PROSPERA
BIOTECH

STUDY TO EVALUATE THE DEGREE OF SKIN SATISFACTION WITH THE COSMETIC CREAMS FOR SENSITIVE SKIN PB-011 AND PB-012 IN ONCOLOGY PATIENTS WITH PALMOPLANTAR POLYNEUROPATHY SECONDARY TO TREATMENT WITH CHEMOTHERAPY OR CHEMOTHERAPEUTIC AGENTS FUSED TO MONOCLONAL ANTIBODIES (IMMUNOCYTOSTATIC).

Study code: 20PB-02

Sponsor: Prospera Biotech S.L.

Study Protocol Compliance Form

Ms. Marta García Escolano as Sponsor, has examined the Protocol nº 20PB-02, version: 1.5, Date: 28/07/2022, entitled:

'STUDY FOR THE EVALUATION OF THE DEGREE OF SKIN SATISFACTION OF THE COSMETIC CREAMS FOR SENSITIVE SKIN PB-011 AND PB-012 IN ONCOLOGICAL PATIENTS AFFECTED BY PALMOPLANTAR POLYNEUROPATHY SECONDARY TO TREATMENT WITH CHEMOTHERAPY OR CHEMOTHERAPEUTIC AGENTS FUSED TO MONOCLONAL ANTIBODIES (IMMUNOCYTOSTATIC)'.

And agrees to conduct the study according to the guidelines of this protocol and to conform to its requirements, subject to its approved ethical and safety considerations.

In Elche, 28th July 2022,

Signed: Dr. Marta García Escolano

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1. SUMMARY

A pilot controlled clinical study is proposed to evaluate and compare the degree of satisfaction and skin comfort with cosmetic creams PB-011 and PB-012 in oncology patients who have developed palmar and plantar peripheral poly-neuropathy due to treatment with chemotherapy or chemotherapeutic agents fused to monoclonal antibodies (immunocytostatic). Both products are cosmetic creams derived from the line Nocisens (for the care of sensitive skin with atopic tendency). The hypothesis to be tested is that care with PB-011 or PB-012 for sensitive skin associated with palmar and plantar peripheral poly-neuropathy in oncology patients will increase their degree of satisfaction and skin comfort. A parallel, randomised, double-blind, masked, double-blind study is proposed in patients who are about to start chemotherapeutic treatment. The study involves two populations: (i) the population where PB-011 cream will be tested; and, (ii) the population that will test PB-012 cream. The duration of the project will be 12 months, and participants will have to apply the cream on their hands once a day during the period of chemotherapy treatment. A sample size of 60 volunteers per population has been estimated to ensure statistical significance. As a relevant qualitative variable for patients who have developed neuropathy, the degree of satisfaction and skin comfort will be assessed by means of a questionnaire.

2. GENERAL INFORMATION

2.1. Study identification

Study code: 20PB-02

Study title: 'Study for the evaluation of the degree of skin satisfaction of the cosmetic creams for sensitive skin PB-011 and PB-012 in oncology patients with palmoplantar polyneuropathy secondary to treatment with chemotherapy or chemotherapeutic agents fused to monoclonal antibodies (immunocytostatic)'.

2.2. Type of study

Multicentre, controlled, parallel, randomised, double-blind, masked, double-blind, randomised study.

2.3. Description of the products under study

Product: Cosmetic creams with Ref. PB-011 and PB-012

Trade name: Nocisens. The formulation with the best acceptance in the study population will be marketed under the name Oncapsisens.

Commercial name: Prospera Biotech S.L

Code and INCI:

- PB-011: Capric Triglyceride, Glyceryl Behenate, Glyceryl Stearate, Hydrogenated Castor Oil, Diethylene Glycol Monoethyl Ether, Tocopherol, Hydroxymethoxyiodobenzyl Glycolamide Perlargonate.
- PB-012: Capric Triglyceride, Glyceryl Behenate, Glyceryl Stearate, Hydrogenated Castor Oil, Diethylene Glycol Monoethyl Ether, Tocopherol.

2.4. Data relating to the sponsor

Dr. Marta García Escolano,

Chief Executive Officer, Prospera Biotech S.L.

Quorum III Building - Miguel Hernández University Science Park

Av. de la Universidad s/n

03202 Elche.

2.5. Identification of the investigators responsible for monitoring

- Dr. Pedro Zapater Hernández.

Department of Pharmacology, Hospital General Universitario de Alicante.

Email: pzapater@goumh.umh.es

- Dra. Asia Fernández Carvajal.

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- Dra. Clotilde Ferrándiz Huertas,

Chief Scientific Officer Prospera Biotech,

Email: cferrandiz@prosperabiotech.com

2.6. Research data

Principal Investigator

- Dr...

  Deparment…

Hospital…

Email:…

Task: recruitment, follow-up and control of patients. Completion of data collection notebook. Final analysis and publication of the results.

- Co-researchers

Name:…

Department: …

Email: …

Task: follow-up and control of patients. Completion of data collection notebook

2.7. Expected duration of the study

The overall duration of the study is expected to be 12 months from the start of recruitment of the populations until the last follow-up control and analysis of the data generated.

The intervention (application of the cosmetic cream) will take place from the beginning to the end of the chemotherapy treatment, with 1 daily application of the product (PB-011 or PB-012) on the hands. If sensory discomfort or, in the worst case, peripheral neuropathy develops during the period of chemotherapy or immunocytostatic treatment, the application shall be increased to twice daily on the affected areas (usually hands and feet). In case of lack of efficacy of the product, the investigator in charge may withdraw the subject from the study after three months of application of the product.

3. INTRODUCCIÓN

The impact of cancer in the western world and the growing number of people affected each year1 means that new, increasingly effective and selective treatments are appearing relatively quickly. However, although these treatments are highly effective in killing tumour cells, they are not their only target. Molecules used in cancer treatments often affect healthy cells, causing side effects (nausea, diarrhoea, anaemia, immunosuppression, fatigue and hair loss). When antineoplastic therapies affect the sensory peripheral nervous system, they can cause peripheral polyneuropathy (NP or CIPN (Chemotherapy-Induced Peripheral Neuropathy)). The prevalence of this disease varies depending on the chemotherapy agent administered, affecting up to 80% of patients treated with taxanes (paclitaxel and/or docetaxel) or up to 95% of patients treated with oxyplatin2. People with PN experience sensory discomfort, mainly in the extremities (numbness, dryness, tingling, burning, stinging, allodynia or hyperalgesia)3 which, over time, can

lead to the interruption of cancer treatment, with the risks that this entails. This condition often persists after the end of cancer treatment, which greatly affects the quality of life of those who suffer from it, as it can be uncomfortable when working, playing sports, carrying out household chores and even when socialising. In addition, the uncomfortable sensations can disturb sleep, which has an impact on mood. In general, people with NP caused by cancer treatments feel a great dissatisfaction with their skin.

Currently, there is no effective treatment for NP, and when the symptomatology is severe and limits patients' daily life, some doctors recommend taking antidepressants, such as duloxetine, or discontinuing chemotherapy treatment4. Although a number of clinical trials aimed at finding an effective treatment for NP have been conducted in recent years, none of them have proven to be effective. Therefore, understanding the mechanisms governing the development of PN and its treatment is a huge challenge in oncology as it is one of the main causes of chemotherapy withdrawal.

The Institute for Research, Development and Innovation in Health Biotechnology of the Miguel Hernández University of Elche (IDIBE-UMH) has been studying the mechanisms that govern skin imbalances for many years. This knowledge has been transferred to Prospera Biotech, and has been used to develop a line of creams for sensitive skin (trade name Nocisens). The mixture of fatty acids, tocopherol and innovative cosmetic ingredients means that Nocisens has a dual action on the stratum corneum. On the one hand, it strengthens the skin's barrier function by preventing water loss, which helps to increase hydration and re-establish the skin's protective function and, on the other hand, it prevents the accumulation of reactive oxygen species in the cells, protecting the skin from their harmful effects. These two actions help Nocisens cosmetic cream to create a feeling of well-being and comfort for the skin.

However, in cosmetics, the degree of acceptance of a product is a key element for adherence to treatment. We have therefore developed two formulations derived from Nocicsens, PB-011 and PB-012, with slightly different texture, composition and properties in order to adapt them to the needs of the sensitive skin characteristic of palmo-plantar neuropathy mediated by chemotherapeutics.

Given that PN induced by treatments with chemotherapy or chemotherapeutic agents fused to monoclonal antibodies (immunocytostatic) is characterised by skin imbalances that affect the quality of life of the people who suffer from it, a parallel, randomised, double-blind, masked study is proposed in patients who are about to begin oncological treatment to compare the

degree of acceptance of PB-011 and PB-012 cosmetic creams in this population. The study involves two populations: (i) the population where PB-011 cream will be tested; and, (ii) the population that will test PB-012 cream. The duration of the project will be 12 months, and participants will have to apply the cream once a day on their hands during the period of chemotherapy treatment. A sample size of 60 volunteers per population has been estimated to ensure statistical significance. As a relevant variable for the patients, the degree of skin satisfaction will be assessed every fortnight by means of a questionnaire only in the case of discomfort in the hands and/or feet.

4. JUSTIFICATION AND STUDY OBJETCTIVES

The toxicity generated during chemotherapy treatments can usually produce skin discomfort or peripheral polyneuropathy. CIPN manifests itself above all in the extremities, mainly in the palmar and plantar regions, giving rise to uncomfortable sensations such as itching, numbness, tingling, pain or dryness, i.e. skin sensitivity. Currently, there is no specific treatment to combat this skin sensitivity and oncology specialists recommend keeping the skin hydrated through the use of cosmetic creams.

Taking into account that these sensations imply a deterioration in the quality of life of patients, our hypothesis is that cosmetic creams for sensitive skin with references PB011 and PB012 could improve comfort and the degree of satisfaction of cancer patients with CIPN. The reason for this hypothesis is that cosmetic creams contain ingredients that reinforce the barrier function of the epidermis and improve the hydration and appearance of the skin. The study has been designed to define which of the two creams produces greater satisfaction in patients.

5. TYPE OF STUDY AND DESIGN

5.1. Development phase

Multicenter, controlled, parallel, randomized, double-blind, masked study.

5.2. Randomization process

The assignment of cosmetic creams PB-011 or PB-012 to patients will be carried out by a simple randomization procedure, using random numbers.

5.3. Masking

To avoid bias, the study is proposed to be blind for patients and researchers and open to third parties (evaluators and those responsible for data analysis). To this end, a qualitative variable will be created, called product, of two degrees that will serve to mask the type of product used in each subject (PB-011/PB-012). The assignment of one product or another will be determined by the order of introduction in the study database. The definition of each degree of this qualitative variable will be in the possession of the main researcher and only when the study has finished and its results have been digitized, will it be transferred to those responsible for the statistical analysis. Both the data notebook and the databases or files used for statistical analysis will be dissociated from the identification data of the subjects under study.

Doctores and other study collaborators will have access to a list containing a fixed order of the products (A/B). For instance: product 1 is A, product 2 is B, product 3 is B… Investigators will assign a cream A/B to participants as they enter in the study (participant 1 will have A, 2 will have B, 3 will have B, etc). This list will be available physically and electronically.

6. SELECTION OF SUJECTS

The inclusion of 120 patients who have been diagnosed with cancer in stages I-III and who are going to start chemotherapy treatment is proposed. Once the treatment is finished, the degree of cutaneous comfort will be compared between the patients who have developed peripheral neuropathy in both groups.

6.1. Inclusion criteria

Patients must meet all the criteria that appear in this section to be included in the study.

- To be older tan 18 year old.
- To be able to complete questionnaires.
- Give informed consent in writing.
- Being able to apply the product under test by oneself.
- To have been diagnosed with stage I-III primary cancer.
- To have received a maximum of one treatment session with chemotherapy (derivatives of taxane, platinum or vincristines).
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2.
- Life expectancy greater than or equal to 6 months.

6.2. Exclusion criteria

Patients who meet one or more of the following criteria will not be eligible to take part in the study despite meeting all the requirements of section 6.1:

- Not being or having been treated with antidepressants, antiepileptics or HIV medication in the last 3 months.
- Pre-existing peripheral neuropathies not related to chemotherapy treatment.
- Pre-existing neurodegenerative or neuromuscular disease or history of stroke.
- Family history of neuropathic diseases.
- Having suffered in the last 6 months: myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or class III/IV heart failure.
- Being receiving investigational treatment (being involved in a clinical trial).
- Evidence or indication of metastasis affecting the Central Nervous System.
- Use of immunosuppressive or immunomodulatory medication that may lead to immunodeficiencies.
- Not being treated with topical palmar and/or plantar medication.
- Known hypersensitivity to capsaicin.
- Having reduced capacity for expression or response to forms.
- Not have been under general anesthesia for at least one month before starting the study.
- Complication of peripheral polyneuropathy symptoms that require the use of specific medication.

6.3. Expected number of subjects and justification

A total of 120 volunteers diagnosed with any type of cancer, in stages I-III, who are about to start or have received a maximum of 1 dose of chemotherapy treatment will be studied.

Two study populations are contemplated: (i) population that will receive the PB-011 cream; (ii) population that will receive the PB-012 cream. Both populations will apply the cream on their hands once a day. If sensory discomfort or, in the worst case, peripheral neuropathy appear during the chemotherapy treatment period, the application will be increased to twice daily on the affected areas (generally hands and feet).

The number of volunteers for the study is 60 for each population. This value is based on: (i) a difference of 2 points between both populations (PB-011 and PB-012), on a satisfaction scale of

0 to 10 points, with 0 being very dissatisfied and 10 very satisfied, or 2 points on the Von Frey scale; (ii) a variability (standard deviation) of 3 points in each population; (iii) a p-value of statistical significance <0.05 and, (iv) a probability of finding a statistically significant difference for the p-value <0.05 of 95%.

6.4. Duration of the recruitment period

The recruitment period is estimated to last at 10 months. Patients should use the cream throughout the treatment period.

7. PRODUCT DESCRIPTION

7.1. Product

Subjects who meet the inclusion/exclusion criteria and who become part of the study may take any medication that their physician deems appropriate, excluding those specified in the exclusion criteria.

Patients participating in the study will apply:

Cosmetic creams Ref. PB-011 and PB-012.

Tradename: Nocisens.

Business owner: Prospera Biotech S.L.

Composition:

- PB-011: Capric Triglyceride, Glyceryl Behenate, Glyceryl Stearate, Hydrogenated Castor Oil, Diethylene Glycol Monoethyl Ether, Tocopherol, Hydroxymethoxyiodobenzyl Glycolamide Perlargonate.
- PB-012: Capric Triglyceride, Glyceryl Behenate, Glyceryl Stearate, Hydrogenated Castor Oil, Diethylene Glycol Monoethyl Ether, Tocopherol.

7.2. Study development

When a subject meets all the inclusion criteria and none of the exclusion criteria and has signed the informed consent document, he/she is electable to enter the study. The researchers will collect the data of each volunteer and notify Prospera Biotech of their inclusion. Patients will

receive the cream when they start the chemotherpaty treatment. Creams will be either sent directly to the participants' home or sent in advance to the centers and stored there at room temperature (15-25ºC) until distributed to participants. The principal investigator will create the Data Notebook for each subject, anonymizing the personal and clinical data in all cases. The type of product to be assigned will be determined by the randomization procedure.

Subjects taking part in the study should apply a sufficient amount of cream to their hands once a day for the duration of their chemotherapy treatment. Those subjects who develop skin sensitivity or peripheral neuropathy should undergo the following procedures:

1. Increase the frecuency of use of the cream to twice a day in all affected areas.

2. Once the chemotherapy treatment is finished: evaluation of the degree of skin satisfaction by means of a questionnaire that assesses the Dermatology Life Quality Index [DLQI] (Annex II) and the degree of satisfaction with the cream (Annex IV). Evaluation of the discomfort generated by peripheral neuropathy through a follow-up questionnaire (Annex III). Measurement of skin sensitivity using Von Frey hairs for patients who voluntarily wish to do so. These procedures will be carried out by the study collaborators of each center. In case of need, Prospera Biotech team could also contribute to make the follow-up (questionnaires) telematicallty.

The study procedures are included in section 8.2.

7.3. Withdrawal criteria

Based on the provisions of the Declaration of Helsinki, the subjects have the right to withdraw from the study at any time and for any reason, being able to express it personally or through their representative. The investigator reserves the right to withdraw any subject from the study in the following cases:

- Subject abandonment: violation of inclusion or exclusion criteria or non-cooperation. In case of withdrawal, the reason is reflected in the Data Notebook.

- By efficacy criteria: if, in the investigator's opinion, the product is not causing any benefit to the subject under study.

- Due to safety criteria: in the event of a serious or unexpected adverse event and that, for this reason, or due to the medication that may be instituted to reverse such event, it is considered that its continuation in the study is not pertinent.

8. STUDY DEVELOPMENT AND EVALUATION OF THE RESPONSE

8.1. Study variables

Main Variable: degree of skin satisfaction/comfort with the skin in the palmar and plantar regions, evaluated by means of the DLQI questionnaire.

Secondary Variables:

- Skin sensitivity quantifiable by the Von Frey filament test for patients who voluntarily so wish.
- Follow-up of discomfort skin sensations experienced by patients, evaluated by means of a brief questionnaire.

8.2. Collection of variables

The main variable, degree of skin satisfaction/comfort, will be evaluated using the DLQI[12, 13] questionnaire available in ANNEX II.

Mechanical sensitivity will be assessed by means of the Von Frey filament test in patients who voluntarily want to undergo it. The pain threshold and mechanical allodynia of patients with post-chemotherapy polyneuropathy will be measured before starting the study and once the chemotherapy treamtment is over, expressing the threshold in the minimum number of pressure units that trigger pain in patients with the corresponding filament. of Von Frey approved.

The follow-up of the patients will be carried out through the usual oncological control during treatment. If the patients develop sensory or skin discomfort during this period, at the end of the treatment a check-up will be carried out using the following questionnaires:

- Follow-up of discomfort sensations available in a questionnaire derived from the Leonard Scale (ANNEX III).
- Degree of skin satisfaction by means of the Dermatology Life Quality Index [DLQI] (Annex II).
- Degree of satisfaction with the cream (Annex IV).

9. ADVERSE EVENTS

An adverse event is considered to be any adverse medical event that occurs in a clinical research subject to whom a product has been administered, even if it does not necessarily have a causal relationship with this treatment. An adverse event can also be any unfavorable or unexpected sign, including an abnormal laboratory finding, symptom, or illness temporarily associated with the use of an investigational product, related or not. An adverse event is considered to be any adverse medical event that occurs in a clinical research subject to whom a product has been administered, even if it does not necessarily have a causal relationship with its use. An adverse event can also be any unfavorable or unexpected sign, including an abnormal laboratory finding, symptom, or illness temporarily associated with the use of an investigational product, related or not.

Due to the fact the products in study are already commercialized, no adverse effects are expected. However, the recording of adverse events is an important aspect of study documentation, so the rules to follow are described below:

9.1. Detection and documentation of adverse events

Adverse events can be detected either by the subject himself or by the investigator, but it is the investigator's responsibility to record them. The Data Notebook will have a section for recording adverse events (Annex V) in which the investigator, or one of his collaborators, must describe events of this type in detail. The method of detecting adverse events can be either by direct communication from the subject under study, by exploration by the investigator, or by the subject's response to a question asked by the investigator or by any collaborator of the study.

In any case, the existence of an adverse event must be duly documented and the nature of the event, the date of detection and the start date if they do not coincide, the duration, severity and possible relationship with the event must be recorded at each visit. product under study.

The subjects in whom an adverse event is detected will be subjected to additional follow-up by the researchers, who will control the evolution of the adverse events until they have disappeared, decreased or stabilized. Follow-up information for these subjects should be brought to the attention of the study monitor.

In addition to documenting the occurrence of any unexpected events, investigators should assess their intensity based on the following scale:

- Mild: adverse event that causes minimal discomfort, tolerable by the subject and that does not interfere with their daily activities.
- Moderate: An adverse event bothersome enough to interfere with normal daily activities.
- Severe: event or adverse reaction that requires hospitalization of the subject or prolongs it, that endangers his or her life, causes invalidity or permanent incapacity, gives rise to some anomaly or congenital malformation, or that produces his or her death). For notification purposes, those suspected adverse events or adverse reactions that are considered important from a medical point of view, even if they do not meet the above criteria, will also be treated as serious.

Unexpected adverse reaction: adverse event whose nature or severity does not correspond to the information in the product's technical data sheet.

9.2. . Assessment of causality

The investigator should make every effort to explain each adverse event and assess its relationship, if any, to treatment with the study product. Causality should be assessed using the following categories:

- Definitive: The adverse event follows a reasonable time sequence from the time of product administration and follows a known response pattern of the study product and cannot be reasonably explained by other factors such as the subject's clinical condition or other therapeutic interventions or concomitant medications administered to the subject and, in addition, one or more of the following: a) appears immediately after administration of the drug; b) improvement when discontinuing drug administration; c) reappears upon reintroduction of the drug.

- Probable: The adverse event follows a reasonable time sequence from the time of product administration and follows a known response pattern to the study product and cannot be reasonably explained by other factors such as the subject's clinical condition or other therapeutic interventions or concomitant medications administered to the subject.

- Possible: The adverse event follows a reasonable time sequence from the time of administration of the product and/or follows a known response pattern of the product under study, although it could be caused by other factors such as the clinical condition

of the subject or other therapeutic interventions or concomitant medications administered to the subject.

- Unlikely: The adverse event is more likely to be caused by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant medications administered to the subject and does not follow a known response pattern of the study product.

- Unrelated: The adverse event is clearly related to other factors such as the subject's clinical status, therapeutic interventions, or concomitant medications administered to the subject.

9.3. Procedures for immediate notification of serious or unexpected events

A severe adverse event is considered to be any adverse medical event that at any dose:

- Causes the death of the subject.

- Puts life in danger.

- Requires hospitalization of the subject or the extension of an existing hospitalization.

- Causes significant or permanent disability/invalidity or a congenital abnormality/birth defect or overdose (accidental or deliberate).Produce la muerte del sujeto.

The principal investigator will immediately notify the promoter of all serious adverse events. The initial communication will be followed by detailed written communications. In the initial and follow-up communications, the study subjects will be identified by means of a specific code number for each of them. In the event that a death of a subject participating in a trial has been reported, the investigator will provide the promoter and the Clinical Research Ethics Committees involved with all the additional information requested.

The principal investigator will communicate serious and unexpected adverse events to the promoter by telephone, email or fax within 24 hours of the investigator becoming aware of the adverse event. The prior report made by telephone, email or fax must be followed by a complete report that includes a copy of the relevant data collected or recorded in the center or other documents produced as a result of the adverse event.

10. ETHICAL ASPECTS

10.1. General Considerations

This study must be carried out in accordance with the protocol and with the standards of good clinical practice, as described in:

- Harmonized Tripartite Standards of the ICH E6, for Good Clinical Practice of 1996.
- Regulation (EU) No 536/2014 of the European Parliament and of the Council, of April 16, 2014.
- ROYAL DECREE 1090/2015, of December 4, which regulates clinical trials with medicines, the Research Ethics Committees with medicines and the Spanish Registry of Clinical Studies.
- Declaration of Helsinki and amendments regarding medical research in human beings.

The researcher agrees, by signing this protocol, to follow the instructions and procedures described in it and therefore will comply with the principles of Good Clinical Practice on which it is based. Once the protocol is signed, it must not be modified without the written agreement of both the promoter and the principal investigator, and with the consent of the Research Ethics Committee.

A signed and dated document confirming that the protocol, the informed consent form and the patient information sheets have been approved by the Ethics Commite must be delivered to the promoter, together with the name and position of the president and members of the Ethics Commite.

10.2. Information to volunteers

The investigator must explain to each subject the nature of the study, its purposes, procedures, expected duration and the potential risks and benefits related to participation in the study, as well as any inconvenience that this may entail. Each of the participants must be informed that tehir participation in the study is voluntary and that they can withdraw from the study at any time, without this affecting their subsequent medical treatment or their relationship with their treating physician.

Informed consent will be provided in standard writing, in language easily understood by the participant. The subject must have sufficient time to read and understand the explanations before dating and signing the informed consent and must receive a copy of the signed

document. No subject can be included in the study without having previously given their informed consent.

10.3. Confidentiality and Access to data

The confidentiality of the personal data of the subjects will be maintained, although subject to the need, on the part of the monitor, to verify the original data against the clinical history of the subject. Only the date of birth and the study code will appear in the data collection notebook and in all study correspondence. The promoter will not keep any document with the name of any subject. At all times, the REGULATION of the European Union 2016/679 of April 27, 2016 will be respected and complied with. Organic Law 3/2018, of December 5th, on the Protection of Personal Data and guarantee of digital rights.

All information disclosed by the promoter to the researcher will be treated as strictly confidential. The investigator will only use this information for the study described in this protocol. It also undertakes not to disclose said information to third parties, except to other colleagues or employees who participate in the execution of the study and who are also bound by confidentiality obligations.

**Depending on the nature of the contact data, it is possible that the email is identifying a patient (example: namesurname@.....com). In these cases, if patients do not wish to transfer data that may be identifying, an anonymized email can be created (Patient code@prosperabiotech.com) or they can choose to follow up by telephone contact.*

10.4. Econocmic report

Given that there is no deviation from the conditions of use established in the product instructions, the center promoting the study (PROSPERA BIOTECH) will provide both creams to the subjects.

The detailed relation of the costs of this study is contemplated in ANNEX XI.

10.5. Insurance police

An insurance policy has been contracted with Berkley company with address at Paseo de la Castellana 141, Planta 18, 28046 Madrid. This insurance covers personal damage caused to the subjects as a result of the study, as well as economic damage arising directly from the same, in accordance with Royal Decree 1090/2015, of December 4. In addition to the legal civil liability of the study promoter, the legal civil liability of the researcher and his collaborators, that of the

hospital or center where the study is carried out, as well as that of the owner of the study, is covered.

11. PRACTICAL CONSIDERATIONS

11.1. Responsibilities of all study participants

Investigator: The investigators will abide by the Good Clinical Practice standards and will know and follow the Standard Operating Procedures (SOPs) of the relevant Clinical Trials Unit. All the information collected during the execution of the project will be recorded directly in the data collection notebook, which is attached as Annex I. When a correction is made, the date and the initials of the person who makes it must be noted.

Auxiliary Personnel: The auxiliary personnel will follow the instructions given by the investigator.

Monitor. The montor must attest that the information compiled in the protocol is true, for which you must have all kinds of facilities from the research team to carry out their work.

Promoter: will be responsible for ensuring compliance with the relevant legal regulations and for supplying the product under study.

11.2. Protocol deviations

When a situation that causes a deviation from the protocol occurs, the deviation will be only for that subject. Investigators present in such circumstances will fully document the deviation and reason on the Data Notebook. In the event that the deviation has to do with the inclusion/exclusion criteria, the investigators will contact the clinical monitor by telephone in order to inform them of such deviation.

11.3. Collection and filing of documentation

There will be a documentation file for all the data, which will be kept for 5 years after the end of the study. This file must contain the following elements:

- Approval by the Ethical Committe of the protocol and the informed consent form.
- Copy of the written consent form and the approved protocol with any amendments if applicable.
- Any correspondence related to the study with the promoter, during the course of the study.

- Any correspondence with the Ethics Committe.
- Signed acceptance of the protocol.
- Curriculum vitae of the principal investigator and of the other investigators who make up the research team.
- Register of signatures of the members of the research team.
- Communications of serious adverse events.
- Contract between the promoter and the hospital when applicable
- Copies of Data Notebook.

11.4. Amendents to the protocol

Neither the investigator, nor the monitor, nor the promoter will modify this protocol without first obtaining the consent of the other parties. The modification must be documented in writing. Any change in the research activity, except those necessary to eliminate an immediate apparent risk to the volunteer, must be reviewed and approved by the Ethics Committe before implementation. The promoter must send the amendments to the protocol to the health authorities, and the modifications may require the review and approval of the Ethics Committe.

11.5. Investigator Acceptance

The researcher commitment is included, if needed, in the documentation submitted to the Ethics Committe.

12. STATISTICAL ANALYSES

The analysis of the results of this study will be approached from two perspectives. On the one hand, the modified intention-to-treat (MITT) population will be analyzed, which corresponds to all those subjects who have used the product at least once and for whom satisfaction data is available. On the other hand, a per-protocol analysis will be carried out in which all randomized subjects who have followed the study instructions until the end of the study will be included.

The clinical evaluation data may be analyzed as quantitative or qualitative variables. In the first case, the results will be expressed as mean ± standard deviation, minimum and maximum. In the case of qualitative variables, the results will be expressed as frequency and percentage. For all the parameters to be measured (both clinical variables and responses to questionnaires) there will be a baseline measurement taken before the start of the protocol that will serve as a control measurement. The change in the main variable (degree of satisfaction) will be analyzed

using the paired Student's T test. The change in the secondary variables will be studied according to their nature (qualitative or quantitative variables) and applying the corresponding test in each case: Chi square, Student's T, ANOVA, Kruskal-Wallis or Mann-Whitney U. The impact of each variable on the main variable will be assess, especially the impact of treatment, diagnosis, age and gender.

13. REFERENCES

1. Roy PS, Saikia BJ. Cancer and cure: A critical analysis. Indian J Cancer. 2016;53(3):441-2.
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ANNEX I: DATA NOTEBOOK

See attached document

ANNEX II: DERMATOLOGY LIFE QUALITY INDEX

See attached document

ANNEX III: QUESTIONNAIRE FOR THE MONITORING OF DISCOMFORT DUE TO PERIPHERAL POLYNEUROPATHY

See attached document

ANNEX IV: SATISFACTION QUESTIONNAIRE

Tittle: Study for the evaluation of the degree of skin satisfaction of cosmetic creams PB-011 and PB-012 for sensitive skin in oncological patients affected by a palmoplantar polyneuropathy secondary to taxanes.

Principal Investgator: Jesús Mauel Poveda Ferriols

Reference: 20PB-02

1. Has applying the cream to your hands and/or feet caused you any discomfort?

Nothin									**Many**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

2. Has the application of the cream to your hands and/or feet generated any kind of skin reaction?

Nothin									**Many**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

3. How would you define your degree of satisfaction with the cream?

Nada									**Mucho**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

If, sensorial discomfort or CIPN have appeared during the chemotherapy treatment please answer also:

1. When you apply the cream to your hands and/or feet, do you feel any relief from any of the sensations that bother you?

YES	NO

2. Has the application of the cream generated comfort in your skin sensitivity on the hands

and/or feet?

Nothing									**A lot**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

ANNEX V: NOTIFICATION OF POSSIBLE ADVERSE REACTIONS

Subject identification:

Protocol	20PB-02	**Nº notification**	
Subject identification number		**Report type**	Initial ☐ Follow-up ☐

Reaction Characteristics:

Study inclusion date:	**Adverse Event Description:**
Date of first application:	
Date of adverse reaction appearance:	
Severity Adverse Reaction	Mild ☐ Moderate ☐ Severe ☐
Consequence Adverse Reaction	

Information on the product under study:

Suspicious Product	**Doe**	**Route**	**Starting date:**
			End date:
Did the adverse effect subside when suspending the application of the product?			**Did the effect reappear when applying the product again?**
YES ☐ NO ☐ NOT APPLICABLE ☐			☐ YES ☐ NO NOT APPLICABLE

Information to take into account and medical history:

Concomitant Medication	**Reason of Prescription**	**Had the patient experienced or recorded the side effect before?**	
		YES☐ NO ☐	
		When?	
		What was it related to?	
Other relevant data from the clinical history:			

Investigator Name:

Position:

Is additional documentation attached? YES☐ NO☐

Which?

ANNEX VI: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2.Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3.The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, promoters, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the promoter and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well

as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for

its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, promoters, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, promoters, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be

published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ANNEX VII: PATIENT INFORMATION SHEET

Through this document you can find out about the study in which you are being offered to participate. Take the time you need to read it carefully and ask your doctor any questions you may have.

Objective

To evaluate and compare the degree of skin satisfaction and comfort of cancer patients with cosmetic creams for sensitive skin PB011 and PB-012 after having developed sensitivity as a result of chemotherapy treatment.

Procedure description

If you agree to participate in this study, you will need to apply a cosmetic hand cream once a day during the course of your chemotherapy treatment. If at any time you decide to withdraw from the study and stop applying the product, notify your oncologist.

If, during treatment, you develop sensitivity or sensory discomfort, you can increase the dose of cream to twice a day. At the end of cancer treatment, you will be asked for your opinion through two short questionnaires. In addition, your doctor may request the analytical or radiological tests that he considers appropriate to control your health status and to diagnose any change in it that may occur due to the progress of your disease.

All the procedures of this study have been approved by an Ethics Committee and are governed by the principles contained in the Declaration of Helsinki.

Beneffits

The daily application of the product under study is expected to produce an increase in the degree of skin satisfaction and comfort in people undergoing chemotherapy derived sensitivity. This will result in an improvement in your quality of life. You must take into account that the action of the product is not immediate. The efficacy of the test cream is based on a slow process of reinforcing the skin's natural protection barrier. Therefore, the beneficial effects of the product will begin to be observed between 4-8 weeks of continuous application. Bearing this in mind, we strongly urge you not to desist from applying the product if you notice an improvement in your skin discomfort, as this could lead to a reactivation of the discomfort.

Risks

The products under study are two creams derived from the NOCISENS cosmetic line (marketed for the treatment of sensitive skin). They have passed all the relevant quality and safety controls in volunteers, being certified as dermatologically safe products, presenting no adverse skin effects. In addition, they do not present any contraindication. Therefore, the topical application of these products does not pose a risk to your health. However, if during the course of the study you suffer any type of adverse skin reaction, you should notify your doctor as soon as possible and follow his instructions. Any new information about the product that may appear during the course of the study will be communicated to you as soon as possible.

Conditions of participation

Your participation in this study is completely voluntary. If you decide to participate, you are free to withdraw from it when you deem it appropriate without having to give any explanation and without this decision entailing any type of penalty, or changes in your treatment or relationship with the doctors who treat you. Participation or non-participation in this study will not affect your medical care.

This study aims to answer relevant questions to, in the future, improve the quality of life of people like you. The costs of the study and the insurance policies are financed by PROSPERA BIOTECH S.L.

The promoter of the study has an insurance policy that conforms to current legislation (Royal Decree 1090/2015, of December 4) and whose purpose is to provide any compensation and indemnity in the event of damage to your health or injuries that may occur in connection with your participation in the study.

Confidentiality

During the course of the study, it is possible that the doctors and researchers participating in it have access to clinical data about your history, your illness and your current situation, as well as the information that you provide in consultations. We are aware of the sensitive nature of said information and, therefore, we undertake to keep it confidentially at all times. Your name or any data that can identify you will be excluded from the study databases, being replaced by a code. Only the doctor who treats you in consultation and the promoter of the research project may have access to the correspondence between your personal data and the identification code. At all times, the current regulations on the processing of personal data regulated by the REGULATION of the European Union 2016/679 of April 27, 2016 will be respected.

Due to the exceptional situation of the COVID-19 pandemic experienced in 2020, the monitoring of the study will be carried out electronically through a web application or telephone contact. To do this, you must provide your contact information (email and/or telephone). In the event that your email address is identifying (example: namesurname@....com) and you do not wish to provide it, you may be provided with an anonymized address (studycode@prosperabiotech.com).

The results of the study may be published in the media, magazines, and scientific conferences; assigned to public or private research centers; or become part of the material intended for teaching or research. However, your personal data will always be excluded from the information that is transferred.

You may, at any time, exercise your rights of access, rectification, cancellation and opposition, communicating it in writing or sending an e-mail to info@prosperabiotech.com or mgarcia@prosperabiotech.com

Contact data:

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Project promoter: PROSPERA BIOTECH

Dra. Marta García Escolano

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ANNEX VIII: INFORMED CONSENT FORM FOR THE PATIENT

Tittle: Study for the evaluation of the degree of skin satisfaction of cosmetic creams PB-011 and PB-012 for sensitive skin in oncological patients affected by a palmoplantar polyneuropathy secondary to taxanes.

Principal Investgator: Jesús Mauel Poveda Ferriols

Reference: 20PB-02

I, _____, with ID nº_____,

(name and surname) (ID)

- I have read the information sheet and have had sufficient time to consider my decision.
- I have been able to ask questions and all of them have been answered satisfactorily.
- I have received sufficient information about the study and understand that my participation in the study is voluntary.
- I have spoken with _____.

(Investigator name and surname)

I understand that I can withdraw from the study:

- Whenever I want.
- Without having to explain.
- Without this affecting my medical care.

I freely give my consent to participate in the study and, therefore, I give my consent for the access and use of my data under the conditions detailed in the information sheet.

And therefore I sign:

In_____ on _____ ___, 20___

(place) (date)

Patient signature	Investigator Signature
Date:	Date:

ANNEX IX: INFORMED CONSENT REVOCATION SHEET

Tittle: Study for the evaluation of the degree of skin satisfaction of cosmetic creams PB-011 and PB-012 for sensitive skin in oncological patients affected by a palmoplantar polyneuropathy secondary to taxanes.

Principal Investgator: Jesús Mauel Poveda Ferriols

Reference: 20PB-02

I, _____, with ID nº_____, revoke the consent given on the date _____ and I do not wish to continue participating in the study entitled: "Study for the evaluation of the degree of skin satisfaction of cosmetic creams PB-011 and PB-012 for sensitive skin in oncological patients affected by a palmoplantar polyneuropathy secondary to taxanes".

And therefore I sign:

In_____ on _____ ___, 20___

(place) (date)

Patient signature	Investigator Signature
Date:	Date:

ANNEX X: ECONOMIC REPORT

See attached document