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APPLICATION NUMBER:

761081Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology
351(k) Biosimilar Review

| | |
|--|---|
| 351(k) BLA Number | 761081 |
| Applicant | Pfizer, Inc |
| Submission Date | June 22, 2017 |
| Submission Type | Standard |
| Link to EDR | \\CDSESUB1\evsprod\BLA761081\761081.enx |
| Brand (Generic) Name | Trazimera (trastuzumab) |
| Dosage Form and Strength | Multidose vial nominally containing 440 mg TRAZIMERA as a lyophilized, sterile powder or cake. |
| Route of Administration | Intravenous infusion |
| Proposed Indication(s) | <p>Adjuvant Breast Cancer</p> <ul style="list-style-type: none"> • As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel • As part of a treatment regimen with docetaxel and carboplatin • As a single agent following multi-modality anthracycline based therapy <p>Metastatic Breast Cancer</p> <ul style="list-style-type: none"> • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease <p>Metastatic Gastric Cancer</p> <ul style="list-style-type: none"> • In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease |
| Associated IND | 110,427 |
| Reference Product Information (U.S.-licensed) | |
| Brand (Generic) Name | Herceptin (Trastuzumab) |
| Dosage Form and Strength | Multidose vial containing 440 mg of lyophilized, sterile powder or cake |
| OCP Review Team Signers | |
| OCP Review Team | Christy S. John, Ph.D. Sarah J. Schrieber, Pharm.D. |
| OCP Final Signatory | Nam Atiqur Rahman., Ph.D. |

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1. EXECUTIVE SUMMARY

This Biologic License Application (BLA) for PF-05280014 has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for PF-05280014 as a proposed biosimilar to US-licensed Herceptin licensed under BLA 103792 by Genentech. The applicant is seeking licensure for the treatment of HER2 overexpressing breast cancer, and the treatment of HER2-overexpressing metastatic gastric cancer or gastroesophageal junction adenocarcinoma for which US-licensed Herceptin is currently approved. The application included pharmacokinetic (PK) similarity data and a comparative clinical study to support a demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin. Study B3271001 was a single-dose, randomized, double-blind, 3-arm, parallel group study in 105 healthy male subjects designed to determine the PK similarity of PF-05280014, US-licensed Herceptin, and EU-approved Herceptin following a single 6 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of the PK endpoint (AUC_{0-inf}) were within the specified limits of 80 to 125%. The results of the study established the PK similarity between PF-05280014 and US-licensed Herceptin. The study also established the PK portion of the scientific bridge between PF-05280014, US-licensed Herceptin, and EU-approved Herceptin, which supports the use of EU-approved Herceptin in the comparative clinical Study B3271002

Overall, Study B3271001 supports a demonstration of PK similarity between PF-05280014 and US-licensed Herceptin, as well as the PK portion of the scientific bridge between PF05280014, US-licensed Herceptin, and EU-approved Herceptin. The scientific bridge along with the analytical similarity allows for relying on data from the study using EU-approved Herceptin as a comparator product for the overall biosimilarity assessment.

The incidence of immunogenicity for PF-05280014 and EU-approved Herceptin was compared in a multiple-dose, parallel-arm study in 707 patients with breast cancer (B3721002). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or PK endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for PF-052850014 as compared to EU-approved Herceptin, and supports the demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin.

In conclusion, the PK and immunogenicity results from Study B3271001 and Study B3271002 support a demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity between PF-05280014 and US-licensed Herceptin.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of PF-05280014 based on demonstration of PK similarity between PF-05280014 and US-licensed Herceptin.

| Review Issue | Recommendations and Comments |
|---|---|
| Pivotal evidence of PK similarity | The results of Study B3271001 demonstrate PK similarity between PF-05280014 and US-licensed Herceptin, as well as establish the PK portion of the scientific bridge between PF-05280014, US-licensed Herceptin, and EU-approved Herceptin. The 90% CI of the geometric mean ratio for each product pairwise comparison for the primary specified PK endpoint of AUC_{0-inf} fell within the specified margin of 80 to 125%. |
| Evidence of immunogenicity comparability | The results of Study B3271002 indicate similar incidence of anti-drug antibodies (ADA) for PF-05280014 to EU-approved Herceptin. |

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

PF-05280014 is a proposed biosimilar to US-licensed Herceptin. US-licensed Herceptin (trastuzumab) is a humanized IgG₁κ monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as antibody dependent cellular toxicity (ADCC) activity. PF-05280014 is produced using a mammalian cell line (b) (4)

Details on the clinical pharmacology of US-licensed Herceptin can be found in the product label (USPI).

In Study B3271001, the 90% CI for the geometric mean ratios of the primary PK endpoint of AUC_{0-inf} and secondary PK endpoint of C_{max} was within the specified limits of 80% to 125% in the pairwise comparisons between PF-05280014, US-licensed Herceptin, and EU-approved Herceptin, as summarized in **Table 1**.

Table 1. Summary statistical analyses for PK similarity (Study B3271001)

| Comparison | Geometric Mean Ratio* (90% CI) | |
|--|--------------------------------|-------------------------|
| | AUC _{0-inf} | C _{max} |
| PF-05280014 vs US-licensed Herceptin | 104.1 (95.4, 112.8) | 103.7 (95.5, 124.3) |
| PF-05280014 vs EU-approved Herceptin | 90.7 (83.5, 98.7) | 93.8 (85.0, 103.5) |
| EU-approved Herceptin vs US-licensed Herceptin | 114.2 (105.1, 124.2) | 114.3 (105.1, 124.3) |

*Presented as percent

Overall, the submitted clinical pharmacology study adequately demonstrated similarity of PK among PF-05280014, US-licensed Herceptin, and EU-licensed Herceptin. The PK results support a demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin, and add to the totality of the evidence to support a demonstration of biosimilarity of PF-05280014 and US-licensed Herceptin.

The incidence of immunogenicity for PF-05280014 and EU-approved Herceptin was compared in a multiple-dose, parallel-arm study in 707 patients with metastatic breast cancer (B3721002). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or PK endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for PF-05280014 as compared to EU-approved Herceptin, and supports the demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin.

2.2 Outstanding Issues

None

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 Describe relevant regulatory history for the review of this 351(k) BLA.

PF-05280014 is a proposed biosimilar to US-licensed Herceptin. The applicant is seeking licensure for the treatment of adjuvant and metastatic breast cancer and metastatic gastric or gastroesophageal adenocarcinoma indications for which US-licensed Herceptin is currently approved.

3.2 Clinical Pharmacology Review Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?

The applicant conducted one clinical pharmacology study and one comparative clinical study, as described in **Table 2**.

Table 2. Summary of relevant clinical studies

| Study # | Title | Subjects | Objectives | Route/Dose/Duration |
|----------|--|--|---|----------------------------|
| B3271001 | 3-arm, double-blind, randomized (1:1:1), parallel-group, single-dose study comparing the PK of PF-05280014, US-trastuzumab, and EU-trastuzumab administered to healthy male subjects. | Healthy male (N=105) | PK similarity | Single 6 mg/kg IV infusion |
| B3271002 | Double-blind, randomized clinical study evaluating the efficacy, safety, PK, and immunogenicity of PF-05280014 in combination with paclitaxel vs. EU-trastuzumab with paclitaxel in patients with HER2-positive, metastatic breast cancer in the first-line treatment setting. | Metastatic breast cancer female, (N=707) | Comparative, efficacy, safety, immunogenicity | IV infusion 8 mg/kg |

Study B3271001 was used to support PK similarity. This study was a single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of PF-05280014 (n = 35), US-licensed Herceptin (n = 35), and EU-approved Herceptin (n = 35) administered as a single 6 mg/kg IV infusion over 90 minutes to healthy male subjects. The primary PK endpoint evaluated was AUC_{0-inf}. PK similarity was concluded if the 90% CI of the geometric mean ratio for each pairwise comparison for AUC_{0-inf} between PF-05280014, US-licensed Herceptin, and EU-approved Herceptin was within the specified limits of 80% to 125%. The study design of Study B3271001 is considered adequate due to the following reasons:

1. A single-dose, parallel group design is appropriate for trastuzumab because the product has a long half-life (ranging from 2 to 12 days).

2. A study in healthy subjects is considered safe and more sensitive compared with that in patients with potentially confounding factors such as underlying disease, concomitant medications, and other factors.
3. Considering PK assay sensitivity, dose-exposure linearity, and tolerability, a single IV dose of 6 mg/kg trastuzumab is considered appropriate for a PK similarity study.

Study B3271002 was a comparative clinical study in patients with HER2-positive MBC. Refer to Clinical review for further details.

3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?

In Study B3271001, the PK similarity criteria of AUC_{0-inf} was that the 90% CI of the geometric mean ratio should lie within 80-125%. This margin proposed by the applicant was acceptable.

PK serum samples were collected on Day 1 at pre-dose, 1.5, 3, 8, 24, 48, 72, 96, 168, 336, 504, 672, 1008, and 1680 hours post-dose.

3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. Trastuzumab levels were measured in serum by a validated enzyme-linked immunosorbent assay (ELISA). See **Section 4.1.1** for details.

3.2.4 Is PK similarity met?

Yes, PK similarity between PF-05280014 and US-licensed Herceptin was demonstrated, where the 90% CI of geometric mean ratios of the primary PK endpoint for each product pairwise comparison was contained within defined criteria of 80 to 125% (Table 1). Also, as shown in Figure 1, the PK profiles of PF-05280014, US-licensed Herceptin, and EU-approved Herceptin overlay each other. A summary of the 6 mg/kg single IV dose PK parameters from Study B3271001 for each product is shown in **Table 3**.

Figure 1. Mean serum trastuzumab concentration vs. time profile (Study B3271001)

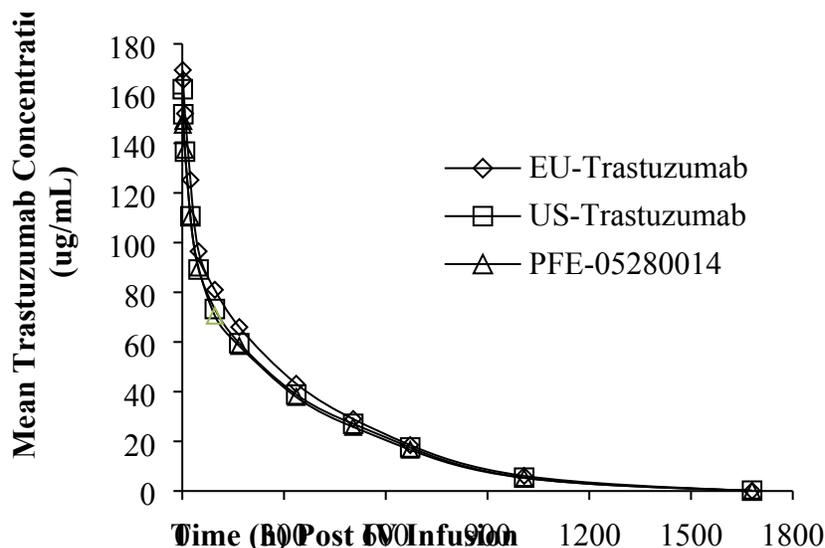


Table 3. Summary of PK parameters (Study B3271001)

| PK parameters | Geometric Mean (% CV) | | |
|---------------------------------|-----------------------|------------------------------|------------------------------|
| | PF-05280014 (n=35) | US-licensed Herceptin (n=35) | EU-approved Herceptin (n=35) |
| C _{max} (µg/mL) | 160 (27%) | 151 (29%) | 171 (17%) |
| AUC _{0-inf} (µg/mL*hr) | 36,781 (19%) | 35,442 (26%) | 40,517 (17%) |
| CL (L/hr/kg) | 0.16 (19%) | 0.17 (26%) | 0.15 (17%) |

% CV: coefficient of variation, CL: clearance

Immunogenicity

3.2.6 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?

Yes. For Study B3721002, detection, confirmation and titration of ADAs were accomplished using a highly sensitive electrochemiluminescence (ECL) method ((b) (4)-1135 at (b) (4) using a Meso Scale Discovery workbench Software. The method sensitivity, low positive control and high positive control of the ADA method were 3.11 ng/mL, 20 ng/mL, and 100 ng/mL, respectively. The assay detection limit was 0.1038 ng/mL and the relative assay sensitivity was 3.11 ng/mL.

Refer to the immunogenicity assay review by the Office of Biological Products review for details regarding the assays.

3.2.7 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

The sampling schedules in the studies were appropriate to minimize interference from the presence of the product in the samples, if the ADA assay is not drug-tolerant. The sampling schedules for the studies were as follows:

- Study B3271001: Predose on Day 1 and post-dose on Day 15, 29, 43 and day 71 or at early termination.
- Study B3271002: Pre-dose Cycles 1 (baseline), 3, 5, 8, every 3 cycles thereafter, and at end of treatment.

3.2.8 What is the incidence of anti-drug antibodies (ADA)? (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study.)

In the single dose PK similarity Study B3271001, the EU-approved Herceptin arm had one positive ADA subject sample following dosing (1/35, 2.9%), which was nAb negative.

In Study B3271002, positive ADA samples were observed at pre-dose (baseline) in each treatment arm, for which approximately 65% were neutralizing. However, there were no treatment emergent ADAs observed in either the PF-05280014 or EU-Herceptin treatment arm (Table 4).

Table 4. Immunogenicity results for binding ADA and nAb in Study B3271002

| | | ADA, % (n) | | nAb, % (n) | |
|--------------|-----|----------------|--------------------|---------------------|--------------------|
| Treatment | N | Baseline | Treatment-emergent | Baseline | Treatment-Emergent |
| PF-05280014 | 349 | 8.6% (n=30) | 0% | 66.7% (20 of 30) | 0% |
| EU-Herceptin | 353 | 4% (n=14) | 0% | 64.3% (9 of 14) | 0% |

ADA=Anti-drug-antibody
nAb=Neutralizing antibody

The data indicate that there is no increase in immunogenicity risk for PF-05280014 as compared to EU-approved Herceptin, and supports the demonstration that there are no clinically meaningful differences between PF-05280014 and US-licensed Herceptin. Of note, a scientific

bridge was established between PF-05280014, US-licensed Herceptin, and EU-approved Herceptin, supporting the relevance of comparative data, including immunogenicity data, generated using EU-approved Herceptin to support a demonstration of no clinically meaningful differences between PF-05280014 and US-licensed Herceptin.

3.2.9 Do the anti-drug antibodies (ADA) have neutralizing activity?

No patient tested positive for neutralizing antibodies following administration of PF-05280014 or EU-approved Herceptin (**Table 4**).

3.2.10 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?

No apparent impact of ADA on PK, activity, or safety endpoints was observed from Study B3271002 (data not shown).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetics

4.1.1.1 How are the concentrations of the pharmacologically active moieties (parent and/or any relevant catabolites) measured in the plasma and other matrices in the clinical pharmacology studies?

Total serum trastuzumab samples were determined using a validated Enzyme-Linked Immunosorbent Assay (ELISA).

This validation study was conducted in accordance with Pfizer Global Research & Development WWPDMS SOPs No. 16 (Pfizer Validation Study No. B3279001, (b) (4) Pfizer Global Clinical Bioanalytical Best Practices and the method validation plan. A summary of the ELISA assay validation for PF-085200, EU-Herceptin US-licensed Herceptin is show in **Table 5**.

In this assay, samples containing trastuzumab are diluted in 600 mM acetic acid to dissociate potential HER-2-drug complexes. Acid-dissociated samples are neutralized with 1.5M Trisbase. Then, trastuzumab is captured onto a microtiter plate coated with a recombinant human HER-2. The bound trastuzumab is detected with the enzyme conjugate, goat anti-human horseradish peroxidase (HRP). TMB (3,3',5,5'-tetramethylbenzidine) is utilized as substrate for signal generation and colorimetric readout. Sample concentrations are determined by interpolation from a calibration curve (prepared from EU-trastuzumab) generated using 5-parameter logistic regression with the weighting 1/Y. Full details of the method including reagents and instruments are documented in the analytical method appended to the validation study report. This ELISA method has been fully validated in evaluation of assay performance with respect to precision, accuracy, selectivity, specificity, dilution linearity, target- and ADA-interference, and tested

stability. Accuracy and precision of the method has been demonstrated using validation samples (VS) for EU-trastuzumab, US-trastuzumab, and PF-05280014 prepared at 5 concentrations each (validation samples lower limit of quantification [VSL LOQ] 0.500 µg/mL, validation samples lower [VSL] 1.50 µg/mL, validation samples mid [VSM] 15.0 µg/mL, validation samples high [VSH] 75.0 µg/mL and validation samples upper limit of quantification [VSU LOQ] 100 µg/mL).

Table 5. ELISA assay validation for PF-05280014, US-licensed Herceptin, and EU-approved Herceptin

| | | |
|---|---|-----|
| ^{(b) (4)} Project # | 15-1223 WWPDM SOPs No. 3, 15, 16 | |
| Pfizer Validation Plan Number | B3279003 | |
| Material for calibration curve & concentration | EU-Trastuzumab, Lot #: 12-000656 (H0775B01) US-Trastuzumab-US, Lot#: 991942 PF-05280014, Lot #: 12-000813 (Z00515) | |
| Material for QC and concentration | EU-Trastuzumab, Lot #: 12-000656 | |
| Minimum required dilution (MRD) | 1:1000 in buffer | |
| Matrix | Human serum | |
| Source & lot of reagents | Recombinant HER2 coated plate HRP-conjugated goat anti-human IgG Fc antibody (^{(b) (4)}), Cat # 109-035-098 | |
| Sample Volume (µL) | 10 µL | |
| Sample Storage | -20 and -70 °C | |
| Validated assay range (LLOQ to ULOQ) | 0.5 to 100 µg/mL | |
| Regression, Weighting | Four or five parameter logistic, 1, 1/Y or 1/Y ² | |
| QC Concentrations (Validation Sample) | 1.5, 15.0, 75.0, 100 and 750 µg/mL | |
| | Method validation summary | |
| Standard curve performance in all validation runs | Number of standard calibrators from LLOQ to ULOQ: 10 | Yes |
| | Cumulative accuracy (%bias) from LLOQ to ULOQ: -2.3 to 3.2% | Yes |
| | Cumulative precision (%CV) from LLOQ to ULOQ: <13.2% | Yes |
| QCs performance during accuracy & precision | <u>Cumulative accuracy (%bias) in 5 QCs</u> EU-Trastuzumab: -3.6 to 6.7% US-Trastuzumab: -6.9 to 4.0% PF-05280014: -4.4 to 6.7% | Yes |
| | <u>Inter-assay %CV in 5 QCs:</u> EU-Trastuzumab: <7% US-Trastuzumab: <8% PF-05280014: <12% | Yes |

| | | |
|---|--|-----|
| | Percent total error (TE) in 5 QCs: EU-Trastuzumab: <14% US-Trastuzumab: <13% PF-05280014: <19% | Yes |
| Selectivity | EU-Trastuzumab: 10 out of 10 Lots Passed US-Trastuzumab: 9 out of 10 Lots Passed PF-05280014: 9 out of 10 Lots Passed | Yes |
| Dilutional Linearity & hook effect | Up to 750 µg/mL, highest dilution factor 500 No hook effect | Yes |
| Hemolysis* | EU-Trastuzumab: 6 out of 6 Lots %RE < 20% PF-05280014: 6 out of 6 Lots %RE < 20% | Yes |
| Lipemia* | EU-Trastuzumab: 5 out of 6 Lots %RE < 20% PF-05280014: 6 out of 6 Lots %RE < 20% | Yes |
| Interference (Specificity Evaluation- Interference of ADA tested using PC, an affinity purified rabbit anti-trastuzumab polyclonal antibody) | EU-Trastuzumab: up to 10 µg/mL of PC US-Trastuzumab: up to 10 µg/mL of PC PF-05280014: up to 10 µg/mL of PC | Yes |
| Bench-top/process stability | Room Temperature Bench-Top Stability of EU-Trastuzumab, US-Trastuzumab, and PF-05280014 in Human Serum was 21.9 hours | Yes |
| Freeze-thaw stability | Freeze/Thaw Matrix Stability of EU-Trastuzumab, US-Trastuzumab, and PF-05280014 in Human Serum at -20 and -70 C was 5 cycles | Yes |
| Frozen serum storage stability (days) | At least 774 Days at - 20°C and - 70°C | Yes |

*Reported in Addendum 2 to Pfizer Validation Study No. B3279001, (b) (4) Project No. 15-1223. Evaluated for samples collected in Study B3271002.

Performance of validated ELISA method ((b) (4) Project Number 15-1249) during the sample analysis for study B3721002 is summarized in **Table 6**.

Table 6. Summary of ELISA method performance in support of Study B3721001

| | | |
|---|--|-----|
| (b) (4) Code | 15-1249 | |
| Assay passing rate | <ul style="list-style-type: none"> 90% of the assay met the method acceptance criteria. | Yes |
| Standard curve performance | <ul style="list-style-type: none"> Cumulative bias range: -0.8 to 3.0% Cumulative precision: ≤ 6%CV | Yes |
| QC performance | <ul style="list-style-type: none"> Cumulative bias range: -4.7 to 3.3% Cumulative precision: ≤ 9.4%CV TE: ≤ 12.7% | Yes |
| Study sample analysis/ stability | All samples analyzed within the established storage stability. | |

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/s/

CHRISTY S JOHN
03/07/2018

SARAH J SCHRIEBER
03/07/2018

NAM ATIQRUR RAHMAN
03/08/2018
I concur.