DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125431/0

BLA APPROVAL

GlaxoSmithKline LLC
Attention: Susan Watts, Ph.D.
Director, Therapeutic Groups
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA) dated and received January 14, 2013, submitted under section 351(a) of the Public Health Service Act for Tanzeum (albiglutide) for injection, for subcutaneous use.

We acknowledge receipt of your amendments dated February 13, 18, and 27, March 5 and 7, April 8, 10, 19, and 26, May 15 (2), 20, 24, and 29, June 4, 7, 10, 14 (3), 18, 19, and 28, July 12, August 5, 8, 12, 16, 19, 23, and 30, September 2 and 30, October 4, 8, 10, and 31, November 8 (2), 18, 22, and 28, and December 12, 13, 18 and 20 (2), 2013, and January 8, 10, 21, and 22, February 11 and 25, March 7, 14, 25, and 28, and April 8, 9 (2), 10, and 11, 2014.

LICENSING

We have approved your BLA for Tanzeum (albiglutide) for injection, for subcutaneous use effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Tanzeum (albiglutide) under your existing Department of Health and Human Services U.S. License No. 1727. Tanzeum (albiglutide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Tanzeum (albiglutide) drug substance at GlaxoSmithKline LLC in Conshohocken, Pennsylvania. The final formulated product will be manufactured, filled, assembled into auto-injectors, labeled, and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, Tanzeum, and will market it in 30 mg or 50 mg in a single-dose pen for injection.

DATING PERIOD

The dating period for Tanzeum (albiglutide) shall be 12 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of (b) (4) (b) (4). The dating period for your drug substance shall be (b) (4) (b) (4) Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Tanzeum to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Tanzeum, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125431/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Tanzeum was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric study for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of Tanzeum (albiglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).

Final Protocol Submission:	October 2014
Study Completion	April 2020
Final Report Submission:	October 2020

Submit the protocol to your IND 065177, with a cross-reference letter to this BLA.
Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess either a signal of a serious risk of cardiovascular events or a serious risk of medullary thyroid carcinoma associated with Tanzeum (albiglutide).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2. A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Tanzeum (albiglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Tanzeum (albiglutide).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2014
Study Completion:	December 2029
Final Report Submission:	December 2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-

diabetic medications, including Tanzeum (albiglutide) for injection, for subcutaneous use, to definitively exclude unacceptable cardiovascular toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3. A randomized, double blind, placebo-controlled trial evaluating the effect of Tanzeum (albiglutide) on the incidence of major adverse cardiovascular events (MACE) in subjects 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 albiglutide to that observed in the placebo group is less than 1.3. This trial must also assess the following adverse events: development of thyroid cancer, hematologic malignancies, pancreatic cancer, pancreatitis, overall injection site reactions, immunological reactions including serious hypersensitive reactions, serious hypoglycemia events, hepatic events, hepatic enzyme elevations (including gamma-glutamyl transpeptidase [GGT]), serious gastrointestinal events, appendicitis, atrial fibrillation/flutter, pneumonia, worsening renal function, and diabetic retinopathy.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2014
Trial Completion:	May 2019
Final Report Submission:	November 2019

Submit the protocols to your IND 065177, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," "**Required Postmarketing Correspondence Under 505(o)**."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4. A study evaluating gallbladder ejection fractions in albiglutide treated subjects to further characterize the effect of albiglutide on gallbladder motility.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2015
Study Completion:	August 2016
Final Report Submission:	February 2017

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

5. To develop, validate, and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	August 2015

6. To develop, validate, and implement a neonatal Fc receptor binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	May 2015

7. To conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product. In addition, develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in

the relevant containers. Provide the information and data in accordance with 21CFR601.12.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: April 2015

8. To conduct a bulk drug substance stability study using samples stored for the desired shelf life in the (b) (4). Stability testing should be performed on drug substance aliquots removed following (b) (4) (b) (4).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2015

9. To implement CAPAs (corrective action/preventative action) to establish a (b) (4) for bulk drug substance.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Implementation date: June 2015
Final Report Submission: August 2015

Submit clinical protocols to your IND 065177 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tanzeum (albiglutide) to ensure the

benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis.

We have also determined that a communication plan is necessary to support implementation of the REMS

Your proposed REMS, emailed to us on April 13, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Tanzeum (albiglutide) into interstate commerce.

At least 24 hours prior to issuing the Dear Healthcare Provider letter(s) that are required as part of the REMS described above, submit an electronic copy of the letter to this NDA, and to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

The REMS assessment plan should include, but is not limited to, the following:

a) REMS communication plan activities:
    (1) Number of healthcare providers and professional societies targeted by the REMS.
    (2) Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the healthcare providers did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
    (3) Number of REMS Factsheets distributed to healthcare providers during the 12 months after product launch.
    (4) Date when REMS website went live and number of total and unique site visits during the assessment period.
b) Evaluation of healthcare providers' understanding of:
    (1) The potential risk of medullary thyroid cancer.
    (2) The risk of pancreatitis.

(3) The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.

(4) Appropriate albiglutide patient population characteristics.

c) Safety surveillance:

(1) Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.).

(2) Evaluation and postmarketing case reports of pancreatitis.

(3) Evaluation and postmarketing case reports of medullary thyroid cancer.

(4) Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125431 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125431 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125431
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125431
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment

Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

CURTIS J ROSEBRAUGH
04/15/2014