

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204629Orig1s000**

**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.

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NDA/BLA # 204629  
Product Name: Jardiance (empagliflozin) tablets

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PMR/PMC Description: A single-dose pharmacokinetic and pharmacodynamic trial of empagliflozin in pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus.

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PMR/PMC Schedule Milestones: Study/Trial Completion: June 2015  
Final Report Submission: December 2015

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

Empagliflozin is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data was available.

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.”

This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of empagliflozin in pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus.

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, open-label, parallel group, single-dose trial to evaluate the pharmacokinetics and pharmacodynamics of three doses of empagliflozin (5 mg, 10 mg, 25 mg) in the pediatric population ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. Randomization will be stratified by gender (at least 1/3 but no more than 2/3 of patients to be female), age (at least 2/3 to be less than 15 years of age), and background therapy (metformin or drug naïve).

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)
- 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

*Continuation of Question 4*

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

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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)

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Other

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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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

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

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(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.

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NDA/BLA # 204629  
Product Name: Jardiance (empagliflozin) tablets

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PMR/PMC Description: A 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of empagliflozin for the treatment of pediatric patients 10 to 17 years (inclusive) with type 2 diabetes mellitus as an add-on to metformin, followed by a 28-week double-blind, placebo- or active-controlled extension period. The efficacy and safety study should have at least 30% of randomized subjects 10 to 14 years (inclusive) of age and at least one-third (but not more than two-thirds) of subjects in both age subsets (10 to 14 years [inclusive] and 15 to 17 [inclusive]) will be female. Secondary safety endpoints should include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. This trial should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>November 2015</u>
	Study/Trial Completion:	<u>February 2019</u>
	Final Report Submission:	<u>August 2019</u>
	Other:	_____

6. 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

Empagliflozin is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data was available.

7. 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.”

This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to assess the efficacy and safety of empagliflozin compared with placebo when added to metformin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). Secondary safety endpoints will include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. SGLT2 inhibitors alter body weight, renal transport of several minerals (i.e., calcium, magnesium and phosphorus), parathyroid hormone and vitamin D metabolism.

8. 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?

9. 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 24-week randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin for the treatment of pediatric subjects 10 to 17 years (inclusive) with type 2 diabetes mellitus, as add-on to metformin, followed by a 28-week double-blind, placebo- or active-controlled extension period. At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third (but not more than two-thirds) of subjects in both age subsets (10 to 14 years [inclusive] and 15 to 17 years [inclusive]) will be female. Secondary safety endpoints will include the effect of empagliflozin on mineral and bone metabolism, and the effect of empagliflozin on growth. This trial should not be initiated until after the data from the juvenile animal study have been submitted to and reviewed by the Agency.

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)
  - 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
- 

10. 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

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

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(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.

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NDA/BLA # 204629  
Product Name: Jardiance (empagliflozin) tablets

PMR/PMC Description: A study to evaluate empagliflozin toxicity in juvenile rats

PMR/PMC Schedule Milestones:

Study/Trial Completion: November 2014  
Final Report Submission: May 2015

11. 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

A juvenile animal toxicity study is required to support pediatric clinical safety/efficacy studies required under PREA, since there are, as of yet, insufficient data on the SGLT2 inhibitor class to establish the risks associated with pediatric exposures to these agents. These data are not necessary to support approval of this drug for use in adults.

12. 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.”

Renal development and function, body growth/maturation and bone development are potential areas of concern for SGLT2 inhibitors based on theoretic and empiric grounds. Juvenile rats treated with other SGLT2 inhibitors are generally more sensitive to caloric loss, osmotic diuresis, and volume depletion than adult rats, resulting in slower weight gain and body growth and evidence of increased fat metabolism (urinary ketones). The juvenile animal study will address concerns regarding potential treatment-related effects on renal development and function, weight gain and body growth, exacerbation of calcium homeostasis disruption and excessive bone accretion, and gastrointestinal tract changes, as well as the reversibility of any effects in juvenile animals.

13. 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?

14. 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.

### **Study Design**

**Age at start of dosing:** post natal Day 21

**Duration of dosing:** from 21 to 90 days (~10 weeks)

**Recovery:** 8 weeks.

**Doses:** 0, 1, 10, 30, 100 mg/kg/day

**Dose volume:** 10 mL/kg/day

**Vehicle:** 0.5% Natrosol (Hydroxyethylcellulose) in Water

**Route of administration:** oral gavage

**Frequency:** once a day

**Species:** Rat (Wistar (CrI:WI(Han)))

**No. animals:** 12/sex/group main study, 8/sex/group for recovery. TK cohort: 3/sex for controls, 9/sex for G2-G4

**Toxicokinetics:** DD1 and Week 10. Time points: 0, 1, 2, 4, 8, 24 hours

**Parameters:** clinical signs, body weights, body growth (crown/rump lengths), food consumption, ophthalmology, hematology, coagulation, serum chemistry, urinalysis (including volume, enzymatic creatinine, glucose, albumin, electrolytes (at least calcium, sodium, phosphorus)), tibia and femur length and width, sexual maturation

**Biomarker collections:** Serum and urine will be collected at the end of study for potential renal biomarker analysis if warranted by changes in routine clinical pathology or microscopic kidney findings.

**Pathology:** Macroscopic examination, organ weights and tissue retention (standard tissues plus humerus, skull, ulna, left femur, left tibia). Microscopic examination: kidney, stomach, bone, plus left femur and tibia, humerus, ulna, skull decalcified and cortical and cancellous bone evaluated from control and high dose animals and gross observations for all animals.

**Collection for specialized bone endpoints:** Right tibia, right femur and L3-L4 Main and Recovery subsets will be retained frozen for possible Peripheral Quantitative Computed Tomography (pQCT) and other evaluations if warranted by microscopic findings in the bones.

### **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)
  - 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)

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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

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15. 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

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

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(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.

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NDA/BLA # 204629  
Product Name: Jardiance (empagliflozin) tablets

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PMR/PMC Description: A randomized, double-blind, placebo-controlled trial evaluating the effect of empagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with empagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of empagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening renal function.

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PMR/PMC Schedule Milestones: Study/Trial Completion: June 2015  
Final Report Submission: December 2015

16. 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

Patients with diabetes mellitus are at increased risk of cardiovascular events and cardiovascular death. There are concerns surrounding anti-diabetics that though they improve glycemic control that they may actually increase the risk of cardiovascular events/death. As part of the development of new anti-diabetic agents, sponsors have been required to meet a prespecified cardiovascular risk margin. An estimate of cardiovascular risk derived from a meta-analysis of cardiovascular data across Phase 2 and 3 programs has provided sufficient evidence that empagliflozin does not unacceptably increase cardiovascular risk above the pre-approval risk margin specified in the FDA Guidance to Industry. The Guidance also stipulates a more stringent risk margin would need to be demonstrated post-approval. This study is intended to fulfill that requirement.

17. 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 empagliflozin therapy does not result in an unacceptable increase in risk for MACE, i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

The applicant has already provided sufficient evidence that empagliflozin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded an unacceptable level of 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 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with canagliflozin to that observed with placebo is less than 1.3.

Signals for potential liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions will also be further assessed in this trial. Estimated glomerular filtration rate (eGFR) will also be monitored over time to assess for any worsening renal function.

18. 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?

19. 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 trial evaluating the effect of empagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus at high risk of cardiovascular disease. The primary endpoint will be the time to first occurrence of any of the following adjudicated components of cardiovascular death, non-fatal MI, and non-fatal stroke.

The long-term effects of empagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions that were noted in the clinical program will also be assessed. Estimated glomerular filtration rate (eGFR) will also be monitored over time to assess for any worsening renal function.

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)
  - 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
-

20. 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?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
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- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

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

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(signature line for BLAs)

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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.**  
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/s/  
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JENNIFER R PIPPINS  
08/01/2014

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)**

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

## Memorandum

**Date:** July 16, 2014

**To:** Patricia Madara, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Kendra Y. Jones, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 204629  
OPDP labeling comments for JARDIANCE<sup>®</sup> (empagliflozin) tablets,  
for oral use

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OPDP has reviewed the proposed draft prescribing information (PI) and carton container labels for JARDIANCE<sup>®</sup> (empagliflozin) tablets, for oral use (Jardiance) submitted for consult on June 12, 2014.

### Prescribing Information

OPDP's comments on the proposed draft PI are based on the version sent from Pat Madara on July 8, 2014, and are provided directly on the marked version below.

### Carton/Container Labels

OPDP's comments on the proposed draft carton/container labels are based on the version sent from Pat Madara on June 30, 2014. Please note, OPDP recommends removing the intervening matter between the proprietary name and established name of the proposed carton/container label.

### Patient Information

OPDP's comments on the proposed draft patient labeling (PPI) were provided under separate cover in conjunction with the Division of (DMPP) on July 11, 2014.

Thank you for the opportunity to comment on the proposed draft labeling.

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

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

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/s/  
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KENDRA Y JONES  
07/16/2014

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

**PATIENT LABELING REVIEW**

Date: July 11, 2014

To: Jean-Marc Guettier, M.D.  
Director  
**Division of Metabolic and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, MSN, FNP-BC, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Twanda Scales, RN, MSN/Ed.  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Kendra Y. Jones  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): JARDIANCE (empagliflozin)

Dosage Form and Route: Tablets

Application Type/Number: NDA 204629

Applicant: Boehringer Ingelheim Pharmaceutical, Inc.

## 1 INTRODUCTION

On June 2, 2014, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) submitted for the Agency's review a Resubmission for empagliflozin tablets to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Reference is made to the Agency's Complete Response letter dated March 4, 2014. This resubmission includes a complete response addressing the deficiencies identified in the Agency action letter.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) on June 12, 2014, and June 12, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JARDIANCE (empagliflozin) tablets.

## 2 MATERIAL REVIEWED

- Draft JARDIANCE (empagliflozin) tablets PPI received on June 2, 2014, and received by DMPP on July 8, 2014.
- Draft JARDIANCE (empagliflozin) tablets PPI received on June 2, 2014, and received by OPDP on July 8, 2014.
- Draft JARDIANCE (empagliflozin) tablets Prescribing Information (PI) received on June 2, 2014, revised by the Review Division throughout the review cycle and received by DMPP on July 8, 2104.
- Draft JARDIANCE (empagliflozin) tablets Prescribing Information (PI) received on June 2, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on July 8, 2014.

## 3 REVIEW METHODS

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 PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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TWANDA D SCALES  
07/11/2014

KENDRA Y JONES  
07/11/2014

MELISSA I HULETT  
07/11/2014

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**CLINICAL INSPECTION SUMMARY**

**DATE:** March 3, 2014

**TO:** William H. Chong, M.D., Clinical Reviewer  
Karen Mahoney, M.D., Clinical Team Leader  
Patricia Madara, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**FROM:** Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 204629

**APPLICANT:** Boehringer Ingelheim Pharmaceuticals, Inc.

**DRUG:** Empagliflozin

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATIONS:** An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

CONSULTATION REQUEST DATE: July 22, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: January 5, 2014

DIVISION ACTION GOAL DATE: March 5, 2014

PDUFA DATE: March 5, 2014

## I. BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is seeking approval for empagliflozin tablets to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Empagliflozin is a novel selective inhibitor of sodium-dependent glucose co-transporter 2 (SGLT-2). The Applicant is proposing to commercialize only the 25 mg dose strength.

Inspections were requested for the following studies:

- **Protocol 1245.19** *A randomized, double-blind, placebo-controlled parallel group efficacy and safety trial of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin*

The study began October 12, 2010 and completed April 11, 2012. It was a multi-centered trial with 69 trial sites in 8 countries (Canada, China, Greece, India, Philippines, Thailand, Ukraine, and the United States). There were 762 subjects enrolled and 499 randomized.

- **1245.20** *A phase III randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 and sitagliptin administered orally over 24 weeks, in drug naïve patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise*

The study began August 12, 2010 and completed March 19, 2012. This was a multi-centered trial with 124 trial sites in 9 countries (Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, and the United States). There were 1616 subjects enrolled and 986 randomized.

- **1245.23 (Met + SU) and 1245.23 (Met only)** *A phase III randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea*

This international, multi-centered trial comprised two independent substudies of identical design. Patients with a stable dose regimen of metformin were to be entered in one substudy (metformin background), and patients with a stable dose regimen of

metformin plus a sulphonylurea were to be entered in the second substudy (metformin plus sulphonylurea background). The two substudies were analyzed separately.

The study trial began July 29, 2010 and completed February 3, 2012. There were 148 trial sites; for the substudy with metformin-only background medication, patients were recruited by 136 centers; for the substudy with metformin plus sulphonylurea background medication, patients were recruited by 129 centers. The sites were in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the United States). There were 2256 subjects enrolled and 1307 randomized. There were also 172 subjects in the open label treatment phase. There were 970 enrolled patients with metformin only as background medication. Of these, 710 patients started the placebo run-in period and 638 patients were randomized. There were 1010 enrolled patients with metformin plus sulphonylurea as background medication. Of these, 740 patients started the placebo run-in period and 669 patients were randomized.

- **1245.28** *A phase III randomized, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104-week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment*

The study began August 26, 2010 and is still ongoing. August 31, 2012 was database lock for the interim analysis. This is a multi-centered trial with 173 trial sites in 23 countries (Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Hong Kong, India, Italy, Malaysia, Mexico, The Netherlands, Norway, the Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the UK, and the US). There were 2637 patients screened, 1678 started the placebo run-in period, 1549 patients were randomized and 1545 patients were treated.

- **1245.33** *A phase IIb, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulphonylurea therapy and insufficient glycaemic control*

The study began November 11, 2009 and completed May 9, 2012. This multi-centered trial was conducted in 97 sites in 7 countries (Denmark, France, Ireland, Republic of Korea, Portugal, United Kingdom, and the United States). There were 826 patients screened, 532 patients began the placebo run-in, and 494 patients were randomized.

- **1245.36** *A phase III, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg and 25 mg administered once daily) as add on to pre-existing antidiabetic therapy over 52 weeks in patients with type 2 diabetes mellitus and renal impairment and insufficient glycaemic control*

The study began September 3, 2010 and completed July 26, 2012. It was a multi-

centered trial with 127 trial sites in 15 countries (Canada, France, Hong Kong, India, Malaysia, Netherlands, Philippines, Poland, Portugal, Russia, Slovakia, South Africa, Spain, United Kingdom and the United States). There were 1317 patients enrolled, 741 patients randomized and 738 patients were treated.

Of the six pivotal Phase 3 trials, one trial (1245.28) is ongoing and remains blinded following the interim analysis provided in the original NDA, and patients from three trials (1245.19, 1245.20, 1245.23) continued in a blinded extension study at the same sites.

There have been several issues regarding site implementation of the protocols that have been brought to the attention of the review team. These issues were also considered when deciding on site selection and what topics needed focus during the inspections.

➤ **Multiple Subject Enrollment**

In a letter dated April 12, 2013, Boehringer-Ingelheim Pharmaceuticals Inc. submitted an amendment to IND (b) (4) and IND 102145 (linagliptin + empagliflozin) describing the Sponsor's identification and investigation of subjects participating in the same trial at multiple investigator sites discovered through the company's Site Escalation process. The investigation results confirmed that 25 subjects, representing 64 subject numbers/data points, were screened and/or randomized at more than one study site for the 1218.74 trial. Ten subjects, representing 21 subject numbers/data points were confirmed as participating at more than one investigator site for the 1275.1 trial. The sites involved were:

- Study 1218.74
  - Eduardo Almaguer
  - Eddie Armas
  - Pierre Blemur
  - Yavir Escovar
  - Ana Fandino
  - Humberto Fernandez-Miro
  - Leonel Perez-Limonte
  - Alejandro Pla
  - Dolores Sanchez-Cazau
  - Erik Van Ginkel
  - Gilbert Weiner
  
- Study 1275.1
  - Ramon Berenguer
  - Barbara Biggs
  - Arsenio Columbie
  - Yavi Escovar
  - Robert Eyzaguirre
  - David Wyatt
  - Nandini Kohli
  - Aziz Laurent
  - Jung Oh
  - Luis Carlos Quinter

- Joanna Van

Investigation by the sponsor of the multi-site participation of subjects in these clinical studies indicated that the root cause was subject fraud. The Office of Scientific Investigations (OSI) compared these sites to those involved with the studies to be inspected. OSI also requested a descriptive summary of the corrective and preventive action (CAPA) plan to be implemented by Boehringer Ingelheim (BI) globally for all currently ongoing and future clinical studies to avoid future occurrence of similar events. The plan details were reviewed and found to be acceptable. The plan focuses on the following main actions:

1. Analyze available data to further assess possibility of subjects participating in multiple sites in other ongoing BI clinical studies
2. Develop/implement a systematic reporting process to aide in detection of multi-site participation in future clinical studies
3. Raise awareness of patients, investigators, and BI's clinical trial teams

FDA field investigators were alerted to the potential for multiple subject enrollments regarding the trials for inspection and were instructed to specifically look for any possibility at the inspected sites.

➤ **Site Closures**

There were several reports sent to FDA regarding site closures throughout the drug development program. In June 13, 2013 the review team requested a list of all sites closed under IND 102145 for empagliflozin tablets. The sponsor responded June 26, 2013 with a list of all site closures reported to the IND, the location of the site, reason for closure and a hyperlink to each site closure letter submitted.

Principal Investigator Name (Last, First)	Trial #	Site #	Location	Serial # /sequence	Date Reported	Reason for closure
Abdel-Salam, Suzanne	1245.20 1245.23	20001 20001	Canada	61/7	3/14/11	For Cause
Ahmed, Azazuddin Ahmed, Follow-up	1245.31	10001	Chicago, IL	156/103 203/150	4/20/12 10/1/12	For Cause
Arena, Charles	1245.25 1245.28 1245.33	10080 10023 01049	Salt Lake City, UT	136/83	2/17/12	Breach of Contract
Behnke, Andrew	1245.33	01041	Carlisle, PA	52/paper	11/16/10	Breach of Contract
Cranford, James	1245.25	10043	Birmingham, AL	277/223	6/21/13	For Cause
Mach, Minh	1245.25	10083	Valencia, CA	185/132	7/26/12	For Cause
Marquez, Farid Marquez, Follow-up	1245.25	10157	Hialeah, FL	154/101 162/109	4/9/12 5/9/12	For Cause
Nassim, Omid	1245.23 1245.25	10095 10058	Huntington Park, CA	137/84	2/17/12	For Cause
Rivas, Joseph	1245.23	10109	Huntington Park, CA	138/85	2/17/12	For Cause
Rohas, Wilson	1245.49	51001	Peru	195/142	9/6/12	For Cause
Ubani, Agnes	1245.25	10178	Tampa, FL	202/149	9/28/12	For Cause
Waseem, Malika	1245.19	10160	Essex, MD	139/86	2/17/12	For Cause
Wittmer, Bret	1245.25	10006	Madisonville, KY	151/98	3/23/12	For Cause

- Azazuddin Ahmed: A for-cause inspection was pending and it was decided to combine with the application inspections. See inspection findings below. *The data from this site was*

*not included in the analyses.*

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 204629 in accordance with Compliance Programs 77348.810 and 348.811. General as well as focused instructions were also provided with this assignment.

## II. RESULTS (by Site):

<b>Name of Clinical Investigator/ Site #</b>	<b>Protocol # and # of Subjects Randomized</b>	<b>Inspection Date</b>	<b>Pending Classification</b>
Daniel Streja/ 10131	1245.19 15 subjects	10/23, 24, 28- 29/2013	NAI
Ernie Riffer/ 10108	1245.20 21 subjects	10/21-23/2013	NAI
Jeff Unger/ 10154	1245.20 13 subjects	10/4,7-10, 15-17, 21/2013	NAI
Joseph (Jose) Rivas/ 10109	1245.0023 (Met + SU) 2 subjects  1245.0023 (Met only) 13 subjects	10/24-25, 28-31, 11/1, 11/8, 11/14/2013	VAI
Andrew Lewin/ 10074	1245.0023 (Met + SU) 16 subjects  1245.0023 (Met only) 20 subjects	10/08-09/2013	NAI
Azazuddin Ahmed/ 10001	1245.0023 (Met + SU) 14 subjects  1245.0023 (Met only) 11 subjects  1245.31 13 subjects	10/08-11/08/ 2013; 12/10-16/2013	OAI

Danny Sugimoto/ 01044	1245.33 11 subjects	12/17-1/2/2014	VAI
Michael O'Mahony/ 20034	1245.19 19 subjects  1245.23 (Met + SU) 10 subjects  1245.23 (Met only) 9 subjects	11/18-27/2013	NAI
Howard Conter/ 20071	1245.28 10 subjects	11/25-29/2013	VAI
Thomas Elliott/ 20028	1245.23 (Met + SU) 9 subjects  1245.23 (Met only) 4 subjects	11/4-8/2013	VAI
Graham Ellis/ 76022	1245.36 36 subjects	11/11-14/2013	NAI
Monojit Mukhopadhyay/ 91211	1245.28 12 subjects  1245.36 3 subjects	11/18-21/2013	NAI
Jamal Ahmad/ 91209	1245.28 15 subjects  1245.36 5 subjects	11/25-28/2013	NAI
Yaoming Xue/ 86002	1245.20 20 subjects  1245.23 (Met + SU) 12 subjects  1245.23 (Met only) 5 subjects	10/14-18/2013	VAI

Boehringer Ingelheim Pharmaceuticals, Inc.	All studies	12/4-18/2013	NAI
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Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending close-out letter to the site.

**1. Daniel Streja, M.D.**

Medical Director

Infosphere Clinical Research, Inc.

7345 Medical Center Drive, #430

West Hills, CA 91307

All correspondences should be addressed to: 7345 Medical Center Drive, #310

- a. What was inspected:** Inspection included the review of informed consent forms for 100% of the patients enrolled, inclusion/exclusion criteria, adverse events (AEs), concomitant medications, source documents, case report forms (CRFs), Institutional Review Board (IRB) approvals and communications, monitoring logs, 1572's, financial disclosures, delegation of duties, training and test article accountability. Eleven subject records (all subjects that completed the study) were reviewed.
- b. General observations/commentary:** For study 1245.19, there were 22 subjects screened, 15 subjects enrolled, and 11 subjects that completed the study. [REDACTED] <sup>(b) (4)</sup> was the IRB of record. The first subject was screened 7/30/2011. The last subject was screened 9/27/2011 but failed the inclusion/exclusion criteria. Source documents were organized, complete and legible. All 15 randomized subjects met inclusion/exclusion criteria. All primary and secondary endpoints were verifiable. There was no under-reporting of adverse events. There were eleven monitoring visits recorded. There were no issues with drug accountability. There was one subject (#12371) who had started using Chantix on 2/26/2012, but the medication was not electronically recorded onto the Concomitant Therapy CRF.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate

serious deviations/findings that would impact the validity or reliability of the submitted data.

## 2. Ernie Riffer

Clinical Research Advantage, Inc.  
Central Phoenix Medical Clinic  
Suite 191  
7600 North 15th Street  
Phoenix, AZ 85020

- a. What was inspected:** Inspection included the review of informed consent forms for 100% of the patients enrolled, inclusion/exclusion criteria, adverse events (AEs), CRFs, concomitant medications, source documents, IRB approvals and communications, monitoring logs, 1572's, financial disclosures, delegation of duties, training and test article accountability. Records from all enrolled subjects (21) were reviewed.
- b. General observations/commentary:** For study 1245.20, there were 26 subjects screened, 21 subjects enrolled, and 17 subjects who completed the study. The first subject was screened on 1/20/2011. The study was closed on 6/12/2012. Six subjects were given open label treatment with empagliflozin. [REDACTED] (b) (4) [REDACTED] was the IRB of record. There were no issues noted with inclusion/exclusion or randomization. All 21 subject records were reviewed for adverse events and there was no under-reporting of AEs. All 21 subject records were compared to the data line listings for the primary endpoint and there were no discrepancies. Key secondary endpoints were reviewed for subjects 024981, 024983, 024985, 024987, 024989, 024991, 024993, 024996, 024999, 020355 and 020357. All were verifiable. Concomitant medications were reviewed for subjects 024982, 024984, 024986, 024988, 024990, 024992, 024995, 024997, 020352 and 020356. No discrepancies were noted. The following records were reviewed fully during the treatment period (Visit 3-7): 024981, 024983, 024985, 024987, 024989, 024991, 024993, 024996, 020355 and 020357. No discrepancies were noted. There were no issues with test article accountability. Monitoring occurred monthly; written reports were available for review.

There was a protocol deviation listed regarding the unblinding of Subject 024986 where the PI did not agree with the conclusion of the sponsor. The deviation in the data listing states, "Medication code broken without just cause but more than 7 days after treatment discontinuation". However, the subject's serum creatinine level went from 0.98 mg/dl at baseline to 2.14 mg/dl and the glomerular filtration rate (GFR) went from 59 ml/min at baseline to 24 ml/min at Week 12. The PI suspected an allergic reaction to the study drug. The subject was prescribed prednisone for treatment of "acute interstitial nephritis and suspected allergic reaction to the study medication". Due to the reaction, Dr. Riffer unblinded the study drug for patient safety, saying that the patient needed to know if she was allergic to sitagliptin or empagliflozin to prevent future

occurrence and possible irreparable damage to her kidneys. The subject was discontinued from study drug. After study drug was discontinued, the patient's creatinine and GFR levels returned to normal.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

### 3. Jeffery Unger

14726 Ramona Avenue  
Suite 100  
Chino, CA 91710

- a. **What was inspected:** There were 20 subject files (including screen failures) reviewed 100% for informed consent, adverse events, and progress notes. There were nine subject files (completed and dropped subjects) reviewed entirely with complete data verification. IRB approvals and communications, correspondence binder, drug accountability, financial disclosure, delegation of duties, training, qualifications, and monitoring reports were reviewed.
- b. **General observations/commentary:** For study 1245.20, there were 30 subjects screened, 14 subjects enrolled (1 did not receive product), and 7 subjects that completed the study. There was no under-reporting of adverse events. The primary efficacy endpoint data and the secondary endpoint data were verifiable.

A review of records did not reveal concerns related to data capture at this site. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were several discussion points:

1. The site never received a Spanish ICF (4th version) for study 1245.20; the English version had been submitted by the sponsor to the IRB and approved. The affected subjects (21701, 21705, 22118) all were initially consented on Version 3 but were not reconsented on Version 4 as the sponsor did not submit the translated version. The inspector noted repeated communications from the site asking for the updated version.
2. The initial monitor assigned to the site did not provide monitoring reports and was eventually let go by the sponsor; the site repeatedly requested the reports. The site was issued the wrong glucose monitoring logs (weekly vs. daily) by the monitor. Twelve subjects were randomized without the daily

Home Blood Glucose monitoring log. This deviation is not found in the data line listings. The IRB had been notified. After the monitor was let go, there was a three-month gap before another monitor was assigned to the site.

3. Two subjects (22106, 22108) were randomized without the hematology results, which were drawn but samples were too old to be analyzed. The site instituted a process control measure with flagging to avoid a similar episode. This deviation is not found in the data line listings. The IRB had been notified.
4. For all subjects, the data line listing Table H concerning the blood pressures appear to be individual results; from the source documents, these are averaged results.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

#### 4. Joseph (Jose) Rivas

Time Clinical Research, Inc.  
2620 Zoe Avenue  
Huntington Park, CA 30255

- a. **What was inspected:** Areas covered during the inspection include PI oversight, conduct of the study, study recruitment, informed consent, 1572s, financial disclosure, training, qualifications, screening and enrollment, monitoring, source documents, drug accountability, review of the eCRF, primary and secondary efficacy endpoint data, IRB correspondence and approval, correspondence between sponsor and site, and general and specific instructions included in the assignment. All subject records (22) were reviewed.

- b. **General observations/commentary:** The FDA inspector attempted to pre-announce the inspection of Dr. Joseph Rivas (Site #10109). It was difficult as he did not answer the phone at the listed site. Dr. Rivas did not have any of the medical records for Study 1245.23. All records were stored at Time Clinical Research, Inc. Time Clinical Research, Inc. is owned solely by (b) (4)

(b) (4)  
also owns another clinical research organization called (b) (4)  
which is also located at the same location. (b) (4) secures  
studies for her site and contracts with physicians to serve as the Principal Investigator. The IRB for the inspected study was (b) (4)  
(b) (4)

For Study 1245.23, 22 subjects were screened, 15 subjects were enrolled and 11 subjects completed the study. All subjects were given a choice on whether they wanted to sign the informed consent forms in either English or Spanish.

Nineteen of the 22 subjects that were screened/enrolled chose to sign the informed consent forms in Spanish. Consent was obtained for all 22 subjects prior to their enrollment into the study and the appropriate IRB approved version of the ICF was utilized. Subjects were re-consented with newer IRB approved consent forms if they were still in the study.

The clinical investigator's study related source documents at the site were organized, complete and legible. A separate three ring binder was maintained for test article accountability. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint data was verifiable. There was no evidence that there were duplicate subjects who were screened and randomized at multiple investigator sites.

The site's case report forms were electronic records. Data was entered into the site's electronic CRF's (case report forms) via remote data capture (RDC). The eCRF data was available to the FDA inspector on a CD-R. Information that was created or modified on the eCRF had an audit trail which included date/time stamps, the name of the individual inputting the data and also identified the change that was made in order to ensure data authenticity and integrity. Dr. Rivas maintained other study related information in addition to source documentation and the informed consent forms, including correspondence and regulatory documents contained within binders, investigational product records, monitor sign-in logs, subject enrollment logs which include the subjects that consented to the study. All pertinent information was reported to the sponsor, such as IRB approval. There were no discrepancies.

Training was provided through a Live Investigator Webcast which covered the specific protocol, a Boehringer Ingelheim US Diabetes General Session Live Investigator Meeting Webcast, and at the trial initiation visit by the monitor on 2/2/11. There was no documentation showing that three of the study coordinators received training. Dr. Rivas said that they were all trained and that he went over the protocol; however records were not maintained of this training.

It was observed that the site's Temperature Logs for the Drug Room had the maximum storage temperature reaching 86°F on a number of days. According to the protocol, the trial medication "must be kept in its tightly closed original packaging under the recommended storage conditions on the label". According to the packaging, the storage conditions should be (b) (4) (59°-77°F).

FDA was notified February 17, 2012 that the sponsor had closed the site based on failure to adhere to the signed agreement (Form FDA 1572), the general investigational plan, Good Clinical Practice, ICH guidelines, and Federal Regulations. There was lack of clinical investigator (CI) oversight, enrollment of subjects who did not meet entry criteria, failure to secure clinical documents to support eligibility, and failure to approve RDC entries in a timely manner. All 15 enrolled subjects had completed the trial before the site was closed.

The FDA inspector was asked to review all of the subject records referenced in the sponsor allegation, and verify and document the allegations. The inspection revealed that the firm had made corrections to observations noted on the Study Site Closure For Cause letter from the sponsor (complaint), as well as confirmed some of the allegations.

At the conclusion of the inspection, a one-item Form FDA 483 was issued for the following:

**1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.**

- Per protocol section 3.3.3, “Exclusion criteria” #1, subjects are excluded from the study if they have uncontrolled hyperglycemia with a glucose level >240 mg/dL (>13.3 mmol/L) after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day).

One out of 15 subjects randomized into the study met exclusion criteria #1 and was not excluded from the study based on elevated blood glucose levels of >240 mg/dL. Subject #37140 was screened for the study on 4/4/11, was enrolled in the placebo run-in period on 4/11/11 and was randomized into the study on 4/25/11. On six occasions during the placebo run-in period the source documentation indicates that the blood glucose levels were greater than 240 mg/dL on the first reading of the day as listed in the table below:

Date	FPG Results
4/11/11	360 mg/dL
4/17/11	276 mg/dL
4/18/11	292 mg/dL
4/19/11	286 mg/dL
4/21/11	262 mg/dL
4/23/11	272 mg/dL

- Per protocol section 5.3.3, “Meal tolerance tests”, a MTT (meal tolerance test) will be an optional (not in the open label arms) part of this trial.

Three out of 15 subjects (subject # 37121, 37125 and 37127) placed into the open label arm of the study had a meal tolerance test performed at Visit 3 which was an optional test for subjects enrolled into the double blind study only.

**OSI Comment:** Dr. Rivas responded to the 483 item. He acknowledged that Subject #37140 was inadvertently randomized on 4/25/11 due to oversight. He also

acknowledged that the meal tolerance test should not have been performed on the three subjects. All deviations had been previously reported to the IRB and sponsor. Corrective actions have included staff training and the institution of a weekly meeting at the site with the PI and staff as well as a monthly meeting to retrospectively look at the protocol adherence. The PI will also review all the procedures on the day of the visit of the subjects at all times.

Four discussion items not included on the FDA-483 were addressed during the close-out of the inspection regarding the following: 1) ensuring that the study drug is stored under appropriate temperatures; 2) documenting in the source documents when the site contacted or attempted to contact a subject regarding their missed appointment in the event that the subject's next visit is out of window; 3) including the subject number on all pages of medical history source documents and; 4) providing subjects with Spanish translated forms that are available during the study when the subject signs a Spanish version of the informed consent form.

**c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. (Note: From review of the clinical study report, although the site was closed, the sponsor included this site's data in the analyses).

## 5. Andrew Lewin

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**a. What was inspected:** All 45 subjects' informed consents were reviewed. All randomized subjects' source records were compared to the data line listings for the primary efficacy endpoint. All records were compared to the adverse event data listings.

**b. General observations/commentary:** There were 45 subjects screened, 36 subjects randomized, and 32 subjects completing the study. The first patient was screened on 6/29/2010 and the trial closed 2/3/2012. There was no under-reporting of adverse events and the primary efficacy endpoint was verifiable.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

**c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**6. Azazuddin Ahmed**

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- a. What was inspected:** This was a for-cause inspection to confirm the findings found at the site by the sponsor. The sponsor had terminated the site's participation in study 1245.31 due to noncompliance and possible fraudulent activities by an employee at his site. The clinical investigator (CI) reported to the sponsor in April 2012 before interim database lock that the primary study coordinator for study 1245.31 had been recording multiple unscheduled visits for three subjects in the study which did not occur. This was substantiated when the CI contacted the three subjects to verify the allegations; the coordinator was also taking stipends that were to be allocated to the subjects had they actually had the unscheduled visits; and the coordinator had submitted blood samples from one subject and labeled the samples as if they were from two other subjects. The sponsor conducted an extensive investigation May 2012 into the past and present studies conducted by the CI, done by an external consultant. Fifteen patients with potentially fraudulent data had participated in trial 1245.31. The sponsor audit revealed that the data integrity concerns extended beyond the data identified by the CI and revealed that CI oversight and supervision was insufficient. This extended into the preceding study 1245.23. The data from these 25 subjects were excluded from all analyses (efficacy and safety).

The findings led to the initiation of procedures described in the BI SOP "001-MCS-80-609 Corporate Standard Operating Procedure: Serious Non-Compliance and Suspected Fraud in Medicine & QRPE. Version 4.0," which deals with the corrective actions taken as a result of fraud at Dr. Ahmed's site. (This document was requested by OSI from the Sponsor for review).

The inspection also extended to include study 1218.74 "A multicenter, international, randomized, parallel group, double blind study to evaluate cardiovascular safety of linagliptin with glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk- Carolina Protocol".

- b. General observations/commentary:** In Study 1245.23, the site had enrolled a total of 25 patients. For Study 1245.31, 13 subjects were screened, 13 subjects were randomized, and 13 subjects were active when the site was closed. The clinical study report says that 15 subjects were rolled over into the 1245.31 trial, but only 13 subjects could be confirmed at the site inspection. Of note, the letter dated April 20, 2012 informing the FDA about the site closure also mentions 13 subjects, not 15.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

### **OBSERVATION 1**

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically,

- A. The Principal Investigator did not ensure that all associates and colleagues assigning in the investigation were meeting the commitments of the study protocols and regulations. For example:
- i. BI Trial 1245.31: The Principal Investigator discovered laboratory results for an unscheduled visit dated 3/10/2012 for Subject 47701. The Principal Investigator contacted the subject and confirmed that the patient's visit and blood collection had never occurred. The Principal Investigator contacted at least two more subjects (47702 and 48431) who also confirmed that the unscheduled visits and blood collections had never occurred. Further investigation confirmed approximately forty-eight (48) unscheduled visits involving approximately twelve (12) subjects where there were no physician orders for the blood sample redraws. Study coordinator (b) (4) submitted the requisition forms for each laboratory test. Dr. "AA" confirmed that each unscheduled visit identified was not assessed medically by Dr. "AA". There was no case report forms (CRFs) filled out for those visits. Dr. "AA" stated that the validity of the data related to the blood collections could not be confirmed.
  - ii. BI Trial 1245.23: Approximately seventeen unscheduled visits with laboratory results which could not be confirmed by Dr. "AA" were noted. (b) (4) study coordinator submitted the requisition forms for each laboratory test. There were no CRFs filled out for those visits; there were no physician orders for repeat laboratory tests; there were no progress notes for the unscheduled visits. Dr. "AA" stated that the validity of the data related to the blood collections could not be confirmed.
  - iii. BI Trial 1245.31: Numerous blood collection values for the Fasting Plasma Glucose (FPG) laboratory results were the same and related in date span and results. There were no CRFs filled out for those visits; there were no physician orders for repeat laboratory tests; there were no progress notes for the unscheduled visits. Dr. "AA" stated that the validity of the data related to the blood collections could not be confirmed. For example:

Subject No.	Visit No.	Date Lab Drawn	Draw Time	Lab Test	Results
47702	Unscheduled	11/18/2011	09:40	FPG	143
48432	Unscheduled	11/18/2011	09:40	FPG	143

47701	Unscheduled	03/10/2012	08:15	FGP	104
48431	Unscheduled	03/10/2012	08:15	FGP	104

- iv. BT Trial 1245.23: Numerous blood collections values for the Fasting Plasma Glucose (FPG) laboratory results were the same and related in date span and results. There were no CRFs filled out for those visits; there were no physician orders for repeat laboratory tests; there were no progress notes for the unscheduled visits. Dr. “AA” stated that the validity of the data related to the blood collections could not be confirmed. For example (not all inclusive):

Subject No.	Visit No.	Date Lab Drawn	Draw Time	Lab Test	Results
30680	7	11/04/2011	10:37	FGP	120
30678		11/04/2011	10:40	FGP	120

- v. BT Trial 1218.74: Numerous blood collections values for the Fasting Plasma Glucose (FPG) laboratory results were the same and related in date span and results. There were no CRFs filled out for those visits; there were no physician orders for repeat laboratory tests; there were no progress notes for the unscheduled visits. Dr. “AA” stated that the validity of the data related to the blood collections could not be confirmed. For example (not all inclusive):

Subject No.	Visit No.	Date Lab Drawn	Draw Time	Lab Test	Results
27813	3	01/31/2012	10:30	FGP	125
27816	3	01/31/2012	08:50	FGP	125
26292	6	03/05/2012	08:45	FGP	144
26296	6	03/05/2012	09:00	FGP	144
26265	1a	08/17/2011	10:00	HbGA1c	7.4
26266	1a	08/18/2011	09:05	HbGA1c	7.4

- B. The Principal Investigator, Dr. “AA”, failed to ensure that the study coordinators who were responsible for obtaining informed consent, making CRF/eCRF entries, maintaining essential documents, and dispensing/administering study drug had adequate educational and/or professional experience prior to participating in Protocols 1245.31, 1245.23 and 1218.74.
- i. (b) (4) study coordinator for protocols 1245.31 and 1245.23 obtained medical histories and performed medical assessments for numerous subjects without supervision from the principal investigator. (b) (4) was purportedly trained as a medical doctor at the (b) (4). However, there was no documentation present that indicated any

- license for (b) (4) to practice in the United States. The Trial Staff List did not indicate delegation of (b) (4) to perform medical assessments and past medical history. The principal investigator failed to list (b) (4) on the Form FDA 1572.
- ii. (b) (4) study coordinator for protocol 1218.74 obtained medical histories and performed medical assessments for numerous subjects without supervision from the principal investigator. For example, (b) (4) medically assessed Subject 26261. The subject records included a Note to File stating “Subject 26261’s medical records state that the subject had diverticulitis. After speaking with the patient today, patient states they do not have or ever had diverticulitis and is asymptomatic.” This was signed by (b) (4) study coordinator on 12/15/2011. The Trial Staff List did not indicate delegation of (b) (4) to perform medical assessments and past medical history. The principal investigator failed to list (b) (4) on the Form FDA 1572.

- C. The Principal Investigator failed to follow the protocols to ensure all subjects’ medical records from other providers were received prior to randomization of the subjects into the studies. The source documents were inadequate to substantiate inclusion/exclusion criteria for the following:
  - i. Trial 1245.31: Approximately five subjects’ medical records were not received from the previous physician.
  - ii. Trial 1245.23: Approximately eleven subjects’ medical records were not received from the previous physician. The principal investigator failed to maintain/store medical records for approximately nine subjects who subsequently were rolled-over for enrollment into study 1245.31. Those medical records were filed with the second study and were not easily available for review. The principal investigator failed to have a set of medical records available for both studies.
  - iii. Trial 1218.74: Approximately eleven subjects’ medical records were not received from the previous physician.
- D. The Principal Investigator failed to ensure assessment of subject eligibility was documented prior to the following subjects being enrolled into the study:
  - i. Trial 1245.31: Subject Eligibility Worksheet were not signed prior to the subjects’ Visit 1 date for the following:

Subject	Visit 1 Date	Date Eligibility Worksheet Signed	Comments
47703	07/26/2011	08/11/2011	Eligibility reviewed worksheet was not available on that date
47708	09/01/2011	09/06/2011	Eligibility “reviewed by phone”
47709	09/01/2011	09/06/2011	Eligibility “reviewed by phone”

- ii Trial 1218.74 was not followed for inclusion/exclusion criteria. Numerous subjects received prohibited medication (sulphonylurea) and were later enrolled into the Beta Cell sub-study for MTT (meal tolerance test). For example (not all inclusive):
- a. Subject 27826 was prescribed glipizide (sulphonylurea) and metformin. There was no documentation noted by the principal investigator assessing the subject's use of the prohibited medication. The subject did not have any medical records from their previous primary care physician on file. Source documents indicated the medical history was verbally obtained from the subject dated 3/10/2012 by (b) (4), the study coordinator. The file did not include the subject's Concomitant Medication Form. A handwritten list of current medications was indicated on back of the subject's Medical History Form.
  - b. Subject 27827 was prescribed glipizide (sulphonylurea), which was indicated on the subject's Concomitant Medication Form. There was no documentation noted by the principal investigator assessing the subject's use of the prohibited medication. The subject did not have any medical records from their previous primary care physician on file. Source documents indicated the medical history was verbally obtained from the subject dated 3/12/2012 by (b) (4), the study coordinator.
  - c. Subject 27828 was prescribed glipizide (sulphonylurea), which was indicated on the subject's Concomitant Medication Form. There was no documentation noted by the principal investigator assessing the subject's use of the prohibited medication. The subject did not have any medical records from their previous primary care physician on file. Source documents indicated the medical history was verbally obtained from the subject dated 3/13/2012 by (b) (4), the study coordinator. The principal investigator failed to review and sign the subject's Concomitant Medication Form.

**OSI Comment:** Dr. Ahmed responded that these subjects were screen failures and were never enrolled into the study.

## **OBSERVATION 2**

Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects. Specifically,

- A. The Drug Accountability Logs for Protocols 1245.31, 1245.23 and 1218.74 were not inventoried by the principal investigator or other study colleagues who were delegated to perform the task. The Drug Accountability Logs included a handwritten notation that stated that the study drugs were "dispensed before inventory". The logs did not include any initials or signature of the clinical site staff. (*In Dr. Ahmed's*

*response, he states that the referenced handwritten notation was made by the study monitor).*

- B. The pre-printed Investigational Product Dispensing Form for protocol 1245.31 included the incorrect number of blisters and/or tablets dispensed. The accuracy of the number of drug product dispensed and subsequently returned by the subjects could not be verified due to the inaccurate accounts identified. The primary study coordinator (b) (4) who dispensed the study drugs failed to correct the numbers of drug product dispensed. Dr. "AA", Principal Investigator" signed each form dated 9/24/2012. However, Dr. "AA" failed to identify each discrepancy. For example, for the following subjects:
- i. Subject 47706 Visit 4 dated 3/09/2012 pre-printed form indicated 14/294 blisters/tablets dispensed. The correct amounts that should have been dispensed were 14/196 blisters/tablets.
  - ii. Subject 47707 pre-printed form indicated 14/294 blisters/tablets dispensed for Visits 2-4 dates 10/17/2011, 12/22/2011, and 3/10/2012. The correct amounts that should have been dispensed for each were 14/196 blisters/tablets.
  - iii. Subject 47708 Visit 4 dated 3/13/2012 pre-printed form indicated 14/294 blisters/tablets dispensed. The correct amounts that should have been dispensed were 14/196 blisters/tablets.
  - iv. Subject 47709 Visit 1 dated 9/01/2011 pre-printed form indicated 7/147 blisters/tablets dispensed. The correct amounts that should have been dispensed were 7/98 blisters/tablets. Visits 2-4 dates 10/13/2011, 12/29/2011, and 2/23/2012 pre-printed form indicated 14/296 blisters/tablets dispensed. The correct amounts that should have been dispensed for each visit were 14/196 blisters/tablets.
  - v. Subject 47710 Visit 1 dated 9/07/2011 pre-printed form indicated 7/147 blisters/tablets dispensed. The correct amounts that should have been dispensed were 7/98 blisters/tablets. Visit 2 dated 10/22/2011 pre-printed form indicated 14/294 blisters/tablets dispensed. The correct amount that should have been dispensed were 14/196 blisters/tablets.

**OSI Comment:** In Dr. Ahmed's response, he states that the sponsor supplied the wrong labeled forms. When the error was initially discovered, the forms were to be corrected until updated forms could be obtained but the corrections were not consistently applied. He is confident that all the calculations were based upon the known study dispense count of 196 tablets, although there is no documentation of such.

- C. Study drug accountability was not properly maintained to adequately document use by each subject and demonstrate reconciliation of all investigational products.

- i. Protocol 1245.31: Subject 47710's source documents indicated that subject left the investigational product at home. There was no further information to indicate whether the investigational product was returned. For example:
  - a. The Investigational Product Dispensing Form included a handwritten notation for Visit 1 dated 9/07/2011 which stated, "Not returned 5/15/2012". The dispenser's initials for (b) (4). The study coordinator (b) (4) dispensed the study drug for (b) (4), the study coordinator who was primarily responsible for this study.
  - b. The Investigational Product Dispensing Form included a handwritten notation for Visit 2 dated 10/22/2011 which stated, "returned not able to calculate" the dispenser's initials indicated for (b) (4). The study coordinator (b) (4) dispensed the study drug for (b) (4), the study coordinator who was primarily responsible for this study.
- ii. Protocol 1218.74: Numerous subjects did not return all dispensed products. The treatment compliance calculations were not performed using the actual number of tablets returned but from the subjects' verbal reports for the missing drug products. For example:
  - a. Subject 27816, Kit No. 508612, one card of investigational product was not returned due to the subject stating "losing it".
  - b. Subject 26253, Kit No. 501916, one card of investigational product was not returned due to the subject stating "losing it".
  - c. Subject 262 253, Kit No. 616378, one card of investigational product was not returned due to the subject stating "losing it".

### **OBSERVATION 3**

Failure to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

Specifically,

- A. Protocol 1218.74: The principal investigator failed to report an SAE for Subject 26297 to the sponsor within 24 hours of discovery. The subject experienced chest tightness on 1/24/2012. The progress note dated 4/18/2012 indicated that the SAE required reporting to the sponsor. The SAE was reported to the sponsor dated 4/27/2012.

**OSI Comment:** Dr. Ahmed states that it was determined that the event was not an SAE as the subject was not hospitalized. He acknowledged that the progress notes did not include this updated information. He has since changed the SOP on "Subject Documentation and Medical Records".

**OBSERVATION 4**

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically,

- A. Protocol 1245.31: There was no source document maintained by the principal investigator of an SAE for Subject 47710. The subject was hospitalized due to an infection in the left toe. The principal investigator failed to obtain medical records related to the SAE and further provide the sponsor with documentation pertaining to the SAE. (*Dr. Ahmed acknowledged the lack of supporting documents. He states the medical records were received after the sponsor closed the site.*)
- B. Protocol 1218.74: Numerous Adverse Event Forms for Subject 26294 were not completed contemporaneously by the principal investigator. The adverse event Forms included handwritten notations stating “Late entry. Reviewed on the date of the visit. Signed late”. The principal investigator signed and dated the entries on 2/2/2012. The source documents did not include any information referencing the dates each adverse event was reported by the subject or the dates the events were submitted to the sponsor. For example:
1. An adverse event of fatigue which started on 10/31/2011.
  2. An adverse event of lightheadedness which started on 11/01/2011.
  3. An adverse event of hypoglycemia which started on 11/15/2011.
  4. An adverse event of dizziness which started on 11/19/2011.
  5. An adverse event of headache which started on 11/20/2011.
  6. An adverse event of fatigue which started on 11/23/2011.
  7. An adverse event of dizziness which started on 11/26/2011.
  8. An adverse event of weakness which started on 2/17/2012.

**OSI Comment:** Dr Ahmed acknowledged the deficiencies and enhanced his SOP “Subject Documentation and Medical Records” and site staff underwent training.

- C. Protocol 1218.74: Subject 29269 reported a toothache and headache that continued over various study visits. The study coordinator <sup>(b) (4)</sup> recorded the events. There was no documentation that medical intervention occurred.

There were also several discussion items at the close-out meeting:

1. Numerous medical record release forms sent to the subjects’ previous physicians were on a fax cover sheet letterhead that included another sub-investigator name, and a different establishment name. The use of the form did not accurately inform the medical records department receiving the request that the intended purpose of the release was for research that was conducted by Dr. “AA”, Principal Investigator at Apex Medical Research

- (AMR), Inc.
2. Subject 47709 Weekly Home Blood Glucose Monitoring (WHGM) Log and Food Log were not reviewed in a timely manner. The HBGM Log was filled out by the subject from 9/06/2011 to 10/13/2011. The principal investigator signed the log dated 1/02/2012. The Food Log was filled out by the subject from 10/10/2011 to 10/12/2011. The principal investigator signed the log dated 3/24/2012.
  3. Protocol 1245.23: Several Informed Consent forms included discrepancies in relation to the subjects' primary care physician (PCP). For example:
    - a. Subject 30670 marked, "No, I do not want the study doctor to inform my PCP/specialist of my taking part in the study". The subject's source document indicated that the principal investigator is the subject's PCP.
    - b. Subject 30681 marked, "No, I do not want the study doctor to inform my PCP/specialist of my taking part in the study" and "The study doctor is my PCP/specialist" and that the principal investigator is the subject's PCP.
  4. Protocol 1218.74: Numerous subjects' files were filed in an accordion file with other files. Only a single sheet of paper separated one file from the next. The file system made it difficult to access a single file. The file system has a great possibility to misfile documents with another subject's documents.

**OSI comment:** Dr. Ahmed did respond to the 483 items. He acknowledged the misconduct of the study coordinator, saying that it was identified internally and reported to the sponsor and IRB within 12 days of discovery. An initial Misconduct Investigation and CAPA Plan were developed May 21, 2012 (which was submitted with the response). An updated version was submitted to the FDA investigator and also with the response. Improvements detailed in the CAPA include (1) hiring of additional resources such as a physician, nurse practitioner, site manager, an onsite dedicated phlebotomist service and a quality control manager (2) revisions to existing SOPs and creation of new SOPs to better define investigator oversight requirements, process for documented approval by Investigator of any unscheduled visits, and documentation requirements for all progress notes and other study related activities (3) creation and delivery of new site training programs to include instruction on GCP, ethics, and SOP revisions.

- Dr. Ahmed listed the hired staff and provided their curriculum vitae. A recent internal audit was done to gauge the effectiveness of the changes. The results of the audit were also sent with the response.
- A new "Unscheduled Visits SOP" was developed and submitted with the response, which requires all such visits to be approved by the PI or sub-PI. New case report forms were developed. Training on the SOP was sent with the response.

- A new SOP “Subject Payments” was developed to ensure payments are made via check only with multiple staff signing off.
  - Ethics training was introduced with documentation sent with the response.
  - An SOP “Obtaining Medical Records” was written and sent with the response.
  - An SOP “Patient Management” was written which no longer allows telephone approval of subjects for enrollment. An investigator will now be on site during all open clinic hours, allowing onsite review of required documentation. Training documentation on this SOP was submitted with the response.
- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. The audit confirmed the sponsor’s findings indicating serious deviations/findings that would impact the validity or reliability of the submitted data. Although steps have been taken by the site to diminish the chances of similar occurrences in the future, the data from this site for 1245.23 and 1245.31 are not reliable. This is also reflected in the sponsor’s decision to exclude all data at the site from analyses.

## 7. Danny Sugimoto

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- a. What was inspected:** Informed consent forms for all subjects were reviewed. IRB approvals and communications, staff training and qualifications, monitoring logs, and drug accountability were reviewed. Five subject files were reviewed for inclusion/exclusion criteria, efficacy and safety endpoints, adverse events, protocol deviations, discontinuation, concomitant medications and a comparison of source documents vs. eCRFs.

The pending complaint on file was also evaluated.

- b. General observations/commentary:** There were 20 subjects screened, nine subjects randomized, and two subjects transferred from another site (11 total). In general, the firm’s record-keeping was very sloppy. The study coordinator made many corrections in the source document worksheets (e.g. study medical compliance calculations) and needed to correct a lot of data entry errors in the eCRFs as a result of the monitoring visits – more than seen with other inspections of this type. However, there was no indication that there was falsification of the data. There was evidence of under-reporting of AEs, specifically urinary tract infections. Primary efficacy endpoint data was

verifiable.

Regarding the pending complaint, a monitor for another IND (b) (4) claimed that the study coordinator was under-trained and very overwhelmed and making up data, drug accountability was lacking, and there were subjects (11) that were consented with the wrong informed consent document. The study coordinator referenced in the complaint was not the same as the study coordinator for Study 1245.33. The site did not have any issues with consent forms for this study.

Regarding staff training and oversight:

- The Delegation Log lists (b) (4) as trial staff from 10/8/2009 – 9/5/2012. (b) (4) dispensed study medication for this trial on numerous occasions, including 10/28/2010, 1/18/2011, 4/3/2011, (Subject #6491) and 1/19/2011 (Subject #6495). There is no record that she attended any training in the conduct of this study.
- The Delegation Log lists (b) (4) as Sub-Investigator in this study from 10/8/2009 – 9/5/2012. The Site Training Form indicates that (b) (4) received training on the study on 10/23/2009 after the trial had begun.
- There is no record that study staff received training for Protocol Amendments #1 and #3.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

### **OBSERVATION 1**

Investigational drug disposition records are not adequate with respect to quantify and use by subjects. Specifically,

- A. There were two discrepancies between the amount of study drug returned by subjects to the Investigator and the amount of study drug returned by the Investigator to the sponsor. Study records indicate the following:
  - i. Subject 6491. On 3/30/2010, the subject was dispensed Med. No. 20777, including 36 tablets of Bottle A and 36 tablets of Bottle B. On 5/11/2010, the subject returned 33 tablets for Bottle A and 33 tablets for Bottle B. On 5/22/2012, the field monitor indicated that an empty inventory of Med No. 20777 was returned to the Sponsor.
  - ii. Subject 5778. On 9/20/2011, the subject was dispensed Med. No. 27605, including 36 tablets of Bottle A and 36 tablets of Bottle B. On 12/06/2011, the subject returned 31 tablets for Bottle A and 31 tablets for Bottle B. On 5/22/2012, the field monitor indicated that a full inventory of Med. No. 27605 was returned to the sponsor.

- B. There was incomplete recordkeeping for study medication dispensation. Study records indicate the following:
- i. Subject 6504. On 4/12/2010, the subject was dispensed Med. No. 20728 and 20731. There is no documentation of the number of tablets dispensed for Med No. 20731.
  - ii. Subject 6495. On 5/14/2010, the subject was dispensed Med. No. 20919, 20923, and 20927. The site did not maintain documentation of kits 20923 or 20927 by affixing the Med. No. stickers to the Investigational Product Accountability Form.

## **OBSERVATION 2**

An investigation was not conducted in accordance with the investigational plan. Specifically,

- A. The protocol defines exclusion criteria #1 as uncontrolled hyperglycemia with a glucose level > 240 mg/dl after an overnight fast or > 400 mg/dl in a randomly performed measurement during placebo run-in with confirmation by a second measurement.
- i. Dr. Sugimoto signed the Inclusion/Exclusion Criteria Worksheet for Subject 6495 on 12/21/2009 indicating that this subject met inclusion/exclusion criteria. He did not review the subject's glucose testing results until 12/23/2009.
  - ii. Dr. Sugimoto signed the Inclusion/Exclusion Criteria Worksheet for Subject 6509 on 6/2/2010 indicating that this subject met inclusion/exclusion criteria. He did not review the subject's glucose testing results until 6/4/2010.
  - iii. Dr. Sugimoto signed the Inclusion/Exclusion Criteria Worksheet for Subject 6491 on 12/15/2009 indicating that this subject met inclusion/exclusion criteria. He did not review the subject's glucose testing results until 12/22/2009.
- B. The protocol defines an asymptomatic urinary tract infection (UTI) as an adverse event if a subject's urinalysis (UA) is positive for white blood cells (WBC) and/or nitrate. It further instructs Investigators to have the subject return to the site in order to evaluate symptoms and obtain a repeat urine sample for confirmatory testing. The following subjects showed WBCs in their urine and Dr. Sugimoto failed to instruct them to return to the site for follow-up or report the adverse event:
- i. Subject 6495. On 12/21/2009, 5/14/2010, and 1/19/2011 the subject's UA was positive for WBCs. The investigator failed to instruct him to return to the site for follow-up or report the adverse event.
  - ii. Subject 6509. On 6/21/2010, 12/14/2011, and 1/11/2012, the subject's UA was positive for WBCs. The investigator failed to instruct him to return to the site for follow-up or report the adverse event.
  - iii. Subject 6499. On 2/3/2010 and 4/28/2010, the subject's UA was positive for WBCs. The investigator failed to instruct her to

return to the site for follow-up or report the adverse event.

**OSI Comment:** The PI responded to the 483 deficiencies. He believes the drug accountability discrepancies occurred in marking a partial bottle as Full and a partial bottle as Empty on the Sponsor Drug Return form. The SOP for drug accountability was updated to specifically address return of drug to sponsor to include a double check of all study drugs being returned to the sponsor. Training on this SOP was also expanded to semi-annually from annually.

The PI acknowledged that there was human error with the incomplete record keeping for study medication dispensation. For Subject 6495, the labels for the kits were lost. The Control of Investigational Drug SOP was updated to include that a second study coordinator confirm that the drug kit labels are placed in the correct section of the source document and that the documentation of dispensed drug is complete. Training on this SOP and drug accountability training was expanded to semi-annually from annually. The study schemas were also updated to include a section for drug labels and written documentation being performed as completed.

Regarding the WBCs in the UAs for several subjects, the PI stated that he misinterpreted the protocol. Since the UAs were negative for nitrates, he interpreted them as being normal. [In case of suspected UTI (symptomatic or asymptomatic) during the trial, a urine culture sample was to be taken and sent to the central laboratory for confirmation of the diagnosis. For immediate identification of asymptomatic UTIs, a dipstick-test (leukocyte esterase for WBCs and nitrite) was to be performed at the site at each safety visit with urinalysis. In case of a positive result at the site, a urine culture sample was to be taken and sent to the central laboratory for confirmation of the diagnosis].

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

## 8. Michael O'Mahony

The London Road Diagnostic Clinic  
481 London Road  
Sarnia, Ontario Canada

- a. **What was inspected:** For Study 1245.19, 100% verification of presence of CRFs, worksheets, medical records and informed consent forms (ICFs). Fourteen records were reviewed for primary efficacy/secondary efficacy endpoints. For Study 1245.23, 100% verification of presence of CRFs, worksheets, medical records and ICFs. Nineteen records were reviewed for primary efficacy/secondary efficacy endpoints. Staff training, qualifications,

IRB review and approval, and drug accountability were also reviewed.

- b. **General observations/commentary:** None of the records (medical records, worksheets) were electronic. The medical records were disorganized (loose papers, out-of-date order, etc.); however, they appeared to be complete. For Study 1245.19, there were 24 subjects screened and 19 subjects enrolled. There was no under-reporting of adverse events and the primary efficacy endpoint data was verifiable. For Study 1245.23, there were 26 subjects screened and 19 subjects enrolled. There was no under-reporting of adverse events and the primary efficacy endpoint data was verifiable.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued. However, there were several discussion items:

- Screening/enrollment logs did not include formal first, middle and last names
- On a few screening forms, the information was signed off prior to receipt of screening labs, which then disqualified some patients
- There were a few discrepancies in records; i.e. some subjects were listed as a different race in some instances (appeared to be entry error)
- Dr. O'Mahony is in private practice and all the patients were from his practice. In the medical files (dictated notes), there was no time of visit or updated list of medications. The flow sheet from the front cover was removed and replaced when patients entered a study. The original flow sheet filled out by patients or staff was discarded. The PI was told of the need to keep this information as it is part of the medical history and source documentation.
- Subject 10058 had ulcerative colitis, Crohn's disease, total removal of the small intestine and a colostomy bag. The site contacted the sponsor to see if this patient could be included. The only problem mentioned in the email was the colostomy bag. The sponsor said it was up to the PI to determine if malabsorption was a problem by reviewing the history and lab results; the PI was told to comment in the CRF. The only mention in the CRF was that there were no current problems so the subject was entered. There is no information as to what was used to determine his status (lab work, etc.).
- For Subject 31430, the medical chart appeared to be a Xerox copy of original files. However, the FDA inspector reported that this was not provable.
- For a few of the patients on Study 1245.23, there were notes concerning the patients' FPG readings; however, the subjects' logs were not present. Per the study coordinator, sometimes the patients did not return the logs but she always verified the readings with the subjects' glucose meter. However, she did not record this information anywhere.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not

available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

**9. Howard Conter, M.D.**

MSHJ Research Associates Inc.  
2717 Gladstone St.  
Suite 106  
Halifax, NS Canada

- a. What was inspected:** There were 10 subject records reviewed. The inspection included 100% of all enrolled subjects' informed consent forms, review of staff training and qualifications, Clinical Trial Agreement with the sponsor, IRB approval and correspondences, financial disclosure forms, sponsor/IRB correspondence, delegation of duties, drug accountability records, monitoring log
- b. General observations/commentary:** During the course of the study, visits were conducted at 2717 Gladstone St. in Halifax until April 2013 when the location was closed and visits were conducted at the above listed physical address. The [REDACTED] (b) (4) [REDACTED] served as the ethics committee of oversight. There were 15 subjects screened, 10 subjects enrolled, and 4 subjects completed the study. The first subject was consented on January 5, 2011. This subject was randomized on February 7, 2011. The last subject was enrolled on June 8, 2011 and was randomized on July 6, 2011. The site did not participate in the extended phase of the trial. This site did not participate in the meal tolerance or body composition sub-studies.

The source documentation on file was organized, complete, and legible. Source documentation included, but was not limited to, informed consent forms, medical history, physical examinations, ECGs, laboratory results, food intake, blood glucose, and medication diaries, dietary counseling, subject questionnaires, and study drug dispensing records. During the course of the study, source data was entered directly into electronic case report forms. Comparison was made of the source records to the data listings provided with the assignment including, but not limited to HbA1c values, laboratory results, waist circumference, adverse and serious adverse events, concomitant medications, and hypo and hyper glycemic events. There were no discrepancies noted. Review of the monitoring reports did not disclose and significant deviations from the protocol or issues of noncompliance by the investigator or his staff. There were no discrepancies in the dispensing and use of investigational product.

Back in 2002, a sponsor terminated the site's involvement in another IND

(b) (4) for possible falsification of patient diaries and/or patients, several protocol violations, drug accountability and inadequate record-keeping. The IND is still open but it has been inactive for several years. During this inspection, there were no issues found of scientific misconduct or any egregious issues in documentation practices.

For Study 1245.28, the investigator failed to report an adverse event and failed to follow up on a positive urine dipstick test. Other adverse events were properly reported and there were no other significant deviations noted. Subject 80455 (b) (6)'s background metformin use was documented as both 1000 mg and 2000 mg, and doses administered during Visit 9 were documented as December 15, 2011, when the IVRS did not dispense the study drug until December 21, 2011.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

#### **OBSERVATION 1**

An investigation was not conducted in accordance with the investigational plan. Specifically,

1. The urine dipstick test conducted for Subject 80457 (b) (6) at Visit 2 was positive; however, there was no urine culture conducted in follow-up. (*OSI Comment: Lab results for the same visit note that a urine culture was not required. However, Section 5.2.3 of the protocol states that in the case of a positive result of a dipstick test, a urine culture sample has to be taken and sent to the central lab to confirm the presence or absence of a urinary tract infection.*)
2. An ear/sinus infection and subsequent concomitant medication was noted by Subject 80461 on the Weekly Home Blood Glucose Monitoring Log (20 September 2011), but was not noted in the adverse event log or in source documentation for Visit 8.

#### **OBSERVATION 2**

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

1. Progress notes documenting Subject 80455 medical history document a metformin background therapy of 1000 mg daily. Source documents reviewed for Visit 2 have a recorded total daily dose 2000 mg of metformin. (*OSI Comment: The protocol preferred a maximum tolerated dose of  $\geq 1500$  mg; however, with the discrepancy in the records, it is unclear as to the dose the subject was taking. At the close-out meeting, the study coordinator claimed the subject was on 2000 mg metformin.*)
2. IVRS confirmation at Visit 9 for Subject 80455 document the visit was

conducted on December 21, 2011. Worksheets for this visit document that the dose was taken on December 15, 2011 with the doses dispensed by the IVRS on December 21, 2011. (*OSI Comment: At the close-out meeting, the study coordinator stated that there was a note to file regarding this issue and that it was decided not to have the dates crossed out again, so they were left as is*).

Verbal items discussed with management included completing the delegation of authority log (The end date on the delegation of authority log was not signed by Dr. Conter), monitoring of the drug storage temperature during closed office hours, and counseling subjects (which often was not done per protocol regarding proper diet, exercise, and study drug compliance). Dr. Conter has served as a principal investigator since 1992. He informed the FDA investigator that he decided to close the research firm MSHJ Research Associates, and will no longer be conducting clinical research.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

#### 10. Thomas Elliott, MBBS, FRCPC

B.C. Diabetes Research  
2775 Laurel Street  
Rm 4178  
Vancouver, BC V5z 1m9  
Canada

- a. What was inspected:** There was review of the records of all enrolled subjects and all consents (screened and enrolled), staff qualifications, Clinical Trial Agreement (instead of a 1572), delegation of duties, test article accountability/disposition, IRB approvals, and enrollment logs. Also reviewed was the Health Canada/IRB required “Qualified Investigator Undertaking” (QIU) Form.
- b. General observations/commentary:** There were 15 subjects enrolled in the study and 13 completed (screened number was not captured). It was confirmed that no subjects were enrolled concurrently in any two protocols or at any other sites. The PI’s use of a non-validated electronic medical record system was demonstrated to be unreliable when confirming hardcopy raw data captured on worksheets for the protocol, but appeared adequate for clinical practice. The PI expectations of written and unwritten standard procedures was not always adhered to, and not always documented completely.

There was no evidence of under-reporting of adverse events. The primary

efficacy endpoint was verifiable. There were no instances when the raw primary efficacy endpoint data did not agree with the eCRF. However, there were three instances noted of data/eCRF conflict (the site completely omitted entering on the eCRF a Concomitant Therapy drug, hydrochlorothiazide; the subject's weight of 65.6 kg. was entered into the eCRF incorrectly as 65.5 kg.; a Concomitant Therapy drug strength was recorded as 5 mg, but entered into eCRF as 2.5 mg with no medical records /documentation to support eCRF value). These appeared to be isolated events.

An investigation was also conducted regarding the pending complaint. The sponsor of another IND discovered at the trial close-out visit that there were issues with improper record retention. All essential documents, informed consent forms, and subject case histories were scanned and immediately shredded without a validated quality control process. A review by the sponsor found a number of missing pages. It was verified during the inspection that all the raw data was destroyed for one of the two studies that had been conducted. An affidavit and records were obtained. The destruction was purported to be accidental/unintentional. The PI stated that he would no longer destroy any raw data and had no plans to digitalize records without a sponsor's concurrence and having a validated process to do so.

At the conclusion of the inspection, a Form FDA 483 was issued for the following:

#### **OBSERVATION 1**

Failure to provide adequate opportunity for subjects to read, review, and consult resources on content of the ICFs for protocol B110773. Specifically, ICFs were signed on the day of the first scheduled procedures and there is not complete accurate data to indicate subjects were provided a complete IRB approved copy in advance of date signed.

**OSI Comment:** The written SOP for the site directs that consenting is to be performed well in advance of Visit 1 for the study, and then final signatures of the subject and the PI are to be obtained at enrollment. The study coordinator said during the inspection that all consents were given to subjects in advance, but she failed to document the events.

#### **OBSERVATION 2**

Failure to adhere to the inspectional plan for study B110773. Specifically,

- A. Subject 31241's physical exam was performed after the scheduled V2 visit, when first drug dispensing occurred. (*OSI Comment: The medication provided at V2 is placebo run-in.*)
- B. Subject 31241's lab results contained eight out-of-specification data that were not signed/determined/reviewed in a timely manner, where the original report to the PI was 2 April 2011, and the review was documented 11 May 2011, more than six weeks past receipt.

- C. Subject 31247's lab results contained five out-of-specification data that were not signed/determined//reviewed in a timely manner, original reported 6 April 2011, and PI review documented 11 May 2011, more than five weeks post receipt.

**OSI Comment:** Dr. Elliott acknowledged the findings during the inspection and agreed that he did not review the labs in a timely manner. This will be corrected for future studies.

- D. In all subjects (14 total), it was documented (via "Note to File") and confirmed that the physical exam process includes a delegated person to record the findings on the exam raw data record while the PI performed the exam, then the PI would sign the record after the exam was recorded. (*OSI Comment: PEs were frequently completed/annotated in another person's hand writing but signed and dated by the PI. The FDA investigator suspected that the PEs were being done by the staff and not the PI, but this was never confirmed*).
- E. Subject 31241's case history contains PI letters addressed to subjects' primary care provider where the PI makes unsubstantiated statements of safety and efficacy of the study drug, at times of enrollment and ending of study site.

### **OBSERVATION 3**

Failure to prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,

- A. Subject 31253's concomitant therapy data includes hydrochlorothiazide 25 mg and it was not captured in the eCRF.
- B. Subject 31247's V3 weight value recorded on the raw data is 65.6 kg, but entered as 65.5 kg on the eCRF (weight was key secondary efficacy endpoint)
- C. Subject 31241's concomitant therapy worksheet has bisoprotocol 5 mg daily, but was entered into eCRF as bisoprotocol 2.5 mg daily.
- D. The study "Subject Master List" of subjects indicates the hospital/chart identification number to be "PI data" for 10 of 14 subjects. The "PI data" is determined to be maintained on an electronic health record (EHR) software system (Diabetes Patient Database), which is unreliable, and can be found inaccurate, and not containing current information of case histories for subjects enrolled. There is no hardcopy patient record of data in the EHR.
- E. Raw data for another protocol was destroyed inadvertently.

**OSI Comment:** There were many instances where the status of the study medications was inaccurate. The PI indicated during the inspection that he is in the process of replacing his EHR with another software version.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was

submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 11. Graham Ellis

Helderberg Clinical Trials Centre  
Suite 7G and H Arun Place  
Sir Lowry's Pass Road  
Somerset West 7129 ZAF Africa

- a. **What was inspected:** There was 100% review of 25 out of 36 randomized subject files. There was a 100% check of primary endpoints, informed consent, AEs, SAEs (including the review of CRFs and clinic visit notes) for all 69 subject files, as applicable.
- b. **General observations/commentary:** There were 69 subjects screened, 36 subjects randomized, and 34 subjects completed the study. The primary efficacy endpoint was verifiable. There was no evidence of under-reporting of AEs. Concerns regarding AE reporting for a study subject were clarified during the inspection. (The investigator listed symptoms leading to a diagnosis of a condition that was reported as an AE). For Subject 2955, the site re-classified the Renal Function Worsening as an SAE (not an AE as stated in the data listing).

There were no deficiencies observed pertaining to the drug accountability records. Overall drug compliance for study subjects completing the study was approximately between 87%-100%. Concerns regarding the timeliness of the site's annual continuous review submission to the Ethics committee were discussed. The site received approval in August but submitted their annual re-approval submission a little after a year (in November of the next year). The Ethics committee sent an e-mail stating in part that they expect the application for annual re-approval within one year of entering the first participant at the approved site. That being the case, the submission was submitted in a timely manner.

It was noted during the inspection that Visit 10 laboratory results for two study subjects were initially sent from the laboratory and later deleted by the laboratory. The laboratory responded that since the Visit 10 results for study subjects 2944 and 2946 were suspected to have been "mixed up", the decision was made at the central laboratory to delete the results for the initial bloods taken. The clinical investigator believes the mix up took place at the central lab and not at the site. For subject 3875, PK blood sample for the 8th hour "time point" wasn't collected. The site reported this as a deviation.

There was a recent inspection of Dr. Ellis for a different application (BLA

125431). Although there was not a Form FDA 483, there were several protocol violations discussed that the PI said he would correct.

1. The site used the wrong version of the informed consent form with some subjects and re-consented subjects late
2. The process to document when new protocols and informed consent forms were received and implemented was deficient
3. The site did not keep records of which refrigerator the test article was stored in while the study was ongoing
4. Amylase/lipase testing was not performed for one subject as required by the protocol.
5. An SAE fax notification form was not sent within 24 hours (only the eCRF was completed within this time frame) as was required by the protocol.

The FDA field investigator was able to verify corrections implemented by the site to these issues.

There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

## 12. Monojit Mukhopadhyay

Diabetic Clinic & Research Centre  
46A, Ritchie Road  
Kolkata 700019 India

- a. What was inspected:** All informed consent forms for all subjects were reviewed. Also inspected were monitoring and sponsor correspondence, financial disclosures, staff credentials, subject source records, drug accountability, enrollment logs, IRB approvals and correspondence, and case report forms. Three subject records for Study 1245.28 were fully reviewed and three subject files for Study 1245.36 were fully reviewed. A pending complaint from 2012 was also evaluated.
- b. General observations/commentary:** For Study 1245.28, there were 14\* subjects screened, 12 subjects enrolled, and 11 subjects completed. \*Due to initial screen failures, subjects 86119/86124 and 86117/86270 were re-enrolled under new subject numbers. The first subject was screened October 25, 2010 and the last subject follow up was July 19, 2013. For Study 1245.36, there were 7 subjects screened, 3 subjects enrolled and 3 subjects completed. There were no duplicate subjects enrolled at the site.

Information about the trial was given to potential patients several weeks before screening. The informed consent form was provided in English, Hindi and Bengali. All source documents were organized and kept in individual three-ring binders. The records were all legible, complete and kept in good condition. There were no issues noted regarding subject selection, randomization, protocol required procedures, or drug dosing. There were no concerns regarding the Drug Accountability Logs. Primary and secondary efficacy endpoints were verifiable.

Not all complaints/abnormal findings recorded in the progress notes were seen in the sponsor AE data listings. The PI explained that the complaints/abnormal findings he mentioned therein were not unexpected; that is why they were not reported to the sponsor. For example, for Study 1245.36 Subject 3289 at Visit 8 and 9 the blood pressure was elevated. Subject 3286 at Visit 6, 7, and 8 had elevated blood pressure. Dr. Mukhopadhyay stated that for both subjects he stopped their hypertension medication because of elevated potassium in the blood due to renal failure. Stopping this one medication caused the subject's blood pressure to rise, which was demonstrated in the recorded blood pressure readings. Because this event was not unexpected, he stated, it was not reported as an adverse event. *(OSI Comment: Per the protocol, it states "Changes in vital signs including BP, pulse rate, ECG, physical examination, and laboratory tests will be only recorded as AEs if they are not associated with an already reported AE, symptom or diagnosis, and the investigational drug is either discontinued, reduced or increased, or additional treatment is required, i.e. concomitant medication is added or changed" AND "Expected fluctuations or expected deterioration of the underlying disease and other preexisting conditions should not be recorded as an AE unless at least one of the following criteria is met: the worsening of the disease constitutes an SAE; the investigational drug is discontinued or the dose is reduced or increased; additional treatment is required, i.e. concomitant medication is added or changed; An unexpected deterioration from baseline has occurred in the opinion of the investigator".*

On January 3, 2012, OSI received a report from another sponsor alleging that Dr. Mukhopadhyay's site engaged in falsification of data in the course of recording study results. The study monitor observed that the study coordinator had pre-populated some of the source worksheet fields (i.e., height, weight, informed consent form narrative, and checked that required laboratory samples were collected) for a subject because she was going to be on leave. During a follow-up monitoring visit, the monitor confirmed that the subject's worksheet was corrected as necessary during the actual subject visit. Following the discovery of pre-recorded data, the study coordinator was replaced and site personnel retrained on good documentation practices including recording information on source documents in real-time not in advance. The site was not closed.

Regarding the pending complaint of falsification, the FDA inspector could not determine that falsification took place for the trials referenced, nor could it be demonstrated that Dr. Mukhopadhyay's oversight of the study was deficient.

At the conclusion of the inspection, a one-item Form FDA 483 was issued for the following:

#### **OBSERVATION 1**

There was no statement in the informed consent document that noted the possibility that the Food and Drug Administration might inspect the records.

**OSI Comment:** The site was not under IND and data was submitted by the sponsor under 21 CFR 312.120. Furthermore, the informed consent language does state that "health authorities" may be inspecting the records. When the FDA Form 483 was submitted to headquarters, a down-grade to NAI was determined.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

### **13. Jamal Ahmad**

Professor of Endocrinology  
Jawaharlal Nehru Medical University  
Centre For Diabetes and Endocrinology  
Faculty of Medicine  
Aligarh Muslim University  
Aligarh, 202002 India

- a. What was inspected:** All informed consent forms for all subjects were reviewed. Also inspected were monitoring and sponsor correspondence, financial disclosures, staff credentials, subject source records, drug accountability, enrollment logs, IRB approvals and correspondence, and case report forms. For Study 1245.28, five subject charts were fully reviewed. For Study 1245.36, two subject charts were fully reviewed.
- b. General observations/commentary:** For Study 1245.28, there were 17 subjects screened, 15 subjects enrolled, and 10 completed the study. The first subject was screened December 20, 2010 and the last subject follow up visit was June 20, 2012. For Study 1245.36, there were nine subjects screened, five subjects enrolled, and five subjects completed the study. The first subject was screened March 28, 2011 and the last subject follow up visit was May 9, 2012. There were no subjects that had duplicate enrollment.

The source records for both studies were almost illegible with handwritten notes

that were very poorly written as “diabetes notes”. Each page did not contain the subject ID number so it was very hard to link documents to subjects. The only records consistently kept with patient binders were the laboratory results, IVRS, ECGs and electronic visit tracking print-outs. All other worksheets such as inclusion/exclusion checklists, food diaries, doctor’s consultations, vitals, home blood glucose monitoring, etc. were intermittent or absent with the information, instead, kept in the diabetes notes. Adverse events and concomitant medications were hand-written in the diabetes notes. It did not allow for efficient review of the records. [The lack of use of the worksheets for the trials was discussed with the PI. There is no requirement in the protocol that this data be recorded on the forms. He chose to handwrite everything].

There were no issues noted in regards to subject selection, randomization, or administration of investigational product. Informed consents were in the languages of English, Hindi, and Urdu. There was adequate documentation to confirm each subject, subject availability during the study, exposure to test article, laboratory testing, and staff participation. There were no issues found regarding test article accountability. Primary and secondary efficacy endpoints were verifiable.

Adverse events reported in eCRFs were found in source notes after discussion with the PI, but the FDA inspector could not determine if adverse events were recorded in the notes but not reported in the eCRF because the quality of the handwritten notes were so poor. The inspection became focused on verifying that procedures were done.

For Subject 3241, the inclusion/exclusion criteria checklist was signed April 18, 2011 but the laboratory tests were not reported until April 21, 2011. This was brought to the attention of Dr. Ahmad. He showed that the subject’s home blood glucose monitoring log from April 4, 2011 to April 17, 2011 never exceeded 240 mg/dl, which qualified the subject for the trial. Drug compliance check forms were missing for Visits 3-10. Dr. Ahmad responded by showing notes of compliance in the source records. An asymptomatic UTI was not recorded in the eCRF. Dr. Ahmad stated that the leucocyte esterase and nitrite testing of the urine were negative so he did not consider it a UTI. [In case of suspected UTI (symptomatic or asymptomatic) during the trial, a urine culture sample was to be taken and sent to the central laboratory for confirmation of the diagnosis. For immediate identification of asymptomatic UTIs, a dipstick-test (leukocyte esterase for WBCs and nitrite) was to be performed at the site at each safety visit with urinalysis. In case of a positive result at the site, a urine culture sample was to be taken and sent to the central laboratory for confirmation of the diagnosis].

FDA was notified July 12, 2012 that another sponsor (IND (b) (4)) terminated the CI site due to non-compliance of GCP. Noncompliance including multiple inter and intra-patient physiologically unexplainable ECG results were

observed, AEs were not adequately identified and therefore not reported to the sponsor, and CI oversight of the study conduct was deficient. The FDA investigator followed up regarding this complaint. The ECGs viewed were very crude, single ECG strips with the leads and the subject ID handwritten on the ECG strip. Source notes mention that ECGs are within normal limits. It was impossible to judge if all AEs were reported due to the illegible handwriting.

At the conclusion of the inspection, no Form FDA 483 was issued; however, there were numerous concerns discussed with Dr. Ahmad regarding documentation organization, completeness and legibility.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although this was a difficult inspection with the handwriting of the investigator and time on site being limiting factors, data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

#### 14. Yaoming Xue

Nanfang Hospital  
No. 1838 Guangzhou Dadaobei  
Guangzhou, 510515 China

- a. **What was inspected:** Records reviewed during the inspection included Investigator Agreements, financial disclosures, drug accountability logs, study enrollment logs, screening logs, consent forms, e-case report forms, source documents, monitoring visit correspondence, sponsor correspondence, IRB correspondence and training records. For Study 1245.20, the files for 11 subjects enrolled in the study were reviewed (23531, 23532, 23533, 23534, 23537, 23545, 23546 [did not complete study], 23547, 23549 [did not complete study], 23558, and 23559). This review verified documentation of the results of HbA1c, blood pressure, weight, blood chemistry and urine tests, and ECGs for Visits 3 and 7. Raw data from the subject files were compared to e-CRF data and to the drug inventory log. For Study 1245.23, the files for 11 subjects enrolled in the study were reviewed (32572, 32573, 32575, 32576, 32577, 32586, 32590, 32591, 32592 [did not complete the study], 32593, 32921 and 32925). Subjects 32921 and 32925 were the only subjects enrolled in the sub-study.
- b. **General observations/commentary:** The IRB approval of Protocol 1245.20 was provided by (b) (4). There were 29 subjects screened, 20 subjects enrolled, and 17 subjects that completed the study. For Protocol 1245.23, the central hospital IRB approval was provided by (b) (4). There were 35 subjects screened, 17 subjects enrolled, and 15 subjects who completed the study. The informed consent was provided both in English and Chinese.

Each subject file contained a dispensing log for dispensing bottles of the test article. There were no issues with drug accountability. Each subject file documented each visit and the tests performed during each visit, which included blood pressure, weight, and blood chemistry testing for HbA1c

At the conclusion of the inspection, a two-item Form FDA 483 Inspectional Observations was issued for the following:

1. Inspection of clinical study Protocol 1245.20 revealed a lack of raw data. Specifically, (A) no ECG was available for subject #23545's visit #3 (May 17, 2011) and (B) no ECG was available for subject #23546's visit #3 (5/20/2011).
2. Inspection of clinical study protocol 1245.23 revealed conflicting data. Specifically, a visit #7 record indicates subject #32577 withdrew from the study on about Sep. 30, 2011, but the Subject Enrollment Log indicates the subject completed the study.

**OSI Comment:** The issues cited were isolated events. Dr. Xue responded to the 483 items and his response is acceptable. He acknowledged that the ECG print-outs were not available in the patient binders for the two subjects mentioned. In the future, the original ECG tracings and photocopies will be pasted into the notebooks of the progress notes. The study coordinator and investigator will cross-check and ensure all protocol required documentations are available and filed after each subject visit. Checklists will be developed according to the trial flow chart as a tool to ensure all completed procedures are documented. Regarding Subject 32577, Dr. Xue acknowledged the error in the data at Visit 7 and the enrollment log. The subject verbally informed the site staff about trial withdrawal on [REDACTED] <sup>(b) (6)</sup> and came back on Visit 7 on October 29, 2011 to return the trial related materials. Trial related procedures were not performed at that time. In the future, the study coordinator and sub-investigator will cross-check the data at each subject visit to ensure data is consistent across the progress notes and enrollment log.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

#### 15. Boehringer Ingelheim Pharmaceuticals Inc.

900 Ridgebury Road  
Ridgefield, CT 06877-0368

The inspection was conducted at the Boehringer Ingelheim Pharmaceuticals, Inc. campus office located at [REDACTED] <sup>(b) (4)</sup>

- a. What was inspected:** This inspection covered sponsor/monitor practices related to Clinical Trials 1245.19, 1245.20, 1245.23, 1245.28, 1245.33 and 1245.36 conducted in support of NDA 204629. Regulatory documents for all sites inspected were reviewed. Documentation was reviewed during this inspection for selected sites/personnel for the following: 1) organization and personnel including review of written agreements with contract research organizations, 2) registration of studies on ClinicalTrials.gov, 3) selection and monitoring of clinical investigators including agreements, non-compliance, and training (including protocol specific and GCP training), 4) selection of monitors, monitoring procedures, plans and reports for the fourteen selected clinical sites, 5) Quality Assurance (QA) including the audit plan and QA audits, 6) safety and adverse event reporting, 7) data collection and handling including Standard Operating Procedures (SOPs), 8) record retention, 9) financial disclosure, 10) electronic records including transmission of data and system security, and 11) test article integrity and accountability. Issues noted during the review of the clinical study report were also evaluated.
- b. General observations/commentary:** Copies of requested records and standard operating procedures (SOP) were reviewed. Records were reviewed to verify that there was documentation to show that the firm met the general responsibilities of a sponsor. Studies 1245.19, 1245.20, 1245.23, 1245.28, 1245.33 and 1245.36 were registered on ClinicalTrials.gov by the sponsor. In addition, the related informed consent documents include the required statement referencing ClinicalTrials.gov. An FDA 1572 Investigator Agreement form was present in each file of investigators located in the U.S. Financial disclosure forms for the sites were present in each file. No financial interests with the sponsor were reported.

Monitoring written procedures and manuals were reviewed with the monitoring reports for the sites inspected. The curriculum vitae (CV) and training documentation of the site monitors for the sites inspected were reviewed. According to the documentation provided, the monitors were qualified and trained prior to participation in the study. Overall, monitoring of clinical investigators appeared to be adequate. However, it was noted that the firm did have personnel issues (no reports submitted) with two monitors at two different sites (Unger and Lewin), both of whom were fired. As a result, one site (Unger-Site 10154) was not initially monitored within the monitoring plan requirements. Both sites were re-monitored by other monitors assigned to the sites in accordance with the monitoring plan.

Written procedures and records for reconciliation of the clinical database with the safety database (Aris-G) were reviewed, including SAE reconciliation SOPs 001-MCS-05-504, versions 4 and 5 and variation 1, documentation for the six trials which included the database lock checklist containing an item on SAE reconciliation to outline that it has been done, and the database lock meeting minutes which described

any outstanding issues right before database lock or the fact that there were none. In addition, the final SAE reconciliation program output for Studies 1245.19, 1245.23 and 1245.33 was available for review. There were no inspectional observations concerning SAE reconciliation. There was no evidence of under-reporting of adverse events or late-reported serious adverse events (SAE) found.

The list of global product complaints which included complaints from the clinical sites was reviewed. The majority of the complaints were related to temperature excursions and some damaged kits. There were no complaints concerning product integrity. Certificates of analyses for selected batches were all within specifications. The approved test article product labels for each clinical trial and found that they were compliant with 21 CFR 312.6. There were no reports to indicate that the test article was recalled, withdrawn or returned.

The Data Monitoring Committee (DMC) was assessed. Selection of members was based on recommendations, but the firm now has a written procedure which relies more on vendors with whom the firm has prior experience and preferred providers. The DMC operates in accordance with a written charter. Data was transferred at least three weeks prior to the meeting. Meetings are held approximately quarterly and the sponsor is only allowed to participate during the open session. Records are currently stored with the DMC but will be transferred after completion of the last trial to the sponsor. No issues were noted.

The Clinical Events Committee (CEC) was already established for the linagliptin studies. (b) (4) is a preferred provider for adjudication services. Reconciliation of adjudication results with adverse events is similar to the SAE reconciliation and is performed by the Trial Data Manager (TDM). A copy of the output of the reconciliation program for Study 1245.23 was reviewed. A manual check was performed because the program was not yet finished. Documentation was supplied to show that the CEC data sets were checked manually and signed on 3/22/2012. Also reviewed was the transfer of the vote from the CEC via (b) (4) to the sponsor BI. The CEC reconciliation/ adjudication results match with the AE code and date reconciliation performed by BI.

Documentation was reviewed regarding non-compliance with study drug and antidiabetic background medication recorded in the IVRS which differed from the antidiabetic background medication that they received. The importance of entering the correct background medication data in the IVRS was stressed to the staff. In addition, clinical investigators and study coordinators were alerted to be more careful in a newsletter sent in March 2011. These subjects were excluded in the per-protocol analysis and a sensitivity analysis was performed on the primary and secondary endpoints which reportedly found small differences. There were no inspectional observations concerning this matter.

The FDA inspector was asked to follow-up on the following observations from FDA inspection of Site 10154 (Jeffrey Unger):

- Reportedly, Site 10154 (Jeffrey Unger) did not receive a Spanish ICF (Version 3). The sponsor provided documentation to show that the IRB notified Dr. Unger in a letter dated 3/23/2011 that the Spanish version ICF was available electronically.
- Reportedly, the monitor did not provide monitoring reports. This was confirmed at the inspection. The monitor did not submit reports to the sponsor and was subsequently fired.
- Reportedly, the sponsor issued the wrong glucose monitoring logs (weekly vs. daily) to the site. The sponsor provided documentation to show that both daily and weekly home blood glucose monitoring logs were provided to this site on 11/30/2010.

In addition, the sponsor reported to the review division that several sites, which were conducting clinical research under IND 102145, were closed due to GCP non-compliance. Site selection was evaluated. There is global sponsor criterion for site selection and then each country adapts it to meet local requirements. SOP 001-MCS 40-211 requires the Trial Clinical Managers (TCMs) to provide Site Feasibility Questionnaires for site identification and selection. Copies of Site Feasibility Questionnaires for all of the clinical trials listed above were reviewed, with the exception of Study 1245.33, which was started prior to implementation of the SOP 001-MCS 40-211 concerning site selection. Comparison of the questionnaires to the protocol found that they appeared to meet the protocol requirements. Suitable sites were further evaluated and trained. There was documentation to show that the sites were trained either at an Investigator Meeting or at a site initiation visit prior to participation in the trial. Regulatory release was issued before the test article was shipped to the sites. There were no inspectional observations concerning site selection, initiation and training.

An extensive review of monitoring reports and sponsor correspondence for several of the closed sites was performed to confirm the reported GCP non-compliance. The monitoring reports were reviewed along with sponsor correspondence to determine when the monitor discovered and reported the noncompliance and what corrective measures, if any, were put into place by the sponsor before termination. Overall monitors did identify GCP non-compliance at each of the sites closed.

An extensive review of sponsor records found that the sponsor appeared to have taken appropriate steps in an attempt to bring noncompliant sites into compliance. If this could not be achieved, investigator sites were closed and the site closures were reported to the FDA. Specifically, the monitoring reports, letters sent to the clinical investigator Dr. Ahmed, and sponsor correspondence were reviewed. The monitor documented major non-compliance concerning the site's failure to follow procedures concerning documentation of subject consent. This issue was reported to BI compliance and the matter was resolved with additional training. The clinical investigator notified the sponsor of the study fraud in Study 1245.23 in a letter dated 3/22/2012 and personally to the monitor during a monitoring visit on 3/28/2012. Documentation shows that a Critical Alert form was received by BIPI Compliance on 3/28/2012. A committee of

senior management met on 4/9/2012 and a decision to close the site for Studies 1245.23 and 1245.31 was made on 4/11/2012. The FDA, CI and IRB were notified of this decision. The sponsor also looked at those studies in which the study coordinator, who allegedly committed the fraud, participated.

In addition to the protocols listed above, some of the clinical investigators were conducting research under Protocol 1245.25 entitled “A phase III, multicenter, international, randomized, parallel group, double blind cardiovascular safety study of BI 10773 (10 and 25 mg administered once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk.” The firm also provided records regarding the site closures related to this protocol for review.

In addition, the sponsor informed the FDA review division in April 2013 that subjects were screened and randomized at multiple investigator sites for two other studies (Studies 1218.74 and 1275.1). Records concerning this matter were reviewed during this inspection and the firm provided a timeline in which corrective action is expected to be implemented. The projected time frame for implementation of the corrective action will be in the second quarter of 2014. The sponsor has encountered several challenges in attempts to implement the corrective action due to the global privacy laws. The firm is searching for an interactive voice response system (IVRS) vendor with the capability to detect multi-site participation. The CI will enter the subject’s date of birth and initials if allowed by a country’s privacy laws and gender into the IVRS. If the system detects a potential duplicate subject, the IVRS will notify the CI to ask for subject verification and notify the BIPI clinical team with details of the investigator’s address and relevant subject numbers. Meanwhile, the firm has raised the awareness of this issue, both to sponsor personnel and has included it in the training of clinical investigators in order to raise their awareness of the issue. In addition, the firm is changing the informed consent form (ICF) template to include a statement that the subject should not participate in more than one clinical trial at a given time due to safety issues. The ICF template is currently in the review process.

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There were no objectionable conditions noted and no Form FDA 483, Inspectional Observations, was issued. However, there were several discussion items:

1. Monitoring Issue-The sponsor identified performance issues (i.e. trips reports were not completed by the monitor in accordance with the monitoring plan) with two monitors at two different sites (Unger and Lewin). Although the monitors were fired and the sites subsequently re-monitored, the sponsor should have addressed the performance issues in a more timely fashion. Specifically, one site initiation and two monitoring visits were conducted at Dr. Unger’s site in March and April 2011. There are no reports for these visits in the file; reportedly, the monitor did not submit them. The next monitoring visit was not done until almost three months later on July 25th. The significance of this observation is that during this time period, the

clinical investigator screened approximately 30 subjects for the clinical trial and randomized approximately 15 into the study.

One initiation and two monitoring visits were conducted at Dr. Lewin's site in January and March 2011. There are no reports for these visits in the file; reportedly, the monitor did not submit them. The CRA manager did go out to the site with the site monitor on April 6, 2011, but the report was not completed until May 18, 2011. During this time period, thirty subjects had been screened and approximately 15 randomized before the sponsor had any written information concerning this site. Although there were reportedly personnel issues that needed to be addressed, the sponsor should have considered placing a screening hold on both sites until there was written documentation of the monitoring visits.

The sponsor has implemented a trip report tracking process since the time this occurred and reportedly has 85% compliance of receiving written trip reports within 10 days. The FDA inspector stressed that this should continue to be monitored and the compliance rate should improve. In addition, the firm should aggressively address non-compliance. It was stressed that the firm should also establish a written plan for addressing re-monitoring when there are personnel issues.

2. During the previous inspection, it was observed that IND Safety Reports were not distributed via TOPCALL in accordance with regulatory time frames to two out of 28 clinical investigators. At the time, the sponsor promised to investigate to determine a root cause and to correct. Since these clinical trials occurred during the same time period, correction could not be verified. Correction will be verified during an inspection at a later date.
  3. In regards to the firm's investigation of subjects participating in the same clinical trial at multiple investigator sites, FDA will continue to monitor implementation of the corrective action plan during future inspections.
  4. Sponsor staff was provided with a copy of FDA Guidance Document entitled "Guidance for Clinical Investigators, Industry and FDA Staff- Financial Disclosure by Clinical Investigators". In the past, in addition to having investigators complete a financial disclosure form prior to participating in a study, BI also required all investigators to complete financial disclosure forms after completion of the study, whether or not the investigator had any changes to financial disclosure to report. The sponsor recently changed the SOP to only require completion of financial disclosure forms by all investigators prior to participating in a clinical trial. It is now the responsibility of the investigators to notify BI of any changes to disclosure i.e., change from no disclosure to disclosure or additional disclosure not previously reported.
- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this sponsor appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the

submitted data.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of seven domestic and seven foreign clinical sites as well as the sponsor. Additional sites had been added for inspection because the Office of Scientific Investigations (OSI) had pending for-cause inspections at those sites. It was felt that moving forward with inspections of these pending sites would be advantageous towards the assessment of the data integrity of the application.

Observations noted above for Drs. Streja, Riffer, Unger, Rivas, Lewin, Conter, Elliott, Mukhopadhyay, Ahmad, Xue and the sponsor are based on review of the Establishment Inspection Reports. Observations noted above for Drs. Ahmed, Sugimoto, O'Mahony, and Ellis are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

One site, Dr. Azazuddin Ahmed (Site 1001) was issued a Form FDA 483 citing inspectional observations and pending classification is Official Action Indicated (OAI). The sponsor had closed this site and has determined not to use the data in any of the analyses. OSI was able to confirm the unreliability of the data.

Five clinical sites inspected, Drs. Rivas, Sugimoto, Conter, Elliott, and Xue were each issued a Form FDA 483 citing inspectional observations and classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for all five sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

Eight clinical sites, Drs. Streja, Riffer, Unger, Lewin, O'Mahony, Elliott, Mukhopadhyay, Ahmad, and the sponsor were not issued a Form FDA 483; classifications for each of these inspections are NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

In general, based on the inspections of the 14 clinical study sites (representing 19 protocol sites) and the sponsor, the inspectional findings support validity of the data as reported by the sponsor under this NDA.

*{See appended electronic signature page}*

Cynthia F. Kleppinger, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
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Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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CYNTHIA F KLEPPINGER  
03/03/2014

JANICE K POHLMAN  
03/04/2014

KASSA AYALEW  
03/04/2014

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

**PATIENT LABELING REVIEW**

Date: December 20, 2013

To: Jean-Marc Guettier, M.D.  
Director (Acting)  
**Division of Metabolic and Endocrinology Products  
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Twanda Scales, RN, MSN/Ed.  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Kendra Y. Jones  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRADENAME (empagliflozin)

Dosage Form and Route: Tablets

Application Type/Number: NDA 204629

Applicant: Boehringer Ingelheim Pharmaceutical, Inc.

## 1 INTRODUCTION

On March 5, 2013, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) submitted for the Agency's review an Original New Drug Application (NDA) for empagliflozin tablets to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) on March 13, 2013, and March 12, 2013, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (empagliflozin) tablets.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (empagliflozin) tablets PPI received on March 5, 2013, revised by the Review Division throughout the review cycle and received by DMPP on December 16, 2013.
- Draft TRADENAME (empagliflozin) tablets PPI received on March 5, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 16, 2013.
- Draft TRADENAME (empagliflozin) tablets Prescribing Information (PI) received on March 5, 2013, revised by the Review Division throughout the review cycle and received by DMPP on December 16, 2013.
- Draft TRADENAME (empagliflozin) tablets Prescribing Information (PI) received on March 5, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 16, 2013.

## 3 REVIEW METHODS

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 PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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TWANDA D SCALES  
12/20/2013

KENDRA Y JONES  
12/20/2013

MELISSA I HULETT  
12/20/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)**

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

## Memorandum

**Date:** December 17, 2013

**To:** Patricia Madara, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Kendra Y. Jones, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 204629  
OPDP labeling comments for empagliflozin

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OPDP has reviewed the proposed draft prescribing information (PI) for empagliflozin submitted for consult on March 12, 2013.

OPDP's comments on the proposed draft PI are based on the version located in the eRoom entitled, "11Oct13 NEW company proposed PI+PPI.doc" (last modified December 13, 2013) and are provided on the marked version provided directly below.

Please note, OPDP will provide comments on the proposed draft patient labeling (PPI) under separate cover.

Thank you for the opportunity to comment on the proposed draft PI.

If you have any questions, please contact Kendra Jones at 301.796.3917 or [Kendra.jones@fda.hhs.gov](mailto:Kendra.jones@fda.hhs.gov).

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KENDRA Y JONES  
12/17/2013

**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, Labeling and Packaging Review**

Date: November 25, 2013

Reviewer: Reasol Agustin, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Jardiance (empagliflozin) Tablets, 10 mg and 25 mg

Application Type/Number: NDA 204629

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2013-655

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

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and prescribing information for Jardiance (Empagliflozin), NDA 204629, for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

The applicant, Boehringer Ingelheim, submitted a request for review of the proposed label and labeling for Jardiance (empagliflozin) on November 19, 2013, as part of NDA 204629.

### 1.2 PRODUCT INFORMATION

- Active Ingredient: Empagliflozin
- Indication of Use: Indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 10 mg and 25 mg
- Dose and Frequency: One tablet orally daily
- How Supplied: Bottles containing 30 tablets, 90 tablets, (b) (4)  
Blistercards 30 tablet blister cards (3x10); 30 tablet blister carton. Professional sample bottle containing 7 tablets. Professional sample 7 tablet blister card (1x7).
- Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Store in a safe place and keep out of reach of children.
- Container and Closure System: HDPE Bottle, 60 and 375cc; Closure- two piece, (b) (4) with an induction seal liner. Blister: Aluminum (b) (4)

## 2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 19, 2013 (Appendix A)
- Unit-Dose Blister card Labels submitted November 19, 2013 (Appendix B)

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

- Unit-Dose Carton Labeling submitted November 19, 2013 (Appendix C)
- Professional Sample Container and Blister card Labels submitted November 19, 2013 (Appendix D),
- Professional Sample Carton Labeling submitted November 19, 2013 (Appendices E)
- Insert Labeling submitted October 11, 2013 (not included)

### 3 CONCLUSIONS

DMEPA concludes that the proposed container and unit dose labels as well as carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

### 4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

#### A. Container Label and Carton Labeling

1. Revise the font color of the proprietary name (b) (4) color) or revise the color scheme of the 25 mg strength (b) (4) color), so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the same (b) (4) color font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.
2. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name, taking into account all factors, including typography, layout, contrast, and other printing features, in accordance with 21 CFR 201.10(g)(2).
3. Please change the (b) (4) block on either 10 mg strength or 25 mg strength, as having (b) (4) color blocks on two strengths decreases the differentiation between the two strengths.

#### B. Commercial and Sample Unit-dose Blisters

1. If feasible, revise the color of the strength statement to the same color scheme as the container labels to better differentiate the strengths (i.e. 10 mg-(b) (4) and 25 mg-(b) (4)). Additionally, see comment A.1 regarding 25 mg color scheme.
2. If space permits, revise the strength statement from “x mg” to state “xx mg per tablet”.

#### C. Commercial and Sample Unit-dose Carton Labeling

1. Revise the color of the strength statement to the same color scheme as in the container labels to better differentiate the strengths (i.e. 10 mg-(b) (4)

and 25 mg (b) (4)). Additionally, see comment A1 regarding 25 mg color scheme.

2. Revise the strength statement on the principal display panel from “XX mg per tablet” to read “XX mg”.
3. For commercial unit-dose carton labeling, revise the quantity statement (b) (4) to read “3 blister cards. Each card contains 10 tablets” to clarify the quantity statement.

D. Professional samples container labeling

1. Container Label

Revise the color of the strength statement to the same color scheme as in the container labels to better differentiate the strengths (i.e. 10 mg (b) (4) and 25 mg (b) (4)). Additionally, see comment A1 regarding 25 mg color scheme.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

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REASOL AGUSTIN  
11/25/2013

YELENA L MASLOV  
11/25/2013

## Clinical Consultation Review

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: 19 October 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology(OPE) , Office of Surveillance and Epidemiology (OSE)

TO: Jean Marc Guettier, M.D., Acting Director, Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs II (OND II), Eric Colman, M.D., Deputy Director, DMEP  
Amy Egan, M.D. Deputy Director for Safety, DMEP  
Karen Mahoney, M.D., Clinical Team Leader, DMEP  
William Chong, M.D., Medical Reviewer, DMEP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of empagliflozin for treatment of diabetes mellitus, NDA 204629, submitted 5 March 2013 by Boehringer Ingelheim Pharmaceuticals, proposed as monotherapy for adults with type 2 diabetes mellitus, and also with other anti-diabetic agents

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### Documents reviewed:

- 1) Consultation request dated 22 May 2013 entered into DARRTS as FRM CONSULT-06 (OSE Consult) by Patricia Madara of DMEP, with initially desired completion date 21 June, forwarded by Marguerita Tossa of OSE, with revised date for completion 31 July 2013
  - 2) Set of narrative reports and laboratory data (187 pages) forwarded by Dr. Chong on 29 July 2013 for 14 patients studied in various empagliflozin trials
  - 3) Data for 10 clinical trials, as discussed between Drs. Guo and Chong during August entered into eDISH program and available for analyses 23 August 2013
  - 4) Consultation to DMEP by Dr. Leonard Seeff sent 22 August 2011 (requested 1 August) for opinion on hepatic events\ patient 4003, M88 fatal outcome, IND 102145, OSE 2011-2651
  - 5) Minutes 13 September of mid-cycle meeting 3 September, concerns about elevated transaminases and multiple Hy's Law cases, as well as for increased incidence of lung cancer and melanoma (for which request had been sent also to DHOP on 22 May, asking for a reply by 5 October), and notice of a planned advisory committee meeting 13 December 2013
  - 6) OSE consultation tracking number #2013-1216 sent by Ms. Tossa on 8 October 2013
  - 7) Updated draft partial clinical review section 7.3.5.2. Liver adverse events/Hepatic injury from Dr. William Chong 9 October 2013, requesting response by 14 October
  - 8) Selected pertinent medical literature from NIH PubMed program
-

The request from the review division asked for 30-day response to questions about increased frequency of reported elevations of “liver enzymes” in subjects treated with empagliflozin compared with those randomized to comparator drugs. Some of the cases had reasonable other explanations for causes of the findings, but some were less clear. Opinion was requested about the likelihood that the study drug (empagliflozin) caused those elevations and imbalances. Two documents were attached to the request: 1) An excerpt from the Summary of Clinical Safety (as provided by the sponsor in the NDA submission), and 2) the DMEP clinical reviewer’s summary (Dr. Chong) of subjects with liver abnormalities of uncertain significance. Rapid response in 30 days or less, was requested because DMEP was considering taking this NDA for review by an advisory committee (date not specified).

Cases of concern selected by Dr. Chong included 8 for which he provided 2-page summaries for each, with brief clinical information, tabulated serial results for serum enzyme activities for serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin concentration (TBL), with reference upper normal limit values., a little time-course graph for each variable, and the impression of most likely cause.

Selected cases with notable liver test abnormalities in subjects on empagliflozin								
Study	subject	sex age	Empa dose	peak value, xULN				likely cause
				ALT	AST	ALP	TBL	
20	023063	M 49	25	8.5	3.3	1.1	9.5	acute hepatitis A
25	(b) (4)	M 64	25	15.2	9.0	1.4	2.0	drug-induced
28	082492	F 65	25	15.5	17.1	4.4	1.2	unexplained
28	084833	M 48	25	25.8	110.8	1.1	16.1	alcoholic hepatitis
28	088530	M 66	25	8.9	6.4	0.5	1.0	uncertain
33	004003	M 87	25	15.7	15.9	2.3	1.0	drug-induced
38	817006	F 58	5, 25	57.5	36.3	2.4	0.8	alcoholic hepatitis
52	281002	M 73	10, 25	5.7	3.5	0.8	5.6	uncertain

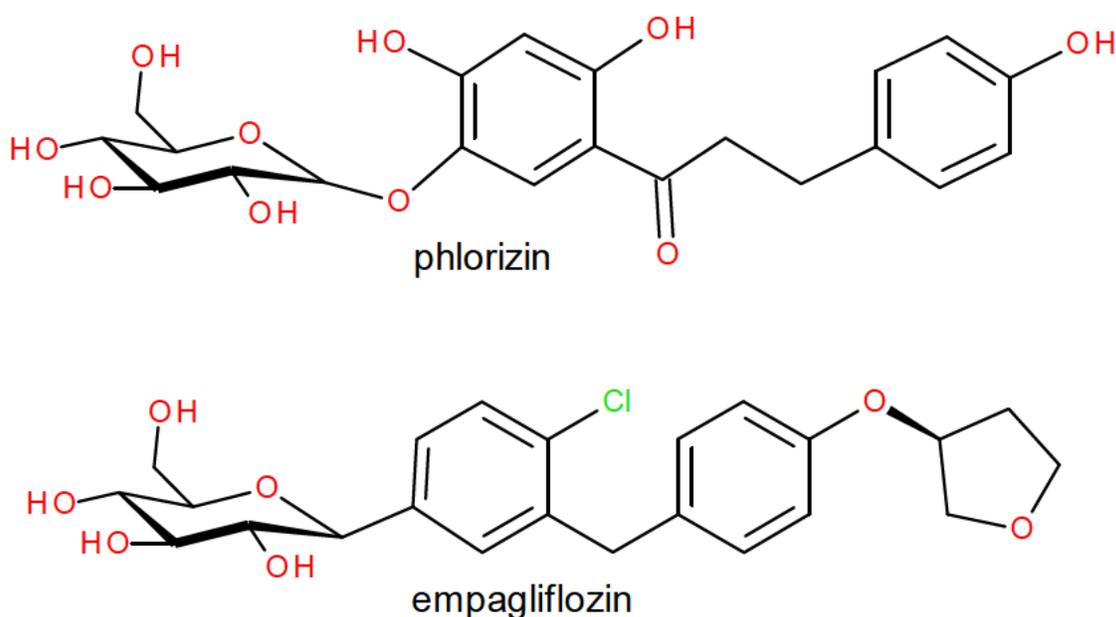
Dr. Chong also provided a Table 2.1.5.2.2.1 listing 7 of the 8 patients shown above, except for the one in Study 52, plus 3 others who had received only 10 mg of empagliflozin (24:008963, 25: (b) (4), 25: (b) (4) – by study:subject number), 2 others who showed liver test abnormalities before receiving empagliflozin (9:009083, 25: (b) (4)), 1 who was randomized to glimepiride (28:082414), and 4 others who showed abnormalities after but not during treatment, including 1 who had received placebo (48:016423), 2 after 25 mg empagliflozin (25: (b) (4); 33:004394), and 1 after 100 mg empagliflozin 4:006059).

This presentation was somewhat confusing, so we requested that DMEP ask the sponsor for data from all of the key clinical trials, formatted for eDISH as detailed by Dr. Guo. This took several weeks to accomplish, but by late August the data were received and entered into eDISH for more analyses of all the data.

While this underway, and while awaiting receipt of the data, we looked into the literature on empagliflozin, finding only 31 published papers, none describing liver or any other toxicity, but only pharmacologic and preliminary efficacy reports. It was found that empagliflozin is one of a new class of –gliflozin drugs, one (canagliflozin) already approved in March 2013, and another

(dapagliflozin) recently resubmitted in July 2013 after a Complete Response on 17 January 2012 following an initial submission 28 December 2010 (NDA 202293) for which concerns had been raised about liver injury and bladder cancer. The –gliflozin class represents a new approach to managing diabetes mellitus, by blocking the renal tubular receptors that reabsorb glucose from glomerular filtrate, thereby reducing blood glucose concentration and increasing sensitivity to insulin, at a cost of increasing the urinary glucose excretion and concentration.

Empagliflozin is active as a selective inhibitor of the proximal tubular sodium-dependent glucose co-transporter-2 receptors (SGLT-2s). The drug is really a phlorizin derivative, with a glucose moiety at one end <sup>(b) (4)</sup> that had been found at Yale to restore sensitivity to insulin in diabetic rats (Rossetti et al., 1987). Derivatives of phlorizin, <sup>(b) (4)</sup> that confer better and more selective properties, such as empagliflozin developed and studied by the sponsors, and also canagliflozin and dapagliflozin developed by others:



The large clinical trials of empagliflozin, co-sponsored by Boehringer Ingelheim and Eli Lilly companies were announced as planned to include 14,500 patients in 12 international phase III studies (Nair, Wilding 2010; clinicaltrials.gov). Even a few cases of elevated serum transaminase elevations with associated increase in bilirubin concentrations, need to be evaluated carefully for incidence, severity, and causality. We have learned that serum enzyme activities, ALT, AST, ALP, and others) are not measures of liver *function* at all, despite commonly being referred to as “liver function tests.” They are simply indicators of injury or damage to cells from which they come, and have important roles inside those cells, but not in circulating plasma where they are measured. They are not specific to liver cells, but the aminotransferases are widely distributed in many types of cells where they function to facilitate carbohydrate and protein metabolism, and alkaline phosphatase is active in bone. Another misunderstanding widely followed is that there is something called “Hy;s Law chemistries.” This is a term and concept that should never be used, because the combination of elevated ALT and TBL is not diagnostic at all of what Zimmerman

called a potentially serious lesion (Zimmerman, 1968), until differential diagnostic medical investigation shows that the findings were at least probably caused by the drug in question and not caused by disease processes (infectious, ischemic, traumatic, other), nor by some other drug than that being evaluated. It is a first principle that “Hy’s Law” requires that the cause be shown to be drug-induced, and that it be shown to result from hepatocellular injury, severe enough to cause jaundice or significant rise in plasma bilirubin concentration indicating diminished whole liver functional capability to clear the plasma of bilirubin normally.

Therefore, simply chasing serum transaminase elevations that are not accompanied or followed by some measure of true liver functional impairment, such as increased bilirubin concentration or prolonged prothrombin time (from reduced whole liver ability to synthesize and nicely regulate the concentration of prothrombin levels, not too high to induce clotting or too low to result in bleeding). It is loss of true liver functional capability that leads to serious clinical problems. At most, serum rtransaminase elevations are indications of need to investigate and follow the patient to make a valid medical diagnosis of what’s really going on and causing the abnormal findings.

The sponsor has expended a great deal of effort in pursuing transaminase elevations that were not followed or accompanied by bilirubin increases, which has generated much false-positive noise. Let us use eDISH, a tool developed to help clinical reviewers to speed quickly through hundreds or thousands of patients or subjects in clinical trials, pick out the few cases of special interest for more detailed investigation as to the probable cause of the findings, to put the issue into better perspective. Dr Guo was given data from 10 clinical trials, along with supplementary narratives for selected patients, to aid this evaluation, Serious drug-induced liver injury that causes clinically important dysfunction is fortunately rare, for drugs being evaluated in NDAs.

The eDISH data considered here includes data on 14619 patients from the following 10 studies:

### Empagliflozin clinical studies - Boehringer Ingeheim NDA 204629

2011		BI 10	BI 25	PLA	sitag						
<b>Studies</b>											
<b>19*</b>		165	168	165		498					
<b>20*</b>		224	310	228	221	983					
<b>23*</b>		445	614	436		1495					
		834	1092	829		(2976)					
<b>2013</b>											
<b>Studies</b>	Emp 1	Emp 5	Emp 10	Emp 25	Emp 25 O	Emp 50	PLA	sitag	metf	glim	
<b>24^</b>	20	40	281	266		70	40	71	79		728
<b>25*</b>			1536	1537			1539				4612
<b>28*</b>				751						769	1520
<b>31*</b>			810	794	244		795	219			2862
<b>33^</b>			167	152			162				481
<b>38^</b>		<b>3</b>	213	212		110	9				544
<b>48*</b>			275	276			266				817
	20	43	3282	3988	244	180	2811	290	79	769	(11643)
			<b>4116</b>	<b>5080</b>			<b>3640</b>				<b>14619</b>

Studies\* listed by sponsor as phase III trials; studies^ as phase II, in Reviewers Guide to NDA 204629, Section 1.2

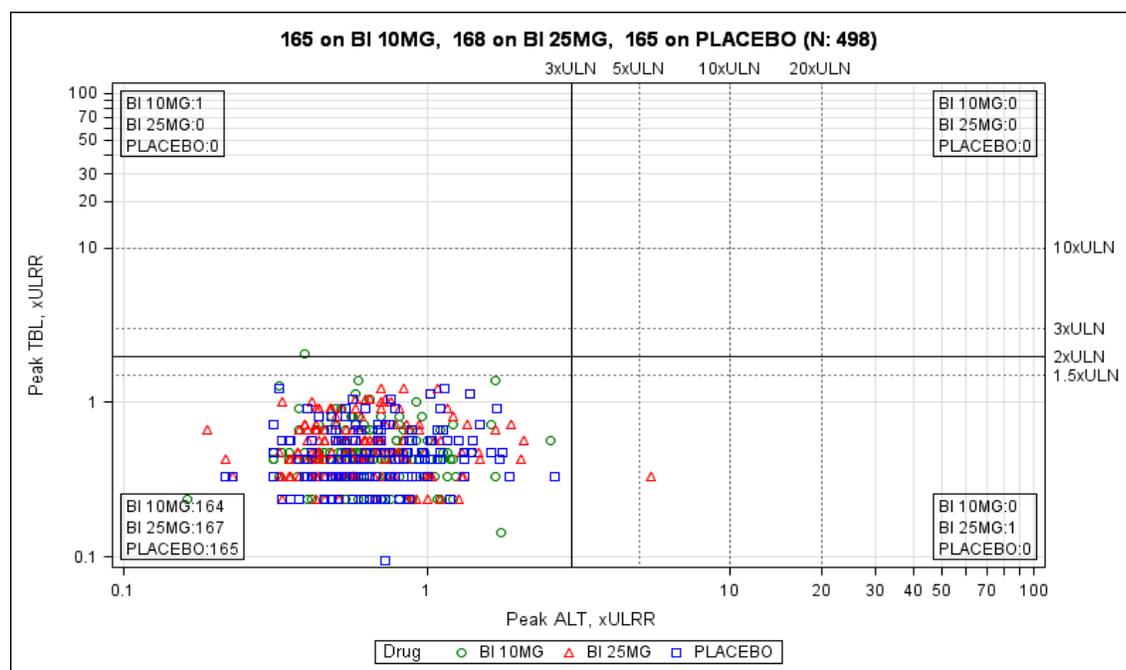
It is evident that the largest dose levels studied were 25 and 10 mg daily of empagliflozin, with substantial numbers of study subjects/patients on placebo for comparison. In this context, let us look at the relative incidence of significantly abnormal liver tests. Bear in mind that the first eDISH plot of ALT values on the abscissa and bilirubin values on the ordinate are in multiples of upper limits of normal and as  $\log_{10}$  values. These are deliberately transformed to compensate for the wide variations in what different laboratories define as normal ranges of test results, and the relatively much greater variation in ALT than bilirubin values.

Among the first three phase III trials 19, 20, and 23 listed as 2011 studies, there were almost 2000 patients randomized to empagliflozin 10 or 25 mg/day, and 829 to placebo, plus 221 to sitagliptin in Study 20. When all of the patients in these three studies were scanned using eDISH, there was one in Study 19 (#011500), two in Study 20 (#023063 and #024155), two in Study 23 (#032675 and #032199) who showed only mild ALT >5xULN with no elevations above normal in TBL. One patient in Study 20 (#023063) showed raised bilirubin as well as ALT increases. Time courses of liver test results for them are shown below, with brief comments on probable clinical causes of the findings:

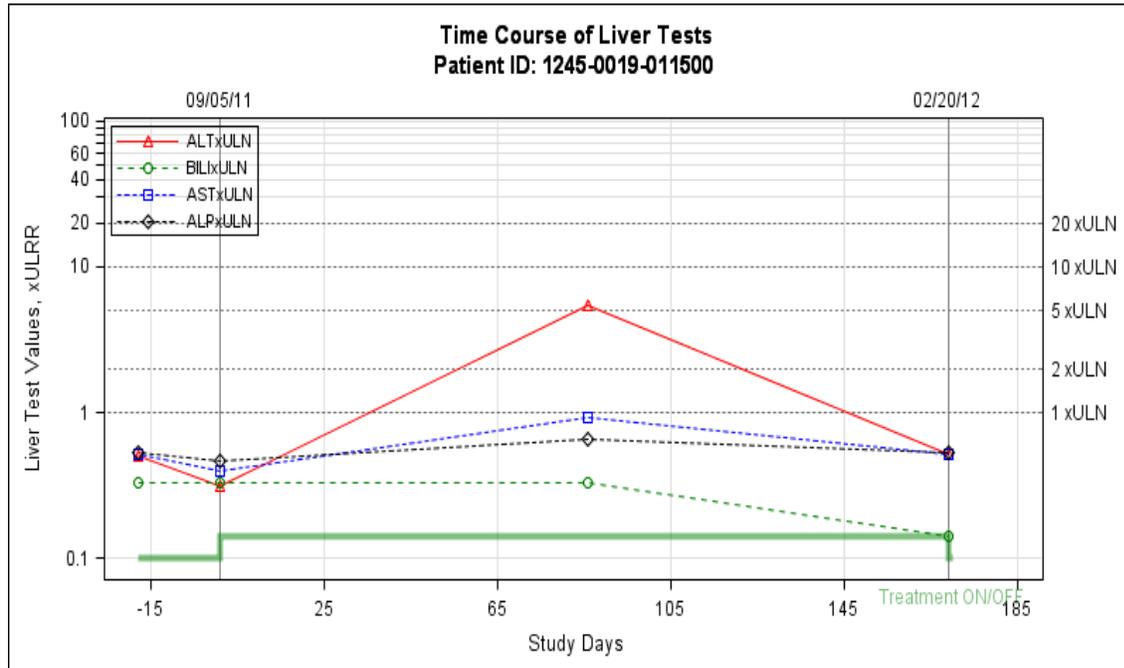
Study 19, the first and smallest of the three, showed the distribution of peak values for the 498 patients as displayed below in the x-y plot of peak ALT values on the abscissa and peak TBL values on the ordinate for each of the almost-500 patients. Each symbol gives the peak observed values for a single patient, plotted as  $\log_{10}(\text{xULN})$  values. This allows visualization of relative changes in test values but decreases the greatly smaller rises of TBL than ALT, and use of ULNs compensates for individual laboratory variations in what they call “normal” ranges. Subsequent graphs suppress the left lower quadrant of normal or near normal values to save memory overload for the Word program, without sacrifice of critical data for patients of clinical interest.

## Study 19

In Study 19 there was just one patient (#011500) with ALT >5xULN but no TBL increase::



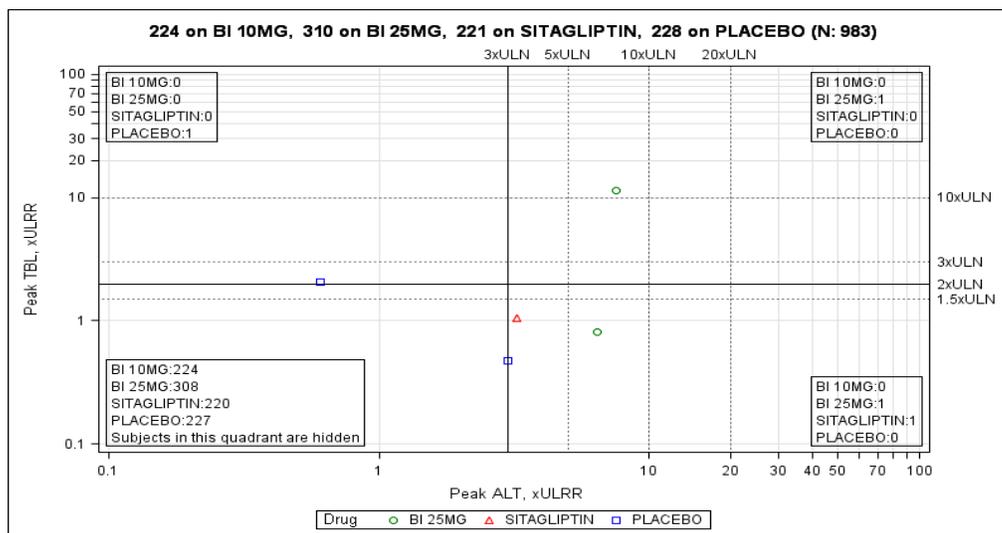
Patient 19: #011500 was an overweight (BMI 30.7) Ukranian man 54.



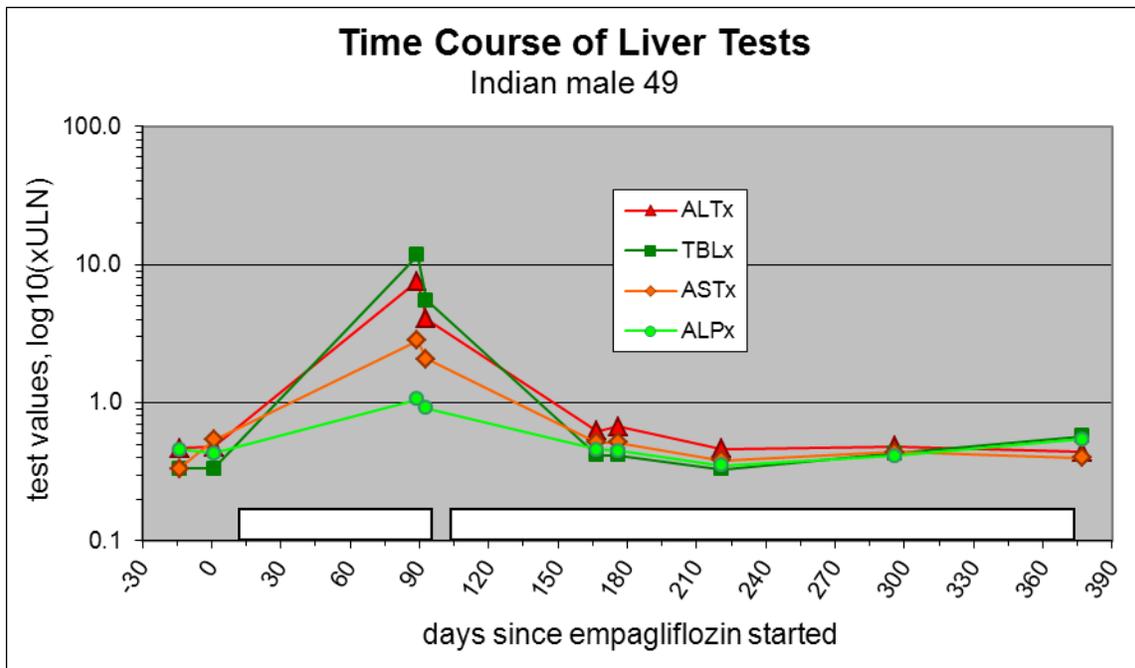
*Comment: Obviously this patient was not very closely watched. Although he had normal values for liver tests before starting on empagliflozin on 5 September 2011, his tests were not checked again for over 12 weeks, at which time his ALT was elevated to 5.4 xULN, with no rise in the other test values. Recheck 12 weeks later showed all values normal. No symptoms or other data were reported; he apparently was not carried over in Study 31, and no narrative was provided. This was not a serious case, even if it might have been transiently caused by exposure to study drug.*

### Study 20

Study 20 included one patient who showed bilirubin as well as ALT elevations:

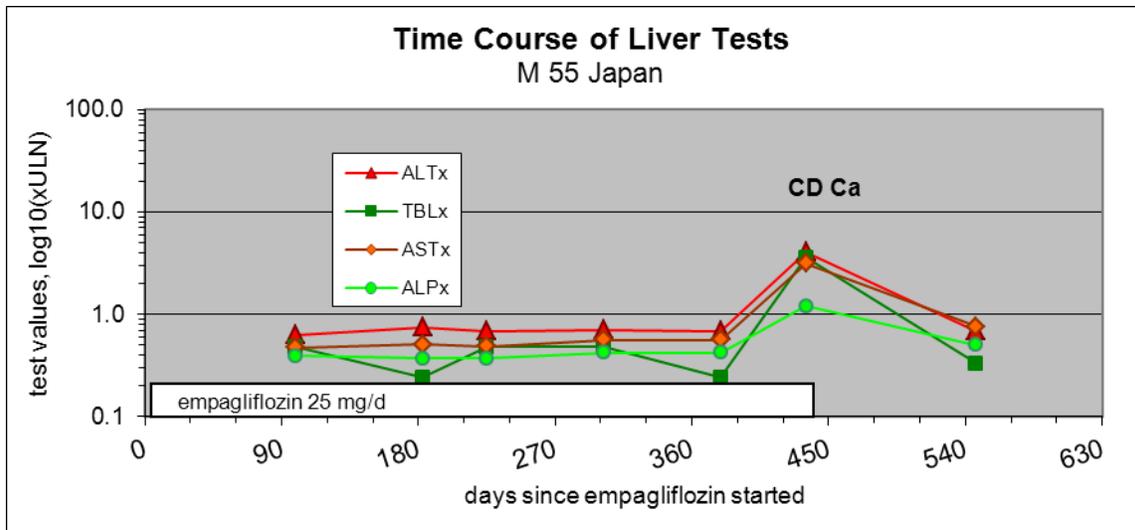


The patient in the right upper quadrant of the graph above was identified as #023063, an Indian male 49 who started empagliflozin (then identified as BI) 25 mg/day on (b) (6). His narrative information indicated that he had loss of appetite, nausea, and vomiting starting about 10 May, six weeks after starting study drug. He developed reddish urine as well the next day and his family physician suspected what he called “infective hepatitis.” Serum tests were negative for hepatitis B surface antigen, and for salmonella markers, and a clinical diagnosis of acute viral hepatitis A was made. Scheduled testing under the protocol at the 12-week check visit on (b) (6) showed elevated ALT 7.6 xULN, AST 2.8 xULN and TBL 11.4 xULN and empagliflozin was stopped. Abdominal ultrasound showed no evidence of biliary obstruction or gallstones. Repeat testing on (b) (6) showed decreasing values of ALT 4.0, AST 2.1, ALP 0.9, and TBL 5.5 xULN, with improving appetite, disappearance of nausea, urine color back to normal, and the investigator restarted empagliflozin on (b) (6). Recheck on (b) (6) showed ALT, AST, and ALP down to the normal range and TBL only 1.7 xULN. The patient was then continued in Study 31 on long-term administration of empagliflozin.



*Comment: The clinical diagnosis of infectious hepatitis appears to have been correct, and there is no evidence that these finding of moderately severe acute liver injury was drug-induced, and giving more drug had no effect on his recovery from the illness, which was not serious, did not require hospitalization. The diagnosis of viral hepatitis A could have been confirmed by testing for appropriate serologic markers, but was not done, or at least not reported. The possibility of acute viral hepatitis E, prevalent in India, does not seem to have been considered. In any case, it was not likely to have been empagliflozin-induced.*

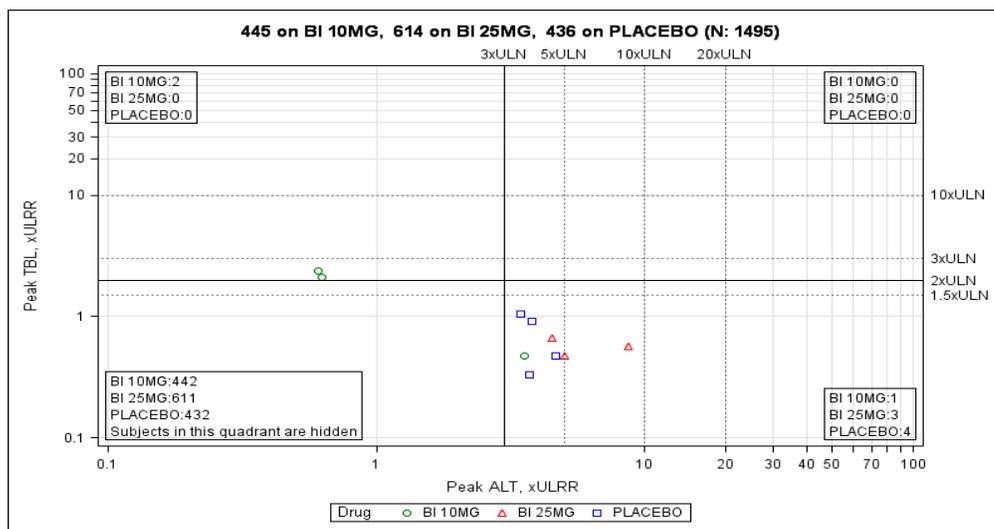
The other case of possible interest in Study 20 was that of patient #0211141, a Jaapanese man 55 randomized to empagliflozin 25 mg/day on (b) (6) who developed whole-body itching in (b) (6) that investigation revealed to be caused by distal common duct carcinoma.



*Comment: It is very unlikely that the abnormal liver test findings in this patient were caused by empagliflozin, but almost certainly by the common duct carcinoma that began to cause pruritus and biliary obstruction almost a year after he started on the study drug. Surgical resection of the tumor in (b) (6) resulted in relief of the biliary obstruction.*

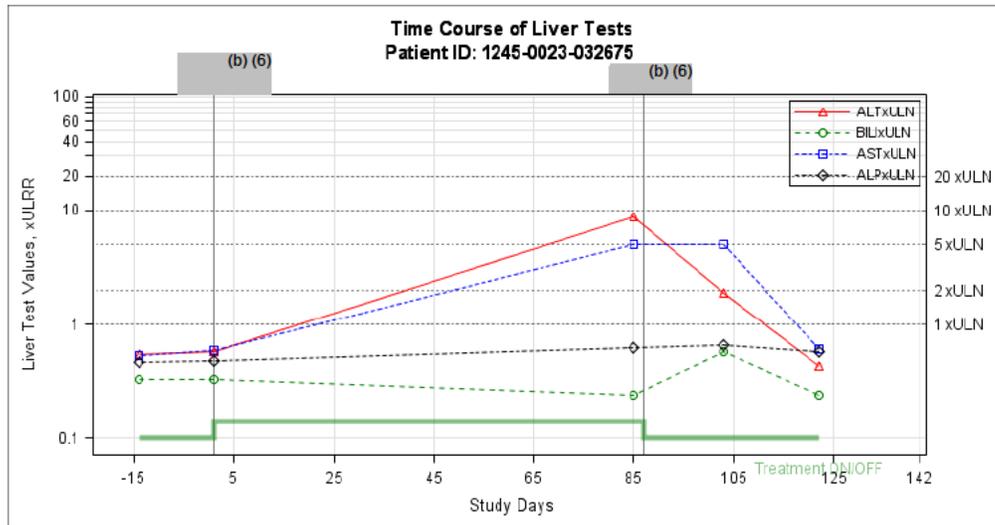
### Study 23

Study 23, the largest of the three studies done in 2011, showed only two cases with ALT >5xULN and none with TBL elevations:



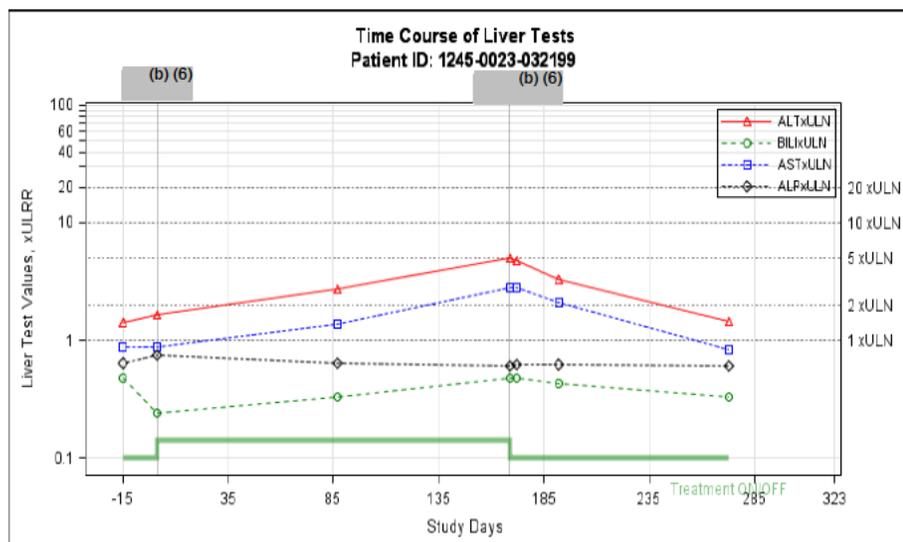
Patient 23: #032675 (red triangle farthest to the right in the lower right quadrant) was a thin (BMI 19.3) Chinese woman of 64 who showed ALT and AST rises to 8.7 and 5.0 xULN 12 weeks after starting empagliflozin 25 mg/day on (b) (6) (see graph of her time course of liver tests, below). On testing (b) (6) later she showed elevated transaminases without symptoms or bilirubin elevation, but investigation showed positive viral hepatitis markers

HBsAg and HBeAb, indicating the probable cause of the findings, and not the empagliflozin. She was discontinued from the study.



*Comment: The diagnosis of chronic asymptomatic hepatitis B was based on finding serum HBsAg 240 ng/mL (normal range 0-0.2 ng/mL, HBeAb 1.99 PEIU/mL (normal range 0-0.2 PEIU/mL), and HBcAb 4.02 PEIU/mL (normal range 0-0.9 PEIU/mL), with normal values for HBsAb and HBeAg. The investigator concluded there was no relationship between these findings and study drug, with which we concur.*

Patient 23: #032199 was an overweight (BMI 30.3) young Chinese woman of 19 started on 25 mg/day of empagliflozin on (b) (6). Even before starting empagliflozin she had very slight ALT elevations of ALT at 1.4 and 1.7 xULN. She showed increases of ALT and AST to 2.7 and 1.4 xULN after 12 weeks, slowly rising even more at 24 weeks to 5.03 and 2.8 xULN, without rises in TBL or ALP. No narrative was provided, and it is not known if she continued into Study 31. Empagliflozin was stopped (b) (6), the elevated enzymes very slowly declined.



*Comment: No firm diagnosis can be made without more clinical information, but it might reasonably be suspected that she had steatohepatitis with mild acute-on-chronic aggravation by study drug, not serious and only a possibility.*

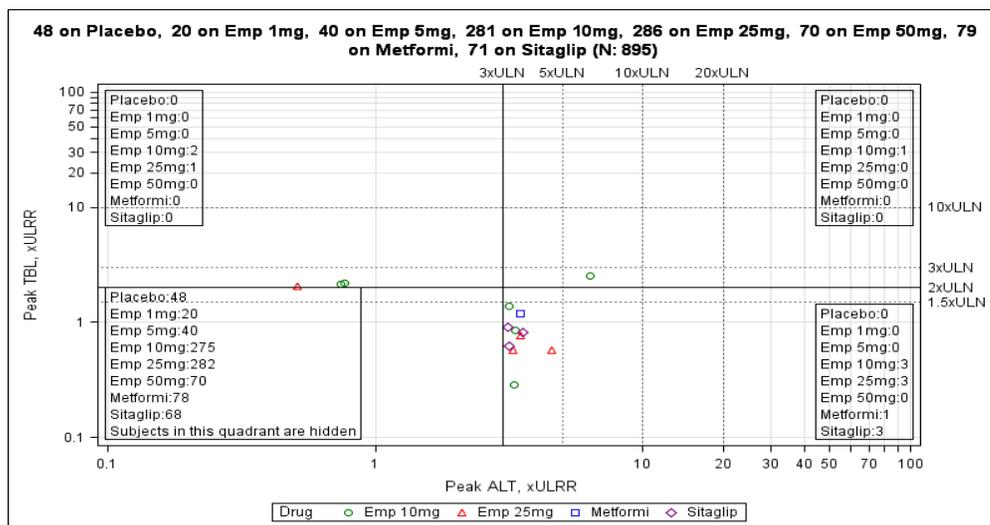
Most but not all of the patients reported for studies 19, 20, and 23 were carried over into the follow-on study 31 and some new ones were added, for whom narratives were provided in the NDA, Section 5.3.5.3, Integrated Safety Studies, List of narratives. The narratives were written for patients showing serious adverse effects (AEs), significant AEs, discontinuation due to AEs, death, or exposure during pregnancy, 280 narratives in all. Among these three studies there was only one of the 2976 patients showed TBL as well as ALT elevations of possible clinical interest, which would give a crude incidence of about 1:3000, before determination of causality. When that patient was found on investigation to have probable acute infectious viral hepatitis A (or perhaps E?), there were no cases meeting the Hy's Law definition when causality was considered, as it must be.

Data were provided for seven additional studies (24, 25, 28, 31, 33, 38 and 48) in which 11,643 additional patients were studied, as summarized in the Table on page 4 above. Among these there were six patients (0.052%) who showed peak ALT and TBL values in the right upper quadrant. When time course and narrative information were used to make an effort at differential diagnosis of the most likely cause, again it was found that alternative explanations were far more likely than empagliflozin-induced liver injury.

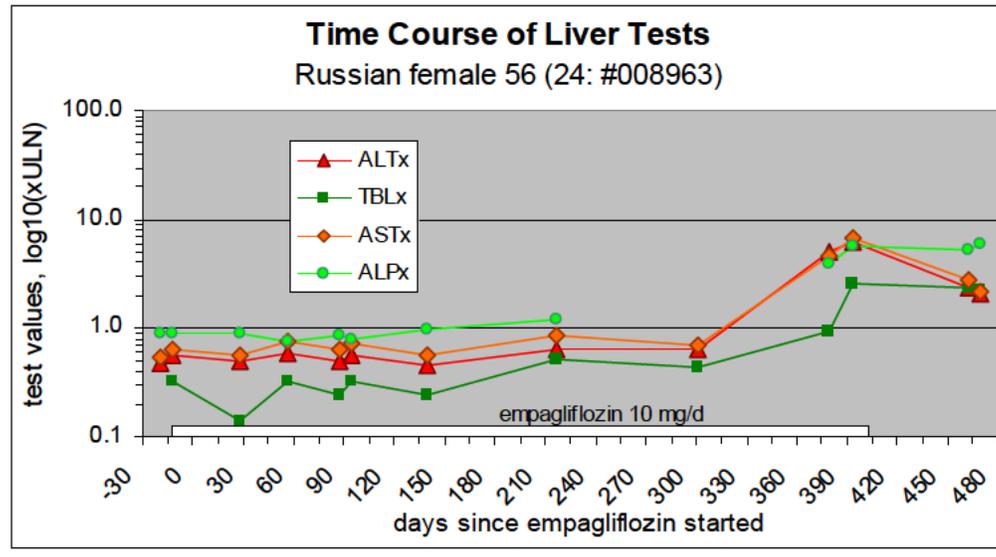
Studies 24, 33, and 38 were phase II studies that explored doses other than the target 10 or 25 mg daily dose of empagliflozin; Study 28 empagliflozin 25 mg daily compared with glimepiride.1 to 4 mg/day. The larger phase III studies 25, 31, and 48 included 2621 patients who were randomized to 10 mg, 2607 to 25 mg empagliflozin/day and 2600 to placebo, 7828 in all.

## Study 24

In Study 24 there was one patient of potential interest for whom information more detailed clinical information was sought, #008693.

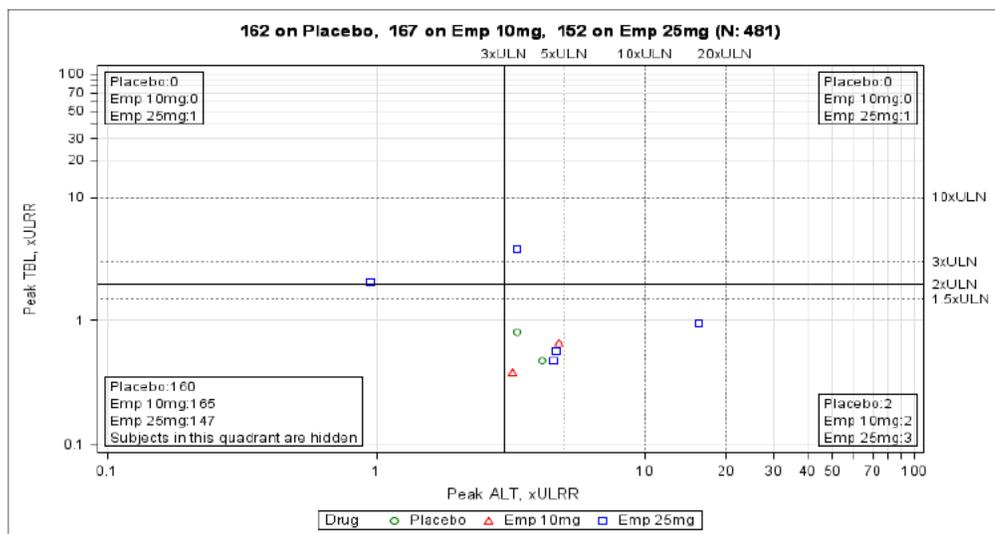


The patient with peak ALT and TBL values in the right upper quadrant was a Russian woman of 56 randomized to 10 mg /day of empagliflozin on (b) (6), which she tolerated for over a year before rises in all three serum enzyme activities, followed by bilirubin rise first noted (b) (6) after starting empagliflozin. Abdominal ultrasound showed gallstones and a partially obstructed common duct. A Klatskin tumor (cholangiocarcinoma of the distal duct) was resected.. Empagliflozin was stopped on (b) (6) considered unrelated to the tumor.



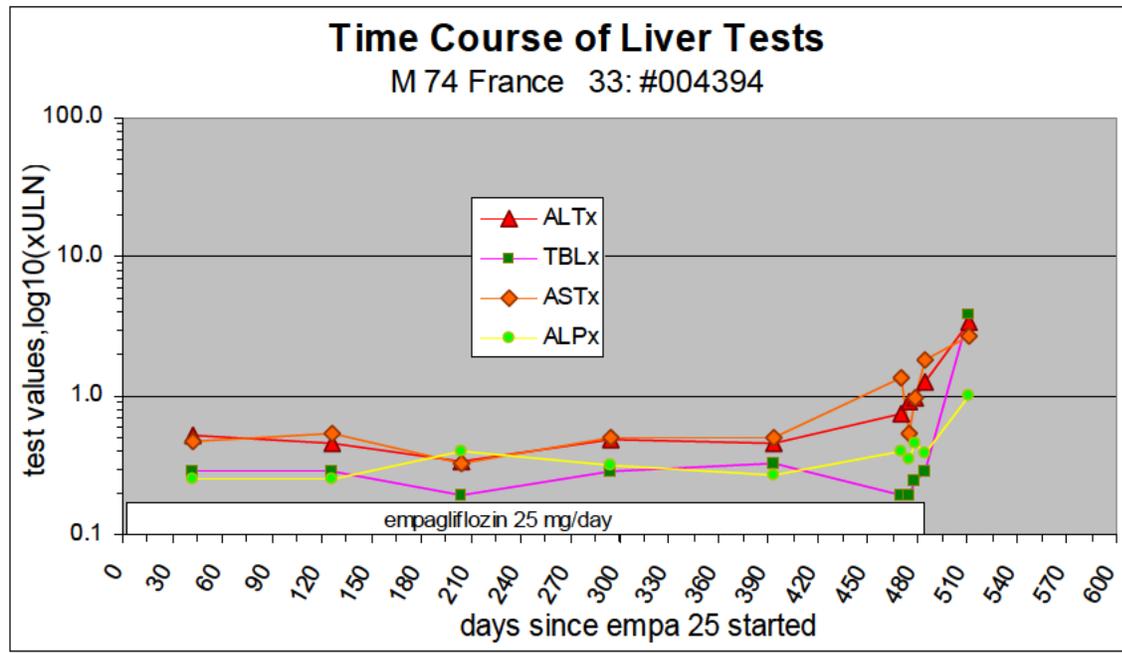
*Comment: There is no evidence at all to support the study drug as a cause of the findings.*

### Study 33



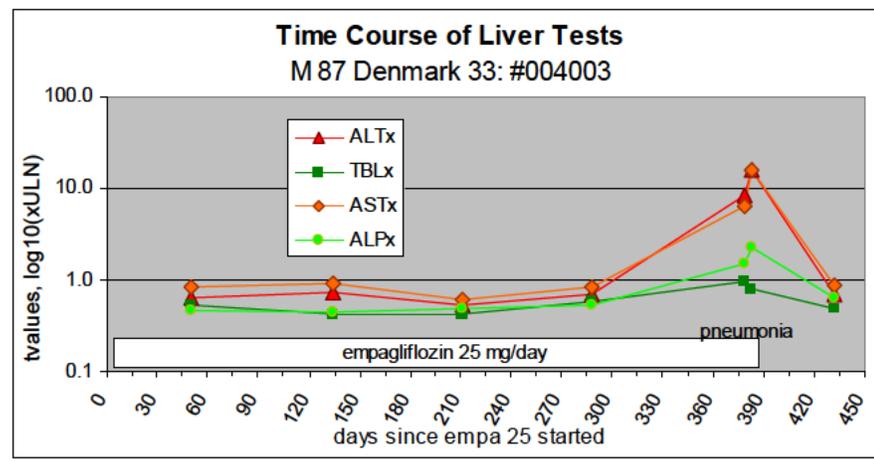
Study 33 was a phase II, 78-week study of efficacy, pharmacokinetics, tolerability, and safety of 10 and 25 mg/day of empagliflozin versus placebo, as add-on to basal insulin therapy.

Patient #004394 was 74-year-old French male randomized to 25 mg/day empagliflozin on (b) (6). After more than 15 months he was found to have slight AST elevation, serum amylase and lipase increases on (b) (6). Empagliflozin was stopped (b) (6) higher AST and ALT were found, again with amylase and lipase elevations but bilirubin and ALP were still normal. By (b) (6) he was jaundiced; pancreatic carcinoma was suspected, confirmed by biopsy (b) (6). He was discontinued from study and scheduled for radical surgery. The investigator considered the findings possibly related to study medication, but sponsor disagreed.



*Comment: The investigator seemed to be overly conservative in thinking the study drug might have caused pancreatic cancer. I concur with the sponsor.*

Another patient in that study, 33: #004003, showed ALT elevations without rise in TBL, but only after a year on empagliflozin 25 mg/day.

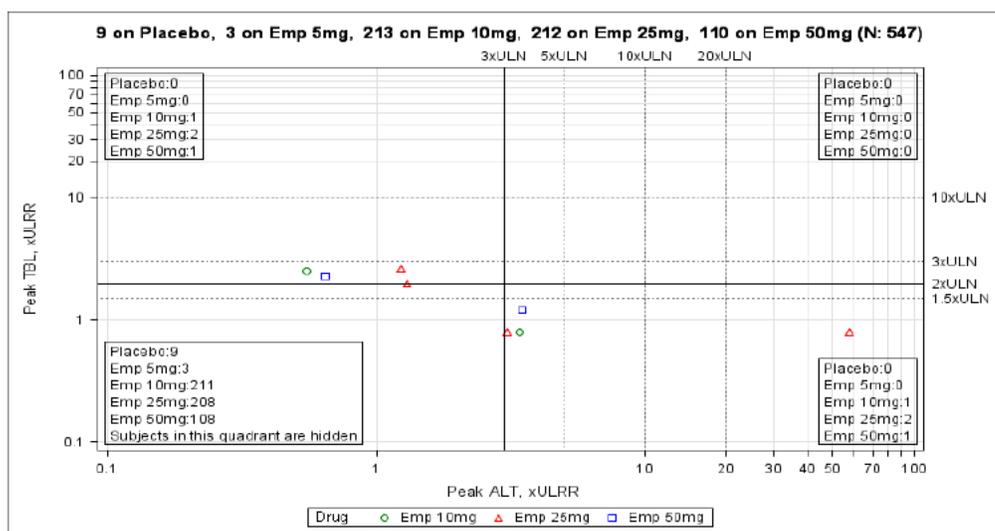


Patient # 004003 was an 87-year-old Danish male who was randomized to empagliflozin on (b) (6) and tolerated it well. On (b) (6) later, he developed pneumonia and was treated with amoxicillin/clavulanic acid, and roxithromycin. He clinically recovered from the pneumonia, and the antibiotics were stopped but (b) (6) study test values showed ALT 8.4, AST 6.4 and ALP 1.5 xULN. Repeat testing on (b) (6) showed even higher values of ALT 15.7, AST 15.9, ALP 2.3 xULN, but TBL was in the normal range on both dates. Empagliflozin was stopped (b) (6). Serologic tests for hepatitis A and B were negative, as they were also for Epstein-Barr virus. Other than stopping medications, no treatment was given, and he recovered. Recheck of liver tests on (b) (6) showed all to be in the normal range. No liver test data during the period of pneumonia treatment were available.

*Comment: It seems only weakly possible that empagliflozin was responsible for the enzyme rises found, and more likely, even probable that the amoxicillin/clavulanic acid was the likely cause of this mild and asymptomatic liver injury.*

### Study 38

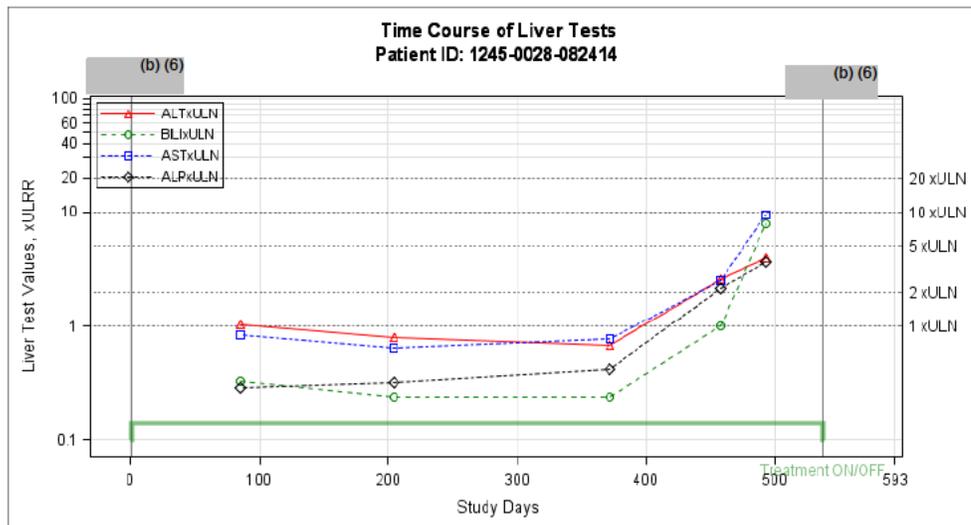
Study 38 was a phase II, 12-week study to compare lower (5 mg) and higher (50 mg) doses of empagliflozin with the expected standard doses of 10 or 25 mg/day, followed by a 40-week study of all subject re-randomized to 10 or 25 mg/day.



Only one patient showed peak test values of clinical interest, patient # 817006, a 58-year old Japanese woman who was randomized on (b) (6) to 5 mg/day in the first 12 weeks, then to 25 mg/day on (b) (6) into the 40-week extension. It was noted in her history that she consumed about a quart (430 mL) of beer daily except for the period 1-21 December, during which the intake doubled to 800 mL/day, which she told the investigator was "more than usual." On (b) (6) her ALT was found to be 57.5 xULN and AST 36.3 xULN, with ALP 2.4 xULN and normal TBL. She complained of fatigue and was hospitalized for evaluation, where she was found moderately hypertensive 164/84 and had rapid heart rate 98/min. Serologic testing was negative for viral markers, not including D or E. She recovered and was discharged on an

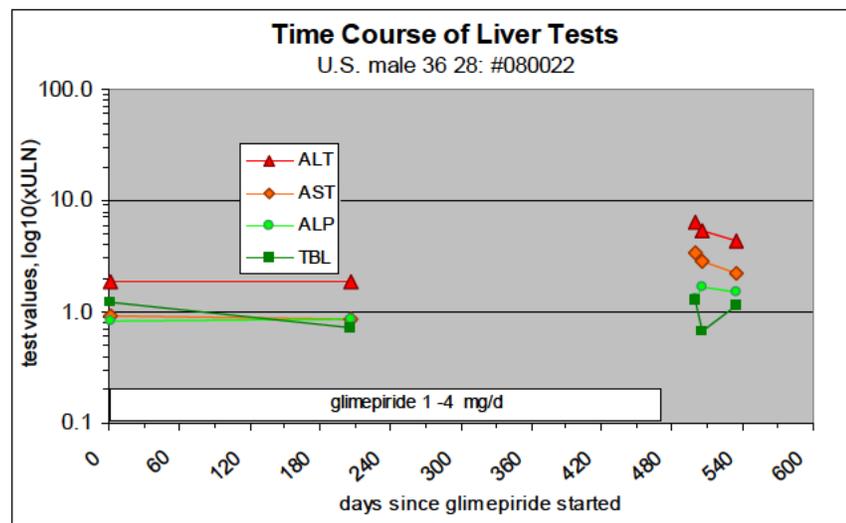


One patient (#082414) on glimepiride showed both TBL and ALT elevations; another (#080022) on glimepiride just ALT elevations >5xULN, and two on empagliflozin (#082492 and #088530) showed ALT elevations only. The patient on glimepiride who showed both ALT and TBL elevations (upper right quadrant) was a 57-year-old Argentinian man randomized to 4 mg/day glimepiride on (b) (6). He began to complain of fatigue and weakness in (b) (6). On (b) (6) ALT was 1.3, AST 3.0, ALP 1.6 and TBL 1.3 xULN. Abdominal echography showed a space-occupying lesion 6 x 3.5 cm in his liver. Repeat tests on (b) (6) showed ALT elevated to 2.6, AST 2, ALP 2.1 ULN but TBL normal. Imaging by computed tomography confirmed the finding of liver tumor. Empagliflozin was stopped (b) (6), and on (b) (6) ALT was 3.9, AST 9.5, ALP 3.7 and TBL 7.8 xULN. Liver biopsy (b) (6) confirmed a diagnosis of hepatocellular carcinoma, from which the patient died on (b) (6).



*Comment: The investigator considered the liver lesion not related to study drug. We concur.*

The other patient on glimepiride (#080022) was an obese (BMI 31.3) white U.S. man 36 years of age randomized (b) (6) to glimepiride titration from 1 to 4 mg/day.

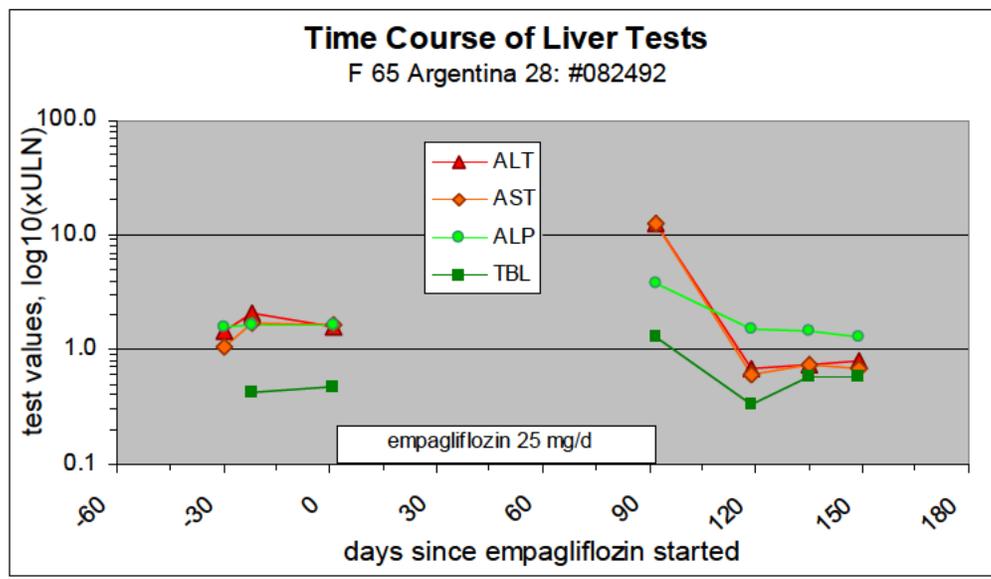


He quit the study, declining to participate further on (b) (6). Follow-up showed abnormalities of liver tests on (b) (6) that were not investigated, but the investigator did not think them related to study medication.

*Comment: This data set is sparse, and the narrative either does not describe what was happening or the patient was not well studied. It appears unlikely that the liver test abnormalities were caused by glimepiride.*

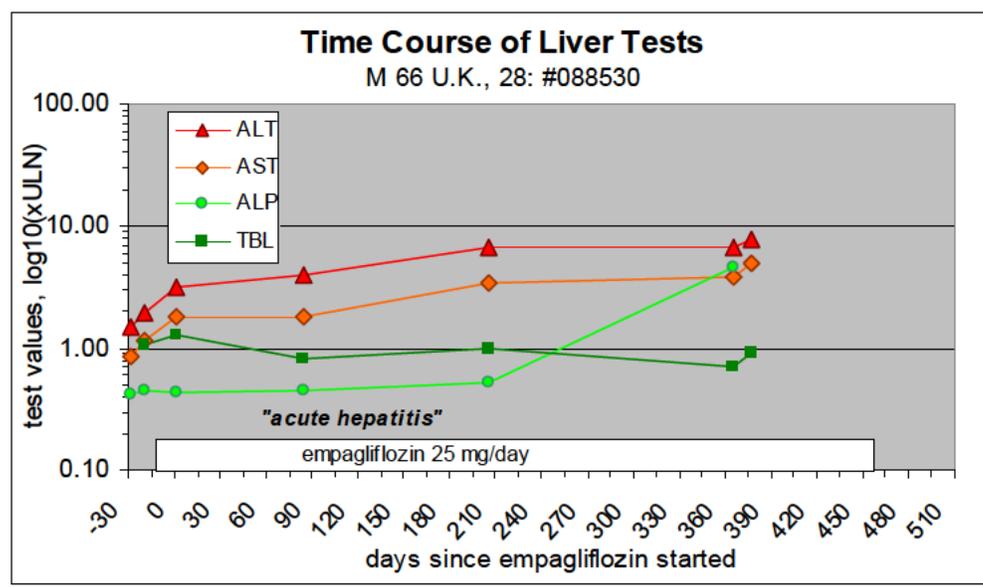
Of the two patients in Study 28 who were randomized to empagliflozin 25 mg/day, and showed peak ALT values >5xULN, the one with the greater elevation (farthest right in the right lower quadrant of the Study 28 graph above, #082492) will be mentioned first.

Patient # 082492 was a plump (BMI 30.4) 65-year-old Argentinian woman who was started on empagliflozin (b) (6). Her pre-treatment serum enzyme activities were slightly elevated but no explanation was provided in the narrative report. She had a history of diabetic neuropathy, osteoarthritis, epigastric pain, varicose veins of the legs, and previous cholecystectomy in 2001. About (b) (6) after starting empagliflozin, she was reported by the investigator to have “acute hepatitis: that was “not serious” but otherwise was not explained further. The acute hepatitis was treated with diclofenac (!) from (b) (6), and domperidone from (b) (6). The serologic tests for vital hepatitis B and C were reported as “unremarkable.” The empagliflozin was stopped on (b) (6) and was attributed by the investigator as causally related. She was stated to have recovered by (b) (6).



*Comment: The narrative provided is not credible. It is unclear why this patient was started in this study without finding out why her liver test values were elevated before she started. Treating acute hepatitis with diclofenac is remarkable, if not just plain wrong. The “acute hepatitis” was not ever explained or justified. Whether this might or might not have been a case of empagliflozin-induced liver injury, as claimed by the investigator, is almost impossible to know, given the confused and questionable information. The BI comment from the sponsor also questioned the opinion of the investigator, as do I.*

The other patient in Study 28 who showed ALT peak values  $>5xULN$  was #088530, a British man of 66 who started empagliflozin 25 mg/day on [REDACTED]<sup>(b) (6)</sup>. He was suspected by the investigator as “using alcohol above the recommended limits” but the patient did not confirm it. He had a history of irritable bowel syndrome, and had some loose stools, flatulence and mild increase in stool frequency before starting empagliflozin. He also had a “long-standing history of fluctuating liver test values, but the investigator thought they were stable acceptable before starting study drug. The symptoms of lethargy, mild palpitations, vomiting recurred on and off, along with scattered mild and unspecific symptoms of many types. A gastroenterology consultant in [REDACTED]<sup>(b) (6)</sup> thought the stooling problem was from diabetic autonomic neuropathy. The investigator assessed the liver test abnormalities as “not causally related to the study drug.”

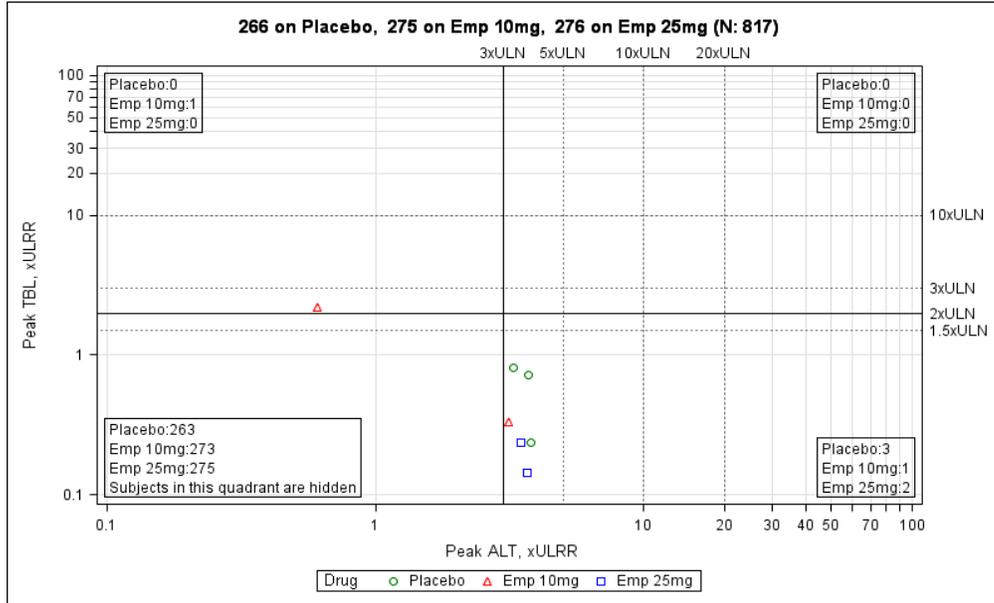


*Comment: It is totally unclear what was going on in this patient's liver, and the investigator clearly did not know (nor care very much, apparently). Empagliflozin did not seem to worsen whatever it might have been, and can scarcely be blamed for causing it. A diagnosis of uncertain is all that can be rendered, and there seems no point in speculating about it as did the sponsor.*

In the three remaining phase III studies, 25, 31, and 48, there were 2621 patients started on 10 mg daily of empagliflozin, 2607 on 25 mg/day, and 2600 on placebo. Most of them were in the large Study 25 for which only interim results are available for data up to 31 August 2012, so that data were submitted only for 1623 on 10 mg, 1632 on 25 mg empagliflozin, and 1619 on placebo, about 62% of the patients entered. Study 31 was a follow-on study from the 2011 Studies 19, 20, and 23 for assessment of long-term safety; the study was still ongoing as of the NDA submission, and included data obtained up to 29 May 2012.

The question of whether a valid and accurate prediction of the likelihood of serious adverse liver effects attributable to empagliflozin is not easy to conclude. There is certainly a very large and rich sample of patients exposed to the study drug, so we can only try to conclude on the basis of what we have so far. The smallest of the three studies in this group is Study 48, including 817 patients, about equally divided between treat on 10 or 25 of empagliflozin, or placebo. No patient in this study showed results of concern, as may be seen immediately below.

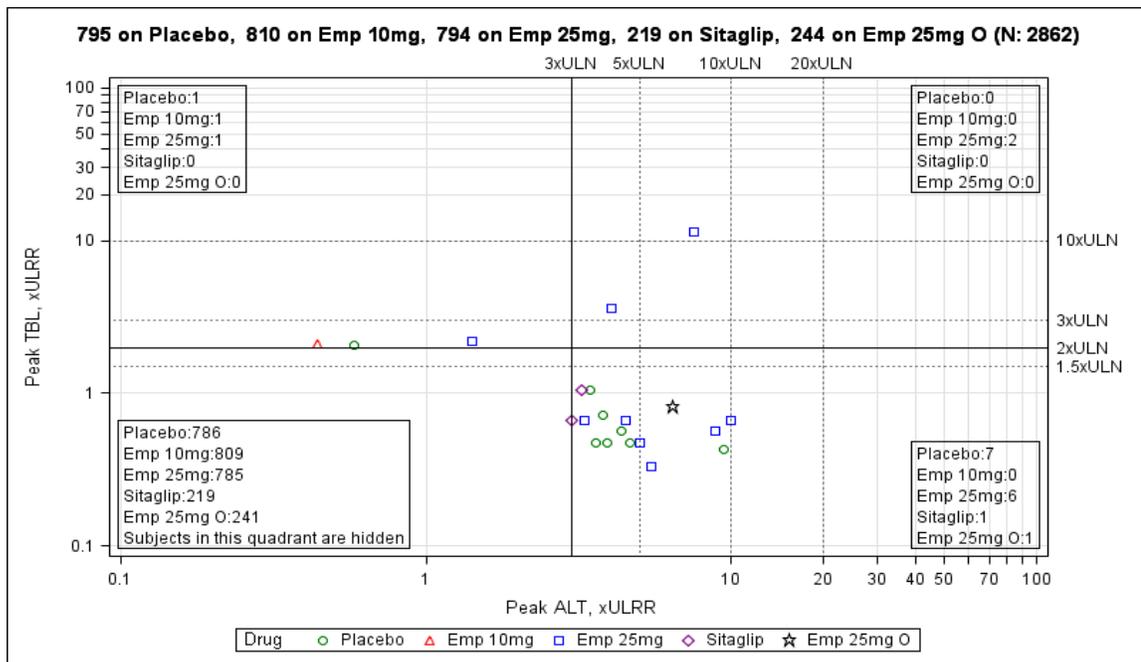
**Study 48**



*Comment: This is a very benign-looking eDISH plot for the 817 patients entered into Study 48, aimed at investigating the target doses of empagliflozin being considered (10 and 25 mg/day), compared to placebo, in patients with hypertension, over a period of 12 weeks.*

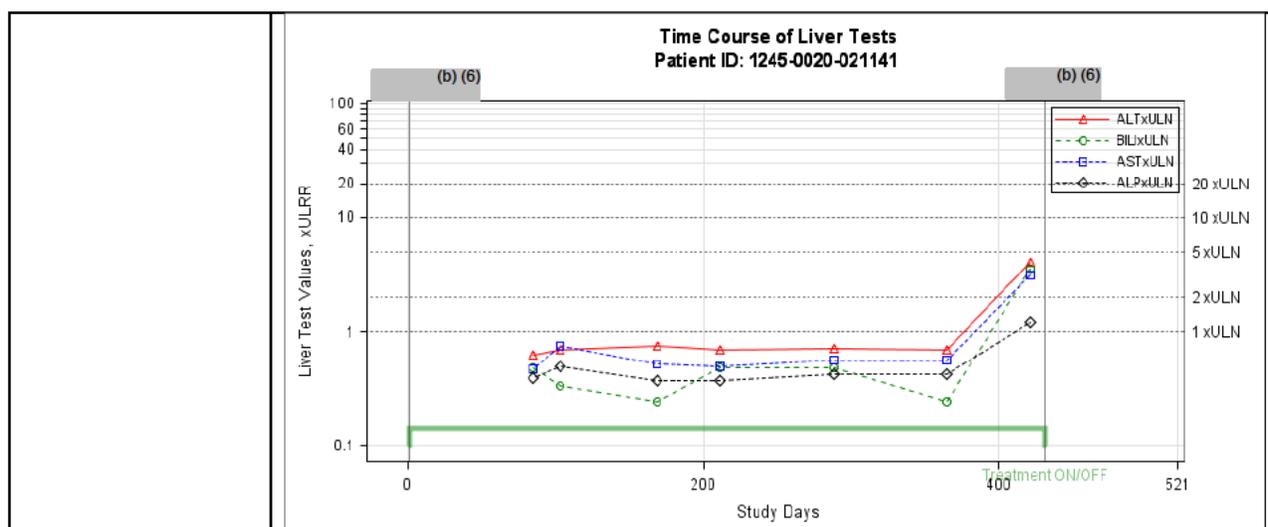
**Study 31**

Study 31 was the long-term follow-on of Studies 19, 20, and 23 that were started earlier:



Looking at the whole group in Study 31, which is still ongoing, there were two patients in the eDISH right upper quadrant, both on 25 mg/day of empagliflozin: #023063 and # 021141. We have already considered #023063 (see above page 7); the Indian man 49 started empagliflozin on (b) (6) rather promptly was diagnosed as having "infective hepatitis" that resolved and for which empagliflozin administration was interrupted for only about a week, and then was restarted. The "rechallenge" with empagliflozin was negative, and the hepatitis subsided despite long-term empagliflozin, strongly indicating that the problem was not empagliflozin-induced.

In addition to him, patient #021141 showed peak ALT 4.1 and TBL 3.6 xULN, but only after more than a year on empagliflozin. He was an overweight (BMI 29.8) Japanese male 55 with a history of steatohepatitis, unspecified pancreatic disease, abdominal pain, and dyslipidemia. He started empagliflozin 25 mg/day on (b) (6) in Study 20 and was rolled over into Study 31 on (b) (6) and continued to show liver tests in the normal range. At the (b) (6) he had a respiratory infection, was given an unspecified antipyretic medication, and then developed whole-body itching, with abdominal discomfort. Symptoms continued, abdominal ultrasonography showed fatty liver and small cysts in liver and kidney, gallbladder, spleen, and pancreas, were poorly visualized. On (b) (6) elevated cancer antigen 19-9 was elevated to 74.5 (ULN 37 u/mL), and carcinoembryonic antigen CEA was twice normal. ALT, AST, ALP, and TBL were all elevated on (b) (6) to 4.1, 3.1, 1.2, and 3.6 xULN, and computed tomography showed a bile duct tumor. Empagliflozin was stopped (b) (6) and pancreaticoduodenectomy was done, resecting the distal bile duct tumor. Study drug was not considered related to the problem.



*Comment: There is almost no likelihood that the bile duct tumor was caused by empagliflozin.*

In addition to this serious case, there were five others in patients on empagliflozin and one in a patient on placebo who showed peak ALT values >5xULN. Of these, two who started first in Study 19: #011500 and Study 23: #032199 have already been discussed above on pages 6 and 9 above. The other four had asymptomatic serum transaminase elevations that did not progress to cause liver dysfunction or symptoms, and were not investigated in detail at the sites, according to the narratives provided. Those four cases are summarized briefly in the following table, but time course data for them are not shown, but available on request:

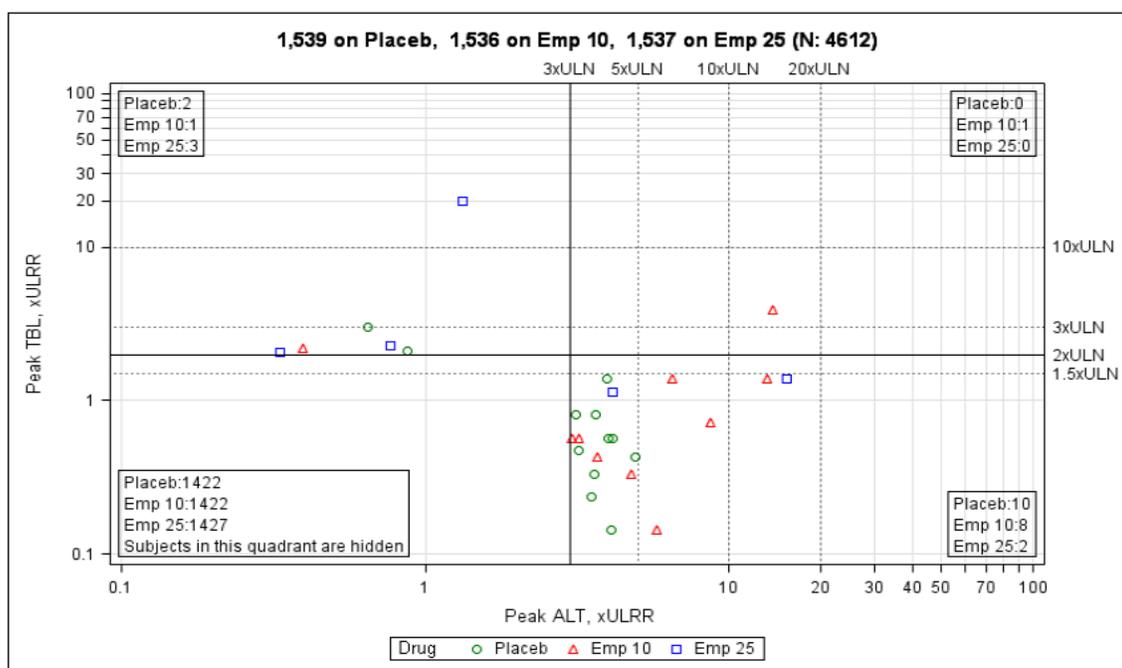
Study 31, follow-on extension of Studies 19, 20, 23							
Study, PtNo	SexAge	location	drug	date start	ALT	TBL	probable cause
19: #011268	F 64	Philippines	E25	(b) (6)	9.97	0.67	not investigated, uncertain
20: #023778	F 50	China	PLA	(b) (6)	9.46	0.43	mild chronic hepatitis B
23: #032675	F 64	China	E25	(b) (6)	8.89	0.59	not investigated, uncertain
20: #023155	F 52	India	E25	(b) (6)	6.43	0.81	not investigated, uncertain

Note: ALT and TBL expressed as peak values, xULN

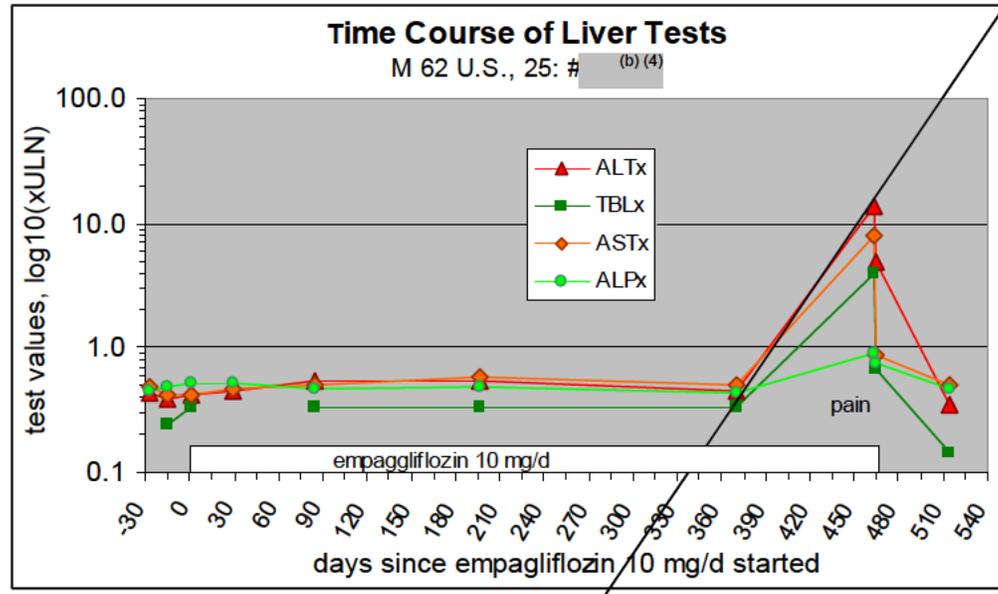
Comment: There is little more to be said about these cases, none of which were serious, nor did the patients have symptoms of liver dysfunction, and they were only of moderate severity because of the peak ALT values. At most they might be considered as **possibly** caused by empagliflozin but other possible causes were not excluded.

### Study 25

This was the largest study of the submission, data on 4612 patients, about equally divided between those on empagliflozin 10 mg/day (1536), empagliflozin 25 mg/day (1537), and placebo (1539). Of them, only one showed peak values of ALT and TBL in the right upper quadrant (b) (4), and there five whose peak ALT values were >5xULN.

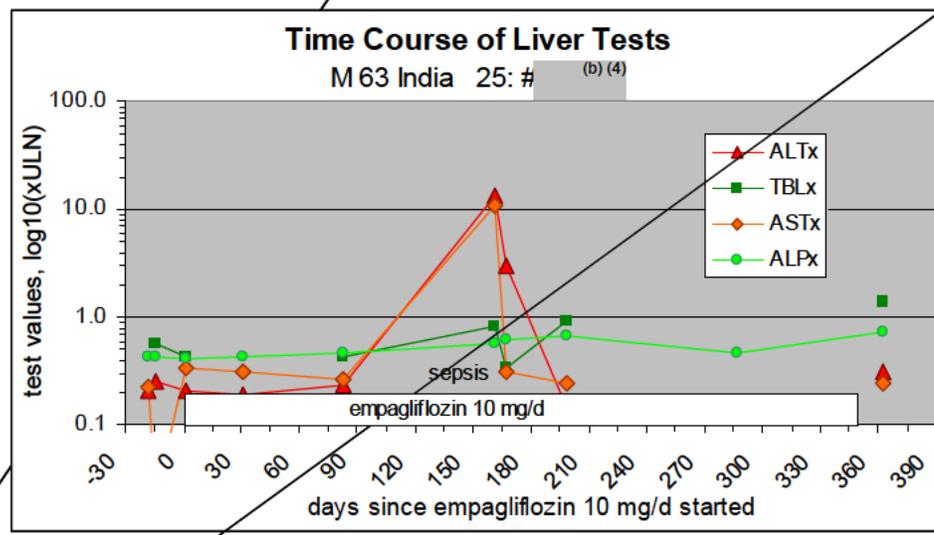


Patient # (b) (4) was a U.S. male 62 randomized to empagliflozin 10 mg/day on (b) (6). He had a history of coronary artery disease, aortic stenosis, hypertension, angioplasty, episodes of heart failure, bee-sting allergy, hypothyroidism, . After more 15 months on empagliflozin, he reported abdominal pain on (b) (6), and his ALT was elevated to 13.9 xULN, AST 8.0 and TBL 3.9 xULN on (b) (6). The pain increased on (b) (6) and CT scan showed cholelithiasis. He was hospitalized and cholecystectomy was done on (b) (6). Follow-up testing on (b) (6) showed all liver test results back to the normal range.



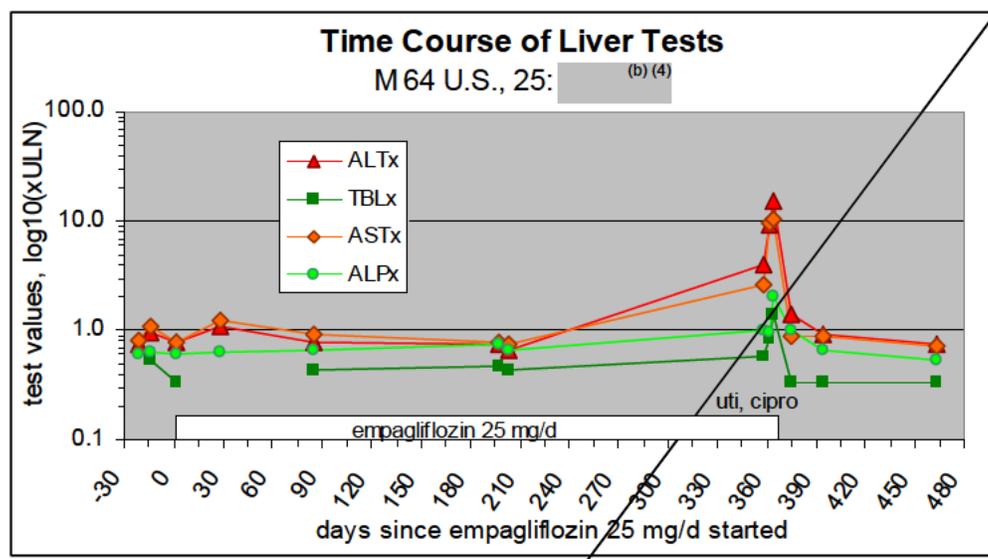
*Comment: The cause of his abnormal liver test values was obviously acute gallbladder disease, with inflammation, relieved by cholecystectomy. Causality by empagliflozin was nil.*

Elevations of serum ALT activity without increase in bilirubin concentration were seen in five patients in Study 25, two of whom showed peak elevations of ALT >5 to 10 xULN. Patient (b) (4) was a thin (BMI 20.0) Indian male 63 when randomized to empagliflozin 10 mg/day on (b) (6). He developed a urinary tract infection, sepsis, and was hospitalized on intensive care in (b) (6). He was treated with antibiotics (b) (6), and was discharged (b) (6) days on empagliflozin, which was continued until (b) (6).



*Comment: The enzyme elevations suggesting acute hepatocellular injury occurred at the time of his severe sepsis and treatment. He had been on empagliflozin for over 5 months without sign of enzyme rise, and tolerated it for another 7 months. Empagliflozin hepatotoxicity very unlikely.*

Patient # (b) (4) was an obese (BMI 35.0) white U.S. male 64 when started on empagliflozin 25 mg/d on (b) (6). In early (b) (6) he developed a urinary tract infection (uti) and was treated with ciprofloxacin for (b) (6). Elevations of his serum enzyme activities (ALT, AST, ALP) began on (b) (6) and peaked on (b) (6), after his antibiotics were stopped.



*Comment: The cause of the enzyme elevations was not investigated, and they disappeared promptly when both empagliflozin and ciprofloxacin were stopped. Although empagliflozin hepatotoxicity is possible, it seems more likely that the effects were induced by the antibiotic. Very slight aminotransferase elevations were noted, and his obesity makes non-alcoholic liver disease a possibility also, but the acute injury in (b) (6) seems most likely ciprofloxacin-induced.*

As may be noted in the ALT-TBL plot for Study 25 above, there were also three patients who showed lesser peak ALT elevations of >5 but <10 xULN, no bilirubin rise, no symptoms, and no evidence of clinical illness. Their data are summarized in the table below, as had been done for the four patients in Study 31, above. None of these patients would have known of the enzyme elevations if not done on schedule under the protocol. It cannot be known whether that values were falling or rising when they happened to be done, except when promptly rechecked. Again, this emphasizes that ALT elevations are not reliable measures of hepatotoxic severity, which is better related to whole-organ dysfunction as measured by bilirubin concentration or prothrombin time (the latter not done in these studies).

Study 25							
Study, Pt No	SexAge	location	drug	date start	ALT	TBL	probable cause
# (b) (4)	F 70	Mexico	E10	(b) (6)	8.62	0.71	Captopril, APAP? uncertain
#	F 50	Korea	E10		6.46	1.38	not investigated, uncertain
#	F 64	Brazil	E10		5.76	0.14	not investigated, uncertain

*Note: ALT and TBL expressed as peak values, xULN*

What may be concluded from this exercise of evaluating serial liver test data for ALT, AST, ALP, activities and TBL concentrations for almost 10,000 (actually 9,683) patients treated with empagliflozin, most of them on 10 or 25 mg/day, for varying periods up to several years? The use of the eDISH program makes it possible fairly quickly to consider all of the data for all of the patients, use the power of the computer to display peak observed values of ALT and TBL for each patients, and at a glance see which ones deserve special attention and more detailed study.

By selecting the few (5) patients who showed peak {ALT >3xULN & TBL >2xULN} its was possible to reduce the massive workload of considering all the patients. Pointing to the symbol representing those patients in the right upper quadrant of the eDISH step-1 ALT-TBL plot very quickly commands eDISH to go get all the test values on all the dates they were determined for the selected patient, which is quite helpful in deciding what may have caused what. The clinical narrative, if well done, is the more powerful tool for making the differential diagnosis of what may have been the most likely cause of the abnormal findings. This is only as helpful as the fine detail and medical information are included, to supplement the information in the case report forms filled out during the studies. It is most valuable if narratives are prepared by a physician skilled and knowledgeable in the art of medical diagnosis. The determination of cause is the most important element of the evaluation using eDISH. The diagnosis cannot be made simply by looking at ALT and TBL values (...which has been used by statisticians wrongly to apply the designation of “chemical Hy’s Law cases.” That should not be done, as we shall see below.)

<b>Cases of special interest in the 10 studies: those with {pALT&gt;3xULN &amp; pTBL&gt;2xULN}</b>							
<i>Study, PtNo</i>	<i>SexAge</i>	<i>location</i>	<i>drug</i>	<i>date start</i>	<i>ALT</i>	<i>TBL</i>	<i>probable cause</i>
20: #023063	M 60	India	E25	(b) (6)	7.6	11.4	acute infectious hepatitis
24: #008693	F 56	Russia	E10		6.3	2.5	cholangiocarcinoma
25: # (b) (4)	M 62	U.S.	E10		13.9	3.9	acute cholecystitis, CD stone
28: #082414	M 57	Argentina	G 4		3.9	7.8	hepatocellular carcinoma
31: #021141	M 55	Japan	E25		4.1	3.6	distal bile duct carcinoma
33: #004394	M 74	France	E25		3.3	3.8	adenocarcinoma pancreas

*Note: ALT and TBL expressed as peak values, xULN*

It is noted that patient 28: #084833, a very obese (BMI 40.35) Czech male 48 started (b) (6) on empagliflozin 25 mg/day was listed by Dr. Chong to have ALT 25.8, TBL 16.1 xULN and AST 110.8 xULN, due to alcoholic hepatitis. He was not so listed for our eDISH analyses nor was a narrative provided. Also of some interest, perhaps secondary, are cases with ALT elevations >10xULN bu no rise of significance of serum bilirubin concentration. There were four more of those:

<b>Cases of secondary interest in the 10 studies: those with pALT&gt;10xULN &amp; pTBL&lt;2xULN}</b>							
<i>Study, PtNo</i>	<i>SexAge</i>	<i>location</i>	<i>drug</i>	<i>date start</i>	<i>ALT</i>	<i>TBL</i>	<i>probable cause</i>
25: # (b) (4)	M 64	U.S.	E25	(b) (6)	15.5	1.4	UTI, ciprofloxacin
25: # (b) (4)	M 63	India	E10		13.3	1.7	UTI,sepsis, antibiotics
28: #082492	F 65	Argentina	E25		12.7	1.3	acute hepatitis unspecified
33: #004003	M 87	Denmark	E25		15.7	0.9	amoxicillin, roxithromycin
38: #817006	F 58	China	E25		57.5	0.8	acute alcoholic hepatitis

*Note: ALT and TBL expressed as peak values, xULN*

The small number of cases is notable, out of nearly 10,000 patients exposed to empagliflozin. Of even less concern were cases in which the peak ALT was >5 but <10xULN, and TBL <2xULN, actually <1.5xULN, as may be seen in the following table:

<b>Cases of some interest in the 10 studies: those with pALT&gt;5 to &lt;10xULN, pTBL&lt;2xULN</b>							
<i>Study, PtNo</i>	<i>SexAge</i>	<i>location</i>	<i>drug</i>	<i>date start</i>	<i>ALT</i>	<i>TBL</i>	<i>probable cause</i>
19: #011500	M 54	Ukraine	E25	(b) (6)	5.44	0.33	not investigated; uncertain
20: #023155	F 52	India	E25		6.43	0.81	no narrative; uncertain
23: #032199	F 19	China	E25		5.03	0.46	not investigated; ?NASH
23: #032675	F 64	China	E25		8.70	0.57	chronic hepatitis B
25: # (b) (4)	F 70	Mexico	E10		8.62	0.71	Captopril, APAP? uncertain
25: #	F 50	Korea	E10		6.46	1.38	not investigated, uncertain
25: #	F 64	Brazil	E10		5.76	0.14	not investigated, uncertain
28: #080022	M 36	U.S.	<b>G1-4</b>		6.48	1.29	not investigated, uncertain
28: #088530	M 66	U.K.	E25		7.88	1.00	not investigated, uncertain
31: #011268	F 64	Philippines	E25		9.97	0.67	not investigated, uncertain
31: #023778	F 50	China	<b>PLA</b>		9.46	0.43	mild chronic hepatitis B
31: #032675	F 64	China	E25		8.89	0.59	not investigated, uncertain
31: #023155	F 52	India	E25		6.43	0.81	not investigated, uncertain

*Note: ALT and TBL expressed as peak values, xULN*

The number of cases for which the probable cause was given as uncertain is unfortunate but may be understandable. These cases were asymptomatic, gave no indication to the investigator, or to themselves, that there may have been a liver problem. Most of them were not investigated further and no diagnosis could be made just from the abnormal serum chemistry values, or even from the time courses of all liver tests in those individuals. It is also possible that the project manager assigned the task of writing a retrospective narrative, from the case report forms and perhaps a MedWatch report, did not note critical bits of possibly diagnostic information.. To make a valid diagnosis of the probable cause of the findings may not have been easy, even for the investigator in the clinic, and few if any of the cases had hospital records.

If we consider mainly the potentially serious cases, there were none found in whom a diagnosis of empagliflozin-induced hepatitis could be made or substantiated by the evidence available or reported to us. A spurious incidence of about 6 per 10,000 thus falls to 0 per 10,000 if probable causality is considered, and focus placed on serious cases that were disabling, hospitalized, had secondary renal or brain failure, need transplantation, or died. Those serious problems are what we really seek to avoid in evaluating new drugs for possible approval for use in far more patients with less observation and reporting that are likely after approval for prescription and marketing.

The liver is a remarkably adaptive organ, can regenerate after resection of two-thirds its mass, then regrows rapidly to its original size and regains full function. For chemical or drug-induced injury that liver is now appreciated to show adaptation and replacement of damaged hepatocytes with new and fully functional cell that have acquired tolerance to the injurious agent. Amazing!

In summary, close inspection and evaluation of this quite large set of controlled clinical studies has shown no indication the empagliflozin is likely to cause serious liver injury or dysfunction. There seems no need to convene a special panel of consultants or advisory committee actions on this issue. These views have been discussed with the primary clinical reviewer on 16 October, and expressed also with his clinical team leader, Division Director, ODE II Director and Deputy on the previous day, 15 October. The time since then has been devoted to filling in all the details into this consultation report and entering it into DARRTS.

Copies of references are available on request. Further commentary and follow-up consultation will be sent after data from completed and reported phase II studies have been received, entered into eDISH, and evaluated. I shall be pleased to attend the meeting of the Advisory Committee in December, to answer any questions if they arise. Your assistance has been much appreciated in the work of this consultative review.

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John R. Senior, M.D.

cc: OSE 2013-1216  
J-M. Guettier, DMEP  
E. Colman, DMEP  
A. Egan, DMEP  
K. Mahoney, DMEP  
W. Chong, DMEP  
S. Iyasu, OPE/OS

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/s/

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JOHN R SENIOR  
10/20/2013

**Consult Request Review**  
**Division of Oncology Products 2 (DOP2)**

**From:** Jennie Chang, Pharm.D., Senior Clinical Analyst, DOP2  
Marc Theoret, M.D., Clinical Team Leader, DOP2

**To:** Bill Chong, M.D.  
Division of Metabolism and Endocrinology Products (DMEP)

**Subject:** Lung neoplasms and malignant melanomas with empagliflozin

**NDA:** 204629

**Product:** Empagliflozin

**Sponsor:** Boehringer Ingelheim

**Date Submitted:** May 22, 2013

**Date Completed:**

**I. BACKGROUND:**

This consult is in response to a request from Bill Chong, M.D., DMEP, to evaluate the cases of lung neoplasms and malignant melanomas. The request states,

“As reported by the Sponsor and noted in our review of NDA-204629 (Empagliflozin), there is an imbalance in the number of cases of lung neoplasms and malignant melanomas occurring  $\geq$  180 days after initiating treatment with Empagliflozin. We are requesting a review and an opinion on the background incidence and an opinion on the likelihood of the study drug contributing to this imbalance.”

Empagliflozin, a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2), is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The recommended dosing schedule for the proposed indication of empagliflozin is 25 mg administered orally once daily.

Melanoma

Approximately 76,690 new cases of melanoma will be diagnosed this year, and 9,480 deaths will occur due to the disease.<sup>1</sup> The age-adjusted incidence rate was 21.1 per 100,000 men and women per year, based on cases diagnosed in 2006-2010 from 18 SEER geographic areas. Median age at time of diagnosis of melanoma is 59 years.<sup>2</sup>

Individuals at increased risk for melanoma are those with light complexions, numerous pigmented lesions (freckles and atypical moles), history of severe sunburns especially during childhood, history of other skin cancers (basal cell and squamous cell carcinomas), and family history of melanoma.<sup>3</sup> Use of tanning beds also has been associated with an increased risk of melanoma.

### Lung Cancer

The leading cause of cancer death in the United States is lung cancer. In 2012, an estimated 226,000 new cases (116,000 in men and 110,000 in women) of lung and bronchial cancer will be diagnosed and 160,000 deaths will occur due to the disease. According to the SEER database, from 2006-2010, the median age at diagnosis for cancer of the lung and bronchus in the U.S. was 70 years of age with approximately 21.3% diagnosed between 55 and 64 years. The age-adjusted incidence rate was about 61 per 100,000 men and women per year.<sup>4</sup>

Risk factors for lung cancer include smoking tobacco, second-hand smoke, exposure to radon gas, asbestos, recurring lung inflammation, tuberculosis, family history, and exposure to other carcinogens (chromium, nickel, and arsenic).<sup>5</sup>

## **II. CONSULT REVIEW**

### NDA Safety Database

To support this NDA, Boehringer Ingelheim submitted safety data from 48 clinical trials, including 13 phase 2b/3 trials, 5 dose-finding phase 2 trials, and 30 phase 1 trials. Some phase III trials were still ongoing at the time of the integrated analysis for this application (1245.25, 1245.28, 1245.31). For these trials, all safety data available at the time of data cut-off for the prespecified interim analysis of each trial are included in the NDA submission. The studies are summarized below:

**Table 1. Trial Groupings for Integrated Safety Analyses**

Shorthand	Description	Main purpose for safety assessment	Trials included	Number of patients treated
SAF-1 <i>mono-therapy</i>	Trials with empagliflozin monotherapy in patients without background antidiabetic therapy	Safety assessment of empagliflozin monotherapy	Phase II: 1245.9, 1245.38 (only until 12 weeks) Phase III: 1245.20, 1245.31 <sub>(monotherapy)</sub> (only patients from 1245.20)	All empa <sup>1</sup> : 1129 Placebo: 420 All comparators <sup>2</sup> : 723
SAF-2 <i>pivotal trials without SU</i>	Pivotal trials, excluding patients receiving an SU as background therapy	Integrated benefit-risk-assessment; assessment of hypoglycaemic events (corresponds to efficacy set EFF-1)	Phase III: 1245.19, 1245.20, 1245.23 <sub>(met)</sub>	All empa <sup>1</sup> : 1211 Placebo: 600 All comparators <sup>2</sup> : 823
SAF-3 <i>pivotal trials with extension</i>	Pivotal trials and their extension, including all patients	Integrated benefit-risk-assessment (corresponds to efficacy set EFF-2)	Phase III: 1245.19, 1245.20, 1245.23 <sub>(met)</sub> , 1245.23 <sub>(met+SU)</sub> , 1245.31	All empa <sup>1</sup> : 1652 Placebo: 825 All comparators <sup>2</sup> : 1048
SAF-4 <i>all patients without other conditions</i>	All trials in patients with type 2 diabetes and without special medical conditions	Safety of empagliflozin in patients with type 2 diabetes mellitus not confounded by severe comorbidities	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III: 1245.19, 1245.20, 1245.23 <sub>(met)</sub> , 1245.23 <sub>(met+SU)</sub> , 1245.28, 1245.31, 1245.48	All empa <sup>1</sup> : 4523 Placebo: 1584 All comparators <sup>2</sup> : 2738
SAF-5 <i>all patients</i>	All trials in patients with type 2 diabetes	Adverse events in subgroups and identification of rare adverse events	Phase I: 1245.2, 1245.4, 1245.44 Phase II: 1245.9, 1245.10, 1245.15, 1245.24, 1245.33, 1245.38 Phase III: 1245.19, 1245.20, 1245.23 <sub>(met)</sub> , 1245.23 <sub>(met+SU)</sub> , 1245.25, 1245.28, 1245.31, 1245.36, 1245.48	All empa <sup>1</sup> : 8197 Placebo: 3522 All comparators <sup>2</sup> : 4676
SAF-6 <i>healthy subjects</i>	All trials in healthy subjects (presented in the SCS only)	Safety assessment of empagliflozin in all healthy subjects	Phase I: 1245.1, 1245.3, 1245.5, 1245.6, 1245.7, 1245.8, 1245.16, 1245.17, 1245.18, 1245.27, 1245.30, 1245.40, 1245.41, 1245.43, 1245.45, 1245.50, 1245.51, 1245.58, 1245.63, 1245.79, 1275.3, 1276.5, 1276.9	All empa <sup>3</sup> : 393 Placebo: 59 All comparators <sup>3</sup> : 305

Met = metformin, SU = sulphonylurea

<sup>1</sup>'All empa' includes all patients treated with any dose of empagliflozin in a randomised treatment group. In addition, 257 patients were treated with open-label empagliflozin 25 mg in trials 124.20, 1245.23<sub>(met)</sub> and 1245.23<sub>(met+SU)</sub>

<sup>2</sup>'All comparators' includes all patients treated with placebo or an active comparator

<sup>3</sup>'All empa' comprises subjects treated with empagliflozin alone in at least 1 treatment period. 'All comparator' comprises subjects treated with any active comparator drug alone in at least 1 treatment period. Some of the subjects contributing to the numbers for 'All empa' and 'All comparator' (in total 289 subjects) were co-administered empagliflozin and other active drugs in other treatment periods of the same trial.

Source: Table 5.1: 1, Trial groupings for integrated safety analyses. 2.5 Clinical Overview, page 56. NDA 204629, Boehringer Ingelheim, February 5, 2013.

In the clinical program, 6808 patients were exposed to empagliflozin for  $\geq 24$  weeks, 4415 patients exposed for  $\geq 52$  weeks, and 1486 patients exposed for  $\geq 76$  weeks.<sup>6</sup>

## Melanoma and Lung Cancer Cases

Malignancies were evaluated from safety trial pool SAF-5, SAF-3 and study 1245.25. Standardized MedDRA query (SMQ) 20000091 “Malignant or unspecified tumours” and SMQ 20000092 “Malignancy related conditions”, excluding PT “acanthosis nigricans” were used to query the safety data. Cases were manually reviewed by Boehringer Ingelheim and were grouped according to malignancy, as shown in Table 2. For melanoma, six cases were observed in the empagliflozin group and none in the comparator arm. Additionally, six cases of lung cancer were observed in the empagliflozin group and none in the comparator arm; however, one case of small cell lung cancer in the placebo group was submitted subsequent to the initial NDA submission on August 15, 2013, under SDN 17.

**Table 2. Incidence of Selected Types of Malignancies in SAF-5 – Events Occurring After 6 Months of Treatment With Empagliflozin or Comparator**

	Placebo	Empa 10	Empa 25	All random. empa <sup>1</sup>	All comparators <sup>2</sup>
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	3522 (100)	3630 (100)	4602 (100)	8400 (100)	4676 (100)
Patients with breast cancer <sup>3</sup>	1 (0.03)	1 (0.03)	0	1 (0.01)	2 (0.04)
Patients with bladder cancer <sup>4,6</sup>	0	2 (0.06)	0	3 (0.04)	1 (0.02)
Patients with renal cancer <sup>5</sup>	2 (0.06)	0	0	0	2 (0.04)
Patients with melanoma <sup>6</sup>	0	2 (0.06)	4 (0.09)	6 (0.07)	0
Patients with lung cancer <sup>7</sup>	0	2 (0.06)	3 (0.07)	6 (0.07)	0

<sup>1</sup> Empagliflozin doses included: 1 to 100 mg

<sup>2</sup> Including placebo, sitagliptin, metformin, and glimepiride

<sup>3</sup> PTs included: breast cancer, breast cancer female

<sup>4</sup> PTs included: bladder cancer, bladder neoplasm, transitional cell carcinoma

<sup>5</sup> PTs included: renal cancer, renal cancer stage II

<sup>6</sup> PTs included: malignant melanoma, malignant melanoma in situ

<sup>7</sup> PTs included: bronchial carcinoma, lung cancer metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified

Source data: RMP [U13-1175] and [U12-2707, Appendix 2, Table 5.17.5.17]

Source: Table 2.1.5.8: 2: Number of patients with selected types of malignancy in SAF-5 – patients treated for >6 months and reported events after 6 months. 2.7.4 Summary of Clinical Safety for Empagliflozin, page 157. NDA 204629, Boehringer Ingelheim, February 5, 2013.

N.B.: Although not included in the table, an additional case of small cell lung cancer in the comparator group was submitted to NDA 204629, SDN 17, on August 15, 2013, so placebo = 1 for patients with lung cancer.

Boehringer Ingelheim presented the following cases of melanoma and lung cancer as shown in Tables 3 and 4 below:

**Table 3. Cases of Melanoma Observed After Exposure to Empagliflozin for >6 Months**

Patient/study No.	Age [years] /gender	Preferred term	Treatment	Start day <sup>1</sup>	Serious	Outcome
(b) (4)/1245.25	59/M	Malignant melanoma	Empa 10	236	Required hospitalisation	Not recovered <sup>2</sup>
/1245.25	69/M	Malignant melanoma	Empa 10	345	Other	Not recovered
3402/1245.24	78/F	Malignant melanoma	Empa 25	238	No	Recovered
(b) (4)/1245.25	67/M	Malignant melanoma	Empa 25	216	No	Recovered
1815/1245.36	62/M	Malignant melanoma	Empa 25	233	Other	Not recovered <sup>2</sup>
80040/1245.28	68/F	Malignant melanoma in situ	Empa 25	351	Other	Recovered

PTs included: malignant melanoma, malignant melanoma in situ

<sup>1</sup> Relative to the first dose of randomised (or open-label) study medication

<sup>2</sup> Follow up sufficient

Source data: [U12-2707, Appendix 2, Listing 5.17.5.18]

Source: Table 2.1.5.8: 3: Number of patients with selected types of malignancy in SAF-5 – patients treated for >6 months and reported events after 6 months. 2.7.4 Summary of Clinical Safety for Empagliflozin, page 158. NDA 204629, Boehringer Ingelheim, February 5, 2013.

**Table 4. Cases of Lung Cancer Observed After Exposure to Empagliflozin for >6 Months**

Patient/study No.	Age [years] /gender	Preferred term	Treatment	Start day <sup>1</sup>	Serious	Outcome
(b) (4)/1245.25	72/M	Lung neoplasm malignant	Empa 10	241	Fatal/required hospitalisation	Fatal
/1245.25	66/M	Lung neoplasm malignant	Empa 25	427	Required hospitalisation	Not recovered
6859/1245.33	69/M	Lung neoplasm malignant	Empa 10	461	Disabled	Not recovered <sup>2</sup>
20704/1245.31	69/M	Bronchial carcinoma	Empa 25	472	Other	Not recovered
809006/1245.38	53/M	Lung cancer metastatic	Empa 10 <sup>3</sup>	194	Required hospitalisation/other	Not recovered <sup>2</sup>
34564/ 1245.31 <sub>(met+SL)</sub>	61/M	Lung squamous cell carcinoma stage unspecified	Empa 25	371	Required hospitalisation	Not recovered <sup>2</sup>

PTs included: bronchial carcinoma, lung cancer metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified

<sup>1</sup> Relative to the first dose of randomised (or open-label) study medication

<sup>2</sup> Follow up sufficient

<sup>3</sup> Randomised to empagliflozin 5 mg for the first 12 weeks; re-randomised to empagliflozin 10 mg thereafter

Source data: [U12-2707, Appendix 2, Listing 5.17.5.18]

Source: Table 2.1.5.8: 2: Number of patients with selected types of malignancy in SAF-5 – patients treated for >6 months and reported events after 6 months. 2.7.4 Summary of Clinical Safety for Empagliflozin, page 158. NDA 204629, Boehringer Ingelheim, February 5, 2013.

In response to an FDA information request sent on July 29, 2013, Boehringer Ingelheim submitted on August 16, 2013 (SDNs 17 and 18) additional information in regard to the melanoma and lung cancer cases, including patient risk factors for lung cancer or

melanoma, pathology reports (with molecular results if performed), staging evaluations, treatments administered, and outcomes of the malignancies.

*Summary of Melanoma Cases*

As shown in Table 3, Boehringer Ingelheim identified six cases of melanoma in patients who were treated with empagliflozin; however, one case (patient #3402 in study 1245.24) was excluded as the patient developed melanoma prior to initiation of empagliflozin, not on-treatment. All serious adverse event (SAE) narratives and supplemental information provided by the Boehringer Ingelheim were reviewed. Of the five cases, all patients were White and median age at time of melanoma diagnosis was 67.5 years. Two-thirds of the patients were men. Geographic distribution of the cases was as follows: United States (n=2), foreign (n=4). A line-listing with details of the each case is presented in Appendix 1. Table 5 summarizes the demographics and characteristics of the melanoma cases:

**Table 5. Demographics and Characteristics of Melanoma Cases**

<b>Characteristic</b>	<b>N=5</b>
<b>Dose of empagliflozin</b>	
10 mg	2
25 mg	3
<b>Geographic location of report</b>	
United States	2
Europe	2
South Africa	1
<b>Age, years</b>	
Range	59-69
Mean	65
Median	67
<b>Gender</b>	
Male	4
Female	1
<b>Time-to-onset, days</b>	
Range	216-351
Mean	276
Median	236
<b>Treatment</b>	
Excision	5
<b>Outcome</b>	
Recovered	2
Not recovered	3
<b>Confounders</b>	
Prior history of basal cell carcinoma and/or melanoma	2
Sun exposure	1
Unknown	2

Individual review of the cases revealed that all patients were White. Additionally, three patients had confounders that may have increased their risk for melanoma. One patient

had a prior history of basal cell carcinoma and melanoma. Another patient had a history of basal cell carcinoma and squamous cell carcinoma of the skin, and also acute lymphoblastic leukemia. A third patient had “sun-damaged skin”, per source documents. Therefore, only two cases of melanoma were observed in patients without additional risk factors for development of melanoma.

#### *Summary of Lung Cancer Cases*

As shown in Table 4, review of the cases submitted by the Boehringer Ingelheim revealed that there were seven cases of lung cancer in patients exposed to empagliflozin; however, one case (Patient #809006 in Study 1245.38) was incorrectly included in the cases of lung cancer as the actual diagnosis was colon cancer with metastases to the lung. This patient was excluded from the analysis below. All SAE narratives were reviewed. Of the six cases, the patients were either White (n=5) or Asian (n=1) and median age at time of lung cancer was 69 years. All patients were men. Geographic distribution of the patients was as follows: Europe (4), Canada (1), and South Korea (1). All cases of lung cancer were non-small cell lung cancer (NSCLC): five cases of squamous cell carcinoma and one case of adenocarcinoma. The median time to onset was 394 days. All cases were confounded by a history of smoking tobacco, and two cases had additional confounders, asbestos exposure and prior history of lung cancer. A line-listing with details of each case is presented in Appendix 2.

The demographics and characteristics of the cases are summarized in Table 6:

**Table 6. Demographics and characteristics of lung cancer cases**

Characteristic	N=6
<b>Dose of empagliflozin</b>	
10 mg	3
25 mg	3
<b>Geographic location of report</b>	
Europe	4
Canada	1
South Korea	1
<b>Age, years</b>	
Range	61-72
Mean	68
Median	69
<b>Gender</b>	
Male	6
Female	0
<b>Lung cancer histology</b>	
Non-small cell lung cancer, squamous	5
Non-small cell lung cancer, adenocarcinoma	1
<b>Time-to-onset, days</b>	
Range	167-472
Mean	394
Median	427
<b>Treatment</b>	
Chemotherapy	5
Radiation	1
<b>Outcome</b>	
Fatal	2
Not recovered	3
Unknown	1
<b>Confounders</b>	
Smoking tobacco	6
Ex-smoker	2
Current	4
Prior history of lung cancer	1
Asbestos exposure	1

### III. DISCUSSION

An imbalance in the number of cases of lung neoplasms and malignant melanomas occurring  $\geq 180$  days after initiating treatment with empagliflozin has been observed in the clinical trials supporting NDA 204629.

Nonclinical toxicology studies demonstrated that empagliflozin did not increase the incidence of tumors in female rats at doses up to the highest dose of 700 mg/kg/day, which is 72 times the clinical area-under-curve (AUC) exposure of 25 mg. In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day, which is

approximately 26 times the clinical exposure of 25 mg. These tumors are common in rats and are unlikely to be relevant to humans. Additionally, empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day, which is approximately 62 times the clinical exposure of 25 mg. However, there was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 700 mg/kg/day, which is approximately 45 times the clinical exposure of 25 mg. This finding was not observed at a lower dose of empagliflozin administered to male mice; at 300 mg/kg/day, which is approximately 11 times the clinical exposure of 25 mg, renal tumors were not observed. The relevance to humans of renal tumors observed in toxicology studies, which occurred exclusively in male mice at empagliflozin exposures exceeding the clinical exposure, is unknown. Nonclinical toxicology studies did not report melanoma or lung cancers; however, use of animal models to predict tumorigenesis in humans has inherent limitations.

The relationship of empagliflozin to the observation of an increased number of melanoma and NSCLC cases observed in the empagliflozin arms is uncertain. The median age at time of diagnosis of melanoma and lung cancer was 67 years and 69 years, respectively. According to the SEER database, from 2006-2010, the median age at diagnosis for melanoma was 59 years and for lung cancer, 70 years. All patients with melanoma or lung cancer exposed to empagliflozin were at higher risk for development of these malignancies based on demographic and other baseline characteristics.

As provided by the Boehringer Ingelheim in Table 2.1.5.8: 1, of 2.7.4, “Summary of Clinical Safety”, the incidence rate of lung cancer in the empagliflozin-exposed group is 150 cases per 100,000 patient-years. The incidence of lung cancer in high-risk individuals is estimated at about 600 cases per 100,000 person years based on results of the National Lung Screening Trial (NLST).<sup>7</sup> According to the Surveillance Epidemiology and End Results (SEER) database, the incidence rate was 61.4 per 100,000 men and women per year, based on cases diagnosed in 2006-2010. The incidence rate of lung cancer in the empagliflozin-exposed group is higher than the general population, but lower than the rate in high-risk individuals. The NLST was a screening trial and patients were followed with low-dose CT or chest radiography; therefore, an increase in the incidence rate would be expected.

For melanoma, the incidence rate in the empagliflozin-exposed group is 120/100,000 patient-years. In the general population, the incidence rate was 21.1 per 100,000 men and women per year in 2006-2010, according to SEER. The incidence rate of melanoma in the empagliflozin-exposed group is higher than the general population; however, the attribution of empagliflozin to melanoma cannot be adequately determined. Manual review of the cases revealed that many were confounded.

Another SGLT-2, canagliflozin (Invokana, NDA 204042), was FDA-approved on March 29, 2013. No cases of melanoma or lung cancer were observed and no imbalance in any malignancies with canagliflozin was noted, per the medical officer’s review.<sup>8</sup> Additionally, an exploratory analysis of postmarketing adverse events with canagliflozin using Empirica, a computer-based system of disproportionality analyses for

postmarketing adverse event signal detection, did not identify any adverse event reports of melanoma or NSCLC.

#### **IV. CONCLUSION**

In conclusion, whether the cases of melanoma and lung cancer associated with administration of empagliflozin is a true signal or a chance finding is unclear. Considering the uncertainties in the data available to assess the risk of developing melanoma and NSCLC in patients exposed to empagliflozin, we recommend the following:

1. Boehringer Ingelheim should collect data in a clinical trial on the relative risk and risk difference of lung cancer and melanoma in patients exposed to empagliflozin versus placebo in a clinical trial setting with a median duration of follow up of at least 5 years, in which risk factors are collected. Detailed information on the histopathological diagnosis and molecular characteristics of all observed cases of lung cancer and melanoma should be collected.
2. Consider a consultation with Office of Surveillance and Epidemiology (OSE) for a pharmacovigilance review of the data on empagliflozin exposure and lung cancer and melanoma in the postmarketing setting. A pharmacovigilance review should also be conducted for comparison for canagliflozin as it is in the same therapeutic class as empagliflozin.
3. Boehringer Ingelheim should consider conducting mechanistic studies to better understand the potential risk of empagliflozin-induced malignant transformation.

## Appendix 1. Melanoma cases

Pt. ID/Study no.	Age	Gender	Race	Location	PT term	Biopsy	Dose	Time to onset	Outcome	Confounders	Treatment	Comments
(b) (4) 1245.25	59	M	White	South Africa	malignant melanoma	yes	empa 10	236	not recovered	basal cell carcinoma in 2011 and melanoma in 1992	excision	none
1245.25	69	M	White	Poland	malignant melanoma	yes	empa 10	345	not recovered	none documented	excision	none
1245.25	67	M	White	U.S.	malignant melanoma	yes	empa 25	216	recovered	source doc says sun damaged skin	excision	none
1815/1245.36	62	M	White	Portugal	malignant melanoma	yes	empa 25	233	not recovered	none documented	excision	none
80040/1245.28	68	F	White	U.S.	malignant melanoma in situ	yes	empa 25	351	recovered	mother had basal cell carcinoma; pt also had squamous cell carcinoma of skin and h/o acute lymphoblastic leukemia	excision	none
3402/1245.24	78	F	White		malignant melanoma	yes	empa 25	238	recovered	h/o melanoma	excision	pt did not have qualifying AE, melanoma was pretx

\* Cases in green were not included in the analyses in the consult, refer to “Confounder” column for an explanation.

## Appendix 2. Lung cancer cases

Pt. ID/Study no.	Age	Gender	Country	Preferred Term	Agent	Time to onset, days	Outcome	Smoker	Biopsy	Comments	Scans	Treatment	Exact diagnosis
(b) (4) 1245.25	72	M	Spain	lung ca	empa 10	241	fatal	ex-smoker since 2005	yes		yes	chemotherapy	squamous cell
1245.25	66	M	Austria	lung ca	empa 25	427	not recovered	ex-smoker	unknown	COPD	yes	chemotherapy	squamous cell
6859/1245.33	69	M	Portugal	lung ca	empa 10	461	not recovered	current smoker	yes	COPD	yes	chemotherapy	squamous cell
20704/1245.31	69	M	Canada	bronchial carcinoma	empa 25	472	not recovered	current smoker. 70 pack year, 1 pack per day x 60 years	yes	COPD, asbestos exposure in 1950s, and uncle died of lung cancer	yes	radiation	squamous cell
34564/1245.31	61	M	Korea	lung squamous cell ca stage unspecified	empa 25	371	fatal	CRF says ex-smoker, but hosp recs say current smoker 1/2 per day	unknown	prior hx lung cancer in 2005 & COPD	yes	chemotherapy + radiation	squamous cell
4331/1245.33	69	M	France	lung ca	empa 10	193	not recovered	current smoke x 20 yrs	yes	this case not included in the Table 2.1.5.8: 4, just in Summary of Clinical Safety	yes	chemotherapy	adenocarcinoma
809006/1245.38*	53	M		lung cancer metastatic	empa 10	194	not recovered			incorrectly dx'ed, colon ca w/ lung mets	n/a	n/a	

\* Cases in green were not included in the analyses in the consult, refer to "Confounder" column for an explanation.

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<sup>1</sup> Siegel, R, Naishadham, D., and Jemal, A, 2013, Cancer Statistics, 2013, CA Cancer J Clin, 63:11-30.

<sup>2</sup> NCCN guidelines version 2.2013 melanoma. Accessed at [http://www.nccn.org/professionals/physician\\_gls/pdf/melanoma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf) on July 24, 2013.

<sup>3</sup> Tsao H, MB Atkins, and AJ Sober, 2004, Management of cutaneous melanoma, N Engl J Med, 351:998-1012.

<sup>4</sup> Surveillance Epidemiology and End Results (SEER) database. Accessed at <http://seer.cancer.gov/statfacts/html/lungb.html> on September 9, 2013.

<sup>5</sup> NCCN guidelines version 2.2013 non-small cell lung cancer. Accessed at [http://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf) on August 22, 2013.

<sup>6</sup> Table 5.1: 1, Trial groupings for integrated safety analyses. 2.5 Clinical Overview, page 56. NDA 204629, Boehringer Ingelheim, February 5, 2013.

<sup>7</sup> National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl Med. 2011;365:395-409.

<sup>8</sup> Kwon, HJ. FDA medical review of canagliflozin (Invokana), NDA 204042. Accessed at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/204042Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000MedR.pdf) on August 22, 2013.

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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.**  
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/s/  
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JENNIE T CHANG  
10/16/2013

MARC R THEORET  
10/17/2013

# DGCPC/OSI CONSULT: Request for Clinical Inspections

**Date:** 7/10/2013

**To:** Ann Meeker-O'Connell, Acting Division Director, DGCPC  
Susan Thompson, M.D., Acting Branch Chief, GCPAB  
Janice Pohlman, M.D., M.P.H., Team Leader, GCPAB  
CDEROCDSIPMOs@fda.hhs.gov  
Cynthia Kleppinger, M.D., Senior Medical Officer, GCPAB  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** *William H. Chong, Medical Officer, Division of Metabolism and Endocrinology Products*  
*Karen Mahoney, Team Leader, Division of Metabolism and Endocrinology Products*

**From:** *Patricia Madara, Project Manager, Division of Metabolism and Endocrinology Products*

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA #204629

IND#: 102145

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Phone: (203) 798-9988

Regulatory Point of Contact: Daniel Coleman, Ph.D., Sr. Associate Director, Regulatory Affairs

Regulatory Point of Contact Phone: (203) 798-5081

Regulatory Point of Contact Email: daniel.coleman@boehringer-ingelheim.com

Drug Proprietary Name:

Generic Drug Name: Empagliflozin

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

DGCPC/OSI Consult: version: 09/28/2011

Page 2-Request for Clinical Inspections

PDUFA: 3/5/2014

Action Goal Date: March 5, 2014

Inspection Summary Goal Date: January 5, 2014

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).*

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
20034 O'Mahony, Michael The London Road Diagnostic Clinic, 481 London Road Sarnia, ON . CAN Canada phone: fax: email:	1245_0019	19	Efficacy v placebo as TZD add on +/- met
	1245_0023 (Met + SU)	10	BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	9	BI 10773 vs placebo as add on to MFN/SU
10131 Streja, Daniel Infosphere Clinical Research, Inc., 7345 Medical Center Drive, #430 West Hills, CA 91307 USA United States phone: fax: email:	1245_0019	15	Efficacy v placebo as TZD add on +/- met
10108 Riffer, Ernie Clinical Research Advantage, Inc, Central Phoenix Medical Clinic, Suites 190 & 191, 7600 North 15th Street Phoenix, AZ 85020 USA United States phone: fax: email:	1245_0020	21	Ph III, 24 wk, mono vs. placebo

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
10154 Unger, Jeffery Jeffery Unger, MD, Suite 100, 14726 Ramona Avenue Chino, CA 91710 USA United States phone: fax: email:	1245_0020	13	Ph III, 24 wk, mono vs. placebo
10001 Ahmed, Azazuddin Apex Medical Research, AMR, Inc, Second Floor, 2555 South Dr. Martin Luther King Drive Chicago, IL 60616 USA United States phone: fax: email:	1245_0023 (Met + SU)	14	BI 10773 vs placebo as add on to MFN/SU BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	11	
76022 Ellis, Graham Helderberg Clinical Trials Centre, Suite 7G and H Arun Place, Sir Lowry's Pass Road Somerset West, NA 7129 ZAF Africa phone: fax: email:	1245_0036	36	52-wk renal safety study
10160 Waseem, Malika Firdous Malika Waseem, MD, 709 Eastern Boulevard Essex, MD 21221 USA United States phone: fax: email:	1245_0019	9	Efficacy v placebo as TZD add on +/- met

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
20028 Elliott, Thomas Vancouver Diabetes Research Centre, 2775 Laurel Street, Rm 4178 Vancouver, BC . CAN Canada phone: fax: email:	1245_0023 (Met + SU)	9	BI 10773 vs placebo as add on to MFN/SU BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	4	
10109 Rivas, Joseph Time Clinical Research Inc, 2620 Zoe Avenue Huntington Park, CA 30255 USA United States phone: fax: email:	1245_0023 (Met + SU)	2	BI 10773 vs placebo as add on to MFN/SU BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	13	
91211 Mukhopadhyay, Monojit Consultant Diabetologist, Diabetic Clinic & Research Centre, 46A, Ritchie Road Kolkata, NA 700019 IND Asia/Pacific phone: fax: email:	1245_0028	12	Effect+ safety BI 10773 + met vs SU+met
	1245_0036	3	52-wk renal safety study
20071 Conter, Howard MSHJ Research Associates Inc., 2717 Gladstone St , Suite 106 Halifax, NS . CAN Canada phone: fax: email:	1245_0028	10	Effect+ safety BI 10773 + met vs SU+met

<b>Site # (Name, Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
91209 Ahmad, Jamal Professor of Endocrinology, Jawaharlal Nehru Medical University, Centre For Diabetes and Endocrinology, Faculty of Medicine, Aligarh Muslim University, Aligarh, NA 202002 IND Asia/Pacific phone: fax: email:	1245_0028	15	Effect+ safety BI 10773 + met vs SU+met
	1245_0036	5	52-wk renal safety study
1044 Sugimoto, Danny Cedar-Crosse Research Center, 800 S. Wells Street, Suite M-15 Chicago, IL 60607 USA United States phone: fax: email:	1245_0033	11	Ph IIb add on to LA insulin
86002 Xue, Yaoming Nanfang Hospital, No. 1838 Guangzhou Dadaobei Guangzhou, NA 510515 CHN Asia/Pacific phone: fax: email:	1245_0020	20	Ph III, 24 wk, mono vs. placebo
	1245_0023 (Met + SU)	12	BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	5	BI 10773 vs placebo as add on to MFN/SU
10074 Lewin, Andrew National Research Institute, Suite 302, 2010 Wilshire Boulevard Los Angeles, CA 90057 USA United States phone: fax: email:	1245_0023 (Met + SU)	16	BI 10773 vs placebo as add on to MFN/SU
	1245_0023 (Met only)	20	BI 10773 vs placebo as add on to MFN/SU

**III. Site Selection/Rationale**

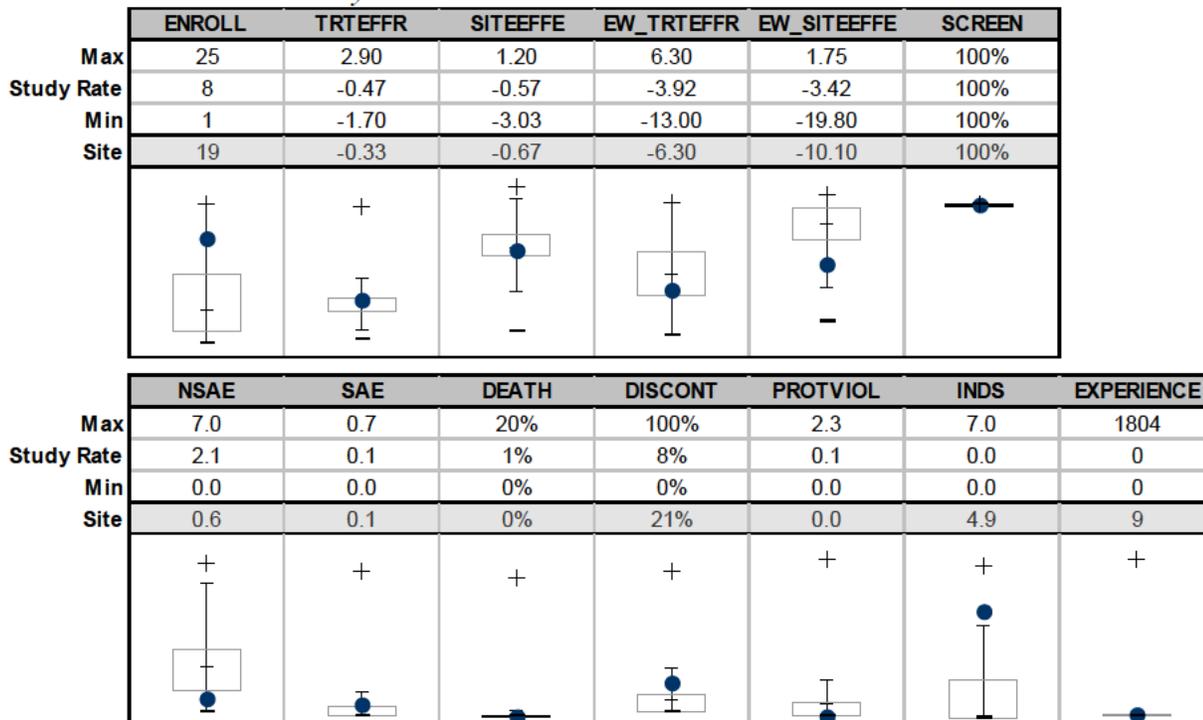
*Site Information*

<b>STUDY:</b>	1245_0019	<b>SITEID:</b>	20034
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<b>NAME</b>	O'Mahony, Michael		
<b>LOCATION</b>	The London Road Diagnostic Clinic, 481 London Road Sarnia, ON, CAN .		
<b>PHONE/FAX</b>	/		
<b>EMAIL</b>			

<b>RANK</b>	2	<b>FINLDISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	16.5	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

high enrollment, participated in multiple studies

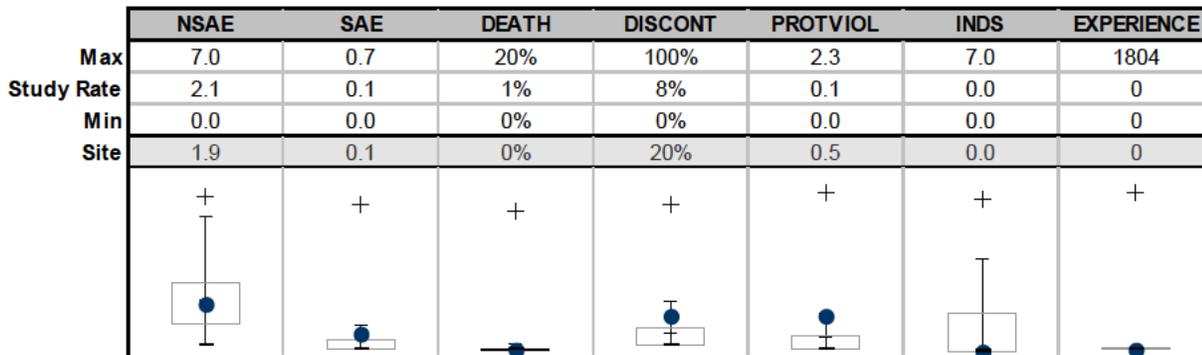
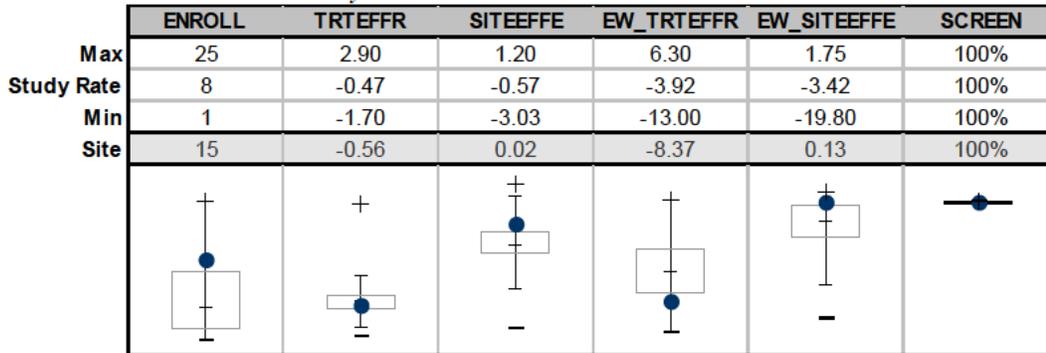
*Site Information*

<b>STUDY:</b>	1245_0019	<b>SITEID:</b>	10131
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<b>NAME</b>	Streja, Daniel
<b>LOCATION</b>	Infosphere Clinical Research, Inc., 7345 Medical Center Drive, #430 West Hills, CA, USA 91307
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	9	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	13.0	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

participated in multiple studies, proximity to other inspection site selection

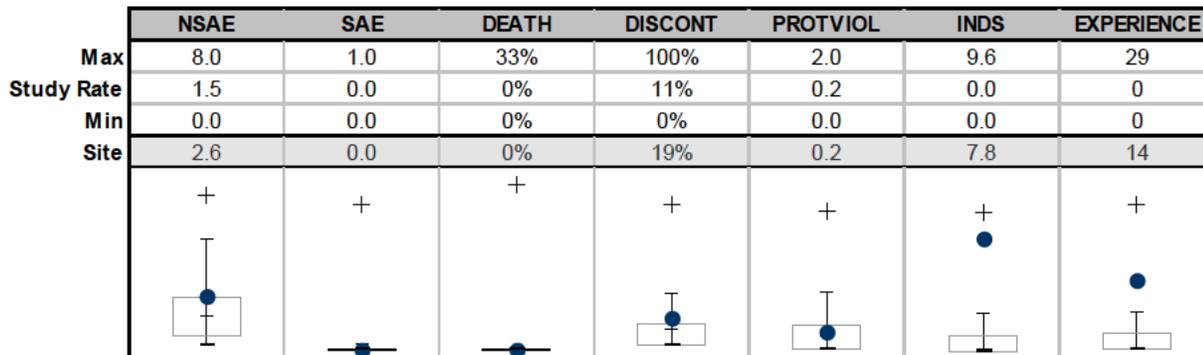
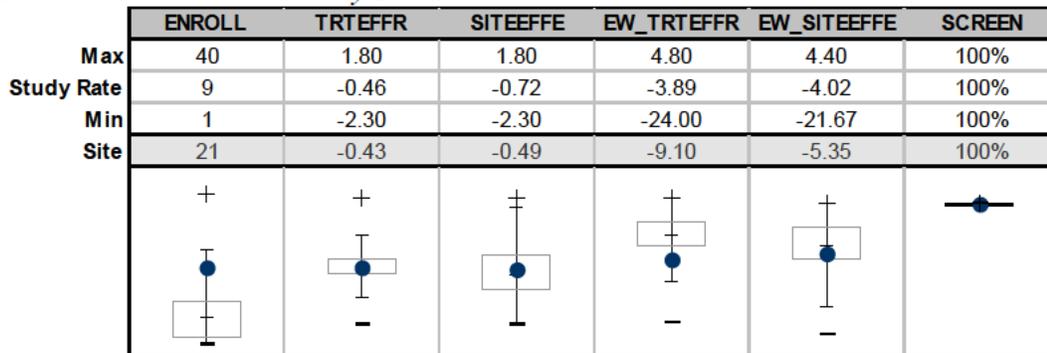
*Site Information*

<b>STUDY:</b>	1245_0020	<b>SITEID:</b>	10108
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<b>NAME</b>	Riffer, Ernie
<b>LOCATION</b>	Clinical Research Advantage, Inc, Central Phoenix Medical Clinic, Suites 190 & 191, 7600 North 15th Street Phoenix, AZ, USA 85020
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	2	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	17.2	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

previous complaint, high enrollment

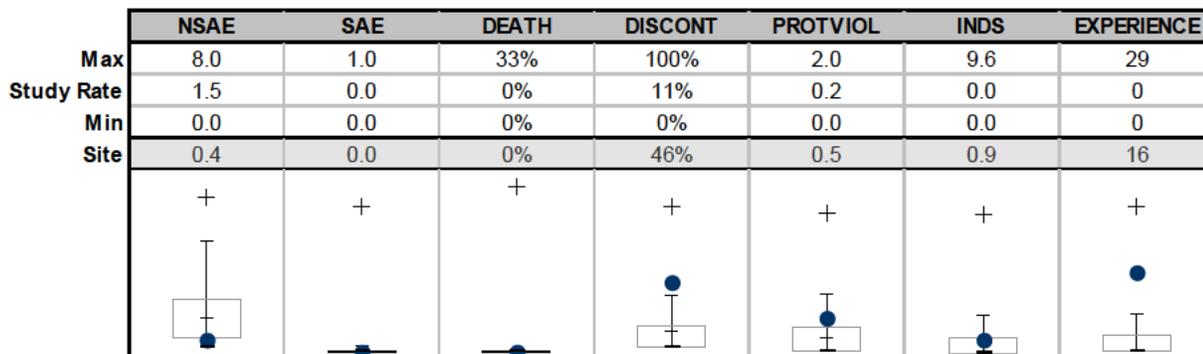
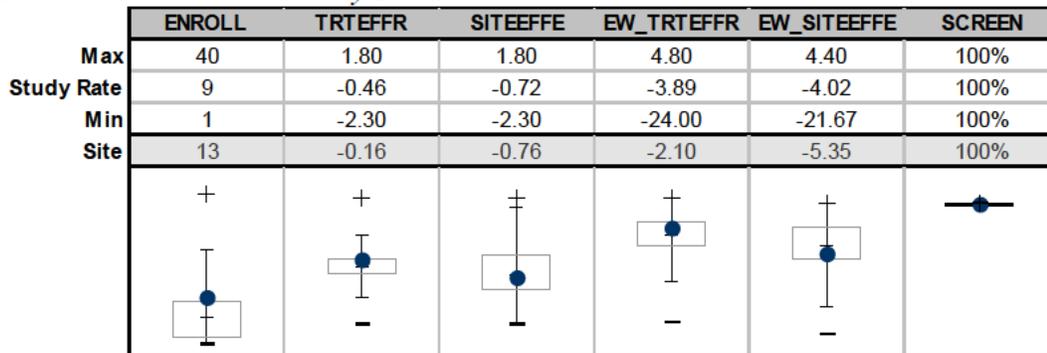
*Site Information*

<b>STUDY:</b>	1245_0020	<b>SITEID:</b>	10154
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<b>NAME</b>	Unger, Jeffery
<b>LOCATION</b>	Jeffery Unger, MD, Suite 100, 14726 Ramona Avenue Chino, CA, USA 91710
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	10	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	10.4	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

high discontinuation, proximity to other inspection site selection

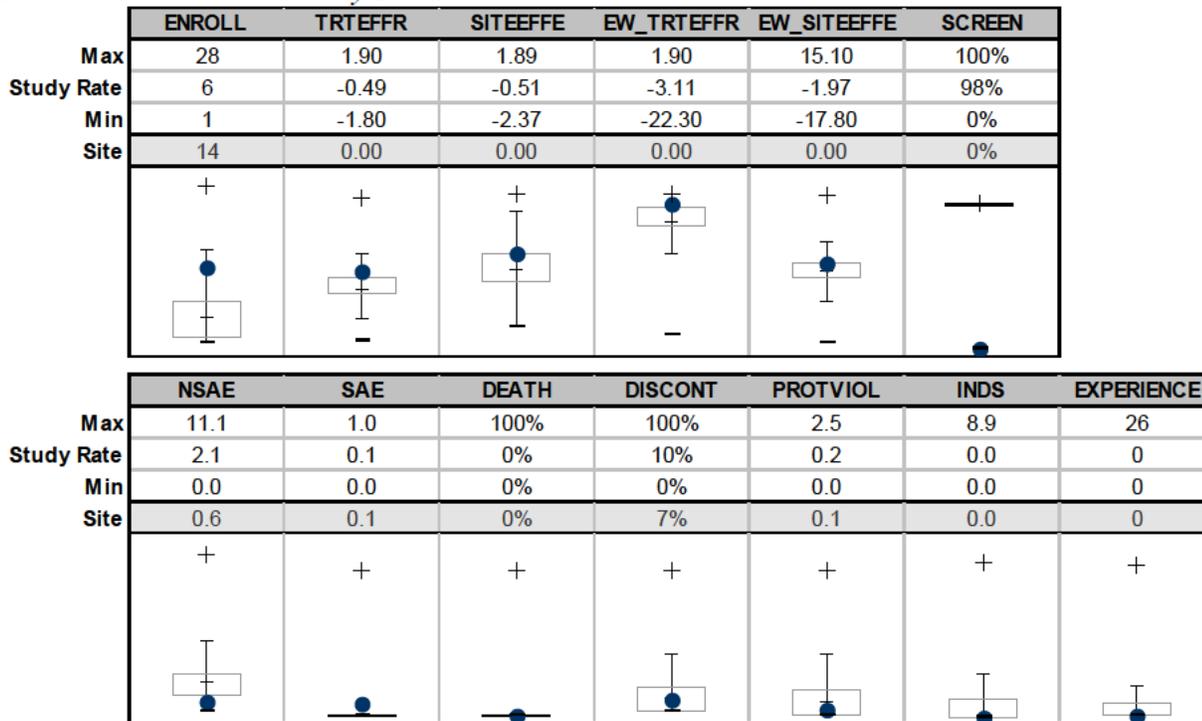
*Site Information*

<b>STUDY:</b>	1245_0023(Met + SU)	<b>SITEID:</b>	10001
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<b>NAME</b>	Ahmed, Azazuddin
<b>LOCATION</b>	Apex Medical Research, AMR, Inc, Second Floor, 2555 South Dr. Martin Luther King Drive Chicago, IL, USA 60616
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	20	<b>FINLDISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	8.2	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

2 complaints pending, please combine PDUFA inspection with complaint investigation

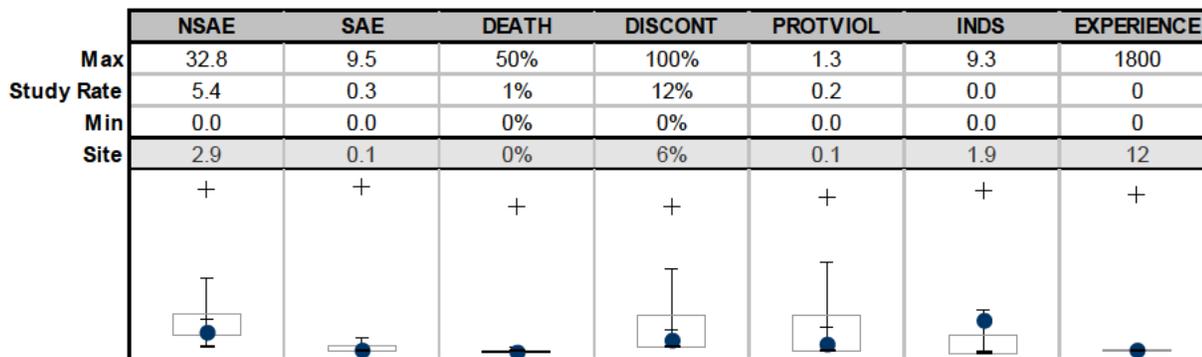
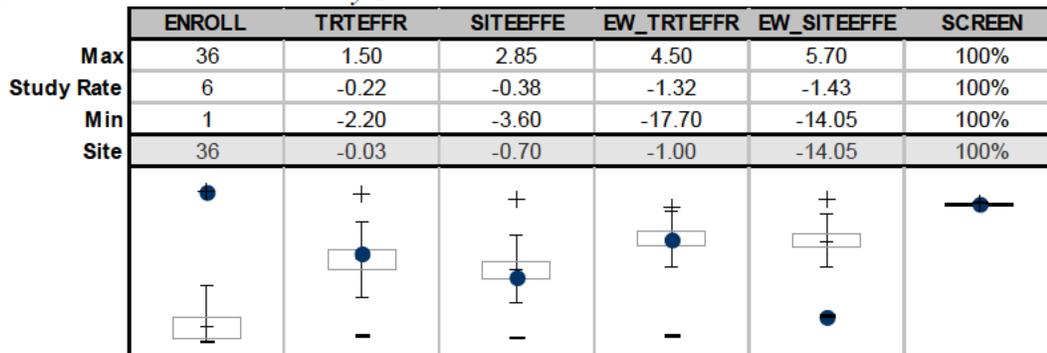
*Site Information*

<b>STUDY:</b>	1245_0036	<b>SITEID:</b>	76022
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<b>NAME</b>	Ellis, Graham
<b>LOCATION</b>	Helderberg Clinical Trials Centre, Suite 7G and H Arun Place, Sir Lowry's Pass Road Somerset West, NA, ZAF 7129
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	5	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	12.4	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

high enrollment, inspection of site planned for another application, please combine inspections

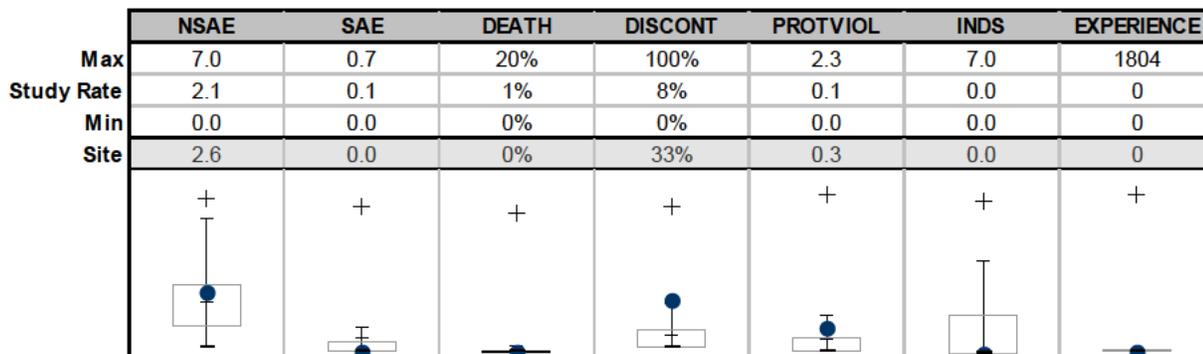
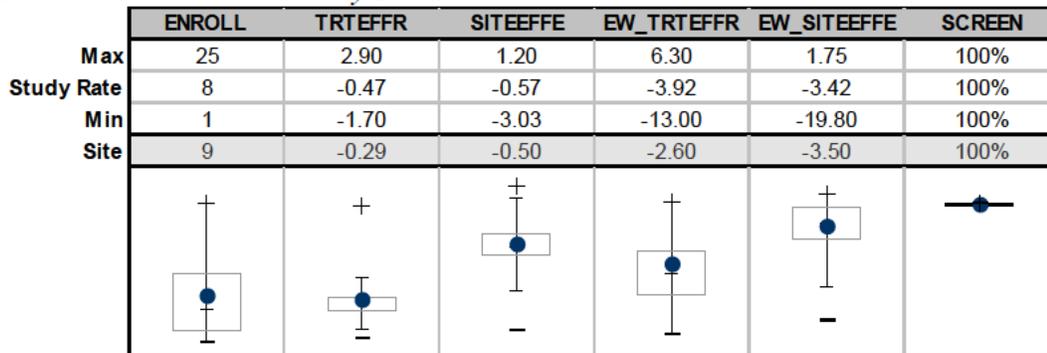
*Site Information*

<b>STUDY:</b>	1245_0019	<b>SITEID:</b>	10160
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<b>NAME</b>	Waseem, Malika Firdous		
<b>LOCATION</b>	Malika Waseem, MD, 709 Eastern Boulevard Essex, MD, USA 21221		
<b>PHONE/FAX</b>	/		
<b>EMAIL</b>			

<b>RANK</b>	24	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	7.7	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

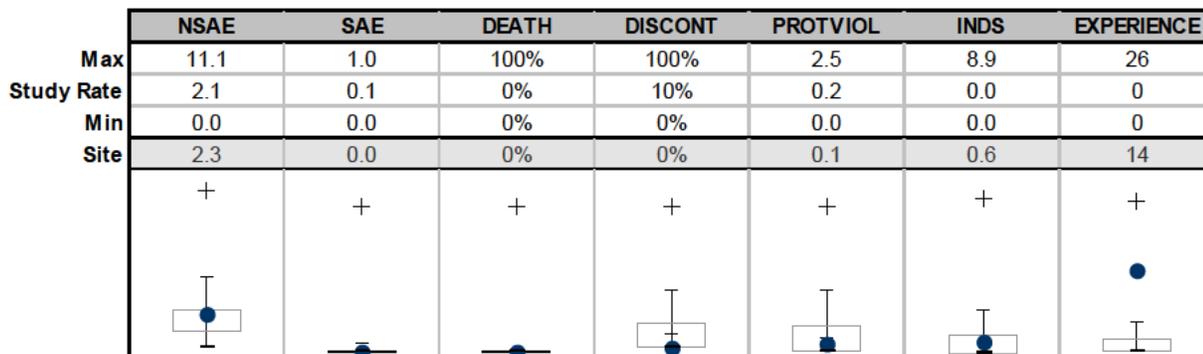
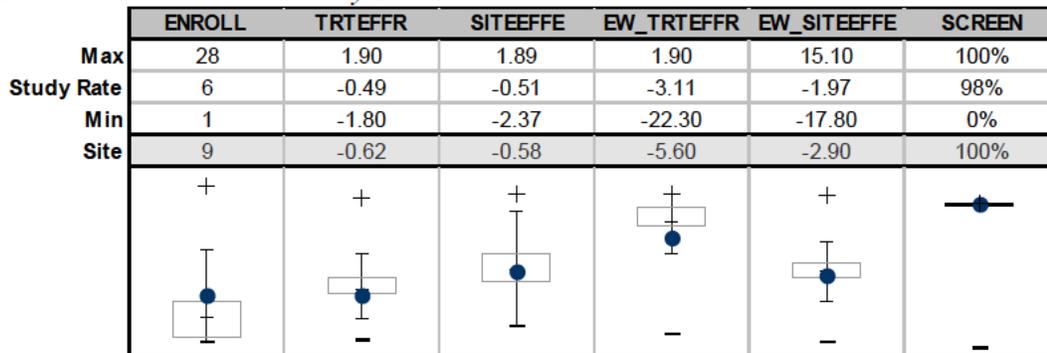
*Site Information*

<b>STUDY:</b>	1245_0023(Met + SU)	<b>SITEID:</b>	20028
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<b>NAME</b>	Elliott, Thomas
<b>LOCATION</b>	Vancouver Diabetes Research Centre, 2775 Laurel Street, Rm 4178 Vancouver, BC, CAN .
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	9	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	10.7	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

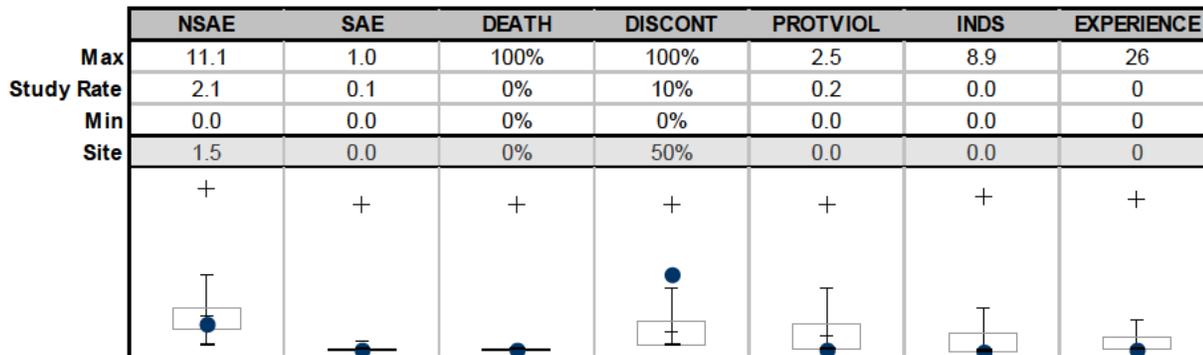
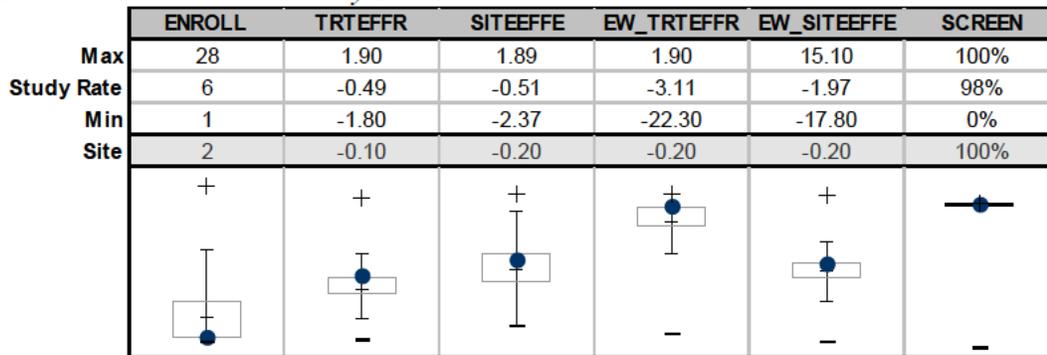
*Site Information*

<b>STUDY:</b>	1245_0023(Met + SU)	<b>SITEID:</b>	10109
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<b>NAME</b>	Rivas, Joseph
<b>LOCATION</b>	Time Clinical Research Inc, 2620 Zoe Avenue Huntington Park, CA, USA 30255
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	38	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	6.4	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA investigation

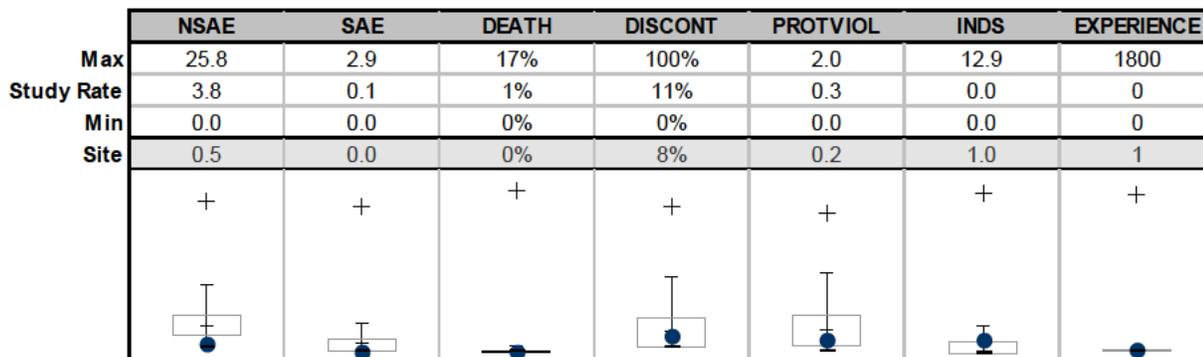
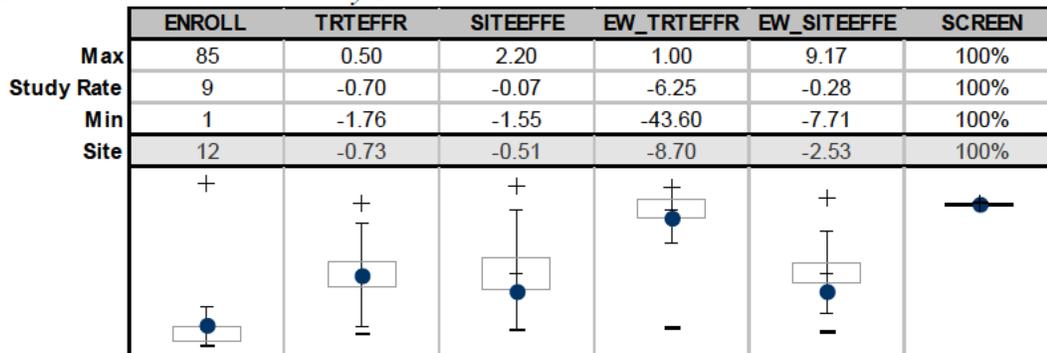
*Site Information*

<b>STUDY:</b>	1245_0028	<b>SITEID:</b>	91211
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<b>NAME</b>	Mukhopadhyay, Monojit
<b>LOCATION</b>	Consultant Diabetologist, Diabetic Clinic & Research Centre, 46A, Ritchie Road Kolkata, NA, IND 700019
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	8	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	8.4	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

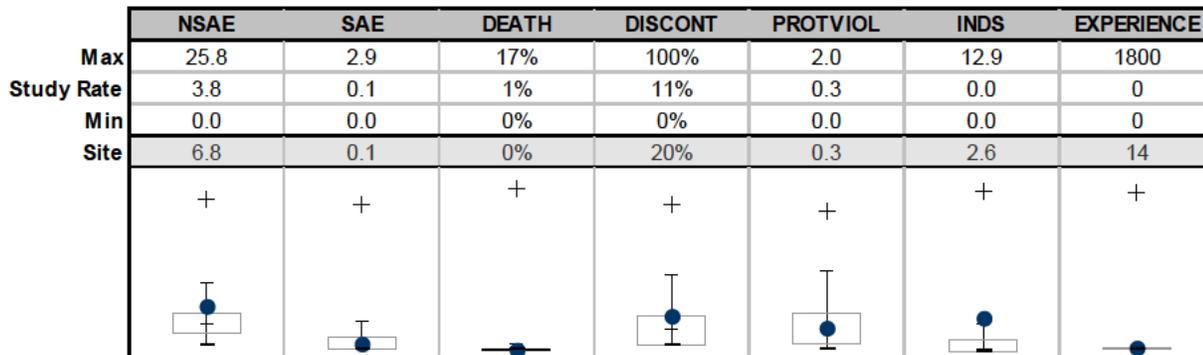
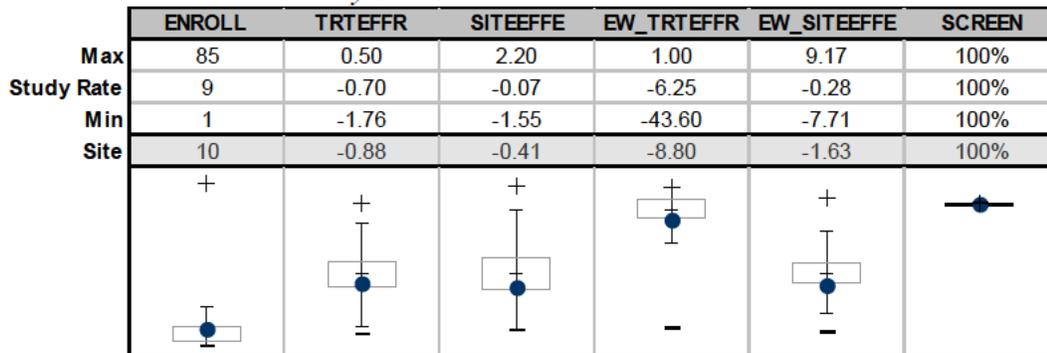
*Site Information*

<b>STUDY:</b>	1245_0028	<b>SITEID:</b>	20071
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<b>NAME</b>	Conter, Howard
<b>LOCATION</b>	MSHJ Research Associates Inc., 2717 Gladstone St , Suite 106 Halifax, NS, CAN .
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	10	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	8.0	<b>OAI</b>	0	<b>TSLI</b>	2

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

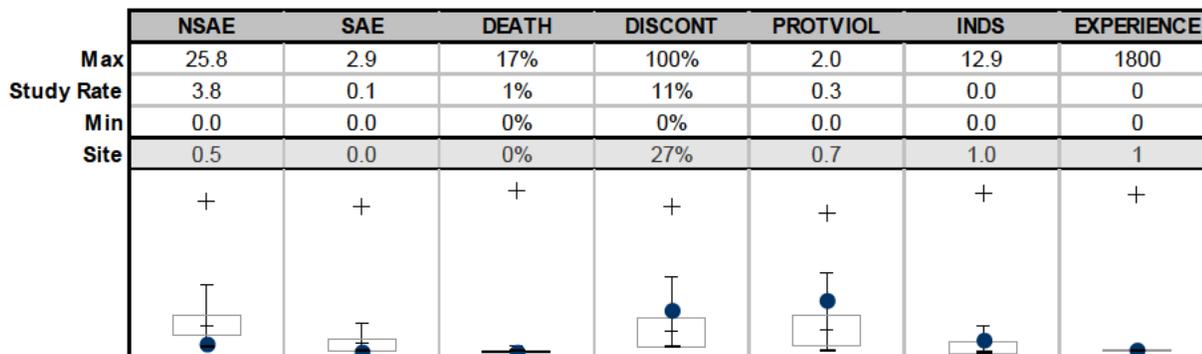
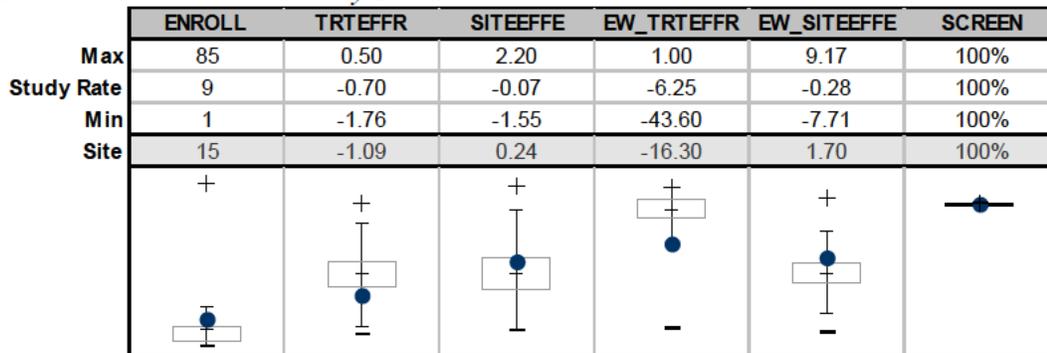
*Site Information*

<b>STUDY:</b>	1245_0028	<b>SITEID:</b>	91209
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<b>NAME</b>	Ahmad, Jamal
<b>LOCATION</b>	Professor of Endocrinology, Jawaharlal Nehru Medical University, Centre For Diabetes and Endocrinology, Faculty of Medicine, Aligarh Muslim University, Aligarh, NA, IND 202002
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	6	<b>FINLDISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	8.8	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

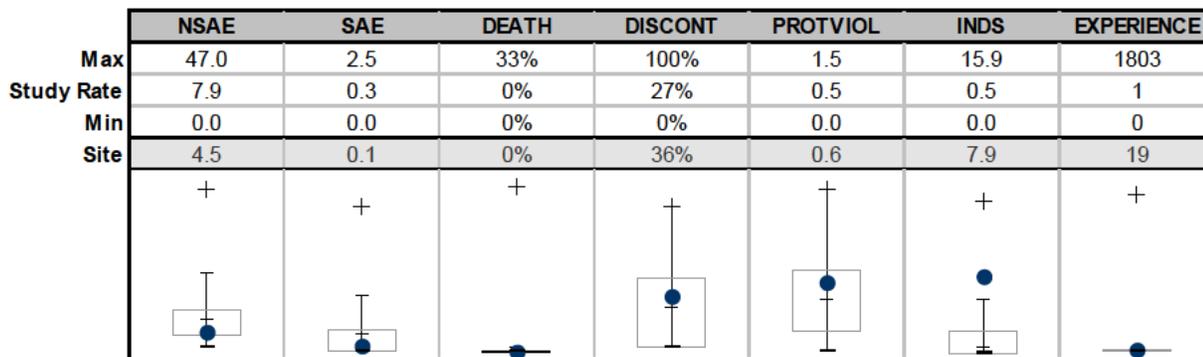
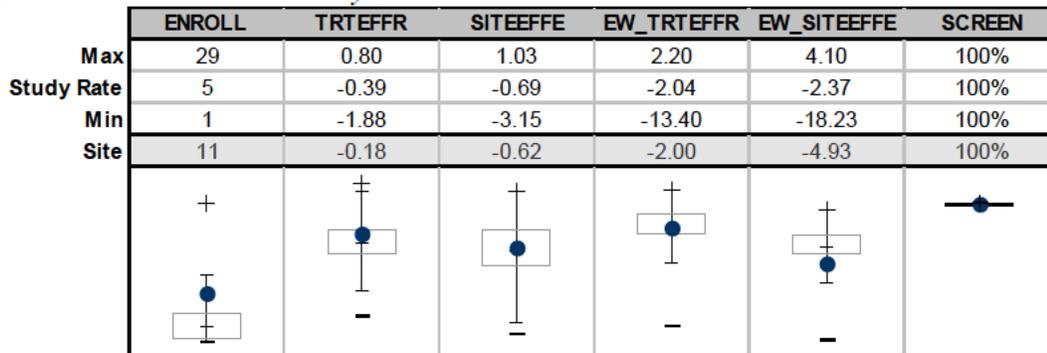
*Site Information*

<b>STUDY:</b>	1245_0033	<b>SITEID:</b>	1044
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<b>NAME</b>	Sugimoto, Danny
<b>LOCATION</b>	Cedar-Crosse Research Center, 800 S. Wells Street, Suite M-15 Chicago, IL, USA 60607
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	4	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	12.4	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

complaint investigation pending, please combine with PDUFA inspection

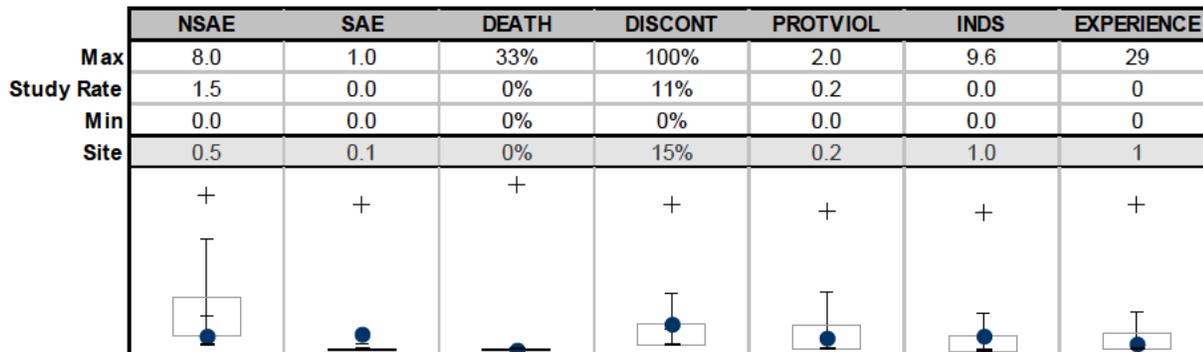
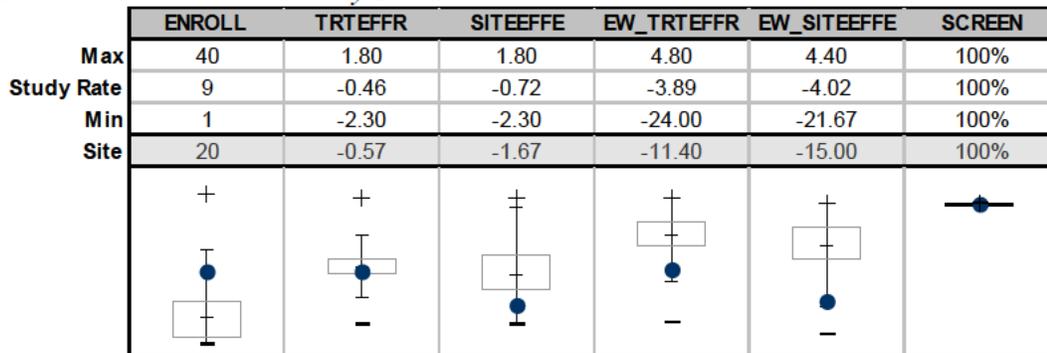
*Site Information*

<b>STUDY:</b>	1245_0020	<b>SITEID:</b>	86002
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<b>NAME</b>	Xue, Yaoming
<b>LOCATION</b>	Nanfang Hospital, No. 1838 Guangzhou Dadaobei Guangzhou, NA, CHN 510515
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	1	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	18.8	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

high enrollment, participated in multiple studies

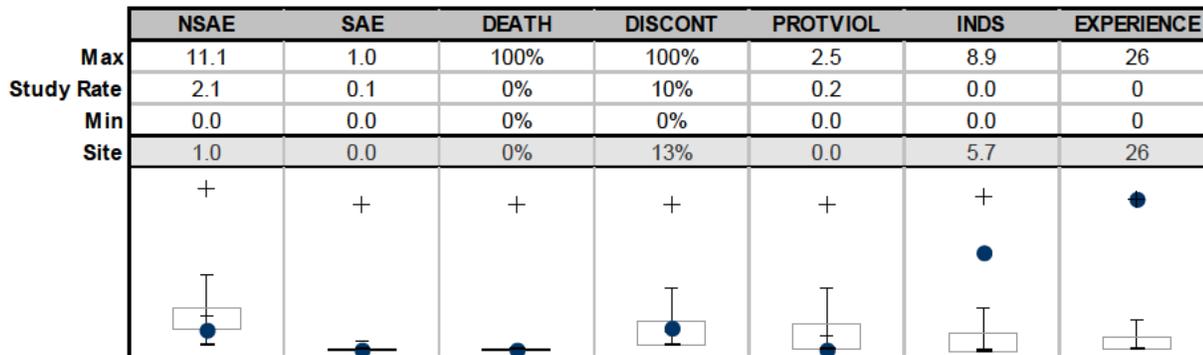
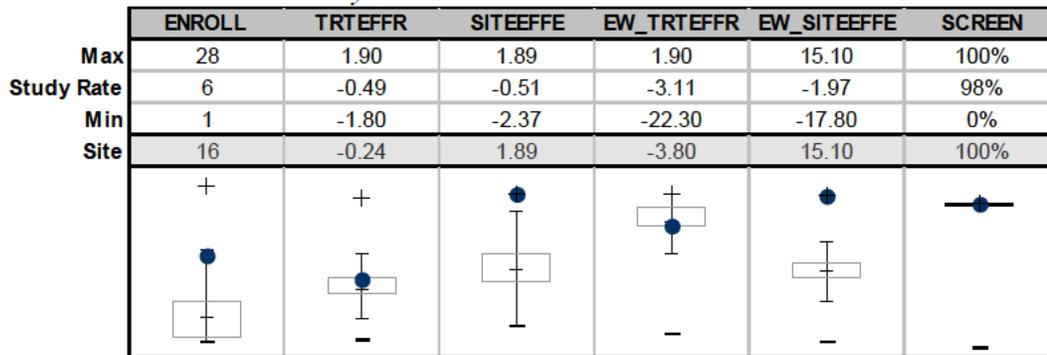
*Site Information*

<b>STUDY:</b>	1245_0023(Met + SU)	<b>SITEID:</b>	10074
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<b>NAME</b>	Lewin, Andrew
<b>LOCATION</b>	National Research Institute, Suite 302, 2010 Wilshire Boulevard Los Angeles, CA, USA 90057
<b>PHONE/FAX</b>	/
<b>EMAIL</b>	

<b>RANK</b>	6	<b>FINLISC</b>	-1	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	12.5	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

high enrollment, participated in multiple studies

*We are requesting the OSI consult for site inspections as this is a New Molecular Entity NDA. Additionally, several sites have pending complaint investigations.*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). High enrollment and participation in multiple pivotal studies. Inspection being scheduled for another application. Pending complaint investigations.

**Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

**There are pending complaint investigations for several of these sites and we would like to combine the PDUFA inspection with these pending investigations.**

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.**

Concurrence: (as needed)

- Medical Team Leader
- Medical Reviewer
- Division Director (for foreign inspection requests or requests for 5 or more sites only)  
See attached email from Division Director, Mary Parks

**\*\*\*Things to consider in decision to submit request for OSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

## Madara, Patricia

---

**From:** Parks, Mary H  
**Sent:** Monday, July 22, 2013 10:45 AM  
**To:** Madara, Patricia  
**Cc:** Mahoney, Karen M (Diabetes Team Leader); Chong, William (FDA); Kleppinger, Cynthia  
**Subject:** RE: Empa OSI site selection memo

Hi Pat

I have signed off on these in the past but am happy if you sign off too w/ my email as record of concurrence. All depends on what the process requires. If you need my sig just plunk into DARRTS.

Thanks,  
Mary

---

**From:** Madara, Patricia  
**Sent:** Monday, July 22, 2013 8:52 AM  
**To:** Parks, Mary H  
**Cc:** Mahoney, Karen M (Diabetes Team Leader); Chong, William (FDA); Kleppinger, Cynthia  
**Subject:** FW: Empa OSI site selection memo

Hi Mary;

For NDA 204629 (empagliflozin), Bill and Karen worked intensively with OSI to select clinical sites for inspection, using the new OSI inspection tool for determining appropriate sites.

Since there are more than five sites and some are foreign, I believe we need your concurrence.

Please let me know if you usually sign off on these things in darrrts, otherwise I will assume your agreement is sufficient.

Many thanks. Pat

---

**From:** Mahoney, Karen M (Diabetes Team Leader)  
**Sent:** Friday, July 19, 2013 8:45 AM  
**To:** Madara, Patricia; Chong, William (FDA)  
**Subject:** RE: Empa OSI site selection memo

A few edits.  
KMM

---

**From:** Madara, Patricia  
**Sent:** Wednesday, July 17, 2013 11:19 AM  
**To:** Chong, William (FDA)

**Cc:** Mahoney, Karen M (Diabetes Team Leader)

**Subject:** RE: Empa OSI site selection memo

This is a totally new procedure so let me check with Cynthia and get back to you. I also need to find out if I have to do something.....

Stay tuned. Pat

---

**From:** Chong, William (FDA)

**Sent:** Wednesday, July 17, 2013 11:17 AM

**To:** Madara, Patricia

**Cc:** Mahoney, Karen M (Diabetes Team Leader)

**Subject:** Empa OSI site selection memo

Pat,

I'm attaching the updated, completed site inspection memo. What am I supposed to do with it? I've cc'd Karen for her to look it over, but am I supposed to check it into DARRTS?

Bill

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

/s/  
-----

PATRICIA J MADARA  
07/22/2013

# **REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION**

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

**Application: NDA 204629**

**Application Type: New NDA**

**Name of Drug: empagliflozin tablets, 10 mg and 25 mg**

**Applicant: Boehringer Ingelheim**

**Submission Date: March 5, 2013**

**Receipt Date: March 5, 2013**

## **1.0 Regulatory History and Applicant's Main Proposals**

Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and is being developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Original IND 102145 was opened on April 10, 2008, to study empagliflozin as a treatment for type 2 diabetes. The End-of-Phase 2 meeting was held on January 21, 2010 and the PreNDA meeting was on January 18, 2012. The NDA was submitted on March 5, 2013.

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3.0 Conclusions/Recommendations**

No SRPI format deficiencies were identified in the review of this PI.

## 4.0 Appendix

---

### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

## Selected Requirements of Prescribing Information (SRPI)

Comment:

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**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).**"

Comment:

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

Comment:

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- N/A** 12. All text must be **bolded**.  
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”  
Comment:

### Dosage Forms and Strengths

## Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
*Comment:*
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
*Comment:*
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
*Comment:*
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
*Comment:*
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
*Comment:*
- YES** 35. If a section or subsection from 201.56(d)(1) 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.”  
*Comment:*

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
*Comment:*
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
*Comment:*
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”*

### Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“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.”*

### Comment:

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “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)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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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.**  
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/s/  
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PATRICIA J MADARA  
05/17/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 204629 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: empagliflozin Dosage Form: tablet Strengths: 10 mg and 25 mg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):		
Date of Application: 3/5/13 Date of Receipt: 3/5/13 Date clock started after UN:		
PDUFA Goal Date: 3/5/14		Action Goal Date (if different): 3/5/14
Filing Date: 5/4/13		Date of Filing Meeting: 4/23/13
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 - NME		
Proposed indication(s)/Proposed change(s): indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	XX Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 102145				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	XX			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		XX		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>XX Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p>XX Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th data-bbox="203 1482 495 1524">Application No.</th> <th data-bbox="495 1482 771 1524">Drug Name</th> <th data-bbox="771 1482 1060 1524">Exclusivity Code</th> <th data-bbox="1060 1482 1349 1524">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td data-bbox="203 1524 495 1566"></td> <td data-bbox="495 1524 771 1566"></td> <td data-bbox="771 1524 1060 1566"></td> <td data-bbox="1060 1524 1349 1566"></td> </tr> <tr> <td data-bbox="203 1566 495 1608"></td> <td data-bbox="495 1566 771 1608"></td> <td data-bbox="771 1566 1060 1608"></td> <td data-bbox="1060 1566 1349 1608"></td> </tr> <tr> <td data-bbox="203 1608 495 1623"></td> <td data-bbox="495 1608 771 1623"></td> <td data-bbox="771 1608 1060 1623"></td> <td data-bbox="1060 1608 1349 1623"></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>XX</p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			XX	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: 5 yrs  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	XX			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		XX		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			XX	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) XX All electronic <input type="checkbox"/> Mixed (paper/electronic)  XX CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	XX			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	XX			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	XX			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	XX			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	XX			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	XX			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	XX			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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...”</i></p>	XX			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			XX	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			XX	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	XX			
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>			XX	
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	XX			
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	XX			Received as an amendment
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		XX		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	XX			
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		XX		
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	XX Carton labels XX Immediate container labels <input type="checkbox"/> Diluent XX Other (specify) blisters			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	XX			
Is the PI submitted in PLR format? <sup>4</sup>	XX			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	XX			
<b>OTC Labeling</b>	<b>XX Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			XX	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			XX	
If representative labeling is submitted, are all represented SKUs defined?			XX	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			XX	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		XX		QT IRT already reviewed study report under IND 102145
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> May 4, 2010	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> September 28, 2012	XX			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> November 25, 2008	XX			Carci SPAs only
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT  
MEMO OF FILING MEETING

**DATE:** April 23, 2013

**BLA/NDA/Supp #:** 204629

**PROPRIETARY NAME:** TBD

**ESTABLISHED/PROPER NAME:** empagliflozin

**DOSAGE FORM/STRENGTH:** 10 mg and 25 mg tablet

**APPLICANT:** Boehringer Ingelheim

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes

**BACKGROUND:** Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and is being developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). SGLT-2 plays an important role in the kidneys and is responsible for most renal glucose reabsorption in T2DM patients. Retention of excess glucose by this pathway contributes to persistent hyperglycemia. Empagliflozin is an NME that will be reviewed under “The Program.” It is the third member of this class to be reviewed for this indication.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	Y
	CPMS/TL:	Mahreen Hai	Y
Cross-Discipline Team Leader (CDTL)	Karen Mahoney		Y
Clinical	Reviewer:	William Chong	Y
	TL:	Karen Mahoney	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Manoj Khurana	Y
	TL:	Lokesh Jain	N
Biostatistics II (efficacy) + VII (safety)	Reviewer:	Dongmei Liu+Janelle Charles	Y
	TL:	Todd Sahlroot + Mat Soukup	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mukesh Summan	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	TBD	
	TL:	TBD	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	NN	
	TL:	NN	
Product Quality (CMC)	Reviewer:	Joe Leginus	Y
	TL:	Su Tran	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	NN	
	TL:	NN	
CMC Labeling Review	Reviewer:	CMC reviewer	Y
	TL:	CMC TL	MC TL
Facility Review/Inspection	Reviewer:	Steven Hertz (PM)	Y
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Reasol Agustin	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NN	
	TL:	NN	

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		N
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:	NN	
Other reviewers	Biopharmaceutics: Houda Mahayni		Y
Other attendees	Sara Stradley, Acting ADRA		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<p>XX Not Applicable  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p>XX YES  <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b> none</p>	<p><input type="checkbox"/> Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  XX FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<p>XX YES  <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety</i></li> </ul>	<p><input type="checkbox"/> YES  Date if known:  <input type="checkbox"/> NO  XX To be determined</p> <p>Reason:</p>

<ul style="list-style-type: none"> <li>○ <i>or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	XX Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	XX Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> raw data requested</p>	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE  XX Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES XX NO
<p><b>BIostatISTICS</b></p> <p><b>Comments:</b> Biostats VII requested info</p>	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE  XX Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable XX FILE <input type="checkbox"/> REFUSE TO FILE  XX Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<p>XX Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable  XX FILE  <input type="checkbox"/> REFUSE TO FILE  XX Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?  <p style="margin-left: 20px;"><b>If no</b>, was a complete EA submitted?</p> <p style="margin-left: 20px;"><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> </li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable  XX YES  <input type="checkbox"/> NO  <input type="checkbox"/> YES  <input type="checkbox"/> NO  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p>Comments:</p>	<p>XX Not Applicable  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable  XX YES  <input type="checkbox"/> NO  XX YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p>XX Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>

<p><b><u>CMC Labeling Review</u></b></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p>XX YES <input type="checkbox"/> NO</p> <p>XX YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>none</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p>XX YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p>XX YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p>XX YES <input type="checkbox"/> NO</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Curt Rosebraugh</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): August 26, 2013</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): not listed</p>	

<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
XX	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>XX Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>XX Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). <b>DONE</b>
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). <b>N/A</b>
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. <b>N/A</b>
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter <b>N/A</b>
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) <b>N/A</b></li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter No issues found
XX	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <b>N/A</b></p> <p><a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a>]</p>
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

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 OND ADRA or OND IO.

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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.**  
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/s/  
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PATRICIA J MADARA  
05/17/2013