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SUMMARY

This was a comprehensive foreign surveillance inspection of a clinical investigator, Eduardo Patricio Yáñez Ruiz, MD. A previous inspection of Dr. Yáñez occurred on 07/11/2022-07/15/2022 and was classified as NAI. This inspection was pre-announced and conducted by the Office of Bioresearch Monitoring Inspectorate (OBMI) in relation to BLA 7(b) (4) and BLA (b) (4). It was Prescription Drug User Fee Act (PDUFA) funded, requested by the Office of Scientific Investigations in the Center for Drug Evaluation and Research. The inspection was conducted in accordance with Compliance Program 7348.811, Clinical Investigators and Sponsor-Investigators, and is associated with eNSpect OP ID 336675.

The inspection covered two clinical trials under the following protocols: Study (b) (4) (b) (4): “(b) (4) ”, and Study (b) (4) ((b) (4)): “(b) (4) . The sponsor for both studies was (b) (4) The site screened 13 subjects and enrolled eight in (b) (4), and screened 18 subjects and enrolled 16 in (b) (4). Blinding did not occur in either of these studies.

Discussion items during the previous inspection were late study visits and late sampling per the protocol. A Form FDA 483, Inspectional Observations, was issued to Dr. Eduardo Yáñez, Clinical Investigator, at the close of the inspection for enrolling subjects that did not meet all eligibility criteria in two studies. There were three discussion items: tracking of protocol deviations, legibility of written records, and Informed Consent Form use. No samples were collected, and no refusals were encountered.

ADMINISTRATIVE DATA

Inspected firm:	Eduardo Patricio Yáñez Ruiz, MD
Location:	Hochstetter 298 Temuco, Araucanía, 4800827, Chile
Phone:	+56 9 7431 6500

FAX:	N/A
Mailing address:	Hochstetter 298 Temuco, Araucanía, 4800827, Chile
Email address:	eyanez@jameslind.cl
Dates of inspection:	01/12/2026-01/16/2026, 01/19/2026-01/22/2026
Days in the facility:	9
Participants:	**Gavin W. Pierce, Investigator**

Non-FDA Participants: None

At the beginning of the inspection on 01/12/2026, I, Gavin W. Pierce, presented my credentials to Dr. Eduardo Patricio Yáñez Ruiz at the opening meeting. The following other attendees were present: Dr. Patricio Yáñez, Ms. (b) (6), Ms. (b) (6), Ms. (b) (6), Ms. Claudia Soto, and Mr. (b) (6). The inspection was conducted with the guidance provided in the Inspection Assignment Memorandums (**Attachment 4 & Attachment 5**). For brevity, Dr. Yáñez will refer to Dr. Eduardo Yáñez, Clinical Investigator, in this report, except where Dr. Patricio Yáñez is specified.

Ms. Soto and Ms. (b) (6) were the primary contacts throughout this inspection. Dr. Yáñez, Ms. Camus, Ms. (b) (6), Mr. (b) (6), and Mr. (b) (6) were regularly available for discussions throughout the inspection, as well as Ms. Bárbara Camus during the second week.

As during the previous inspection, copies of unredacted subject records were not able to be collected due to Chilean Law. Copies of the applicable regulations were provided: Resolución 5174 EXENTA (**Exhibit 1, Pages 1-18; see Pages 13-14**), and Ley 20584 (**Exhibit 1, Pages 19-37**). As necessary, the firm provided redacted copies of subject records that removed identifying information.

The FMD-145 copy of this report and FDA correspondence should be directed to Dr. Eduardo Yáñez at eyanez@jameslind.cl, and the mailing address Hochstetter 298 Temuco, Araucanía, 4800827, Chile.

HISTORY

Dr. Yáñez continues to serve as Clinical Investigator for clinical trials that are regulated by FDA at James Lind Centro de Investigación del Cáncer. A list of the trials that he has served as CI on over the past five years was collected (**Exhibit 2**). An organizational chart of the study team was provided

(**Exhibit 3**). Office hours are (b) (4), (b) (4), and (b) (4) (b) (4)

The sponsor for this trial was (b) (4) and the Contract Research Organization (CRO) was (b) (4) The study team completed a questionnaire assessing site eligibility for (b) (4) and (b) (4) before being selected as a study site. Prospective subjects were referred through physician and committee referrals, and though either prospective subjects or their friends or relatives contacting the James Lind Center in search of research trials.

There are currently 52 active clinical trials at the research institution, four of which are actively recruiting. The study teams for (b) (4) and (b) (4) overlap and are comprised primarily of staff from the James Lind Centro de Investigación del Cáncer, in addition to select other employees from Clínica Alemana Temuco.

INTERSTATE (I.S.) COMMERCE

Dr. Yáñez participated in clinical research regulated by FDA and was not involved in the distribution or marketing of regulated products.

JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

The clinical trials covered during this inspection were submitted in support of BLA (b) (4) and BLA (b) (4) and are thus under the jurisdiction of FDA.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Eduardo Patricio Yáñez Ruiz, Clinical Investigator: Dr. Yáñez has been a Clinical Investigator at James Lind Centro de Investigación del Cáncer for 22 years. His responsibilities in these studies include eligibility assessments, consenting, checking on patients' conditions throughout their participation, assessing medical history, reviewing records, and study oversight including training of study staff. He spends 100% of his time on research.

Bárbara Camus, Director: Ms. Camus is the lead director for both studies as well as the supervisor for the Regulatory Affairs Department. Ms. Camus was unavailable during the first week of the inspection. She actively participated in the remainder of the inspection, starting on 01/19/2026.

(b) (6), **Pharmacy Supervisor:** Ms. (b) (6) has been with the institution for three years. Her responsibilities include overseeing the investigational pharmacy, including receipt, storage, disposition, documentation, and quality controls of investigational products and pharmaceuticals used in the course of research at the institution.

(b) (6), **Study Coordinator:** Ms. (b) (6) is the primary study coordinator for both ASCENT-03 and ASCENT-04. She has been with the Center for three years.

Claudia Soto, Study Director: Ms. Soto is the subdirector of both (b) (4) and (b) (4) and reports to Ms. Camus. Additionally, she is a study coordinator supervisor. She began working at the Center in 2021.

(b) (6), **Data Entry Supervisor:** Mr. (b) (6) oversees data entry for (b) (4) and (b) (4). He provided information regarding data systems and audit trails during the inspection.

(b) (6), **Regulatory Staff:** Mr. (b) (6) has been with the institution since 2022. He works in the Regulatory Affairs Department and provided information relating to regulatory matters in Ms. Camus' absence.

(b) (6), **Pharmacist, Oncologic Preparation Unit (Clínica Alemana Temuco):** Dr. (b) (6) oversees receipt and preparation of the investigational product (IP) for administration at Clínica Alemana Temuco. He provided information regarding this process and a tour of where the IP was prepared on 01/15/2026.

(b) (6) **Registered Nurse (Clínica Alemana Temuco):** Ms. (b) (6) is one of the nurses who administers the IP to subjects for both (b) (4) and (b) (4). She explained the administration process and monitoring of subjects' condition on 01/15/2026.

CLINICAL SITE TRAINING

I reviewed documentation of training for Dr. Yáñez and other study staff. There were Site Initiation Visits (SIVs) on 01/10/2023 for (b) (4) and on 01/27/2023 for (b) (4)4. These SIVs were conducted jointly by the sponsor and CRO and included a range of training materials for study staff. Trainings are recorded in on logs and stored in regulatory binders.

Meetings for both studies are generally conducted ad hoc in an informal manner. There is an additional formal meeting monthly at the Research Center that covers all active research studies, including (b) (4) and (b) (4). I reviewed documents for the qualification of investigators

and training records. Renewal histories of medical licenses were not entirely available for review. Medical license renewals for the physicians on the study all had an expiration date of 12/31/2025 during my review. Dr. Yáñez explained that in Chile, renewal of medical certifications is not mandatory following initial certification, and that there was currently a national change in the documentation process which was causing delays in getting license date renewals. Dr. Yáñez began practicing medicine before the initial certification process in Chile went into effect; however, he has since completed subsequent medical license renewals. I did not observe deficiencies with respect to certifications and educational qualifications or to documentation of training activities.

AUTHORITY AND ADMINISTRATION

Study visits occurred at Hochstetter 298 (James Lind Research Center) and at Clinica Alemana Temuco, 645 Senador Estébanez Temuco, Araucanía, Chile. Preparation of and administration of the treatments occurred at Clinica Alemana Temuco, while remaining study activities occurred at James Lind Research Center.

The Form 1572s, Statements of Investigators, can be found in **Exhibits 4-5**. The site used Delegation of Authority (DOA) logs to delineate responsibilities for each of the staff members involved in the study (**Exhibits 6-7**). The site maintained subject identification code lists, however, these were not collected due to Chilean regulations regarding Protected Health Information and Personally Identifiable Information in the research context (**Exhibit 1**). Other pre-screening and screening logs can be found in **Exhibits 8 & 9**.

Pre-Screening was utilized for both studies as a way to parse out potential eligibility between the two; a pre-screening log can be found in **Exhibit 8**. Following pre-screening, there were 13 subjects who underwent screening for (b) (4), and eight were enrolled (**Exhibit 9**). For (b) (4) following pre-screening, there were 18 subjects who underwent screening, and 16 were enrolled.

Due to time constraints, the subject record review focused on documentation of informed consent, screening, concomitant medications, adverse events (AEs) and serious adverse events (SAEs), protocol deviations (PDs), subject discontinuations, and the primary efficacy endpoints. I reviewed ICFs, screening documents, concomitant medications, and primary efficacy endpoint data for all Subjects in (b) (4) and Subjects (b) (6), (b) (6) and (b) (6) in (b) (4) in addition to spot checking adverse events (see **Discussion Item 2**), study visit records, and IP administration records. Serious Adverse Events and protocol deviations were reviewed for all randomized subjects on both studies.

CLINICAL TRIALS .GOV REQUIREMENT

Both clinical studies were registered on https://ClinicalTrials.gov, ID# (b) (4) AND ID# (b) (4). I did not find any discrepancies regarding the registration of these clinical trials.

PROTOCOL

The primary efficacy endpoint for (b) (4) was (b) (4) scores by Blinded Independent Central Review (BICR) between (b) (4) and (b) (4) The primary efficacy endpoint for (b) (4) was similar, incorporating (b) (4) into both groups; (b) (4) as assessed by BICR between (b) (4) with (b) (4) and (b) (4) with (b) (4). Images were assessed both locally and by the BICR. I compared the assignment data line listings (DLL) primary efficacy endpoint data against the site's assessments of disease progression, and the BICR confirmation of disease progression reports the site received. I found the following data discrepancies:

- (b) (4)
  - (b) (6)
    - DLL state 10/23/2023 as date of disease progression by BICR; BICR report states disease progression from 03/14/2024 scan (**Exhibit 10, Pages 1-4**)
  - (b) (6)
    - DLL state 06/12/2024 as date of disease progression by BICR; BICR report states disease progression from 09/04/2024 scan (**Exhibit 10, Pages 5-8**)
  - (b) (6)
    - DLL state 07/10/2024 as date of disease progression by BICR; BICR report states disease progression from 10/03/2024 scan (**Exhibit 10, Pages 9-12**)
- (b) (4)
  - (b) (6)
    - DLL state 07/20/2023 as date of disease progression by INV; site records do not indicate disease progression on this date (**Exhibit 11, Pages 1-4**)
  - (b) (6)
    - DLL state disease progression on 01/05/2024 as assessed by BICR, however, the site did not receive a report of progressive disease for this subject from BICR (**Exhibit 11, Pages 5-7**)
  - (b) (6)
    - DLL state disease progression on 12/13/2023 as assessed by BICR; however, the BICR report states disease progression from 01/30/2024-01/31/2024 scans (**Exhibit 11, Pages 8-13**)
  - (b) (6)

- DLL state disease progression on 12/04/2024 as assessed by BICR; however, the BICR report states disease progression from 02/12/2025 scan (**Exhibit 11, Pages 14-17**)

- (b) (6)
  - DLL state disease progression on 01/28/2025 as assessed by BICR; however, the BICR report states disease progression from 07/08/2025 scan (**Exhibit 11, Pages 18-21**)

Review of the site's CRF entries and audit trails of (b) (4) data, in addition to discussions with the study team, did not reveal any apparent explanations for the discrepancies listed above.

There were four versions of the protocol, in addition to two administrative amendments approved by the EC in Spanish and English for (b) (4); and two versions of the protocol and one administrative amendment approved for (b) (4)

Protocol Deviations

Protocol Deviations were reported to the sponsor by study monitors and not by the site. The site kept monitoring follow up letters that included documentation of discovered protocol deviations, but did not collate these data into logs prior to this inspection. When I asked the site how protocol deviations were tracked and reported, there was some confusion from the study team. See **Discussion Item 1** for further information on protocol deviations.

ETHICS COMMITTEE

The Ethics Committee (EC) used for both studies was (b) (4). The current mailing address for the ethics committee is (b) (4), and the current president is Dr. (b) (4) (b) (4). Lists of pertinent EC approval dates for both studies can be found below:

(b) (4)		
Document	**Approval/Effective Date**	**Exhibit Number**
Initial approval, including: Investigator (Dr. Yáñez) Protocol Amendment 1 ICF Main Version 2.1.1 ICF Cross Treatment Version 1.2.1 ICF Pregnancy Monitoring Version 1.1.1	08/16/2022	**Exhibit 12, Pages 1-3**

ICF Prescreening Version 1.2.1		
ICF Main Version 3.1.2 ICF Cross Treatment Version 2.1.2	12/06/2022	**Exhibit 12, Pages 4-5**
ICF Biopsy Sub-study Version 1.1.1 ICF Pregnancy Monitoring Version 1.1.1	01/10/2023	**Exhibit 12, Pages 6-7**
ICF Genomic Sub-study Version 1.1.1	01/17/2023	**Exhibit 12, Pages 8-9**
Protocol Administrative Amendment 1	08/08/2023	**Exhibit 12, Pages 10-11**
Continuing Review	08/29/2023	**Exhibit 12, Page 12**
Protocol Administrative Amendment 2	01/23/2024	**Exhibit 12, Pages 13-14**
Protocol Amendment 2 ICF Prescreening Version 2.1.1 ICF Main Version 4.1.1	03/12/2024	**Exhibit 12, Pages 15-17**
Protocol Amendment 3	06/25/2024	**Exhibit 12, Pages 18-19**
Continuing Review	07/23/2024	**Exhibit 12, Page 20**
Protocol Amendment 4 ICF Main Version 6.1.1 ICF Cross Treatment Version 3.1.1	03/04/2025	**Exhibit 12, Pages 21-22**
Continuing Review	07/29/2025	**Exhibit 12, Pages 23**

(b) (4)		
Document	**Approval/Effective Date**	**Exhibit Number**
Initial approval, including: Investigator (Dr. Yáñez) Protocol Amendment 1 ICF Prescreening Version 1.1.2 ICF Main Version 2.1.2 ICF Cross Treatment Version 1.1.2 ICF Genomic Sub-study Version 1.1.2 ICF Biopsy Sub-study Version 1.1.2 ICF Pregnancy Monitoring Version 1.2.2	01/17/2023	**Exhibit 13, Pages 1-3**
ICF Main Version 4.1.3 ICF Cross Treatment Version 3.1.3 ICF Biopsy Sub-study Version 1.2.3 ICF Genomic Sub-study Version 1.2.3	04/04/2023	**Exhibit 13, Pages 4-6**
Protocol Administrative Amendment 3	11/07/2023	**Exhibit 13, Pages 7-8**
Continuing Review	01/30/2024	**Exhibit 13, Page 9**
Protocol Amendment 2	03/05/2024	**Exhibit 13, Pages 10-11**

ICF Prescreening Version 2.1.1 ICF Main Version 6.1.1		
Continuing Review	12/19/2024	**Exhibit 13, Page 12**
ICF Main Version 7.1.1 ICF Cross Treatment	03/04/2025	**Exhibit 13, Pages 13-14**

In both studies, there were Continuing Review periods that exceeded one year. In (b) (4), the periods 08/16/2022-08/29/2023 and 07/23/2024-07/29/2025, and in (b) (4) the period of 01/17/2023-01/30/2024.

There were some discrepancies regarding completion of Informed Consent Forms; see **Discussion Item 3**.

The CRO requested that the site did not implement new ICF and Protocol versions until they had been both initially approved by the EC and subsequently cleared for implementation by the CRO. Consequently, there were some delays between EC approval of ICFs and Protocol versions, and their implementation. Study staff provided documentation of these exchanges and approvals.

SUBJECT RECORDS

The majority of study records were stored physically, including subjects' medical records. Case report forms were stored electronically. As medical records were generated and stored as paper documents, the study team did not generally have access to subjects' medical records at external institutions for medical history review and for monitoring of adverse events throughout the study. Medical records from external institutions were only obtained when a subject brought them as physical copies for the study team to review. Concomitant medications were monitored throughout the trial by asking subjects during each visit regarding new, stopped, and continued medications. I verified Serious Adverse Events in the source documents against the data line listings and spot-checked Adverse Events (see **Discussion Item 2**). The monitors were responsible for discovering and reporting adverse events.

Informed Consent Documentation and Process

I reviewed the Informed Consent Forms for both studies and determined they complied with the required elements in 21 CFR 50.25. The requisite ClinicalTrials.gov statement was included in each EC-approved ICF version. The ICFs used in this study were paper documents with wet signatures. Only Spanish ICFs were utilized at this site, which was the preferred language for the included subjects. English versions were also available for review. Signed Informed Consent Forms were not

collected due to Chilean legal restrictions (**Exhibit 1**). The first subject to sign the main ICF for (b) (4) was Subject (b) (6) on 04/18/2023, and Subject (b) (6) on 02/21/2023 for (b) (4). Both studies are still active but not open to enrollment.

Source Records and Case Report Forms

Source documents for subjects enrolled in the clinical trial at this site include the following as applicable: signed ICFs, eligibility assessments, medical history, laboratory results, ECGs, imaging results, and IP accountability records. I did not observe significant deviations regarding records being attributable, contemporaneous, original, complete, consistent, enduring, and available. There were various discrepancies regarding legibility of records (see **Discussion Item 2**) and accuracy (see **Observation 1**).

Electronic Case Report Files were transcribed from source documents into iMedidata. The site was allotted three working days from a subject's visit to transcribe the data into the eCRF. I reviewed select CRF entries and audit trails for primary efficacy endpoints and other data and did not encounter discrepancies with source documents.

OTHER STUDY RECORDS

Administrative study records and communications with the sponsor, monitor, and EC were reviewed, and no discrepancies were found.

ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

The EDC used for this study was iMedidata. Various eCRF captures were provided for comparison with source records and DLL; I did not find discrepancies with reviewed eCRF entries. Clario was used for image storage, interpretation, and transmission. Some documents, including archived protocol versions, were stored electronically. Remaining study records and subject records were stored as physical documents.

INTERVIEWS OF SUBJECTS/PERSONNEL

I did not interview any study subjects during this inspection.

FINANCIAL DISCLOSURE

I reviewed financial disclosure forms for Dr. Yáñez and the other physicians that were part of the study teams. No financial conflicts of interest were reported.

CONTROL OF INVESTIGATIONAL PRODUCT

The site had investigational product on site during the inspection. I inspected the areas where the investigation product was stored, prepared, and administered. The study drug and other drugs used as part of the protocol were received and stored at the James Lind Research Center, while the IP and other drugs are brought to Clinica Alemana for administration to subjects. Once the IP is brought to Clinica Alemana, it does not undergo any further temperature control. Time from IP arrival to subject administration is typically about 30 to 45 minutes. The IP is prepared in a clean room with a negative pressure system. In addition to the drugs required for the control group, prophylactic drugs were supplied by the James Lind Center to Clinica Alemana. Subjects are observed throughout study drug administration and for 30 minutes following.

The pharmacy at James Lind Research Center is used for both approved and study drugs. The ambient temperature and relative humidity are monitored, and the temperature is maintained between 15 and 25°C. Coolers each have two thermometers – a primary and a backup. The thermometers display, in addition to the current reading, the maximum and minimum temperatures since the thermometer was last reset. Additionally, the temperature data is recorded electronically and reviewed periodically. See **VOLUNTARY CORRECTIONS** for additional information regarding the firm's review of storage conditions. I observed storage of (b) (4) for both studies, in addition to partitioned storage of quarantined and expired drugs. I spot-reviewed the site's accountability and administration logs and shipping records for the investigational product and did not encounter deficiencies.

RECORDS CUSTODY AND RETENTION

The Investigator's Site Files and subject records are stored on the second floor of Hochstetter 298. There is an SOP in place for transfer of study records to an offsite storage location following the completion of a trial.

REPORTS TO SPONSOR

I observed the site submitted required reports in accordance with the protocols for the two studies and FDA regulations, save for protocol deviations (see **Discussion Item 1**). I did encounter discrepancies between source documents and the data line listings with respect to disease progression based on (b) (4) scores analyzed by BICR (see **PROTOCOL; Exhibits 10 & 11**).

MONITORING

Monitoring activities were primarily performed by (b) (4) There were 17 IMVs for (b) (4) and 23 IMVs for (b) (4). Both studies also had frequent Site Management Contact Visits (SMCs) conducted virtually via Microsoft Teams. The monitors were effectively responsible for reporting of protocol deviations to the sponsor for both studies, however, there were not any documents available that outlined this protocol.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on Form FDA 483

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator.

Specifically, in each of two studies, (b) (4) and (b) (4) subjects were enrolled despite ineligibility due to not meeting all inclusion criteria or by meeting an exclusion criterion. Due to not meeting all of the screening criteria, the following subjects were not eligible to be enrolled in their respective studies as follows:

Study	Subject Number	Screening Criteria #	Screening Criteria	Finding
(b) (4)	(b) (6)	Exclusion 13	Patients with active Hepatitis B or Hepatitis C	The subject was not tested for Hepatitis C at screening.
		Inclusion 2ai	"***Patients who received taxane, gemcitabine, or other platinum agents in the (neo)adjuvant chemotherapy setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo) adjuvant chemotherapy administration, whichever occurred last) and first	The subject received their last dose of docetaxel on 05/30/2023, and was diagnosed with metastatic triple-negative breast cancer on (b) (6).

(b) (4)	(b) (6)		documented local or distant disease recurrence."	
		Inclusion 8	Adequate hepatic function, including serum albumin > 3 g/dL.	The subject's serum albumin at screening was 2.8 g/dL.
		Exclusion 9	"Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate (with the exception of those treated with chemotherapy) provided they have stable CNS disease imaging assessments; one performed during screening) for at least 4 weeks prior to enrollment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases***"	The subject last received radiotherapy for brain lesions on 10/31/2023. The subject was screened on 11/06/2023, prior to a post-treatment MRI of the brain on 11/07/2023. The subject was then randomized on 11/15/2023.
		Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	The subject last received paclitaxel on 04/04/2023, and disease progression was noted 10/14/2023.
		Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the	The subject received their last dose of paclitaxel on 12/12/2023,

			(neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	and disease progression was noted on 07/15/2024.
(b) (4)	(b) (6)	Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	The subject received their last dose of paclitaxel on 12/01/2023, and disease progression was noted on 06/15/2024.

Documentation of and relating to the screening deficiencies listed above can be found as follows:

- (b) (6)
  - Screening documents: **Exhibit 14, Pages 1-31; see Pages 1, 30-31**
  - Letter notifying Ethics Committee: **Exhibit 14, Page 32**
  - Email communications: **Exhibit 14, Pages 33-42**
- (b) (6)
  - Screening documents: **Exhibit 15, Pages 1-21; see Pages 5-6, 14, 21**
- (b) (6)
  - Screening documents: **Exhibit 16, Pages 1-24; see Pages 10, 13, 17**
  - Letter notifying Ethics Committee: **Exhibit 16, Page 25**

  - Email communications: **Exhibit 16, Pages 25-28**
- (b) (6)
  - Screening documents: **Exhibit 17, Pages 1-38; see Page 29**
  - Letter notifying Ethics Committee: **Exhibit 17, Pages 39-40**
  - Email communications: **Exhibit 17, Pages 41-45**
- (b) (6)
  - Screening documents: **Exhibit 18, Pages 1-20; see Pages 7-8, 15**
  - Letter notifying Ethics Committee: **Exhibit 18, Pages 21-23**
  - Email communications: **Exhibit 18, Pages 24-36**
- (b) (6)
  - Screening documents: **Exhibit 19, Pages 1-25; see Pages 1, 4, 10, 21**
  - Letter notifying Ethics Committee: **Exhibit 19, Pages 26-28**
  - Email communications: **Exhibit 19, Pages 37-41**
- (b) (6)
  - Screening documents: **Exhibit 20, Pages 1-24; see Pages 1, 7-8, 20**
  - Letter notifying Ethics Committee: **Exhibit 20, Pages 25-27**
  - Email communications: **Exhibit 20, Pages 28-40**

Prior to this inspection, the inclusions of subjects who did not meet all eligibility criteria had been discovered by study monitors and reported to the Ethics Committee. As a corrective measure, trainings had been issued to address the subject screening process.

During the inspection, Dr. Yáñez expressed his understanding of the finding and explained that he and the study team had misunderstood the protocol with respect to specific screening criteria, leading to the repeated protocol deviations. He explained that each of these subject cases was discussed with the sponsor, and it was determined these subjects were not at significantly increased risks, or likely to experience significantly reduced potential efficacy of the investigational treatments by participating in their respective studies. I discussed the importance of having measures in place to ensure that protocol deviations, including screening, are identified as early as possible so they aren't replicated; and the challenges that can arise with largely relying upon monitors for identification of protocol deviations. Dr. Yáñez and the study team indicated they would be exploring further options to ensure there are not eligibility issues with study subjects moving forward.

REFUSALS

I did not encounter any refusals during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

At the close of the inspection, I issued a Form FDA 483, Inspectional Observations, to Dr. Eduardo Yáñez, Clinical Investigator. I informed him of the administrative, civil, and criminal actions available to the agency in response to findings of noncompliance with the regulations. I informed him that CDER, the center that issued the assignment, would make the final determinations regarding classification of the inspection and compliance with FDA regulations and the Federal Food, Drug, and Cosmetic Act. In addition to Dr. Yáñez, Ms. (b) (6), Mr. (b) (6), Ms. (b) (6), Ms. (b) (6), and Ms. (b) (6) were present at the closeout meeting, as well as Ms. (b) (6), Translator.

The items discussed at closeout, including **OBSERVATION 1** and the Discussion Items, had already been discussed with Dr. Yáñez and the study team throughout the inspection and preceding the final meeting. Consequently, Dr. Yáñez did not have new responses at the time of the closeout meeting. However, he iterated his intention to follow and comply with FDA regulations and indicated that he intended to respond to the Form FDA 483 via email with planned corrective actions within 15 business days.

1. There were not clear procedures for identifying, documenting, and reporting protocol deviations. While some protocol deviations were reported to the Ethics Committee, the site did not directly report protocol deviations to the sponsor and was uncertain if protocol deviations were being identified and reported through the monitor.

   When I requested to review protocol deviations, the site did not have a clear answer on how protocol deviations were reported but indicated that they were being handled by the monitor. During the inspection, the site assembled what they considered to be comprehensive lists of protocol deviations based on their review of records and communications for my review; these can be found in **Exhibit 22** for (b) (4) and **Exhibit 23** for (b) (4). Review of these lists found that while the PDs on the list were present in the Data Line Listings, these protocol deviation lists were not exhaustive. Of additional note is that the protocol deviation lists assembled by the firm during the inspection were inclusive of deviations through the time of the inspection, as opposed to the PDs in the DLLs which were up to the data cutoff dates of 04/02/2025 for (b) (4) and 03/03/2025 for (b) (4).

2. There were significant legibility issues of select handwritten records, to the extent that attempting to interpret these records was prohibitively time consuming. In my review of documents for both studies, I found that select patient records, and in particular, records relating to Adverse Events were often largely or entirely illegible without careful review and interpretation by the study team. In many of these instances, it took three or more individuals, including myself, the interpreter, and members of the study team to decrypt what was written.

These records were largely confined to those written by Dr. (b) (6).

When I discussed my concerns regarding legibility with the study team, Dr. Yáñez apologized and acknowledged that he and the study team shared my concerns with these records. He explained that they had addressed this issue with Dr. (b) (6), and eventually he was seperated from the study team, in part because of the insufficient legibility of his records that resulted in record quality concerns. To aid the inspection and permit review of these records, the study team transcribed what they believed was written in the concomitant medication records. I reviewed these records and conducted spot comparisons with Dr. (b) (6)' written records to confirm they were feasible interpretations of the writing.

3. There were multiple discrepancies regarding the use of Informed Consent Forms. There were instances where the most recent approved version of the ICF was not used, and instances of not all form fields being completed. One of the Main ICF documents signed by Subject (b) (6) was missing the subject signature date. One of the ICF documents signed was not the most current approved version for Subjects (b) (6), and (b) (6)

   I stressed the importance of accurate and complete documentation of informed consent to Dr. Yáñez and the study team. They agreed with the importance of ICF documentation, and provided records of training to address these deficiencies.

ADDITIONAL INFORMATION

No additional information was collected during the inspection.

SAMPLES COLLECTED

I did not collect any samples.

VOLUNTARY CORRECTIONS

During my review of the site's storage of investigational products, I observed that there were not complete records indicating that storage conditions had been reviewed over time, including for products such as (b) (4) that require refrigeration for stability. The firm's procedures included continuous data logging, but the data were not associated with a review signature. Additionally, there were twice daily checks of temperature conditions in the investigational pharmacy, but only the temperatures in that instant were recorded. Dr. (b) (6) explained that the thermometers recorded the maximum and minimum temperatures since they were last checked and reset, but there was not a field on the form to indicate that temperatures were in range. I explained that while their procedure

inferred that temperatures were in range when checked, that this information was not explicitly outlined in their documentation.

Dr. (b) (6) generated an updated form with an additional data field to indicate that when temperatures were checked, the previous maximum and minimum temperatures were within range. The study team began using this form for the remainder of the inspection and provided a copy of this document to illustrate its implementation. Examples of the previous temperature log format can be found in **Exhibit 24, Pages 1 & 3**, and examples of the updated form having been implemented can be found in **Exhibit 24, Pages 2 & 4**.

EXHIBITS COLLECTED

EX 1 Applicable Chilean Regulations – 37 Pages
EX 2 Yáñez Studies – 4 Pages
EX 3 Org Chart – 9 Pages
EX 4 1572s (b) (4) – 32 Pages
EX 5 1572s (b) (4) – 37 Pages
EX 6 DOA Log (b) (4) 12 Pages
EX 7 DOA Log (b) (4) – 12 Pages
EX 8 Pre-Screen (b) (4) Log – 5 Pages
EX 9 Subject Enrollment Log (b) (4) – 1 Page
EX 10 Imaging Reports (b) (4) – 12 Pages
EX 11 Imaging Reports (b) (4) – 21 Pages
EX 12 Ethics Committee Letters (b) (4) – 23 Pages
EX 13 Ethics Committee Letters (b) (4) – 14 Pages
EX 14 (b) (6) Screening – 42 Pages
EX 15 Screening – 21 Pages
EX 16 Screening – 28 Pages
EX 17 Screening – 45 Pages
EX 18 Screening – 36 Pages
EX 19 Screening – 41 Pages
EX 20 Screening – 40 Pages
EX 21 Trainings Records Screening – 9 Pages
EX 22 Protocol Deviations (b) (4) – 1 Page
EX 23 Protocol Deviations (b) (4) – 3 Pages
EX 24 Pharmacy Temperature Monitoring Forms 4 Pages

ATTACHMENTS

ATT 1 Issued Form FDA 483 – 6 Pages
ATT 2 Issued Form FDA 483 Amendment 1 – 6 Pages
ATT 3 Issued Form FDA 483 Amendment 2 – 6 Pages
ATT 4 Inspection Assignment Memo (b) (4) 12 Pages
ATT 5 Inspection Assignment Memo 12 Pages

Gavin W. Pierce -S
Digitally signed by Gavin W. Pierce -S
Date: 2026.03.04 13:03:34 -08'00'

Investigator Gavin W. Pierce

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Avenue Building 51 Silver Spring, MD 20993 301-796-3150 Fax:(301)594-1204	1/12/2026-1/22/2026* FEI NUMBER 3022159116

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Eduardo Patricio Yanez Ruiz, MD, Medical Oncologist

FIRM NAME	STREET ADDRESS
Eduardo Patricio Yanez Ruiz, MD	Hochstetter 298
CITY, STATE, ZIP CODE, COUNTRY Temuco, Region de la Araucania, 4800827 Chile	TYPE ESTABLISHMENT INSPECTED Clinical Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator.

Specifically, in each of two studies, [redacted] (b) (4) and [redacted] (b) (4), subjects were enrolled despite ineligibility due to not meeting all inclusion criteria or by meeting an exclusion criterion. Due to not meeting all of the screening criteria, the following subjects were not eligible to be enrolled in their respective studies as follows:

Study	Subject Number	Screening Criteria #	Screening Criteria	Finding
[redacted] (b) (4)	[redacted] (b) (6)	Exclusion 13	Patients with active Hepatitis B or Hepatitis C	The subject was not tested for Hepatitis C at screening.
		Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant chemotherapy setting can be treated with the same class of chemotherapy	The subject received their last dose of docetaxel on 05/30/2023, and was diagnosed with metastatic triple-

AMENDMENT 2

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			(taxane or gemcitabine/carboplatin if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo) adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	negative breast cancer on 04/16/2024.
(b) (4)	(b) (6)	nclusion 8	Adequate hepatic function, including serum albumin > 3 g/dL.	The subject's serum albumin at screening was 2.8 g/dL.
		xclusion 9	"Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate (with the exception of those treated with	The subject last received radiotherapy for brain lesions on 10/31/2023. The subject was screened on 11/06/2023, prior to a post-treatment MRI of the brain on

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			chemotherapy) provided they have stable CNS disease imaging assessments; one performed during screening) for at least 4 weeks prior to enrollment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases***"	11/07/2023. The subject was then randomized on 11/15/2023.
(b) (4)	(b) (6)	Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever	The subject last received paclitaxel on 04/04/2023, and disease progression was noted 10/14/2023.

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			occurred last) and first documented local or distant disease recurrence."	
(b) (4)	(b) (6)	Inclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	The subject received their last dose of paclitaxel on 12/12/2023, and disease progression was noted on 07/15/2024.
		nclusion 2ai	"***Patients who received taxane, gemcitabine, or platinum agents in the	The subject received their last dose of paclitaxel on

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			(neo)adjuvant setting can be treated with the same class of chemotherapy (taxane or gemcitabine/carboplatin) if ≥ 12 months have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last (neo)adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence."	12/01/2023, and disease progression was noted on 06/15/2024.

***DATES OF INSPECTION**

1/12/2026(Mon), 1/13/2026(Tue), 1/14/2026(Wed), 1/15/2026(Thu), 1/16/2026(Fri), 1/19/2026(Mon), 1/20/2026(Tue), 1/21/2026(Wed), 1/22/2026(Thu)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."