significant and do not meet the CDER criteria to be considered drug related.

Tg.rasH2 Mouse Carcinogenicity Study

AF37702 was administered to Tg.rasH2 mice (25/sex/group) at doses of 0 (vehicle control), 0.1, 0.25, 0.5 mg/kg given intravenously in 20mM phosphate and 0.003% Tween 20 in 4.7% sorbitol, pH range 5.9-6.0 every 3 weeks for 26 weeks. Positive control animals (25/sex/group) were administered urethane at 1000 mg/kg/dose by IP injection on Days 1, 3, and 5. Due to mortalities, all surviving positive control mice were sacrificed on Days 113-114. One animal in each of the 0.1 and 0.25 groups were found dead; however, these deaths were not dose-dependent. Non-neoplastic findings were consistent with the pharmacology of AF37702, and included increased RBCs and indices (HGB, HCT), enlarged spleen, increased spleen weight, increased hematopoiesis in spleen, and erythropoiesis in bone marrow. Splenic hemangiosarcomas were numerically increased in dosed mice, but the incidences were not dose related or statistically significant. Incidences of 20% have been seen in several other Tg.rasH2 studies submitted to CDER. Furthermore, results of statistical analysis of these neoplasms do not meet the CDER criteria to be considered drug related.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms.

Tg.rasH2 Mouse:

- The Committee agreed that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DHP
/HSaber, DHOT
/KRinggold, DHOT
/TScott, DHP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
11/17/2011

DAVID JACOBSON KRAM
11/17/2011



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 15, 2011

From: Shona S. Pendse, MD, MMSc
Medical Officer - Clinical Reviewer
Division of Cardiovascular and Renal Products/OND/CDER

Aliza Thompson, MD, MS
Clinical Team Leader
Division of Cardiovascular and Renal Products/OND/CDER

Through: Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products/OND/CDER

To: Trinh Scott
Regulatory Project Manager
Division of Hematology Products/OND/CDER

Subject: Consult to review the cardiovascular events observed in a trial of administering Peginesatide

This memo is in response to your consult to us requesting that we “evaluate and advise on the significance of the finding of adverse safety for Peginesatide in the not-on-dialysis population versus the on-dialysis.” We received and reviewed the following materials:

1. Your consult to us dated October 6, 2011
2. Sponsor’s submission for NDA 202,799

Background

Peginesatide (AF37702) is a synthetic, PEGylated erythropoietin receptor activator peptide with no amino acid sequence homology to erythropoietin. It is a dimeric peptide that binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors in vitro in a manner similar to that of recombinant erythropoiesis-stimulating agents, or ESAs. The applicant has submitted an NDA for this new molecular entity for the proposed indication of treatment of adult patients with anemia of chronic renal failure on dialysis. Other agents currently marketed in the US for this indication include epoetin alpha (EPOGEN[®]/PROCRIT[®]) and darbepoetin alpha (ARANESP[®]), both of which have been shown to cause adverse cardiovascular (CV) outcomes in randomized trials in patients with chronic kidney disease (CKD). However, the mechanisms that underlie the increase in risk as well as the absolute magnitude of the risk have yet to be delineated. One of the goals of the Phase 3 program for Peginesatide was to capture data on CV events relative to marketed ESAs.

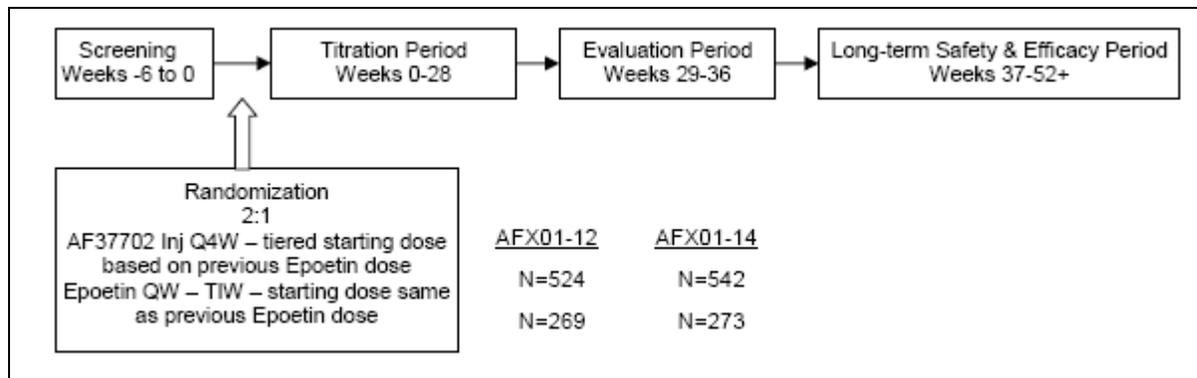
Phase 3 Program: Overview of Trials and Statistical Analysis

The Phase 3 Program consists of four randomized, open-label, active-controlled pivotal trials, all of which were designed to establish non-inferiority relative to other marketed ESAs with regard to effects on raising hemoglobin. Two of the trials were in subjects with CKD on dialysis who were switched from Epoetin therapy to Peginesatide, and two were in subjects with CKD not on dialysis and not on ESA therapy at baseline.

There were notable differences between the dialysis and non-dialysis trials that must be considered. The dialysis trials were conducted, by design, in subjects who were already on Epoetin treatment at baseline (subjects had to be on IV Epoetin alfa for Trial AFX01-12, which was conducted in the US, or on IV or SC Epoetin alfa or beta for Trial AFX01-14, which was conducted in the US and EU). In contrast, for the trials in subjects not on dialysis, subjects were excluded if they had any history of treatment with an ESA within 12 weeks prior to randomization. In addition, the choice of active comparator differed between the trials in the two populations: Epoetin alfa (AFX01-12) or Epoetin alfa or beta (AFX01-14) was used as the comparator in the trials in subjects on dialysis, while Darbepoetin was used in the trials in subjects not on dialysis. Schematic diagrams of the dialysis trials (Figure 1) and the non-dialysis trials (Figure 2) are shown below.

Key eligibility criteria for the dialysis trials included the presence of CKD treated with hemodialysis for ≥ 3 months prior to randomization, ongoing therapy with Epoetin treatment for ≥ 8 weeks before randomization with stable Epoetin doses for 4 weeks before randomization, 4 consecutive Hgb values with a mean ≥ 10.0 g/dL and ≤ 12.0 g/dL during the Screening Period, and no RBC or whole blood transfusion within 12 weeks of randomization. Subjects were excluded if they had any known bleeding or coagulation disorder or poorly controlled hypertension within 4 weeks prior to randomization. Of note, there were no exclusion factors based on recent CV events or CV risk factors other than the aforementioned one related to poorly controlled hypertension (HTN). Eligible subjects were randomized in a 2:1 ratio to either Peginesatide Q4W at starting doses of 0.04 mg/kg to 0.16 mg/kg, based on the subject's prior Epoetin dose, or to continued treatment with Epoetin 1-3 times per week, and followed for a minimum of 52 weeks. Study medication doses were adjusted using individual subject dose adjustment guidelines to maintain Hgb in a target range of 10.0-12.0 g/dL and ± 1.5 g/dL from Baseline during the Titration and Evaluation Periods and in the target range of 10.0-12.0 g/dL during the Long-term Safety and Efficacy Period. The primary efficacy endpoint was the mean change in Hgb between Baseline and the Evaluation Period. Non-inferiority of Peginesatide to Epoetin was established if the lower limit of the two-sided 95% confidence interval (CI) for the difference between the two treatment groups in mean change in Hgb was ≥ -1.0 g/dL.

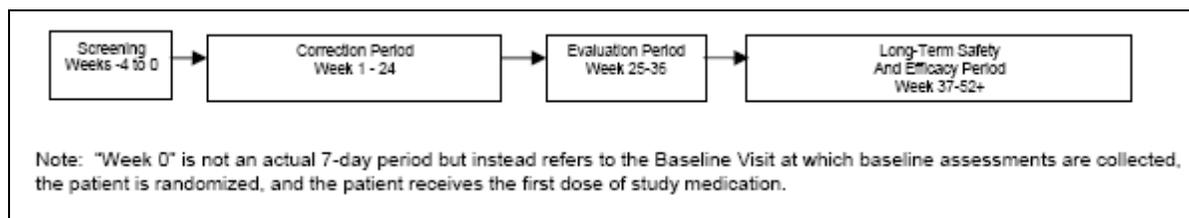
Figure 1: Design and Follow-up for the Phase 3 Dialysis Trials – Sponsor’s Diagram



Key eligibility criteria for the non-dialysis trials included CKD (estGFR<60 mL/min/1.73m²), two consecutive Hgb values ≥ 8.0 g/dL and ≤ 11.0 g/dL within 4 weeks prior to randomization, absence of any ESA therapy within 12 weeks prior to randomization, and the absence of any bleeding or coagulation disorder. Subjects were excluded if they had any known bleeding or coagulation disorder or poorly controlled hypertension within 4 weeks prior to randomization and again, similar to the dialysis trials, there were no other exclusions related to recent CV events or CV risk factors. Following a screening period of up to 4 weeks, eligible subjects were randomized 1:1:1 to either Peginesatide SC at a starting dose of 0.025 mg/kg Q4W, Peginesatide SC at a starting dose of 0.04 mg/kg Q4W, or Darbepoetin alfa SC at a starting dose of 0.75 μ g/kg Q2W and followed for a minimum of 52 weeks (Figure 2). Study medication doses were adjusted for each patient throughout the study, using dose adjustment guidelines specified in the protocol, to increase and maintain Hgb in a target range of 11.0-12.0 g/dL. The primary efficacy endpoint was the same as that in the dialysis trials.

For all of the Phase 3 trials, the protocols did not specify criteria for transfusions, with the need for transfusion being left to the discretion of the investigator or treating physician, though the details as to the number of units transfused was collected as part of the study.

Figure 2: Schematic of Follow-up for the Phase 3 Non-Dialysis Trials – Sponsor’s Diagram



Assessing Cardiovascular Risk

The safety program was designed to evaluate CV events specifically using a blinded adjudicated CV composite safety endpoint (CSE) consisting of six events: all-cause death, stroke, myocardial infarction (MI), and serious adverse events (SAEs) of congestive heart failure (CHF), unstable angina, and arrhythmia. The Phase 3 studies were closed based on projections of when 553 subjects would have experienced a CSE, and a total of 572 subjects experiencing a CSE were ultimately included in the primary CSE analysis. In addition, two modified CSEs, CHOIR-like (death, heart failure, MI, and stroke) and MACE (death, MI, and stroke), were evaluated (The

CHOIR-like CSE was prospectively specified, in contrast to the MACE CSE, which was defined post-hoc, after the preliminary phase 3 and CSE findings were known).

Potential CSE events were adjudicated by an independent Endpoint Review Committee (ERC), whose members reviewed source documentation that had been redacted to blind treatment group, dosing information, and Hgb.

The pre-specified primary endpoint for the pooled CSE analysis was based on the time from randomization in each of the Phase 3 studies to the first occurrence of a CSE event that was positively adjudicated by the ERC. The pre-specified primary statistical analysis of the pooled Phase 3 CSE events was to be based upon a one-sided 95% CI, equivalent to a two-sided 90% confidence interval (CI), and the study was designed to exclude a hazard ratio greater than 1.3 relative to marketed ESAs using the one-sided 95% CI (As previously stated, ESAs have been shown in prior randomized trials to cause an increased risk of adverse CV events). It must be pointed out that this is different from what is usually done – typically the upper limit of the two-sided 95% CI is used.

The pre-specified primary analysis of the CSE was an On-Study analysis, including CSE events other than death that occurred through termination from study and including deaths that occurred through 28 days after study termination. This On-Study analysis, however, included even those subjects who prematurely discontinued study drug and remained in the study and continued to be followed for SAEs. An additional analysis was done which was termed the On-Drug analysis, which included CSE events that occurred through 28 days after the last dose of study drug. The exception to this were events that occurred within 28 days after the last dose of study drug but occurred after initiation of a non-study ESA or following renal transplantation – these events were not included in the On-Drug analysis.

Deaths that occurred through 28 days after termination from study were submitted to the ERC for adjudication of date and primary cause of death. These included death due to a CSE component (other than the component of death itself), sudden death, death due to other unidentifiable cause, and unknown primary cause of death. The criteria for sudden death were either 1) non-traumatic, unexpected death either within one hour from the onset of symptoms or 2) unwitnessed death.

In addition to the analyses evaluating data from all four studies, the CSE was also evaluated separately for the Dialysis and Non-Dialysis trials. Sensitivity analyses censoring subjects after they discontinued study treatment and excluding events that occurred more than 28 days after last dose of study drug were conducted to inform the relatedness of CV events to the randomized study treatment. Additional post-hoc analyses were conducted to understand associations among CSE events, Hgb, and study drug exposure.

All SAE's in the Phase 3 trials reported to Affymax Drug Safety were screened by the Affymax Drug Safety team using Standardized MedDRA Queries (SMQs) to identify potential CSE events, which were then submitted to the ERC for adjudication. In addition, the clinical trial databases for the Phase 3 trials were periodically searched using SMQ event terms for myocardial infarction and stroke. Each potential CSE event was then reviewed independently by two reviewers in the specialty appropriate to the event (i.e., cardiologist or neurologist). If the two reviewers reached agreement on the event, no further review was required. Events in which there was not agreement were then referred for review to a subcommittee consisting of initial two ERC Members in the appropriate specialty area plus one additional ERC Member of the appropriate specialty, and the Chairperson.

Results:

Differences in Dosing of Study Drug

Doses of both Peginesatide and the active comparator were generally lower in the Non-Dialysis trials as compared to the Dialysis trials¹²³⁴⁵⁶. In the trials in subjects not on dialysis (both trials AFX01-11 and AFX01-13), there were two dose groups with different starting doses of Peginesatide. In the Non-Dialysis trials, median doses declined relatively steeply in both the 0.025 mg/kg and 0.04 mg/kg Peginesatide starting dose groups and the darbepoetin group over the course of the studies. Additionally, the mean doses in the two starting dose groups (median weight adjusted doses) were not dissimilar between the two starting dose groups by the end of the study.

Differences in Baseline Demographic Factors:

Table 1 shows the baseline characteristics across the trials. The non-dialysis trials had subjects who were approximately 10 years older than were those in the dialysis trials. In addition, the non-dialysis trials had a lower proportion of males and Blacks than the dialysis trials. With regard to baseline CV risk factors and CV associated medications, the non-dialysis trials had a higher proportion of subjects with hyperlipidemia and diabetes, and higher baseline usage of angiotensin II receptor blockers (ARBs), statins and hypoglycemic medications (including insulin) when compared to those in the dialysis trials. In contrast, the dialysis trials had a greater proportion of subjects with underlying heart failure and hyperphosphatemia, and also had higher baseline hsCRP levels. The significance of these differences in baseline demographic factors remains unclear. Of perhaps greater importance, is the fact that, across the trials, there were no clear differences between baseline demographics of the Peginesatide-treated patients and their active-comparator-treated counterparts.

¹ Utilizing a conversion factor of 219 (one of the numerous published conversion factors for Darbepoetin to Epoetin in subjects with CKD which ranged from 200 to 240), we estimated the Darbepoetin doses for the non-dialysis trials expressed as the equivalent Epoetin doses for comparison. This revealed a mean dose in the Darbepoetin arm of 37 µg Darbepoetin or approximately 8000 U Epoetin, a first dose of 59 µg Darbepoetin (~ 13000 U Epoetin), and a last dose during the study of 24 µg Darbepoetin (~ 5000 U Epoetin). Higher or lower conversion factors produced similar results.

² WHO. Drug Information. <http://www.whooc.no/atcddd/>

³ Sterner G and Prutz KG. Conversion from epoetin beta to darbepoetin: what is the equivalent dose? *Nephrology Dial Transplant* 2008; 23: 4084

⁴ Scott SD. Dose conversion from recombinant human erythropoietin to darbepoetin alfa; recommendations from clinical studies. *Pharmacotherapy* 2002; 22: 160S.

⁵ Tolman C, Richardson D, Barlett C et al. Structured conversion from trice weekly to weekly erythropoietic regimens using a computerized decision-support system: a randomized clinical study. *J Am Soc Nephrology* 2005; 16: 1463.

⁶ Raymond CB et al. Conversion from epoetin alfa to darbepoetin alfa within the Manitoba Renal Program: evaluation of dose ratios. *CANNT J.* 2008; 18(1): 39-43.

Table 1: Baseline Demographic Factors for the Dialysis and Non-Dialysis Trials – Modified from Sponsor’s Table

	Dialysis		Non-Dialysis	
	Peginesatide	Epoetin	Peginesatide	Darbepoetin
Mean Age (years)	58.1	58.1	67.6	66.8
N (%) male	624 (58.5)	297 (54.8)	290 (44.2)	126 (38.5)
Race				
N (%) White	617 (57.9)	299 (55.2)	482 (73.5)	231 (70.6)
N (%) Black	399 (37.4)	211 (38.9)	142 (21.6)	78 (23.9)
Mean BMI (kg/m ²)	28.99	28.70	30.78	30.52
N (%) BMI ≥ 30 kg/m ²	390 (36.6)	185 (34.1)	318 (48.5)	145 (44.3)
Median hsCRP (mg/L)	5.4	5.8	3.1	2.8
N (%) Phos > 2.91 mmol/L	41 (3.9)	13 (2.5)	0	0
N (%) Any CV History	1053 (98.8)	538 (99.3)	654 (93.4)	293 (89.6)
CV Risk History N (%)				
HTN	1039 (97.5)	532 (98.2)	639 (97.4)	316 (96.6)
Diabetes	536 (50.3)	275 (50.7)	444 (67.7)	197 (60.2)
CAD	447 (41.9)	191 (35.2)	264 (40.2)	125 (38.2)
Arrhythmia	224 (21.0)	105 (19.4)	104 (15.9)	43 (13.1)
CVD	187 (17.5)	99 (18.3)	122 (18.6)	59 (18.0)
PVD	257 (24.1)	119 (22.0)	179 (27.3)	65 (19.9)
Hyperlipidemia	629 (59.0)	316 (58.3)	513 (78.2)	242 (74.0)
CHF	446 (41.8)	220 (40.6)	182 (27.7)	77 (23.5)
Cigarette Use	357 (33.5)	171 (31.5)	72 (11.0)	27 (8.3)

Efficacy Results

Although the efficacy findings are not the focus of this review, briefly, the ability of Peginesatide to raise hemoglobin was demonstrated in all four trials according to the pre-specified primary analysis.

Safety Results

Primary CSE Analysis

As mentioned earlier, the primary statistical analysis of the pooled Phase 3 CSE events was to be based upon a one-sided 95% CI using a weighted Cox model, which was obtained using the upper limit of the two-sided 90% CI, and designed to exclude a hazard ratio greater than 1.3 relative to marketed ESAs. The FDA statistical reviewer performed the primary analysis based on a two-sided 95% CI, as is typically done; the results are shown in Table 2. Across both populations, the hazard ratio (HR) for the pre-specified primary CSE analysis is 1.03 (95% CI 0.87, 1.23). Focusing on the non-dialysis trials, the HR is 1.25 (95% CI 0.91, 1.70), and for the

dialysis trials, the HR is 0.93 (95% CI 0.75, 1.15). As can be seen, the upper bounds for the pooled analysis (dialysis and non-dialysis populations) for the primary CSE analysis, MACE, stroke and all-cause mortality are all greater than one (range 1.17 to 1.41).

The individual components of the primary CSE can be seen in

Table 3. In the Non-Dialysis trials, death, arrhythmia, and unstable angina each occurred more frequently in the Peginesatide arm. Arrhythmias included both tachycardic and bradycardic disorders, but there seemed to be a greater frequency of the latter. In contrast, in the dialysis population, these were not seen.

Event rates, hazard ratios, and confidence intervals for the On-Study versus On-Drug analyses for the primary CSE and MACE endpoints can be seen in Table 4 (sponsor's analyses). As can be seen in the table, the hazard ratios for the On-Drug analyses are consistently smaller than for the On-Study analyses.

Of note, there were no obvious imbalances between the groups in the percentage of events sent to the Endpoint Review Committee that were adjudicated as events.

Table 2: FDA Statistical Reviewer Analysis of CSE Events (Time to Event)*

	Dialysis		Non-Dialysis		Dialysis + Non-Dialysis	
	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)	Peginesatide (N=1722)	Comparator (N=869)
CSE (Primary Endpoint)						
N(%) with Events	243 (22.8%)	132 (24.4%)	141 (21.5%)	56 (17.1%)	384 (22.3%)	188 (21.6%)
HR (95%CI)	0.93 (0.75, 1.15)		1.25 (0.91, 1.70)		1.03 (0.87, 1.23)	
MACE						
N(%) with Events	161 (15.1%)	96 (17.7%)	80 (12.2%)	30 (9.2%)	241 (14.0%)	126 (14.5%)
HR (95%CI)	0.83 (0.65, 1.07)		1.28 (0.84, 1.94)		0.94 (0.76, 1.17)	
All-Cause Mortality						
N(%) with Events	136 (12.8%)	68 (12.5%)	73 (11.1%)	24 (7.3%)	209 (12.1%)	92 (10.6%)
HR (95%CI)	0.99 (0.74, 1.33)		1.37 (0.86, 2.17)		1.11 (0.86, 1.41)	
Stroke						
N(%) with Events	122 (11.4%)	72 (13.3%)	53 (8.1%)	23 (7.0%)	175 (10.2%)	95 (10.9%)
HR (95%CI)	0.84 (0.63, 1.13)		1.10 (0.67, 1.80)		0.91 (0.71, 1.17)	

*Analyses done by the FDA Statistical Reviewer using a cox model with the protocol pre-specified stratification variables (email from Dr. Xu to Dr. Pendse dated 11/6/2011)

Table 3: Individual Component Breakdown of the Primary CSE Analysis (On-Study Analysis – by the Time of Study Termination Oct 15, 2009 to Feb 3, 2010) – Modified from Sponsor’s Table

	Dialysis		Non-Dialysis		Dialysis + Non-Dialysis	
	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)	Peginesatide (N=1722)	Comparator (N=869)
Components of Primary Endpoint N (%)						
Death	115 (10.8%)	64 (11.8%)	58 (8.8%)	22 (6.7%)	173 (10.0%)	86 (9.9%)
Stroke	26 (2.4%)	20 (3.7%)	7 (1.1%)	3 (0.9%)	33 (1.9%)	23 (2.6%)
MI	49 (4.6%)	29 (5.4%)	24 (3.7%)	11 (3.4%)	73 (4.2%)	40 (4.6%)
CHF	103 (9.7%)	49 (9.0%)	56 (8.5%)	28 (8.6%)	159 (9.2%)	77 (8.9%)
Unstable Angina	24 (2.3%)	12 (2.2%)	16 (2.4%)	3 (0.9%)	40 (2.3%)	15 (1.7%)
Arrhythmia	63 (5.9%)	35 (6.5%)	37 (5.6%)	13 (4.0%)	100 (5.8%)	48 (5.5%)

Table 4: Event Rates, Hazard Ratios, and CIs for CSE and MACE CSE, for the Phase 3 Trials (On-Study and On-Drug Analyses) – Modified from Sponsor’s Table

	Dialysis		Non-Dialysis		Dialysis + Non-Dialysis	
	Peginesatide (N=1066)	Epoetin (N=542)	Peginesatide (N=656)	Darbepoetin (N=327)	Peginesatide (N=1722)	Comparator (N=869)
CSE (Primary Endpoint)						
On-Study						
N (%) with Events	243 (22.8%)	132 (24.4%)	141 (21.5%)	56 (17.1%)	384 (22.3%)	188 (21.6%)
HR (90% CI) *	0.95 (0.79, 1.13)		1.32 (1.02, 1.72)		1.06 (0.91, 1.22)	
95% CI	[0.77, 1.17]		[0.97, 1.81]		[0.89, 1.26]	
On-Drug						
N (%) with Events	195 (18.3%)	121 (22.3%)	114 (17.4%)	47 (14.4%)	309 (17.9%)	168 (19.3%)
HR (90% CI) *	0.85 (0.70, 1.03)		1.30 (0.98, 1.74)		0.97 (0.83, 1.14)	
95% CI	[0.68, 1.07]		[0.92, 1.84]		[0.80, 1.17]	
MACE-CSE						
On-Study						
N (%) with Events	161 (15.1%)	96 (17.7%)	80 (12.2%)	30 (9.2%)	241 (14.0%)	126 (14.5%)
HR (90% CI)*	0.85 (0.69, 1.05)		1.41 (0.98, 2.01)		0.97 (0.81, 1.16)	
95% CI	[0.66, 1.09]		[0.92, 2.16]		[0.78, 1.20]	
On-Drug						
N (%) with Events	102 (9.6%)	81 (14.9%)	48 (7.3%)	22 (6.7%)	150 (8.7%)	103 (11.9%)
HR (90% CI)*	0.65 (0.51, 0.83)		1.14 (0.74, 1.74)		0.75 (0.60, 0.93)	
95% CI	[0.48, 0.87]		[0.68, 1.89]		[0.58, 0.96]	

* Note: HR is based on one-sided 95% confidence interval

All-Cause Mortality and Cause of Death

As can be seen in Table 5, in the non-dialysis trials, all-cause mortality, and, specifically sudden death and deaths with unknown primary cause, were more common in subjects treated with Peginesatide than with Darbepoetin. Similar findings were not seen in the dialysis trials.

Table 5: Deaths and Primary Cause of Death – Sponsor’s Table

ERC-Adjudicated Deaths and Primary Cause	Dialysis		Non-Dialysis	
	AF37702 Inj. (n=1066)	Epoetin (n=542)	AF37702 Inj. (n=656)	darbepoetin (n=327)
Deaths (On-Study)	115 (10.8%)	64 (11.8%)	58 (8.8%)	22 (6.7%)
Primary Cause of Death as Adjudicated by the ERC				
Cardiovascular and Unknown Causes	72 (6.8%)	40 (7.4%)	38 (5.8%)	10 (3.1%)
Sudden Death	26 (2.4%)	12 (2.2%)	14 (2.1%)	1 (0.3%)
Cardiovascular (CSE + Other CV Cause)	31 (2.9%)	14 (2.6%)	8 (1.2%)	5 (1.5%)
Unknown Primary Cause	15 (1.4%)	14 (2.6%)	16 (2.4%)	4 (1.2%)
Other Non-Cardiovascular Cause	43 (4.0%)	24 (4.4%)	20 (3.0%)	12 (3.7%)

Factors Affecting Interpretation of Trial Findings

Across the studies there were relatively high rates of premature discontinuation from the study, even when excluding death as a cause, with a slight excess in the Peginesatide arms compared to their active comparators (Table 6). Furthermore, there were imbalances in three categories of study discontinuation, with greater numbers in the Peginesatide arm in each: withdrawal of consent for all study activities, loss to follow-up, and “other”, all of which raise concern for bias related to knowledge of treatment assignment.

Across the studies there were also relatively high rates of premature discontinuation of study medication, even when excluding death as a cause (Table 7). Again, there was a slight excess in the Peginesatide arms. Of these premature discontinuations from study medication, a higher percentage in the Peginesatide arms were cited as being due to “lack of efficacy”, adverse events and withdrawal of consent.

Furthermore, when one compares rate of discontinuation from the study and from study medication, it appears that many of the subjects who prematurely discontinued study medication also likely went on to terminate the study.

Table 6: Premature Study Discontinuations (from Phase 3 Trials) – Modified from Sponsor’s Table

	Dialysis		Non-Dialysis		Total	
	Peginesatide N = 1066	Epoetin N = 542	Peginesatide N = 656	Darbepoetin N = 327	Peginesatide N = 1722	Comparator N = 869
Number of Subjects who Prematurely Terminated from Study						
	279 (26.2%)	129 (23.8%)	161 (24.5%)	63 (19.3%)	440 (25.6%)	192 (22.1%)
Primary Reason for Discontinuation from Study						
Consent Withdrawn for all Study Activities	72 (6.8%)	23 (4.2%)	46 (7.0%)	16 (4.9%)	118 (6.9%)	39 (4.5%)
Death	107 (10.0%)	59 (10.9%)	48 (7.3%)	19 (5.8%)	155 (9.0%)	78 (9.0%)
Loss to Follow-up	11 (1.0%)	7 (1.3%)	18 (2.7%)	8 (2.4%)	29 (1.7%)	15 (1.7%)
Other	89 (8.3%)	40 (7.4%)	49 (7.5%)	20 (6.1%)	138 (8.0%)	60 (6.9%)

Table 7: Subjects who Prematurely Discontinued Study Medication from Phase 3 Trials – Modified from Sponsor’s Table

	Dialysis		Non-Dialysis		Total	
	Peginesatide N = 1066	Epoetin N = 542	Peginesatide N = 656	Darbepoetin N = 327	Peginesatide N = 1722	Comparator N = 869
Number of Subjects who Prematurely Discontinued Study Medication						
	329 (30.9%)	144 (26.6%)	188 (28.7%)	77 (23.5%)	517 (30.0%)	221 (25.4)
Primary Reason for Prematurely Discontinuing Study Medication						
Lack of Efficacy	11 (1.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	12 (0.7%)	0 (0.0%)
Adverse Event	47 (4.4%)	12 (2.2%)	48 (7.3%)	16 (4.9%)	95 (5.5%)	28 (3.2%)
Withdrew Consent	64 (6.0%)	19 (3.5%)	45 (6.9%)	17 (5.2%)	109 (6.3%)	36 (4.1%)
Death	89 (8.3%)	53 (9.8%)	36 (5.5%)	17 (5.2%)	125 (7.3%)	70 (8.1%)
Renal Transplant	34 (3.2%)	24 (4.4%)	3 (0.5%)	2 (0.6%)	37 (2.1%)	26 (3.0%)
Loss to Follow-Up	6 (0.6%)	4 (0.7%)	13 (2.0%)	5 (1.5%)	19 (1.1%)	9 (1.0%)
Other	78 (7.3%)	32 (5.9%)	42 (6.4%)	20 (6.1%)	120 (7.0%)	52 (6.0%)

The Phase 3 trials were closed beginning on October 15, 2009, the date by which a total of at least 553 subjects were projected to have experienced a composite safety endpoint (CSE) event. At individual study sites, the trials were closed over a time period from October 15, 2009 to February 3, 2010. Thus, October 15, 2009 was the last date through which subjects were uniformly followed for CSE events and the last date for survey of vital status. As of this date, CSE status was known for 2310/2591 (89.2%) of subjects overall, either by subjects experiencing CSE events or those who had not experienced an event but had completed follow-up for CSE events. Of the 2591 subjects, 106 subjects, or 4.1%, overall, terminated from the study prior to October 15, 2009 without having experienced a CSE event and with unknown vital status by the termination date (Table 8).

Table 8: Follow-up for Composite Safety Endpoint and Vital Status by October 15, 2009 – Sponsor’s Table

	Dialysis		Non-Dialysis		Dialysis + Non-Dialysis		
	AF37702 Injection (N=1066)	Epoetin (N=542)	AF37702 Injection (N=656)	darbepoetin (N=327)	AF37702 Injection (N=1722)	Reference ESA (N=869)	Total (N=2591)
CSE Status Known (i.e., experienced a CSE event, or completed follow-up through 15 October 2009 without experiencing a CSE Event):							
	939 (88.1%)	492 (90.8%)	583 (88.9%)	296 (90.5%)	1522 (88.4%)	788 (90.7%)	2310 (89.2%)
CSE Status Unknown (i.e., terminated from study prior to 15 October 2009 without experiencing a CSE Event):							
	127 (11.9%)	50 (9.2%)	73 (11.1%)	31 (9.5%)	200 (11.6%)	81 (9.3%)	281 (10.8%)
For those with CSE Status Unknown, Vital Status as of 15 October 2009:							
Vital Status Known	89 (8.3%)	31 (5.7%)	37 (5.6%)	18 (5.5%)	126 (7.3%)	49 (5.6%)	175 (6.8%)
Vital Status Unknown	38 (3.6%)	19 (3.5%)	36 (5.5%)	13 (4.0%)	74 (4.3%)	32 (3.7%)	106 (4.1%)

Comments and Recommendations

Erythropoietin, the primary growth factor for erythroid development, is produced in the kidney and released into the bloodstream. It binds to the erythropoietin receptor on the surface of erythroid progenitor cells, activating signaling pathways which stimulate red blood cell production, or erythropoiesis, and inhibition of apoptosis, increasing red blood cell production.

Erythropoiesis-stimulating agents (ESAs) are drugs that stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. Two ESAs are marketed currently in the U.S, epoetin alpha (EPOGEN®/ PROCRI®) and darbepoetin alpha (ARANESP®), both of which have been shown to cause adverse cardiovascular outcomes in multiple randomized trials of ESAs in CKD. Although numerous mechanisms have been postulated, including those related to blood pressure, ESA dose, and hemoglobin concentration, none have been confirmed. In addition, the absolute magnitude of the cardiovascular risk of these agents remains as of yet unknown.

Peginesatide (AF37702) is a synthetic, PEGylated erythropoietin receptor activator peptide with no amino acid sequence homology to erythropoietin which binds to and activates the human erythropoietin receptor in a manner similar to that of recombinant ESAs. The applicant has submitted an NDA for this new molecular entity for the proposed indication of treatment of adult patients with anemia of chronic renal failure on dialysis.

One of the goals of the Phase 3 program for Peginesatide was to capture data on cardiovascular risk relative to marketed ESAs. The Phase 3 program consists of four randomized, open-label, active-controlled pivotal non-inferiority trials – two in subjects with CKD on dialysis and two in subjects with CKD who were not on dialysis. These studies were designed to exclude an upper bound of 1.3 relative to marketed ESAs based upon a one-sided 95% CI. Of note, typically non-inferiority studies are designed and analyzed based on a 2-sided 95% confidence interval.

The pre-specified primary safety analysis was a composite safety endpoint (CSE) consisting of consisting of all-cause death, stroke, myocardial infarction (MI), congestive heart failure (CHF), unstable angina, and arrhythmia. Pooled primary CSE analyses of these trials showed an overall

HR (for dialysis and non-dialysis taken together) of 1.03 with an upper bound of 1.23 (FDA statistical reviewer's two-sided 95% CI analyses). Ignoring other aspects of study design or conduct that may have impacted the findings, the results cannot exclude a possible ~20% increased risk for adverse cardiovascular outcomes with Peginesatide treatment relative to marketed ESAs. When we separate the populations, as the applicant has done, the dialysis studies yield a HR of 0.93 with upper bound of 1.15, and the non-dialysis studies yield a HR of 1.25 with an upper bound reaching 1.70. In the non-dialysis trials, the individual components of the composite that were driving the increased risk in the Peginesatide-treated subjects were death, arrhythmia, and unstable angina.

Given the differential findings in the dialysis and non-dialysis populations, the sponsor proposed limiting the indication to dialysis patients. This raises an important question – is there a biologically plausible mechanism whereby there would be greater adverse cardiovascular effects with Peginesatide treatment in one population versus the other? We can think of no obvious biologically plausible mechanism for such a differential in risk. Moreover, if you focus on the 95% confidence intervals as opposed to the point estimates, they overlap, suggesting that there may be no difference between the two populations with regard to cardiovascular risk with Peginesatide relative to marketed ESAs.

Finally, several elements of the trial design and conduct suggest that the true cardiovascular risk of Peginesatide relative to marketed ESAs may be greater than the results of these trials suggest. An open-label trial raises concerns for bias. One method for introduction of bias is preferential discontinuation and loss to follow-up of patients who were sicker and more likely to have adverse outcomes. Whether or not this occurred in these trials is not clear. However, we do note the relatively high rates of study discontinuation/follow up and the slight excess of discontinuations from the study in the Peginesatide arms. With regard to the issue of premature discontinuation of study medication, the slight excess in discontinuations in the Peginesatide arm (and in particular, the slight excess in discontinuation for an adverse event) may in part explain the fact that the on-drug analysis looked more favorable than the on-study analysis for the Peginesatide groups compared to the active controls. Finally, we note that a greater number of Peginesatide-treated subjects who prematurely discontinued from the study had CSE status unknown at the end of the trials.

Perhaps the most critical issue is that these trials characterized the risk of Peginesatide relative to marketed ESAs. Why, unless the other agent offers significant advantage over marketed ESAs, would one tolerate 1.3 times greater risk of adverse CV outcomes above and beyond that of marketed ESAs? The fact that we do not know the safety profiles of the chosen comparators makes it extremely difficult to evaluate the safety of Peginesatide against the backdrop of these active comparators. It is concerning, nonetheless, that the available data do not allow for the exclusion of excess risk with Peginesatide therapy relative to existing ESA comparators, in a population with a high absolute risk of CV disease at baseline.

There are challenges to developing drugs in this area, where the benefit shown thus far is a reduction in the use of transfusions. With regard to the path forward for these products, we can think of two potential routes by which to evaluate drug candidates while also adequately characterizing potential cardiovascular risks of therapy. One such method is to conduct a placebo-controlled non-inferiority study that seeks to rule out some level of cardiovascular risk. The second is to conduct an active-controlled study against a marketed ESA that seeks to show superiority in reduction of adverse CV events.

With regard to the conduct of placebo-controlled non-inferiority studies, two questions that arise are the choice of the NI margin for such a trial and secondly, the ethical issues surrounding use

of a placebo. In trials of diabetes mellitus, the margins that have been used were 30% increase in risk. The choice of margin for trials of ESAs merits further discussion. Clearly, the absolute level of cardiovascular risk at baseline should factor into the selection of a margin. For a population with a low level of absolute risk, one might tolerate a larger margin. In contrast, for a population with a high level of absolute risk of cardiovascular events, a smaller margin would be preferable. Given that the absolute risk of cardiovascular disease in the CKD population (both dialysis and non-dialysis) is high, a margin such as 1.3 may not be appropriate. In trials of new therapies for the anemia of CKD, it may be reasonable to select a non-inferiority margin based on our understanding to date of the magnitude of risk of ESAs. For example, if ESAs were thought to have a relative risk of 1.3 for increasing adverse cardiovascular events, one might select a margin which excludes this level of risk. By doing so, one has effectively shown that the new therapy has less risk than marketed ESAs, hence offering an advantage over the marketed ESAs. The choice of margin may merit further discussion, and may be best served by discussion with the larger community, with the discussion informed by the data that have been collected thus far. Other factors will also need to be taken into consideration, such as the feasibility of the trial (i.e. sample size constraints). With regard to use of placebo, such an approach may not be acceptable in the dialysis population in which anemia is typically more severe than it is in the non-dialysis population.

In sum, given our current understanding of the data, Peginesatide does not appear to offer any advantage beyond those of marketed ESAs in the proposed population (dialysis patients). Indeed, existing data raise the possibility that adverse cardiovascular effects may be greater with Peginesatide than with currently marketed ESAs.

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