ONDQA, Division of Pre-Marketing Assessment I
CMC REVIEW (DMEP)

IND: 113,480 Review Date: 15-Dec-2011

Initial IND Submission: 14-Oct-2011 (Serial # 000)

Amendment: 05-Dec-2011 (Serial # 001)

Applicant: Transition Therapeutics Inc./ 101 College Street, Suite 220/ Toronto, Ontario/ Canada M5G 1L7
Phone: (416) 260-7770. Fax: (416) 260-2886
USA Agent: Mr. Michael Kim/ Senior Consultant/ PARAXEL Consulting/ PARAXEL International, LLC
4600 East West Drive Highway, Suite 350, Bethesda, MD 20814
Tel: (858) 795-6291. Fax: (301) 634-8040. Email: rnichael.kim@parexel.com.

Product Name(s): TT401 (polyethylene glycolylated (PEGylated) oxyntomodulin (OXM) analog) for Injection

Dosage Form/ Strength / and Route of administration: Lyophilized powder for reconstitution/ 1.0 – 10.0 mg/mL / Subcutaneous Injection

Placebo: Commercially available 0.9 % sodium chloride for injection, USP or sterile water for injection, USP will be used as the placebo in study DPO-101.

Pharmacological Category and/or Principal Indication: Steroid. Specific antagonist of the Type II glucocorticoid receptor (GR-II) and the progesterone receptor/ Type 2 diabetes mellitus/ obesity

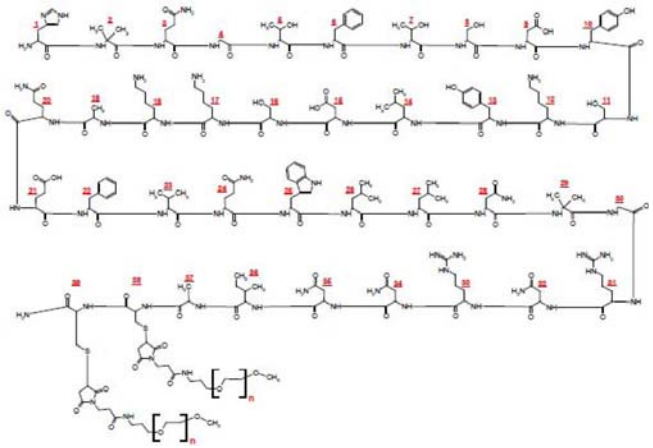
Structural Formula and Chemical Name:

TT401 (PEGylatedOXM) analog)

Formula: $C_{2063}H_{4023}N_{63}O_{989}S_2$ (as free base)

MW: 20.5 kDa (where n = ~460)

CAS #: Not yet assigned.



H-His[1]-Aib-Gln-Gly-Thr[5]-Phe-Thr-Ser-Asp-Tyr[10]-Ser-Lys-Tyr-Leu-Asp[15]-Ser-Lys-Lys-Ala-Gln[20]-Glu-Phe-Val-Gln-Trp[25]-Leu-Leu-Asn-Aib-Gly[30]-Arg-Asn-Arg-Asn-Asn[35]-Ile-Ala-Cys[PEG]-Cys[PEG]-NH_2

Remarks: This amendment provides a response to the Agency requests dated 09-Nov-2011 and 18-Nov-2011, and additional CMC information.

Conclusion and Recommendation: From the CMC viewpoint the proposed Phase I clinical study, described under protocol DPO-101, may continue to proceed.

	Xavier Ysern, PhD	Review Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII
Init.	Ali Al-Hakim, PhD	Branch Chief/ CDER/ ONDQA/ DNDQA III/ Branch VII

Filename: /ind/113312_1.doc

Review Notes

Part of the information requested by the Agency on November 18, 2011, is one question/comment (Question 10) from CMC. Agency's Question 10, shown in bold, is followed by the Applicant response.

Question 10 (CMC). Please provide the specifications for the starting material PEG (~20 kDa) Maleimide and a description of the efforts to control its molecular weight variation (currently the actual number of repeating PEG units ranges from ~ 414 to 505).

Response: The specifications for the starting material PEG (~20 kDa) are included in the enclosed Certificate of Analysis. The PEG average molecular weight is controlled by the manufacturer within the release specification limits of 18.5 - 22.5 kDa (414 – 505 repeating PEG units). This molecular weight is confirmed by PolyPeptide Laboratories Inc. using MALDI-TOF mass spectrometry prior to release of the PEG starting material for use in manufacturing.

Comment: The Applicant has chosen not control the range of the molecular weigh of the starting material PEG (~20 kDa) beyond that controlled by the supplier and included in the specifications for the starting material PEG (~20 kDa) as given in their Certificate of Analysis.

In addition, the Applicant provides additional stability data. The available results from the ongoing stability study (details referred to the Applicant's amendment submission), as provided by the Applicant, are given below

Batch ENG1105 – Non-GMP (2 week and 1 month data)

Accelerated Storage Conditions (25 ± 2 °C/65 ± 5 % RH)

After 1 month storage at the accelerated storage condition, 25 ± 2 °C / 60 ± 5 % RH, the TT401 drug product purity was 98.0 % and 98.7 % by RP-HPLC and SEC-HPLC at release and 97.9 % and 98.2 % respectively at 1 month. The related substance at RRt 1.03 by RP-HPLC was initially 1.6 % and was 1.7 % after 1 month, and the substance at RRt 0.90-0.92 by SEC-HPLC changed from 1.3 % to 1.8 % following 1 month storage. The potency (relative EC50) at the GLP-1 receptor was 86 % and 84 % at release and 1 month, respectively, and the potency (relative EC_{50}) at the glucagon receptor was 90 % and 88 % at release and following 1 month storage at accelerated conditions. Water content increased from 1.2 % at time 0 to 3.2 % at 1 month.

Long-term Storage Conditions (5 ± 3 °C/ambient RH)

After 1 month storage at the long-term condition of 5 ± 3 °C, the purity by RP-HPLC or SECHPLC of TT401 drug product batch ENG1105 showed no notable change and no change in related substances was observed after 1 month storage. The potency (relative EC_{50}) at the GLP-1 receptor was 86 % both at release and 1 month, and the potency (relative EC_{50}) at the glucagon receptor was 90 % and 93 % at release and following 1 month storage at the long-term condition. Water content changed from 1.2 % at time 0 to 2.5 % at 1 month.

Batch B110543– GMP (1 month data)

Accelerated Storage Conditions (25 ± 2 °C/65 ± 5 % RH)

At the accelerated storage condition, the purity by RP-HPLC and SEC-HPLC was 98.1 % and 97.8 % respectively at release and 98.0 % and 97.6 % after 1 month. The related substance at RRt 1.03 by RP-HPLC was initially 1.6 % and was 1.7 % after 1 month, and the substance at RRt 0.88 by SEC-HPLC changed from 2.2 % to 2.4 % following 1 month storage. The potency (relative EC50) at the GLP-1

receptor was 93 % both at release and 1 month, and the potency (relative EC_{50}) at the glucagon receptor was 110 % and 99 % at release and following 1 month storage at accelerated conditions. Water content changed from 1.5 % at time 0 to 2.1 % at 1 month. The pH of the reconstituted solution was 5.6 both at time 0 and 1 month. The physical appearance of the drug product or the reconstituted solution did not change following 1 month storage at the accelerated condition.

Long-term Storage Conditions (5 ± 3 °C/ambient RH)

After 1 month storage at the long-term condition, the purity by RP-HPLC or SEC-HPLC of TT401 drug product batch B110543 showed no change and no change in related substances was observed. The potency (relative EC_{50}) at the GLP-1 receptor was 93 % and 96 % at release and 1 month, respectively, and the potency (relative EC_{50}) at the glucagon receptor was 110 % at release and 104 % following 1 month storage at the long-term condition. Water content changed from 1.5 % at time 0 to 2.4 % at 1 month. The pH of the reconstituted solution was 5.6 at time 0 and 5.7 at the 1 month time point. The physical appearance of the drug product or the reconstituted solution did not change following 1 month storage at the long-term condition.

Based on the results obtained under accelerated and long-term storage conditions for TT401 drug product, a shelf-life of 6 months, under the storage condition of 5 ± 3 °C are proposed by the Applicant for the drug product.

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

/s/

XAVIER J YSERN
12/15/2011

ALI H AL HAKIM
12/15/2011