# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211875Orig1s000

# CLINICAL PHARMACOLOGY REVIEW(S)

# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | 211875 |
| **Link to EDR** | \\CDSESUB1\evsprod\nda211875\0016\ |
| **Submission Date** | April 24, 2020 |
| **Submission Type** | 505(b)(2) resubmission after Complete Response, Listed Drug: ABRAXANE ® |
| **Brand Name** | NA |
| **Generic Name** | HBT-001 (Paclitaxel protein-bound particles for injectable suspension (albumin-bound)) |
| **Dosage Form and Strength** | Lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution. |
| **Route of Administration** | 260 mg/m$^2$ IV infusion over 30 minutes every 3 weeks |
| **Proposed Indication** | 1. Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.<br>2. Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.<br>3. Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. |
| **Applicant** | HBT Labs |
| **Associated IND** | IND-129370 |
| **OCP Review Team** | Wentao Fu, Ph.D.; Salaheldin Hamed, Ph.D. |

## 1. SUMMARY OF APPLICATION

HBT Labs has submitted a resubmission to NDA 211875 addressing the CMC deficiencies in the Complete Response (CR) letter dated June 14, 2019 to the original NDA 211875 submission. There is no new clinical pharmacology data in current resubmission. In the original submission, PK bioequivalent (BE) were established between HBT-001 and ABRAXANE when 260 mg/m$^2$ administrated intravenously over 30 minutes under overnight fasting conditions in Study HBT-001-BE-01. The Study Integrity and Surveillance clinical sites inspection concluded that the clinical data from Study HBT-001-BE-01 are reliable to support a regulatory decision. Please refer to the Clinical Pharmacology Reviews (Reference ID 4436559 and 4448856) and

Bioequivalence Establishment Inspection Report Review (Reference ID 447390) for the original NDA 211875 submission in DARRTs for details.

The resubmission now includes all the current indications for Abraxane. The original submission only included the breast cancer indication and carved out the indications for non-small cell lung cancer and adenocarcinoma of the pancreas. The proposed drug product and ABRAXANE® are the same with respect to dosage form, route of administration and strength. Following ABRAXANE intravenous infusion, paclitaxel exhibited linear drug exposure (AUC) across clinical doses ranging from 80 to 300 mg/m$^2$.

The proposed dosing regimen of HBT-001:

- Metastatic Breast Cancer: 260 mg/m$^2$ intravenously over 30 minutes every 3 weeks
- Non-Small Cell Lung Cancer: 100 mg/m$^2$ intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle
- Adenocarcinoma of the Pancreas: 125 mg/m$^2$ intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211875 submission. This NDA is approvable from a clinical pharmacology perspective.

## 1.2 Post-Marketing Requirements and Commitments

None.

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# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | 211875 |
| **Link to EDR** | Application 211875 - Sequence 0001 - 0001 (1) 08/29/2018 ORIG-1 /Multiple Categories/Subcategories |
| **Submission Date** | August 29, 2018 |
| **Submission Type** | 505(b)(2), Listed Drug: ABRAXANE ® |
| **Brand Name** | NA |
| **Generic Name** | HBT-001 (Paclitaxel protein-bound particles for injectable suspension (albumin-bound)) |
| **Dosage Form and Strength** | Lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution. |
| **Route of Administration** | 260 mg/m$^2$ IV infusion over 30 minutes every 3 weeks |
| **Proposed Indication** | For the treatment of metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated |
| **Applicant** | HBT Labs |
| **Associated IND** | IND-129370 |
| **OCP Review Team** | Wentao Fu, Ph.D.; Pengfei Song, Ph.D. |

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# 1. EXECUTIVE SUMMARY

In this 505(b)(2) application, the applicant seeks the approval of HBT-001(paclitaxel protein-bound particles for injectable suspension (albumin-bound)) [redacted (b) (4)]. Evidence demonstrated pharmacokinetic (PK) bioequivalence (BE) between HBT-001 and Listed Drug ABRAXANE® in patients with metastatic breast cancer. The proposed drug product and ABRAXANE® are the same with respect to dosage form, route of administration and strength.

The proposed dosing regimen of HBT-001:

- 260 mg/m$^2$ intravenously over 30 minutes every 3 weeks

This clinical pharmacology review focused on following issues:

- Whether bioequivalence (BE) is demonstrated between HBT-001 and ABRAXANE.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211875 submission. This NDA is approvable from a clinical pharmacology perspective pending on the scheduled OSIS clinical sites inspection results.

The key review issues with specific recommendations and comments are summarized below:

| Review Issue | Recommendations and Comments |
|---|---|
| **Evidence of PK Similarity of HBT-001 and ABRAXANE under Overnight Fasted Conditions** | A Phase 1 trial provides evidence establishing PK bioequivalent (BE) between HBT-001 and ABRAXANE when 260 mg/m$^2$ administrated intravenously over 30 minutes under overnight fasting conditions. |
| **General dosing instructions** | HBT-001 is 260 mg/m$^2$ intravenously over 30 minutes every 3 weeks |

## 1.2 Post-Marketing Requirements and Commitments

None.

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology, Pharmacodynamics and Clinical Pharmacokinetics

Paclitaxel is an anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

### 2.1.1 Clinical Pharmacokinetics

This review focuses on BE between HBT001 and ABRAXANE (b) (4). Please refer to clinical review in DARRTs dated 5/15/2019 by Dr. Preeti Narayan for detail on safety review of Study HBT001-BE-01. Paclitaxel total (albumin-bound and unbound) and free plasma concentrations of HBT001 and ABRAXANE were studied in BE Study HBT001-BE-01 in patients with breast cancer. The proposed commercial formulation of HBT001 was used in the study. The study was a Phase 1, multicenter, randomized, open-label, 2-period, 2-sequence, crossover, 2-stage group sequential design study assessing the BE of a single dose of HBT001 versus ABRAXANE. Study treatments were administered as a single IV dose in 3-week cycles. Period 1 in Cycle 1 (Period 1 and washout period of three weeks) and Period 2 in Cycle 2 (Period 2 and follow-up period) evaluated the pharmacokinetics (PK) of paclitaxel following dosing with HBT001 or ABRAXANE, Table 1.

Table 1. Study HBT001-BE-01 Design

| Sequence | Period 1 in Cycle 1 | Period 2 in Cycle 2 |
|---|---|---|
| AB | A | B |
| BA | B | A |

A: HBT001 (Test); B: ABRAXANE (Reference)

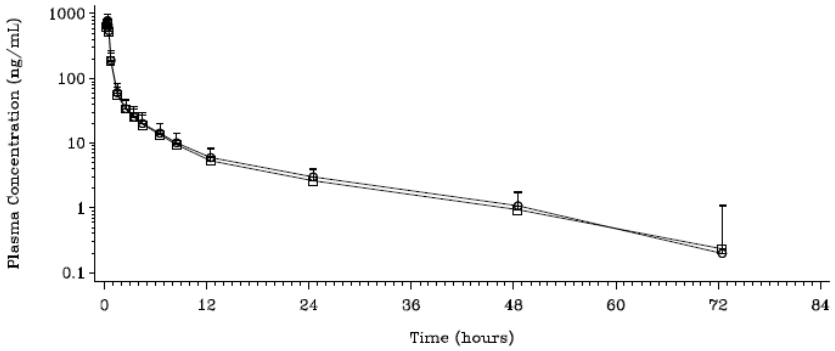
*Source Clinical Study Report Protocol number HBT001-BE-01.*

A total of 22 subjects were randomly assigned and 21 subjects completed Cycles 1 and 2. All 22 subjects were included in the safety population and 21 subjects were included in the PK population. One subject (subject (b) (6)) was withdrawn prior to Cycle 2; therefore, PK sample analysis was not conducted, and no PK data were generated for this subject.

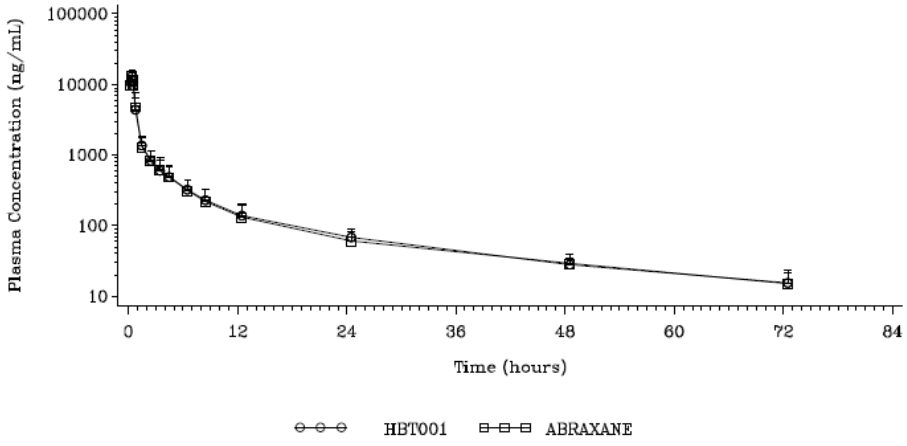
Following a single-dose 30 minutes IV infusion of HBT001 or ABRAXANE in subjects with breast cancer, unbound paclitaxel total and free PK profiles were similar between HBT001 and ABRAXANE, Figure 2. Pharmacokinetic plasma sample collection time points included pre-dose sampling (within 10 minutes before the start of infusion), sampling during infusion (15 and 25 minutes after the start of infusion), and post-infusion sampling (0 [immediately after the end of infusion], 2, 15, and 60 minutes, and 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after the end of the infusion). In summary, the PK parameters from HBT001 and ABRAXANE are very similar, Table 2. The statistical analysis $AUC_{0-t}$, $AUC_{0-inf}$ and $C_{max}$ of unbound paclitaxel and total paclitaxel meet BE criteria, Table 4.

Figure 1. Mean Paclitaxel Plasma Concentration Time Plots

a. Free Paclitaxel




b. Total Paclitaxel




*Source Figure 11-1 and Figure 11-2 of Clinical Study Report Protocol number HBT001-BE-01.*

Table 3. Summary of Plasma PK Parameters

a. Mean (CV) PK Parameters of Unbound Paclitaxel

| Parameter (unit) | Treatment HBT001 (n=21) | Treatment ABRAXANE (n=21) |
|---|---|---|
| $AUC_{0-t}$ (ng•h/mL) | 756 (26.3) | 718 (27.1) |
| $AUC_{0-inf}$ (ng•h/mL) | 760 (23.1)[a] | 755 (26.8)[b] |
| $C_{max}$ (ng/mL) | 819 (20.5) | 778 (14.9) |
| $T_{max}$ (h)[c] | 0.42 (0.25, 0.54) | 0.42 (0.25, 0.54) |
| $K_{el}$ (1/h) | 0.0612 (29.2)[a] | 0.0642 (36.0)[b] |
| $t_{1/2}$ (h) | 12.22 (27.7)[a] | 12.00 (30.4)[b] |

b. Mean (CV) PK Parameters of Total Paclitaxel

| Parameter (unit) | Treatment HBT001 (n=21) | Treatment ABRAXANE (n=21) |
|---|---|---|
| $AUC_{0-t}$ (ng•h/mL) | 15700 (24.4) | 15700 (26.5) |
| $AUC_{0-inf}$ (ng•h/mL) | 16200 (23.9) | 16200 (26.3) |
| $C_{max}$ (ng/mL) | 13800 (21.6) | 13600 (18.2) |
| $T_{max}$ (h)[a] | 0.42 (0.25, 0.54) | 0.42 (0.26, 0.75) |
| $K_{el}$ (1/h) | 0.0392 (16.6) | 0.0386 (19.6) |
| $t_{1/2}$ (h) | 18.10 (15.7) | 18.65 (20.1) |

*Source Table 11-2 and 11-3 of Clinical Study Report Protocol number HBT001-BE-01.*

Table 4. Study HBT001-BE-01 BE Assessment Summary

**Table 1** **Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE Studies (Without $AUC_{0-inf}$ Exclusions)**

| Unbound Paclitaxel (No. of subjects completed = 21)[a] Dose (260 mg/m²) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | | | |
|---|---|---|---|---|---|---|
| **Fasting Bioequivalence Study (Study No. HBT001-BE-01)** | | | | | | |
| **Parameter** | **HBT001** | **N** | **ABRAXANE** | **N** | **Ratio** | **90% CI[c]** |
| $AUC_{0-t}$ | 704 | 21 | 672 | 21 | 104.69 | (95.80, 114.41) |
| $AUC_{0-inf}$ | 734 | 21 | 692 | 20[b] | 106.14 | (96.82, 116.37) |
| $C_{max}$ | 788 | 21 | 763 | 21 | 103.23 | (94.93, 112.25) |

| Total Paclitaxel (No. of subjects completed = 21)[a] Dose (260 mg/m²) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals | | | | | | |
|---|---|---|---|---|---|---|
| **Fasting Bioequivalence Study (Study No. HBT001-BE-01)** | | | | | | |
| **Parameter** | **HBT001** | **N** | **ABRAXANE** | **N** | **Ratio** | **90% CI[c]** |
| $AUC_{0-t}$ | 14900 | 21 | 15000 | 21 | 99.91 | (92.69, 107.69) |
| $AUC_{0-inf}$ | 15400 | 21 | 15400 | 21 | 99.71 | (92.52, 107.45) |
| $C_{max}$ | 13300 | 21 | 13300 | 21 | 100.28 | (92.92, 108.23) |

[a] Subject (b) (6) was excluded from the PK population and did not have PK samples analyzed because the subject did not complete both periods of the study.

[b] $AUC_{0-inf}$ is missing from the statistical analysis for Subject (b) (6) because the terminal phase parameters were not estimable.

[c] A 91.08% CI is reported since alpha=0.0446 to control overall Type 1 error in the 2-stage design used in this study.

*Source Table 1 of Clinical Study Report Protocol number HBT001-BE-01 Addendum.*

## 2.2 General Dosing

Recommended dosage of HBT-001 is 260 mg/m$^2$ intravenously over 30 minutes every 3 weeks. The dosage is the same as recommended dosage of ABRAXANE. The dosage is supported by the BE between HBT-001 and ABRAXANE when 260 mg/m$^2$ administrated intravenously over 30 minutes under overnight fasting conditions.

## 2.3 Outstanding Issues

The OSIS clinical site inspection was requested and is pending.

## 2.4 Summary of Labeling Recommendations

There is no labeling review in this review cycle, given a Complete Response action due to deficient manufacturing site inspection results.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 General Pharmacology and Pharmacokinetic Characteristics

The summary of clinical pharmacology and pharmacokinetics information is listed below. Please refer to original ABRAXANE ® (NDA 21660) and TAXOL (NDA 20262) submission for review of paclitaxel distribution, metabolism and excretion information.

| **Pharmacology** | | | |
|---|---|---|---|
| **Mechanism of Action** | Paclitaxel is a microtubule inhibitor | | |
| **Active Moieties** | Paclitaxel | | |
| **General Information** | | | |
| **Bioanalysis** | Total and free paclitaxel concentrations were measured using validated LC-MS/MS methods. | | |
| **Drug exposure at steady state following the therapeutic dosing regimen** | No accumulation expected for free and total paclitaxel exposure. After single dose (N=21) under overnight fasted conditions, geometric mean (CV%) $C_{max}$ and $AUC_{0\text{-}inf}$ values for total paclitaxel were 13800 ng/mL (21.6%) and 16200 ng·h/mL (23.9%), respectively; geometric mean (CV%) $C_{max}$ and $AUC_{0\text{-}inf}$ values for free paclitaxel were 819 ng/mL (20.5%) and 760 ng·h/mL (23.1%), respectively | | |
| **Minimal effective dose or exposure** | Not available. HBT-001 single dose was the only dosing regimen studied in the clinical trial in patients with metastatic breast cancer. | | |
| **Maximal tolerated dose or exposure** | Not available for HBT-001. | | |
| **Dose Proportionality** | Not available for HBT-001. The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m$^2$ and the pharmacokinetics of paclitaxel for ABRAXANE. | | |
| **Total Paclitaxel HBT-001/ABRAXANE Least Squares Geometric Mean Raio (90% Confidence Intervals)** | BE | | |
| | $C_{max}$ | $AUC_{last}$ | $AUC_{INF}$ |
| | 1.003 (0.9292, 1.082) | 0.9991 (0.9269, 1.077) | 0.9971 (0.9252, 1.075) |
| **Free Paclitaxel HBT-** | BE | | |

| | | | |
|---|---|---|---|
| **001/ABRAXANE Least Squares Geometric Mean Raio (90% Confidence Intervals)** | $C_{max}$ | $AUC_{last}$ | $AUC_{INF}$ |
| | 1.032 (0.9493, 1.123) | 1.045 (0.9580, 1.144) | 1.061 (0.9682, 1.164) |

## 3.2 Clinical Pharmacology Review Questions

### *3.2.1 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes.

### *3.2.2 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?*

The percentage of dose changes related to the recommended dose of alternative dosing regimen and management strategy are expected to be the same for ABRAXANE. Refer to ABRAXANE submission under NDA 21660.

### *3.2.3 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?*

Drug-drug interaction studies have not been performed with HBT-001. The drug interactions with HBT-001 are expected to be the same for ABRAXANE. Refer to ABRAXANE submission under NDA 21660.

### *3.2.4 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?*

The to-be-marketed formulation is the same as the clinical trial formulation.

# 4. APPENDICES

## 4.1 Summary of Bioanalytical Method Validation and Performance

**Were relevant metabolite and biomarker concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

Yes, Total (albumin-bound and unbound) and free plasma concentrations of paclitaxel were measured in the clinical pharmacology and biopharmaceutics studies in this submission.

**For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The total and free concentration of paclitaxel in plasma was measured in the clinical trials and was appropriate.

**What bioanalytical methods are used to assess concentrations?**

Free paclitaxel plasma samples were analyzed according to (b) (4) Method LCMSC 637.3 V 2 Project RIMW2, entitled "Quantitation of Unbound Paclitaxel in Human Plasma Ultrafiltrate via HPLC with MS/MS Detection.". The calibration range was 1 ng/mL (LLOQ) to 1000 ng/mL (ULOQ) with 8 calibration standards. Each calibration curve was calculated using a linear (1/concentration$^2$ weighted) least-squares regression algorithm.

Total (albumin-bound and unbound) paclitaxel plasma samples were analyzed according to (b) (4) Method LCMSC 637.1 Project BWZ2, entitled "Quantitation of Unbound Paclitaxel in Human Plasma Ultrafiltrate via HPLC with MS/MS Detection.". The calibration range was 10 ng/mL (LLOQ) to 10,000 ng/mL (ULOQ) with 8 calibration standards. Each calibration curve was calculated using a linear (1/concentration$^2$ weighted) least-squares regression algorithm.

The ability to analyze samples with insufficient volume for a full aliquot was validated by analyzing six replicate QCs, containing 320 ng/mL paclitaxel, as 2.5-fold dilutions in Runs 1BWZ2-A. These samples had an unacceptable positive bias (16.1%). These samples had been prepared using a repeater pipette. The samples were prepared using an adjustable pipette and were analyzed in Run 6BWZ2-A and were acceptable. The ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate QCs, containing 20000 ng/mL paclitaxel, as ten-fold dilutions in Run 1BWZ2-A. The intraassay quality control data for the diluted QC pools met the performance criteria specified in the method validation plan and applicable (b) (4) SOPs.

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