CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022271Orig1s000

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/BLA #	022271
Product Name:	Nesina (alogliptin)
PMR/PMC Description:	A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the pharmacokinetics of alogliptin and to determine the dose(s) for the subsequent phase 3 study that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10-13 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	12/31/2013
	Final Report Submission:	06/30/2014
	Other:	

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

Alogliptin is ready for approval for the treatment of type 2 diabetes mellitus (T2DM) in adults; however, the pediatric studies have not been completed.

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."

Deferred pediatric study required under PREA to assess the pharmacokinetics of alogliptin in pediatric patients ages 10 to 17 years (inclusive) with T2DM and to establish the dose(s) to be used in the phase 3 efficacy and safety study.

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.

A phase 1 pharmacokinetic dose finding study of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with T2DM. At least 25% of randomized subjects will be 10-13 years of age.

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)
Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with T2DM

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)

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/BLA #	022271 Nesina (alogliptin)
Product Name:	203414 Kazano (alogliptin and metformin hydrocholoride)
PMR/PMC Description:	Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin compared to placebo when added to metformin for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10 to 17 years (inclusive). At least 30% of randomized subjects will be 10-14 years of age, and at least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/31/2015
	Study/Trial Completion:	07/31/2019
	Final Report Submission:	01/31/2020
	Other:	

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

   Alogliptin is ready for approval for use in adults; however, the pediatric studies have not been completed.

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."

Deferred pediatric study required under PREA to assess the efficacy and safety of alogliptin compared with placebo when added on to metformin for the treatment of T2DM in pediatric patients ages 10 to 17 years (inclusive).

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.

A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin compared to placebo when added on to metformin in pediatric patients 10 through 17 years (inclusive) with T2DM. At least 30% of randomized subjects will be 10-14 years of age. At least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

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)
Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with T2DM

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)

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/BLA #	022271
Product Name:	Nesina (alogliptin)
PMR/PMC Description:	Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin compared to placebo for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10 to 17 years (inclusive). At least 30% of randomized subjects will be 10-14 years of age, and at least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/31/2015
	Study/Trial Completion:	11/30/2020
	Final Report Submission:	05/31/2021
	Other:	

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

   Alogliptin is ready for approval for use in adults; however, the pediatric studies have not been completed.

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."

Deferred pediatric study required under PREA to assess the efficacy and safety of alogliptin compared with placebo as monotherapy for the treatment of T2DM in pediatric patients ages 10 to 17 years (inclusive).

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.

A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with T2DM. At least 30% of randomized subjects will be 10-14 years of age, and at least 1/3 and not more than 2/3 of subjects in both age subsets (10-14 years and 15-17 years) will be female.

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)
Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with T2DM

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)

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/BLA # Product Name:	022271 Nesina (alogliptin) 022426 Oseni (alogliptin and pioglitazone) 203414 Kazano (alogliptin and metformin hydrochloride)
PMR/PMC Description:	An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with alogliptin – both foreign and domestic cases. Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/31/2013
	Interim Report Submissions:	03/31/2014
		03/31/2015
		03/31/2016
		03/31/2017
		03/31/2018
		03/31/2019
		03/31/2020
		03/31/2021
		03/31/2022
	Study/Trial Completion:	01/31/2023
	Final Report Submission:	09/30/2023
	Other:	

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

Review of clinical trial and Japanese postmarketing data has revealed cases of hepatotoxicity for which no satisfactory or convincing diagnosis, other than the use of alogliptin, was found. Given the low incidence of this safety signal, enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of this drug.

A serious risk of pancreatitis is a potential safety concern related to the DPP4 inhibitor class of drugs, including alogliptin. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of the drug.

A serious risk of hypersensitivity is a potential safety concern related to the DPP4 inhibitor class of drugs, including alogliptin. This risk may be enhanced by concomitant administration of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Enhanced pharmacovigilance is required to generate additional data to better assess this serious risk related to the long-term use of the drug and concomitant medication administration.

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 goal of the enhanced pharmacovigilance study is to gather additional data on known and potential serious risks related to the long-term use of alogliptin.

The program will include:

a) Active query of reporters to obtain additional clinical information related to reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions. The sponsor should actively query reporters for the following information:

1) For reports of serious hepatic abnormalities the sponsor should actively query reporters for liver-related laboratory (including viral serology), imaging and pathology results, duration of alogliplitin exposure, and other risk factors for hepatic abnormalities.
2) For reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis the sponsor should actively query reporters for related laboratory values (including triglyceride, lipase, and amylase values), confirmatory imaging and pathology results, duration of alogliptin exposure, and other risk factors for pancreatitis.
3) For reports of severe hypersensitivity reactions the sponsor should actively query reporters for concomitant medication use (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers), biopsy results, duration of alogliptin exposure, and other risk factors for hypersensitivity reactions.

b) Expedited reporting to FDA of all initial and follow-up reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis with a serious outcome, and severe hypersensitivity reactions.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal and hemorrhagic/necrotizing pancreatitis, and 10 years from the date of approval for reports of hepatic abnormalities and severe hypersensitivity reactions.

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.

Enhanced pharmacovigilance program for reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis (HNP), and severe hypersensitivity reactions in patients treated with alogliptin for a period of 5 years from the date of approval for fatal pancreatitis and HNP and 10 years from the date of approval for hepatic abnormalities and severe hypersensitivity reactions to collect data that will be analyzed to better define these risks. The enhanced pharmacovigilance program includes the following:

a) Active query of reporters to obtain additional clinical information related to reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions.

b) Expedited reporting to FDA of all initial and follow-up reports of serious hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis with a serious outcome, and severe hypersensitivity reactions.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

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)
Enhanced pharmacovigilance

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)

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/BLA #	022271
Product Name:	Nesina (alogliptin)
PMR/PMC Description:	A randomized, double-blind, placebo-controlled trial evaluating the effect of Nesina (alogliptin) on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The primary objective of the trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Nesina (alogliptin) to that observed in the control group is less than 1.3. The long-term effects of Nesina (alogliptin) on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety will be evaluated. The trial must include at least 200 Nesina (alogliptin)-treated patients with moderate renal impairment and 100 Nesina (alogliptin)-treated patients with severe renal impairment. .

PMR/PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	12/31/2013
	Final Report Submission:	09/30/2014
	Other:	

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

Interim analysis of cardiovascular outcomes trial "A multicenter, randomized, double-blind, placebo-controlled study to evaluate CV outcomes following treatment with alogliptin in addition to standard of care in subjects with T2DM and acute coronary syndrome" demonstrated that the upper bound of the 95% confidence interval for the risk ratios comparing the incidence of major adverse cardiovascular events (MACE) with alogliptin to the incidence of MACE with placebo is <1.8. However, the duration of study was not sufficient to address the risk definitively (i.e., demonstrate an upper bound of the 95% CI <1.3).

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."

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry, "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". This trial is intended to demonstrate that alogliptin therapy does not result in an unacceptably increased risk for major adverse cardiovascular events (MACE), i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

The sponsor has already provided sufficient evidence that alogliptin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded unacceptable cardiovascular risk. Therefore, consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with alogliptin to that observed in the control group is less than 1.3.

The trial must also assess adverse events of special interest including the long-term effects of alogliptin on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety.

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.

A randomized, double-blind, placebo-controlled cardiovascular outcomes trial to be conducted in subjects with type 2 diabetes and acute coronary syndrome. The primary endpoint will be the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

The trial must also assess adverse events of special interest including the long-term effects of alogliptin on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety.

The trial must include at least 200 alogliptin-treated patients with moderate renal impairment and 100 alogliptin-treated patients with severe renal impairment.

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/

AMY G EGAN
01/24/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

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

Memorandum

Date: January 18, 2013

To: Rich Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DPDP
Kendra Y. Jones, Regulatory Review Officer, DCDP

Subject: **OPDP Labeling Review**
NDA #022271 NESINA (alogliptin) tablets
#022426 OSENI (alogliptin and pioglitazone) tablets
#203414 KAZANO (alogliptin and metformin HCl) tablets

OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (Med Guide), and carton/container labeling for the products listed above consulted from DMEP to OPDP on January 7, 2008, October 1, 2008, August 3, 2011, December 7, 2011, and September 17, 2012. OPDP has reviewed the proposed version of these documents accessed from the eRoom on January 16, 2013 and offers the following comments.

Comments regarding the PI and Med Guide are provided in the marked versions below. OPDP has reviewed the proposed carton/container labeling submitted on January 9, 2013, January 11, 2013 and January 17, 2013 and does not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
01/18/2013

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

PATIENT LABELING REVIEW

Date:	January 18, 2013
To:	Mary Parks, M.D., Director **Division of Metabolic and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name:	NESINA (alogliptin)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 22271
Applicant:	Takeda Global Research and Development Center, Inc.

1 INTRODUCTION

On December 21, 2007, Takeda Global Research and Development Center, Inc. (Takeda) submitted a New Drug Application (NDA 22271) for NESINA (alogliptin) tablets indicated for the treatment of Type 2 Diabetes. The Agency issued a Complete Response Letter on April 25, 2012. On July 26, 2012, Takeda submitted for the Agency's review a Complete Response to Issues Identified in Action Letter amending all issues identified in the Agency's April 25, 2012, Complete Response Letter. On September 18, 2012 the Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for NESINA (alogliptin) tablets.

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Medical Policy Programs **(**DMPP) to review the Applicant's proposed Medication Guide for NESINA (alogliptin) tablets.

2 MATERIAL REVIEWED

- Draft NESINA (alogliptin) tablets, Medication Guide (MG) received on July 26, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 7, 2013.
- Draft NESINA (alogliptin) tablets, Prescribing Information (PI) received on July 26, 2012, and received by DMPP January 7, 2013.

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 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 document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- 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 is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG is 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.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/18/2013

MELISSA I HULETT
01/18/2013

LASHAWN M GRIFFITHS
01/18/2013

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 Memo

Date:	January 18, 2013
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg; Kazano (Alogliptin and Metformin) Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg; Oseni (Alogliptin and Pioglitazone) Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg
Application Type/Number:	NDA 022271, NDA 203414, and NDA 022426
Applicant/sponsor:	Takeda Pharmaceuticals America, Inc

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

1 INTRODUCTION

This review evaluates the revised professional sample blister and bottle tray labeling for Nesina (Alogliptin) Tablets, 12.5 mg and 25 mg, Kazano (Alogliptin and Metformin) Tablets, 12.5 mg/500 mg and 12.5 mg/1000 mg, and Oseni (Alogliptin and Pioglitazone) Tablets, 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg submitted by the Applicant on January 17, 2013.

In this submission, the Applicant revised the trademark statement which is currently presented as (b) (4) to read "<TAKEDA PRODUCT> is a trademark of Takeda Pharmaceutical Company Limited registered with the U.S. Patent and Trademark Office and is used under license by Takeda Pharmaceuticals America, Inc."

2 MATERIAL REVIEWED

The revised professional sample blister and bottle tray labeling submitted to the Agency on January 17, 2013 were evaluated to assess whether the revision is acceptable from a medication safety perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised professional sample blister and bottle tray labeling for Nesina (Alogliptin), Kazano (Alogliptin and Metformin), and Oseni (Alogliptin and Pioglitazone) submitted on January 17, 2013 are acceptable from the medication error perspective.

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/s/

REASOL AGUSTIN
01/18/2013

YELENA L MASLOV
01/18/2013

M E M O R A N D U M

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

CONSULT REVIEW MEMO

DATE: January 14, 2013

TO: Mehreen Hai and Richard Whitehead, Regulatory Project Managers
Valerie Pratt, M.D. and Karen Mahoney, M.D. Clinical Reviewers
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Treatment Assignment for Subject 8413-006/402

NDA: 22271

APPLICANT: Takeda Global Research and Development Center, Inc.

DRUG: Nesina (alogliptin)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: January 7, 2013

I. BACKGROUND:

On January 7, 2013, the Office of Scientific Investigations (OSI) was requested to comment on treatment assignment for Subject 8413-006/402.

In April 2012, Takeda received a Complete Response letter from FDA for both the alogliptin and SYR-322-4833 NDAs, requesting additional clinical and postmarketing data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. In response to this request, on July 26, 2012, Takeda submitted an updated safety profile of alogliptin with available data from recently completed and ongoing clinical trials along with additional postmarketing data from Japan. In Module 2.7.4 of the NDA resubmission, in-text Table 3.d, under "new case reported after May 15 2012" Subject 8413-006/402 (Subject 8413 at site 006 in study 402) is listed as alogliptin 25 mg.

On January 7, 2013, FDA DMEP review division received an e-mail from the sponsor informing the review division that the sponsor discovered an error in the treatment code and that Subject 8413-006/402 was randomized to placebo, not to alogliptin as originally reported in the NDA submission of July 26, 2012. The e-mail also contained an explanation for the error. The review division forwarded this e-mail to Office of Scientific Investigations (OSI) and requested advice from OSI concerning methods to determine the correct treatment assignment for the subject **(E-mail Attachment 1)**. The sponsor discovered the error while they were in the process of updating Table 3f (Markedly abnormal values for hepatic parameters of Study 402). Takeda re-ran the table with a new database cut, with six months of additional data. Takeda attributes that error, in part, due to the fact that this subject was a late breaker case that occurred following the database cut off and that the table in 2.7.4 was manually generated at the time of the NDA resubmission.

II. RESULTS:

OSI requested and reviewed the following documentation and documents concerning this subject:

1. E-mails from Eugenio Andraca-Carrera and Mary Parks providing timelines for this subject and information that the subject started on treatment on November 16, 2011 and is randomized to placebo according to the dataset Sequence 0070 (71) submitted on 7/27/2012 **(E-mail Attachment 2).**

2. Takeda's response to FDA information request submitted via e-mail on January 9, 2013 containing the case report form (CRF) and the site's investigational product accountability log. The dosing log from Page 36 of the eCRF for Subject 8413-006 and the product accountability log **(Attachment 3)** were compared. All nine medication ID #'s on the subject eCRF are noted to be from placebo lots. In addition, included are two Takeda certificates of release for the bulk product lots that were dispensed to this subject, bulk lot Z641V081 and bulk lot 1025001A. The following are the nine "med ID#'s":

i. 22889862
ii. 20117545
iii. 22715106
iv. 22068829
v. 22128993
vi. 21642842
vii. 21945408
viii. 220907254
ix. 20660869

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data listing submitted to the NDA on June 27, 2012 and the additional documents submitted, specifically the eCRF and the medication log, demonstrate that the subject received placebo. The medication ID numbers entered in the CRF by the investigator are placebo lots per the site level inventory provided. This also matches Takeda's certificate of release for the drug lot as being placebo.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{*See appended electronic signature pag*e}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

ATTACHEMENT 1

Leibenhaut, Susan

From	Parks, Mary H
Sent	Monday, January 07, 2013 3:45 PM
To	Leibenhaut, Susan
Cc	Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject	RE: NDA22271 alogliptin: Information Request

Correction - Jan 25th is the AGD

From: Parks, Mary H
Sent: Monday, January 07, 2013 3:42 PM
To: Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: FW: NDA22271 alogliptin: Information Request

Hi Susan

We have an unusual situation arise that I'm wondering if you can help advise us on. In the course of reviewing the NDA in this subject line we were down to a decision on approval for one case of liver toxicity in a clinical trial. We had numerous info requests on this case, including having this patient be called back in to have bloods drawn to rule out hepatitis. They did bring him back in and ruled out hepatitis E as a possible cause. Just today we got the email below telling us that they discovered an error in the treatment code and that this patient was randomized to placebo. Below are the company's explanations for this error, which essentially eliminated the safety concern. Frankly, I'm not able to verify their explanation below and this last minute discovery just makes me a little nervous, especially since they've known about this case for several months now and we've had several requests to them on him.

We have an opportunity to tcon w/ them so I was wondering from your experience w/ clinical site inspections are there specific documents you look at to make sure someone is randomized AND received treatment as reported to FDA? We have a AGD of Jan 29th so I seriously doubt OSI will be able to inspect this site (Russia) but any documentation that OSI can recommend we request be sent in would be helpful.

Thanks,
Mary

From: Whitehead, Richard
Sent: Monday, January 07, 2013 10:40 AM
To: Parks, Mary H; Pratt, Valerie
Cc: Hai, Mehreen
Subject: FW: NDA22271 alogliptin: Information Request

Mary,

Let me know if this answer your question or you want additional clarification.

Rich

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, January 07, 2013 10:28 AM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request

Dear Rich,
In the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg. At the time of the resubmission, since this was a late breaker case (occurred after database cut-off), there was no program assisted narrative generated from the clinical database, which would have identified the subject treatment as placebo. In the clinical database, which is unblinded, this subject was correctly assigned to the placebo treatment arm in all the summary statistical tables (e.g., demographics, exposure, AEs and laboratory tables). We have validated the treatment assignment codes of the data and the IVRS randomization code which confirms this patient is indeed on the placebo treatment arm.

In the Pharmacovigilance safety database of SAEs, this subject still remains blinded. This case was not a SUSAR therefore was not unblinded for the purpose of an IND expedited safety report. All CIOMS for this subject indicate that the treatment code is not broken.

We would be glad to have a teleconference with the Agency to provide any additional details or clarity on this issue.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M (b) (6)
F 224-554-7870
sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda hhs.gov]
Sent: Monday, January 07, 2013 7:54 AM
To: Cosner, Sandra (TGRD)
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request

Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. We ask that you provide your response by noon, today. Let me know if you have any questions and please confirm receipt of this email notification.

Please explain how you were able to determine that subject 8413-006/402 was assigned to placebo and yet state that this "case currently remains blinded as this is an ongoing study in the safety database". Did you not have to unblind the case to determine treatment assignment?

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Sunday, January 06, 2013 10:11 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Jan. 4 Information Request

Dear Rich,

During our evaluation of FDA's latest information request from Friday, Jan. 4 for an update of Table 3f (Markedly abnormal values for hepatic parameters of Study 402), Takeda re-ran the Table with a new database cut (with 6 months of additional data) and has unfortunately learned of an incorrect treatment code on the case of interest in Study 402; subject 8413-006/402 (TPG2012A01058) that was provided to FDA in the July 2012 NDA resubmission. Takeda had inadvertently assigned this case to the alogliptin 25 mg treatment code and subsequently upon this latest review learned that this subject was in fact on placebo.

We would like to reassure the Agency that the statistical tables and outputs from the clinical database are accurate. In addition, the safety database is accurate and this case currently remains blinded as this is an ongoing study in the safety database. This error was in part due to the fact that this subject was a late breaker case that occurred following the database cut off and that the table in 2.7.4 was manually generated. Because this error was discovered, the team is putting extra effort in QCing all the data in all manually generated hepatic tables from the NDA resubmission (i.e., Tables 3c, 3d and 3i) to confirm these are accurate. The team is also re-checking all current data, randomization codes, and conducting QC checks against previous and current database cut offs. Takeda apologizes and regrets very much that this error has occurred. We understand this case was of specific interest to both Takeda and FDA and we wanted to notify you as soon as we had confirmed this error. Through our investigation, we are ensuring that no other such mis-assignments exist. The case will be properly reflected in our submission that we will be sending to you by the end of the day tomorrow (Jan 7) as per the data you requested last week, at which time the quality control of the other tables will have been completed as well.

We understand the Agency is meeting Monday, January 7 for the second round of labeling comments and potentially later in the week for the end-of-review wrap-up meeting. If the Division has any concerns or would like any additional clarification on this issue, Takeda would gladly be available for a teleconference to further review the details of this finding and provide clarity or additional assurances ensuring data integrity.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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From: Whitehead, Richard [mailto:Richard.Whitehead@fda hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAM NE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

ATTACHEMENT 2

Leibenhaut, Susan

From	Parks, Mary H
Sent	Tuesday, January 08, 2013 8:58 AM
To	Leibenhaut, Susan; Andraca-Carrera, Eugenio
Cc	Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject	RE: NDA22271 alogliptin: Information Request

The patient was started on treatment on November 16, 2011. On study day 181 during a scheduled visit his ALT/AST values were found to be > 5xULN. On Study Day 187 he was subicteric w/ bili > 2xULN and ALT/AST now > 10xULN. So if we say about 6 months into the study, he was first noted to have liver abnormalities mid-May that progressed into June.

I don't recall when the report came in (Valerie - do you know?) but we have sent numerous info requests since then (and 7/27/12) so if they submitted to us in 7/27/12 that he was on placebo they certainly did divulge that info in the course of all the info requests.

From: Leibenhaut, Susan
Sent: Tuesday, January 08, 2013 8:50 AM
To: Parks, Mary H; Andraca-Carrera, Eugenio
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: RE: NDA22271 alogliptin: Information Request

Can you tell me the timeline for when the liver injury occurred/was reported relative to when the dataset was created submitted?
Susan

From: Parks, Mary H
Sent: Tuesday, January 08, 2013 8:42 AM
To: Andraca-Carrera, Eugenio; Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: RE: NDA22271 alogliptin: Information Request

Thanks. This is helpful and is sufficient to convince me that he did receive placebo. If you told me a dataset was just submitted yesterday w/ this treatment assignment, I might push harder on the company.

How do others feel?

Mary

From: Andraca-Carrera, Eugenio
Sent: Tuesday, January 08, 2013 8:22 AM
To: Parks, Mary H; Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: RE: NDA22271 alogliptin: Information Request

Hi Mary

Patient 8413-006/402 was not included in the submission I used for my review of this application.

However, I found this patient in a SAS dataset submitted later to NDA 022426 Sequence 0070 (71) on 7/27/2012.

Patient 8413-006/402 is recorded as being randomized to Placebo QD.

From: Parks, Mary H
Sent: Monday, January 07, 2013 7:25 PM
To: Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer); Andraca-Carrera, Eugenio
Subject: RE: NDA22271 alogliptin: Information Request

Susan

Thanks for the quick response w/ suggestion. I'm cc'ing Eugenio as he reviewed this trial for an interim CV analysis with the previous submission; however, it may be that this patient wasn't enrolled until after his review was completed as he started drug in Nov 2011.

Eugenio - you heard about this patient at today's labeling meeting. His patient ID number is **Patient 8413-006/402**
Any possibility you can look at the SAS datsets to see if he's in there and can determine if he was assigned to pbo or alogliptin?

Thanks,
Mary

From: Leibenhaut, Susan
Sent: Monday, January 07, 2013 6:15 PM
To: Parks, Mary H
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: RE: NDA22271 alogliptin: Information Request

All,
I was hoping to find some independent information, outside of Module 2, concerning this subject to determine treatment arm. However, I can't find it. it appears from the information below that this subject would be in the line listings in Study 402 Site 8413. The line listings for this site indicate only 2 subjects enrolled at this site. Subject 001 was in the Alogliptin arm and Subject 002 was not randomized. This study (the CV endpoint study) was ongoing at the time of submission, so I am assuming that the site was not yet fully enrolled when the initial line listings were submitted. **Is it possible that there is a SAS dataset with all enrolled subjects for this site that would contain treatment assignment in order to corroborate with the sponsor explanation?**

According to item below "in the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg." Is this the Table on Page 53 of the July 17 resubmission in the ISS?

I will be discussing this issue with others in OSI to see if they can offer any insight into this or any suggestion for documents to request.
Thanks,
Susan

From: Parks, Mary H
Sent: Monday, January 07, 2013 3:45 PM
To: Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: RE: NDA22271 alogliptin: Information Request

Correction - Jan 25th is the AGD

From: Parks, Mary H
Sent: Monday, January 07, 2013 3:42 PM
To: Leibenhaut, Susan
Cc: Whitehead, Richard; Hai, Mehreen; Pratt, Valerie; Mahoney, Karen M (Endocrine Clinical Reviewer)
Subject: FW: NDA22271 alogliptin: Information Request

Hi Susan

We have an unusual situation arise that I'm wondering if you can help advise us on. In the course of reviewing the NDA in this subject line we were down to a decision on approval for one case of liver toxicity in a clinical trial. We had numerous info requests on this case, including having this patient be called back in to have bloods drawn to rule out hepatitis. They did bring him back in and ruled out hepatitis E as a possible cause. Just today we got the email below telling us that they discovered an error in the treatment code and that this patient was randomized to placebo. Below are the company's explanations for this error, which essentially eliminated the safety concern. Frankly, I'm not able to verify their explanation below and this last minute discovery just makes me a little nervous, especially since they've known about this case for several months now and we've had several requests to them on him.

We have an opportunity to tcon w/ them so I was wondering from your experience w/ clinical site inspections are there specific documents you look at to make sure someone is randomized AND received treatment as reported to FDA? We have a AGD of Jan 29th so I seriously doubt OSI will be able to inspect this site (Russia) but any documentation that OSI can recommend we request be sent in would be helpful.

Thanks,
Mary

From: Whitehead, Richard
Sent: Monday, January 07, 2013 10:40 AM
To: Parks, Mary H; Pratt, Valerie
Cc: Hai, Mehreen
Subject: FW: NDA22271 alogliptin: Information Request

Mary,

Let me know if this answer your question or you want additional clarification.

Rich

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, January 07, 2013 10:28 AM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request

Dear Rich,
In the manually created in-text table of 2.7.4 of the NDA resubmission, Table 3.d, this subject (8413-006/402) was erroneously listed as alogliptin 25 mg. At the time of the resubmission, since this was a late breaker case (occurred after database cut-off), there was no program assisted narrative generated from the clinical database, which would have identified the subject treatment as placebo. In the clinical database, which is unblinded, this subject was correctly assigned to the placebo treatment arm in all the summary statistical tables (e.g., demographics, exposure, AEs and laboratory tables). We have validated the treatment assignment codes of the data and the IVRS randomization code which confirms this patient is indeed on the placebo treatment arm.

In the Pharmacovigilance safety database of SAEs, this subject still remains blinded. This case was not a SUSAR therefore was not unblinded for the purpose of an IND expedited safety report. All CIOMS for this subject indicate that the treatment code is not broken.

We would be glad to have a teleconference with the Agency to provide any additional details or clarity on this issue.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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From: Whitehead, Richard [mailto:Richard.Whitehead@fda hhs.gov]
Sent: Monday, January 07, 2013 7:54 AM
To: Cosner, Sandra (TGRD)
Cc: Hai, Mehreen

Subject: RE: NDA22271 alogliptin: Information Request

Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. We ask that you provide your response by noon, today. Let me know if you have any questions and please confirm receipt of this email notification.

Please explain how you were able to determine that subject 8413-006/402 was assigned to placebo and yet state that this "case currently remains blinded as this is an ongoing study in the safety database". Did you not have to unblind the case to determine treatment assignment?

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Sunday, January 06, 2013 10:11 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Jan. 4 Information Request

Dear Rich,

During our evaluation of FDA's latest information request from Friday, Jan. 4 for an update of Table 3f (Markedly abnormal values for hepatic parameters of Study 402), Takeda re-ran the Table with a new database cut (with 6 months of additional data) and has unfortunately learned of an incorrect treatment code on the case of interest in Study 402; subject 8413-006/402 (TPG2012A01058) that was provided to FDA in the July 2012 NDA resubmission. Takeda had inadvertently assigned this case to the alogliptin 25 mg treatment code and subsequently upon this latest review learned that this subject was in fact on placebo.

We would like to reassure the Agency that the statistical tables and outputs from the clinical database are accurate. In addition, the safety database is accurate and this case currently remains blinded as this is an ongoing study in the safety database. This error was in part due to the fact that this subject was a late breaker case that occurred following the database cut off and that the table in 2.7.4 was manually generated. Because this error was discovered, the team is putting extra effort in QCing all the data in all manually generated hepatic tables from the NDA resubmission (i.e., Tables 3c, 3d and 3i) to confirm these are accurate. The team is also re-checking all current data, randomization codes, and conducting QC checks against previous and current database cut offs. Takeda apologizes and regrets very much that this error has occurred. We understand this case was of specific interest to both Takeda and FDA and we wanted to notify you as soon as we had confirmed this error. Through our investigation, we are ensuring that no other such mis-assignments exist. The case will be properly reflected in our submission that we will be sending to you by the end of the day tomorrow (Jan 7) as per the data you requested last week, at which time the quality control of the other tables will have been completed as well.

We understand the Agency is meeting Monday, January 7 for the second round of labeling comments and potentially later in the week for the end-of-review wrap-up meeting. If the Division has any concerns or would like any additional clarification on this issue, Takeda would gladly be available for a teleconference to further review the details of this finding and provide clarity or additional assurances ensuring data integrity.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

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From: Whitehead, Richard [mailto:Richard.Whitehead@fda hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAM NE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and

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ATTACHEMENT 3

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN LEIBENHAUT
01/14/2013

SUSAN D THOMPSON
01/14/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 8 November 2012

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)
Leonard B. Seeff, M.D., Hepatology Consultant (Hill Group), OPE

TO: Mary Parks, M.D., Director, Division of Metabolic and Endocrine Products (DMEP), Office of New Drugs (OND)
Amy Egan, M.D., Medical Team Leader, DMEP
Valerie Pratt, M.D., Medical Reviewer, DMEP

VIA: Gerald Dal Pan, M.D. M.H.P., Director, OSE; Acting Director OPE

SUBJECT: Hepatic safety of alogliptin (NDA 022271), alogliptin/pioglitazone (NDA 022426), and alogliptin/metformin (NDA 203414), Takeda

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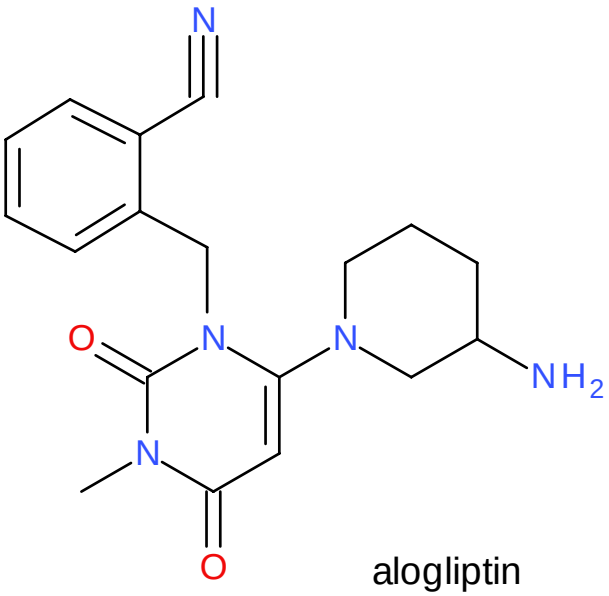
Documents reviewed:
1) Consultation request dated 15 October 2012 from Dr. Pratt via Mr. Rich Whitehead and Ms. Margarita Tossa, with requested response date 9 November, OSE tracking #2012-2411.
2) Takeda summary dated 4 October 2012, provided clinical details on cases showing either ALT >10xULN or {ALT/AST >3xULN & BILI >2xULN}
3) Previous consultation reports by Dr. Leonard Seeff of 21 February and 8 May 2012
4) Summary minutes of end-of-review meeting 29 June 2012; Takeda and FDA/ODE II/DMEP

Alogliptin, a dipeptidyl peptidase-4 compound (SYR-322) was approved in Japan in April 2010 and marketed by Takeda as an oral drug with brand name NESINA® for treatment of patients with type 2 diabetes mellitus. The original new drug application (NDA 022271) in the United States submitted in December 2007 was not approved 29 June 2009, citing inadequate information. A resubmission 25 July 2011, along with NDA 022426 for an alogliptin/pioglitazone combination, was also not approved 25 April 2012 because of residual concerns about rare hepatotoxicity and differing opinions of consultants on whether or not caused by alogliptin hypersusceptibility. The sponsor assembled a group of well known hepatologists (b) (4) as a Liver Safety Evaluation Committee (LSEC) to review cases of special interest and concern as to whether alogliptin was the probable cause of liver injury or dysfunction observed. As has been noted by other sets of reknowned experts in hepatology serving in the drug-induced liver injury network (DILIN) of the National Institutes of Health, experts do not always agree on the likelihood of causation by administered drugs, in cases for which there may be other possible causes such as several types of acute viral hepatitis, autoimmune hepatitis, alcohol-induced hepatitis, from other drugs or substances also taken concurrently, genetic and metabolic liver diseases, and others.

The dipeptidyl peptidase-type 4 inhibitors reduce inactivation of glucagon-like peptide-1, which lowers blood glucose and decreases gastric emptying. Three other agents of this class have been approved for use in the United States, including sitagliptin (JANUVIA®, Merck Sharp Dohme; 16 October 2006), saxagliptin (ONGLYZA®, Squibb; 31 July 2009), and linagliptin (TRADJENTA®, Boehringer Ingelheim; 2 May 2011), and others are under development.

Among these agents, alogliptin has perhaps the simplest structure:



alogliptin

With respect to the stated concerns about possible hepatotoxicity of alogliptin in some people, as mentioned above, there have been no published reports (byPubMed search) of significant or serious liver injury from the considerable experience in Japan since it was approved there in 2010. That does not mean that there actually have been no cases, just none published. We should evaluate the data carefully, however, concerning this issue, in light of some of the rather serious post-marketing cases reviewed by Dr. Seeff in his previous consultations of February and May. We recognize that experts don't always agree on the likelihood of causal association, and that opinions are highly dependent on adequate clinical information to exclude other possible causes of findings observed or reported. Such information is often or usually missing from spontaneous reports from busy practicing physicians, but lack of information is nor reassuring.

We shall not repeat here the findings and conclusions reached by Dr. Leonard Seeff in February and May of this year that considered those mainly post-marketing cases from Japan. Review of the same cases by the sponsor's consultants, (b) (4), showed that they did not always concur with each other, nor did Dr. Seeff when he looked at presumably the same information as they had done. In this consultation, we shall focus on cases forwarded to us in the consultation request of 15 October 2012, which included 11 cases from clinical trials who showed ALT peak elevations >10xULN, and 5 cases with {ALT>3xULN & BILI>2xULN}. 1 of which was the same (305/5304-055). In citing the cases by number, we shall try to be more consistent than was the sponsor, using the convention of Study/Site-Subject to identify the person of interest.

Dr. Seeff took the lead in reviewing the 11 cases with ALT elevations >10xULN, and I focused on the 5 potential "Hy's Law" cases. We emphasize the point that there really is no such thing as a "biochemical Hy's Law" case, as suggested by the sponsor and reiterated in your consultation request. The intent of setting low threshold limits of {ALT>3xULN & BILI>2xULN}.was not for making diagnosis, but simply as conservative levels for screening possible cases to follow by investigating them further by medical process to estimate the most likely or probable cause of the findings observed or reported. As Dr. Hyman Zimmerman repeatedly stated and wrote, "drug-induced hepatocelluar jaundice is a serious lesion," with substantial mortality. The very first idea of that advice was that there had to be evidence to support the cause of the finding as from a drug administered, which requires ruling out or excluding other possible causes, including diseases such as acute viral hepatitis of several types, alcoholic and autoimmune hepatitis, diseases of iron or copper deposition, other drugs, biologics, generics, or dietary supplements also taken. There is no known pathognomonic biomarker or indicator of drug-induced liver injury, even biopsy, and certainly not by imaging. The process of investigating a patient for what caused a problem is a medical exercise in differential diagnosis, and cannot be done by statistical approaches.

First, the 11 cases from Studies 303, 305, 307, 311, 395. 402, and 831:

Peak ALT Values >10 x ULN

303/3128-003 (*Study/Site-Subject*)

This 73 year old man with a history of cholelithiasis, cholecystectomy, malaria and onychomycosis who was receiving treatment with fluconazole and ranitidine, was started on (ALT 144 IU/L; AST 103 IU/L, ALP 150 IU/L, total serum bilirubin 0.74 mg/dl), with values returning to normal when re-tested 6 days later. On day 8, he apparently developed acute abdominal pain and 7 days later, all 3 serum enzymes, ALP in particular, were found again to be abnormal. He was diagnosed as having a bile duct stone and, indeed, 5 days later, had a total serum bilirubin value of 4.07 mg/dl. with continuing elevation of the ALP level. A day later,alogliptin treatment was permanently discontinued and values returned to normal thereafter. Also noted was fatty liver disease on US.

Comment (LBS): This was not an instance of alogliptin hepatotoxicity, but rather transient gall stone obstruction. Noteworthy is that the term "Hy's law" was mentioned which is of course incorrect until a diagnosis of dili is reached. Raised aminotransferases and serum bilirubin caused by other conditions should not be called Hy's law.

303/5505-016

This 46 year old obese male being treated with metformin was started on treatment with alogliptin on September 6, 2010. Liver-related chemistries were normal at baseline and remained normal until day 274 when he had an ALT of 356 IU/L, and an AST of 260 IU/L with a normal serum bilirubin value. At this point, the drug was withdrawn and 8 days later, all values had returned to normal (even unusually low). As best as can be determine, treatment was re-started without evidence of further enzyme elevation. No information is supplied regarding an effort to seek cause for the abnormality other than to say that he had had "alcohol use," whatever that means. Accordingly, the cause for the single set of biochemical abnormality remains unknown.

Comment (LBS): This is yet another instance in which there is a single set of moderately increased aminotransferase levels for which no cause was identified. That this is almost certainly not alogliptin dili is evident from the prolonged latency after starting treatment of approximately 9 months and the lack of recurrence after re-starting treatment. However, what the actual cause is cannot be determined from the information presented.

305/5039-003

This 56 year old male with a history of cataracts, diarrhea, headaches and increased GGT levels, who was receiving metformin and ibuprofen, was started on treatment with alogliptin on July 27, 2009. Both prior to starting treatment, and continuing thereafter until day 57, he had very mild elevations in his ALT levels, all other routine liver-related chemistries being normal. On day 113, he suddenly developed an ALT level of 321 IU/L and an AST of 166 IU/L. Treatment apparently continued until day 134 when he voluntarily withdrew from treatment. By day 141, his ALT level had fallen to 54 IU/L. It is then stated that he had hemochromatosis which might, according to the narrative, have been responsible for the abnormal serum enzymes This seems hardly likely.

Comment (LBS): We are faced once again with a single set of aminotransferase abnormalities consistent with mild hepatocellular injury. The cause is entirely unclear. Since the drug was withdrawn and the chemistries fell thereafter to almost normal values, dili cannot be absolutely ruled out. However, no information is presented to show that other potential causes for the liver abnormality were sought. Regardless, this represents only minimal and transient, indeed trivial liver dysfunction. In the absence of any other explanation, it is conceivable that alogliptin might have led to the single set of enzyme elevations but this is not really drug-induced liver injury.

305/5304-055 (*see also below as potentially more serious)*

A 54 year old man with a history of anxiety who was taking metformin, atorvastatin, ursodeoxycholic acid, aspirin, vitcofol and multivitamins was started on treatment with alogliptin on March 29, 2010. His baseline liver chemistries were normal, but they became slightly abnormal (ALT 85 IU/L, AST 51 IU/L) on day 29. He was apparently worked up for etiology, and was diagnosed to have developed acute hepatitis E based on a positive test for IgM anti-HEV. The aminotransferase level increased 9 days later and treatment was discontinued on day 48 when the values had increased even further. The values peaked 3 days after discontinuing alogliptin (ALT 1036 IU/L, AST 578 IU/L), the bilirubin level rising to 2.37 mg/dl. By day 79, all values had returned to normal.

Comment (LBS): Very nice case. The diagnosis could easily have been dili until work up revealed acute HEV infection.

307/9019-009

This 47 year old man with a history of hypertriglyceridemia, hypercholesterolemia, diabetic neuropathy, gout and obesity who had been receiving treatment with pioglitazone, began treatment with alogliptin on November 13, 2006. He was also being treated with metformin, paracetamol, pseudoephedrine, fenofibrate, and nutria min C resist(?). His baseline liver chemistries were abnormal (ALT 430 IU/L; AST 190 IU/L, t. bilirubin 1.3 mg/dl). On day 5, alogliptin was discontinued and on day 8, the last time he was seen in this study, both serum enzymes were still moderately elevated. The subject was referred to his primary care physician and apparently was lost to follow-up thereafter.

Comment (LBS): This is clearly not alogliptin dili since enzyme elevations were already present at baseline. The diagnosis is not known even though the patient was referred to his PCP for further evaluation, none of which was forthcoming. Alogliptin was discontinued 5 days after starting treatment.

311/9003-009 (*previously reviewed*)

This 49 year old male with a history of hyperlipidemia, drug hypersensitivity (?) and anxiety, who was being treated with pioglitazone, fluoxetine, buspirone, trazidone, and ezetimibe, was started on treatment with alogliptin on June 16, 2006. He had an unexplained slight elevation in his ALT and GGT levels at baseline which had returned to normal 2 weeks later. On day 32, he was suddenly found to have an ALT level of 646 IU/L, an AST level of 585 IU/L, and slight increases in the levels of total serum bilirubin and ALP but still in the normal range. Alogliptin was withdrawn and 10 days later, the values were back to normal. It is implied that alogliptin treatment was re-started without giving a date, without further elevation of the serum enzymes and that he voluntarily withdrew from the study on day 91. Inexplicably, there is reference to a set of values obtained on day 208, all of which were normal. The single set of abnormal values is ascribed to "alcohol intake" without further explanation.

Comment (LBS): I do not know the cause for the single set of moderately abnormal aminotransferase values but cannot consider them to be due to alcohol intake. First, there is no information given as to how much alcohol was taken and for how long, and the pattern of enzyme elevation is decidedly unlike that seen in alcoholic liver disease. Moreover, the values had returned to normal 10 days later. It is also unlikely that alogliptin was responsible since, as best as I can glean from the skimpy information given, the patient was started back on alogliptin without re-emergence of enzyme abnormalities. I'm not sure what the cause of the single spike in enzymes is and wonder whether the sample tested was actually from someone else.

395/3054-001

This was a 67 year old female with a medical history of dyslipidemia and cholecystectomy who was begun on treatment with alogliptin on April 10, 2007. Her baseline ALT level was a smidgen above normal, but the ALT and other liver chemistries reported were all normal until day 112. At this time, the ALT increased to 257 IU/L and the AST to 118 IU/L with normal total serum bilirubin and ALP values. One week later, the ALT had decreased to 128 IU/L and the AST to 70 IU/L. Alogliptim was apparently not discontinued yet the aminotransferase levels became normal on day 141 and remained normal through day 183. The reason for the transient slight elevation in aminotransferase levels without concomitant hyperbilirubinemia remains unclear although it is stated that an ultrasound revealed fatty liver (which must have spontaneously disappeared if the raised enzymes were a result of this occurrence). Also, there is mention of hepatitis A infection reported on day 169 (well after the first enzyme obtained from the sponsor be obtained regarding whether a follow-up ultrasound was performed and what the specific serologic findings were that led to a diagnosis of hepatitis A.

Comment (LBS): The sponsor attributes the short-lived increases in serum enzymes 112 days after starting alogliptin treatment to fatty liver disease and/or hepatitis A. The data made available are insufficient to confirm either of these two diagnoses. Although I cannot absolutely rule out a role for alogliptin, I think it extremely unlikely. In any case, the "liver disease" was trivial.

402/8070-002
This 60 year old man with a history of atherectomy (?), peripheral artery angioplasty, myocardial infarction, coronary artery bypass and multiple other medical problems including chronic hepatitis C, was started on treatment with alogliptin on June 24, 2010. Throughout the entire 610 days of follow-up, and even prior to starting treatment, he had persistently abnormal aminotransferase levels, the ALT always exceeding the AST, with normal serum bilirubin and alkaline phosphatase levels. The patient was also receiving multiple other medications, several with a known history of having caused dili in the past. No information is given regarding hepatitis C (or other forms of viral hepatitis) serologic markers, but almost certainly the persistently elevated serum enzyme levels are a consequence of chronic hepatitis C. Of note is that on day 42, his ALT level peaked at 267 IU/L with an AST value of 277 IU/L at which time, alogliptin was discontinued. Nevertheless, the serum enzymes levels remained abnormal throughout his follow-up although at a lower level.
Comment (LBS): Without question, the observed aminotransferase abnormalities in this patient were not a consequence of alogliptin treatment but presumably rather of chronic hepatitis C. Moreover, even after alogliptin treatment was withdrawn, serum enzymes remained abnormal showing an absence of dechallenge.

402/8260-010 This 58 year old female with a history of dyslipidemia, myocardial infarction, unstable angina, and hypertension was begun on treatment with alogliptin on February 22, 2011. Starting with completely normal liver-related chemistries, she was found to have a single set of abnormalities 92 days later (ALT 293 IU/L; AST 149 IU/L; ALP 129 IU/L, and T. Bilirubin 1.65 mg/dL). At the tiome, she was also receiving multiple other medications (cloipidogrel, metformin, simvastatin, carvedilol, spironolactone, gliclazide, isosorbide dinitrate and mononitrate, and aspirin). Alogliptin was withdrawn. Just prior to the elevated values, she was diagnosed with unstable angina and she had cardiac catheterization, revealing coronary obstruction, followed by successful coronary artery angioplasty. Ten days later, the aminotransferase levels returned to normal and she was started back on alogliptin treatment without developing abnormal chemistries. Continued follow-up values while on alogliptin treatment remained normal.
Comment (LBS): This was clearly not a case of alogliptin hepatotoxicity but the single set of abnormal values resulted presumably from her cardiac disease. Moreover, re-challenge with the drug did not result in repeat liver dysfunction.

402/8521-002
An 81 year old female with a history of chololithiasis, cardiac failure, and myocardial infarction presenting with hypertension, angina pectoris, osteochondrosis, the post-cholecystectomy syndrome, and presbyopia was started on treatment with alogliptin on January 25, 2011. At the time of starting treatment she had abnormal baseline liver-related abnormal chemistries (ALT 349 IU/l; AST 259 IU/L, and ALP 134 IU/L. These tests were abnormal also 12 days before starting treatment (why was she treated?). The values remained persistently abnormal through day 36, falling gradually to normal by day 94. On day 85, she was diagnosed to have acute pancreatitis. There is also notation that the patient had underlying hepatitis C but without supporting serologic evidence presented. Moreover, she continued to be treated with alogliptin until day 372 but the liver chemistries remained normal from day 197 onward.

Comment (LBS): Clearly, with abnormal liver chemistries noted even prior to starting treatment, and with normal values noted for several months even after re-starting treatment, the abnormalities cannot be attributed to treatment with alogliptin. The cause for the abnormalities remains unclear, although it is suggested that it might be a result of chronic hepatitis C (no serologic results given), chronic pancreatitis, or underlying cardiac disease.

402/8664-005

This 59 year old male with multiple medical problems (angina pectoris, mitral valve prolapse, diabetic nephropathy, dyslipidemia and an enlarged prostate) who was receiving treatment with aspirin, captopril, clopidogrel, isosorbide, metoprolol, atorvastatin, and, trimetazadine, was begun on treatment with alogliptin on April 29, 2011. Prior to baseline, he had a slightly elevated ALT value, 78 IU/L, but it was normal at baseline and remained normal until day 263 when he was found to have an ALT of 256 IU/L, an AST value of 57 IU/L, a serum bilirubin value of 1.65 mg/dl and a ALP of 213 IU/L. Both alogliptin and atorvastatin were discontinued and the values decreased slightly by day 267 and were almost back to normal by day 277. Alogliptin appears to have been re-started (but the information on this is obtuse and no re-start date is mentioned). Serum enzymes thereafter remained normal. The sponsor attributed the abnormalities to atorvastatin based on evidence of dechallenge. As usual, no mention is made of efforts to identify cause.

Comment (LBS): Yet another instance of delayed hepatocellular injury without a specific cause being identified. Although attributed to atorvastatin dili, there is no information on how long that drug had been in use, it would have been less likely if atorvastatin was being received for a prolonged period. I am uncertain what the cause was for the raised aminotransferases, and although the likelihood is low, alogliptin cannot be completely ruled out although I am skeptical of this diagnosis. Unfortunately, other causes were not sought. As usual, this was a trivial finding.

831/2508-002

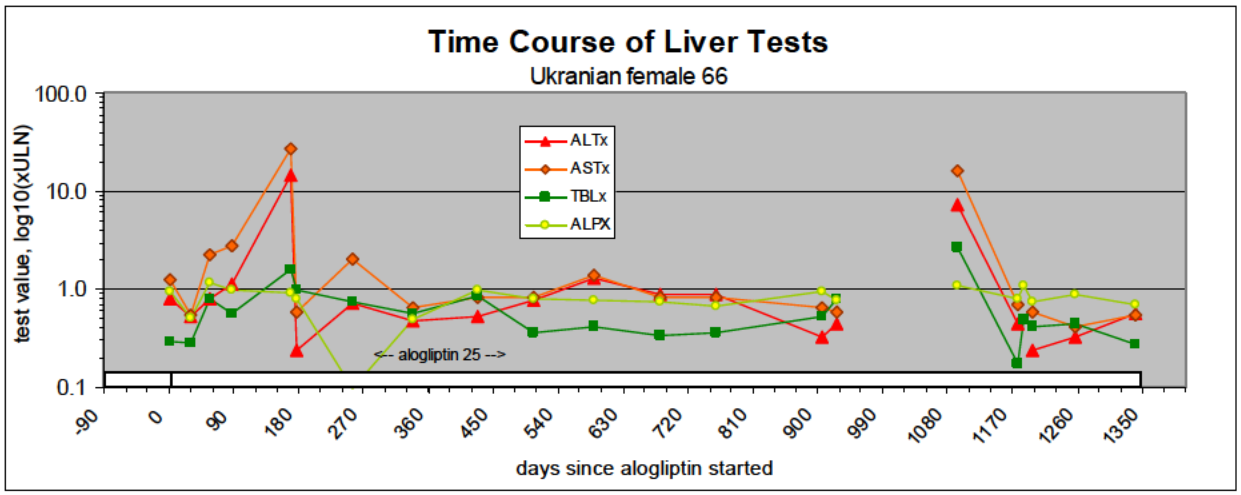
This 49 year old male with hypoacusis and an umbilical hernia began treatment with alogliptin on July 31, 2007. The ALT and AST values preceding treatment and at baseline were mildly abnormal but returned to normal between days 15 and 68. On day 64, he was diagnosed serologically with acute hepatitis B (serologic results not reported), and on day 86, was found to have an ALT value of 689 IU/L and an AST of 515 IU/L. Five days later (day 91), his ALT value had risen to 1771 IU/L and his AST to 1345 IU/L with normal ALP and serum bilirubin values. Alogliptin treatment was discontinued on day 107, and one month later, his serum enzymes had returned to normal. It is unfortunate that the hepatitis B serology defining acute hepatitis B is not made available in this obviously shortened report. It would be worth knowing how the acute HBV infection was acquired.

Comment (LBS): This is presumably an instance of short-lived acute hepatitis B without available confirmatory serologic evidence, but still this diagnosis seems likely.

Possibly More Serious Cases: ALT/AST >3x ULN; Total Bilirubin >2x ULN

012/961-2501 (*Study/Site-Subject*)

This is a somewhat complicated narrative of a 66 year old woman with a history of cardiac disease, hypertension and obesity who had previously been enrolled in another trial in which she had received alogliptin; during treatment, she was found to have very mild increases in his ALT, LDH, and GGT, but treatment continued. In the present study, she received alogliptin and nifedipine and her liver-related chemistries remained normal until day 169 when she was found to have a single set of abnormal values (ALT 360 IU/L, AST 602 IU/L, total bilirubin 1.73 IU/L) after which the values returned to normal remaining normal until month 39 when, once again, a single set of abnormal values was found (ALT 180 IU/L, AST 356 IU/L, total bilirubin 2.91 mg/dl). Treatment continued and the enzyme and bilirubin values returned to normal. The patient was entirely asymptomatic. The attending physician considered the abnormalities as laboratory errors.



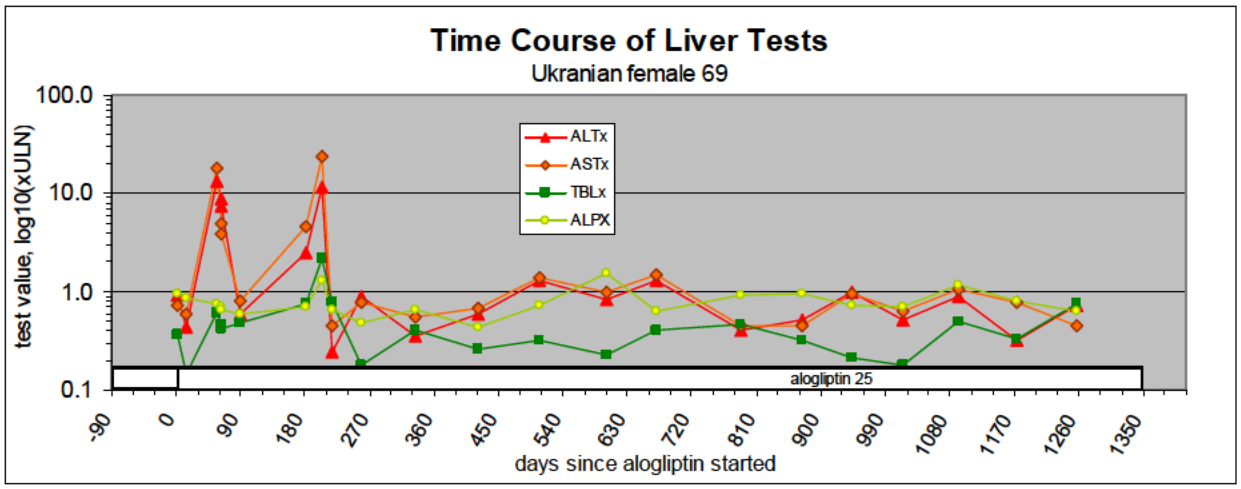
Comment (JRS): Inspection of the data and graphic display shows that this woman tolerated alogliptin very well, but had periodic abnormalities AST > ALT with no cholestasis. She had known heart disease and congestive failure, and the enzyme elevations corresponded to episodes of congestive failure (with centrilobular liver congestion). Probably cardiac, not drug-induced.

Comment (LBS): Single abnormal sets of values 6 and 39 months after starting treatment considered to be a laboratory error by the attending physician. The cause is otherwise unclear and could represent laboratory error or perhaps bouts of congestive heart failure. This is not drug hepatotoxicity.

012/961-3006

This was a 69 year old female with a history of hypertension and cerebral atherosclerosis who had participated in an earlier study using pioglitazone but because of apparent lack of efficacy, was rolled into a new open-label study receiving alogliptin on November 16, 2007. In the first study, she had had low level GGT elevations throughout. She was also receiving an ACE

inhibitor. Baseline and 2 week follow-up laboratory values were normal, but on day 56 (Week 8), she was found to have an ALT of 333 IU/L and an AST value of 396 IU/L with normal ALP and total serum bilirubin values. Similar abnormalities were noted on day 62 and day 63 repeated because the specimen was said to be unsatisfactory. Thereafter, the values dropped back to normal despite continuing treatment with the drug.. Then on day 182 (month 60), the enzymes increased again (ALT 62 IU/L, AST 100 IU/L) increasing further on day 203 (ALT 290 IU/L, AST 530 IU/L, total bilirubin 2.35 IU/L.). Apparently, drug treatment continued, and the bilirubin and aminotransferase values returned to normal and remained normal until day 1337. The narrative suggests that the first abnormality was a result of alcohol use over the holidays and the second bout to exposure to an insecticide. No other etiologies were sought.



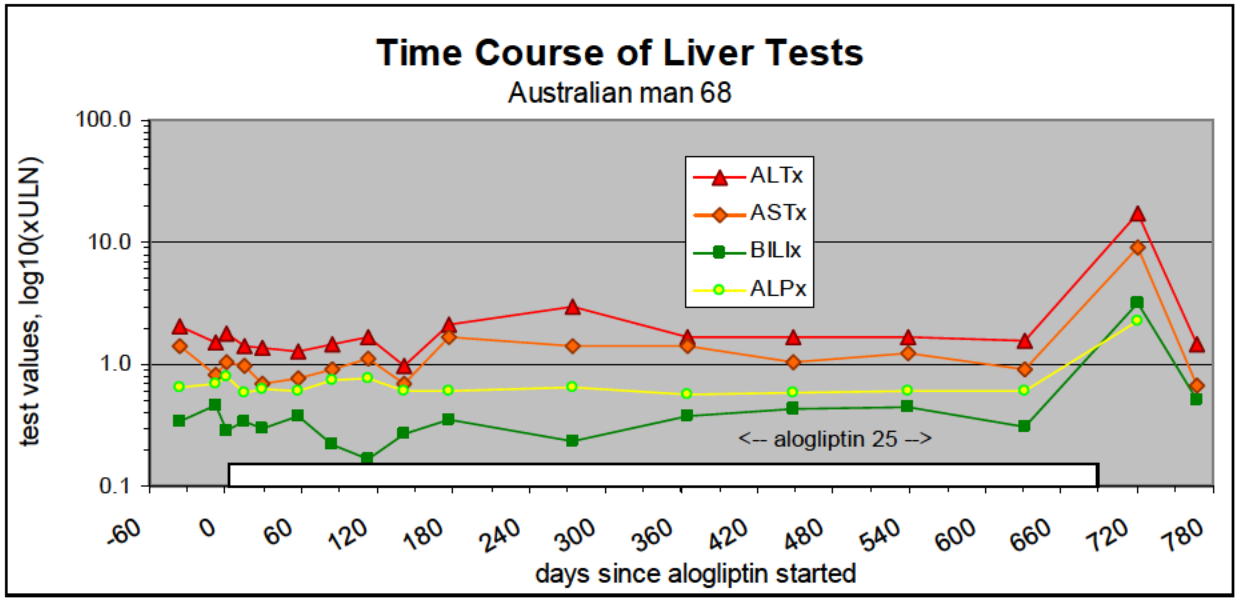
Comment (JRS): The two rather sharp increases in AST and ALT in January and May 2008, were attributed to preceding alcohol and insecticide exposure, but not convincingly. Alogliptin administration continued, and did not appear causative. The pattern of AST > ALT is seen in recurrent alcoholic hepatitis but usually at lower levels of activity, suggesting heart insufficiency as a factor (not mentioned in the narrative). The case was not well worked up or explained.

Comment (LBS): There were two episodes of fairly prominent liver abnormalities, one associated with jaundice. I cannot say what the causes were. The type of abnormality first seen is quite unlike that caused by alcohol. I cannot speak to the second episode that conceivably might have been due to toxic exposure to an insecticide, as is suggested in the narrative. Were it not for the fact that alogliptin treatment continued throughout, I would have been suspicious that it might have played a role. However, the second episode was quite late and liver abnormalities did not re-occur with continued use of alogliptin so therefore I will eliminate alogliptin as the cause for the observed biochemical abnormalities.

305/5312-001

This 68 year old male with a history of hypertension, hyperlipidemia and bruising of his arms started on the study drug on June 30, 2010. The patient was also receiving celecoxib, esomeprorozole, atorvastatin, telmisartan, oxycodone, paracetamol and metformin. Beginning prior to starting the study drug and continuing throughout follow-up until day 631, he had minimal elevations in his ALT levels, the other chemistries remaining normal. On day 721, he was found to have an ALT value of 429 IU/L, an AST value of 198 IU/L, an ALP value of 160

IU/L (4 x higher than the previous values), and a total serum bilirubin value of 3.49 mg/dl. He was hospitalized and worked up for gall stone obstruction which seemed confirmed by an US examination. Magnetic resonance evaluation revealed choledocholithiasis, following which he underwent an ERCP with sphincterotomy and gallstone removal. Screening for hepatitis A, B, and C were all negative.

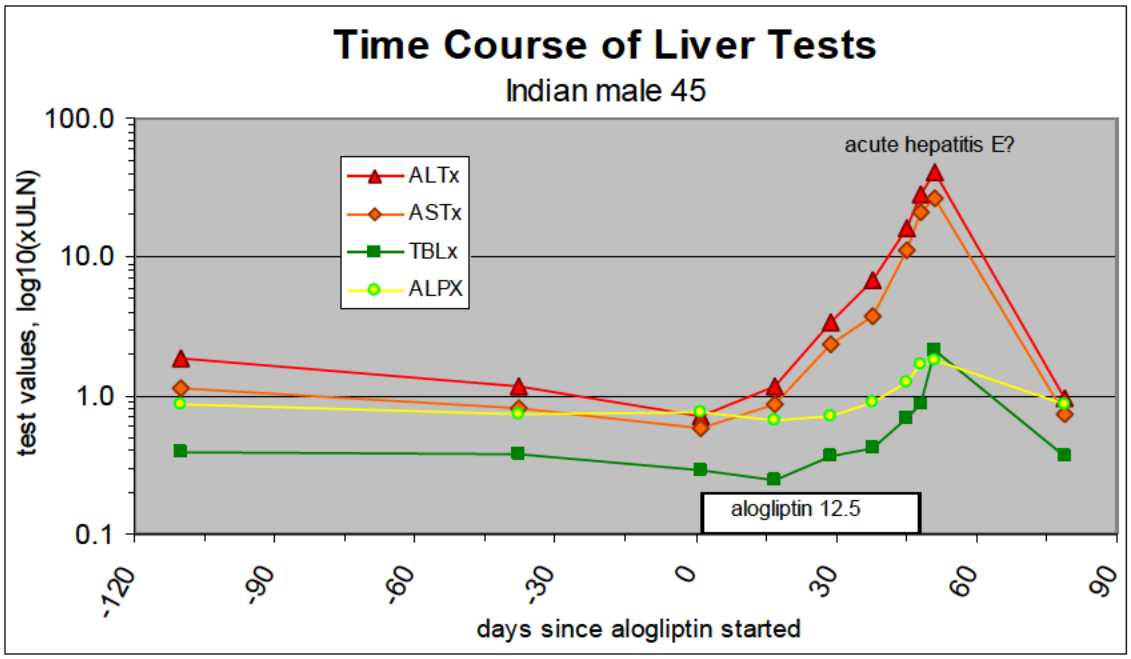


Comment (JRS): The slight but persistent ALT elevations were never investigated or explained, but the patient tolerated alogliptin well for two years. At that point a common duct stone was confirmed, then removed, with resolution. The aminotransferases elevations were relatively greater then the rise in alkaline phosphatase, so there may may have been some hepatocellular injury in addition to the cholestasis caused by the gallstone.

Comment (LBS): This is clearly an instance of obstructive jaundice caused by a gall stone. That finding and the fact that liver dysfunction occurred on day 721 completely eliminates a diagnosis of alogliptin hepatotoxicity.

305/5304-055 (*see also above)*

A 54 year old man with a history of anxiety who was taking metformin, atorvastatin, aspirin, ursodeoxycholic acid, vitcofol and multivitamins with minerals, was started on treatment with alogliptin 12.5 mg/kg/day on March 29, 2010. His baseline liver chemistries were normal, but his ALT had been modestly elevated 4 months before. On alogliptin treatment, they became slightly abnormal (ALT 85 IU/L, AST 51 IU/L) on day 29, then markedly so on day 38 but his serum bilirubin had not yet risen. Because of the rising aminotransferase levels, alogliptin was stopped on day 48. The aminotransferaes contined to rise for three days more and serum bilirubin then reached 2.15xULN. He was worked up for etiology, and was diagnosed to have developed acute hepatitis E based on a positive test for IgM anti-HEV. By day 79, all liver test values returned to the normal range.



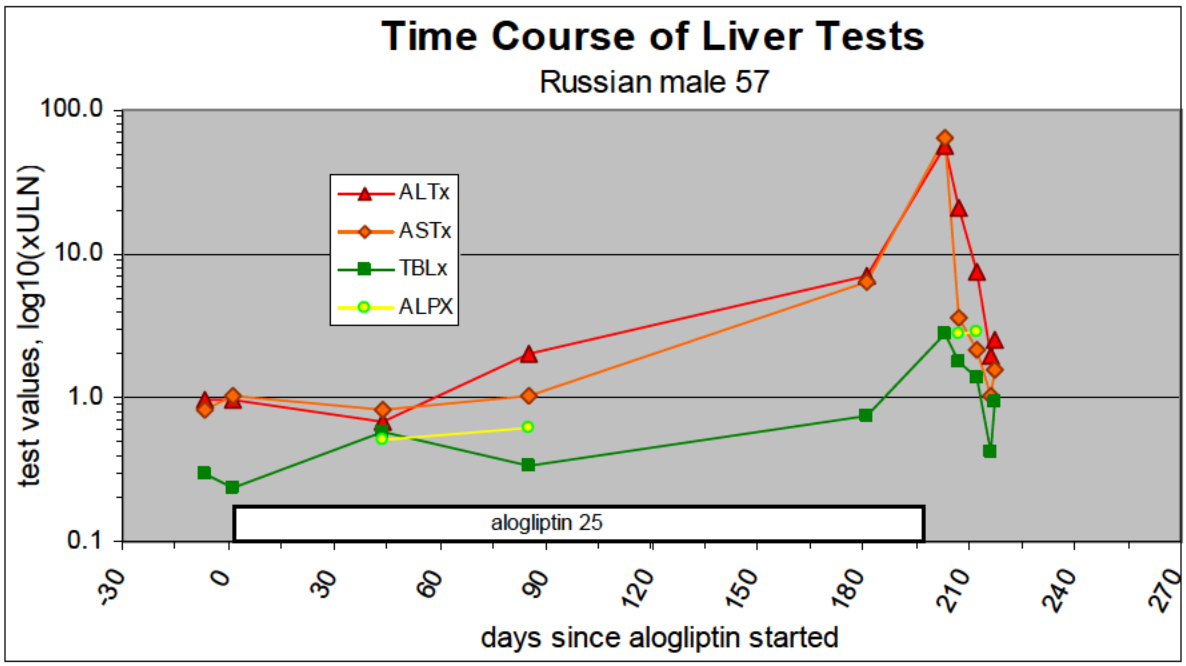
Comment (JRS): This subject showed aminotransferase activity rises about four weeks after starting alogliptin, with sharp subsequent increases that led to stopping the drug three weeks later. The investigator found acute-phase IgM antibodies against acute viral hepatitis E, which subsided within four weeks. Although this case was investigated alertly, it was not reported to the sponsor until September 2010 and norto the FDA by the sponsor until April 2011.

Comment (LBS): Very nice case. The diagnosis could easily have been dili until work up revealed acute HEV infection.

402/8413-006

A 57 year old male with a history of unstable angina, myocardial infarction, congestive cardiac failure, associated with hyperlipidemia, peptic ulcer, and hypertension was started on study drug on November 16, 2011. He was also receiving atorvastatin, clopidogrel, metoprolol, perindopril, and glibenclamide. At baseline and follow-up to day 85, all liver-related chemistries were normal. On day 85 (February 8), his ALT had risen from the previous 17 IU/L to 50 IU//L. No comment is made of this slight abnormality. On the next-reported testing day (day 181, May 14, almost 3 months following the first abnormality) his ALT was 176 IU/L, AST was 142 IU/L without elevation of his serum bilirubin. By day 203 (May 14, about 3 weeks later), the next value shown, he had undoubtedly developed an acute hepatitis as indicated by an ALT of 1410, an AST of 1390, and a raised serum bilirubin of 3.03 mg/dl. There is a comment in the narrative that the patient had drunk "200 ml of vodka 2 days prior to this visit" displaying the first set of abnormalities inferring that this event had something to do with the observed biochemical abnormalities that is almost certainly not correct as indicated by the high ALT/AST ratio and the subsequent marked increase in both serum enzymes. Serologic work-up failed to implicate hepatitis A, B, and C, he is reported to be positive for IgG anti-HAV; no testing for hepatitis E

was reported. The study drug was discontinued on day 207, as was atorvastatin, following which the chemistries improved, falling eventually to normal.



Comment (JRS): This pattern is not typical of acute alcoholic hepatitis because of the very high peak values of the transaminases at 56 and 63 xULN for ALT and AST, but more likely an acute viral infection that was not diagnosed, such as acute hepatitis A or E with no chronicity. A weak attempt was made to rule out other causes but no explanation was found. Alogliptin causation cannot be excluded.

Comment (LBS): This patient developed an acute hepatitis beginning apparently almost 3 months after starting the study drug. The serum bilirubin was transiently increased. There is a paucity of reported testing with a gap of almost 3 months between the first identified ALT value and the next reported test showing a quadrupling of the A LT value. About 3 weeks later, the enzyme elevations indicate clearly that the patient had developed an acute hepatitis that subsided thereafter, concomitantly with the withdrawal of both alogliptin and atorvastatin, although this may have been coincidental. An important question is whether the sequence, beginning 3 months after starting treatment and terminating about 4 months later was a result of the same insult. If so, although strangely protracted, it would be within the latency period of potential alogliptin dili. On the other hand, if there were in fact two insults, it is possible that the high enzymes occurring later were a result of some other etiology than dili. Serologic data excluded a diagnosis of acute hepatitis A, B, and C, but testing for hepatitis E was not reported, so this cannot be entirely excluded. This case was poorly reported or poorly worked up by the involved physician. . I doubt that atorvastatin accounted for the liver injury. IT IS IMPORTANT IN THIS CASE TO LEARN WHETHER THE STUDY MEDICATION WAS ALOGLIPTIN. IF SO, IT CANNOT BE RULED OUT AS A CAUSE FOR THE ACUTE HEPATITIS. UNLESS ACUTE HEPATITIS E OR SOME OTHER UNDEFINED ETIOLOGY IS IDENTIFIED, I WOULD GRADE ALOGLIPTIN DILI AS AT LEAST POSSIBLE, VERGING ON PROBABLE.

Two more Japanese post-marketing cases:

TCI12012A05586

This 64 year old male (referred to as 'she' in the narrative), was started on treatment with lansoprazole on August 4, 2012, and then on sulfamethoxazole/trimethoprim on August 20, 2012. He had apparently been receiving oral prednisolone for transverse myelitis following which he was found to have an elevated HbA1c. He was therefore started on treatment with alogliptin on August 27, 2012. On (b) (6), the patient developed a fever and by the next day, was seen in the outpatient department to have a rash on his limbs and trunk; he also had oral mucosal eruption. On the same day, his ALT was 134 IU/L, his AST 83 IU/L, his ALP 195 IU/L, and his total bilirubin, 0.2 mg/dl. By the next day, the rash had spread even more and now his ALT value was 1057 IU/L, his AST was 640 IU/L, his ALP was 188 IU/L, and his bilirubin remained normal. All three dugs – alogliptin, sulfamethoxazole/trimethoprim, and lansoprazole - were then discontinued. He was seen by dermatology who recommended increasing his dose of prednisolone and also placed him on an anti-allergy drug. Over the following 5 days, his abnormal liver chemistries began to improve although they were still abnormal when he was reported to have been seen last (b) (6)). He showed peripheral eosinophilia, and his skin biopsy was quite abnormal.

Comment (LBS): In my view, this is an impressive case of drug-induced liver injury but I would attribute the liver injury first to sulfamethoxazole/trimethoprim and second to lansoprazole, the latter less likely than the former. I am not aware that alogliptin cause an immunoallergic form of drug induced liver injury and therefore would place it third in likelihood, swamped I believe by the greater likelihood that one of the other two drugs was responsible for the liver injury. It would be interesting to have additional follow-up on this case.

TCI2012A05429

This 80 year old man with a suspected diagnosis of hemophagocytic syndrome (?) started treatment with alogliptin on May 8, 2012; no further information regarding this event is provided. It is then stated that he was started on ursodeoxycholoc acid at another hospital without indicating the reason; perhaps it was because he was found to have jaundice and an increase in his aminotransferase levels apparently on (b) (6) (the dates reported are confusing). It appears that he stopped treatment with alogliptin on that date. No laboratory values are provided and no information given on what evaluation was done to determine the cause of the liver dysfunction, other than to repeat a presumptive diagnosis of hemophagocytic syndrome. He was apparently also receiving azosemide, allopurinol, and furosemide. His jaundice is then reported to have deepened but again, no values are mentioned. He was given pulsed steroid therapy, but his blood pressure began to decline, becoming "stable." As later reported. He was then reported to have died on (b) (6) without ant description of his medical problem, his treatment, the course of the disease, and the circumstances surrounding his death. Importantly, there is absolutely no information regarding the cause of his liver disease.

Comment: This is a glaringly inadequate report surrounding the cause for the liver injury in this patient, the course of the illness, and the basis for his death. There is absolutely no way of establishing even a presumptive diagnosis to identify a cause for the liver disease and of his death. In my view, it is mandatory for the sponsor to provide the needed information, especially since the patient died without being able to determine whether the death was liver-related.

Summary

This consultation involved a review of 17 cases, 15 of which were pre-marketing cases and 2, post-marketing cases. In the former group, 11 were selected based on ALT values of greater than 10 times the upper limit of normal, and 4 based on what is referred to as "biochemical Hy's law cases." It must be emphasized and re-emphasized that the term "Hy's law cases" should be utilized only for persons found to have increased ALT and bilirubin levels with some confidence (at least probably) caused by drug-induced liver injury. We should not use the term "biochemical Hy's Law," and should discourage sponsors from using it. Hy's law **requires** assessment of the probable cause as drug-induced, which is a medical process of differential diagnosis, and cannot be concluded just by statistical methods.

Among 10 cases with only raised aminotransferase values, most had only single sets of abnormal values that were difficult to pinpoint as to cause, some had other causes likely to be responsible for the abnormalities (cardiac disease, perhaps acute hepatitis B, C, or E, gallstone obstruction). Unfortunately, the data provided were regularly quite limited, creating difficulty in reaching a reasonable diagnosis. Indeed, even when the abnormalities were attributed to an acute viral hepatitis infection, the diagnosis had to be taken on good faith because the actual serologic confirmation was not provided.

Among the 5 cases of both ALT and bilirubin elevation, 3 appeared to have other causes for the abnormalities (cardiac disease or gallstone obstruction), whereas one of them (**402/8413-006**) represents, in our view, a possible/probable case of alogliptin hepatotoxicity, or at least in which that cannot be excluded. This patient developed an acute hepatitis presentation approximately 3 months after starting treatment. Serologic testing for hepatitis A, B, C were reported negative (hepatitis E was not evaluated), and the abnormal values subsided after discontinuation of the study drug. Unfortunately, there were important prolonged gaps between testing of the liver panel making it difficult to determine what the sequence of abnormalities really was.

One of the two post-marketing cases was almost certainly a result of drug-induced liver disease but not necessarily a result of alogliptin. The clinical manifestations suggested strongly that it might have been the result of one of two additional drugs received, either sulfamethoxazole/ trimethoprim or lansoprazole. The second case in which the patient developed liver disease together with jaundice was so poorly reported that it is impossible to determine what the cause was for the reported liver disease. Moreover, the patient died without being able to determine whether the liver disease accounted for the death.

Finally, a comment about implicating alcohol as a cause for observed liver abnormalities. It is unusual for an occasional drinker to develop more than a mild increase in AST levels if they happen to have a "weekend binge." Alcoholic hepatitis generally occurs in chronic alcoholism, with recurrent episodes following binges. Moreover, almost always, the AST value exceeds that of the ALT, and the ALT value extremely rarely exceeds 100 U/L. Only a minor fraction of advanced alcoholics, about 15-20%, ever develop serious liver disease, despite drinking maximal amounts of alcohol humanly possible. There is indeed a major factor of dose-related toxicity of alcohol, but also a very important factor of individual susceptibility that is still "idiosyncratic."

Recommendations

1. The recently provided information on cases reported in clinical trials shows that most of the serious liver injury or dysfunction has some other causative explanation than alogliptin-induced, but there still remain cases in which no satisfactory or convincing alternative causative diagnosis was found or could be determined by review of the clinical informationj supplied.

2. We are still concerned about the inadequate investigation or reporting of patients receiving alogliptin after approval (so far, Japan only, but there will be many more if alogliptin is approved in the United States). This is a general problem all over the world, and we realize it will not be solved just by labeling. The sponsor should assume more responsibility for safe use of this drug and advise prescribers to be somewhat cautious in its use, to check liver tests (serum ALT, AST, ALP, BILI) twice before starting it, then monitor ALT at least monthly for six months, and to repeat testing for elevations above 2xULN or 2xB (B, average of pre-treatment baseline values) within a week to confirm. If still elevated or worse, consider temporary interruption of alogliptin therapy and investigate for probable cause using full liver set (ALT, AST, ALP, BILI) and other tests as needed for diagnosis, with prompt reporting of the cases and details about them.

3. That said, we concur with the DMEP reviewers that alogliptin is approvable.

4. It is in the best interest of the sponsor, as well as of patients to be treated, to be cautious and vigilant about the hepatic safety of alogliptin until much more experience with it can be gained worldwide. It not sufficient to call cases “confounded” because there may be some other possible cause of the findings, and certainly no service to the patient.

John R. Senior, M.D. & Leonard B. Seeff, M.D.

cc: V. Pratt, DMEP
A. Egan, DMEP
M. Parks, DMEP
G. Dal Pan, OSE

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/s/

JOHN R SENIOR
11/10/2012
Major contribution by Dr. Leonard Seeff

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:	October 19, 2012
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name:	Nesina (Alogliptin) Tablets, 6.25 mg, 12.5 mg, 25 mg
Application Type/Number:	NDA 022271
Applicant/sponsor:	Takeda Pharmaceuticals America, Inc
OSE RCM #:	2012-1778

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1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Nesina (Alogliptin) Tablets submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE Review #2011-2602, dated November 29, 2011.

2 MATERIAL REVIEWED

The revised container label and carton labeling submitted to the Agency on January 24, 2012 (See Appendices) and OSE Review #2011-2602, dated November 29, 2011, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised container labels and carton labeling submitted on January 24, 2012 address all of DMEPA's concerns. However, we have additional comments.

1. All Container Labels and Carton Labeling; All Strengths

    a. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXX-xx). Pharmacists use the middle portion of the NDC number to ensure the correct product is dispensed.

2. Blister Card Container Labels; 12.5 mg and 25 mg

    a. The blister cards (b) (4) on the packaging. This presentation decreases the contrast and visibility of important information, which affects readability. Remove (b) (4) of the packaging and follow the bottle presentation with partial coloration (i.e. color block around the strength presentation) and white background with black lettering.

    b. Revise the day designation on the inner card (i.e. Mon, Tues., etc.) to read (b) (4) Patients may begin therapy on any day of the week. As proposed the patient may wait until Monday to begin therapy.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Margarita Tossa at 301-796-4053.

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

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/s/

REASOL AGUSTIN
10/19/2012

YELENA L MASLOV
10/21/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1

Date:	8 May 2012
To:	Hylton Joffe, M.D., Team Leader Division of Metabolic and Endocrine Products
Reviewer:	Leonard Seeff, MD, Hepatologist Office of Surveillance and Epidemiology
Through:	Allen Brinker, MD, MS, Medical Team Leader Division of Pharmacovigilance 1
Drug Names:	alogliptin (Nesina) alogliptin & pioglitazone (Oseni) sitaglitin (Januvia) sitagliptin & metformin (Janumet)
NDA Numbers:	22-271 (alogliptin) 22-426 (algliptin & pioglitazone) 21-995 (sitagliptin) 22-044 (sitagliptin & metformin)
Applicant/sponsor:	Takeda (alogliptin)
OSE RCM #:	2012-468
Issue:	Update: Review of cases of liver injury in association with alogliptin submitted by the sponsor. In addition: review cases of liver injury in association with sitagliptin collected from the AERS database.

INTRODUCTION

This review includes an update to a previous review[1] based on additional data provided for selected cases and new cases of liver injury associated with alogliptin. Material included in these cases was received periodically as documents from the alogliptin sponsor and in the setting of a teleconference held with the alogliptin sponsor and their representatives on April 16, 2012. In addition, this review includes 8 cases of liver injury in association with sitagliptin submitted to FDA's Adverse Event Reporting System (AERS) database. These 8 cases were also described in a recent separate and independent review[2] by DVP Reviewers Bezabeh and Boyd.

As employed in the original consult request, this consult utilized the following grading system for likelihood of causality and disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.[3] These scales are outlined in the following two tables.

Likelihood of Causality

Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥95	Causality is "beyond a reasonable doubt"
2	Highly Likely	75-94	Causality supported by "clear and convincing evidence"
3	Probable	50-74	Causality supported by the "preponderance of the evidence"
4	Possible	25-49	Less than the preponderance of evidence but still possible
5	Unlikely	<25	Causality unlikely or excluded

[1] Memorandum dated 21 February 2012. Leonard Seeff to Hylton Joffe: Review of cases of liver injury in association with alogliptin.
[2] Memorandum dated 2 April 2012. Sarita Boyd and Shewit Bezabeh: Serious hepatoxicity in association with sitagliptin, saxagliptin, and linagliptin.
[3] Fontana RJ, Seeff LB, Andrade RJ, Bjornsonn E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:730-42.

Disease Severity Scales

Score	Grade	Definitions
1	Mild	Elevated ALT and/or Alk P but serum bilirubin <2.5 mg/dL and INR <1.5
2	Moderate	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl or INR ≥1.5
3	Moderate-Severe	Elevated ALT and/or Alk P and bilirubin or INR and new or prolonged hospitalization due to dili
4	Severe	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl and there is one of the following: -Hepatic failure (INR ≥1.5, ascites or encephalopathy -Other organ failure (renal/pulmonary) d/t dili
5	Fatal	Death or liver transplant from dili

Alogliptin Case Narratives (n=16)

ERD2010A00037

This 41 year old man from India with a history of renal calculi was entered into a multicenter, double-blind, active-controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin in persons with type 2 diabetes. Other medications the patient was receiving included rabeprazole, domperidone, metformin, aspirin, atorvastatin, ursodiol, cefadroxil, clavulanate, and pantoprazole.

The baseline values for ALT ranged from 13 to 18 IU/L, the AST from 14 to 15 IU/L, the alkaline phosphatase (ALP) 60 to 66 IU/L, and the bilirubin 0.71 to 1.23 mg/dL. The patient was started on the blinded study drug on October 24, 2009 and several values of the liver-related tests obtained over the following 3 to 4 months remained quite normal. However, approximately 4 months after starting the test drug (January 27, 2010), the ALT was found to be 130 IU/L, the AST 61 IU/L, the ALP 83 IU/L, and the bilirubin 1.17 mg/dL. The patient apparently remained asymptomatic. Repeat testing 2 weeks later revealed an increase in the ALT to 208 IU/L although the other liver-related tests had returned to normal. At this point, the test drug was discontinued. Repeat testing 1 week later identified that the ALT had now returned to normal. Additional work-up, including abdominal ultrasonograpy and testing for HBsAg and anti-HCV yielded negative results. Regarding the other drugs received, the data provided are a little unclear but it appears that rabeprozole and domperidone treatment continued whereas the study drug was withdrawn followed by the return to normal of the ALT value.

Comment: This patient, with baseline liver chemistry tests that are completely normal, developed a moderate increase in the ALT value and a mild increase in the AST value approximately 4 months after beginning treatment with the blinded study drug. At this time, his serum bilirubin value was only minimally increased and he remained completely asymptomatic. Repeat testing two weeks later demonstrated a further increase in the ALT value while the other liver tests returned completely to normal. The test drug was then discontinued and a repeat test of the ALT 3 to 4 days later was now normal. Only minimal additional work-up was reported that included negative results for acute hepatitis B and C with testing for hepatitis A and E not reported, but both would seem unlikely to be the cause for the abnormalities. Also not reported and also unlikely to be the cause of the liver dysfunction because of its transient presentation was evidence of autoimmune hepatitis, as well as alcohol induced liver injury (AST elevation almost always exceeds ALT elevation) and nonalcoholic steatohepatitis (abnormality too transient). Injury from the other drugs received is ruled out by the fact that the ALT abnormalities waned even though these drugs were continued whereas normalization of the ALT followed discontinuation of the study drug. Thus, given the evidence of two elevated ALT values, both exceeding the AST values, in the absence of an alternative explanation for these noted abnormalities, drug-induced liver injury from the study drug cannot be excluded although clearly the injury was extremely mild and transient. I rate this as a low possible but mild case of alogliptin hepatotoxicity.

TCI2011A03640

This 64 year old Japanese male with diabetes mellitus and diabetic nephropathy was switched from treatment of his diabetes with voglibose to alogliptin on January 18, 2011 because of increased HbA1c and serum glucose levels. His baseline ALT was normal but baseline values for AST, AP and serum bilirubin were not reported. Soon after starting alogliptin, he developed nausea and vomiting as well as "stomach heaviness." Four days later (January 22), having received 4 doses of alogliptin, he stopped using the drug although his nausea persisted. He noted darkening of his urine. Liver-related tests performed for the first time on February 8 (approximately 2 weeks after stopping treatment), revealed an ALT of 869 IU/L, an AST of 625 IU/L, an ALP of 1169 IU/L, and a serum bilirubin value of 0.5 mg/dL. He also complained of itching. Over the next several months, even though he remained nauseated, his liver tests, with the exception of the ALP, slowly returned to normal, the AST value by February 19 and the ALT value by April 2 (taking into account the timing of blood testing). However, the abnormal ALP values resolved more slowly, falling to its lowest level (268 IU/L) on August 20, 2011. Only 2 values of serum bilirubin are reported, neither of which were abnormal. It is then stated that he was hypoalbuminemic and developed deteriorating renal function and dialysis was being contemplated but it is not stated that this was undertaken. What is stated categorically is that he was not evaluated further for a potential etiology, i.e., he did not undergo testing for the hepatitis viruses or for autoimmune markers, and he did not have a liver biopsy performed. Moreover, despite the pattern of liver tests that followed a mixed but predominantly cholestatic pattern, presumably representing

intrahepatic cholestasis based on the absence of jaundice or of biliary tree pain, no imaging procedures were performed.

Comment: This patient developed nausea, vomiting, and stomach "heaviness" shortly after starting alogliptin which presumably led him to discontinue treatment with alogliptin on his own accord after having received 4 doses of the drug. It is unclear whether these symptoms were a consequence of developing liver disease, as identified 2 weeks later based on the first set of liver chemistries evaluated, or on developing renal failure, the beginning date of which is not reported. Thus it is not clear whether the latency between starting alogliptin and development of liver disease occurred one week (when symptoms occurred) or three weeks (when biochemical dysfunction was identified) after starting the drug. The biochemical abnormalities that developed showed mixed hepatocellular/cholestatic liver injury, the cholestatic pattern predominating. In keeping with this is that he also had pruritus that persisted for some time after identification of the abnormal liver tests. He is not reported to have developed jaundice and the 2 serum bilirubin values provided were normal. No work-up was done to exclude the viral hepatitides or autoimmune liver disease, but it is decidedly unlikely that these would have yielded positive results given the pattern of liver injury. Also, although it would have been useful to have had imaging procedures performed to completely rule out extrahepatic obstruction, there is in fact no support for this diagnosis. He had been taking other drugs (allopurinol, amlodipine) but had been receiving them for well over a year, thus excluding them as possible causes for the liver injury. Thus, in the absence of a plausible alternative etiology, a diagnosis of alogliptin hepatotoxicity is probable even though it is uncertain whether the latency to injury occurred after one or after three weeks of starting treatment with the drug. However, it was not a life-threatening form of liver disease that can be graded as mild.

TCI2010A05612

This 64 year old man from Japan with type 2 diabetes was started on treatment with alogliptin on September 21, 2010 because of ever increasing HbA1c levels. Baseline levels for the ALT and AST values are not reported but his baseline ALP level was 323 IU/L and his serum bilirubin value, 0.59 mg/dL. Two months after starting treatment with alogliptin (November 10, 2010), even though asymptomatic, he was found to have developed quite abnormal liver-related tests (ALT 230 IU/L, AST 108 IU/L, ALP 1,260 IU/L, serum bilirubin 0.87 mg/dL). Alogliptin treatment was discontinued a day later (November 11, 2010) and he was started on treatment with glycyrrhizin/glycine/cysteine and later, ursodeoxycholic acid. An abdominal ultrasound revealed steatosis, and testing for hepatitis A, B and C were all negative, but testing for hepatitis E as well as for autoimmune markers was not performed. Over the course of the following 6 weeks, the ALT and AST values returned to normal, whereas the ALP value remained high although it began to decline but was still abnormal (ALP 588 IU/L) on December 29 2010, the last set of values shown. At no time was the serum bilirubin value increased. Other drugs the patient was receiving were candasartan and atorvastatin, but the liver chemistries

improved despite continuation of these drugs but following withdrawal of alogliptin. No further information on outcome or additional evaluation is reported.

Comment: Two months after starting treatment with alogliptin, the patient developed abnormal liver-related biochemical tests showing a mixed hepatocellular/cholestatic pattern, with the cholestasis predominating; the bilirubin value remained normal throughout and he was asymptomatic. Even though the biochemical pattern does not fit that of viral hepatitis, he was screened for and found to be negative for viral hepatitis markers. Because of liver test abnormalities showing a mixed although predominantly cholestatic pattern of injury, an abdominal ultrasound was performed presumably seeking evidence of a gallstone or dilatation of the biliary ducts, but none was found. Thus, this patient developed abnormal liver chemistries consistent with that of intrahepatic cholestasis 2 months after starting alogliptin, the abnormalities improving upon withdrawal of the drug. No other etiology for the liver abnormalities is apparent, and liver injury from other drugs he was receiving is ruled out by the improvement of the liver chemistries despite continued use of these drugs. It is thus my opinion that this patient probably developed alogliptin-related drug induced liver injury. The severity of the liver injury can be graded as moderate.

TCI2011A01464

This 75 year old man from Japan with type 2 diabetes was admitted to hospital because of a giant hematoma on his back. He had been treated with voglibose and pioglitazone but the pioglitazone was withdrawn on hospitalization and replaced with alogliptin on (b) (6). A day earlier, ALT, AST and serum bilirubin baseline values were normal (ALT 21 IU/L, AST 26 IU/L , serum bilirubin 0.77 mg/dL) but no baseline ALP is shown. One week later, he was found to have very mild elevations in his aminotransferase levels (ALT 67 IU/L, AST 56 IU/L) with unchanged ALP and serum bilirubin values. Both ALT and AST values peaked 3 days later (89 IU/L for both) but continued to remain mildly abnormal through (b) (6) the last set of values reported. The serum bilirubin values remained normal throughout the reported follow-up period, which unfortunately lasted for only one week. Thus, with the exception of a single baseline normal value for the ALT and AST, all values for the aminotransferases thereafter remained mildly abnormal with minimal fluctuation. Despite the short observation period, the mostly unwavering mildly abnormal ALT values raises the suspicion of a pre-existing form of chronic liver disease, yet no effort was made to perform testing for chronic hepatitis B or C, for markers of autoimmune hepatitis, or for evidence to support the possibility of nonalcoholic steatohepatitis (NASH). An imaging study reported that the liver "had a blunt margin" and a hepatic cyst was reported to be present. The narrative summary raises the issue of possible chronic liver disease but then suggests that the identified abnormalities began a week after starting the drug and that the abnormal values appeared to be improving (unimpressive to me) thus suggesting a temporal relationship between starting the drug and development of liver injury with possible improvement on stopping the drug (i.e., a dechallenge). I am not convinced that this was the case, or that an initial single "normal" aminotransferase value followed a

week later by mildly abnormal values persisting and fluctuating through the last set of tests precludes the possibility of pre-existing chronic liver disease. It is a pity that hepatitis serology was not performed without which it is not possible for me to reach a firm diagnostic conclusion.

Comment: This patient was reported to have had normal ALT and AST values at the time of starting treatment with alogliptin with the identification of mild increases in both values one week later that persisted in being mildly abnormal with slight fluctuations throughout the relatively short period of biochemical follow-up. Alkaline phosphatase and bilrubin values remained normal. The issue for me is whether the abnormalities were precipitated by the drug or whether the patient already had mild viral-related chronic liver disease or NASH despite the report of a single abnormal baseline level. In this instance, if it is the drug, the latency is quite short and the aminotransferase values are very mild and, over the course of the short follow-up period, persistently abnormal with the type of fluctuations seen in patients with chronic hepatitis C. Unfortunately, hepatitis viral markers were not obtained. With the absence of these markers and of further follow-up of the serum aminotransferases, I am unable to reach a reasonable diagnostic conclusion. Specifically, I am unable to make a diagnosis of alogliptin hepatotoxicity but I am also unable to exclude the possibility of this diagnosis. Moreover, the injury appears to be mild. On the basis of the insufficient available data, I believe that there is a very low possibility that the patient developed alopgliptin-induced liver injury although I am unwilling to exclude the possibility that the patient actually had pre-existing chronic liver disease. This latter would require information on hepatitis virus serology and on additional biochemical follow-up.

TCI2011A01670

This 67 year old Japanese female with diabetes mellitus was started on treatment with alogliptin on February 1, 2011. No baseline pre-treatment values are reported, but liver-related tests obtained 2 weeks later (January 15, 2011), while on treatment, revealed normal values for the ALT (17 IU/L) with a slightly elevated ALP value (233 IU/L) on the same day. Approximately 10 days after that (February 26, 2011), routine testing revealed an ALT value of 331 IU/L, an AST value of 76 IU/L, an ALP of 353 IU/L, and a direct serum bilirubin value of 0.3 mg/dL. She also had a slightly elevated serum amylase value. She is reported to have had chronic kidney disease and to be a regular user of alcohol without specifying how much drinking of alcohol she actually did. The alogliptin was discontinued on the same day (February 25, 2011). Over the course of 3 weeks, her ALT value returned to normal as did the AST value, but although ALP values declined, they were still abnormal 3 weeks later. Her serum bilirubin value remained normal throughout. She was treated with glycyrrhizin/glycine/cysteine and liver extract/ flavine adenine dinucleotide and then with ursodeoxycholic acid. She is not reported to have developed symptoms, and she was not evaluated for hepatitis virus and autoimmune markers or to have undergone imaging procedures. She was reported to also be receiving

candesartan and magnesium oxide but start and stop dates for these products were not reported.

Comment: This patient was found about 3-4 weeks after starting treatment with alogliptin to have moderately increased values for ALT, AST, and ALP. She remained asymptomatic. Her serum bilirubin value was not increased. Treatment with alogliptin was discontinued and over a period of 2 to 3 weeks, her aminotransferase values returned to normal but not her ALP values. Work-up for alternative diagnoses was not performed, but it was apparently assumed that because the liver chemistries improved after stopping alogliptin, it was likely that the liver injury was precipitated by alogliptin. It is unfortunate that markers for viral and autoimmune hepatitis were not done since it is conceivable that viral or autoimmune hepatitis might have played a role. On the other hand, the likelihood of these conditions being responsible is quite low because of the rapid improvement in the aminotransferase values. Thus, liver injury from alogliptin remains a possible diagnosis, the liver dysfunction appearing to be mild and lasting for a short duration.

TCI2011A02538

This 54 year old Japanese man with diabetes mellitus and hypertension had been seen on a number of occasions at the same hospital beginning in 2008. He was tested and found to be negative for hepatitis B and C. He received a number of drugs including pioglitazone, acarbose, cilnidipine, olmesartan, nifedipine, mecobalamin, and epalrestat. There is background information suggesting the occurrence of alcoholic liver disease but without other supporting information. There is also mention of fluctuating aminotransferase values, ranging between 10 and 30 IU/L but rising to between 50 and 70 IU/L on occasion for reasons not stated. On October 18, 2010, he is reported to have an ALT of 32 IU/l, an AST of 36 IU/L, and a total bilirubin of 0.5 mg/dL. On October 19, 2010, clinidipine and nifedipine were switched to azalnidipine and generic nifedipine. On October 26, he was started on alogliptin. About 6 weeks later (December 6, 2010), he had a single spike in his liver chemistries (ALT 198 IU/L, AST 194 IU/L, total serum bilirubin 1.2 mg/dL). An ALP value was not reported at this time. Repeat testing a little over 2 weeks later revealed that ALT, AST, and serum bilirubin values had returned to normal although ALP levels were slightly increased. On December 20, 2010, alogliptin, azelnidipine, and generic nifedipine were all discontinued and replaced with glimepiride, cilnidipine, and generic nifedipine and he also began treatment with glycyrrhizin/glycine/cysteine. As noted above, markers for hepatitis B and C were found to be negative. No markers for autoimmune liver disease were performed nor were imaging procedures. Thus, the liver "disease" is characterized by a single spike in the aminotransferases and serum bilirubin levels, followed by a return to normal by the time of the next set of tests performed 18 days later. It is a great pity that retesting of the serum enzymes was not done until 2 weeks after identifying a fairly brisk abnormality that would probably have confirmed the identified abnormalities.

Comment: It is unclear what etiology of liver disease to append to this case. About 6 weeks after starting several drugs, one of which is alogliptin, he developed a single spike in both aminotransferase values and a minimal increase in the serum bilirubin level, all returning to normal when testing was repeated for the first time after the observed abnormality 18 days later. Is it conceivable that there was an error in the tests performed or that the sample tested had actually belonged to someone else? Or was this a legitimate single abnormality that might have again been abnormal if repeat testing had been performed earlier. Regarding etiology if the finding was valid, hepatitis viral infections B and C seem ruled out as are other etiologies because of the transient nature of the abnormality. It is not really appropriate to attempt to assign an etiology to a single abnormal serum enzyme because of the uncertainty of whether this is a legitimate event. Nevertheless, if the finding of the single abnormal spike of both the ALT and AST was indeed valid, without being able to impugn another etiology, the likelihood that the single abnormality represented a reaction to alogliptin cannot be entirely ruled out. Thus, there is a very low possibility that alogliptin was responsible for the identified abnormality that might have been confirmed had re-testing not been delayed for 18 days. If correct, the liver disease that developed was trivial.

TCI2011A04039

This 77 year old man from Japan with diabetes mellitus was admitted to hospital on (b) (6) for treatment of "arteriosclerosis obliterans with percutaneous transluminal angioplasty" which was performed 2 days later. The following day (b) (6) he was started on treatment with alogliptin. Baseline ALT and AST values on (b) (6) were normal (both 10 IU/L). Three days later he developed anorexia, and a day after that, he began vomiting. Laboratory testing on (b) (6) revealed an ALT value of 106 IU/L, an AST value of 125 IU/L, an ALP value of 336 IU/L, and a serum bilirubin value of 0.3 mg/dL. By the next day, the values for the aminotransferases peaked (ALT 627 IU/L, AST 669 IU/L) whereas the ALP value peaked 5 days after the initial abnormality (349 IU/L). Bilirubin values remained normal throughout. Alogliptin was discontinued on (b) (6) The last set of values reported, on (b) (6) revealed marked decreases in both the ALT (60 IU/L) and AST (66 IU/L) levels but not yet to normal values. As noted, the ALP was still abnormal and the serum bilirubin value never became abnormal. At this time, his anorexia and vomiting ceased. There is no mention of testing for hepatitis or autoimmune serology. Other drugs he had been receiving continued. In the belief that the abnormalities were a consequence of the receipt of alogliptin, no effort appears to have been invested in seeking an alternative diagnosis for the liver disease. Still, there is a compelling temporal relationship between starting the drug and the onset of liver test abnormalities, although of very short latency, and stopping the drug was followed by improvement of liver chemistries. Based on the available data, possible explanations for the observed liver injury include a reaction to the alogliptin, although the latency is very short, or induction of cardiac dysfunction following the angioplasty, although there is no evidence to support this likelihood; while neither viral nor autoimmune hepatitides were excluded, the likelihood that either are responsible for the liver injury is low given the rapid improvement in the aminotransferase levels after drug withdrawal.

Comment: This patient, with cardiovascular disease requiring angioplasty, developed anorexia and vomiting 3-4 days after starting treatment with alogliptin; alogliptin treatment was apparently begun one day after the angioplasty. With the onset of vomiting, liver-related tests revealed mild increases in both aminotransferase levels that increased the next day to considerably higher values. Treatment with alogliptin was discontinued with the observed peak values. Two days later, the aminotransferases had fallen to the level of the abnormal values first identified and 2 days after that had fallen to near but not completely normal values. Alkaline phosphatase values were mildly increased but the bilirubin was not increased. Symptoms paralleled the raised aminotransferase values. Unfortunately, based on what is reported, no effort was undertaken to exclude such etiologies as acute viral or autoimmune hepatitis but the rapidity of recovery would suggest that these etiologies are unlikely to have been responsible for the liver injury, which was modest and short-lived. An alternative diagnosis to alogliptin hepatotoxicity, given that he was admitted to undergo angioplasty, is liver dysfunction associated with cardiac failure. However, there is absolutely no mention of cardiac dysfunction. Thus, was it not for the fact that the liver injury was identified after a very short latency of starting treatment, I would have judged this a case of probable alogliptin hepatotoxicity. But given the potential for a cardiac etiology, I am inclined to classify this case as a possible-probable mild case of alogliptin hepatotoxicity.

TCI2011A04874

This 55 year old Japanese male with diabetes was reported to have begun treatment with cefotiam hydrochloride, reason not given, on July 22, 2011. On July31, 2011, the cefotiam was discontinued and on August 1, 2011, was replaced with cefazolin (reason not given), that was administered until August 5, 2011. Alogliptin treatment was begun on July 25, 2011. Baseline values of the liver-related tests are not shown. On August 15, 2011 (15 days after stopping cefotiam, 10 days after stopping cefazolin and 21 days after starting alogliptin), the patient was found to have an ALT value of 233 IU/L, the values remaining in the same increased level (>200 IU/L) on the 3 occasions it was measured over the following 10 days. During the same period, the AST was only slightly increased (65-43 IU/L), the ALP was increased to above 300 IU/L, and the serum bilirubin was measured as slightly exceeding 1.0 mg/dl. No information is provided regarding symptoms, and there is no evidence that the patient was evaluated for other etiologies (viral or autoimmune hepatitis). Treatment with alogliptin was discontinued on August 25 and the aminotransferase values slowly declined; the ALT value was back to near normal by September 8 while the AST value was back to normal by September 1. Alkaline phosphatase values also declined and reached normality by September 22. At no time did the patient have evidence of jaundice.

Comment: This patient, treated with 2 different antibiotics for unstated reasons, and then begun on treatment with alogliptin, was found to have moderate increases in ALT and milder increases in AST 15 days after stopping the one antibiotic, cefotiam, 10 days after stopping the second antibiotic, cefazolin, and 21 days after starting treatment with alogliptin. Unfortunately, baseline levels performed at the outset are either not shown or

were not obtained. The ALT values remained abnormal in the same range until the alogliptin was discontinued at which time they began a decline to near normal values close to one month after stopping the alogliptin. As noted for most of the cases reviewed, based presumably on the likelihood that the alogliptin treatment was responsible for the liver injury, alternative diagnoses were not sought. While a diagnosis of acute viral or autoimmune hepatitis cannot be completely excluded since testing for these disorders was either not undertaken or not reported, these diagnoses seem less likely because of the rapid recovery of the serum enzyme levels. Both antibiotics received have been associated with the development of abnormal liver chemistries, but in this instance, the injury was identified after stopping the drugs, not an unheard-of occurrence. Still, the latency is a little prolonged for both. Taking this all into account, a diagnosis of alogliptin hepatotoxicity cannot be dismissed and, therefore, alogliptin hepatotoxicity represents a possible diagnosis. The manifest liver disease was, however, mild and short-lived.

TCI2011A04573 (significant update and features hyperbilirubinemia)

This was a 77 year old Japanese female patient with a history of spinal stenosis (that had required lumbar surgery), Hashimoto's thyroiditis, and diabetes mellitus. Her diabetes had been treated with voglibose and glimepiride but she had a high HbA1c and peripheral neuropathy. On June 1, 2011, she was started on treatment with levothyroxine for her hypothyroidism, the dose being increased on June 17. On (b) (6) she was started on treatment with alogliptin. Baseline values for the ALT, AST, and serum bilirubin were normal (ALT 22 IU/L, AST 27 IU/L, bilirubin 0.4 mg/dL). Her baseline ALP value was 290 IU/L. On (b) (6) 13 days after starting alogliptin, she was found to have mild increases in liver-related tests (ALT 57 IU/L, AST 56 IU/L), followed by a dramatic increase in the levels about one month later (ALT 1178 IU/L, AST 1070 IU/L, ALP 905 IU/L, serum bilirubin 6.3 mg/dl). She was also found to have increases in serum ammonia levels and coagulation parameters and she was febrile. On (b) (6) because of the continued high elevation in all the liver chemistries, alogliptin treatment was discontinued, and she was begun on treatment with menatetranone, ascorbic acid, and glycyrrhizin/glycine/cysteine, followed 4 days later by treatment with ursodeoxycholic acid. At this time, levothyroxine treatment was discontinued. She appeared to be moving toward fulminant hepatitis and she was transferred to another hospital, presumably an academic institution. Although her serum enzymes began to fall, her coagulation parameters worsened, as did her serum bilirubin that peaked at 33.5 mg/dL on (b) (6). She was treated for encephalopathy with kanamycin and lactulose. She was then started on treatment with corticosteroids, first given intravenously and then switched to oral prednisilone. The serum aminotransferases and bilirubin began to decline, and she was then transferred back to her original hospital. In October, she developed a fever and what was diagnosed as pneumonia, and she was started on treatment with a number of antibiotics. Her pneumonia worsened and she died on (b) (6) at which time her ALT was 30 IU/L, her AST 61 IU/L, her ALP 480 IU/L, and her serum bilirubin 3.8 mg/dL. Work-up had identified negative serology for hepatitis A, B, and C, for EBV and CMV, and negative tests for ANA, ASMA, LKM-1 antibody and AMA. Thus her death,

clearly related to fulminant liver disease or its complications, was not caused by infection with hepatitis viruses, and did not seem related to autoimmune hepatitis as defined by negative tests for all autoimmune hepatitis markers.

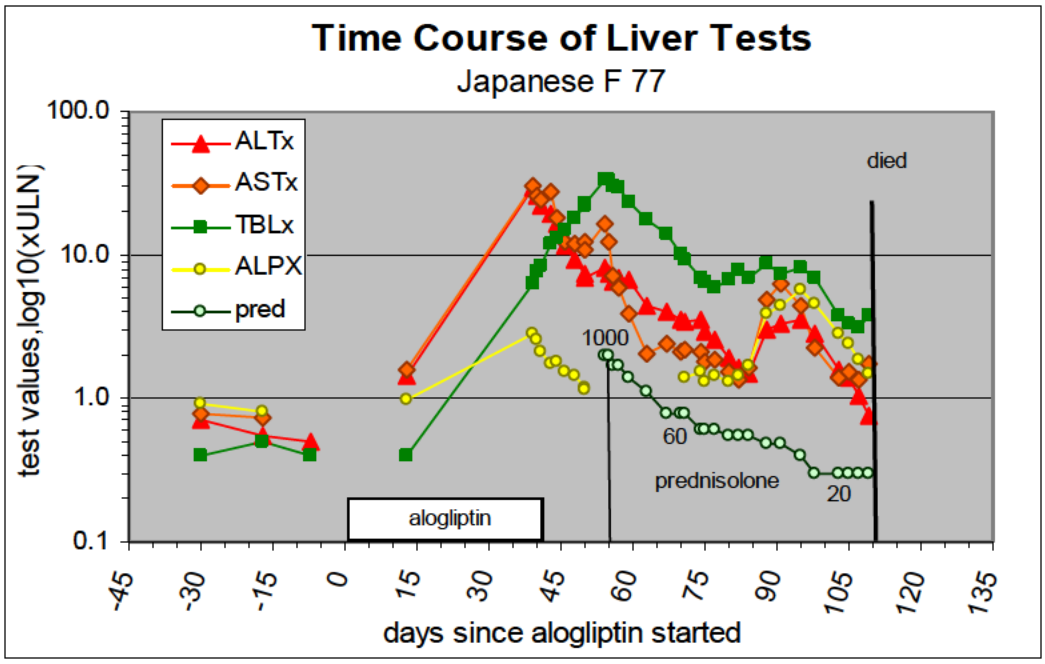
Comment: This 77 year old woman with diabetes mellitus, Hashimoto's thyroiditis and hypertension, who was admitted to hospital for treatment of her hypothyroidism with levothyroxine, developed mild elevations in aminotransferase levels 13 days after starting treatment of her diabetes with alogliptin. The liver dysfunction slowly worsened and she developed jaundice and evidence of impending fulminant hepatitis. Treatment with alogliptin was discontinued after 39 days, followed by discontinuation of the levothyroxine. She was transferred to another hospital presumably because of greater expertise at that hospital, and she was managed there for her advancing hepatic failure. Eventually she was started on treatment with corticosteroids on the assumption that the liver disease was of autoimmune origin in view of her background of diabetes and thyroiditis. This diagnosis was not, however, confirmed by identifying markers of autoimmune liver disease, all of which were negative. The liver disease appeared to improve as defined by a reduction in the liver chemistries, and the patient was transferred back to the original hospital. There she developed a fever and evidence of pneumonia, and despite treatment with a number of antibiotics, she died.

That this patient developed severe liver disease and died as a late sequel to the liver disease seems quite clear. What is to be determined is what the cause was for the liver disease. Viral hepatitis as the cause for the liver injury is ruled out by the negative serology for all the hepatitis viruses but hepatitis E. Autoimmune hepatitis, particularly in an elderly female, needs to be excluded. This diagnosis is based generally on identifying autoimmune markers, but the test results of all markers in this patient were negative that ordinarily would exclude the diagnosis. However, given this patient's background, namely the existence of other autoimmune disorders such as the diabetes and thyroiditis, "idiosyncratic" autoimmune hepatitis needs consideration despite the negativity of all the autoimmune hepatitis. This presumably was the basis for treating this patient with corticosteroids that appeared to lead to the improvement of the liver dysfunction thus supporting the possibility of this diagnosis. However, the apparent rapid response to steroids seems much quicker than is normally the case for idiosyncratic autoimmune hepatitis, and corticosteroids can "wipe out the yellow" even in instances of non-autoimmune acute hepatocellular injury. In my opinion, the absence of positive tests for autoimmune markers is compelling evidence that this patient did not spontaneously develop idiopathic autoimmune hepatitis. Rather, in view of the temporal relationship between starting treatment with alogliptin and developing acute hepatocellular injury two weeks later makes it probable to highly likely that alogliptin was indeed responsible for the fatal liver disease.

Noteworthy is that the hepatology experts assigned by the company to review the cases disagree with my conclusion, (b) (4) assessing the case as unlikely and instead due to autoimmune hepatitis (AIH), while (b) (4) assessed the case as being possibly attributable to alogliptin. The concerning issue is whether the diagnosis was

actually "idiosyncratic" AIH rather than dili from alogliptin. The major issue responsible for the disagreement is that the usual markers of AIH were negative in this patient. In favor of a diagnosis of AIH hepatitis is the fact that the patient was a female, that she had another diagnosis with autoimmune overtones, thyroiditis, and that she appeared to respond to treatment with corticosteroids. In my view, while this diagnosis can certainly not be ruled out, there are features that suggest to me that dili represents a greater likelihood as causation. Clearly, AIH can present for the first time in an elderly female and can occur in the absence of positive immunological tests. However, she is a little older than is usual for a first time onset of AIH and I am compelled by the fact that if she did have an underlying immunological diathesis, all of her markers for AIH were completely negative. That her liver chemistries improved with corticosteroid treatment is clear, but this can also occur with other causes of acute hepatocellular injury. Most of all, however, is that the injury occurred coincidental with use of alogliptin. Is this purely coincidental? I am left with the view that the drug played a role in the induction of the liver disease, either through a direct "idiosyncratic" mechanism or through precipitating liver injury in a patient primed for it because of a so-called autoimmune diathesis. I feel quite strongly that it is not appropriate to assign a score of unlikely to this case; on the other hand, I recognize the validity of the counter argument and therefore I am willing to downgrade my assessment from highly likely to probable.

In a later discussion with the sponsor and the two liver disease experts they employed to review cases, both experts continued to indicate that this patient was unlikely to have developed alogliptin hepatotoxicity, stating that they continued to believe that the diagnosis was that of "idiosyncratic" autoimmune hepatitis because of their stated view that while on treatment with corticosteroids, the liver chemistries underwent a marked improvement, but when steroid treatment was discontinued, there was a rebound in these chemistries that increased again to pretreatment levels. The case was then reviewed once more by Dr. John Senior who developed a figure showing a serial plot of the liver chemistries ranged against the administration of the corticosteroid. The plot indicated that the rebound occurred while steroids were still being received although the dose had been decreased. The plot indicates that corticosteroids continued to be administered virtually up to the time of death. Dr. Senior's consultation follows:



A Japanese woman born in [redacted] was found to have elevated blood sugar in 2009, and was started on voglibose 0.6 mg/day and glimepiride 1 mg/day. In April 2011 she complained of numbness in both hands from palm to fingers, thought due to peripheral neuropathy. Her HbA1c was 6.8%. On 1 Jun 2011 she was found to have hypothyroidism and was started on levothyroxine 25 µg/day, increased to 50 µg/day on 17 June. Alogliptin 25 mg/day was started on 1 July (Day 1) and levothyroxine was increased to 75 µg/day. On 13 Jul ALT and AST were slightly elevated, and markedly so on 8 August, with TBL 6.3 and prolonged prothrombin time. Fever and jaundice were noted 9 August and alogliptin stopped that day (41). She was treated with amino acids, menatetranone, ascorbic acid, glycerryhizin/glycine/cysteine, ursodeoxycholic acid. Levothyroxine was stopped that day. Liver failure was suspected and she was transferred to the reporting hospital on [redacted]. Kanamycin and lactulose were started, then she was started on methyl-prednisolone I.V., reduced by half every second day, then switched to oral prednisolone 60 mg daily and tapered off to 30 mg/day by [redacted], three weeks after being returned to the referring hospital on [redacted]. Fever occurred, pneumonia was diagnosed [redacted]; unresponsive to antibiotics, she died on [redacted]. No autopsy was done.

Other information: History of hypertension since 1997, surgery for lumbar spinal stenosis 2006,Hashimoto disease, hypothyroidism, obesity, hepatic steatosis,
Many CT scans were done, showing normal liver size in [redacted] (1400 mL [redacted]), with left lobe atrophy [redacted]; gallbladder wall thickened, atrophic [redacted] Negative tests [redacted] for ANA, ASMA, ALKM-1, AMA and vs HAV,IgM, HBc IgM, HCV, EBV IgM, CMV IgM but anti-thyroglobulin 29.5, anti-TPO-AB 600. Tests for GGT and LDH paralleled ALT, AST but CPK not changed. No normal laboratory ranges provided, No albumin or globulin data. Serum amylase slightly

increased [redacted] (b) (6) CT of pancreas [redacted] (b) (6) possible pancreatitis. Takeda remarked on 4 November that a lymphocyte stimulation test for alogliptin was negative, and also for levothyroxine, and suggested this problem was caused by autoimmune hepatitis, rather than DILI as diagnosed by the reporting physicians.

Impression: Alogliptin-induced serious hepatotoxicity, with terminal biliary obstructive process, possibly pancreatitis. Death due to pneumonia, sepsis. No good evidence for autoimmune hepatitis.

8635-004/402

The data provided in this case are meager and insufficient to allow a definitive diagnosis. This 65 year old man from Spain with chronic hepatitis (not further defined), dyslipidemia, hypoacusis, musculoskeletal pain, a palatal disorder, strabismus, and type 2 diabetes, was started on treatment with alogliptin on June 14, 2011.The patient was also receiving a number of other drugs that included acetylsalicylic acid, bisoprolol, glyceryl trinitrate, hydrochlorothiazide, olmesartan, omeprazole, simvastatin, gliclazide, and repaglinide. Liver-related chemistries one week before stating alogliptin were an ALT value of 24 U/L, an AST of 16 U/L, an ALP of 40 U/L, and a total bilirubin of 0.4 mg/dL. The values had increased a little at the time of beginning treatment with alogliptin. One month after starting treatment (July 13, 2011), he was found to have an ALT of 196 U/L, an AST 0f 111 U/L, an ALP of 42 U/L and a total serum bilirubin of 0.48 mg/dL. No mention is made of symptoms. Values obtained five days later (the last set shown in the report), showed an increase in the ALT level to 237 U/L, and a virtually unchanged AST value (108 U/L), ALP and serum bilirubin. Absolutely no further evaluation (i.e., viral and autoimmune markers) is reported. Treatment with alogliptin was discontinued on September 9, 2011 (almost 3 months after identifying raised levels of aminotransferases). However, testing for the serum aminotransferases between July 18 and September 9 was either not done (which I doubt) or was not reported. Also not done or not reported were virologic assays for hepatitis or testing for autoimmune markers. More importantly, what the reported “chronic hepatitis” is was not further described and what the outcome of the disease is not known. Regarding possible injury from other drugs he was receiving, it is unclear whether any of them could be implicated because first, their use all continued, and second, the last aminotransferases shown continued to be even more abnormal. It is thus not possible to establish an etiology for the liver dysfunction. Indeed, it is imperative that more information be supplied regarding viral and autoimmune markers and that liver chemistry results beyond those shown be displayed.

Comment: In the absence of needed information (hepatitis and autoimmune markers, start and stop dates of all drugs received, information on clinical manifestations, long-term follow-up data on liver chemistries,), it is not possible to establish an etiologic diagnosis. The sponsor should be required to submit the needed information.

311-9003/009

This case is identified as a subject with an ALT or AST >10x ULN. The data provided are minimal, summarized in a single page. The patient was a 49 year old man with hyperlipidemia, depression and anxiety who presumably had diabetes mellitus although this diagnosis is not mentioned in this single page report. Medications he was taking included fluoxetine, buspirone, trazodone, and ezetimibe. He was apparently a participant in a study drug trial who, in May 2006, was taking pioglitazone during run-in for an alogliptin trial. On June 16, 2006 he was randomized for a double-blind trial and, if I read the supplied information correctly, received alogliptin. During "stabilization", his liver related studies revealed an ALT of 14 mU/mL, an AST of 20 mU/mL, an ALP of 55 mU/mL, and a total serum bilirubin value of 0.3 mg/dL. On the day of randomization, the aminotransferase values were slightly increased to above the ULN (ALT 66 mU/mL and AST 32 mU/mL) as was the ALP (84 mU/mL; normal value 32-72mU/mL). The bilirubin value remained normal. Thirty-two days after starting treatment with alogliptin, the ALT value was found to have increased substantially (ALT 646 mU/mL) as had the AST (585 mU/mL) and the ALP (112 mU/mL); serum bilirubin had also increased but remained within the normal range. There is no comment on whether or not the patient developed associated symptoms. Also, there is no mention of efforts to evaluate the cause for this sudden increase in serum enzymes values (i.e., no tests for hepatitis or autoimmune serology). It is stated that the study drug was interrupted because of the increase in serum enzymes but without stating on which date although, presumably, it was when the abnormalities were first identified. Also not commented upon was what the start and stop dates were for the other drugs the patient was receiving.

Repeat testing was performed 10 days later (study day 42), identifying that the ALT had decreased to 46 mU/mL, the AST to 22 mU/mL, the ALP to 73 mU/mL, and the serum bilirubin to 0.39 mg/dL. By study day 49, all values were now completely normal. In the meantime, the study subject had voluntarily withdrawn from the study. Thus, this patient developed an increase in serum enzymes although not in serum bilirubin about one month after starting alogliptin at which time the drug was stopped, following which there was a rapid fall in enzymes 10 days later to near-normal values. Since efforts to identify an alternative diagnosis to possible drug induced liver injury were not undertaken, the precise basis for the observed abnormality cannot be determined. In view of the rapid improvement in the enzyme levels within 10 days of drug withdrawal, it is unlikely that viral or autoimmune accounted for these abnormalities.

Comment: This 49 year old man developed a fairly marked increase in serum enzymes (ALT, AST) approximately one month after starting treatment with alogliptin, all values declining to near normal when next tested (10 days) later, and to normal when tested 10 days after that. This suggests a link to the use of alogliptin since the latency period of one month is a well-accepted time interval, and the rapid decline to normal values within 20 days of discontinuing use of alogliptin suggests an effect of drug de-challenge. Unfortunately, testing for possible infection with one or other of the viral infections was not performed, nor was testing for markers of autoimmune hepatitis. However, the rapid decline in aminotransferase values with discontinuation of alogliptin is consistent with

the effect of de-challenge. Even if drug-induced liver injury was the actual cause, implicating alogliptin alone is not possible without knowledge of the start and stop dates of the other drugs taken. Thus, it is difficult to reach a definitive diagnosis for the observed liver dysfunction, although it is possible that alogliptin might have been the cause. Nonetheless, the condition can be graded as mild and short-lived.

TCI2011A06892

This 78 year old Japanese man, a heavy drinker, with a diagnosis of gastric cancer and type 2 diabetes, treated with glimepiride and voglibose, was started on treatment with alogliptin on October 26, 2011, the glimepiride being reduced by half. His baseline aminotransferase values were abnormal (ALT 52 IU/L, AST 57 IU/L) while his serum bilirubin level was normal. Subsequent tests of the aminotransferases showed persistent low-grade increases of their levels until approximately 2 months later (December 20, 2011), when his ALT increased to 237 IU/L, his AST to 542 IU/L and his ALP was 542 IU/L. The single test for bilirubin was normal. Alogliptin treatment was withdrawn on this date and he was switched back to glimepiride. An abdominal ultrasound was reported to show no liver abnormalities or dilated intrahepatic ducts but there was suspicion of cancer of the pancreatic tail. Tests for hepatitis B and C were negative. A single follow-up test of his liver chemistries, performed the day after the values had spiked, showed that they had dropped but were still far from normal. Since these are the only tests displayed, the final outcome is unknown. Also unknown is whether he was continuing to drink when the abnormalities were identified.

Comment: Data available in this narrative are insufficient to establish a diagnosis for the observed liver dysfunction. The patient, described as a heavy drinker, had abnormal aminotransferases at baseline that might have been a result of continued heavy drinking or of alcoholic steatohepatitis, although the AST and ALT values were elevated to the same level, unlike alcoholic liver disease where the AST is almost always higher than the ALT value. Two months after starting treatment with alogliptin, he developed a considerable spike in his already abnormal aminotransferase levels, the AST now rising to twice the level of the ALT increase. The value obtained on the following day had dropped considerably although it remained much higher than the baseline abnormal values. No further liver-related test data were reported so the extended outcome is unknown. Hepatitis B and C serologic markers were negative. Clearly, something precipitated a surge in aminotransferase levels that, since it followed 2 months after starting alogliptin treatment, could possibly have been a result of receipt of this drug. But there is insufficient clinical information provided surrounding the period of the spike, such as whether the patient was drinking heavily at the time. Thus, there is a low possibility that alogliptin was responsible for a sudden increase in aminotransferase values, but they dropped considerably in 24 hours and thus, together with the apparent lack of symptoms and of the development of jaundice, this can be considered a trivial issue.

TCI2011A06837 (features hyperbilirubinemia)

This 66 year old Japanese male who had been treated with pioglitazone and glimepiride for type 2 diabetes, was switched from pioglitazone to sitagliptin on October 13, 2011. However, sitagliptin appeared to be ineffective, and on [redacted] (b) (6) was itself replaced by alogliptin. His baseline liver chemistries were normal (ALT 27 IU/L, AST 36 IU/L). His ALP and serum bilirubin levels are not recorded. On a routine visit approximately 1 month later [redacted] (b) (6)), he was found to have an ALT value of 1512 IU/L, an AST of 2188 IU/L, a serum bilirubin of 3.9 mg/dL, and an ALP value of 313 IU/L. Initially reported to have had no symptoms at this time, he later admitted to actually having had some malaise. He was immediately hospitalized and alogliptin treatment was discontinued, and the dose of glimepiride was increased. The serum aminotransferase values declined rapidly over the course of the following week, reaching near normal values within 10 to 14 days, as shown in the last test result provided.

Work up focused on testing for the viruses of hepatitis B and C, both of which were serologically excluded. No imaging procedures were performed. Markers for autoimmune hepatitis were apparently not performed but the issue of potential autoimmune hepatitis was considered by his physician, and the likelihood dismissed based on the evidence of normal values for gamma globulin and the return of the abnormal values to near normal within a relatively short time and without corticosteroid treatment. Other drugs received by the patient included isosorbide, sodium gualenate, famotidine, teprenone, nifedipine, and pravastatin, but they were continued despite which the liver tests improved following withdrawal of the alogliptin. Alcoholic liver disease as a potential diagnosis was excluded by the fact that he was only an occasional drinker and the pattern of liver dysfunction was completely different from that seen in alcoholic hepatitis.

Comment: This 66 year old man developed acute hepatocellular liver injury associated with hyperbilirubinemia approximately one month after starting treatment with alogliptin. With identification of the liver injury, alogliptin was discontinued whereas all other drugs he was receiving continued to be administered. In seeking an etiology, infection with the hepatitis B and C viruses was ruled out (but, of course, not hepatitis E virus infection), as was autoimmune hepatitis based on the absence of hyperglobulinemia and the rapid recovery without immunosuppressive treatment. Although imaging was not done to exclude the possibility of obstructive causes for the liver dysfunction, there were no clinical or biochemical indicators to support the diagnosis. Accordingly, it is my opinion that a diagnosis of alogliptin hepatotoxicity is probable to highly likely the cause of the liver disease of moderate severity.

The liver experts employed by the company have both reached a different conclusion, [redacted] (b) (4) *indicating that data were insufficient to reach a reasonable conclusion whereas* [redacted] (b) (4) *awarded this a case of barely possible alogliptin hepatotoxicity. Both express concern of the rapid improvement in the serum aminotransferases in the face of a drug with a long half-life, a concern with which I agree. Undoubtedly, rapid improvement such as occurred in this case from strikingly increased aminotransferase*

levels to near normal levels within 10 to 14 days is unusual for the common causes of acute hepatocellular injury other than acute congestion or shock. However, unless not reported, the narrative does not provide any information that even suggests the presence of cardiac disease or the occurrence of dramatic hypotension. The other issue raised to dismiss dili is that the lymphocyte stimulation test was negative. Since this test is not approved for this purpose in the U.S., and since its validity is uncertain, I cannot hang my hat on the results reported here as an indicator that dili was excluded. Clearly missing is the lack of test results for hepatitis A and E. One or other of these viruses might well have been responsible although hepatitis A is relatively uncommon in a 66 year old man (potential risk factors not reported) and hepatitis E is not known to be endemic in Japan (at least to my knowledge). I will therefore remain with my view that alogliptin dili is the probable cause for the liver injury although I will agree that there are some conflicting data that could require assigning a score of probable rather than highly likely.

In later review of this case by both (b) (4)*, it appears that they now both score this case as a probable instance of alogliptin hepatotoxicity.*

TCI2011A06481 (new)

This 53 year old Japanese man was found during a medical check-up to have an elevated blood glucose level of 193 mg/dL. He was admitted to hospital (reason not stated) and began treatment with voglibose. His HbA1c remained high and he was admitted to another hospital (this information is a little confusing since he seems to have been admitted to more than one hospital for reasons not reported other than to stabilize his treatment for diabetes). Changes in treatment occurred because of persistently increased levels of HbA1c so he was switched from voglibose plus nategliunide to glimepiride plus miglitol. Because of a continuingly elevated HbA1c value, he was then switched to sitagliptin and, finally, on July 21, 2011, sitagliptin was discontinued and he was placed on alogliptin. Serum enzymes obtained 2 months prior to starting alogliptin were normal (ALT 18 IU/L, AST 25 IU.L, ALP 226 IU/.L) as were these values obtained about one month after starting alogliptin (ALT 22 IU/L, AST 21 IU/L, ALP 242 IU/L). On (b) (6) , he complained of feeling that was "being strangled," leading to the consideration of angina pectoris. Because his chest X-ray and EKG were normal, the considered diagnosis turned to reflux esophagitis and on (b) (6) he was started on treatment with sodium rabeprazole, rebamipide, and mosapride, prescribed for 3 days, but liver-related abnormalities were noted on the same day (ALT 1583 IU/L, AST 921 IU/L, ALP 447 IU/L; no serum bilirubin value was reported on that date. Apparently, he could not be contacted until 2 days later when he was hospitalized on (b) (6) and the alogliptin was immediately discontinued. Laboratory values at this time had fallen to an ALT of 982 IU/L, an AST of 320 IU/L, and a direct serum bilirubin value of 0.2 mg/dL., the ALP remaining high at 455 IU/L. A work-up for potential etiologies showed that he had not been infected with hepatitis viruses A, B, and C, but no test was reported for hepatitis E. Serology was negative also for markers of autoimmune hepatitis and primary biliary cirrhosis, although he was positive for both IgM and IgG anti-CMV but without

CMV antigenemia. Also unrevealing was a CT and US (presumably of the abdomen but not stated). Over the course of the following 3 weeks, during which the only symptom was pruritis, the serum enzymes returned to normal; the serum bilirubin value was never increased.

Comment: This 53 year old man without a past medical history of any substance was identified to have diabetes mellitus during a routine visit to a doctor. He was placed on oral treatment for diabetes, receiving several different drugs ending up finally with alogliptin. Testing for serum enzymes prior to and one month after starting alogliptin treatment revealed that they were normal. Approximately 3 and a half months after beginning treatment with alogliptin, he developed chest discomfort considered first to be possible angina, ruled out by finding a normal EKG, and then possible reflux esophagitis, prompting anti-reflux medication. However, on that same day, testing for possible liver injury revealed a markedly increased ALT value, an AST value that was also increased but less so than the ALT, and a normal value for the serum bilirubin. Alogliptin was immediately discontinued but on that same day, the liver-related chemistries showed considerable improvement, the values continuing to decline, reaching near normal values 3 weeks later. The serum bilirubin remained normal throughout. Work-up for potential etiologies appeared to rule out viral hepatitis A, B, and C, but not E, autoimmune hepatitis and obstructive liver disease. Tantalizing information for possible CMV infection could be set aside by finding no evidence for CMV antigenemia.

Ruling out almost all alternative diagnoses other than hepatitis E raises a strong suspicion of drug-induced liver injury. Alogliptin is the primary suspect based on an appropriate latency between starting treatment and the recognized development of liver dysfunction, and there is also compelling evidence of dechallenge after discontinuing treatment. Somewhat challenging, however, is that a reduction in the height of the abnormal aminotransferase levels appeared to start even before discontinuing the drug (might this have been the beginning of adaptation to the drug?). The most important alternative diagnoses are excluded with the exception of acute hepatitis E. Putting this all together, it is my opinion that the likeliest explanation for these finding are a hepatologic response to alogliptin. Given that there appeared to be beginning improvement in the serum enzymes even before discontinuing alogliptin, and the fact that testing for hepatitis E was not conducted, I am inclined to grade the as a probable case of alogliptin hepatotoxicity of moderate severity. It might be worthwhile checking to see whether testing for hepatitis E was in fact performed but not reported, but more likely that it was not done but could be performed if blood samples are available.

TCI2012A01179 (new and features hyperbilirubinemia)

This was a 65 year old Japanese male with type 2 diabetes. The narrative indicates that he had had two bouts of jaundice of unknown origin at ages 20 and 39 and that he had had cholecystitis on an unknown date culminating in a chlolecystectomy at age 55 years. He was also reported to have a "drinking habit." He was not reported to have been taking other medications and it is stated specifically that he had not been receiving any herbal products. He was started on treatment with alogliptin on September 20, 2011. A set of biochemical tests about a month after starting drug reported normal liver-related results (ALT 7 IU/L, AST 18 IU/L, total bilirubin 0.05 mg/dL). About 5 months after beginning treatment ((b) (6)), he developed malaise and noticed dark urine. Treatment with alogliptin was discontinued on the next day, and on the day after that (b) (6) [mis-labeled in the narrative as (b) (6)]), liver chemistries revealed an ALT level of 481 IU/L, an AST of 778 IU/L, an ALP value of 1288 IU/L, and a total serum bilirubin value of 14.4 mg/dL. The patient was then hospitalized. He was not reported to have complained of abdominal pain nor was it reported that he was febrile. Presumably because of the marked elevation in the ALP level, he underwent both a CT and US examination of his abdomen that was reported to be unrevealing. Also, the results were negative for testing for hepatitis B and C. The leukocyte count was relatively high but within the normal range. A lymphocyte stimulation test was reported to be negative. Testing about one week later ((b) (6)) revealed that there was a slight increase in his ALT level with a decline in his AST and ALP levels but his total serum bilirubin value was now 19.4 mg/dL. A liver biopsy was performed on (b) (6) reported to show features (not described) not inconsistent with drug-induced liver injury. The last set of tests reported, 2 weeks beyond the previously reported values, showed a marked improvement in the values, although they were not yet back to normal (ALT 65 IU/L, AST 71 IU/L, ALP 336 IU/L, total serum bilirubin 4.4 mg/dL). The patient was then discharged from hospital and no further follow-up information was reported.

Follow-up data indicate that the patient's blood sample (timing not stated) was positive for HEV RNA and anti-HEV IgA indicating apparent acute HEV infection.

Comment: This case represents somewhat of a dilemma for me. Reasonable efforts were made to exclude possible etiologies, although there were no test results for hepatitis A or E or for possible autoimmune hepatitis. However, the pattern of injury and the rate of recovery tend to negate the likelihood that any of these three conditions might have been responsible. In my mind, the two likeliest considerations are the passage of a gallstone or drug-induced liver injury. Items that raise the suspicion of the passage of a stone include the past history of transient jaundice on a couple of occasions without identified cause but also the history of cholecystitis requiring cholecystectomy, the marked increases in both the ALP and total serum bilirubin values relative to the aminotransferase levels, and the somewhat extended latency between starting the drug and the development of jaundice. Important points against it, however, are the reported lack of abdominal pain, fever, and leukocytosis, and the fact that imaging procedures were said to be normal (it might have been more helpful to have performed as ERCP but it is hardly surprising that it was not done). Moreover, the liver biopsy was reported to

show features "not inconsistent with drug-induced liver injury." Unfortunately, the liver biopsy findings were not described. It might have been helpful also to have reported on a serum amylase value.

In favor of potential dili from alogliptin (no other drug or herbal reported to be taken) is that the liver injury developed within 5 months of starting treatment with alogliptin. A consideration for dili, of course, requires excluding other conditions that might have been responsible; in this instance, items not excluded were hepatitis A and E and autoimmune hepatitis, but the pattern of injury does not appear to favor these diagnoses. Moreover, the liver chemistries improved after stopping the drug, consistent with dechallenge if indeed the diagnosis is dili. Also important is that the liver biopsy was not reported to show findings typical for another etiology, especially finings consistent with biliary tree involvement. Often taken as a point against dili, particularly in Japan, is if the lymphocyte stimulation test is negative, but this test is not approved for use in the U.S., and in any case, it has not been subjected to careful scrutiny for validation. Somewhat concerning vis a vis a diagnosis of dili, however, is the relatively long latency period of 5 months, the pattern of liver injury (hepatocellular/cholestatic rather than pure hepatocellular together with a somewhat higher serum bilirubin values than is usually seen). However, these minor misgivings certainly do not preclude a diagnosis of dili. Thus, there are items somewhat unsupportive of both of these diagnoses but I feel that the negative elements are greater for biliary tree disease than for dili and hence, without being able to implicate another cause (although it would have been preferable to definitively exclude hepatitis E and even hepatitis A), I am inclined to consider this a case of possible to probable alogliptin hepatotoxicity.

Follow-up data now indicate that the patient had developed apparent acute hepatitis E infection based on the identification of HEV RNA and IgA anti-HEV thus excluding a diagnosis of alogliptin hepatotoxicity.

TCI2011A02923 (new and features hyperbilirubinemia)

This 64 year old Japanese man with type 2 diabetes was found to have elevated blood glucose and HbA1c levels despite being treated with oral glimeperide and metformin. Accordingly, on March 2, 2011, metformin was discontinued and replaced with alogliptin. Blood testing was performed about one month later (March 30) and although he was without symptoms, he was found to have an ALT value of 358 IU/L and an AST of 204 IU/L. Unfortunately, no levels of the liver chemistries (ALT, AST. ALP, bilirubin) are shown prior to beginning treatment with alogliptin (this would be critically important information). Alogliptin treatment was discontinued on April 6. The next set of blood tests were performed about one week later (April 14, 2011, about 6 weeks after having started treatment with alogliptin and 8 days after discontinuing its use), displaying marked worsening of the aminotransferase levels (ALT 1030 IU/L, AST 362 IU/L), an ALP of 341 IU/L, and a total serum bilirubin value of 1.3 mg/dL. The following day, drip infusion with glycyrrhizin/glycine/cysteine was begun. Four days later (April 18), the ALT was now 1025 IU/L, the AST was 371 IU/L, and the total serum bilirubin value had

increased to 2.1 mg/dL. Drip infusion treatment was repeated. By April 21, the aminotransferase levels had decreased (ALT 755 IU/L, AST 199 IU/L) but not the total serum bilirubin value. On this day, a referral was made to a gastroenterologist at another hospital who prescribed ursodeoxycholic acid and daily treatment with glycyrrhizin/ glycine/cysteine. Work-up at this time identified the presence of HCV RNA, genotype 2. Without further treatment, the abnormal chemistries began to improve, and by July 20, about 4 months after the first identified abnormality, the ALT had returned to normal (ALT 29 IU/L) as had the AST value (AST 27 IU/L) and total serum bilirubin (0.8 mg/dL). One month later, the ALT value had increased again to the same modest level (ALT 138 IU/L) as the month before the identified normal value, with a slight increase also in the AST value (AST 91 IU/L), without any rebound in either the ALP or total serum bilirubin. This prompted a liver biopsy that was interpreted as showing moderate necrosis and inflammation (A2) and fibrous portal expansion. It is stated that treatment was begun with interferon and the about two months later, the aminotransferases returned to normal, the total serum bilirubin remaining normal. All liver-related tests remained normal for the approximately 5 months that followed.

Testing for hepatitis B was negative for HBsAg but positive for anti-HBc. Testing for hepatitis A and E was not performed.

Comment: This is an interesting case representing something of a dilemma. Clearly, the patient had hepatitis C but it is unclear whether he started with acute hepatitis C as suggested by markedly elevated aminotransferase values and mild hyperbilirubinemia that slowly subsided over 4 months or whether he had had existing chronic hepatitis C with a superimposed other acute insult such alogliptin hepatotoxicity. The great pity is that no hepatitis serology or liver chemistries were apparently available in the several months preceding his start of treatment with alogliptin. The one certain fact is that the acute liver injury within 4 weeks of starting alogliptin treatment cannot be explained solely on the basis of chronic hepatitis C alone because it is extraordinarily rare for there to be flares of liver injury of this degree in chronic hepatitis C as can be the case for chronic hepatitis B. Could this apparent acute insult therefore be explained by superimposed dili? The answer is absolutely" yes" despite the fact of difficulty in distinguishing acute superimposed injury in those with already existing chronic elevations of the aminotransferase levels. In this instance, information that the chronic hepatitis preceded the start of alogliptin treatment is lacking making it difficult to determine whether this was acute injury of another origin superimposed on already existing chronic hepatitis C. Had the abnormal values returned to normal in time without treatment, it would have been appropriate to regard this as superimposed acute liver injury. In this case there was a transient return to normal after stopping the drug but the aminotransferase returned to the low level abnormal values that prompted treatment with interferon that might then have been responsible for the persistent normal values that followed. However, I wonder whether the single normal value in a string of abnormal values of about the same degree was real or an error such as a wrong blood sample. If so, the values did seem to be slowly resolving even before treatment with interferon.

Sitagliptin cases collected from the AERS database and included in the recent review[2] by DPV (n=8).

6921611-5

There is sparse information in this AERS report. This was a 68 year old man with a history of hypertension and type 2 diabetes. He was started on treatment with sitagliptin on April 27. 2010. Concomitant therapy included candesartan. His aminotransferase values prior to treatment with sitagliptin were as follows: ALT 23 IU/L, ALT 24 IU/L. About one month later (May 22, 2010), he is reported to have developed bilirubinuria and clinical jaundice, but no liver-related tests are reported on this date. However, approximately 10 days after that, at the time of visit to a clinic, he is found to have an ALT of 1373 IU/L and an AST of 752 IU/L. Sitagliptin was then discontinued and 15 days later (June 17, 2010), his liver chemistries were apparently improving, although the values are not shown. No further information is offered.

Comment: Unfortunately, this report is incomplete with respect to determining whether it represents hepatotoxicity. There is minimal information on the patient's medical history or on the events surrounding his acute "liver injury." there is only a single set of liver chemistries reported during the acute event whereas sequential values are needed, it is reported that he is improving without showing the data and, of course, no tests for alternative etiologies, such as viral or autoimmune hepatitis, are reported. Nevertheless, in view of the temporal relationship between starting the drug and the identified onset of apparent liver injury with a reasonable latency period, and the fact that stopping the drug was apparently associated with improvement of the liver chemistries (i.e., dechallenge), dili cannot be ruled out. According, it is my view that this is a possible case of sitagliptin hepatotoxicity.

5989197-X

Once again, the data in this case are so skimpy that it is not possible to reach an etiologic diagnosis. The report involves a 73 year old female with apparent penicillin and sulfonamide allergies who was treated with sitagliptin beginning on (b) (6) She was also receiving plavix, lipitor, hydrochlorothiazide actonel, prozac , altace, enablex and nexium. On (b) (6) (one week after starting treatment with sitagliptin), she was reported to have developed jaundice and was hospitalized. No laboratory results were reported for this day. Sitagliptin was discontinued the following day. Three days later, she was noted to have a total serum bilirubin value of 5.6 mg/dL, the only biochemical test reported for the entire course. On (b) (6), it is reported that "the patient recovered from jaundice"' again with no laboratory data shown.

Comment: The data shown are grossly inadequate to reach any conclusion regarding etiology. If this were dili, it occurred after a very short latency and appears to have

recovered unusually promptly, especially given the fact that she was jaundiced. Even though is possible that sitagliptin was responsible, I'm inclined to cast doubt on this possibility and to assess this case as unlikely to be sitagliptn-related dili.

7912249-1

As seems to be usual, the available data in this report are grossly deficient. This was a 53 year old man with diabetes who was begun on treatment with sitagliptin on an unspecified date. The patient was taking other drugs that included atorvastatin, aspirin, glilazide, hydrochlororhiazide, pregabalin, merthyldopa, telmisartan, esomeprazole, and vitamins. On April 26, 2008, the patient was found to have an ALT value of 275 IU/L, an AST of 152 IU/L, and total/direct serum bilirubin value of 72/52 (said to be increased but units uncertain unless it is micromoles), and a GGT value of 1558 IU/L. No date is given for start of sitagliptin so the latency cannot be determined. Thee days later, the ALT is now 159 IU/L, the AST 87 IU/L, and the bilirubin has returned to normal. No information is reported regarding whether the sitagliptin was discontinued.

Comment: As with the above case, the data presented are insufficient to reach a decision regarding the etiology of the liver dysfunction for the same reasons mentioned above.

7236251-0

This was a 64 year old man with type 2 diabetes and venous insufficiency who was started on sitagliptin on March 18, 2009. He was also taking metformin and atorvastatin. He developed jaundice and arthralgias in June 2009. The sequence of events thereafter are difficult to sort out. In May 2010 almost 14 months after starting sitagliptin, he had an ALT and AST value 10 x ULN with slight hyperbilirubinemia. Over a period of 4 months, the aminotransferase levels fell to 2 x ULN and appeared to normalize by November 2010. Tests for hepatitis A, B, C and E were all negative. He was also negative for ASMA and AMA. Treatment with atorvastatin was discontinued in January, 2010 but abnormal liver chemistries persisted. He was hospitalized in (b) (6), sitagliptin was discontinued, and he underwent a liver biopsy, read as drug induced hepatitis. No further follow-up was reported.

Comment: Complicated case, very difficult to sort out events. It appears that the patient underwent treatment with sitagliptin and atorvastatin, and developed jaundice approximately 3 months later. No aminotransferase levels are reported at the time but the values were found to be increased 14 months later. They gradually declined and about 6 months later, returned to normal. Thus, the duration of the liver abnormalities was quite prolonged. A liver biopsy performed later was said to have findings consistent with drug induced liver injury without specifying the basis for this. Other etiologies for the liver disease, such as viral hepatitis A, B, C, E and autoimmune hepatitis were ruled out. Thus, drug induced liver injury cannot be ruled out. If this is correct, sitagliptin seems a likely candidate since, although atorvastatin use can be associated with raised ALT levels,

actual hepatotoxicity from this and other statins is relatively uncommon. Thus, in my view, this is a case of possible sitagliptin hepatotoxicity.

7312908-8

This 56 year old man was started on treatment with sitagliptin for type 2 diabetes on (b) (6) The patient was also receiving tiotropium bromide. He had normal baseline aminotransferase levels (ALT 28 IU/L, AST 21 IU/L). Five days after starting treatment ((b) (6)), he developed left parietal thoracic pain and was hospitalized. Liver-related chemistries reported on that date consisted of the following: ALT 6 x ULN, bilirubin slightly increased. ALP levels were not reported. Sitagliptin was discontinued and replaced with metformin. Thereafter, the abnormal values returned to normal and remained normal. No further information is supplied.

Comment: There is insufficient information to assess the cause of this apparently blunted liver dysfunction occurring five days after starting sitagliptin, at the same time that he developed acute thoracic pain. The specific cause is uncertain – could the raised ALT value come from a non-liver source such as muscle? Unfortunately, no other serum enzymes, such as AST, CPK, LDH are reported. However, I believe it unlikely that this was a case of sitagliptin hepatotoxicity.

5339297-2

This is a report of a 54 year old man with a long history of non-ischemic cardio-myopathy. Because he had A-V dissociation, he had had a cardiac defibrillator placed on (b) (6). One to two months later, he was started on treatment with sitagliptin because of diabetes. The only other drug that he was taking was lisinopril and possibly ciprofloxacin. Following the earlier procedure, he began to develop intermittent pain (presumably chest but not specified) provoked by effort and relieved by rest. He underwent cardiac catheterization but because no abnormalities were found, he was referred to a gastroenterologist who found an abnormal US evaluation of the gallbladder, prompting a laparoscopic cholecystectomy on (b) (6) The patient did have postoperative problems that required ventilation. He was discharged from hospital on (b) (6), reportedly with normal serum enzymes. He was readmitted to hospital for 2 days about 2 weeks later with a possible diagnosis of pneumonia. On (b) (6), he is reported to be not feeling well and was found to have abnormal chemistries, but no actual values were reported. He was then again admitted to hospital and on (b) (6), he was found to have an ALT value of 6554 IU/L, an AST of 12874 IU/L, an ALP of 73 IU/L, and a serum bilirubin of 2.6 mg/dL. He was identified to have acute congestive heart failure. He was admitted to the ICU and the next day (b) (6) his ALT has fallen to 3500 I/L, his AST has dropped to 3000 IU/L, but his bilirubin had increased to 6.3 mg/dL. He also showed marked coagulopathy. Unfortunately, there are no comments about any blood pressure changes during this period. However, the abnormal tests began to return to normal, and he was discharged from hospital on (b) (6)

(b) (6). The ALT returned to normal on February 14, 2007. The patient's physicians believed that the observed biochemical dysfunction was a consequence of sitagliptin hepatotoxicity.

Comment: Although injury from silagliptin cannot be completely ruled out, the dramatic increase in the aminotransferase levels followed by a marked reduction in the values the following day suggest that the abnormalities were far more likely to be of cardiovascular origin. Indeed, the extreme height of the serum enzymes followed by a marked reduction the following day is far more reminiscent of shock, although none was reported. However, it was probably not measured sufficiently frequently. Thus it appears that the liver dysfunction in this case was probably of cardiac origin and not a result of sitagliptin hepatotoxicity.

7549829-1

This 63 year old man with hypertension and dyslipidemia was placed on treatment with sitagliptin in January, 2009. At the same, time, he was also given atorvastatin. Other drugs he was receiving included olmesartan and metformin. At the time of starting sitagliptin treatment, his liver chemistries were normal (ALT 23 IU/L, AST 20 IU/L). On April 4, he was found to have abnormal aminotransferase levels for the first time (ALT 132 IU/L, AST 68 IU/L). Atorvastatin was discontinued although the precise date is not given. Despite this, the values continued to rise and on May 11, the ALT was 341 IU/L, the AST 203 IU/L, the ALP 716 IU/ L, and the serum total and direct bilirubin, 57/44 (presumably micromoles). Sitagliptin was discontinued on May 18. Workup revealed that serologic tests for hepatitis A, B and C, as well as ANA and ASMA were all negative. The ALT value peaked at 400 IU/L on May 25, while the ALP peaked at 909 IU/L on May 18. Presumably because of the marked increase in the ALP, an MRI was performed on the biliary system which is recorded as normal. Over the course of the following 2 months, the liver chemistries slowly declined and on July 23, the ALT was now 116 IU/L, the AST 97 IU/L, the ALP 205 IU/L, and the total serum bilirubin, 9.0 micromoles. Continued follow up thereafter to May 2011 showed that aminotransferases remained mildly abnormal throughout, with minor fluctuations.

Comment: This patient developed abnormal liver chemistries approximately three months after starting treatment with both sitagliptin and atorvastatin. The injury pattern was mixed, with elevations of both the aminotransferases and ALP. There was mild hyperbilirubinia. Workup was negative for all viral hepatitis markers with the exception of hepatitis E, and was negative also for autoimmune serologic markers. There is no evidence that the patient had cardiac disease that might have accounted for the abnormalities. Concern that the liver dysfunction might have been of cholestatic origin because of the somewhat unusually increased ALP level, prompted an effort to rule out biliary obstruction which was done by conducting an MRI of the biliary system that was reported to be normal. Thus, potential dili rises to the top as a cause for the abnormalities. The two possibly implicated drugs are atorvastatin and sitagliptin. Atorvastatin seems less likely since the biochemical values continued to rise even after

discontinuing the drug. On the other hand, the values began to fall after sitagliptin was discontinued. Accordingly, it is my view that the patient probably developed sitagliptin hepatotoxicity.

6037181-2

Information pertaining to this patient is presented in a mere 9 lines. This was a 69 year old female with apparently no pertinent past medical history of note who was started on treatment with sitagliptin on an unknown date but possibly early in the year 2008. Liver-related tests were said to be normal 6 months before beginning treatment with sitagliptin. The only information provided is that in June 2008, she was found to have an AST of 600 and an ALT of 198. No further aminotransferase values are given and the only other laboratory value mentioned is a serum bilirubin value of 10 (no units given but presumably mg/dL because there is mention of jaundice later in the narrative). Surprisingly, according to the narrative, sitagliptin was only discontinued in September, 2008, and by November 14, liver-related tests were now normal. It is noteworthy that the reporting physician regarded the liver injury as life threatening, but the patient's hospitalization was not motivated by the evidence of liver disease but rather by the underlying disease. Finally, the physician refused to provide the patient's name, date of birth or the name of the hospital. No other information given.

Comment: The insufficient data provided (sequential laboratory values, work-up for alternative etiologies, etc.) makes it impossible to reach any etiologic conclusion for this case. Sitagliptin hepatotoxicity can be neither ruled in nor ruled out. Because these events occurred in 2008, it might not be possible to derive and additional information.

SUMMARY /CONCLUSIONS

Siltagliptin Cases: The cases of possible sitagliptin liver injury submitted for review were mostly lacking in sufficient information to permit definitive or even a possible diagnosis. However, a diagnosis of sitagliptin-related liver injury was considered possible in two instances but without conviction, largely because important alternative diagnoses were not ruled out. One additional case was considered to be a probable case of sitagliptin dili, because almost all alternative diagnoses, with the exception of hepatitis C, were excluded. This latter case was relatively mild. Accordingly, I agree with the findings of the DPV review[2] that spontaneous cases collected to date do not suggest a novel signal for hepatotoxicity in recipients of sitagliptin and current labeling for sitagliptin appears sufficient.

Alogliptin Cases: The primary focus of the case reviews described herein is consideration of whether or not liver abnormalities identified among persons treated with alogliptin result from injury caused by the drug. Case narratives represent updates to previous information (included in the initial review[1]) and new cases received in the

interim. In view of the population of patients who receive this drug, it would not be surprising to observe evidence of liver dysfunction since these are individuals who are highly susceptible to such conditions as nonalcoholic steatohepatitis, severe cardiovascular disease, gall stones, and in view of their age, malignancies such as pancreatic cancer, all of which may induce liver dysfunction. And indeed, in an earlier review of over 50 cases in which recipients of alogliptin were found to have liver-related biochemical test abnormalities, the majority were considered to have causes other than alogliptin hepatotoxicity. However, this was not the case for the 16 cases described here; 6 cases were scored as probable instances of alogliptin hepatotoxicity (not always agreed upon by the liver disease experts selected by the sponsor to review potential cases of dili), 1 as possible/probable, 3 as possible, 4 as low possible, 1 as acute hepatitis E, and 1 with insufficient data to reach a conclusion. In 3 of the 6 cases scored as probable, the serum bilirubin value exceeded 2.1 mg/dl. One of these 3 patients died as a consequence of impending fulminant hepatitis although the primary basis for death was probably pneumonia that developed in the context of corticosteroid therapy given for possible "idiosyncratic" autoimmune hepatitis

As regards the features of liver injury among those considered to be possible or probable cases, most occurred after a relatively short latency (as early as one week), most did not present with symptoms but were identified through the planned study screening, some presented as mixed hepatocellular/cholestatic liver injury, and most were of short duration (although some were not studied appropriately, namely responding to an identified abnormality by repeating the testing shortly after identifying the abnormality). In summary, even if attributable to receipt of alogliptin, once the drug was discontinued (I am uncertain what specific criteria were used for drug discontinuation), the apparent liver injury appeared to be trivial.

This case series includes 4 cases with a bilirubin value greater than 2.1 mg/dl. One of them, first considered to be a probable case of alogliptin hepatotoxicity, was subsequently identified to have what appears to be acute hepatitis E virus infection and thus the diagnosis was obviously changed to "not alogliptin hepatotoxicity." Among the remaining 3 cases, all considered probable cases of alogliptin hepatotoxicity, 1 was a female considered possibly to have developed autoimmune hepatitis that prompted treatment with corticosteroids that probably was responsible for her terminal pneumonia, accounting for her demise. This patient was negative for all serologic markers of autoimmune hepatitis The second was a man who developed liver dysfunction after a relatively short latency, the liver disease lasting for a relatively short period of time. The third patient appeared to have developed either acute hepatitis C or superimposed acute hepatotoxicity on already existing chronic hepatitis C. No past history was available when the case was first evaluated accounting for the uncertainty. Subsequently, information became available indicating that the patient indeed had had chronic hepatitis C for some time, and since it is extraordinarily rare for persons with chronic hepatitis C to develop relatively short-lived flares associated with jaundice, a diagnosis of superimposed drug-induced liver injury could now be made with confidence.

Since these cases occurred in the postmarketing setting, it is unknown if they confer the same degree of regulatory concern as would 3 such cases identified during registrational trials. However, given the imbalance in the frequency of ALT abnormalities noted in the pre-marketing trials between those who received alogliptin and those in the control group, it seems prudent to consider whether these data taken together suggest that further study is needed regarding possible hepatotoxicity of alogliptin before general marketing of the drug is permitted in the US.

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/s/

MARGARITA V TOSSA
05/08/2012

ALLEN D BRINKER
05/08/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1 – Memo to File

Date:	25 April 2012
To:	Hylton Joffe, M.D., Team Leader Division of Metabolic and Endocrine Products
Reviewer:	Leonard Seeff, MD, Hepatologist Office of Surveillance and Epidemiology
Through:	Allen Brinker, MD, MS, Medical Team Leader Division of Pharmacovigilance 1
Drug Name:	alogliptin (Nesina)
NDA Number:	22-271
Applicant/sponsor:	Takeda
OSE RCM #:	2012-468
Issue:	Update: Review of cases of liver injury in association with alogliptin including cases collected through spontaneous reporting programs and cases from registrational trials

Memo to File:

This brief text is intended to document receipt of additional information on specific cases of potential alogliptin-associated liver injury received at or near the end of the review cycle. This information includes updates included on a previous review[1] and new cases.

This information has been reviewed by OSE but due to the lateness of receipt a full assessment will be made when we receive the resubmission.

[1] Memorandum dated 21 February 2012; Leonard Seeff to Hylton Jaffe. Review of cases of livery injury in association with alogliptin.

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/s/

MARGARITA V TOSSA
04/25/2012

ALLEN D BRINKER
04/25/2012

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

REVIEW DEFERRAL MEMO

Date:	**April 19, 2012**
To:	Mary Parks, MD, Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review Deferred: Medication Guide (MG)
Drug Name:	Alogliptin tablets
Application Type/Number:	NDA 22271
Applicant/Sponsor:	Takeda Global Research & Development Center, Inc.
OSE RCM #:	2011-2666

1 INTRODUCTION

On July 25, 2011, Takeda Global Research & Development Center, Inc. (Takeda) submitted a Class 2 re-submission Complete Response, for Alogliptin tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, to all issues identified in the Agency's June 26, 2009 Complete Response Letter. On April 5, 2012, Takeda submitted for the Agency's review a response to FDA Information Request. Reference is also made to an FDA Information Request on April 2, 2012.

On August 4, 2011, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG), for Alogliptin tablets. This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG), for Alogliptin tablets.

2 CONCLUSIONS

Due to outstanding clinical deficiencies DMEP plans to issue a Complete Response (CR) letter and will not review patient labeling this cycle. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

TWANDA D SCALES
04/19/2012

MELISSA I HULETT
04/20/2012

LASHAWN M GRIFFITHS
04/20/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 022271 (Resubmission)

Name of Drug: Alogliptin tablets

Applicant: Takeda Pharmaceuticals

Labeling Reviewed

The NDA resubmission was submitted and received on July 25, 2011, and contained labeling in SPL format. Preliminary comments and edits from certain disciplines were sent to Takeda on January 26, 2012. The company sent back revised labeling (in Word format) by email on February 9, 2012. This revised label was used for this review.

Background and Summary Description

NDA 022271 is for alogliptin tablets, a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Alogliptin is a fourth-in-class new molecular entity. The suggested dose is 25 mg taken once daily with or without food. Dosage form and strengths are 25 mg, 12.5 mg and 6.25 mg tablets.

This NDA was submitted on December 27, 2007, and was issued a Complete Response letter on June 26, 2009. Takeda resubmitted the NDA on July 25, 2011, and on November 16, 2011, the review clock was extended by 3 months, resulting in a PDUFA goal date of April 25, 2012.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. In the Highlights, under Dosage and Administration, the applicant has used an [redacted] (b) (4) This is not acceptable, [redacted] (b) (4) .
2. In the Highlights, under Use in Specific Populations, [redacted] (b) (4) category should be removed.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant, along with other labeling comments identified by the review team, during the week of February 20 – 24, 2012, as previously agreed to. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies, and the resubmitted labeling will be used for further labeling discussions.

Mehreen Hai, Ph.D.	February 17, 2012
Regulatory Project Manager	Date
Lina Aljuburi, Pharm.D., M.S.	February 21, 2012
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**
  - ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

    http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
  - ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**
  - ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

☒ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Note: The word "clinical" has been omitted. Also, this statement is listed under the heading "ADVERSE REACTIONS" instead of under the sub-heading "Clinical Studies Experience".

☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

☐ This section is required and cannot be omitted.

☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"

Note: The words "(Patient Information)" have been omitted.

- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

MEHREEN HAI
03/06/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1

Date:	21 February 2012
To:	Hylton Joffe, M.D., Team Leader Division of Metabolic and Endocrine Products
Reviewer:	Leonard Seeff, MD, Hepatologist Office of Surveillance and Epidemiology
Through:	Allen Brinker, MD, MS, Medical Team Leader Division of Pharmacovigilance 1
Drug Name:	alogliptin (Nesina)
NDA Number:	22-271 (alogliptin) 22-426 (alogliptin & pioglitazone)
Applicant/sponsor:	Takeda
OSE RCM #:	2012-37
Issue:	Review of a cases of liver injury in association with alogliptin

INTRODUCTION

In an updated request dated 3 Jan 2012, DMEP requested OSE hepatology review of selected cases of liver injury in association with alogliptin. This was requested, in part, since the alogliptin sponsor has had two external hepatologists review selected liver cases of interest that have been reported with alogliptin in the clinical trial database and in the postmarketing setting ((b) (4) conducted an unblinded review of the cases and (b) (4) conducted a blinded review of the cases). DMEP reviewed the case material and narrowed the specific cases for review from more than 50 (original consult request) down to 11 (new consult). In the updated consult request, DMEP requested review of an additional 2 cases that were not adjudicated by the sponsor.

BACKGROUND

Alogliptin is an orally active DPP4 inhibitor indicated for treatment of type 2 diabetes mellitus as an adjunct to diet and exercise. DPP4 inactivates glucagon-like peptide 1 (GLP-1) by N-terminal cleavage. GLP-1 is released from the L-cells in the gut after meals, which potentiates glucose-dependent insulin secretion from pancreatic β cells, leading to increased hepatic glucose metabolism. GLP-1 also suppresses glucagon secretion, which delays gastric emptying and independently contributes to reduced blood glucose concentrations. DPP4 inhibition has been shown to reduce blood sugar and glycated hemoglobin (HbA1c) in vivo in healthy and diabetic animal models and in diabetic patients.

Alogliptin is approved for marketing in Japan. Three DPP4 inhibitors, sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta) are currently marketed in the U.S. and globally for treatment of type 2 diabetes.

Although animal studies for alogliptin hepatotoxicity have been negative to date, the most recent assessment of human data includes an imbalance in the number and percentage of trial subjects with elevations in serum ALT values. The following table was cited and included in the NDA Complete Response (DRAFT) review currently underway by Dr. Valerie S.W. Pratt of DMEP:

Table 1. Number and percentage of subjects with markedly abnormal ALT values (All completed, controlled phase 2, studies)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline			During Treatment		
Parameter (Criterion)	All Comparators (a) N=4215	Alogliptin 25 mg N=4829	All Alogliptin (b) N=7187	All Comparators (a) N=4074	Alogliptin 25 mg N=4680	All Alogliptin (b) N=7011
ALT (>20×ULN)	0	0	0	0	1 (<0.1%) [0.0]	2 (<0.1%) [0.1]
ALT (>10×ULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	0	6 (0.1%) [0.2]	8 (0.1%) [0.2]
ALT (>8×ULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	1 (<0.1%) [0.0]	9 (0.2%) [0.4]	11 (0.2%) [0.3]
ALT (>5×ULN)	2 (<0.1%)	4 (0.1%)	6 (0.1%)	6 (0.1%) [0.3]	17 (0.4%) [0.7]	21 (0.3%) [0.6]
ALT (>3×ULN)	10 (0.2%)	23 (0.5%)	30 (0.4%)	39 (1.0%) [1.8]	52 (1.1%) [2.1]	71 (1.0%) [2.1]

Source: November 7, 2011 liver-safety submission Table 8

A summary table containing the cases and adjudication assessments is included at the end of this document.

Current Evaluation: Assessment of potential drug-induced liver injury of the present cases uses the grading system for likelihood of attribution and liver disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.*

Likelihood of Causality

Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥95	Causality is "beyond a reasonable doubt"
2	Highly Likely	75-94	Causality supported by "clear and convincing evidence"
3	Probable	50-74	Causality supported by the "preponderance of the evidence"
4	Possible	25-49	Less than the preponderance of evidence but still possible
5	Unlikely	<25	Causality unlikely or excluded

Disease Severity Scales

Score	Grade	Definitions
1	Mild	Elevated ALT and/or Alk P but serum bilirubin <2.5 mg/dL and INR <1.5
2	Moderate	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl or INR ≥1.5
3	Moderate-Severe	Elevated ALT and/or Alk P and bilirubin or INR and new or prolonged hospitalization due to dili
4	Severe	Elevated ALT and/or Alk P and serum bilirubin ≥2.5 mg/dl and there is one of the following: -Hepatic failure (INR ≥1.5, ascites or encephalopathy -Other organ failure (renal/pulmonary) d/t dili
5	Fatal	Death or liver transplant from dili

*Fontana RJ, Seeff LB, Andrade RJ, Bjornsonn E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:73-742

ERD2010A00037

This 41 year old man from India with a history of renal calculi was entered into a multicenter, double-blind, active-controlled study to evaluate the durability of the efficacy and safety of alogliptin compared to glipizide when used in combination with metformin in persons with type 2 diabetes. Other medications the patient was receiving included rabeprazole, domperidone, metformin, aspirin, atorvastatin, ursodiol, cefadroxil, clavulanate, and pantoprazole.

The baseline values for ALT ranged from 13 to 18 IU/L, the AST from 14 to 15 IU/L, the alkaline phosphatase (ALP) 60 to 66 IU/L, and the bilirubin 0.71 to 1.23 mg/dL. The patient was started on the blinded study drug on October 24, 2009 and several values of the liver-related tests obtained over the following 3 to 4 months remained quite normal. However, approximately 4 months after starting the test drug (January 27, 2010), the ALT was found to be 130 IU/L, the AST 61 IU/L, the ALP 83 IU/L, and the bilirubin 1.17 mg/dL. The patient apparently remained asymptomatic. Repeat testing 2 weeks later revealed an increase in the ALT to 208 IU/L although the other liver-related tests had returned to normal. At this point, the test drug was discontinued. Repeat testing 1 week later identified that the ALT had now returned to normal. Additional work-up, including abdominal ultrasonograpy and testing for HBsAg and anti-HCV yielded negative results. Regarding the other drugs received, the data provided are a little unclear but it appears that rabeprozole and domperidone treatment continued whereas the study drug was withdrawn followed by the return to normal of the ALT value.

Comment: This patient, with baseline liver chemistry tests that are completely normal, develops a moderate increase in the ALT value and a mild increase in the AST value approximately 4 months after beginning treatment with the blinded study drug. At this time, his serum bilirubin value is only minimally increased and he remains completely asymptomatic. Repeat testing two weeks later demonstrates a further increase in the ALT value while the other liver tests return completely to normal. The test drug is then discontinued and a repeat test of the ALT 3 to 4 days later is now normal. Only minimal additional work-up is reported that includes negative results for acute hepatitis B and C with testing for hepatitis A and E not reported, but both would seem unlikely to be the cause for the abnormalities. Also not reported and also unlikely to be the cause of the liver dysfunction because of its transient presentation is evidence of autoimmune hepatitis, as well as alcohol induced liver injury (AST elevation almost always exceeds ALT elevation) and nonalcoholic steatohepatitis (abnormality too transient). Injury from the other drugs received is ruled out by the fact that the ALT abnormalities waned even though these drugs were continued whereas normalization of the ALT followed discontinuation of the study drug. Thus, given the evidence of two elevated ALT values, both exceeding the AST values, in the absence of an alternative explanation for these noted abnormalities, drug-induced liver injury from the study drug cannot be excluded although clearly the injury was extremely mild and transient. I rate this as a possible, mild case of alogliptin hepatotoxicity.

TCI2011A03640

This 64 year old Japanese male with diabetes mellitus and diabetic nephropathy was switched from treatment of his diabetes with voglibose to alogliptin on January 18, 2011 because of increased HbA1c and serum glucose levels. His baseline ALT was normal but baseline values for AST, AP and serum bilirubin were not reported. Soon after starting alogliptin, he developed nausea and vomiting as well as "stomach heaviness." Four days later (January 22), having received 4 doses of alogliptin, he stopped using the drug although his nausea persisted. He noted darkening of his urine. Liver-related tests performed for the first time on February 8 (approximately 2 weeks after stopping treatment), revealed an ALT of 869 IU/L, an AST of 625 IU/L, an ALP of 1169 IU/L, and a serum bilirubin value of 0.5 mg/dL. He also complained of itching. Over the next several months, even though he remained nauseated, his liver tests, with the exception of the ALP, slowly returned to normal, the AST value by February 19 and the ALT value by April 2 (taking into account the timing of blood testing). However, the abnormal ALP values resolved more slowly, falling to it lowest level (268 IU/L) on August 20, 2011. Only 2 values of serum bilirubin are reported, neither of which were abnormal. It is then stated that he was hypoalbuminemic and developed deteriorating renal function and dialysis was being contemplated but it is not stated that this was undertaken. What is stated categorically is that he was not evaluated further for a potential etiology, i.e., he did not undergo testing for the hepatitis viruses or for autoimmune markers, and he did not have a liver biopsy performed. Moreover, despite the pattern of liver tests that followed a mixed but predominantly cholestatic pattern, presumably representing intrahepatic choilestasis based on the absence of jaundice or of biliary tree pain, no imaging procedures were performed.

Comment: This patient developed nausea, vomiting, and stomach "heaviness" shortly after starting alogliptin which presumably led him to discontinue treatment with alogliptin on his own accord after having received 4 doses of the drug. It is unclear whether these symptoms were a consequence of developing liver disease, as identified 2 weeks later based on the first set of liver chemistries evaluated, or on developing renal failure, the beginning date of which is not reported. Thus it is not clear whether the latency between starting alogliptin and development of liver disease occurred one week (when symptoms occurred) or three weeks (when biochemical dysfunction was identified) after starting the drug. The biochemical abnormalities that developed showed mixed hepatocellular/cholestatic liver injury, the cholestatic pattern predominating. In keeping with this is that he also had pruritus that persisted for some time after identification of the abnormal liver tests. He is not reported to have developed jaundice and the 2 serum bilirubin values provided were normal. No work-up was done to exclude the viral hepatitides or autoimmune liver disease, but it is decidedly unlikely that these would have yielded positive results given the pattern of liver injury. Also, although it would have been useful to have had imaging procedures performed to completely rule out extrahepatic obstruction, there is in fact no support for this diagnosis. He had been taking other drugs (allopurinol, amlodipine) but had been receiving them for well over a year, thus excluding them as possible causes for the liver injury. Thus, in the absence of a plausible alternative etiology, a diagnosis of alogliptin hepatotoxicity is probable even

though it is uncertain whether the latency to injury occurred after one or after three weeks of starting treatment with the drug. However, it was not a life-threatening form of liver disease that can be graded as mild.

TCI2010A05612

This 64 year old man from Japan with type 2 diabetes is started on treatment with alogliptin on September 21, 2010 because of ever increasing HbA1c levels. Baseline levels for ALT and AST values are not reported but his baseline ALP level is 323 IU/L and his serum bilirubin value is 0.59 mg/dL. Two months after starting treatment with alogliptin (November 10, 2010), even though asymptomatic, he is found to have developed quite abnormal liver-related tests (ALT 230 IU/L, AST 108 IU/L, ALP 1,260 IU/L, serum bilirubin 0.87 mg/dL). The alogliptin was discontinued a day later (November 11, 2010) and he is started on treatment with glycyrrhizin/glycine/cysteine and later, ursodeoxycholic acid. An abdominal ultrasound reveals steatosis, and testing for hepatitis A, B and C are all negative. Tests for autoimmune markers were not performed. Over the course of the following 6 weeks, the ALT and AST values returned to normal, whereas the ALP value remained high although it began to decline but was still abnormal (ALP 588 IU/L) on December 29 2010, the last set of values shown. At no time was the serum bilirubin value increased. Other drugs the patient was receiving were candasartan and atorvastatin, but the liver chemistries improved despite continuation of these drugs but following withdrawal of alogliptin. No further information on outcome or additional evaluation is reported.

Comment: Two months after starting treatment with alogliptin, the patient develops abnormal liver-related biochemical tests showing a mixed hepatocellulat/cholestatic pattern, with the cholestasis predominating; the bilirubin value remains normal throughout and he is asymptomatic. Even though the biochemical pattern does not fit that of viral hepatitis, he is screened for and found to be negative for viral hepatitis markers. Because of liver test abnormalities showing a mixed although predominantly cholestatic pattern of injury, an abdominal ultrasound is performed presumably seeking evidence of a gallstone or dilatation of the biliary ducts, but none is found. Thus, this patient develops abnormal liver chemistries consistent with that of intrahepatic cholestasis 2 months after starting alogliptin, the abnormalities improving upon withdrawal of the drug. No other etiology for the liver abnormalities is apparent, and liver injury from other drugs he is receiving is ruled out by the improvement of the liver chemistries despite continued use of these drugs. It is thus my opinion that this patient probably developed alogliptin-related drug induced liver injury. The severity of the liver injury can be graded as moderate.

TCI2011A01464

This 75 year old man from Japan with type 2 diabetes was admitted to hospital because of a giant hematoma on his back. He had been treated with voglibose and pioglitazone but

the pioglitazone was withdrawn on hospitalization and replaced with alogliptin on (b) (6). A day earlier, ALT, AST and serum bilirubin baseline values were normal (ALT 21 IU/L, AST 26 IU/L , serum bilirubin 0.77 mg/dL) but no baseline ALP is shown. One week later, he is found to have very mild elevations in his aminotransferase levels (ALT 67 IU/L, AST 56 IU/L) with unchanged ALP and serum bilirubin values. Both ALT and AST values peak 3 days later (89 IU/L for both) but continue to remain mildly abnormal through (b) (6) the last set of values reported. The serum bilirubin values remain normal throughout the reported follow-up period, which unfortunately lasts for only one week. Thus, with the exception of a single baseline normal value for the ALT and AST, all values for the aminotransferases thereafter remain mildly abnormal with minimal fluctuation. Despite the short observation period, the mostly unwavering mildly abnormal ALT values raises the suspicion of a pre-existing form of chronic liver disease, yet no effort is made to perform testing for chronic hepatitis B or C, for markers of autoimmune hepatitis, or for evidence to support the possibility of nonalcoholic steatohepatitis (NASH). An imaging study reported that the liver "had a blunt margin" and a hepatic cyst was reported. The narrative summary raises the issue of possible chronic liver disease but then suggests that the identified abnormalities began a week after starting the drug and that the abnormal values appeared to be improving (unimpressive to me) thus suggesting a temporal relationship between starting the drug and development of liver injury with possible improvement on stopping the drug (i.e., a dechallenge). I am not convinced that this was the case, or that an initial single "normal" aminotransferase value followed a week later by mildly abnormal values persisting and fluctuating through the last set of tests precludes the possibility of pre-existing chronic liver disease. It is a pity that hepatitis serology was not performed without which it is not possible for me to reach a firm diagnostic conclusion.

Comment: This patient is reported to have had normal ALT and AST values at the time of starting treatment with alogliptin with the identification of mild increases in both values one week later that persisted in being mildly abnormal with slight fluctuations throughout the relatively short period of biochemical follow-up. Alkaline phosphatase and bilrubin values remain normal. The issue for me is whether the abnormalities were precipitated by the drug or whether the patient already had mild viral-related chronic liver disease or NASH despite the report of a single abnormal baseline level. In this instance, if it is the drug, the latency is quite short and the aminotransferase values are very mild and, over the course of the short follow-up, persistently abnormal with the type of fluctuations seen in patients with chronic hepatitis C. unfortunately, hepatitis viral markers were not obtained. With the absence of these markers and of further follow-up of the serum aminotransferases, I am unable to reach a reasonable diagnostic conclusion. Specifically, I am unable to make a diagnosis of alogliptin hepatotoxicity but I am also unable to exclude the possibility of this diagnosis. Moreover, the injury appears to be mild. On the basis of the insufficient available data, I believe that there is a very low possibility that the patient developed alopgliptin-induced liver injury although I am unwilling to exclude the possibility that the patient actually had pre-existing chronic liver disease. This latter would require information on hepatitis virus serology and on additional biochemical follow-up.

TCI2011A01670

This 67 year old Japanese female with diabetes mellitus was started on treatment with alogliptin on February 1, 2011. No baseline pre-treatment values are reported, but liver-related tests obtained 2 weeks later (January 15, 2011), while on treatment, revealed normal values for the ALT (17 IU/L) with a slightly elevated ALP value (233 IU/L) on the same day. Approximately 10 days after that (February 26, 2011), routine testing revealed an ALT value of 331 IU/L, an AST value of 76 IU/L, an ALP of 353 IU/L, and a direct serum bilirubin value of 0.3 mg/dL. She also had a slightly elevated serum amylase value. She is reported to have chronic kidney disease and to be a regular user of alcohol without specifying how much drinking of alcohol she actually did. The alogliptin was discontinued on the same day (February 25, 2011). Over the course of 3 weeks, her ALT value returned to normal as did the AST value, but although ALP values declined, they were still abnormal 3 weeks later. Her serum bilirubin value remained normal throughout. She was treated with glycyrrhizin/glycine/cysteine and liver extract/ flavine adenine dinucleotide and then with ursodeoxycholic acid. She is not reported to have developed symptoms, and she is not evaluated for hepatitis virus and autoimmune markers or to undergo imaging procedures. She is reported to also be receiving candesartan and magnesium oxide but start and stop dates for these products are not reported.

Comment: This patient was found about 3-4 weeks after starting treatment with alogliptin to have moderately increased values for ALT, AST, and ALP. She remains asymptomatic. Her serum bilirubin value is not increased. Treatment with alogliptin is discontinued and over a period of 2 to 3 weeks, her aminotransferase values return to normal but not her ALP values. Work-up for alternative diagnoses is not performed, but it is assumed that because the liver chemistries improved after stopping alogliptin, it was likely that the liver injury was precipitated by alogliptin. It is unfortunate that markers for viral and autoimmune hepatitis were not done since it is conceivable that viral or autoimmune hepatitis might have played a role. On the other hand, the likelihood of these conditions being responsible is quite low because of the rapid improvement in the aminotransferase values. Thus, liver injury from alogliptin remains a possible diagnosis, the liver dysfunction appearing to be mild and lasting for a short duration.

TCI2011A02538

This 54 year old Japanese man with diabetes mellitus and hypertension had been seen on a number of occasions at the same hospital beginning in 2008. He is tested and found to be negative for hepatitis B and C. He receives a number of drugs including pioglitazone, acarbose, cilnidipine, olmesartan, nifedipine, mecobalamin, and epalrestat. There is background information suggesting the occurrence of alcoholic liver disease but without other supporting information. There is also mention of fluctuating aminotransferase values, ranging between 10 and 30 IU/L but rising to between 50 and 70 IU/L on occasion for reasons not stated. On October 18, 2010, he is reported to have an ALT of 32 IU/l, an AST of 36 IU/L, and a total bilirubin of 0.5 mg/dL. On October 19, 2010, clinidipine and nifedipine are switched to azalnidipine and generic nifedipine. On

October 26, he is started on alogliptin. About 6 weeks later (December 6, 2010), he has a single spike in his liver chemistries (ALT 198 IU/L, AST 194 IU/L, total serum bilirubin 1.2 mg/dL). ALP is not reported at this time. Repeat testing a little over 2 weeks later reveals that ALT, AST, and serum bilirubin values have returned to normal although ALP levels are slightly increased. On December 20, 2010, alogliptin, azelnidipine, and generic nifedipine were all discontinued and replaced with glimepiride, cilnidipine, and generic nifedipine and he also begins treatment with glycyrrhizin/glycine/cysteine. As noted above, markers for hepatitis B and C were found to be negative. No markers for autoimmune liver disease were performed nor were imaging procedures. Thus, the liver "disease" is characterized by a single spike in the aminotransferases and serum bilirubin levels, followed by a return to normal by the time of the next set of tests performed 18 days later. It is a great pity that retesting of the serum enzymes was not done until 2 weeks after identifying a fairly brisk abnormality that would probably have confirmed the identified abnormalities.

Comment: It is unclear what etiology of liver disease to append to this case. About 6 weeks after starting several drugs, one of which is alogliptin, he develops a single spike in both aminotransferase values and a minimal increase in the serum bilirubin level, all returning to normal when testing is repeated for the first time after the observed abnormality 18 days later. Is it conceivable that there was an error in the tests performed or that the sample tested had actually belonged to someone else? Or was this a legitimate single abnormality that might have again been abnormal if repeat testing had been performed earlier. Regarding etiology if the finding was valid, hepatitis viral infections B and C seem ruled out as are other etiologies because of the transient nature of the abnormality. It is not really appropriate to attempt to assign an etiology to a single abnormal serum enzyme because of the uncertainty of whether this is a legitimate event. Nevertheless, if the finding of the single abnormal spike of both the ALT and AST was indeed valid, without being able to impugn another etiology, the likelihood that the single abnormality represented a reaction to alogliptin cannot be entirely ruled out. Thus, there is a very low possibility that alogliptin was responsible for the identified abnormality that might have been confirmed had re-testing not been delayed for 18 days. If correct, the liver disease that developed was trivial.

TCI2011A04039

This 77 year old man from Japan with diabetes mellitus was admitted to hospital on (b) (6) for treatment of "arteriosclerosis obliterans with percutaneous transluminal angioplasty" which was performed 2 days later. The following day (b) (6) he is started on treatment with alogliptin. Baseline ALT and AST values on (b) (6) were normal (both 10 IU/L). Three days later he develops anorexia and a day after that, begins vomiting. Laboratory testing on (b) (6) revealed an ALT value of 106 IU/L, an AST value of 125 IU/L, an ALP value of 336 IU/L, and a serum bilirubin value of 0.3 mg/dL. By the next day, the values for the aminotransferases peaked (ALT 627 IU/L, AST 669 IU/L) whereas the ALP value peaked 5 days after the initial abnormality (349 IU/L). Bilirubin values remain normal throughout. Alogliptin was discontinued on (b) (6). The last

set of values reported, on (b) (6) reveals marked decreases in both the ALT (60 IU/L) and AST (66 IU/L) levels but not yet to normal values. As noted, the ALP was still abnormal and the serum bilirubin value never became abnormal. At this time, his anorexia and vomiting ceased. There is no mention of testing for hepatitis or autoimmune serology. Other drugs he had been receiving continued. In the belief that the abnormalities were a consequence of the receipt of alogliptin, no effort appears to have been invested in seeking an alternative diagnosis for the liver disease. Still, there is a compelling temporal relationship between starting the drug and the onset of liver test abnormalities, although of very short latency, and stopping the drug is followed by improvement of liver chemistries. Based on the available data, possible explanations for the observed liver injury include a reaction to the alogliptin, although the latency is very short, or induction of cardiac dysfunction following the angioplasty, although there is no evidence to support this likelihood; while neither viral nor autoimmune hepatitides were excluded, the likelihood that either are responsible for the liver injury is low given the rapid improvement in the aminotransferase levels after drug withdrawal.

*Comment: This patient, with cardiovascular disease requiring angioplasty, develops anorexia and vomiting 3-4 days after starting treatment with alogliptin; alogliptin treatment was apparently begun one day after the angioplasty. With the onset of vomiting, liver-related tests reveal mild increases in both aminotransferase levels that increase the next day to considerably higher values. Treatment with alogliptin is discontinued with the observed peak values. Two days later, the aminotransferases have fallen to the level of the abnormal values first identified and 2 days after that have fallen to near but not completely normal values. Alkaline phosphatase values are mildly increased but the bilirubin is not increased. Symptoms parallel the raised aminotransferase values. Unfortunately, based on what is reported, no effort is undertaken to exclude such etiologies as acute viral or autoimmune hepatitis but the rapidity of recovery would suggest that these etiologies are unlikely to be responsible for the liver injury, which is modest and short-lived. An alternative diagnosis to alogliptin hepatotoxicity, given that he was admitted to undergo angioplasty, is liver dysfunction associated with cardiac failure. However, there is absolutely no mention of cardiac dysfunction. Thus, was it not for the fact that the liver injury was identified after a very short latency of starting treatment, I would have judged this a case of probable alogliptin hepatotoxicity. But given the potential for a cardiac etiology, I am inclined to classify this case as a possible-probable mild case of alogliptin hepatotoxicity.***

TCI2011A04874

This is a 55 year old Japanese male with diabetes who is reported to have begun treatment with cefotiam hydrochloride, reason not given, on July 22, 2011. On July31, 2011, the cefotiam is discontinued and on August 1, 2011, is replaced with cefazolin (reason not given), that is administered until August 5, 2011. Alogliptin treatment is begun on July 25, 2011. Baseline values of the liver-related tests are not shown. On August 15, 2011 (15 days after stopping cefotiam, 10 days after stopping cefazolin and 21 days after starting alogliptin), the patient is found to have an ALT value of 233 IU/L,

the values remaining in the same increased level (>200 IU/L) on the 3 occasions it is measured over the following 10 days. During the same period, the AST is only slightly increased (65-43 IU/L), the ALP is increased to above 300 IU/L, and the serum bilirubin is measured as slightly exceeding 1.0 mg/dl. No information is provided regarding symptoms, and there is no evidence that the patient was evaluated for other etiologies (viral or autoimmune hepatitis). Treatment with alogliptin is discontinued on August 25 and the aminotransferase values slowly decline; the ALT value is back to near normal by September 8 while the AST value is back to normal by September 1. Alkaline phosphatase values also decline and reach normality by September 22. At no time does the patient have evidence of jaundice.

Comment: This patient, treated with 2 different antibiotics for unstated reasons, and then begun on treatment with alogliptin, is found to have moderate increases in ALT and milder increases in AST 15 days after stopping the one antibiotic, cefotiam, 10 days after stopping the second antibiotic, cefazolin, and 21 days after starting treatment with alogliptin. Unfortunately, baseline levels that would identify normal values at the outset are not shown or were not obtained. The ALT values remain abnormal in the same range until the alogliptin is discontinued at which time they begin a decline to near normal values close to one month after stopping the alogliptin. As is the case for most of the cases reviewed, based presumably on the likelihood that the alogliptin treatment was responsible for the liver injury, alternative diagnoses were not sought. While a diagnosis of acute viral or autoimmune hepatitis cannot be completely excluded since testing for these disorders was either not undertaken or not reported, these diagnoses seem less likely because of the rapid recovery of the serum enzyme levels. Both antibiotics received have been associated with the development of abnormal liver chemistries, but in this instance, the injury was identified after stopping the drugs, not an unheard-of occurrence. Still, the latency is a little prolonged for both. Taking this all into account, a diagnosis of alogliptin hepatotoxicity cannot be dismissed and, therefore, alogliptin hepatotoxicity represents a possible diagnosis. The manifest liver disease was, however, mild and short-lived.

TCI2011A04573

This is a 77 year old Japanese female patient with a history of spinal stenosis that had required lumbar surgery, Hashimoto's thyroiditis, and diabetes mellitus. Her diabetes had been treated with voglibose and glimepiride but she had a high HbA1c and peripheral neuropathy. On June 1, 2011, she was started on treatment with levothyroxine for her hypothyroidism, the dose being increased on June 17. On (b) (6) she was started on treatment with alogliptin. Baseline values for the ALT, AST, and serum bilirubin were normal (ALT 22 IU/L, AST 27 IU/L, bilirubin 0.4 mg/dL); Her baseline ALP value was 290 IU/L. On (b) (6) 13 days after starting alogliptin, she was found to have mild increases in liver-related tests (ALT 57 IU/L, AST 56 IU/L), followed by a dramatic increase in the levels about one month later (ALT 1178 IU/L, AST 1070 IU/L, ALP 905 IU/L, serum bilirubin 6.3 mg/dl). She was also found to have increases in serum ammonia levels and coagulation parameters and she was febrile. On (b) (6) because of

the continued high elevation in all the liver chemistries, alogliptin treatment was discontinued. And she was begun on treatment with menatetranone, ascorbic acid, and glycyrrhizin/glycine/cysteine, followed 4 days later by treatment with ursodeoxycholic acid. At this time, levothyroxine treatment was discontinued. She appeared to be moving toward fulminant hepatitis and she was transferred to another hospital, presumably an academic institution. Although her serum enzymes began to fall, her coagulation parameters worsened, as did her serum bilirubin that peaked at 33.5 mg/dL on (b) (6). She was treated for encephalopathy with kanamycin and lactulose. She was then started on treatment with corticosteroids, first given intravenously and then switched to oral prednisilone. The serum aminotransferases and bilirubin began to decline, and she was then transferred back to her original hospital. In October, she developed a fever and what was diagnosed as pneumonia, and she was started on treatment with a number of antibiotics. Her pneumonia worsened and she died on (b) (6) at which time her ALT was 30 IU/L, her AST 61 IU/L, her ALP 480 IU/L, and her serum bilirubin 3.8 mg/dL. Work-up had identified negative serology for hepatitis A, B, and C, for EBV and CMV, and negative tests for ANA, ASMA, LKM-1 antibody and AMA. Thus her death, clearly a result of fulminant liver disease or its complications, was not caused by infection with hepatitis viruses, and did not seem related to autoimmune hepatitis as defined by negative tests for all autoimmune hepatitis markers.

Comment: This 77 year old woman with diabetes mellitus, Hashimoto's thyroiditis and hypertension, who was admitted to hospital for treatment of her hypothyroidism with levothyroxine, developed mild elevations in aminotransferase levels 13 days after starting treatment of her diabetes with alogliptin. The liver dysfunction slowly worsened and she developed jaundice and evidence of impending fulminant hepatitis. Treatment with alogliptin was discontinued after 39 days, followed by discontinuation of the levothyroxine. She was transferred to another hospital presumably because of greater expertise at that hospital, and she was managed there for her advancing hepatic failure. Eventually she was started on treatment with corticosteroids on the assumption that the liver disease was of autoimmune origin in view of her background of diabetes and thyroiditis. This diagnosis was not, however, confirmed by identifying markers of autoimmune liver disease, all of which were negative. The liver disease appeared to improve as defined by a reduction in the liver chemistries, and the patient was transferred back to the original hospital. There she developed a fever and evidence of pneumonia, and despite treatment with a number of antibiotics, she died.

That this patient developed severe liver disease and died as a consequence seems quite clear. What is to be determined is what the cause was for the liver disease. Viral hepatitis as the cause for the liver injury is ruled out by the negative serology for all the hepatitis viruses but hepatitis E. Autoimmune hepatitis, particularly in an elderly female, needs to be excluded. This diagnosis is based generally on identifying autoimmune markers, but the test results of all markers in this patient were negative that ordinarily would exclude the diagnosis. However, given this patient's background, namely the existence of other autoimmune disorders such as the diabetes and thyroiditis, autoimmune hepatitis must be considered despite the negativity of all the autoimmune hepatitis. This presumably was the basis for treating this patient with corticosteroids that appeared to lead to the

improvement of the liver dysfunction thus supporting the possibility of this diagnosis. However, the apparent rapid response to steroids seems much quicker than is normally the case for autoimmune hepatitis, and corticosteroids can "wipe out the yellow" even in instances of non-autoimmune acute hepatocellular injury. In my opinion, the absence of positive tests for autoimmune markers is compelling evidence that this patient did not spontaneously develop idiopathic autoimmune hepatitis. Rather, in view of the temporal relationship between starting treatment with alogliptin and developing acute hepatocellular injury two weeks later makes it probable to highly likely that alogliptin was indeed responsible for the fatal liver disease.

Noteworthy is that the hepatology experts assigned by the company to review the cases disagree with my conclusion, (b) (6) assessing the case as unlikely and instead due to autoimmune hepatitis (AIH), while (b) (6) assessed the case as being possibly attributable to alogliptin. The concerning issue is whether the diagnosis was actually "idiopathic" AIH rather than dili from alogliptin. The major issue responsible for the disagreement is that the usual markers of AIH were negative in this patient. In favor of a diagnosis of AIH hepatitis was the fact that the patient is a female, that she had another diagnosis with autoimmune overtones, thyroiditis, and that she appeared to respond to treatment with corticosteroids. In my view, while this diagnosis can certainly not be ruled out, there are features that suggest to me that dili represents a greater likelihood as causation. Clearly, AIH can present for the first time in an elderly female and to occur in the absence of positive immunological tests. However, she is a little older than is usual for a first time onset of AIH and I am compelled by the fact that if she did have an underlying immunological diathesis, all of her markers for AIH were completely negative. That her liver chemistries improved with corticosteroid treatment is clear, but this can also occur with other causes of acute hepatocellular injury. Most of all, however, is that the injury occurred coincidental with use of alogliptin. Is this purely coincidental? I am left with the view that the drug played a role in the induction of the liver disease, either through a direct "idiosyncratic" mechanism or through precipitating liver injury in a patient primed for it because of a so-called autoimmune diathesis. I feel quite strongly that it is not appropriate to assign a score of unlikely to this case; on the other hand, I recognize the validity of the counter argument and therefore I am willing to downgrade my assessment from highly likely to probable.

8635-004/402

The data provided in this case are meager and insufficient to allow a definitive diagnosis. This 65 year old man from Spain with chronic hepatitis (not further defined), dyslipidemia, hypoacusis, musculoskeletal pain, a palatal disorder, strabismus, and type 2 diabetes, was started on treatment with alogliptin on June 14, 2011.The patient was also receiving a number of other drugs that included acetylsalicylic acid, bisoprolol, glyceryl trinitrate, hydrochlorothiazide, olmesartan, omeprazole, simvastatin, gliclazide, and repaglinide. Liver-related chemistries one week before stating alogliptin were an ALT value of 24 U/L, an AST of 16 U/L, an ALP of 40 U/L, and a total bilirubin of 0.4 mg/dL. The values had increased a little at the time of beginning treatment with

alogliptin. One month after starting treatment (July 13, 2011), he was found to have an ALT of 196 U/L, an AST 0f 111 U/L, an ALP of 42 U/L and a total serum bilirubin of 0.48 mg/dL. No mention is made of symptoms. Values obtained five days later (the last set shown in the report), showed an increase in the ALT level to 237 U/L, and a virtually unchanged AST value (108 U/L), ALP and serum bilirubin. Absolutely no further evaluation (i.e., viral and autoimmune markers) is reported. Treatment with alogliptin was discontinued on September 9, 2011 (almost 3 months after identifying raised levels of aminotransferases). However, testing for the serum aminotransferases between July 18 and September 9 was either not done (which I doubt) or was not reported. Also not done or not reported were virologic assays or testing for autoimmune markers. More importantly, what the reported "chronic hepatitis" is was not further described and what the outcome of the disease is not known. Regarding possible injury from other drugs he was receiving, it is unclear whether any of them could be implicated because first, their use all continued, and second, the last aminotransferases shown continued to be even more abnormal. It is thus not possible to establish an etiology for the liver dysfunction. Indeed, it is imperative that more information be supplied regarding viral and autoimmune markers and that liver chemistry results beyond those shown be displayed.

Comment: In the absence of needed information (hepatitis and autoimmune markers, start and stop dates of all drugs received, information on clinical manifestations, long-term follow-up data on liver chemistries,), it is not possible to establish an etiologic diagnosis. The sponsor should be required to submit the needed information.

311-9003/009

This case is identified as a subject with an ALT or AST >10x ULN. The data provided are minimal, summarized in a single page. The patient was a 49 year old man with hyperlipidemia, depression and anxiety who presumably had diabetes mellitus although this diagnosis is not mentioned in this single page report. Medications he was taking included fluoxetine, buspirone, trazodone, and ezetimibe. He was apparently a participant in a study drug trial who, in May 2006, was taking pioglitazone during run-in for an alogliptin trial. On June 16, 2006 he was randomized for a double-blind trial and, if I read the supplied information correctly, received alogliptin. During "stabilization", his liver related studies revealed an ALT of 14 mU/mL, an AST of 20 mU/mL, an ALP of 55 mU/mL, and a total serum bilirubin value of 0.3 mg/dL. On the day of randomization, the aminotransferase values were slightly increased to above the ULN (ALT 66 mU/mL and AST 32 mU/mL) as was the ALP (84 mU/mL; normal value 32-72mU/mL). The bilirubin value remained normal. Thirty-two days after starting treatment with alogliptin, the ALT value was found to have increased substantially (ALT 646 mU/mL) as had the AST (585 mU/mL) and the ALP (112 mU/mL); serum bilirubin had also increased but remained within the normal range. There is no comment on whether or not the patient developed associated symptoms. Also, there is no mention of efforts to evaluate the cause for this sudden increase in serum enzymes values (i.e., no tests for hepatitis or autoimmune serology). It is stated that the study drug was interrupted because of the increase in serum enzymes but without stating on which date although, presumably, it was when the

abnormalities were first identified. Also not commented on were the start and stop dates for the other drugs the patient was receiving.

Repeat testing was performed 10 days later (study day 42), identifying that the ALT had decreased to 46 mU/mL, the AST to 22 mU/mL, the ALP to 73 mU/mL, and the serum bilirubin to 0.39 mg/dL. By study day 49, all values were now completely normal. In the meantime, the study subject had voluntarily withdrawn from the study. Thus, this patient developed an increase in serum enzymes although not in serum bilirubin about one month after starting alogliptin at which time the drug was stopped, following which there was a rapid fall in enzymes 10 days later to near-normal values. Since efforts to identify an alternative diagnosis to possible drug induced liver injury were not undertaken, the precise basis for the observed abnormality cannot be determined. In view of the rapid improvement in the enzyme levels within 10 days of drug withdrawal, it is unlikely that viral or autoimmune accounted for these abnormalities.

Comment: This 49 year old man developed a fairly marked increase in serum enzymes (ALT, AST) approximately one month after starting treatment with alogliptin, all values declining to near normal when next tested (10 days) later, and to normal when tested 10 days after that. This suggests a link to the use of alogliptin since the latency period of one month is a well-accepted time interval, and the rapid decline to normal values within 20 days of discontinuing use of alogliptin suggests an effect of drug de-challenge. Unfortunately, testing for possible infection with one or other of the viral infections was not performed, nor was testing for markers of autoimmune hepatitis. However, the rapid decline in aminotransferase values with discontinuation of alogliptin is consistent with the effect of de-challenge. Even if drug-induced liver injury was the actual cause, implicating alogliptin alone is not possible without knowledge of the start and stop dates of the other drugs taken. Thus, it is difficult to reach a definitive diagnosis for the observed liver dysfunction, although it is possible that aloigliptin might have been the cause. Nonetheless, the condition can be graded as mild and short-lived.

ADDITIONAL CASES

TCI2011A06892

This 78 year old Japanese man, a heavy drinker, with a diagnosis of gastric cancer and type 2 diabetes, treated with glimepiride and voglibose, was started on treatment with alogliptin on October 26, 2011, the glimepiride being reduced by half. His baseline aminotransferase values were abnormal (ALT 52 IU/L, AST 57 IU/L) while his serum bilirubin level was normal. Subsequent tests of the aminotransferases showed persistent low-grade increases of their levels until approximately 2 months later (December 20, 2011), when his ALT increased to 237 IU/L, his AST to 542 IU/L and his ALP was 542 IU/L. The single test for bilirubin was normal. Alogliptin treatment was withdrawn on this date and he was switched back to glimepiride. An abdominal ultrasound was reported to show no liver abnormalities or dilated intrahepatic ducts but there was suspicion of

cancer of the pancreatic tail. Tests for hepatitis B and C were negative. A single follow-up test of his liver chemistries, performed the day after the values had spiked, showed that they had dropped but were still far from normal. Since these are the only tests displayed, the final outcome is unknown. Also unknown is whether he was continuing to drink when the abnormalities were identified.

Comment: Data available in this narrative are insufficient to establish a diagnosis for the observed liver dysfunction. The patient, described as a heavy drinker, had abnormal aminotransferases at baseline that might have been a result of continued heavy drinking or of alcoholic steato-hepatitis, although the AST and ALT values were elevated to the same level, unlike alcoholic liver disease where the AST is almost always higher than the ALT value. Two months after starting treatment with alogliptin, he develops a considerable spike in his already abnormal aminotransferase levels, the AST now rising to twice the level of the ALT increase. The value obtained on the following day has dropped considerably although it remains much higher than the baseline abnormal values. No further liver-related test data are reported so the extended outcome is unknown. Hepatitis B and C serologic markers are negative. Clearly, something precipitated a surge in aminotransferase levels that, since it followed 2 months after starting alogliptin treatment, could possibly have been a result of receipt of this drug. But there is insufficient clinical information provided surrounding the period of the spike, such as whether the patient was drinking heavily at the time. Thus, there is a low possibility that alogliptin was responsible for a sudden increase in aminotransferase values, but they dropped considerably in 24 hours and thus, together with the apparent lack of symptoms and of the development of jaundice, this can be considered a trivial issue.

TCI2011A06837

This 66 year old Japanese male who had been treated with pioglitazone and glimepiride for type 2 diabetes, was switched from pioglitazone to sitagliptin on October 13, 2011. However, sitagliptin appeared to be ineffective, and on (b) (6), was itself replaced by alogliptin. His baseline liver chemistries were normal (ALT 27 IU/L, AST 36 IU/L). His ALP and serum bilirubin levels are not recorded. On a routine visit approximately 1 month later (b) (6)), he is found to have an ALT value of 1512 IU/L, an AST of 2188 IU/L, a serum bilirubin of 3.9 mg/dL, and an ALP value of 313 IU/L. Initially reported to have had no symptoms at this time, he later admitted to actually having had some malaise. He was immediately hospitalized and alogliptin treatment was discontinued, and the dose of glimepiride was increased. The serum aminotransferase values declined rapidly over the course of the following week, reaching near normal values within 10 to 14 days, as shown in the last test result provided.

Work up focused on testing for the viruses of hepatitis B and C, both of which were serologically excluded. No imaging procedures were performed. Markers for autoimmune hepatitis were apparently not performed but the issue of potential autoimmune hepatitis was considered by his physician, and the likelihood dismissed

based on the evidence of normal values for gamma globulin and the return of the abnormal values to near normal within a relatively short time and without corticosteroid treatment. Other drugs received by the patient included isosorbide, sodium gualenate, famotidine, teprenone, nifedipine, and pravastatin, but they were continued despite which the liver tests improved following withdrawal of the alogliptin. Alcoholic liver disease as a potential diagnosis is excluded by the fact that he was only an occasional drinker and the pattern of liver dysfunction was completely different from that seen in alcoholic hepatitis.

Comment: This 66 year old man developed acute hepatocellular liver injury associated with hyperbilirubinemia approximately one month after starting treatment with alogliptin. With identification of the liver injury, alogliptin was discontinued whereas all other drugs he was receiving continued to be administered. In seeking an etiology, infection with the hepatitis B and C viruses was ruled out (but, of course, not hepatitis E virus infection), as was autoimmune hepatitis based on the absence of hyperglobulinemia and the rapid recovery without immunosuppressive treatment. Although imaging was not done to exclude the possibility of obstructive causes for the liver dysfunction, there were no clinical or biochemical indicators to support the diagnosis. Accordingly, it is my opinion that a diagnosis of alogliptin hepatotoxicity is probable to highly likely causing a liver disease of moderate severity.

The liver experts employed by the company have both reached a different conclusion, (b) (4) *indicating that data were insufficient to reach a reasonable conclusion whereas* (b) (4) *awarded this a case of barely possible alogliptin hepatotoxicity. Both express concern of the rapid improvement in the serum aminotransferases in the face of a drug with a long half-life, a concern with which I agree. Undoubtedly, rapid improvement such as occurred in this case from strikingly increased aminotransferase levels to near normal levels within 10 to 14 days is unusual for the common causes of acute hepatocellular injury other than acute congestion or shock. However, unless not reported, the narrative does not provide any information that even suggests the presence of cardiac disease or the occurrence of dramatic hypotension. The other issue raised to dismiss dili is that the lymphocyte stimulation test was negative. Since this test is not approved for this purpose in the U.S., and since its validity is uncertain, I cannot hang my hat on the results reported here as an indicator that dili was excluded. Clearly missing is the lack of test results for hepatitis A and E. One or other of these viruses might well have been responsible although hepatitis A is relatively uncommon in a 66 year old man (potential risk factors not reported) and hepatitis E is not known to be endemic in Japan (at least to my knowledge). I will therefore remain with my view that alogliptin dili is the probable cause for the liver injury although I will agree that there are some conflicting data that could require assigning a score of probable rather than highly likely.*

SUMMARY /CONCLUSIONS

The primary focus of the case review described herein is consideration of whether or not liver abnormalities identified among persons treated with alogliptin result from injury caused by the drug. In view of the population of patients who receive this drug, it would not be surprising to observe evidence of liver dysfunction since these are individuals highly susceptible to such conditions as nonalcoholic steatohepatitis, severe cardiovascular disease, gall stones, and in view of their age, malignancies such as pancreatic cancer, all of which may induce liver dysfunction. And indeed, in an earlier review of over 50 cases in which recipients of alogliptin were found to have liver-related biochemical test abnormalities, the majority were diagnosed to have causes other than alogliptin hepatotoxicity. However, this was not the case for the 13 cases described here; no diagnosis could be reached in 3 cases because of the insufficiency of the reported data; in 6 cases, there was no other alternative diagnosis to alogliptin hepatotoxicity although the cases were not fully compelling and thus were scored as possible alogliptin drug-induced liver injury; the association appeared more compelling in two further instances and hence were scored as probable instances of alogliptin hepatotoxicity; and finally, a diagnosis of alogliptin hepatotoxicity appeared more compelling and hence were scored as probable to highly likely instances of drug-induced liver injury from alogliptin in two additional cases.

As regards the features of liver injury among those considered to be possible or probable cases, none were associated with jaundice, most occurred after a relatively short latency (as early as one week), most did not present with symptoms but were identified through the planned study screening, some presented as mixed hepatocellular/cholestatic liver injury, and most were of short duration (although some were not studied appropriately, namely responding to an identified abnormality by repeating the testing shortly after identifying the abnormality). In summary, even if attributable to receipt of alogliptin, once the drug was discontinued (I am uncertain what specific criteria were used for drug discontinuation), the apparent liver injury appeared to be trivial.

Both cases scored as probable to highly likely presented with jaundice and evidence of severe hepatocellular injury. In one instance, an elderly female, the acute illness progressed to fulminant hepatitis even though the drug was discontinued, and she finally died after having developed pneumonia, possibly a consequence of treatment with corticosteroids. The second case, a middle-aged man, recovered after discontinuation of the drug.

In this regard, in the draft review by Dr. Pratt, the same 2 cases (TCI2011A04573 and TCI2011A06837) identified as moderate to severe liver disorders were considered to be associated with alogliptin. Since these cases occurred in the postmarketing setting, it is unknown if they confer the same degree of regulatory concern as would 2 such cases identified during registrational trials. However, given the imbalance in the frequency of ALT abnormalities noted in the pre-marketing trials between those who received alogliptin and those in the control group, it seems prudent to consider whether these data

taken together suggest that further study is needed regarding possible hepatotoxicity of alogliptin before general marketing of the drug is permitted in the US.

Cases of specific interest evaluated by DPV (Dr. Seeff) as a subset of cases from the December 7, 2011 submission including assessments by [redacted] (n=11) plus 2 additional cases.					
Subject #	**Treatment**	**Preferred Term**	**[redacted] Unblinded Assessment**	**[redacted] Blinded Assessment**	**Dr. Seeff's Assessment for CDER**
Serious Clinical Case (n=1)					
ERD2010A00037	Alo 12.5	ALT increased	Possible/ probable	Possible	Possible
Serious Postmarketing Cases (n=1)					
TCI2011A03640	Nesina 6.25	Liver disorder	Possible	Possible	Probable
Nonserious Postmarketing Cases (n=6)					
TCI2010A05612	Nesina 25	Hepatic function abnormal	Possible	Possible	Probable
TCI2011A01464	Nesina 12.5	Liver disorder	Possible	Probable	Possible
TCI2011A01670	Nesina 25	Hepatobiliary disease Blood amylase increased	Possible	Possible	Possible
TCI2011A02538	Nesina	Liver disorder	Possible	Possible	Possible
TCI2011A04039	Nesina 25	Hepatic function abnormal Vomiting Decreased appetite	Possible	Possible	Possible/ Probable
TCI2011A04874	Nesina 25	Hepatic function abnormal	Possible/ Insufficient data	Possible	Possible
Biochemical Hy's Law Postmaketing Case (n=1)					
TCI2011A04573	Nesina 25	Liver disorder	Unlikely	Possible	Probable to Highly Likely
Clinical Cases of ALT >5xULN (n=2)					
8635-004/402	Alo 25	ALT >8xULN	Unlikely	Possible	Insufficient data
311-9003/009	Alo 12.5	ALT >20xULN	Unlikely	Possible	Possible
Additional Cases (n=2)					
TCI2011A06892	Alo (no dose)	ALT=237			Possible
TCI2011A06837	Alo (no dose)	ALT=1,512; Bili=3.9			Probable to Highly likely

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/s/

MARGARITA V TOSSA
02/22/2012

ALLEN D BRINKER
02/22/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 3, 2012

TO: Mehreen Hai, Ph.D. Regulatory Project Manager
Valerie Pratt, M.D. Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 22271

APPLICANT: Takeda Global Research and Development Center, Inc.

DRUG: Nesina (Alogliptin)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: August 9, 2011

DIVISION ACTION GOAL DATE: April 25, 2012

PDUFA DATE: April 25, 2012

I. BACKGROUND:

NDA 22-271 is a resubmission of an application for a new molecular entity, Alogliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. The sponsor originally submitted the NDA in 2008 for the indication of an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The FDA issued a CR letter requesting that the applicant conduct a cardiovascular outcome trial to determine whether the product increases cardiovascular risk.

The protocols inspected included:

1. Protocol SYR-322_402 entitled, "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment with Alogliptin in Addition to Standard of Care in Subjects with Type 2 Diabetes and Acute Coronary Syndrome"

2. Protocol 01-06-TL-322OPI-004 entitled "A Multicenter, Randomized, Double-Blind Study to Determine the Efficacy and Safety of the Addition of SYR-322 25 mg versus Dose Titration from 30 mg to 45 mg of ACTOS® Pioglitazone HCl in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Control on a Combination of Metformin and 30 mg of Pioglitazone HCl Therapy" and

3. Protocol SYR-322_303 entitled "A Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Alogliptin Compared to Glipizide in Elderly Subjects with Type 2 Diabetes."

A total of 6 clinical sites and the sponsor were inspected for this application. Clinical sites were chosen for inspection because of large numbers of study subjects, participation in more than one study, history of protocol violations and complaints, and ranking in the "risk based model site selection tool." Protocol SYR-322_402 is ongoing, and has enrolled 2134 subjects at over 600 clinical sites world-wide. Three foreign sites were inspected for this protocol. Protocol SYR-322_303 was conducted from June 25, 2008 to August 30, 2008 and enrolled 441 subjects at 110 study sites in 15 countries. Protocol 01-06-TL-322OPI-004 enrolled 803 subjects at 235 clinical sites in 16 countries. For each of these two protocols, one foreign and one domestic site were inspected.

The sponsor was inspected because of issues found during inspection of the Lagrosa site to evaluate sponsor's oversight of the study.

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Sponsor	Protocol #/Site # # Subjects Randomized*	Inspection Date	Final Classification
Dr. Oscar R. Minuchin Clalit Healthcare Services Linn Clinic Diabetes and Lipids Department 145 A Jaffa Road Haifa, Israel	Protocol SYR-322_402/ Site # 8538/ 16 subjects Protocol SYR-322_303/ Site #3304/ 9 subjects	October 30 to November 3, 2011	NAI
Sergiy Polyvoda, MD, PhD, DM, Professor 10 Orekhivske shose, Zaporizhzhya, 69600, Ukraine	Protocol SYR-322_402/ Site # 8520/ 30 subjects	October 10 to 14, 2011	NAI
Roberto Botelho Instituto do Coração do Triângulo Mineiro S/C Ltda Rua Artur Bernardes, 239 Uberlândia, MG 38400-368, Brazil	Protocol SYR-322_402/ Site #8247/ 21 subjects	November 16 to 19, 2011	NAI
Adriana Dumitrescu, MD SC Centrul Medical "Sanatatea Ta" SRL 28, Armoniei St, 2nd sector 020725, Bucharest, Romania	Protocol 01-06-TL-322OPI-004/ Site #0886/ 31 subjects	October 24 to 26, 2011	NAI
Jeffrey B. Rosen, MD Clinical Research of South Florida 275 Alhambra Circle Coral Gables, FL 33134	Protocol 01-06-TL-322OPI-004/ Site #1037/ 18 subjects	September 12 to 26, 2011	VAI
Pedro F. Lagrosa, MD Time Clinical Research Inc. 2640 Zoe Ave. Huntington Park, CA 90255	Protocol SYR-322_303/ Site # 3018/ 24 subjects	August 23 to November 2, 2011	(b) (7)(A)
Takeda Global Research & Development Center, Inc. One Takeda Parkway Deerfield, IL 60015	Protocol SYR-322_402 Protocol SYR-322_303 Protocol 01-06-TL-322OPI-004	November 28 to December 8, 2011	Pending (Preliminary classification NAI)

*Protocol SYR-322_402 is an ongoing study and the numbers in the chart above from the NDA interim study report may not agree with the numbers of subjects randomized at the time of inspection of the clinical site. This was discussed with the Dr. Pratt on January 26, 2012.

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Dr. Oscar R. Minuchin**
Clalit Healthcare Services, Linn Clinic, Diabetes and Lipids Department
145 A Jaffa Road, Haifa, Israel

a. **What was inspected**: For Protocol SYR-322_402 at this site, 24 subjects were screened, and 17 subjects were enrolled into the study. An audit of all randomized subjects' records was conducted. During the inspection the following areas were covered: protocol compliance, test article accountability and storage, informed consent process, data accuracy, and site training and monitoring. This is an ongoing study, and the primary endpoint is occurrence of major adverse cardiovascular event (MACE). For Protocol SYR-322_303, a total of 11 subjects were screened, and 9 subjects were randomized into the study. A review of consent form documents from all screened subjects, and a review of the 9 enrolled study subjects' records were 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.

b. **General observations/commentary:** For the two protocols, there was no evidence of under-reporting of adverse events noted. Source documents were compared with the data listings submitted by the sponsor to the NDA and no significant discrepancies were noted. Compared to the chart above, there is an additional subject randomized into the study for Protocol SYR-322_402, and this may be attributed to the ongoing nature of the study. No violations were noted, and no Form FDA 483 was issued at the conclusion of the inspection.

c. **Assessment of data integrity**: The studies appear to have been conducted adequately, and the data generated by this site for the two protocols appear acceptable in support of the respective indication.

2. **Sergiy Polyvoda, MD, PhD, DM, Professor**
10 Orekhivske shose, Zaporizhzhya, 69600, Ukraine

a. **What was inspected**: At this site, Protocol SYR-322_402 was conducted. A total of 48 subjects were screened and 44 enrolled into the study. An audit of 11 subjects' records was conducted. During the inspection the following areas were given coverage: protocol compliance, test article accountability and storage, informed consent process, data accuracy, and site training and monitoring.

b. **General observations/commentary:** There was no evidence of any unreported instances of cardiac events that met the primary endpoint. There were additional subjects randomized into the study compared to the chart above and this may be attributed to the ongoing nature of the study. No violations were noted, and no Form FDA 483 was issued at the conclusion of the inspection.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. **Roberto Botelho**
Instituto do Coração do Triângulo, Mineiro S/C Ltda
Rua Artur Bernardes, 239, Uberlândia, MG 38400-368, Brazil

a. **What was inspected:** For Protocol SYR-322_402 at this site, a total of 32 subjects were screened and 25 enrolled into the study. Two subjects (#8247018 and #8247004) died and one subject (#8247001) withdrew consent after experiencing coronary artery bypass grafting complicated by infected chest suture. An audit of all 32 subjects' records, including informed consent, was conducted. During the inspection the following areas were given coverage: IRB review and approval of protocol, sponsor monitoring, consenting of subjects, adherence to the protocol, drug accountability, and training of study staff. Source documents were compared with the data listings submitted by the sponsor to the NDA, and no significant discrepancies were noted.

b. **General observations/commentary:** Protocol SYR-322_402 is an ongoing study, and the primary endpoint is occurrence of major adverse cardiovascular event (MACE). There were additional subjects randomized into the study compared to the chart above and this may be attributed to the ongoing nature of the study. There was no evidence of under-reporting of adverse events. No violations were noted, and no Form FDA 483 was issued at the conclusion of the inspection.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. **Adriana Dumitrescu, MD**
SC Centrul Medical, "Sanatatea Ta" SRL
28, Armoniei St, 2nd sector, 020725, Bucharest, Romania

a. **What was inspected:** For Protocol 01-06-TL-322OPI-004, at this site, 47 subjects were screened and 31 subjects enrolled into the study. 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. There was evaluation of IRB review, sponsor monitoring, consenting of subjects, site training and adherence to the protocol, adverse events reporting, and drug accountability. An in depth audit of 15 subjects' records, including informed consent, was conducted.

b. **General observations/commentary:** For the primary endpoint, HbA1C, all subjects' source laboratory reports were compared to the line listings provided from the NDA. There was no evidence of under-reporting of adverse events noted. No violations were noted, and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. **Jeffrey B. Rosen, MD**
Clinical Research of South Florida, 275 Alhambra Circle
Coral Gables, FL 33134

a. **What was inspected:** For Protocol 01-06-TL-322OPI-004 at this site, 35 subjects were screened, 18 subjects were randomized, and 11 subjects completed the study. There were no deaths or SAEs reported. No subjects discontinued from the study because of adverse events. One subject on placebo, Subject 10374503, was lost to follow-up. Four subjects from the placebo group (Subjects 10374508, 10374512, 10374524, and 10374526) and one subject from the active group (Subject 10374513) discontinued due to lack of efficacy. An audit of 10 subject's records was conducted.

b. **General observations/commentary:** The primary efficacy endpoint, hemoglobin A1C, was verified. Documents inspected included study related records, screening and enrollment logs, CRFs, eCRFs, source documents, 100% of the signed informed consent documents, and drug accountability records. A Form FDA 483 was issued because the CI failed to maintain adequate case histories. The following are examples:

1. Pain and discomfort, or anxiety and depression were noted by 10 subjects on the subject self-administered EQ-5D QOL assessment (Subjects 10374501, 10374504, 10374507, 10374508, 10374512, 10374520, 10374521, 10374526, 10374527, 10374532), but these symptoms were not further addressed in office notes. This most likely did not impact data integrity because adverse events were elicited from the subjects at each study visit in the normal manner using general questions. Thus, the CI's failure to review the EQ-5D forms should not have resulted in a change in the reporting rate for true adverse events. Also noted in the EIR was that, four months after completing the study, Subject 10374504 was admitted to the hospital for coronary artery bypass surgery. This did not impact data integrity because this event occurred outside of the reporting requirements for the protocol. The subject was seen for the Visit 16/Week 52 End of Treatment/Study Termination on August 4, 2008 and the event occurred on (b) (6) months after the termination of the study. According to protocol Section 10.2.1 "Collection and Reporting of Adverse Events": "Spontaneously reported SAEs will be collected for at least 30 days after the last dose of study drug(s)."

2. Subject 10374507 experienced "left knee pain" and was given Xanax, Motrin or Mobic and Ultram ER 100. This was not reported as an AE nor was it reported on the concomitant medication log for this study.

There was no other evidence of under-reporting of adverse events.

Dr. Rosen responded adequately. In a letter dated October 6, 2011, he stated that the standard procedure at his site will be amended so that the quality of life assessments will be reviewed by the investigator.

c. **Assessment of data integrity:** Although regulatory violations were noted as per above, these are considered isolated in nature and unlikely to significantly impact data reliability. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. **Pedro F. Lagrosa, MD**
Time Clinical Research Inc., 2640 Zoe Ave.
Huntington Park, CA 90255

Note: (b) (7)(A)

(b) (7)(A)

a. **What was inspected:** With respect to this application, one of the three pivotal studies, Protocol SYR-322_303, was inspected. For Protocol SYR-322_303 according to the NDA there were 24 subjects at this site. An audit of 11 enrolled subjects' records was conducted. The review included a comparison of source documentation to (CRFs) and data listings submitted to the NDA. Specific records reviewed included, but were not limited to, adverse event reporting; inclusion/exclusion criteria; test article accountability; informed consent form approvals; monitoring records; adherence to protocol-specified procedures. In

addition to the audit, subject and employee interviews and affidavits were obtained.

b. **General observations/commentary:** Following the inspection, a Form FDA 483 was issued to Dr. Lagrosa. The following observations were noted on the Form FDA 483:

(b) (7)(A)

[redacted]

Reviewer note: *The violations cited on the Form FDA 483 noted above were based on record review of the source data at the site.*

(b) (7)(A)

[redacted]

(b) (7)(A)

[redacted]

Reviewer Note: (b) (7)(A)

[redacted]

[redacted] (b) (7)(A)

c. **Assessment of data integrity:** [redacted] (b) (7)(A) As discussed with the review division in a series of e-mails in December 2011, the data from this site are not considered reliable in support of the application. [redacted] (b) (7)(A)

7. **Takeda Global Research & Development Center, Inc.**
One Takeda Parkway, Deerfield, IL 60015

Note: Observations noted for this site are based on communications with the FDA investigator and review of a draft EIR. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** This inspection covered sponsor activities for Protocol SYR-322-402 for clinical investigators (CIs) Minuchin, Polyvoda and Botelho; for Protocol 01-06-TL-322OPI-004 for CIs Dumitrescu, Rosen and Jasper Hein; and for Protocol SYR-322-303 for CIs Minuchin and Lagrosa. The inspection reviewed the following: organizational duties and responsibilities, CRO contracts, sponsor SOPs, monitoring and auditing program, sponsor-clinical site correspondence, sponsor site audits, data management and drug accountability. A review of Takeda's procedures to ensure sites are adhering to GCPs in foreign countries including Takeda's SOPs for informed consent forms and document translations was conducted. A detailed review was conducted of the monitoring reports, including reports documenting the [redacted] (b) (4) monitor's review and verification of source documents compared to the eCRFs for 14 of the 24 subjects enrolled at Dr. Lagrosa's sites. The documents verified by the monitor included ECGs, medical histories and informed consent forms.

b. **General observations/commentary:** Takeda contracted with [redacted] (b) (4) a contract research organization (CRO), to conduct the responsibilities of monitoring and

selection of investigators.

During the FDA inspection, all misconduct investigations for the 3 protocols identified in the assignment were reviewed. There were 5 misconduct investigations for Protocol 01-06-TL-322OPI-004, 1 investigation for Protocol SYR-322-303 and 2 investigations for Protocol SYR-322-402. The sponsor terminated the following 3 clinical sites from the protocols reviewed during this inspection as a result of misconduct investigations: John Spence, MD (Florida) and Narendra Gupta, MD (Georgia) from their participation in Protocol 01-06-TL-322OPI-004 and Eric Lowe, MD (Florida) from Protocol SYR-322-402. Misconduct investigations documented Drs. Spence, Gupta and Lowe were terminated for GCP non-compliance and/or quality issues. Takeda sent letters to the Agency within 2 days of terminating their sites. Takeda did not include data from Dr. Spence, Dr. Gupta and Dr. Lowe's sites in the clinical study report.

Data from 3 additional sites for Protocol 01-06-TL-322OPI-004 in which Takeda conducted misconduct investigations, but were not terminated, were also noted. These included Dr. Balli in Texas, Dr. Saadeh in Maryland and Dr. Hein in Germany. No discrepancies with SOPs were noted with the investigations at Dr. Balli and Dr. Saadeh's sites; however, the FDA investigator noted isolated deficiencies with the timing and assessment of the misconduct investigation at Dr. Hein's site. Specifically, numerous GCP non-compliance and data collection issues were detected at Dr. Hein's site from June 2008 to May 2009 for the single subject enrolled into the study. Attempts to bring the site into compliance were unsuccessful and Takeda decided to not use the site's data in the per-protocol analyses in March 2009 due to data integrity issues; however the site was not terminated. Ms. Dalton stated the site was not terminated because only one subject was randomized at the site and this subject completed the last visit prior to Takeda's determination of GCP non-compliance at the site. It was verified that Dr. Hein's site was reported to the Ethics Committee for GCP non-compliance by Takeda. The FDA investigator verified that Takeda obtained prompt compliance when serious deviations occurred at clinical investigator sites, with the exception of Dr. Hein's site for Protocol 01-06-TL-322OPI-004. With respect to oversight of Dr. Hein's site, the explanation as per above appears reasonable. Takeda appears to have executed sponsor responsibilities pertinent to sponsored studies adequately. No regulatory violations were noted and no Form FDA 483 was issued.

Concerning sponsor and CRO actions regarding the Lagrosa site, on August 18, 2008, (b) (7)(A) The Clinical Team Manager from (b) (4) and Study Manager from Takeda

conducted a co-monitoring visit on October 1, 2008 to address a corrective action plan regarding reporting of GCP issues.

(b) (7)(A) Takeda performed a directed quality assurance audit at this site on October 7, 2008 and GCP issues were identified. However, the exact nature of these concerns is unclear as the EIR has not been received. Based on preliminary communications with the field, it appears that corrective actions were implemented by Takeda/(b) (4) E-mail communication and weekly meeting minutes between (b) (4) and Takeda were provided as documentation of the steps taken to bring Dr. Lagrosa's site in compliance. (b) (7)(A)

During the closeout meeting for inspection of the sponsor held on December 8, 2011, (b) (7)(A) Takeda did not identify any significant GCP concerns related to Dr. Lagrosa's conduct of the Takeda study during their audit.

Reviewer note: (b) (7)(A) *An inspection of the site for the conduct of Protocol SYR-322-303 was conducted by FDA from March 23 to April 15, 2009. No significant GCP issues were identified during the earlier inspection of this site as it relates to Protocol SYR-322-303, and the final classification was VAI and NAI for Dr. Oganyan and Dr. Lagrosa, respectively. FDA's inspection of this site for Protocol SYR-322-303 appears to be in line with Takeda's audit related findings (October 2008), and it appears that no significant GCP violations impacting data reliability were identified by FDA or Takeda.*

(b) (7)(A)

(b) (7)(A)

For the inspection assignment of Takeda issued for review of this NDA, the field investigator was specifically instructed to investigate concerns about monitoring at the Lagrosa site. Based on preliminary communications with the field and a preliminary report, it appears that Takeda followed their procedures concerning the monitoring of the Lagrosa site. (b) (7)(A)

c. **Assessment of data integrity:** In general, Takeda's oversight over this study appears to have been adequate. No significant concerns have been raised regarding adequacy of monitoring for this study. The issues noted at the Lagrosa site appear to be an isolated instance. (b) (7)(A) As further evidence for the adequacy of monitoring of the clinical trials sponsored by Takeda, there were sites that were removed from participation in studies due to GCP non-compliance, indicating that there appears to have been monitoring of clinical sites that was adequate so that non-complaint sites were removed. The other clinical sites noted above appear to have been adequately monitored during the clinical trials and the sponsor appears to have met their responsibilities.

In general, the studies appear to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication, with the exception of the data from Dr. Lagrosa's site for the respective study.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites and the sponsor were inspected in support of this NDA. For the five clinical sites and the sponsor there were no violations noted or only minor violations noted that did not impact data integrity. The primary endpoint data were verified and there was no evidence of underreporting of adverse events. However, data from Dr. Lagrosa's site are considered unreliable. OSI recommends that the data from this site for the respective study be removed from any analysis in support of this NDA. (b) (7)(A) No significant concerns are raised regarding data from other sites involved in the conduct of this study, especially given that Takeda appears to have adequately monitored the conduct of this clinical investigation, and where appropriate, has secured compliance or terminated sites with significant issues of GCP noncompliance as discussed above.

Based on results of these inspections it appears that data submitted by the Applicant in support of the requested indication, except for the data generated by Dr. Lagrosa's site, are considered reliable.

Note: Classification noted for Dr. Lagrosa is not final and is based on preliminary reviews of the EIR, additional reports and supporting documents. Classification noted above for Takeda, the sponsor, is based on communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and further review of the Establishment Inspection Reports (EIR).

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/

SUSAN LEIBENHAUT
02/09/2012

TEJASHRI S PUROHIT-SHETH
02/09/2012

MEMO TO FILE

NDA #:	22271
Sponsor:	Takeda
Drug:	Nesina (Aloglitpin)
Submission Date:	July 25, 2011
Memo Date:	January 24, 2012
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Jayabharathi Vaidyanathan, Ph.D. (Acting)
RE:	Labeling Comments

Labeling Comments

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/s/

SANG M CHUNG
01/24/2012

JAYABHARATHI VAIDYANATHAN
01/24/2012

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:	November 29, 2011
Reviewer:	Anne C. Tobenkin, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name(s) and strengths:	Nesina (Alogliptin) Tablets, 6.25 mg, 12.5 mg, 25 mg
Application Type/Number:	NDA 022271
Applicant/sponsor:	Takeda
OSE RCM #:	2011-2602

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

1 INTRODUCTION

This review evaluates the proposed container labels, carton, and insert labeling for Nesina (Alogliptin) Tablets for NDA 022271 for areas of vulnerability that could lead to medications errors. The review responds to a request from the Division of Metabolism and Endocrinology Products (DMEP). The proposed proprietary name, Nesina, was found acceptable in OSE review # 2011-2601.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 25, 2011 proprietary name submission.

- Established Name: Alogliptin
- Indication of Use: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or combination therapy
- Route of administration: Oral
- Dosage form: Tablet
- Dose: One tablet (6.25 mg, 12.5 mg, 25 mg)
- How Supplied: Bottles of 30, 90 or 500 and Physician samples of 7 (b) (4) tablets
- Storage: Room temperature
- Container and Closure System:
  - (b) (4) on 30 and 90 count bottles.
  - (b) (4) on institution 500 count bottle.
  - (b) (4)
  - 7 day Blister physician sample, no child-resistant closure noted

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted July 25, 2011
- Carton Labeling submitted July 25, 2011
- Insert Labeling submitted July 25, 2011

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

3 CONCLUSIONS AND RECOMMENDATIONS

The proposed labels and labeling introduce vulnerability to confusion that can lead to medication errors. We note that the insert labeling utilizes error prone symbols, the labels and labeling present the proprietary name in a (b) (4) used in the strength presentation of the 25 mg tablets and the established name is not prominent. In addition, (b) (4). We recommend the following revisions be implemented prior to the approval of this NDA.

A. Insert Labeling

The symbols '<' and '>' utilized throughout the labeling are dangerous symbols that appear on the List of Error-Prone Abbreviations, Symbols, and Dose Designations. These symbols are often mistaken and used as opposite of intended. As part of a national campaign to avoid the use of dangerous abbreviations and symbols, FDA agreed not to use such symbols in the approved labels and labeling of products. We recommend you replace all instances of the symbol '<' with the phrase "less than" and the symbol '>' with the phrase "greater than."

B. General Comments (All strengths)

1. The proprietary name, Nesina, is presented in a (b) (4) To avoid selection errors, revise the appearance of the proprietary name so that it appears in (b) (4) utilized in highlighting the strengths.
2. Increase the visibility of the established name by increasing the size of the font.

C. Nesina Bottles (All strengths and sizes)

1. Decrease the prominence of the quantity statement so that the proprietary name, established name, and strength are more prominent.

D. Nesina Blister Label Samples (12.5 mg, 25 mg)

1. Include a statement which communicates that the blister pack (b) (4) to keep out of reach of children.

E. Nesina Blister Carton Labeling (12.5 mg, 25 mg)

1. See comment D1 above.

If you have further questions or need clarifications, please contact OSE Project Manager, Margarita Tossa, at 301-796-4053.

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/s/

ANNE C TOBENKIN
11/29/2011

LUBNA A MERCHANT
11/29/2011

CAROL A HOLQUIST
11/29/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: February 18, 2009

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Reviewer
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Nancy Carothers, RN
Patient Product Information Reviewer
Patient Labeling and Education Team
Division of Risk Management (DRISK)

Subject: Memo to file re: Review of Patient Labeling (Patient Package Insert

Drug Name(s):
- Nesina (alogliptin) Tablets, NDA 22-271
- TRADENAME (alogliptin and pioglitazone) Tablets, NDA 22-426

Applicant/sponsor: Takeda Global Research & Development Center, Inc.

OSE RCM #: 2008-59; 2008-1617

DMEP requested that the Patient Labeling and Education Team of DRISK review proposed patient labeling for two New Drug Applications submitted by Takeda Global Research & Development Center, Inc.:

- Nesina (alogliptin) Tablets, NDA 22-271
- TRADENAME (alogliptin and pioglitazone) Tablets, NDA 22-426

DMEP does not plan to address labeling during this review cycle; therefore, we will defer our reviews until such time as DMEP plans to hold labeling discussions. Please send us new consult requests at that time.

Please let us know if you have any questions.

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/s/

Sharon Mills
2/18/2009 01:35:40 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/18/2009 02:11:57 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: September 26, 2008

FROM: Sriram Subramaniam, Ph.D.
Sean Y. Kassim, Ph.D.
Samuel H. Chan, Pharm.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 9/30/08
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-271, Nesina(alogliptin) tablets, 12.5mg and 25mg, sponsored by Takeda Global Research & Development, Inc.

TO: Mary H. Parks, M.D.
Director, Division of Metabolism & Endocrinology Products (HFD-510)

At the request of the Division of Metabolism and Endocrinology Products, the Division of Scientific Investigations audited the clinical and analytical portions of the following bioequivalence study:

Study Number: **SYR-322-027**
Study Title: **"An open-label, Randomized, 2-Period Crossover Study to Determine the Bioequivalency of the Phase 3 SYR-322 Tablets (12.5mg and 25mg) With the Commercial SYR-322 Tablets (12.5mg and 25mg) in Healthy Adult Subjects"**

The clinical portion and analytical portions of the above study were conducted at MDS Pharma Services (MDS) in Phoenix, AZ and (b) (4) respectively. Following the inspection of the clinical facility (July 14-25, 2008) and the analytical facility (b) (4) Form FDA 483s were issued.

Clinical Facility Observations

MDS responded to the Form 483 observations by letter dated August 20, 2008 (Attachment 1). (b)(4) responded to the Form 483 observations by letter dated September 8, 2008 (Attachment 2). The observations and our evaluations follow.

1. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.**

   a. **Two of the 28 subjects records reviewed had adverse events documented on the general physical examination (source) that were not reported on the case report form (CRF).**

   During the inspection, approximately 39% of subject records were reviewed. The review revealed the following AEs in the source data were not reported in the CRFs:

   - Subject# 0001/006 (b)(6) had mild conjunctivitis in the left eye during post-study physical examination.
   - Subject# 0001/101 (b)(6) had "1 cm cellulitis right upper lip for 3 days" during the interim physical examination. These events were not reported in the CRF.

   b. **Four of the 46 source documents and/or case report forms (CRF) reviewed had transcription errors noted for the urine collection for pharmacokinetic (PK) time and/or total volume collected. (See Table 1)**

Table 1

Site No. /Subject number	Treatment Period/Dose	Scheduled Time of study	Source Record		CRF	
			Collection date/time	Volume (mL)	Collection date/time	Volume (mL)
0001/059	2/Day 1-3 25mg Phase 3 tablet	0 to 24 hours post dose	10-4-06 /07:45	2,040	10-4-06 /07:52	1,000
0001/066	1/Day 1-4 25mg commercial tablet	-12 to 0 hours pre-dose	9-26-06 /08:18	360	09-26-06 /06:35	560
0001/070	2/Day1-3 25mg commercial tablet	0 to 24 hrs post dose	10-4-06 /07:45	2,560	10-4-06 /07:58	1,700
0001/083	2/Day1-3 25mg commercial tablet	0 to 24 hrs post dose	10-4-06 /07:50	16,040	10-4-06 /07:50	16,040

During the inspection, approximately 64% of the subject records were reviewed for urine collection data. Based on this limited audit, the times and volumes of urine collection were not accurately reported in the CRFs for the subjects in Table 1. The times and volumes recorded in the source data should be used for the study. Also, MDS could not explain the abnormally high urine volume collection for subject# 0001/083.

In their response, MDS agreed with the observations in 1 (a) and (b) above. MDS attributed the discrepancies to transcription errors and promised to correct the objectionable practices for future studies. MDS also promised to report these errors to the sponsor.

Analytical Facility Observations

Failing dilution quality control (QC4, Dil 4 for SYR110324) concentrations without assignable cause, generated from an acceptable validation run (2FCO2-B), were not reported in (b)(4) validation report FCO2.

(b)(4) did not include all acceptable data to validate dilution integrity. As described in the Form 483 observations, validation data from an acceptable run for dilution integrity was excluded solely because dilution QCs

were inaccurate. Nonetheless, during the inspection, (b)(4) included all dilution QC data for SYR110324 (metabolite M-1) and found the performance of the dilution QCs were acceptable. In addition, dilution QC results analyzed with diluted study samples were acceptable. Therefore, the observation does not impact the study results.

Conclusion:

Based on the above findings, DSI concludes inaccuracies in reporting AEs and urine collection times and volumes in the CRFs for the study SYR-322-027. As the data audited was limited, the sponsor should provide an accurate list of AEs and urine collection times and volumes for the study. The remaining data is acceptable for agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam signed by Subramaniam

Sriram Subramaniam, Ph.D.

Sean Y. Kassim, Ph.D.

Samuel H. Chan, Pharm.D.

Final Classifications:
VAI - MDS Pharma Services, Phoenix, AZ
VAI - (b)(4)

cc:
HFD-45/RF
DSI/Vaccari
HFD-48/Kassim/Subramaniam/Chan/Patague/CF
HFD-510/Marchick
HFD-870/Chung/Choe
Draft: SYK 9/8/08 SHC 9/8/08
Edit: SS 9/25/08 MKY 9/26/08
DSI:5846; O:\BE\EIRCOVER\22271tak.alo
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/s/

Samuel Chan
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DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 4, 2008

TO: Julie Marchick, Regulatory Project Manager
Joanna Zawadzki, M.D. Medical Officer
Division of Metabolic and Endocrine Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-271

APPLICANT: Takeda Global Research & Development Center

DRUG: Nesina *(*alogliptin*)*

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus as monotherapy and in combination therapy with a thiazolidinedione (either alone or in combination with metformin or a sulfonylurea), metformin, a sulfonylurea or insulin (either alone or in combination with metformin)

CONSULTATION REQUEST DATE: March 14, 2008

DIVISION ACTION GOAL DATE: October 24, 2008
PDUFA DATE: October 27, 2008

I. BACKGROUND:

NDA 22-271 is an application for a new molecular entity, alogliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 inhibitors prolong the activity of incretin hormones by blocking their degradation. Incretin hormones are released from the gut throughout the day and levels are increased in response to ingestion of a meal. These hormones enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner.
The goals of the inspections were assessment of safety and of the primary efficacy endpoint, glycosylated hemoglobin (HbA1c) change from baseline at Week 26.
There were no sites enrolling large numbers of subjects in any one of the studies. Most of the investigators randomized less than 10 subjects per protocol. Investigators who participated with the greatest number of randomized subjects in all studies were selected for inspection.

The protocols inspected include:

A. SYR-322-MET-008, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR-322 When Used in Combination with Metformin in Subjects with Type 2 Diabetes
B. SYR-322-TZD-009, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Pioglitazone in Subjects with Type 2 Diabetes
C. SYR-322-PLC-010, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) Compared with Placebo in Subjects with Type 2 Diabetes
D. SYR-322-INS-011, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Insulin in Subjects with Type 2 Diabetes

II. RESULTS (by Site):

Name of CI, or Sponsor Location	**Protocol #: and # of Subjects:**	**Inspection Date**	**Final Classification**
CI #1 Marc Rendell, MD Creighton Diabetes Center 601 N. 30th St., Ste. 6715 Omaha, NE 68131	Protocol A. SYR-322-MET-008/ 20 subjects enrolled/18 subjects randomized Protocol D. SYR-322-INS-011/ 17 subjects enrolled/10 subjects randomized	July 1-8, 2008	NAI

CI #2 Fatima Phillips, M.D. Clinical Research Solutions, Inc 205 North Banana River Drive, Suite 102 Merritt Island, FL 32952	Protocol B. SYR-322-TZD-009/ 19 subjects enrolled and randomized Protocol C. SYR-322-PLC-010/ 10 subjects enrolled/8 subjects randomized	April 30-May 28, 2008	Pending (Preliminary classification OAI)
SPONSOR Takeda Global Research & Development Center One Takeda Parkway Deerfield, IL 60015	Protocol A. SYR-322-MET-008/ Protocol B. SYR-322-TZD-009 Protocol C. SYR-322-PLC-010 Protocol D. SYR-322-INS-011	July 8-14, 2008	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Marc Rendell, MD
   Creighton Diabetes Center
   601 N. 30th St., Suite 6715
   Omaha, NE 68131

a. **What was inspected:** Regarding SYR-322-MET-008, 27 subjects were screened, 18 subjects were randomized and 18 subjects completed the study. There were no deaths or SAEs reported. One subject (subject 8003) on active treatment experienced adverse events and discontinued from the study. One subject (subject 8027) on active treatment discontinued due to lack of efficacy. Regarding SYR-322-INS-011, 28 subjects were screened, 10 subjects were randomized and 10 subjects completed the study. There was one SAE of atrial fibrillation on active treatment. There were no deaths reported. One subject (subject 5024) on active treatment and three subjects on placebo (Subjects 5002, 5007, 5020) discontinued due to lack of efficacy.

   An audit of 100% of informed consent documents, subject records for adverse event reporting and endpoint data and 50% of source documents for eligibility criteria was conducted. No regulatory violations were noted.

b. **General observations/commentary:** No significant regulatory observations were noted with Dr. Rendell's conduct of the study.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Fatima Phillips, MD
Clinical Research Solutions, Inc.
205 North Banana River Drive, Suite 102
Merritt Island,
FL 32952

a. **What was inspected:** Regarding SYR-322-TZD-009, 19 subjects were randomized and 17 subjects completed the study. Records for 14 of the 19 randomized subjects (74%) were reviewed for completeness, accuracy, protocol deviations and compliance with applicable regulations.

Regarding SYR-322-PLC-010, 11 subjects were screened, 8 subjects were randomized, and 7 subjects completed the study. Records for 10 of the 11 enrolled subjects were reviewed for completeness, accuracy, protocol deviations and compliance with applicable regulations.

b. **General observations/commentary:** The inspection found the following:

- Dr. Phillips did not maintain adequate and accurate records. Specifically, Dr. Phillips did not maintain source documents for subject medical history or medication history for Type 2 Diabetes Mellitus (DM) to establish the eligibility of the subjects enrolled in the trials. The FDA inspector repeatedly requested source documents that could verify eligibility criteria. Dr. Phillips stated that the site did not maintain any medical charts or records for the study subjects outside of the subject case report files. This finding was presented to Dr. Phillips in an FDA Form 483 at the close-out for the inspection.

  In a response to FDA on June 28, 2008, Dr. Phillips submitted items designated as "source documents" for two subjects, one for each of the two studies inspected. The documents consist of a single page with small spaces for "Disease", "Pertinent Medical Hx" and three lines to fill in "Meds." These items were not adequate to establish whether the subject met eligibility criteria such as previous medications for DM and status of control of DM. For Subject (b) (6) enrolled in SYR-322-PLC-010, source documentation submitted by Dr. Phillips was only the patient intake form documenting that the patient has DM currently treated with diet. There was no record of a medical history in the subject files to document whether the subject met other criteria for eligibility. For Subject (b) (6) enrolled in SYR-322-TZD-009 medical history was recorded on a "source document worksheet" provided by the sponsor containing the checklist of the eligibility criteria. Pertinent items on the copy of the source document submitted are not legible (blacked-out) so subject diagnosis and medication cannot be determined.

- Dr. Phillips may not have obtained adequate informed consent. Specifically, the informed consent for subject (b) (6) -9041 appears to have been signed by someone other than the subject. The subject's name on the informed consent does not have the same spelling or writing as the signature on all corresponding clinical sign-in sheets. In her response submitted to FDA, Dr. Phillips stated that this was an isolated occurrence. She states that the subject was contacted and the subject stated that she consented to participation and has used an altered version of her identity in the past during participation in clinical research. Further investigation by FDA of this finding is pending.

c. **Assessment of data integrity**: The source documents to verify the eligibility criteria are inadequat (b) (7)(A) However, neither of these observations adversely impact data acceptability. Of note, regarding eligibility criteria, Dr. Phillips had adequate documentation by way of laboratory results to show that the subjects in fact had DM. (b) (7)(A)

3. Takeda Global Research & Development Center
   One Takeda Parkway
   Deerfield, IL 60015

a. **What was inspected**: The inspection included review of monitoring reports, training records, and drug shipping records for the above protocols.

b. General observations/commentary: Subject screening and monitoring visits began in January 2006; however, the monitoring plan was not established until April 2006. The timeframes established in the monitoring plan were not followed. For monitoring reports reviewed examples were noted when the CRO conducting the monitoring did not perform interval monitoring visits within the specified timeframe of +/- 6 weeks. Examples were also noted when the monitors did not prepare their reports within two to three business days, and when the reports were not received by the sponsor (Takeda) within 25 business days from the visit. Weekly monitoring reports were also not performed as required. A few examples were also noted when the monitoring report was not reviewed by Takeda within 30 days as required by Takeda written procedures. No regulatory violations were noted and a Form 483 was not issued.

c. Assessment of data integrity: Data generated by this sponsor appear acceptable in support of the pending application.

Observations noted above based on this sponsor inspection are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above, the inspection of clinical investigator Dr. Rendell found no regulatory violations. Inspection of the sponsor, Takeda Global Research & Development Center found no regulatory violations and our preliminary assessment is based on communication with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

The inspection of clinical investigator Dr. Phillips found that the source documents to verify the eligibility criteria are inadequate (b) (4)

However, neither of these observations adversely impact data acceptability. Of note, regarding eligibility criteria, Dr. Phillips had adequate documentation by way of laboratory results to show that the subjects in fact had DM. (b) (4)

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Susan Leibenhaut
9/9/2008 03:38:46 PM
MEDICAL OFFICER

Constance Lewin
9/9/2008 03:50:25 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Metabolism and Endocrinology Products

Application Number: 22-271

Name of Drug: Nesina (alogliptin) Tablet

Applicant: Takeda Global Research & Development Center, Inc.

Material Reviewed:

Submission Date(s): December 27, 2007

Receipt Date(s): December 27, 2007

Submission Date of Structure Product Labeling (SPL): December 27, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by May 16, 2008. This updated version of labeling will be used for further labeling discussions.

Highlights

Dosage and Administration

- Do not use (b) (4) in Highlights (b) (4)

(b) (4)

End of Highlights

- For a new NDA, the revision date will be the month/year that the application is approved. The preferred format is "Revised: Month Year" or "Revised: Month/Year".

(b) (4)

FPI

- All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly.

17 Patient Counseling Information

- There is no requirement that the (b) (4) be a subsection under the Patient Counseling Information section. (b) (4)

General

- Remove the header and footer from each page

Additional (Non-PLR-Related) Comments

The Division is requesting changes to the labeling of all oral-antidiabetic drugs to appropriately reflect the findings of efficacy and safety of these products and to better inform prescribers when selecting an oral anti-diabetic drug for their patients. The following sections of the label should be modified as described below:

1. Under **INDICATIONS and USAGE**
   In the Highlights of Prescribing Information and in the Full Prescribing Information, replace (b) (4) with the following sentence:

   "Nesina is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

2. Under Important Limitations of Use
   In the Highlights of Prescribing Information and in the Full Prescribing Information, add a statement listing the major classes of anti-diabetic drugs that have not been studied in combination with your drug, but which are likely to be used in combination with your drug (e.g., sulfonylureas, insulin, etc.).

   "Nesina has not been studied in combination with Drug A."

3. Under **WARNINGS and PRECAUTIONS**
   In the Highlights of Prescribing Information and in the Full Prescribing Information, the following statement should be added to reflect the absence of macrovascular outcome data for all oral anti-diabetic drugs:

   "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Nesina or any other oral anti-diabetic drug."

4. Under **CLINICAL STUDIES**
   Add a statement at the beginning of this section describing how your drug has been studied.

   "Nesina has been studied as monotherapy and in combination with Drug A, Drug B, and Drug C."

Reviewed by:
Julie Marchick, MPH
Regulatory Project Manager

Supervisory concurrence:
Lina AlJuburi, PharmD, MS
Chief, Project Management Staff

Drafted: JM/01.11.08
Revised: JM/03.06.08
Finalized: JM/03.11.08

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Marchick
3/11/2008 10:17:51 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-271 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Nesina
Established Name: alogliptin tablets
Strengths: 25 mg, 12.5 mg, 6.25 mg

Applicant: Takeda Global Research & Development Center
Agent for Applicant (if applicable): N/A

Date of Application: December 27, 2007
Date of Receipt: December 27, 2007
Date clock started after UN: N/A
Date of Filing Meeting: TBD
Filing Date: February 25, 2008
Action Goal Date (optional): October 24, 2008 User Fee Goal Date: October 27, 2008

Indication(s) requested: As an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM [redacted] (b) (4)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☐ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

  3. This application is an eCTD NDA. YES ☒

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? X YES, Did not specify Years NO ☐

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes
- List referenced IND numbers: 69,707
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) November 28, 2005 NO ☐

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 30, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) February 25, 2005 – Carcinogenicity protocol NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? **N/A** YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? **N/A** YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐

If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
If EA submitted, consulted to EA officer, OPS? YES ☒ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? **N/A** YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 12, 2008

NDA #: 22-271

DRUG NAMES: Nesina (alogliptin) Tablets

APPLICANT: Takeda Global Research & Development Center

BACKGROUND: NDA 22-271 for alogliptin tablets was submitted for review on December 27, 2007. Alogliptin is a dipeptidyl-peptidase IV (DPP-IV) inhibitor. The Sponsor proposes that alogliptin be indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM (b) (4)

ATTENDEES: Mary Parks, Hylton Joffe, Joanna Zawadzki, Janice Derr, Todd Sahlroot, David Carlson, Todd Bourcier, Stephen Moore, Sally Choe, Andrea Slavin, Julie Marchick, Lina AlJuburi, Lee Ripper, Anthony Charity, Jennifer Qin, Jena Weber, Lucan Bi, Kathryn Gaines

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Joanna Zawadzki
Secondary Medical:	Hylton Joffe
Statistical:	Janice Derr
Pharmacology:	David Carlson
Statistical Pharmacology:	N/A
Chemistry:	Chien Hua Niu
Environmental Assessment (if needed):	TBD
Biopharmaceutical:	Sang Chung
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Andrea Slavin
OPS:	N/A
Regulatory Project Management:	Julie Marchick
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐

If no, explain:

- Advisory Committee Meeting needed? **TBD** YES, date if known _____ NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	☒	FILE	☐	REFUSE TO FILE	☐	
STATISTICS	N/A	☐	FILE	☒	REFUSE TO FILE	☐	
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐	

- Biopharm. study site audits(s) needed? YES ☒ NO ☐

PHARMACOLOGY/TOX	N/A	☐	FILE	☒	REFUSE TO FILE	☐	

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY			FILE	☒	REFUSE TO FILE	☐	

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? **N/A** YES ☐ NO ☐

  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center

Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Julie Marchick MPH
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Marchick
3/6/2008 10:35:19 AM
CSO

Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation: Thorough QT Study Review

IND or NDA	IND 69707
Brand Name	
Generic Name	SYR-332
Sponsor	Takeda Global Research and Development
Indication	Type 2 Diabetes Mellitus
Dosage Form	Film-coated tablets
Therapeutic Dose	12.5 mg and 25 mg QD
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not defined
Application Submission Date	12 Jan 2007
Review Classification	IND Study Review
Date Consult Received	29 Jan 2007
Date Consult Due	07 May 2007
Clinical Division	DMEP / HFD 510
PDUFA Date	Not Applicable

1 SUMMARY

1.1 BACKGROUND

In this amendment to IND 69707, Takeda Global Research and Development (TGRD) submits reports for two QT studies as well as an expert consultant's (b) (4) interpretation of the two studies. The first study, SYR-322-004, was performed by a previous sponsor during 30 Jun 2005 to 16 Sep 2005. TGRD states that the design of the study was inadequate so undertook a second QT study, SYR-322-019, during 11 Jan 2006 to 10 Mar 2006.

The focus of this review is on pivotal TQT study SYR-322-019. A formal review of the first study, SYR-322-004, was not performed by the QT-IRT.

1.2 OVERALL SUMMARY OF FINDINGS

- In 'thorough QT study' SYR-32-019 the effects of administering two supratherapeutic doses (50 mg and 400 mg) of SYR-322 on the QTc were assessed after a single dose and at steady state after seven days of repeat dosing. The mean steady state Cmax for the dose groups were 301 ng/ml and 2844 ng/ml, respectively, which represent a 2-fold and 19-fold increase in exposure over the highest clinical dose (25 mg).
- At 0.5 h after dosing on day 7, the 400 mg dose of SYR-332 resulted in a lengthening of the QTcI to 7 ms with an upper one-sided 95% confidence bound of 13 ms which is more than the value of 10 ms identified as the threshold of regulatory concern in the ICH E14 guidance (Table 22). In study SYR-32-004, the maximum mean effect of administering 400 mg of SYR-322 on the QTcF occurred at Tmax (1 h post dosing) and was 8 ms (upper one-sided 95% bound of 11 ms).

- SYR-322 undergoes very little metabolism and is predominantly excreted unchanged in the urine (Table 1). Therefore, subjects with impaired renal function are expected to have the highest exposure to SYR-322. In study SYR-3232-006 (renal impairment study), subjects with severe renal impairment had a 27% increase in Cmax and 3.5-fold increase in AUC. Subjects with end-stage-renal disease had an increase of 32% in Cmax and 4.8-fold increase in AUC. Hence, the observed exposures after administration of repeated doses of 400 mg of SYR-322 are far in excess of the expected "worst-case scenario."
- Repeat dosing of the second supratherapeutic dose, 50 mg of SYR-332, did not result in a lengthening of the QTc to greater than 10 ms at any timepoint.
- Therefore, study SYR-322 is reassuring that exposures reasonably likely to occur after a dose of 25 mg of SYR-322 are unlikely to result in a clinically significant effect on the QTc.
- A linear mixed-effects model was used to describe the relationship between SYR-322 concentrations and ΔΔQTcF. The relationship was flat with a population slope of 1.6 ms per 1000 ng/ml SYR-322. This slope is consistent with the slope reported by the sponsor (Figure 1). Based on this relationship, the mean ΔΔQTcF is 5 ms (90% confidence interval of 3 to 6 msec) at a mean Cmax of 2844 ng/ml Table 31. The major difference in the results between the two methods is the C-QTc approach uses all the data collected and is less sensitive to outlying data points.

1.3 Responses to Questions Posed by Review Division

None.

1.4 Reviewer's Comments

1. In SYR-32-019, 400 mg of moxifloxacin was administered daily for seven days. Moxifloxacin should be administered as a single dose for assay sensitivity. Repeat dosing of moxifloxacin is not optimal because plasma concentrations accumulate resulting in larger effects on the QTc than desired for assay sensitivity

2 PROPOSED LABEL

Not applicable.

3 BACKGROUND

3.1 Indication

Treatment for type 2 diabetes mellitus

3.2 Drug Class

Inhibitor of dipeptidyl peptidase IV (DPP-IV)

3.3 Market Approval Status

Not approved for marketing in the USA.

3.4 PRECLINICAL INFORMATION

The sponsor states in the background information:

"The potential cardiac effects of SYR-322 have been investigated in 2 in vitro models, the human ether-à-go-go-related gene (hERG) potassium channel model and the canine Purkinje fiber model. In voltage-clamped Chinese hamster ovary (CHO) and CHO-K1 cells that were stably transfected with the hERG gene, SYR-322, tested at concentrations of 3 and 30 µmol/L, had no inhibitory effect on hERG channel current. In addition, SYR-322 (HCl salt), tested at concentrations of 1, 10, and 30 µmol/L, did not prolong action potential repolarization in isolated canine Purkinje fibers.
The cardiac safety of SYR-322 has also been evaluated in dogs. In free-moving telemetrized beagle dogs, SYR-322, administered as a single oral dose of 7.5, 15, or 25 mg/kg, had no physiologically significant dose- or time-dependent effects on body temperature, heart rate, serum troponin levels, blood pressure (systolic, diastolic, and mean arterial), or ECG readings (PR interval, RR interval, QRS duration, QT interval, and QTc interval). In addition, in the repeat-dose toxicity studies in dogs, SYR-322 had no effects on ECG readings or troponin levels when administered for up to 9 months at dosages of up to 200 mg/kg/day."

3.5 PREVIOUS CLINICAL EXPERIENCE

The sponsor's states in the clinical study report for SYR-322-019:

"SYR-322 has been evaluated in 7 completed clinical studies: a single-dose pharmacokinetic study in healthy male subjects (Study SYR-322-001); a multiple-dose pharmacokinetic study in subjects with type 2 diabetes (Study SYR-322-002); 4 drug-drug interaction studies in healthy subjects (Studies SYR-322-005, SYR-322-015, SYR-322-016, and SYR-322-018) [13-16]; and a phase 2 dose-ranging safety and efficacy study in subjects with type 2 diabetes (Study SYR-322-003). SYR-322 is also being evaluated in ongoing clinical studies, including several additional pharmacokinetic studies; 5 phase 3 safety and efficacy studies in subjects with type 2 diabetes; and an open-label, long-term safety study in subjects with type 2 diabetes. To, date, SYR-322 has been safe and well tolerated in these clinical studies at doses up to 800 mg. Currently, 12.5 mg and 25 mg SYR-322 are being studied in phase 3 clinical trials."

3.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features of SYR-322's clinical pharmacology.

Table 1- Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

<table>
<tr><th></th><th></th><th>Annotation</th></tr>
<tr><td>Therapeutic dose (Anticipated)</td><td colspan="2">12,5 mg and 25 mg QD</td><td>Pending results from phase 3 studies</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">Human:
SYR-322 was well-tolerated at the highest doses tested in the single-rising dose (800 mg) and the multiple-rising dose (400 mg QD for 14 days) clinical studies.</td><td>SYR-322-001
SYR-322-002</td></tr>
<tr><td></td><td colspan="2">NOAEL:
<table><tr><th>Species</th><th>Duration of Dosing</th><th>NOAEL (mg/kg/day)</th><th>AUC(0-24) (ng·hr/mL)</th><th>Cmax (ng/mL)</th></tr><tr><td>Mouse</td><td>13 weeks</td><td>500</td><td>21,733</td><td>95,832</td></tr><tr><td>Rat</td><td>26 weeks</td><td>400</td><td>258,579</td><td>23,683</td></tr><tr><td>Dog</td><td>39 weeks</td><td>200</td><td>400,140</td><td>38,800</td></tr></table></td><td>SYR-322-00046.001A
SYR-322/00088
SYR-322/00089</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">Below are adverse events with suspected causal relationship to administration of SYR-322 that occurred at a frequency greater than or equal to twice that observed after administration of placebo or occurred in at least two SYR-322 treated subjects but no placebo subjects in a multiple dosing study with a placebo arm. Causality of the listed events has not been established. None of these events were reported as serious adverse events.

o abdominal pain,
o blurred vision
o constipation
o dizziness
o dry mouth
o dyspepsia
o headache
o hyperglycemia
o musculoskeletal pain
o nausea
o paresthesia
o pharynx discomfort
o rash (including maculopapular rash)
o somnolence
o upper abdominal pain
o weight decreased</td><td>Investigator Brochure, Edition 5 (Appendix A: List of Expected Adverse Drug Reactions for SYR-322)</td></tr>
<tr><td rowspan="2">Maximum dose tested</td><td>Single dose</td><td>800 mg</td><td>SYR-322-001</td></tr>
<tr><td>Multiple dose</td><td>400 mg QD for 14 days</td><td>SYR-322-002</td></tr>
</table>

Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

<table>
<tr><th></th><th colspan="2"></th><th>Annotation</th></tr>
<tr><td rowspan="2">Exposures achieved at maximum tested dose</td><td>Single dose:
Mean (%CV)</td><td>• Cmax: 6994 (13%) ng/mL
• AUC(0-inf): 49595 (7%) ng·hr/mL</td><td>SYR-322-001</td></tr>
<tr><td>Multiple dose:
Mean (%CV)</td><td>• Cmax: 2560 (31%) ng/mL
• AUC(0-tau): 20675 (28%) ng·hr/mL</td><td>SYR-322-002</td></tr>
<tr><td>Range of linear PK</td><td colspan="2">Linear within range of SYR-322 doses between 25 mg QD and 400 mg QD for 14 days
<table>
<tr><th>Analyte</th><th>Parameter</th><th>Slope</th><th>90% CI</th><th>P value</th></tr>
<tr><td>SYR-322</td><td>ln AUC(0-tau)</td><td>0.9520</td><td>0.91-1.00</td><td>0.094</td></tr>
<tr><td></td><td>ln Cmax</td><td>1.0080</td><td>0.94-1.07</td><td>0.835</td></tr>
</table></td><td>SYR-322-002</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Accumulation of 34% (AUC[0-24]) and 9% (Cmax).
<table>
<tr><th>Parameter</th><th>Treatment (mg)</th><th>Day 1 GM</th><th>Day 14 GM</th><th>Ratio (Day 14/ Day 1)</th><th>90% CI</th></tr>
<tr><td>AUC(0-24)</td><td>25</td><td>1068</td><td>1430</td><td></td><td></td></tr>
<tr><td></td><td>100</td><td>4801</td><td>6428</td><td>1.34</td><td>1.28-1.40</td></tr>
<tr><td></td><td>400</td><td>15095</td><td>20207</td><td></td><td></td></tr>
<tr><td>Cmax</td><td>25</td><td>135.7</td><td>148.2</td><td></td><td></td></tr>
<tr><td></td><td>100</td><td>578.5</td><td>631.8</td><td>1.09</td><td>0.99-1.21</td></tr>
<tr><td></td><td>400</td><td>2219</td><td>2423</td><td></td><td></td></tr>
</table></td><td>SYR-322-002</td></tr>
<tr><td>Metabolites</td><td colspan="2">Metabolite and activity:
<table>
<tr><th>Metabolite</th><th>DPP4 IC_{50}</th></tr>
<tr><td>M-I (SYR110324)</td><td>5 nM</td></tr>
<tr><td>M-II (SYR135457, N-acetyl metabolite)</td><td>> 50,000 nM</td></tr>
<tr><td>S-enantiomer (SYR111475; not measurable in human plasma)</td><td>1045 nM</td></tr>
</table></td><td>SYR-322/00009</td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/Relative Bioavailability</td><td>The fraction of oral dose absorbed can be estimated from the ADME study where 76% of administered radioactivity was recovered in urine, indicating at least 76% of dose was absorbed. SYR-322 does not undergo extensive metabolism and 63% of the dose is excreted as unchanged drug in urine, which also suggests relatively high oral bioavailability.</td><td>SYR-322-ADME-014
SYR-322-001</td></tr>
<tr><td>Tmax:
Median (range)</td><td>After 25 mg QD for 7 days:
• SYR-322: 2.5 (0.5-3.0) hr
• M-I: 2.5 (0.75-8.0) hr
• M-II: 2.5 (1.5-4.1) hr</td><td>SYR-322-017</td></tr>
<tr><td>Distribution</td><td>Vd/F (L):
Mean (%CV)</td><td>431 (21%) L after single 25 mg dose</td><td>SYR-322-001</td></tr>
</table>

			Annotation
	% bound, human: Mean	In vitro: • 24% at 10 µmol/L • 15% at 100 µmol/L	SYR-322/00016
Elimination	Route (% dose eliminated)	Kidney 63% after single 25 mg dose	SYR-322-001
	Terminal t1/2 (hr): Mean (%CV)	After single 25 mg dose: • SYR-322: 21.4 (21%) hr • M-I: 25.0 (48%) hr	SYR-322-001
	CL/F (L/hr): Mean (%CV)	After single 25 mg dose: • 19.0 (12%) L/hr	SYR-322-001
Intrinsic Factors	Age	Not yet available	SYR-322-022 (data being finalized)
	Sex	Not yet available	SYR-322-022 (data being finalized)
	Race	Not yet available	SYR-322-022 (data being finalized)
	Hepatic Impairment	Not yet available	SYR-322-023 (data being finalized)
	Renal Impairment SYR-322 50 mg single dose	Mean changes in SYR-322: **Mild Renal Impairment:** • 69% and 71% increases in AUC(0-tlqc) and AUC(0-inf), respectively (1.69- and 1.71-fold increases) • 13% increase in Cmax **Moderate Renal Impairment** • 108% and 112% increases in AUC(0-tlqc) and AUC(0-inf), respectively (2.08- and 2.12-fold increases) • 42% increase in Cmax **Severe Renal Impairment** • 219% and 251% increases in AUC(0-tlqc) and AUC(0-inf), respectively (3.19- and 3.51-fold increases) • 27% increase in Cmax	SYR-322-006

Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

			Annotation
		End-Stage-Renal Disease (ESRD) • 281% and 377% increases in AUC(0-tlqc) and AUC(0-inf), respectively (3.81-and 4.77-fold increases) • 32% increase in Cmax	
Extrinsic Factors ***Drug interactions***	***Effect of Other Drugs on SYR-322™***	Mean changes in SYR-322:	
	Cimetidine 400 mg QD	• 7% increase in $AUC_{(0\text{-}tau)}$ • 5% increase in Cmax	SYR-322-005
	Metformin 1000 mg QD	• No change in $AUC_{(0\text{-}tau)}$ • 11% decrease in Cmax	SYR-322-005
	Fluconazole 200 mg QD	• 2% decrease in AUC • 20% decrease in Cmax	SYR-322-016
	Ketoconazole 400 mg QD	• 17% increase in AUC • 22% increase in Cmax	SYR-322-016
	Gemfibrozil 600 mg BID	• 15% increase in AUC • 15% decrease in Cmax	SYR-322-016
	Pioglitazone 45 mg QD	• 10% increases in AUC(0-tau) and Cmax	SYR-322-017

Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

			Annotation
Extrinsic Factors *Drug interactions*	*Effect of SYR-322 on Other Drugs**	Mean changes in the following:	
	SYR-322 100 mg QD	**Drug cocktail containing:** **Caffeine (CYP1A2)** • 5% increase in AUC • 2% decrease in Cmax **Tolbutamide (CYP2C9)** • 3% decrease in AUC • <1% decrease in Cmax **Midazolam (CYP3A4)** • 8% increase in AUC • 13% increase in Cmax **Dextromethorphan (CYP2D6)** • 27% increase in AUC • 32% increase in Cmax **Fexofenadine (P-glycoprotein)** • 34% increase in AUC • 17% increase in Cmax	SYR-322-015
	SYR-322 25 mg QD	**Pioglitazone** • 6% increase in AUC(0-tau) • 5% increase in Cmax	SYR-322-017
	SYR-322 25 mg QD	**Glyburide** • <4% decrease in AUC • 15% increase in Cmax	SYR-322-018
Extrinsic factors *Food effect*	High fat meal	Mean changes in SYR-322: • 5% decrease in AUC • 14% decrease in Cmax *Note: Effect of food on the PK of the proposed commercial formulation is pending	SYR-322-005 SYR-322-026 (study currently ongoing)

		Annotation
Expected High Clinical Exposure Scenario	SYR-322 undergoes very little metabolism and is excreted predominantly (>60%) as unchanged drug in urine. Because renal excretion is the primary route of drug elimination, subjects with severe renal impairment (creatinine clearance less than 30 mL/min) and those with ESRD have markedly increased (about 4-fold) systemic exposure (AUC) to SYR-322 compared to age- and gender-matched subjects with normal renal function. The increased AUC of SYR-322 in subjects with renal impairment is due to prolongation in elimination half-life of SYR-322 and, without dosage adjustment, would result in significant drug accumulation with multiple dosing. There are two possible options for dosage adjustment based on renal function; ie, either reduce the dose or increase the dosing interval. It is noteworthy that after a single 50 mg dose of SYR-322, increases in SYR-322 Cmax in subjects with renal impairment were less than 50% (1.5-fold) compared to control subjects. Assuming linear kinetics, the simulated range of plasma concentrations of SYR-322 for one dose interval after 50 mg QD doses for 7 days (a 2-fold higher than anticipated maximum dose) in subjects with severe renal impairment are between approximately 370 and 620 ng/mL. Using noncompartmental methods, estimated values for pseudo steady-state Cmax and AUC(0-tau) of SYR-322 based on these simulated concentrations are 613 ng/mL and 12231 ng·hr/mL, respectively. The simulated concentration time-curve at steady state shows that there is less than 10% possible additional increase in Cmax or AUC beyond 7 days. For comparison, the mean (min-max) values SYR-322 Cmax and AUC(0-24) after dosing 400 mg QD for 7 days (supratherapeutic dose in QTc study SYR-322-019) were 2844 (1700-5260) ng/mL and 23646 (12786-34162) ng·hr/mL, respectively.	SYR-322-006 SYR-322-019

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted two QT studies for review:

- "Study SYR-322-004, entitled: "A Evaluator-Blinded, Active- and Placebo-Controlled, Multiple-Dose, Crossover Study to Assess the Effects of SYR110322 on the QTc Interval in Healthy Subjects"

  Study Dates: 30 June 2005 to 16 September 2005

- "Study SYR-322-019, entitled: "A Single-Blind, Randomized, Parallel Trial to Define the ECG Effects of SYR-322 Using a Clinical and Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women"

Study Dates: 20 December 2005 to 30 March 2006

The sponsor states,

"An early review of the unblinded data from study SYR-322-004 revealed several limitations in the study design that TGRD believed would significantly confound interpretation of the QT/QTc data; the most critical were the manner in which the continuous digital ECG were collected and analyzed, and the selected Baseline value for the digital ECG analysis. Therefore, to adequately assess the effects of SYR-322 on cardiac repolarization, a new protocol, SYR-322-019, submitted on January 9, 2006 (S/N: 045), was initiated and designed in accordance with FDA Guidance of Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrythmic Potential for Non Antiarrhythmic Drugs (October 2005)."

4.2 QT STUDY

4.2.1 Title

An Evaluator-Blinded, Active- and Placebo-Controlled, Multiple-Dose, Crossover Study to Assess the Effects of SYR110322 on the QTc Interval in Healthy Subjects

4.2.2 Protocol Number

SYR-322-004

4.2.3 Sponsor Analysis

"On Day 6, after administration of SYR-322 100 or 400 mg for 6 days, the upper bound of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcF interval was <10 msec at all time points except at 1 hour postdose for the 400 mg dose; the upper bound was 11.32 msec at this time point. After administration of moxifloxacin 400 mg QD for 6 days, this upper bound was >10 msec at all time points except at 24 hours postdose, ranging from 12.99 to 23.80 msec across the 0.5 to 12 hours postdose time points."

The sponsor's consultant, [redacted] (b) (4) states:
"The assay sensitivity results using moxifloxacin showed placebo corrected results larger than expected in that during the hours 2-6 moxifloxacin mean changes were 13-20 ms vs. the expected around 10 ms change (upper confidence intervals were close the mid 20s vs. expected mid-teens). This suggests that the SYR-322 changes may have been also larger than what might otherwise be observed in a better powered, time matched, double delta analysis."

4.2.4 Study Limitations

The study limitations of the sponsor's first TQT study, SYR-322-004, as described by [redacted] (b) (4) are:

- The 7-day washout between treatment periods was not sufficient. Some subjects had measurable SYR-322 concentrations at the pre-dose time point (Sponsor's Table 15.2.5.1, page 290 of 4586 in SYR-322-004 report).
- The lack of time-matched baseline ECGs

Reviewer's comment: A full time-matched baseline period may not be necessary in TQT studies using a crossover design.

- The use of the Fridericia method for correcting QT (QTcF) interval for heart rate instead of individual heart rate-corrected QTc (QTcI).

Reviewer's comment: The heart-rate correction method rarely changes study outcome. Unless the drug has a significant effect on heart rate, QTcF is adequate.

- The lack of blinding.

Reviewer's comment: Blinding TQT studies may help to minimize bias in ECG interpretation.

Although not noted by [redacted] (b) (4), we view the administration of multiple doses of moxifloxacin in SYR-322-004 as an additional limitation.

4.3 TQT STUDY

4.3.1 Title

A Single-Blind, Randomized, Parallel Trial to Define the ECG Effects of SYR-322 Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women

4.3.2 Protocol Number

SYR-322-019

4.3.3 Objectives

Primary:
Evaluate the time-matched change from baseline in QT interval corrected for heart rate (QTc) between treatment group means based on an individual correction (QTcI) method that provides an optimization of QT correction for heart rate as compared to fixed exponent approaches, such as Bazett or Fridericia.

Secondary:
The secondary objectives of this study included evaluation of the following: QTc with Fridericia correction method and the QTc with Bazett correction method (provided for historic reasons only), heart rate, PR interval, QRS interval, uncorrected QT interval, change in electrocardiogram (ECG) morphological patterns, and correlation between the QTcI change from Baseline and plasma concentrations of the parent and metabolites.

4.3.4 Design

4.3.4.1 Description

This was a single-blind, randomized, placebo- and positive-controlled, 4-arm, parallel-group, single-center study comparing 2 dose levels of SYR-322, moxifloxacin (positive control), and placebo (matching SYR-322).

4.3.4.2 Sponsor's Justification for Design

"To reduce the potential for bias during data collection, subjects were not informed of their treatment assignment. In addition, the central ECG reader, who read and evaluated the continuous digital 12-lead ECG recording data, was kept blinded to subject treatment assignment to reduce potential bias during evaluation of the ECG data. Randomization was used to reduce the potential for selection bias. To avoid the potential for carry-over effect of treatment, a parallel group design was employed for this study rather than a crossover design. As moxifloxacin has been shown to prolong QT interval, this drug was selected as a positive control to assess the sensitivity of the study methods."

4.3.4.3 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.3.4.4 Blinding

This was a single-blind study; subjects were not informed of their treatment assignment. However, the SYR-322 and placebo tablets were identical in appearance, but the commercial moxifloxacin tablets looked different. Therefore, subjects who received moxifloxacin may have been aware of their treatment assignment. The cardiologists at (b) (4) were blinded to all treatment assignments during the ECG analyses.

The blind was broken for Subject 1093, who became pregnant during this study.

4.3.5 Study Subjects

To be eligible to enroll, subjects must have

- Been healthy and age 18 to 45 years
- Weighed at least 50 kg (110 lb) and a body mass index between 18 to 32 kg/m^2
- Had a normal screening electrocardiogram without second- or third-degree atrioventricular block, QRS interval >110 msec, QTc >470 msec, or PR interval >240 msec, or any rhythm other than sinus rhythm that was interpreted by the investigator to be clinically significant.
- Not been pregnant or lactating.

4.3.6 Dosing Regimens

4.3.6.1 Treatment Arms

Subjects were randomly assigned to 1 of the following 4 treatment groups:

- Group A: SYR-322 50 mg once daily (QD)
- Group B: SYR-322 400 mg QD
- Group C: Moxifloxacin 400 mg QD
- Group D: Placebo QD

Subjects were dosed once-daily on the morning of Days 1 through 7.

4.3.6.2 Sponsor's Justification for Doses

"The 50 and 400 mg doses of SYR-322 selected for this study are 2- and 16-fold, respectively, higher than the anticipated maximum therapeutic dose of 25 mg. The supratherapeutic dose of 400 mg was selected in order to evaluate any potential QT interval effects associated with an increased exposure of SYR-322 that may result from drug-drug interactions. Both the 50 and 400 mg doses fall within an acceptable margin of safety based on the available nonclinical and clinical data for SYR-322."

4.3.6.3 Instructions with regard to meals

SYR-322, matching placebo, and moxifloxacin were administered each morning on Days 1 through 7 of the study.

Doses on Days 1 and 7 were administered after a fast of at least 10 hours (included no coffee or orange juice). Subjects continued to fast for an additional 4 hours postdose.

4.3.6.4 Study Assessments

Table 2: Highlights of Schedule of Interventions

Study Day	-1	1	7
Intervention	No treatment	Single dose	Steady State
12-Lead ECGs	Record ECGs# (Baseline)	Record ECGs#	Record ECGs#
PK Samples for drug	None collected	Collected#	Collected#

#Before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing
PK Sampling: additional samples were collected before dosing on days 5 and 6.

4.3.6.5 Sponsor's justification for sampling schedule

No justification was provided.

4.3.6.6 Baseline

The sponsor stated, "ECGs were obtained using a Mortara Instrument H-12 ECG continuous 12-lead digital recorder on Day -1 (Baseline) and on Days 1 and 7 (page 5, 2.0 SYNOPSIS, IND 69707 097 vol 003 of 005.pdf)." Consistent with the sponsor's data, the baseline is the Day -1 time-matched ECG measurements.

4.3.7 ECG Collection

Continuous digital 12-lead ECG data were collected on Days 1 and 7 beginning before dosing and continuing through 23.5 hours after dosing using H- 12 Mortara Instrument. The data from Days 1 and 7 were analyzed at the following time points: approximately 0.5 hours before dosing (0 hour), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing. Subjects were to refrain from talking and were required to be in a supine position for approximately 5 minutes before each digital 12-lead ECG analysis time point.

Three ECGs within one minute were extracted at the central ECG laboratory at each ECG analysis time point and the mean of the 3 replicate ECG measures for each quantitative

ECG variable were calculated. All calculated mean values were rounded up to the next whole number.

The central ECG reader, who read and evaluated the continuous digital 12-lead ECG recording data, was kept blinded to subject treatment assignment to reduce potential bias during evaluation of the ECG data.

4.3.8 Sponsor's Results

4.3.8.1 Statistical Analyses

4.3.8.1.1 Primary Analysis

The sponsor focuses on the QT interval data corrected for heart rate using the individual and Fridericia correction methods (QTcI and QTcF, respectively). The QT interval data corrected for heart rate using the Bazett and Framingham correction methods (QTcB and QTcL, respectively) and the uncorrected QT interval data are not presented [in the main text] (page 58, 11.2 ECG Analyses Results, IND 69707 097 vol 003 of 005.pdf).

The sponsor's findings of the time-matched mean change from (Day -1) baseline in QTcI on Days 1 and 7 are shown in the following tables.

Table 3: Summary of Sponsor's Findings

QTc	Day	SYR-322 50	SYR-322 400
QTcF	Day 1	Upper CIs <10 msec: all time points	Upper CIs <10 msec: all time points
	Day 7	Upper CIs <10 msec: all time points	Upper CIs <10 msec: all time points
QTcI	Day 1	Upper CIs <10 msec: all time points	Upper CIs <10 msec: all time points
	Day 7	Upper CIs <10 msec: all time points	Upper CIs >10 msec: 10.24 at 30 minutes, 10.70 at 1 hour

The findings, above, will be compared with the reviewer's independent statistical analyses.

4.3.8.1.1.1 Sponsor's QT analyses based on QTcI

Table 4: Sponsor's Table 11.a Analysis of Time-Matched LS Mean Change From Baseline in QTcI Interval (msec) on Day 1—Time-Matched Baseline

Time Point	Treatment	LS Mean	Difference from Placebo (a)	
			LS Mean (SE)	90% CI
0.5 hour postdose	SYR-322 50 mg	-0.02	4.09 (2.40)	(0.13, 8.05)
	SYR-322 400 mg	0.18	4.28 (2.39)	(0.33, 8.23)
	Moxifloxacin 400 mg	7.30	11.40 (2.40)	(7.45, 15.36)
	Placebo	-4.11	---	---
1 hour postdose	SYR-322 50 mg	0.01	2.73 (2.33)	(-1.12, 6.58)
	SYR-322 400 mg	1.52	4.24 (2.33)	(0.40, 8.08)
	Moxifloxacin 400 mg	9.94	12.66 (2.33)	(8.81, 16.51)
	Placebo	-2.72	---	---
2 hours postdose	SYR-322 50 mg	1.86	2.23 (2.30)	(-1.57, 6.04)
	SYR-322 400 mg	3.74	4.11 (2.30)	(0.32, 7.90)
	Moxifloxacin 400 mg	12.65	13.03 (2.31)	(9.21, 16.84)
	Placebo	-0.37	---	---
3 hours postdose	SYR-322 50 mg	4.47	3.59 (2.41)	(-0.40, 7.57)
	SYR-322 400 mg	4.53	3.64 (2.41)	(-0.33, 7.62)
	Moxifloxacin 400 mg	15.06	14.18 (2.42)	(10.18, 18.17)
	Placebo	0.88	---	---
4 hours postdose	SYR-322 50 mg	5.22	3.41 (2.36)	(-0.49, 7.31)
	SYR-322 400 mg	4.82	3.00 (2.35)	(-0.88, 6.89)
	Moxifloxacin 400 mg	16.48	14.67 (2.36)	(10.77, 18.57)
	Placebo	1.81	---	---
5 hours postdose	SYR-322 50 mg	4.46	1.77 (2.40)	(-2.20, 5.74)
	SYR-322 400 mg	6.36	3.66 (2.40)	(-0.30, 7.63)
	Moxifloxacin 400 mg	14.65	11.96 (2.41)	(7.97, 15.94)
	Placebo	2.69	---	---
6 hours postdose	SYR-322 50 mg	-0.27	2.06 (2.36)	(-1.83, 5.95)
	SYR-322 400 mg	2.21	4.54 (2.35)	(0.66, 8.43)
	Moxifloxacin 400 mg	8.31	10.64 (2.37)	(6.73, 14.55)
	Placebo	-2.33	---	---
8 hours postdose	SYR-322 50 mg	-1.25	1.26 (2.40)	(-2.70, 5.21)
	SYR-322 400 mg	0.48	2.99 (2.39)	(-0.96, 6.94)
	Moxifloxacin 400 mg	5.21	7.71 (2.40)	(3.75, 11.68)
	Placebo	-2.51	---	---
10 hours postdose	SYR-322 50 mg	-3.04	-0.10 (2.49)	(-4.21, 4.02)
	SYR-322 400 mg	-1.06	1.88 (2.48)	(-2.22, 5.98)
	Moxifloxacin 400 mg	7.99	10.93 (2.51)	(6.79, 15.06)
	Placebo	-2.94	---	---
12 hours postdose	SYR-322 50 mg	0.39	1.57 (2.45)	(-2.48, 5.62)
	SYR-322 400 mg	0.39	1.57 (2.45)	(-2.47, 5.62)
	Moxifloxacin 400 mg	9.00	10.18 (2.46)	(6.12, 14.25)
	Placebo	-1.18	---	---

14 hours postdose	SYR-322 50 mg	1.63	3.61 (2.47)	(-0.47, 7.68)
	SYR-322 400 mg	-0.33	1.65 (2.46)	(-2.41, 5.71)
	Moxifloxacin 400 mg	6.67	8.66 (2.47)	(4.58, 12.74)
	Placebo	-1.98	---	---
16 hours postdose	SYR-322 50 mg	2.56	0.23 (2.70)	(-4.23, 4.68)
	SYR-322 400 mg	3.26	0.93 (2.68)	(-3.51, 5.36)
	Moxifloxacin 400 mg	10.08	7.74 (2.70)	(3.28, 12.19)
	Placebo	2.34	---	---
18 hours postdose	SYR-322 50 mg	7.59	1.22 (2.65)	(-3.15, 5.58)
	SYR-322 400 mg	8.58	2.21 (2.63)	(-2.14, 6.56)
	Moxifloxacin 400 mg	14.31	7.94 (2.65)	(3.57, 12.31)
	Placebo	6.37	---	---
23.5 hours postdose	SYR-322 50 mg	0.55	0.57 (2.31)	(-3.25, 4.39)
	SYR-322 400 mg	2.71	2.73 (2.30)	(-1.07, 6.53)
	Moxifloxacin 400 mg	7.52	7.54 (2.32)	(3.71, 11.37)
	Placebo	-0.02	---	---

On Day 1, after administration of a single dose of SYR-322 50 or 400 mg, the upper bound of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcI interval was <10 msec at all time points (pages 60-61, 11.2.1.1 Time-Matched Mean Change from Baseline in QTcI Interval on Days 1 and 7—Time-Matched Baseline, IND 69707 097 vol 003 of 005.pdf).

On Day 1, after administration of a single dose of moxifloxacin 400 mg, most of the lower bounds of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcI interval were >5 msec .

Table 5: Sponsor's Table 11.b Analysis of Time-Matched LS Mean Change From Baseline in QTcI Interval (msec) on Day 7—Time-Matched Baseline

Time Point	Treatment	LS Mean	Difference from Placebo (a)	
			LS Mean (SE)	90% CI
0.5 hour postdose	SYR-322 50 mg	-2.60	2.68 (2.67)	(-1.73, 7.10)
	SYR-322 400 mg	0.56	5.84 (2.66)	(1.44, 10.24)
	Moxifloxacin 400 mg	12.41	17.69 (2.70)	(13.24, 22.14)
	Placebo	-5.28	---	---
1 hour postdose	SYR-322 50 mg	-0.42	3.52 (2.49)	(-0.58, 7.63)
	SYR-322 400 mg	2.66	6.60 (2.48)	(2.50, 10.70)
	Moxifloxacin 400 mg	14.93	18.87 (2.51)	(14.73, 23.02)
	Placebo	-3.94	---	---
2 hours postdose	SYR-322 50 mg	3.51	4.47 (2.53)	(0.30, 8.65)
	SYR-322 400 mg	3.99	4.95 (2.52)	(0.79, 9.11)
	Moxifloxacin 400 mg	17.78	18.74 (2.55)	(14.53, 22.96)
	Placebo	-0.96	---	---
3 hours postdose	SYR-322 50 mg	3.81	1.60 (2.50)	(-2.53, 5.73)
	SYR-322 400 mg	5.73	3.52 (2.49)	(-0.60, 7.63)
	Moxifloxacin 400 mg	17.74	15.53 (2.53)	(11.36, 19.69)
	Placebo	2.21	---	---
4 hours postdose	SYR-322 50 mg	4.69	2.55 (2.59)	(-1.72, 6.83)
	SYR-322 400 mg	5.61	3.47 (2.58)	(-0.79, 7.74)
	Moxifloxacin 400 mg	18.17	16.04 (2.62)	(11.71, 20.36)
	Placebo	2.14	---	---
5 hours postdose	SYR-322 50 mg	4.75	1.84 (2.65)	(-2.55, 6.22)
	SYR-322 400 mg	5.96	3.05 (2.65)	(-1.32, 7.43)
	Moxifloxacin 400 mg	18.73	15.82 (2.68)	(11.39, 20.24)
	Placebo	2.91	---	---
6 hours postdose	SYR-322 50 mg	-0.25	0.46 (2.63)	(-3.88, 4.80)
	SYR-322 400 mg	1.21	1.93 (2.62)	(-2.40, 6.25)
	Moxifloxacin 400 mg	12.06	12.77 (2.65)	(8.39, 17.15)
	Placebo	-0.71	---	---
8 hours postdose	SYR-322 50 mg	0.29	2.63 (2.65)	(-1.75, 7.00)
	SYR-322 400 mg	1.98	4.32 (2.63)	(-0.03, 8.67)
	Moxifloxacin 400 mg	9.46	11.80 (2.67)	(7.40, 16.20)
	Placebo	-2.34	---	---
10 hours postdose	SYR-322 50 mg	1.46	1.00 (2.57)	(-3.24, 5.25)
	SYR-322 400 mg	3.44	2.98 (2.56)	(-1.25, 7.20)
	Moxifloxacin 400 mg	11.54	11.08 (2.60)	(6.80, 15.37)
	Placebo	0.46	---	---
12 hours postdose	SYR-322 50 mg	-1.58	-0.14 (2.52)	(-4.30, 4.03)
	SYR-322 400 mg	-0.66	0.79 (2.51)	(-3.36, 4.93)
	Moxifloxacin 400 mg	9.43	10.88 (2.54)	(6.68, 15.08)
	Placebo	-1.45	---	---

14 hours postdose	SYR-322 50 mg	-3.66	0.12 (2.47)	(-3.95, 4.19)
	SYR-322 400 mg	-1.62	2.16 (2.46)	(-1.89, 6.22)
	Moxifloxacin 400 mg	5.52	9.30 (2.49)	(5.19, 13.40)
	Placebo	-3.78	---	---
16 hours postdose	SYR-322 50 mg	1.44	0.31 (2.68)	(-4.12, 4.73)
	SYR-322 400 mg	3.76	2.63 (2.67)	(-1.77, 7.04)
	Moxifloxacin 400 mg	11.63	10.50 (2.70)	(6.04, 14.96)
	Placebo	1.13	---	---
18 hours postdose	SYR-322 50 mg	7.23	-0.48 (2.67)	(-4.88, 3.92)
	SYR-322 400 mg	8.14	0.43 (2.65)	(-3.94, 4.81)
	Moxifloxacin 400 mg	15.95	8.24 (2.69)	(3.81, 12.68)
	Placebo	7.71	---	---
23.5 hours postdose	SYR-322 50 mg	-3.33	1.64 (2.54)	(-2.55, 5.83)
	SYR-322 400 mg	-2.78	2.19 (2.53)	(-1.99, 6.36)
	Moxifloxacin 400 mg	3.02	7.98 (2.57)	(3.74, 12.22)
	Placebo	-4.96	---	---

On Day 7, after administration of SYR-322 50 or 400 mg QD for 7 days, the upper bound of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcI interval was <10 msec at all time points except at 0.5 hours and 1 hour postdose for the 400 mg dose. The difference from placebo at these time points for SYR-322 400 mg were 5.84 msec (90% CI, 1.44-10.24 msec) and 6.60 msec (90% CI, 2.50-10.70 msec), respectively (pages 62-63, 11.2.1.1 Time-Matched Mean Change from Baseline in QTcI Interval on Days 1 and 7 Time-Matched Baseline, IND 69707 097 vol 003 of 005.pdf).

On Day 7, after administration of moxifloxacin 400 mg QD for 7 days, most of the lower bounds of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcI interval were >5 msec.

4.3.8.1.1.2 Sponsor's QT analyses based on QTcF

Table 6: Sponsor's Table 11.c Analysis of Time-Matched LS Mean Change From Baseline in QTcF Interval (msec) on Day 1—Time-Matched Baseline

Time Point	Treatment	LS Mean	Difference from Placebo (a)	
			LS Mean (SE)	90% CI
0.5 hour postdose	SYR-322 50 mg	0.11	4.44 (2.31)	(0.63, 8.25)
	SYR-322 400 mg	−0.36	3.97 (2.30)	(0.17, 7.77)
	Moxifloxacin 400 mg	6.75	11.08 (2.31)	(7.27, 14.89)
	Placebo	−4.33	---	---
1 hour postdose	SYR-322 50 mg	0.07	3.13 (2.25)	(−0.59, 6.84)
	SYR-322 400 mg	1.21	4.26 (2.24)	(0.55, 7.96)
	Moxifloxacin 400 mg	9.57	12.63 (2.25)	(8.92, 16.34)
	Placebo	−3.05	---	---
2 hours postdose	SYR-322 50 mg	1.50	1.98 (2.29)	(−1.80, 5.77)
	SYR-322 400 mg	3.35	3.83 (2.28)	(0.06, 7.60)
	Moxifloxacin 400 mg	12.03	12.51 (2.30)	(8.72, 16.30)
	Placebo	−0.48	---	---
3 hours postdose	SYR-322 50 mg	4.15	3.72 (2.38)	(−0.22, 7.65)
	SYR-322 400 mg	3.57	3.14 (2.38)	(−0.79, 7.06)
	Moxifloxacin 400 mg	14.67	14.24 (2.39)	(10.29, 18.18)
	Placebo	0.43	---	---
4 hours postdose	SYR-322 50 mg	4.75	3.12 (2.34)	(−0.74, 6.98)
	SYR-322 400 mg	3.64	2.01 (2.33)	(−1.83, 5.85)
	Moxifloxacin 400 mg	16.10	14.48 (2.34)	(10.62, 18.34)
	Placebo	1.63	---	---
5 hours postdose	SYR-322 50 mg	4.42	1.68 (2.32)	(-2.16, 5.51)
	SYR-322 400 mg	5.38	2.64 (2.32)	(-1.19, 6.46)
	Moxifloxacin 400 mg	14.13	11.39 (2.33)	(7.54, 15.23)
	Placebo	2.75	---	---
6 hours postdose	SYR-322 50 mg	1.26	2.95 (2.17)	(−0.63, 6.53)
	SYR-322 400 mg	2.18	3.88 (2.17)	(0.30, 7.45)
	Moxifloxacin 400 mg	8.29	9.99 (2.18)	(6.39, 13.59)
	Placebo	−1.69	---	---
8 hours postdose	SYR-322 50 mg	0.27	2.11 (2.12)	(−1.39, 5.61)
	SYR-322 400 mg	0.81	2.65 (2.11)	(−0.84, 6.14)
	Moxifloxacin 400 mg	5.12	6.96 (2.12)	(3.45, 10.46)
	Placebo	−1.83	---	---
10 hours postdose	SYR-322 50 mg	-1.99	0.59 (2.24)	(-3.11, 4.28)
	SYR-322 400 mg	-1.23	1.34 (2.23)	(-2.34, 5.02)
	Moxifloxacin 400 mg	7.45	10.02 (2.25)	(6.30, 13.74)
	Placebo	-2.57	---	---
12 hours postdose	SYR-322 50 mg	1.44	1.78 (2.12)	(−1.73, 5.28)
	SYR-322 400 mg	0.35	0.69 (2.12)	(−2.81, 4.19)
	Moxifloxacin 400 mg	8.72	9.06 (2.13)	(5.53, 12.58)
	Placebo	−0.34	---	---

14 hours postdose	SYR-322 50 mg	2.59	4.07 (2.21)	(0.41, 7.72)
	SYR-322 400 mg	-0.16	1.32 (2.20)	(-2.32, 4.96)
	Moxifloxacin 400 mg	6.33	7.81 (2.21)	(4.15, 11.46)
	Placebo	-1.48	---	---
16 hours postdose	SYR-322 50 mg	3.16	0.35 (2.53)	(-3.83, 4.54)
	SYR-322 400 mg	2.95	0.14 (2.52)	(-4.03, 4.30)
	Moxifloxacin 400 mg	9.88	7.07 (2.54)	(2.88, 11.25)
	Placebo	2.81	---	---
18 hours postdose	SYR-322 50 mg	7.60	1.22 (2.49)	(-2.89, 5.34)
	SYR-322 400 mg	8.31	1.94 (2.48)	(-2.16, 6.03)
	Moxifloxacin 400 mg	13.72	7.34 (2.49)	(3.23, 11.46)
	Placebo	6.37	---	---
23.5 hours postdose	SYR-322 50 mg	0.56	0.41 (2.21)	(-3.24, 4.06)
	SYR-322 400 mg	2.30	2.15 (2.20)	(-1.49, 5.79)
	Moxifloxacin 400 mg	6.99	6.84 (2.22)	(3.17, 10.51)
	Placebo	0.15	---	---

On Day 1, after administration of a single dose of SYR-322 50 or 400 mg, the upper bound of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcF interval was <10 msec at all time points (90% CI, 1.44-10.24 msec) and 6.60 msec (90% CI, 2.50-10.70 msec), respectively (pages 64-65, 11.2.1.2 Time-Matched Mean Change from Baseline in QTcF Interval on Days 1 and 7 Time-Matched Baseline, IND 69707 097 vol 003 of 005.pdf).

On Day 1, after administration of a single dose of moxifloxacin 400 mg, most of the lower bounds of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcF interval were >5 msec.

Table 7: Sponsor's Table 11.d Analysis of Time-Matched LS Mean Change from Baseline in QTcF Interval (msec) on Day 7 Time-Matched Baseline

Time Point	Treatment	LS Mean	Difference from Placebo (a)	
			LS Mean (SE)	90% CI
0.5 hour postdose	SYR-322 50 mg	−2.22	3.51 (2.54)	(−0.68, 7.70)
	SYR-322 400 mg	−0.30	5.43 (2.53)	(1.25, 9.61)
	Moxifloxacin 400 mg	11.50	17.23 (2.56)	(13.01, 21.46)
	Placebo	−5.73	---	---
1 hour postdose	SYR-322 50 mg	−0.39	3.58 (2.39)	(−0.36, 7.53)
	SYR-322 400 mg	1.79	5.77 (2.39)	(1.83, 9.71)
	Moxifloxacin 400 mg	13.82	17.79 (2.41)	(13.81, 21.78)
	Placebo	−3.98	---	---
2 hours postdose	SYR-322 50 mg	2.92	4.47 (2.44)	(0.44, 8.49)
	SYR-322 400 mg	2.75	4.29 (2.43)	(0.28, 8.31)
	Moxifloxacin 400 mg	16.35	17.90 (2.46)	(13.83, 21.96)
	Placebo	−1.55	---	---
3 hours postdose	SYR-322 50 mg	3.51	1.74 (2.44)	(−2.30, 5.78)
	SYR-322 400 mg	4.43	2.65 (2.43)	(−1.37, 6.67)
	Moxifloxacin 400 mg	16.75	14.98 (2.47)	(10.91, 19.05)
	Placebo	1.77	---	---
4 hours postdose	SYR-322 50 mg	4.29	2.43 (2.51)	(−1.72, 6.58)
	SYR-322 400 mg	4.73	2.87 (2.50)	(−1.26, 7.01)
	Moxifloxacin 400 mg	17.15	15.29 (2.54)	(11.10, 19.48)
	Placebo	1.86	---	---
5 hours postdose	SYR-322 50 mg	4.56	2.14 (2.62)	(-2.18, 6.46)
	SYR-322 400 mg	5.07	2.65 (2.61)	(-1.66, 6.96)
	Moxifloxacin 400 mg	17.41	14.99 (2.64)	(10.63, 19.34)
	Placebo	2.42	---	---
6 hours postdose	SYR-322 50 mg	0.76	0.88 (2.34)	(−2.99, 4.75)
	SYR-322 400 mg	0.94	1.07 (2.34)	(−2.79, 4.92)
	Moxifloxacin 400 mg	11.03	11.15 (2.37)	(7.25, 15.06)
	Placebo	−0.12	---	---

8 hours postdose	SYR-322 50 mg	1.70	3.22 (2.44)	(–0.80, 7.25)
	SYR-322 400 mg	1.74	3.26 (2.42)	(–0.73, 7.26)
	Moxifloxacin 400 mg	8.83	10.35 (2.45)	(6.51, 14.40)
	Placebo	–1.53	---	---
10 hours postdose	SYR-322 50 mg	2.38	1.28 (2.44)	(-2.74, 5.31)
	SYR-322 400 mg	2.77	1.67 (2.43)	(-2.33, 5.68)
	Moxifloxacin 400 mg	10.40	9.30 (2.46)	(5.24, 13.36)
	Placebo	1.10	---	---
12 hours postdose	SYR-322 50 mg	–0.19	–0.21 (2.18)	(–3.39, 3.81)
	SYR-322 400 mg	–0.60	–0.20 (2.17)	(–3.78, 3.38)
	Moxifloxacin 400 mg	8.62	9.01 (2.20)	(5.38, 12.64)
	Placebo	–0.40	---	---
14 hours postdose	SYR-322 50 mg	-2.41	0.92 (2.24)	(-2.77, 4.61)
	SYR-322 400 mg	-1.39	1.94 (2.23)	(-1.74, 5.61)
	Moxifloxacin 400 mg	4.69	8.03 (2.25)	(4.31, 11.74)
	Placebo	-3.33	---	---
16 hours postdose	SYR-322 50 mg	1.99	0.45 (2.46)	(-3.61, 4.51)
	SYR-322 400 mg	3.35	1.80 (2.45)	(-2.24, 5.84)
	Moxifloxacin 400 mg	10.52	8.97 (2.48)	(4.88, 13.06)
	Placebo	1.55	---	---
18 hours postdose	SYR-322 50 mg	7.66	-0.14 (2.50)	(-4.27, 3.98)
	SYR-322 400 mg	8.27	0.46 (2.49)	(-3.64, 4.57)
	Moxifloxacin 400 mg	15.19	7.38 (2.52)	(3.23, 11.54)
	Placebo	7.81	---	---
23.5 hours postdose	SYR-322 50 mg	–2.44	1.35 (2.31)	(–2.47, 5.17)
	SYR-322 400 mg	–3.26	0.53 (2.30)	(–3.27, 4.34)
	Moxifloxacin 400 mg	2.63	6.42 (2.34)	(2.55, 10.29)
	Placebo	–3.80	---	---

On Day 7, after administration of SYR-322 50 or 400 mg QD for 7 days, the upper bound of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcF interval was <10 msec at all time points (pages 66-67, 11.2.1.2 Time-Matched Mean Change from Baseline in QTcF Interval on Days 1 and 7 Time-Matched Baseline, IND 69707 097 vol 003 of 005.pdf).

On Day 7, after administration of moxifloxacin 400 mg QD for 7 days, most of the the lower bounds of the 2-sided 90% CI around the difference from placebo in LS mean change from Baseline in QTcF interval were >5 msec.

4.3.8.1.2 Categorical Analysis

4.3.8.1.2.1 Categorical analysis of the maximum QTcF interval for Days 1 and 7

Table 8: Sponsor's Table 11.g Categorical Analysis of Maximum QTcF Interval for Days 1 and 7 - Time-Matched Baseline

Study Day Category	No. Subjects (%)			
	SYR-322 50 mg	SYR-322 400 mg	Moxifloxacin 400 mg	Placebo
Day 1				
Total (a)	N=63	N=64	N=65	N=64
Maximum Value				
≤450	63 (100.0)	63 (98.4)	61 (93.8)	62 (96.9)
>450 and ≤480 msec	0	1 (1.6)	2 (3.1)	2 (3.1)
>480 and ≤500 msec	0	0	2 (3.1)	0
>500 msec	0	0	0	0
P-value (b)	0.496	>0.999	0.680	---
Maximum Increase from Baseline				
<30	58 (92.1)	58 (90.6)	50 (76.9)	62 (96.9)
≥30 and <60 msec	5 (7.9)	6 (9.4)	15 (23.1)	2 (3.1)
≥60 msec	0	0	0	0
P-value (c)	0.273	0.273	0.001	---
Day 7				
Total (a)	N=63	N=64	N=62	N=63
Maximum Value				
≤450	61 (96.8)	63 (98.4)	58 (93.5)	62 (98.4)
>450 and ≤480 msec	2 (3.2)	1 (1.6)	4 (6.5)	1 (1.6)
>480 and ≤500 msec	0	0	0	0
>500 msec	0	0	0	0
P-value (b)	>0.999	>0.999	0.207	---
Maximum Increase from Baseline				
<30	57 (90.5)	54 (84.4)	40 (64.5)	55 (87.3)
≥30 and <60 msec	6 (9.5)	10 (15.6)	22 (35.5)	8 (12.7)
≥60 msec	0	0	0	0
P-value (c)	0.778	0.800	0.003	---

4.3.8.1.2.2 Categorical analysis of the maximum QTcI interval for Days 1 and 7

Table 9: Sponsor's Table 11.f Categorical Analysis of Maximum QTcI Interval for Days 1 and 7 - Time-Matched Baseline

Study Day Category	No. Subjects (%)			
	SYR-322 50 mg	SYR-322 400 mg	Moxifloxacin 400 mg	Placebo
Day 1				
Total (a)	N=63	N=64	N=65	N=64
Maximum Value				
≤450	62 (98.4)	63 (98.4)	61 (93.8)	61 (95.3)
>450 and ≤480 msec	1 (1.6)	1 (1.6)	2 (3.1)	3 (4.7)
>480 and ≤500 msec	0	0	2 (3.1)	0
>500 msec	0	0	0	0
P-value (b)	0.619	0.619	>0.999	---
Maximum Increase from Baseline				
<30	60 (95.2)	55 (85.9)	46 (70.8)	62 (96.9)
≥30 and <60 msec	3 (4.8)	9 (14.1)	19 (29.2)	2 (3.1)
≥60 msec	0	0	0	0
P-value (c)	0.680	0.054	<0.001	---
Day 7				
Total (a)	N=63	N=64	N=62	N=63
Maximum Value				
≤450	62 (98.4)	63 (98.4)	58 (93.5)	62 (98.4)
>450 and ≤480 msec	1 (1.6)	1 (1.6)	4 (6.5)	1 (1.6)
>480 and ≤500 msec	0	0	0	0
>500 msec	0	0	0	0
P-value (b)	>0.999	>0.999	0.207	---
Maximum Increase from Baseline				
<30	55 (87.3)	52 (81.3)	36 (58.1)	57 (90.5)
≥30 and <60 msec	8 (12.7)	12 (18.8)	26 (41.9)	6 (9.5)
≥60 msec	0	0	0	0
P-value (c)	0.778	0.203	<0.001	---

4.3.8.1.3 Additional Analyses

(N/A)

4.3.8.2 Safety Analysis

No deaths, SAEs, seizures, or episodes of ventricular tachycardia are reported. Three subjects, all in the 400 mg SYR-322 treatment arm, are reported to have had "vasovagal syncope." Review of sponsor supplied narratives reveal these episodes were all characterized as mild by the investigator. Two are reported to have occurred at time of phlebotomy on day 7 more than 12 hours after dosing. The third event occurred 2.5 hours after dosing ion day 1 and resolved within 1 minute. All of these events resolved without intervention. The sponsor notes that no QT prolongation or tachycardia was noted on the subject's ECGs at the time of these events.

Reviewer's comment: The information provided suggests that the etiology of these events was not related to torsade de pointes.

Of the 257 subjects enrolled, 252 completed the study. Of the five subjects withdrawn, 3 had been randomized to moxifloxacin and 1 to placebo. 1 subject randomized to the 50 mg of SYR-322 treatment arm was withdrawn on day 3 due to pharyngitis, which the sponsor labels not treatment-emergent.

The majority of treatment-emergent adverse events were considered mild in intensity by the investigator; only 2 subjects experienced an event considered moderate in intensity (allergic reaction after dosing with moxifloxacin and headache after dosing with placebo) and no subjects is reported as experiencing a severe adverse event.

4.3.8.3 Clinical Pharmacology

4.3.8.3.1 Pharmacokinetic Analysis

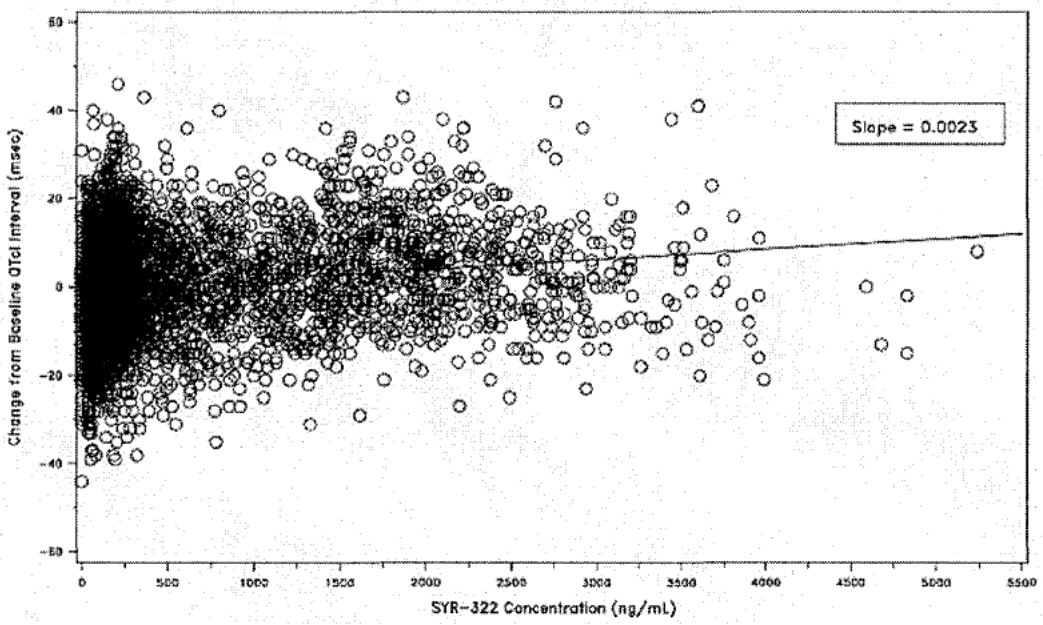
Table 10: Sponsor's Table 11.r Mean (%CV) PK Parameters for SYR-322 and M-I

Parameter (units)	SYR-322 50 mg Day 1 n=64	SYR-322 400 mg Day 1 n=64	SYR-322 50 mg Day 7 n=63	SYR-322 400 mg Day 7 n=64
SYR-322				
AUC(0-23.5) (ng·hr/mL)	2301.76 (13.902)	20161.56 (15.693)	2909.88 (13.844)	23646.49 (17.332)
Cmax (ng/mL)	269.77 (25.095)	2794.22 (26.664)	301.33 (22.835)	2844.06 (25.943)
Cmin(0) (ng/mL)	---	---	47.37 (19.349)	282.56 (26.964)
Tmax (hr) (a)	1.10 (0.60-5.10)	1.10 (0.60-3.22)	1.10 (0.60-4.13)	1.10 (0.60-4.10)
CL/F (L/hr)	---	---	17.51 (13.733)	17.44 (18.501)
M-I				
AUC(0-23.5) (ng·hr/mL)	17.75 (65.137)	164.76 (66.703)	29.33 (60.828)	212.60 (64.213)
Cmax (ng/mL)	1.22 (71.715)	14.01 (68.935)	1.92 (64.857)	16.69 (66.598)
Cmin(0) (ng/mL)	---	---	0.75 (61.785)	4.24 (65.193)
Tmax (hr) (a)	3.10 (0.60-8.10) (b)	2.10 (0.60-6.10)	3.100 (0.60-6.10) (c)	2.100 (0.60-6.15)

Source: Tables 15.2.1.3.
--- = not applicable.
(a) Median (minimum, maximum).
(b) n=60.
(c) n=59.

4.3.8.3.2 Exposure-Response Analysis

Figure 1: Sponsor's Figure 11.a Scatter Plot of Change from Baseline in QTcI Interval vs. SYR-322 Plasma Concentration



Reviewer's comments: The sponsor did not support their analysis with the required diagnostic plots. The reviewer re-analyzed the data with results shown in section 5.2.2.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The statistical reviewer's evaluation is based on the sponsor's data and in accordance with the ICH E14 guideline. The statistical reviewer analyzed the ECG data, ECGALL.XPT; and the demographic data, DEMOG.XPT. These data files were converted to SAS data sets for statistical analyses. The format of the submitted ECG data set was identified as time-matched. The reviewer's analysis data set, ECGALL2.sas7bdat was created based on ECGALL.sas7bdat. The data set DEMO1.sas7bdat was derived from DEMOG.XPT. Nearly all the statistical analyses in this report are based on this analysis data set.

To verify the sponsor's findings, the statistical reviewer independently analyzed the sponsor's ECG data on the **mean change in QTcF from baseline (Day -1) at each time point post-dose.**

5.1.1 Statistical Analysis

Table 11 through Table 13 describes some of the subjects' characteristics.

Table 11: Number of subjects by sex and treatment

	Treatment								Total	
	Placebo		50 mg SYR-322		400 mg SYR-322		400 mg moxifloxacin			
	N	%	N	%	N	%	N	%	N	%
Female	28	43.8	27	42.2	27	42.9	19	29.2	101	39.5
Male	36	56.3	37	57.8	36	57.1	46	70.8	155	60.5
Total	64	100.0	64	100.0	63	100.0	65	100.0	256	100.0

Source: ECGALL2 (DAY= -1 and HOUR= 0.00)

Table 12: Number of subjects by race and treatment

	Treatment								Total	
	Placebo		50 mg SYR-322		400 mg SYR-322		400 mg moxifloxacin			
	N	%	N	%	N	%	N	%	N	%
American Indian or Alaska Native					1	1.6			1	0.4
Asian	1	1.6			1	1.6			2	0.8
Black or African American	16	25.0	14	21.9	11	17.5	10	15.4	51	19.9
White	47	73.4	50	78.1	50	79.4	55	84.6	202	78.9
Total	64	100.0	64	100.0	63	100.0	65	100.0	256	100.0

Source: ECGALL2 (DAY= -1 and HOUR= 0.00)

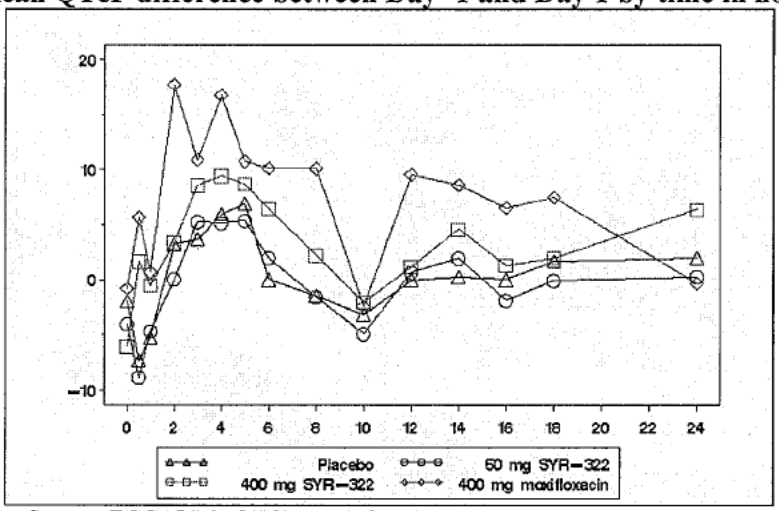
Table 13: Analysis of ages of the subjects

	N	Mean	Min	Max
Overall	256	29.24	19	45
Placebo	64	30.23	19	45
50 mg SYR-322	64	29.92	19	45
400 mg SYR-322	63	29.73	19	45
400 mg moxifloxacin	65	27.11	19	44

Source: ECGALL2 (DAY= -1 and HOUR= 0.00)

Figure 2 depicts the mean QTcF difference between Day -1 and Day 1 by time in hours.

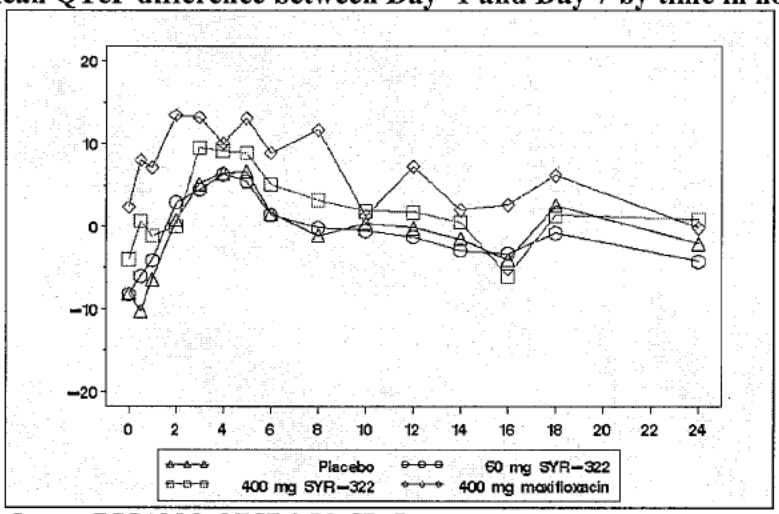
Figure 2: Mean QTcF difference between Day -1 and Day 1 by time in hours



Source: ECGALL2_QTCF_MN_CB_1

Figure 3 depicts the mean QTcF difference between Day -1 and Day 7 by time in hours.

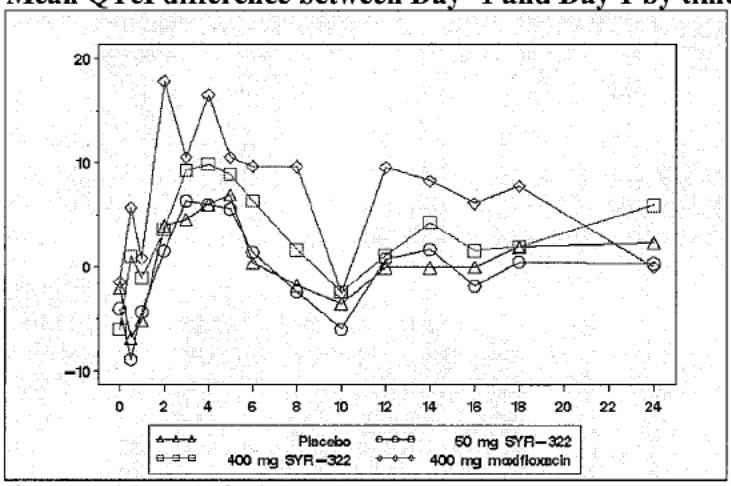
Figure 3: Mean QTcF difference between Day -1 and Day 7 by time in hours



Source: ECGALL2_QTCF_MN_CB_7

Figure 4 depicts the mean QTcI difference between Day -1 and Day 1 by time in hours.

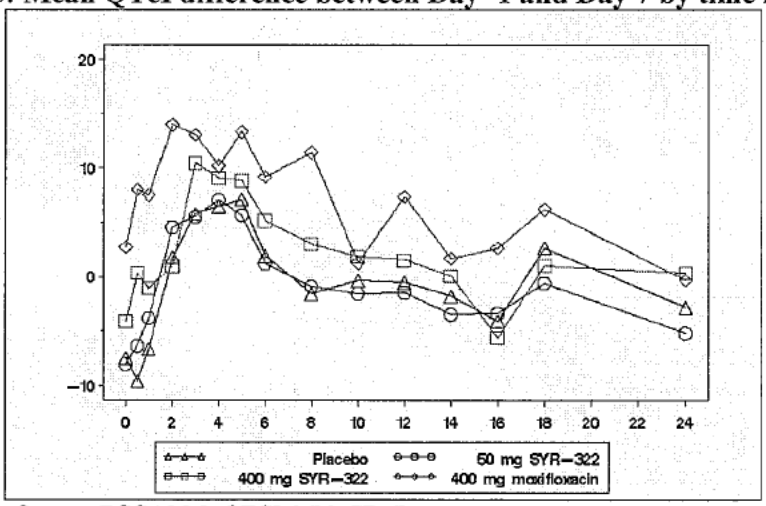
Figure 4: Mean QTcI difference between Day -1 and Day 1 by time in hours



Source: ECGALL2_QTCI_MN_CB_1

Figure 5 depicts the mean QTcI difference between Day -1 and Day 7 by time in hours.

Figure 5: Mean QTcI difference between Day -1 and Day 7 by time in hours



Source: ECGALL2_QTCI_MN_CB_7

The reviewer's inferential statistical analyses were performed using ANCOVA by time point with SAS PROC GLM procedure. Selected results are shown as follows.

Table 14: Number of subjects included in the statistical model

Treatment	#Subjects
Placebo	64
50 mg SYR-322	64
400 mg SYR-322	64
400 mg moxifloxacin	65

Source: ECGALL2

5.1.1.1 Reviewer's ANCOVA results based on QTcF

Table 15: Reviewer's analysis of QTcF difference from placebo at each time point Day 1 post dose for 50 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	-1.91	-9.11	5.29
1.00	1.79	-2.48	**6.07**
2.00	-1.35	-5.41	2.71
3.00	2.22	-1.00	5.44
4.00	0.86	-3.50	5.23
5.00	0.34	-2.71	3.39
6.00	2.26	-0.39	4.90
8.00	0.66	-1.95	3.27
10.00	-0.57	-3.91	2.77
12.00	0.99	-1.63	3.60
14.00	2.55	-0.02	5.12
16.00	-1.89	-4.58	0.79
18.00	0.35	-3.47	4.16
24.00	-0.76	-3.61	2.10

The largest upper limit of the one-sided 95% CIs for the 50 mg SYR-322-placebo difference after baseline adjustment is 6.07 at Hour 1, below the 10 ms threshold. The following picture depicts the CIs for mean change from baseline at each time point.

Figure 6: 90% 2-sided CIs for mean QTcF difference from placebo at each time point Day 1 post-dose for 50 mg SYR-322

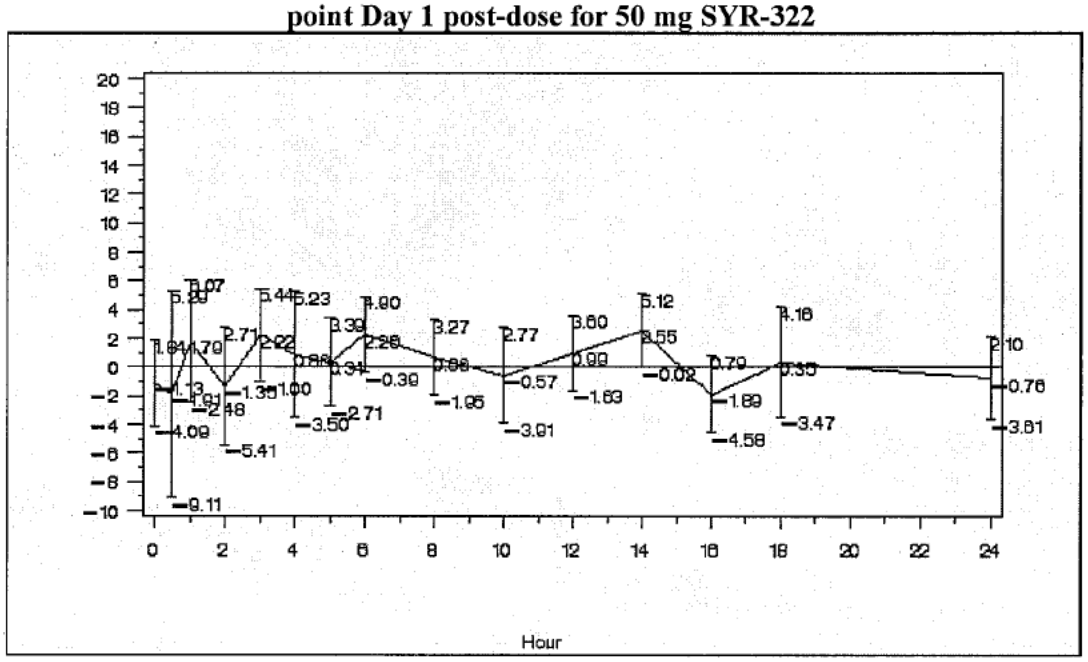


Table 16: Reviewer's analysis of QTcF difference from placebo at each time point Day 7 post dose for 50 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	4.11	-1.23	**9.46**
1.00	3.47	-0.05	6.99
2.00	3.28	-0.20	6.76
3.00	0.17	-3.30	3.65
4.00	1.45	-2.43	5.32
5.00	0.47	-3.29	4.22
6.00	0.16	-2.76	3.08
8.00	1.83	-1.63	5.29
10.00	0.29	-3.21	3.80
12.00	-0.56	-3.43	2.32
14.00	-0.34	-3.18	2.49
16.00	1.53	-3.87	6.92
18.00	-1.10	-4.93	2.74
24.00	-1.46	-5.52	2.61

The largest upper limit of the one-sided 95% CIs for the 50 mg SYR-322-placebo difference after baseline adjustment is 9.46 at 30 minutes, below the 10 ms threshold. The following picture depicts the CIs for mean change from baseline at each time point.

Figure 7: 90% 2-sided CIs for QTcF difference from placebo at each time point Day 7 post-dose for 50 mg SYR-322

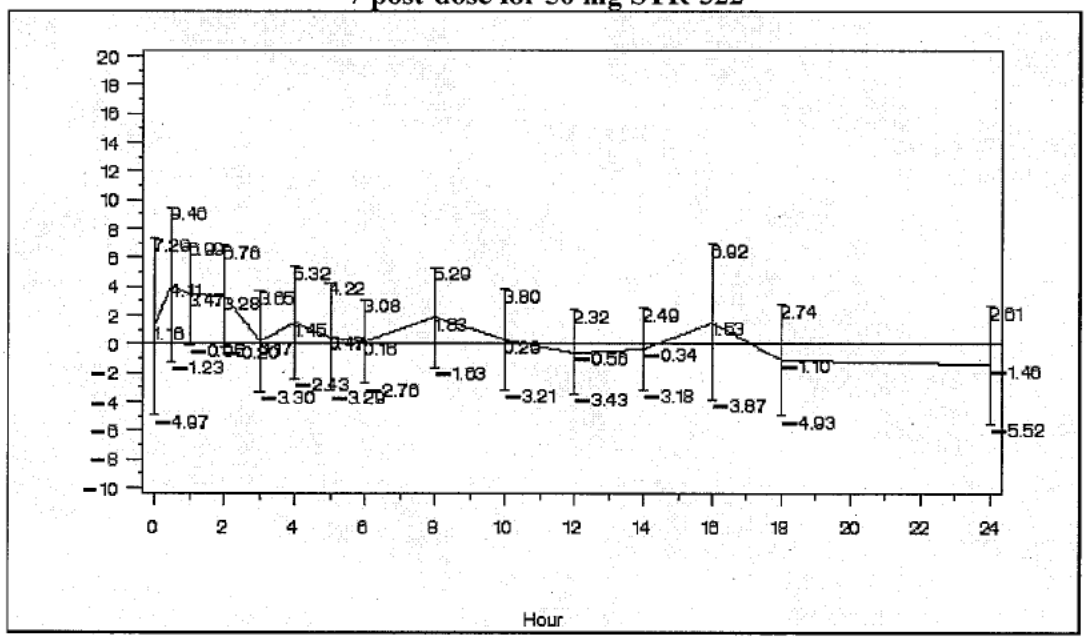


Table 17: Reviewer's analysis of QTcF difference from placebo at each time point Day 1 post dose for 400 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	5.28	1.53	**9.03**
1.00	4.65	1.61	7.69
2.00	1.33	-2.77	5.42
3.00	4.15	0.76	7.54
4.00	2.75	-0.61	6.11
5.00	2.44	-0.96	5.84
6.00	5.13	1.62	8.64
8.00	3.30	0.39	6.21
10.00	1.11	-2.27	4.50
12.00	0.06	-3.99	4.10
14.00	2.74	-0.39	5.88
16.00	0.73	-2.99	4.45
18.00	1.30	-2.12	4.71
24.00	3.40	0.40	6.39

The largest upper limit of the one-sided 95% CIs for the 400 mg SYR-322-placebo difference at day 1 after baseline adjustment is 9.03 at 30 minutes, below the 10 ms threshold. The following picture depicts the CIs for mean change from baseline at each time point Day 1 post-dose for 400 mg SYR-322.

Figure 8: 90% 2-sided CIs for QTcF difference from placebo at each time point Day 1 post-dose for 400 mg SYR-322

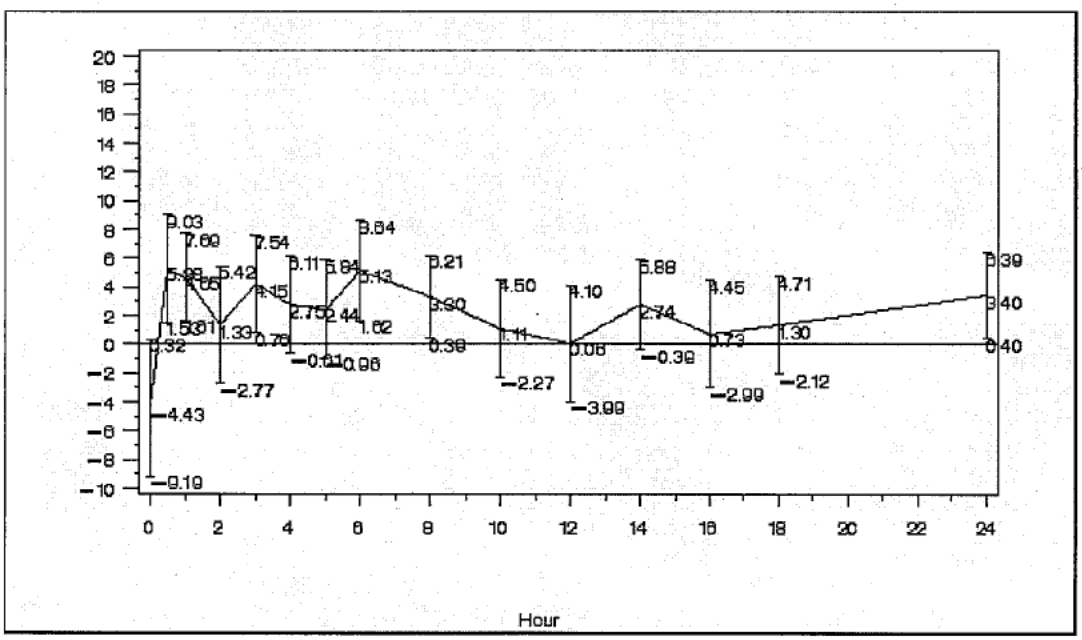
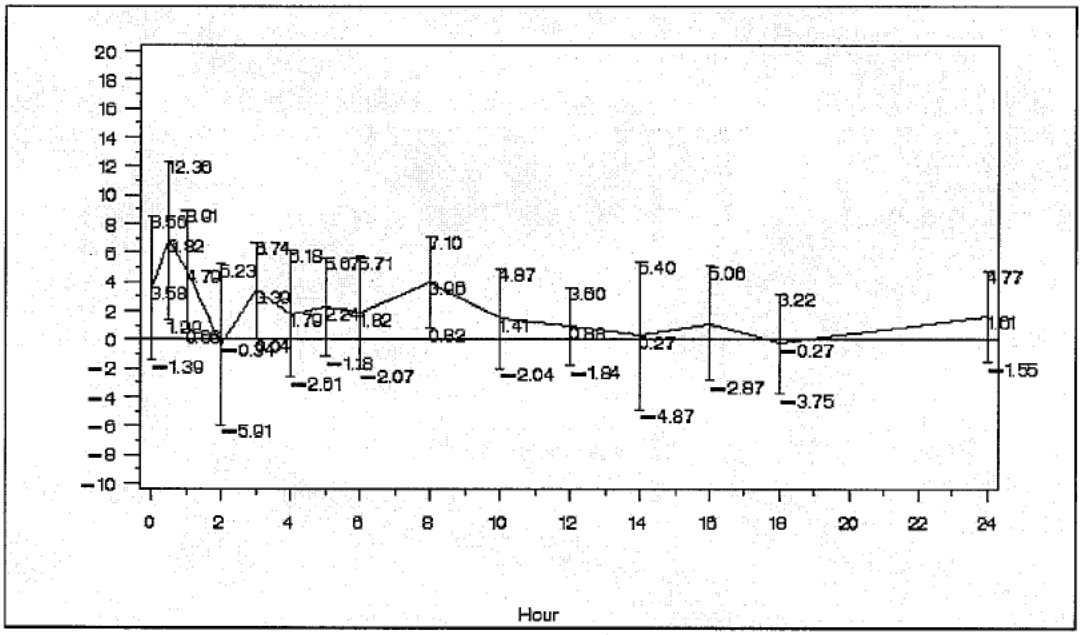


Table 18: Reviewer's analysis of QTcF difference from placebo at each time point Day 7 post dose for 400 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	6.82	1.29	**12.36**
1.00	4.79	0.66	8.91
2.00	-0.34	-5.91	5.23
3.00	3.39	0.04	6.74
4.00	1.79	-2.61	6.18
5.00	2.24	-1.18	5.67
6.00	1.82	-2.07	5.71
8.00	3.96	0.82	7.10
10.00	1.41	-2.04	4.87
12.00	0.88	-1.84	3.60
14.00	0.27	-4.87	5.40
16.00	-2.87	-10.81	5.06
18.00	-0.27	-3.75	3.22
24.00	1.61	-1.55	4.77

The largest upper limit of the one-sided 95% CIs for the 400 mg SYR-322-placebo difference after baseline adjustment is 12.36 at 30 minutes, which is above 10 ms, the level identified as the threshold of regulatory concern in the ICH E14 guideline. The following picture depicts the CIs for mean change from baseline at each time point Day 7 post-dose for 400 mg SYR-322.

Figure 9: 90% 2-sided CIs for QTcF difference from placebo at each time point Day 7 post-dose for 400 mg SYR-322



5.1.1.2 Reviewer's ANCOVA results based on QTcI

Table 19: Reviewer's analysis of QTcI difference from placebo at each time point Day 1 post dose for 50 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	-2.24	-9.46	4.98
1.00	1.64	-2.82	**6.10**
2.00	-0.84	-4.99	3.32
3.00	2.40	-0.81	5.60
4.00	1.37	-3.04	5.77
5.00	0.39	-2.68	3.46
6.00	1.23	-1.53	3.99
8.00	-0.21	-3.13	2.71
10.00	-1.56	-5.04	1.93
12.00	0.86	-1.96	3.68
14.00	2.18	-0.68	5.04
16.00	-1.89	-4.77	0.98
18.00	0.22	-3.83	4.27
24.00	-1.10	-3.95	1.75

The largest upper limit of the one-sided 95% CIs for the 50 mg SYR-322-placebo difference after baseline adjustment is 6.10 at Hour 1, below the 10 ms threshold. The following picture depicts the CIs for mean change from baseline at each time point Day 1 post-dose for 50 mg SYR-322.

Figure 10: 90% 2-sided CIs for QTcI difference from placebo at each time point Day 1 post-dose for 50 mg SYR-322

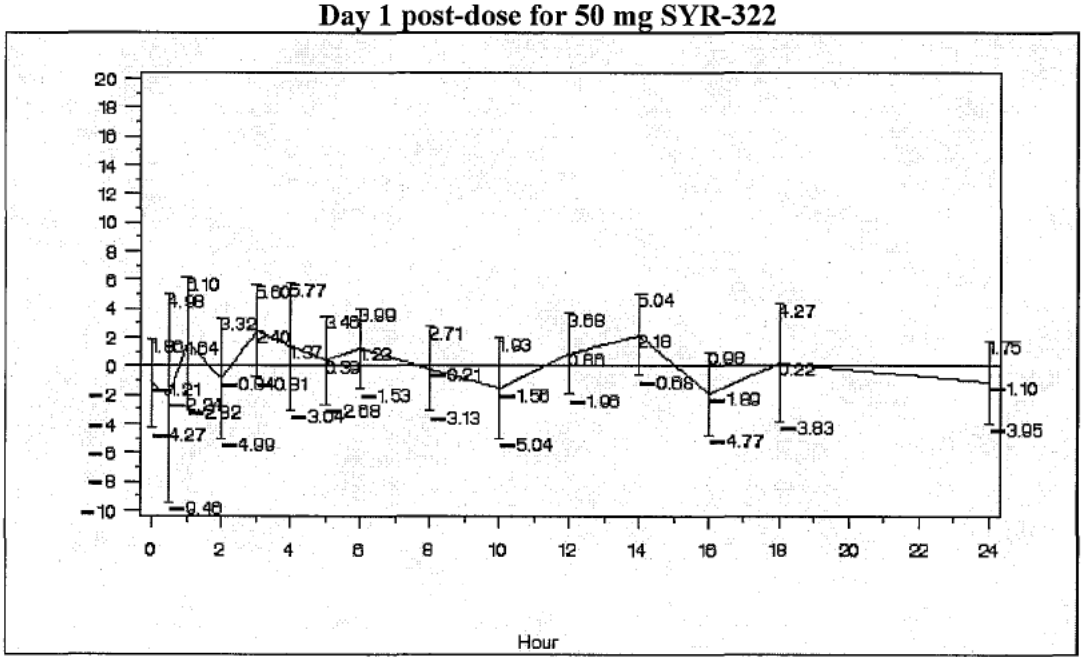


Table 20: Reviewer's analysis of QTcI difference from placebo at each time point Day 7 post dose for 50 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	3.28	-2.16	**8.73**
1.00	3.56	-0.26	7.38
2.00	3.66	0.04	7.27
3.00	0.23	-3.32	3.78
4.00	1.72	-2.31	5.75
5.00	-0.01	-3.82	3.79
6.00	-0.51	-3.59	2.57
8.00	1.08	-2.38	4.53
10.00	-0.19	-3.71	3.34
12.00	-0.76	-3.92	2.40
14.00	-1.11	-4.18	1.97
16.00	1.22	-4.36	6.80
18.00	-1.52	-5.67	2.63
24.00	-1.89	-6.06	2.28

The largest upper limit of the one-sided 95% CIs for the 50 mg SYR-322-placebo difference after baseline adjustment is 8.73 at 30 minutes, below the 10 ms threshold. The following picture depicts the CIs for QTcI difference from placebo at each time point Day 7 post-dose for 50 mg SYR-322.

Figure 11: 90% 2-sided CIs for QTcI difference from placebo at each time point Day 7 post-dose for 50 mg SYR-322

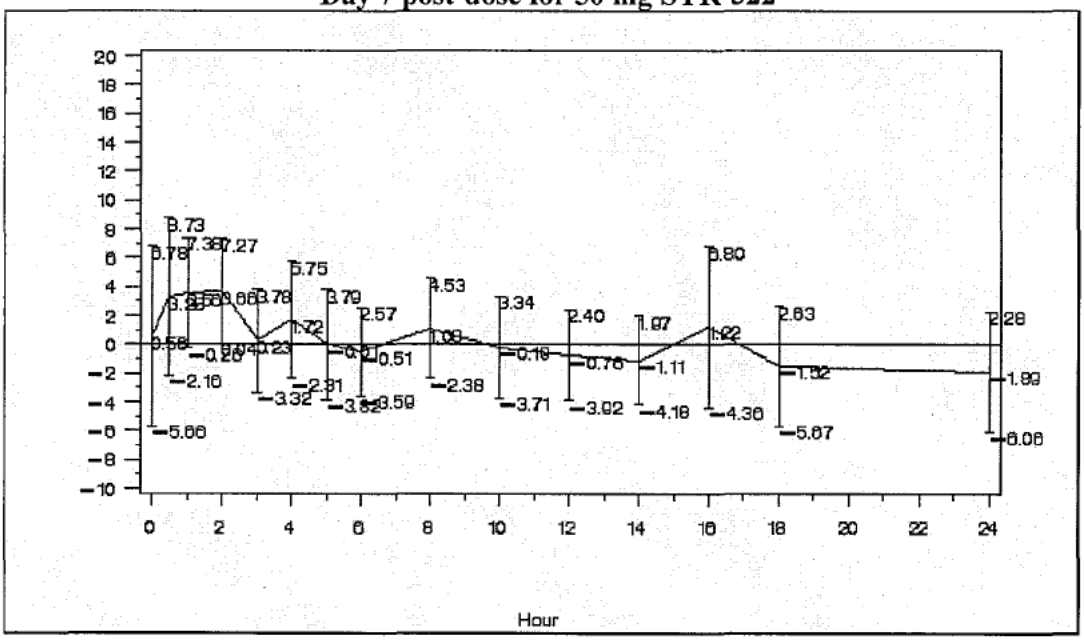


Table 21: Reviewer's analysis of QTcI difference from placebo at each time point Day 1 post dose for 400 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	5.46	1.55	**9.36**
1.00	4.43	1.29	7.56
2.00	1.28	-2.80	5.37
3.00	4.26	0.93	7.59
4.00	3.41	0.09	6.73
5.00	2.94	-0.46	6.34
6.00	5.35	1.52	**9.18**
8.00	3.24	0.06	6.43
10.00	1.38	-2.15	4.91
12.00	0.65	-3.63	4.93
14.00	3.17	-0.36	6.69
16.00	1.36	-2.64	5.36
18.00	1.29	-2.31	4.90
24.00	3.37	0.30	6.43

The largest upper limits of the one-sided 95% CIs for the 400 mg SYR-322-placebo difference after baseline adjustment are 9.36 at 30 minutes, and 9.18 at 6 hours, below the 10 ms threshold. The following picture depicts the CIs for QTcI difference from placebo at each time point Day 1 post-dose for 400 mg SYR-322.

Figure 12: 90% 2-sided CIs for QTcI difference from placebo at each time point Day 1 post-dose for 400 mg SYR-322

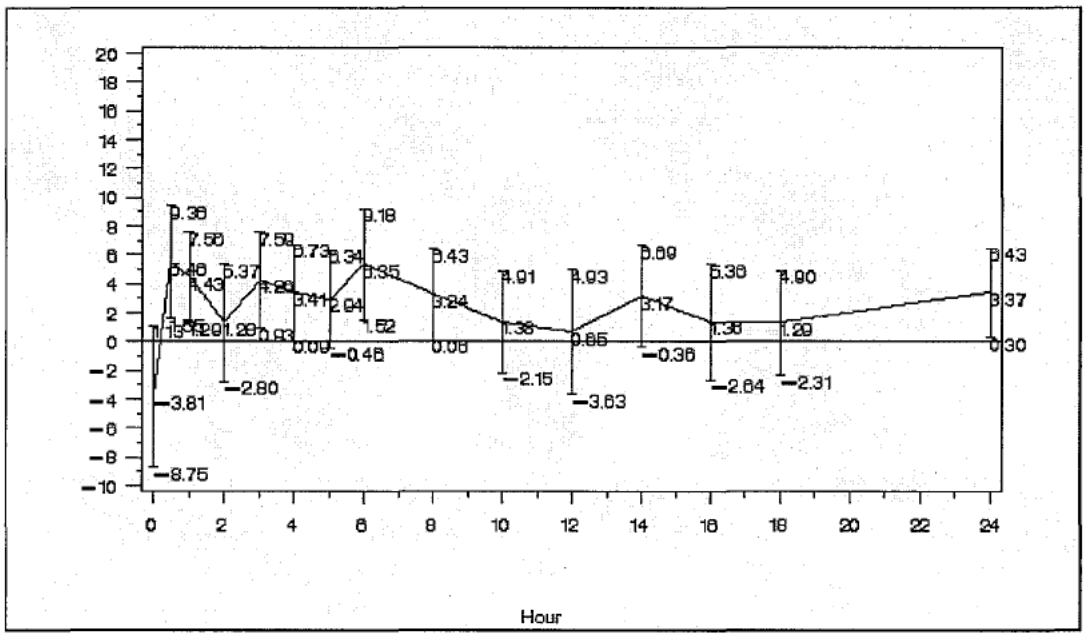
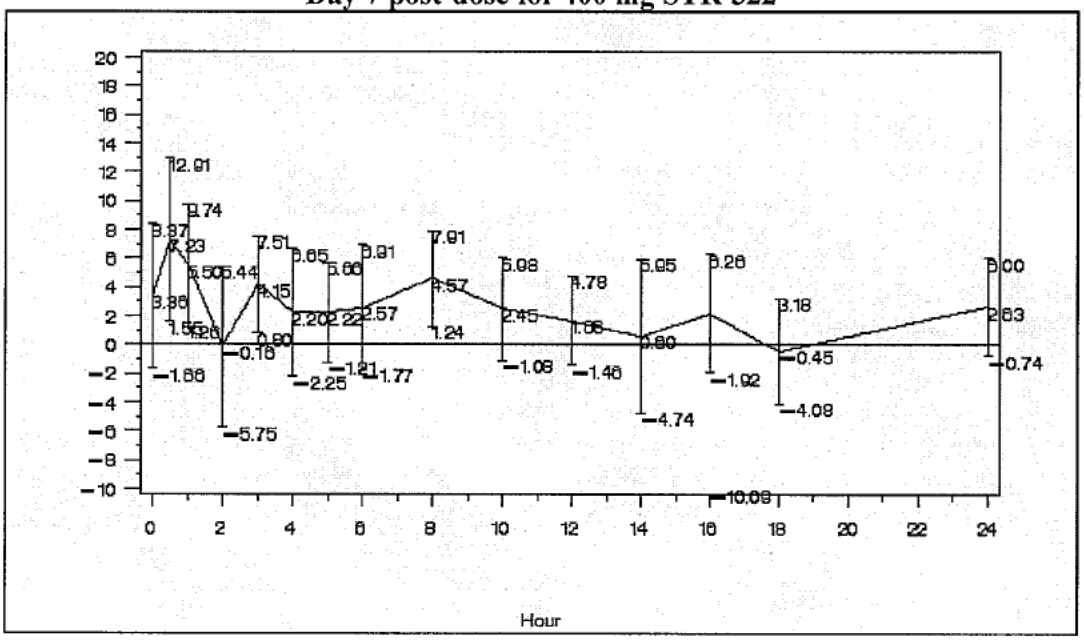


Table 22: Reviewer's analysis of QTcI difference from placebo at each time point Day 7 post dose for 400 mg SYR-322

Scheduled Time in Hours	Treatment Difference	Lower Confidence Limit	Upper Confidence Limit
0.50	7.23	1.55	**12.91**
1.00	5.50	1.26	9.74
2.00	-0.16	-5.75	5.44
3.00	4.15	0.80	7.51
4.00	2.20	-2.25	6.65
5.00	2.22	-1.21	5.66
6.00	2.57	-1.77	6.91
8.00	4.57	1.24	7.91
10.00	2.45	-1.08	5.98
12.00	1.66	-1.46	4.78
14.00	0.60	-4.74	5.95
16.00	-1.92	-10.09	6.26
18.00	-0.45	-4.08	3.18
24.00	2.63	-0.74	6.00

The largest upper limit of the one-sided 95% CIs for the 400 mg SYR-322-placebo difference after baseline adjustment is 12.91 at 30 minutes, above the 10 ms threshold, indicating a potentially significant QTc prolongation. The following picture depicts the CIs for QTcI difference from placebo at each time point Day 7 post-dose for 400 mg SYR-322.

Figure 13: 90% 2-sided CIs for QTcI difference from placebo at each time point Day 7 post-dose for 400 mg SYR-322



The following principle is applied to the analysis of the positive control. The adjusted significance level used is 0.003.

5.1.1.3 Summary of Reviewer's Findings

The reviewer's findings are summarized in Table 23. The numbers for SYR-322 arms in this table represent maximal upper CIs among all the time points.

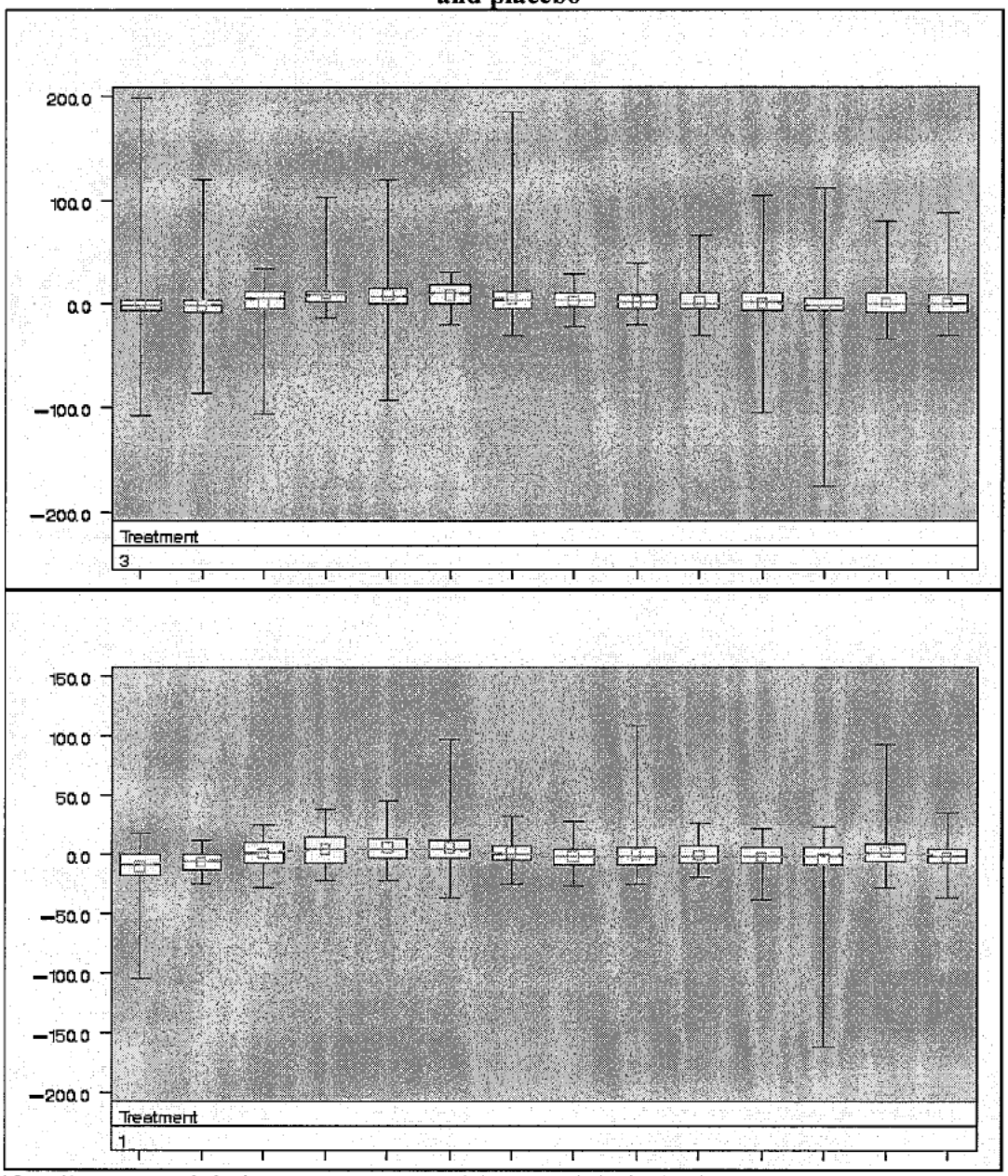
Table 23: Summary of reviewer's findings

QTc	Day	SYR-322 50	SYR-322 400	Moxifloxacin 400
QTcF	Day 1	6.07 msec at 1 hour	9.03 msec at 30 minutes	Lower CIs 5.33 msec and 6.14 msec at 2 and 4 hours
	Day 7	9.46 msec at 30 minutes	12.36 msec at 30 minutes	Lower CI 10.23 msec at 1 hour
QTcI	Day 1	6.10 msec at 1 hour	9.36 msec at 30 minutes	Lower CIs 5.76 msec and 5.98 msec at 2 and 4 hours
	Day 7	8.73 msec at 30 minutes	12.91 msec at 30 minutes	Lower CL 10.62 msec at 1 hour

The reviewer's findings based on QTcF and QTcI are consistent with those of the sponsor, summarized in Table 3 of this report.

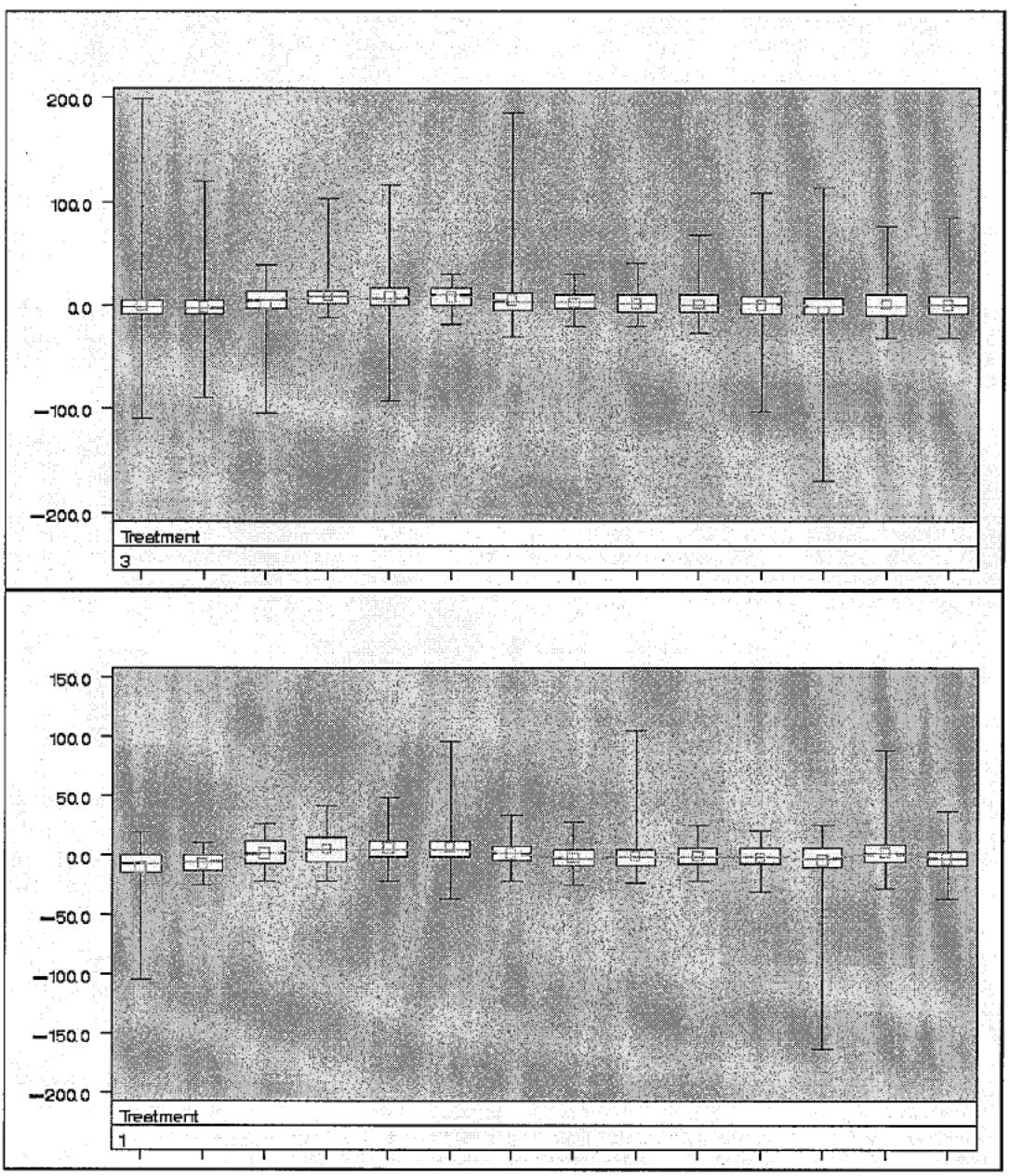
The upper confidence limit for comparing Day 7 400 mg SYR-322 with placebo at 30 minutes was found to be 12.36 based on QTcF. The same number based on QTcI was found to be 12.91. To explore whether the results were influenced by outliers or other data irregularity, the following box plots show the distribution of QTcF change from baseline by time in hours. Comparison between SYR-322 400 mg and placebo based on QTcI is also made. See Figure 14 and Figure 15. Unadjusted means and standard deviations of Day 7 QTcF and QTcI changes from baseline by time point are shown in Table 24and Table 25.

Figure 14: Distribution of QTcF change from baseline by hour for SYR-322 400 mg and placebo



Note: Treatment coded 3 is SYR-322 400 mg and the one coded 1 is placebo

Figure 15: Distribution of QTcI change from baseline by hour for SYR-322 400 mg and placebo



Unadjusted means and standard deviations for Day 7 QTcF and QTcI changes from baseline are shown in Table 24 **and** Table 25**.**

Table 24: Unadjusted means and standard deviations of Day 7 QTcF changes from baseline by time point

Scheduled Time in Hours	Unadjusted Means and Stds by Treatment			
	400 mg SYR-322		Placebo	
	Mean QTCF_MN_Chg	Std QTCF_MN_Chg	Mean QTCF_MN_Chg	Std QTCF_MN_Chg
0.50	0.64	30.41	-10.24	16.87
1.00	-1.11	21.66	-6.36	9.34
2.00	0.04	24.09	0.82	12.68
3.00	9.49	15.89	5.13	13.84
4.00	9.11	21.95	6.43	13.50
5.00	8.89	11.98	6.61	17.31
6.00	5.11	26.19	1.59	10.48
8.00	3.18	10.73	-1.15	11.93
10.00	1.89	11.53	0.42	17.98
12.00	1.73	14.40	-0.15	10.18
14.00	0.53	27.36	-1.49	10.47
16.00	-5.98	36.42	-4.01	22.51
18.00	1.35	15.96	2.59	16.27
24.00	0.89	14.87	-2.07	11.53

Table 25: Unadjusted means and standard deviations of Day 7 QTcI changes from baseline by time point

Scheduled Time in Hours	Unadjusted Means and Stds by Treatment			
	400 mg SYR-322		Placebo	
	Mean QTCI_MN_Chg	Std QTCI_MN_Chg	Mean QTCI_MN_Chg	Std QTCI_MN_Chg
0.50	0.38	30.28	-9.63	16.96
1.00	-1.08	21.56	-6.66	8.85
2.00	0.97	24.32	1.77	12.45
3.00	10.48	15.88	5.81	13.40
4.00	9.11	21.88	6.50	13.40
5.00	8.87	12.26	7.10	16.81
6.00	5.15	26.54	1.93	10.18
8.00	3.05	11.36	-1.59	11.75
10.00	1.88	11.80	-0.35	16.69
12.00	1.54	14.41	-0.53	10.48
14.00	0.08	27.13	-1.79	10.29
16.00	-5.64	36.59	-4.11	22.50
18.00	1.05	15.70	2.67	15.55
24.00	0.37	14.80	-2.81	11.48

Based on the observations of Table 24, Table 25, Figure 14 and Figure 15, the influence of extremely large or small values of QTcF or QTcI changes from baseline at a particular time point is not considered unusual. The statistical reviewer is not concerned about the data irregularity that might bias the statistical findings. After all, the interpretation of the

upper confidence limits greater than 10 msec lies in the hands of experts outside the statistical field.

5.1.2 Categorical Analysis

The results for the categorical analysis are presented in the following tables. These analysis results are consistent with the sponsor's findings. p-values of greater than 0.05 indicates that **SYR-322** in 50 and 400 mg are not positively associated with QTcF of greater then 450 ms. P-values of less than 0.05 for moxifloxacin indicates that moxifloxacin is positively associated with QTcF of greater then 450 ms.

Table 26: MAX QT_CF comparing 50 mg SYR-322 and placebo

Day 1

MAX QT_CF	Treatment		Total
	Placebo	50 mg SYR-322	
(0-450]	60	59	119
(450 above]	4	4	8
Total	64	63	127
Fisher's exact test for 2x2 table of treatment by outlier: P≈1.0000			

Day 7

MAX QT_CF	Treatment		Total
	Placebo	50 mg SYR-322	
(0-450]	62	59	121
(450 above]	1	4	5
Total	63	63	126
Fisher's exact test for 2x2 table of treatment by outlier: P=0.3649			

Table 27: MAX QT_CF comparing 400 mg SYR-322 and placebo

Day 1

MAX QT_CF	Treatment		Total
	Placebo	400 mg SYR-322	
(0-450]	60	62	122
(450 above]	4	2	6
Total	64	64	128
Fisher's exact test for 2x2 table of treatment by outlier: P=0.6799			

Day 7

MAX QT_CF	Treatment		Total
	Placebo	400 mg SYR-322	
(0-450]	62	60	122
(450 above]	1	4	5
Total	63	64	127
Fisher's exact test for 2x2 table of treatment by outlier: P=0.3650			

Table 28: MAX QT_CF comparing 400 mg moxifloxacin and placebo

Day 1

MAX QT_CF	Treatment		Total
	Placebo	400 mg moxifloxacin	
(0-450]	60	53	113
(450 above]	4	12	16
Total	64	65	129
Fisher's exact test for 2x2 table of treatment by outlier: P=0.0590			

Day 7

MAX QT_CF	Treatment		Total
	Placebo	400 mg moxifloxacin	
(0-450]	62	53	115
(450 above]	1	9	10
Total	63	62	125
Fisher's exact test for 2x2 table of treatment by outlier: P=0.0085			

5.2 Clinical Pharmacology Assessments

5.2.1 Assay Sensitivity

Subjects received daily doses of 400 mg oral moxifloxacin for 7 days. The C-QTcF relationship was determined separately on days 1 and 7; and the results are summarized in Table 29. The slope estimates on days 1 and 7 are the same; thereby, confirming assay sensitivity on day 7.

Table 29: C-QTc Relationship for Moxifloxacin

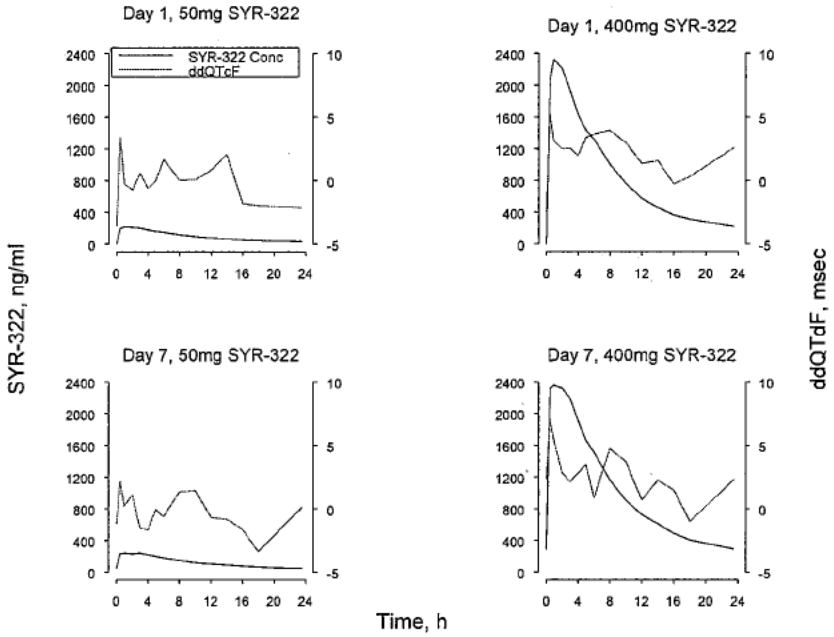
	Estimate (90% CI); p-value	Between-subject variability (SD)
Day 1: ddQTcF = Intercept + slope*concentration		
Intercept, ms	1.1 (-0.2, 2.4) 0.149	3.58
Slope, ms per mcg/mL	4.5 (3.7, 5.3) < 0.0001	0.89
Residual Variability, ms	9.68	--
Day 7: ddQTcF = Intercept + slope*concentration		
Intercept, ms	0.86 (-1.02, 2.74) 0.454	6.1
Slope, ms per mcg/mL	4.2 (3.4, 5.1) < 0.0001	1.9
Residual Variability, ms	9.68	--

5.2.2 C-QTc Relationship for SYR-322

Time-matched ddQTcF ($\Delta\Delta QTcF_{ij} = QTcF_{ij}$- $baseline_{ij}$- $placebomean_{j}$, where baseline is from day -1) was used to explore its relationship with SYR-322 concentrations. The ddQTcF versus SYR-322 concentration is plotted in Figure 16. For the 400 mg dose group, the maximum change in ddQTc occurs within the first hour after dosing which

also corresponds to peak plasma concentrations of SYR-322 (Table 10). These plots also show 1) the mean increase in ddQTcF for the 400 mg group is larger than the mean ddQTcF for 50 mg group; and 2) the mean ddQTcF within each dose group is similar on days 1 and 7.

Figure 16: Time Course of Mean SYR-322 Concentrations and ddQTcF Stratified by Study Day and Dose



A linear mixed effects model was used to describe the relationship between SYR-322 concentrations and ddQTcF. Metabolite concentrations were not used in the model because the largest increase in ddQTcF occurred within the first hour after dosing which corresponds more to the Tmax of SYR-322. Three models were considered: 1) $Y= \beta_0+\beta_1*\ln(\text{SYR-322})$; 2) $Y= \beta_0+\beta_1*\text{SYR-322}$; and 3) $Y= \beta_1*\text{SYR-322}$. Both slope and intercept parameters contained random effect terms. Modeling results are shown in Table 30. Based on the AIC criteria, model 3 was selected as the best model to describe the relationship between SYR-322 concentrations and ddQTcF. Goodness of fit plots for Model 3 are shown in Figure 18.

Table 30: C-QTc Relationship for SYR-322

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcF = Intercept + slope*ln(concentration) ; AIC= 27485		
Intercept, ms	-5.37 (-7.61, -3.14) 0.0001	6.9
Slope, ms per mcg/mL	1.14 (0.78, 1.50) < 0.0001	0.82
Residual Variability, ms	10.3	--
Model 2: ddQTcF = Intercept + slope*concentration ; AIC = 27477		
Intercept, ms	0.26 (-0.55, 1.08) 0.53	4.8
Slope, ms per ng/mL	0.0015 (001, 0.002) < 0.0001	0.0166
Residual Variability, ms	10.3	--
Model 3 : ddQTcF = slope*concentration; AIC= 27475		
Intercept, ms	0 Fixed	4.8
Slope, ms per ng/mL	0.0016 (0.001, 0.002)	0.0166
Residual Variability, ms	10.3	--

Figure 17: Concentration-ddQTcF Relationship

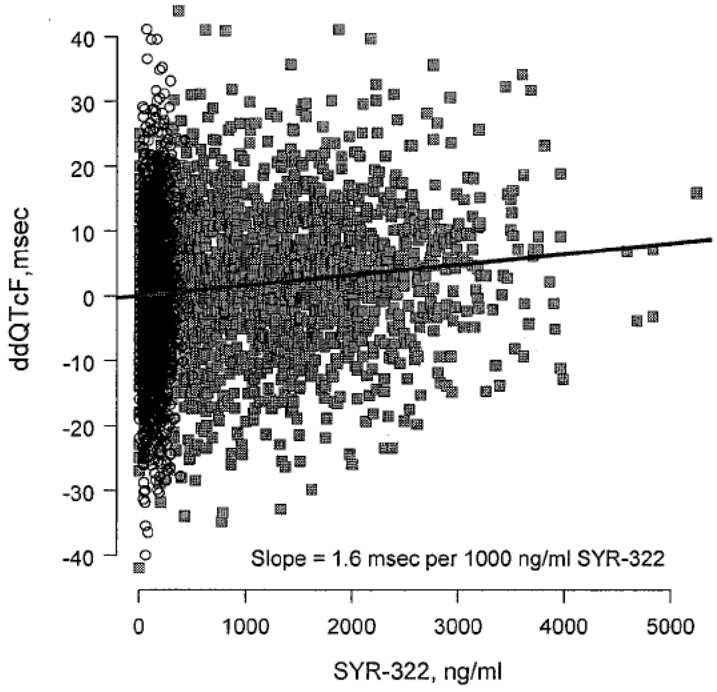
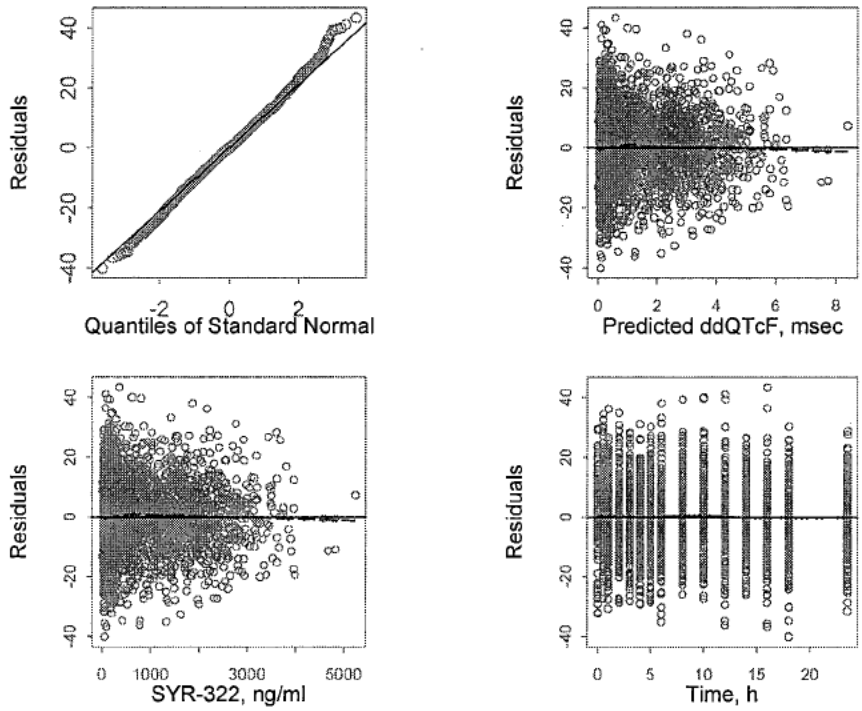


Figure 18: Goodness-of-Fit Plots for Model 3



Over a large range of concentrations, the relationship is flat with a population slope of 1.6 ms per 1000 ng/ml SYR-322. This slope is consistent with the slope reported by the sponsor (Figure 1). Based on the C-QTc relationship, the mean ddQTcF is less than 5 ms at a mean Cmax of approximately 2800 ng/ml Table 31. This exposure is 19-fold larger than the mean Cmax at the highest therapeutic dose (148 ng/ml for 25 mg).

Table 31: Model Predicted ddQTcF at the Mean Cmax by Dose

	ddQTcF, ms	90% CI
50 mg SYR-322		
Day 1	< 1	--
Day 7	< 1	--
400 mg SYR-322		
Day 1	4.5	3.3, 5.7
Day 7	4.6	3.4, 5.8

5.3 CLINICAL ASSESSMENT

The only reported events of possible clinical significance were the three episodes of syncope that occurred in subjects taking the 400 mg of SYR-322. Review of these events indicated that there was no association between these events and QT interval prolongation or ventricular arrhythmia.

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

Assessment	Screening	Check-in	Baseline	Treatment			
	Days -28 to -3	Day -2	Day -1	Day 1	Days 2 to 6	Day 7	Final Visit or ET Visit Day 8 (i)
Informed consent	X						
Check-in		X					
Inclusion/exclusion	X						
Medical history	X	X					X
Demographics	X						X
Physical examination (a)	X	X					X
Baseline			X				
Vital signs	X	X	X	X	X	X	X
Weight, height, and BMI	X (b)	X					X
Clinical laboratory tests (c)	X	X					X
HBsAg, HCV, and HIV	X						
Serum pregnancy test (hCG) (d)	X	X					X
Urine screen (alcohol and drugs)	X	X					
Randomization			X (e)				
Study drug administration				X	X	X	
Standard 12-lead ECG (safety only)	X	X	X	X (f)	X (f)	X (f)	
Continuous digital 12-lead ECG H-12 recording			X (g)	X (g)		X (g)	
Pharmacokinetic sampling				X (h)	X (h)	X (h)	
Adverse event monitoring		X	X	X	X	X	X
Prior/Concomitant medications	X	X		X	X	X	X
Compliance assessment				X	X	X	

ET=Early Termination, BMI=body mass index, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, hCG=human chorionic gonadotropin.
(a) Physical examination included a digital skin assessment.
(b) Height was only calculated at Screening.
(c) Clinical laboratory tests included hematology, serum chemistry, and urinalysis.
(d) Serum pregnancy tests were performed at all applicable time points (women of childbearing potential only).
(e) Randomization was performed at the end of Day -1 or Day 1 immediately before dosing.
(f) A standard 12-lead ECG was obtained at 2 to 3 hours after dosing on Days 1, 3, 5, and 7 for safety evaluation.
(g) Continuous digital 12-lead H-12 ECGs were obtained before dosing (time 0) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing on Days -1, 1, and 7 in triplicate (3 ECGs within 1 minute of the time point).
(h) Pharmacokinetic blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 23.5 hours after dosing on Days 1 and 7. In addition, trough samples were collected within 0.5 hours before dosing on Days 5 and 6.
(i) Final visit procedures were conducted for subjects who discontinued early per Protocol Section 7.6.

6.2 SAS CODES

6.2.1 SAS program used by the statistical reviewer for this report

```
proc glm data=subset_chg_fr_bs order=data;
by hour;
class treatment sex;
model QTCF_MN_CHG = sex treatment QTCF_MN_BASELINE;
lsmeans treatment/pdiff cl alpha=0.00333;
Run;
```

6.2.2 SAS program for C-QTc analysis

```
PROC MIXED IC DATA =OLD2 METHOD=ML;
CLASS ID;
MODEL DDQTCOBS=Cp/ SOLUTION OUTPM=PRED5 CL ALPHA=0.1
ALPHAP=0.1 NOINT DDFM= KENWARDROGER;
RANDOM INT Cp / TYPE=UN SUBJECT=ID;
ods output   SolutionF=parameter5 InfoCrit=infofit5;
RUN;
data qtp5; set pred5; intercept= 'No'; model='5'; if id>9990; tused=(upper-
pred)/StdErrPred;keep tused cp pred StdErrPred DF alpha lower upper model; run;
data para5; set parameter5; intercept= 'No'; model='5'; run;
data fit5; set infofit5;intercept='No';model='5';run;
```

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