# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

# FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): July 31, 2019

# LIXTE BIOTECHNOLOGY HOLDINGS, INC.

| DELAWARE | 000-51476 | 20-2903526 |
|---|---|---|
| (State or other jurisdiction of incorporation) | (Commission File Number) | (IRS Employer Identification No.) |

248 Route 25A, No. 2
East Setauket, New York 11733
(Address of principal executive offices)

(631) 830-7092
(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (See General Instruction A.2. below):

[ ] Written communications pursuant to Rule 425 under the Securities Act of 1933 (17 CFR 230.425)
[ ] Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
[ ] Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
[ ] Pre-commencement communications pursuant to Rule 13e-4(e) under the Exchange Act (17 CFR 240.13e-4(c))

**Item 1.01. Entry into a Material Agreement.**

Effective July 31, 2019, the Company and Grupo Español de Investigación en Sarcomas ("GEIS") entered into a Collaboration Agreement For An Investigator-Initiated Clinical Trial (the "Clinical Trial Agreement"). The Clinical Trial Agreement sets forth the terms under which GEIS will conduct a clinical research protocol to study the safety and/or efficacy of LB-100, the Company's lead compound (the "Study"). The Clinical Trial Agreement is intended to support a Phase 1b/randomized Phase 2 study of doxorubicin, the global standard for initial treatment of advanced soft tissue sarcomas versus doxorubicin plus LB-100. The Company will provide funding for up to 168 patients at a rate specified in the budget which is attached to the Agreement. The Study is to be performed in accordance with a protocol attached to the Clinical Trial Agreement.

The foregoing description of the terms of the Clinical Trial Agreement does not purport to be complete and is subject to and qualified in its entirety by reference to the Clinical Research Agreement, a copy of which are filed with this Form 8-K and incorporated by reference. Portions of the Clinical Trial Agreement will be subject to a FOIA confidential treatment request to the Securities and Exchange Commission pursuant to Rule 24b-2 under the Securities Exchange Act of 1934, as amended.

**Item 8.01. Other Events.**

On August 6, 2019, the Company issued a press release regarding the agreement with GEIS.

**Item 9.01. Financial Statements and Exhibits.**

(d) There is filed as part of this report the exhibit listed on the accompanying Index to Exhibits which exhibit is incorporated herein by reference

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 6, 2019

LIXTE BIOTECHNOLOGY HOLDINGS, INC.

By: */s/ JOHN S. KOVACH*

John S. Kovach, Chief Executive Officer

**INDEX TO EXHIBITS**

| Exhibit No. | Description |
|---|---|
| 10.1 | Clinical Trial Research Agreement[1] |
| 99.1 | Press Release regarding the agreement with Grupo Español de Investigación en Sarcomas |

1 Certain portions of the Exhibit have been omitted based upon a pending request for confidential treatment filed by the Company with the Securities and Exchange Commission.

TEXTED MARKED BY [***] HAS BEEN OMITTED PURSUANT TO A REQUEST FOR CONFIDENTIAL TREATMENT AND WAS FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION

Exhibit 10.1

EXECUTION VERSION

**COLLABORATION AGREEMENT**
**FOR AN INVESTIGATOR-INITIATED CLINICAL TRIAL**

In Madrid, July 31, 2019 ("Effective Date")

**GATHERED**

On the one hand, **Grupo Español de Investigación en Sarcomas (GEIS)** with tax identification number G81890212, and address at C/ Diego de Leon 47, 28006 Madrid, Spain (hereinafter the "Sponsor") represented in this act by Dr. Claudia Valverde Morales, in her capacity as President.

On the other hand, **Lixte Biotechnology Holdings, Inc.** with address at 248 Route 25A No. 2 East Setauket, New York 11733, United States (hereinafter "LIXTE"), represented in this act by John S. Kovach, M.D. in his capacity as Chief Executive Officer.

**MANIFEST**

I. Whereas, the Sponsor is a non-profit clinical research association dedicated to improving the expectations of sarcoma patients, with special interest and experience in conducting clinical trials in soft tissue sarcomas.

II. Whereas, LIXTE is a clinical-stage public pharmaceutical company dedicated to discovering drugs for more effective treatments for cancer.

III. Whereas, the Sponsor intends to carry out the clinical trial entitled **"Randomized phase I/II trial of LB-100 plus doxorubicin vs. doxorubicin alone in first line of advanced soft tissue sarcoma"** (hereinafter the "Trial") in accordance with the trial protocol summarized in Appendix 5 (hereinafter the 'Protocol").

IV. Whereas, the Sponsor has asked LIXTE for financial collaboration and the supply of samples of LIXTE'S proprietary LB-100 drug (the "Trial Drug") in order to conduct the Trial.

V. Whereas, LIXTE, being interested in obtaining information about the efficacy and safety of LB-100 in soft tissue sarcomas, has agreed to collaborate with the Sponsor for the development of the Trial under the conditions detailed in this agreement (the "Agreement") ..

By virtue of this, the parties, stating sufficient legal capacity, agree to formalize this Agreement in accordance with the following·

**I.**
**PURPOSE**

1.1 The purpose of this Agreement is to establish the terms and conditions under which LIXTE will collaborate with the Sponsor in the conduct of the Trial , through financial contribution and the supply of a number of samples of the Trial Drug that are necessary to achieve the

## II.
## COORDINATING INVESTIGATOR, PARTICIPATING SITES, AND PROJECT PARTICIPANTS

2.1 The Sponsor states that Dr. Javier Martin Broto shall perform the functions of coordinating investigator responsible for the practical execution of the Trial ("Coordinating Investigator"), and that he is professionally qualified to lead the Trial.

2.2 The Sponsor represents and warrants that the rest of the participating centers where the Trial is to take place (collectively, the "Participating Sites") have the necessary professional qualifications and experience for conduct of the Trial, and that they will carry out the Trial in accordance with the obligations established in this Agreement.

2.3 In the event of an absence of thirty (30) days or cessation of participation in the Trial by the aforementioned Coordinating Investigator, the Sponsor must notify LIXTE as soon as possible and make best efforts to replace him with another person of similar qualification. Sponsor will provide thirty (30) days' notice to LIXTE, whenever practical, of any change of Coordinating Investigator. LIXTE will have the right to review the qualifications of any Coordinating Investigator replacement and raise any reasonable concerns which LIXTE may have in that regard and, both parties shall seek in good faith to address such concerns.

2.4 Before commencing the Trial, the Sponsor shall have obtained written agreements with the Participating Sites governing conduct of the Trial, which shall contain terms expressing the same commitments assumed by the Sponsor in this Agreement.

2.5 The Sponsor and Coordinating Investigator shall require that all employees, consultants and agents of the Sponsor, the Coordinating Investigator and the Participating Sites who are assigned to perform services under this Agreement ("Project Participants") are made aware of the obligations contained in-this Agreement and are bound by such obligations. In performing the services under this Agreement, the Sponsor and Coordinating Investigator will reasonably allocate personnel with the necessary licenses, qualifications and experience to conduct the Trial in accordance with the Protocol. In particular, Sponsor and the Coordinating Investigator shall ensure that all Project Participants are trained in ICH Harmonised Tripartite Guideline For Good Clinical Practice E6(Rl) Current Step 4 version dated 10 June 1996 (including the Post Step 4 corrections) ("GCP"). LIXTE will have the right, before executing this Agreement, to review the qualifications of any key personnel, including Project Participants whose participation in the Trial is expected for the duration of the Trial, and raise any concerns which LIXTE may have in that regard. In the event that LIXTE has concerns regarding the performance of any Project Participant, the parties shall in good faith seek to resolve such concerns. Sponsor will provide thirty (30) days' notice to LIXTE, whenever practical, of any changes to the Project Participants. Sponsor will provide project-specific training to replacement Project Participants at its own expense. LIXTE will have the right to review the qualifications of any Project Participant replacements and raise any reasonable concerns which LIXTE may have in that regard and, both parties shall seek in good faith to address such concerns.

2.6 The Sponsor and Coordinating Investigator will ensure that Sponsor, its trustees, officers and directors, Coordinating Investigator, Participating Sites, Project Participants and any sub-contractors: (i) are under no contractual or other obligation or restriction that is inconsistent with the Sponsor and Coordinating Investigator's performance of or obligations under this Agreement ; (ii) do not have a financial or other interest in LIXTE or the outcome of the Trial that might interfere with their independent judgment; (iii) have not been and are not under consideration to be (1) debarred from providing services; (2) excluded, debarred or suspended from, or otherwise ineligible to participate in any national or state health care programs; (3) disqualified by any government or regulatory agencies from performing specific services, and are not subject to a pending disqualification proceeding; or (4) convicted of a criminal offense related to the provision of health care items or services, or under investigation or subject to any such action that is pending.

2.7 Neither the Coordinating Investigator, Sponsor, nor any Participating Site may subcontract the performance of any of its/his/her activities under this Agreement to a third party without LIXTE's prior written consent. In the event that LIXTE consents to such subcontracting, Sponsor agrees that (a) such third parties shall perform such activities in a manner consistent with the terms and conditions of this Agreement, and (b) Sponsor remains liable for such third parties' performance.

2.8 The Sponsor shall ensure that all clinical data, trial data, documentation, correspondence, and other information, data, and findings and results generated in the conduct of the Trial ("Trial Data") shall be recorded in a timely, accurate, complete and legible manner. The Sponsor will take all reasonable and customary precautions, including periodic backup of computer files, to prevent the loss or alteration of such Trial Data. In the event that LIXTE is required to use any Sponsor information systems and associated processes in order to obtain access to any Trial Data, Sponsor will provide to LIXTE access rights, at no additional charge, to such systems as is necessary for LIXTE to obtain access to such Trial Data. Such Sponsor systems will be accessible by LIXTE during, at minimum, normal business hours, and the Sponsor will promptly correct any unavailability of, or defect or inadequacy in, such systems to the extent they affect LIXTE's ability to access such Trial Data. In no event will Sponsor use or disclose, or permit any third party to use or disclose, the Trial Data for any commercial purpose or to any commercial entity.

2.9 The Sponsor and Coordinating Investigator will collect, retain and/or use blood, fluid and/or tissue samples collected from subjects of the Trial as may be set forth in the Protocol, and tangible materials directly or indirectly derived from such samples (collectively, "Biological Samples") solely as set forth in the Protocol.

## III.
## COMPLIANCE WITH REGULATIONS

3.1 The Sponsor represents and warrants that it is aware of the laws and regulations applicable to clinical trials of medicinal products for human use and declares that it will comply with, and will cause the Coordinating Investigator and the Participating Sites to comply with, all regulations and guidelines applicable to the Trial, including but not limited to the Declaration of Helsinki of the World Medical Association and the ICH Harmonised Tripartite Guideline For Good Clinical Practice E6(Rl) Current Step 4 version dated 10 June 1996 (including the Post Step 4 corrections) as applied to the monitoring and/or management of clinical trials.

3.2 The Sponsor will (i) notify LIXTE of any communications from or to any regulatory authority having an impact on the Trial; (ii) include LIXTE in any discussions or meetings with a regulatory authority regarding the Trial where appropriate; (iii) supply LIXTE with a copy of any correspondence from a regulatory authority regarding the Trial, including any approval letter, and any other Trial related correspondence; and (iv) allow LIXTE a reasonable opportunity to comment on any correspondence being sent to the regulatory authority by Sponsor regarding the Trial, including any submitted annual reports.

## IV.
## SPONSOR AND COORDINATING INVESTIGATOR RESPONSIBILITIES

4.1 Authorizations.

(a) The Sponsor is responsible for obtaining and maintaining in force the authorizations required to carry out the Trial, and in particular and prior to the start of the Trial: (a) the favorable opinion of the appropriate ethics committee ("Ethics Committee"), (b) the authorization of the Spanish Agency of Medicines and Medical Devices ("AEMPS").

(b) The Sponsor. shall keep LIXTE informed at all times in relation to the process of obtaining reports and authorizations and/or subsequent incidents that may affect the validity or permissibility of the Trial under applicable law (including those that may affect the Participating Sites), as well as the progress _of the Trial.

(c) At LIXTE's request, the Sponsor shall provide to LIXTE a copy of the AEMPS authorization and the Ethics Committee's approval. The Sponsor shall not make any substantial modification to the Protocol without prior authorization from LIXTE.

(d) The Sponsor is responsible for making all necessary arrangements and obtaining all required authorizations for the import and use of the Trial Drug in the. European Union. LIXTE will make reasonable efforts to furnish documentation relating to the Tri!. al Drug required for Sponsor to make such arrangements and obtain such authorizations.

4.2 Regulatory Framework. The Sponsor and the Coordinating Investigator will conduct the Trial (and ensure that the Participating Sites conduct the Trial) in accordance with:

(a) The Protocol;

(b) The regulatory authorization legally required for the conduct of the Trial provided by the AEMPS of Spain;

(c) The conditions established by the Ethics Committee; and

(d) The anti-corruption clauses contained in Appendix 4 to this Agreement.

4.3 Trial Insurance. The Sponsor represents and warrants it will obtain liability insurance adequate to cover the damages that may result from the Trial for the subjects on whom it is to be performed, and that such liability insurance will be adequate to cover damages that may result from the execution of the responsibilities of the Sponsor, the Coordinating Investigator, the Participating Sites, the Project Participants, and any sub-contractors. The Sponsor will provide written evidence of such insurance to LIXTE upon request.

4.4 Information Communication and Publication of Results.

(a) The Sponsor shall keep LIXTE informed of the progress of the Trial, and shall provide any information that LIXTE may request for this purpose. In any case, the Sponsor will send to LIXTE all the results of the Trial (intermediate and final) (including the Trial Data), during the sixty (60) days following the date on which such results become available.

(b) The Sponsor will not communicate to any laboratory or other commercial organization the data of the Trial, other than LIXTE.

(c) The Sponsor shall make public the results of the Trial via a written report within one ye r of the end of the Trial. Prior to publication, the Sponsor will send a draft of the report to LIXTE. Within thirty (30) days of receipt of the report, LIXTE shall provide any comments and/or raise any reasonable concerns LIXTE may have with the report, and both parties shall seek in good faith to address such comments and concerns. If LIXTE determines that Confidential Information or a LIXTE Invention is contained in the report, the Sponsor and Coordinating Investigator shall defer publication or disclosure for up to an additional sixty (60) days from the time LIXTE notifies the Sponsor or Coordinating Investigator that LIXTE desires patent application(s) to be filed on the LIXTE Invention. Sponsor shall include in the report a reference to LIXTE's participation as a "collaborator" (in the section "acknowledgements" or similar).

(d) Notwithstanding the above, the Sponsor will not use the name and/or logos of LIXTE in any advertising, press releases, announcements, communications, or for any promotional purpose, without the prior written consent of LIXTE.

(e) The Sponsor shall register the Trial, at its inception, on the web site www.clinicaltrials.gov, and on other national and international clinical study databases as required.

(f) LIXTE will be legitimated to make public the Trial results through· a summary of them in the registry of clinical trials in the LIXTE web site. In addition, LIXTE will be entitled to make public, at the beginning of the Trial, a summary of the protocol in the clinical trial registry on the LIXTE website.

4.5 Inspections and Audits.

(a) The parties agree that LIXTE, or others designated by LIXTE may, at mutually agreeable times and with prior written notice, during normal business hours, arrange with the Sponsor, Coordinating Investigator or their respective designee:

(i) to examine and inspect qualifications of the Project Participants and Participating Sites required for performance of the Trial according to GCP; and

(ii) to inspect and make copies of all data and supporting Trial documentation to confirm that the Trial is being conducted in conformance with the Protocol and this Agreement, and in compliance with all applicable legal and regulatory requirements.

(b) LIXTE agrees that all inspections and audits will be conducted in accordance with the policies and procedures regarding access to the information systems of the Sponsor or Participating Site, as applicable.

## V.
## DRUG SUPPLY

5.1 LIXTE undertakes to collaborate with the Sponsor by providing the Trial Drug as described in Appendix 2.

5.2 No Trial Drug samples will be delivered to Participating Sites until the Sponsor has obtained the necessary authorizations from the AEMPS and the corresponding Ethics Committee. The Sponsor shall be responsible for the management, handling, custody, including, if applicable, destruction, of the Trial Drug in accordance with current legislation, the Protocol and this Agreement.

5.3 The dispensation of the Trial Drug to the subjects of the Trial will be carried out according to the description of the treatment that appears in the Protocol. Any reformulation or modification in the composition of the Trial Drug is prohibited.

5.4 ‘The Sponsor, Coordinating Investigator and Participating Sites shall use the Trial Drug exclusively for the purpose stipulated in the Protocol and in accordance with the applicable regulations. Unless expressly authorized by LIXTE, the Sponsor shall not make the Trial Drug and/or any related information provided by LIXTE available to any third party, except to the Coordinating Investigator and Participating Sites.

5.5 The Sponsor shall at all times maintain, and shall cause the Coordinating Investigator and Participating Sites to maintain, an updated record of the number and date of dispensation of the Trial Drug samples to each subject of the Trial.

5.6 At the end of the Trial or upon termination of this Agreement, whichever is earlier, the Sponsor will cause the Coordinating Investigator to provide to LIXTE a written account of the quantities of the Trial Drug used in the Trial and will, at LIXTE's election (i) return to LIXTE any and all remaining stock of the Trial Drug or (ii) destroy any remaining stock of the Trial Drug, following the requirements established by applicable legislation.

5.7 Any incidents related. to the delivery of the Trial Drug (e.g. damaged goods, quantity, etc.) should be reported by the Sponsor to LIXTE within fourteen (14) days of delivery.

## VI.
## FINANCIAL COMPENSATION

6.1 In consideration for the performance of the Trial, LIXTE undertakes to collaborate financially with the Sponsor in carrying out the Trial by means of a maximum contribution of ***.

6.2 Payments will be made by bank transfer according to the schedule of milestones established in Appendix 1. The parties may modify the schedule of Appendix 1 via a writing signed by each party's authorized representative.

6.3 The parties acknowledge that the amount to be paid by LIXTE hereunder is reasonable compensation for the work to be performed during conduct of the Trial and that neither Sponsor, any Participating Site, nor Coordinating Investigator has received any other compensation or other inducement in connection with this Agreement or its participation in the Trial

6.4 In the event that the number of patients recruited for the Trial is less than the number set forth in the Protocol, the parties shall meet and confer to discuss in good faith reduction in the payments due from LIXTE pursuant to Appendix 1, taking into account the reduction in expenses of conducting the Trial resulting from the lower number of patients.

6.5 Within thirty (30) days of the occurrence of each milestone set forth in Appendix 1, Sponsor will issue an invoice to LIXTE for the corresponding payment amount. The Sponsor will include in its invoices the protocol number and title of the Trial and will send each invoice pursuant to the notification provisions of Section 14.1. LIXTE shall pay each invoice by bank transfer within thirty (30) days after receipt of such invoice.

6.6 All payments by LIXTE shall be made directly to Sponsor, and not to any Participating Site or the Coordinating Investigator. Sponsor shall be responsible for any payments required to be made to Participating Sites or the Coordinating Investigator.

## VII.
## EXCLUSION OF LIABILITY AND INDEMNITY

7.1 The Sponsor is the exclusive institution responsible for the Trial and LIXTE's participation is only as a collaborator via the contributions described in Sections Five and Six. In all its relations with third parties, including the subjects of the Trial, the Sponsor will not make statements that may indicate or suggest that LIXTE's role in the Tri.al is different.

7.2 LIXTE assumes no liability to the Sponsor, Coordinating Investigator, Participating Sites, Project Participants and/or any third party for any losses, damages, costs; claims, suits and expenses, including the cost and expense of handling and defending such claims, proceedings, investigations and suits arising from the conduct of the Trial. Sponsor exonerates and will indemnify LIXTE from any liability in this regard pursuant to Section 7.3.

7.3 Sponsor shall indemnify and hold harmless LIXTE and its affiliates and their respective officers, directors, employees and agents (the "LIXTE Indemnitees") from and against any losses, damages, costs, claims, suits and expenses, including the cost and expense of handling and defending such claims, proceedings, investigations and suits, arising from a third party claim against any LIXTE Indemnitee to the extent attributable to (i) a material breach of this Agreement by Sponsor, or (ii) the gross negligence, malpractice or wrongful acts of the Coordinating Investigator or participants in the project at any Participating Site; as applicable. In connection with such indemnity, LIXTE agrees: (1) to promptly notify Sponsor of any such claim or suit (provided, however, that Sponsor shall not be released from its obligations under this Section 7.3 if the failure to promptly notify Sponsor does not materially prejudice the defense of such claim, proceeding, investigation or suit); (2) to cooperate fully with Sponsor in defending against such claim or suit; and (3) in the event of suit, to attend hearings and trials and assist in securing and giving evidence, and to use reasonable efforts to obtain the attendance of necessary and proper witnesses. Sponsor shall reimburse LIXTE for all reasonable expenses incurred at Sponsor's request in connection with items (ii) and (iii) above. Sponsor shall have the right to settle any such claim, proceeding, investigation or suit at the Sponsor's sole expense provided that any settlement will not include an admission of liability, wrongdoing or negligence of the LIXTE Indemnitees or incur a financial obligation on behalf of a LIXTE Indemnitee, without their prior written consent. Sponsor shall pay for separate counsel to the extent representation of the LIXTE Indemnitee(s) and Sponsor by the same counsel is a conflict of interest for such counsel.

## VIII.
## PROTECTION OF PERSONAL DATA AND INFORMED CONSENT

8.1 The treatment of the personal data of the subjects participating in the Trial will be in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR), as well as Law 41/2002 of Spain, which regulates the autonomy of the patient, and other applicable laws on data protection and patient autonomy. The Sponsor will comply with and ensure that the Coordinating Investigator and Participating Sites comply with all the requirements established by such regulations.

8.2 All the information or data concerning Trial that are sent by the Sponsor and/or the Coordinating Investigator to LIXTE will be sent in an anonymized, de-identified format, so that LIXTE does not have, in any case, access to the personal data of Trial patients.

8.3 The Sponsor undertakes to ensure that all Participating Sites obtain the informed consent of the subjects included in the Trial, such informed consent to include, without limitation, an adequate description of the Trial, its risks, possible alternatives and each subject's rights and responsibilities.

## IX.
## INDUSTRIAL AND INTELLECTUAL PROPERTY RIGHTS

9.1 The signature of this Agreement shall not affect the ownership of industrial and intellectual property rights of which the parties were the holders before signing it, nor imply the granting of any rights except as expressly stipulated in this document.

9.2 All inventions, discoveries, developments, technology and data resulting from the performance of this Agreement or the Trial, or the use of the Trial Drug, whether patentable or not ("Inventions"), conceived, reduced to practice or made by or on behalf of the Sponsor and/or Coordinating Investigator, solely or jointly with others, that use, relate to, or incorporate the Trial Drug or LIXTE's Confidential Information, or that involve identification or use of biomarkers related to the safety, efficacy or use of the Trial Drug ("LIXTE Inventions"), shall be the sole and exclusive property of LIXTE, shall promptly be disclosed in writing by the Sponsor and Coordinating Investigator only to LIXTE, and Sponsor and the Coordinating Investigator hereby assign to LIXTE all rights, title and interests in and to such Inventions and all intellectual property rights therein. LIXTE shall have the sole and exclusive right to obtain, at its option, patent protection in the United States and other countries on any LIXTE Invention. LIXTE hereby grants to Sponsor a limited, non-exclusive, non-transferable and nonsublicenseable license under such LIXTE Invention, solely for internal non-commercial, academic, research and patient care purposes. LIXTE shall own all rights in the Trial Data, provided that LIXTE hereby grants to Sponsor a limited, non-exclusive, nontransferable and non-sublicenseable license to use and disclose, as necessary, the Trial Data, solely for (i) internal non-commercial, academic, research and patient care purposes and (ii) as required to fulfill its obligations under applicable law as the sponsor of the Trial, subject to Sections 4.4 and 11.

9.3 Other than the funding payments specified herein, LIXTE is not obligated to make any payments to Sponsor in consideration of the licenses set forth herein.

9.4 All Inventions other than LIXTE Inventions shall be owned by Sponsor if invented solely by Sponsor and jointly owned by Sponsor and LIXTE if jointly invented by Sponsor and LIXTE; provided, however, that Sponsor hereby grants to LIXTE a limited, non-exclusive, non-transferable and non-sublicenseable license to use any such Inventions.

9.5 Sponsor shall require that all Project Participants and Participating Sites have assigned to Sponsor their rights to any invention, discovery, development, technology and data resulting from their performance of this Agreement.

9.6 LIXTE will remain at all times the exclusive owner of the Trial Drug, including all its industrial, commercial, and marketing rights.

## X.
## DRUG SAFETY MONITORING

10.1 Sponsor shall make the clinical safety data notifications set forth in Appendix 3 to LIXTE within the time periods prescribed in Appendix 3. In addition, the Sponsor shall notify LIXTE of any other clinical safety data obtained during the Trial within thirty (30) days of such data becoming available, and at any time when requested by LIXTE.

10.2 In accordance with ICH GCP standards and applicable local regulations, the Sponsor is responsible for assessing all clinical safety information obtained during the Trial in order to produce all necessary safety reports. These safety reports shall include, without limitation, the prompt notification of individual cases of suspected serious and unexpected adverse reactions (SUSAR) and the Development Safety Update Reports (DSURs). The Sponsor will be responsible for sending these reports to the competent health authorities, to the relevant Ethics Committee and to the Coordinating Investigator and Project Participants, as appropriate, within the relevant timeframes established by law.

10.3 In the event that LIXTE has its own Investigator's Brochure ('IB") for the Trial Drug, LIXTE will provide the Sponsor throughout the Trial, for information purposes, both the IB and its updates and/or supplements.

10.4 In the event that LIXTE produces safety reports of the Trial Drug, LIXTE agrees, for the duration of the Trial, to send a copy of each such safety report to Sponsor within thirty (30) days of such report's completion.

10.5 In the event that LIXTE prepares periodic SUSAR notification reports to be sent to investigators for the Trial Drug, LIXTE agrees, for the duration of the Trial, to send a copy of each such safety report to Sponsor within thirty (30) days of such report's completion.

10.6 LIXTE will ensure that any urgent safety issues relating to the Trial Drug are reported to the Sponsor by any means that LIXTE, in its absolute discretion, considers approximate.

10.7 The Sponsor will notify LIXTE in advance of any review meetings of the Independent Data Monitoring Committee ("IDMC"), or equivalent. The Sponsor shall provide LIXTE, within thirty (30) days following completion of such meeting, with the minutes of the protocol meetings, and any recommendations or requests addressed to the Sponsor. The Sponsor shall communicate within forty-eight (48) hours any urgent safety issues relating to the LIXTE investigational medicinal product(s) identified at these meetings.

10.8 The Sponsor will notify LIXTE within twenty-four (24) hours after learning of any serious adverse effect or drug reaction affecting any subject in the Trial.

10.9 If a subject of the Trial is injured or becomes ill as a result of participating in the Trial, the Sponsor and/or Coordinating Investigator will be solely responsible for providing, at their expense, the medical treatment necessary to diagnose and treat such injury or illness.

## XI.
## CONFIDENTIALITY

11.1 During the term of this Agreement, the parties may obtain certain Confidential Information, as hereinafter defined, from each other or as a result of performing the Trial. "Confidential Information" shall mean all information provided by LIXTE (including, but not limited to, information about the Trial Drug), as well as all the information obtained during the development of the Trial and the personal data of the subjects recruited in the Trial.

11.2 Sponsor and Coordinating Investigator agree to, and agree to cause the Participating Sites to: (i) use the Confidential Information only in connection with their performance of this Agreement, (ii) treat the Confidential Information as they would their own proprietary and confidential information, and (iii) to take all reasonable precautions to prevent disclosure of the Confidential Information to any third party, except for legal and financial counsel involved in the Trial.

11.3 The foregoing obligations of Section 11.2 shall not be mandatory with respect to information that (i) has been published by LIXTE or is in the public domain for reasons other than non-compliance by the Sponsor, (ii) was previously accredited by evidence in the Sponsor's possession, (iii) is required by law or regulation to be disclosed; provided that the Sponsor shall notify LIXTE of any proceedings or requests that could result in disclosure under this Section 11.3 in sufficient time to permit LIXTE to take the appropriate measures to prevent such disclosures or (iv) is made available to the Sponsor or coordinating Investigator for use or disclosure from any third party having a legal right to do so and who is not under any obligation to keep such information confidential.

11.4 The Sponsor and the Coordinating Investigator agree to maintain, and agree to cause the Participating Sites to maintain, all Confidential Information in the strictest confidence for a period of ten (10) years from the termination of this Agreement.

11.5 Upon LIXTE's written request, the Sponsor shall, and shall cause the Coordinating Investigator and Participating Sites to, promptly deliver to LIXTE or to destroy if so requested, as applicable, all originals, copies, and summaries of documents, materials, and other tangible manifestations of Confidential Information belonging to LIXTE and any other property of LIXTE, as applicable, in its possession or under its control, in whatever media; provided, however, that Sponsor or Coordinating Investigator shall be entitled to retain in confidence under this Agreement, (i) one (1) archived copy of the Confidential Information, including without limitation notes and memoranda, solely for the purpose of administering its obligations or exercising its rights under this Agreement; and (ii) Confidential Information contained in its electronic back-up files that are created in the normal course of business pursuant to its standard protocol for preserving its electronic records.

## XII.
## DURATION

12.1 Except in the cases of early termination described below, this Agreement shall remain in force until the completion of the Trial and the fulfillment of all the obligations contemplated therein.

12.2 The Trial is expected to be carried out in the following stages:

- Administrative start-up: 4 months
- First subject visit (FSV): Q4 2019
- Total recruitment period: 24 months
- Treatment period: 6 months
- Follow-up period: 6 months
- Close-out: 4 months
- Estimated end of study: Q3 2022

## XIII.
## EARLY TERMINATION OF THE AGREEMENT

13.1 Termination for Breach. Either party may terminate this Agreement for any material breach by the other party if it: (i) provides written notification of a material breach to the other party and (ii) the other party fails to cure such material breach within thirty (30) days of receipt of such notification.

13.2 Termination by LIXTE. Without prejudice to LIXTE's right to claim any damages, LIXTE shall be entitled to terminate this Agreement at any time, without any requirement other than prior notice to Sponsor and without having to pay any indemnity to the Sponsor for such early termination.

13.3 Termination for Health or Safety. Finally, either party may immediately terminate this Agreement if: (i) it believes that immediate termination is necessary due to an evaluation of risks to the safety and/or health of the subjects involved in it or (ii) it is informed that approval to conduct the Trial has been withdrawn by AEMPS or other applicable regulatory authority.

13.4 Effect of Termination. In the event of any termination:

(a) The Sponsor shall cause the Coordinating Investigator to issue a report as to remaining amounts of the Trial Drug, and return or destroy such remaining amounts of the Trial Drug pursuant to Section 5.6.

(b) The Sponsor shall return to LIXTE the amount corresponding to those expenses that at the time of the suspension had not yet occurred.

(c) The Sponsor shall return or destroy all Confidential Information or other property of Lixte pursuant to Section 11.5.

13.5 Survival of Provisions. Sections 2.8, 3.1, 4.3, 4.4, 4.5, 6.3, 7, 8, 9, 10, 11, .13, 14 and any other provision required for the interpretation thereof shall survive termination of this Agreement.

## XIV.
## MISCELLANEOUS

14.1 Notices. All communications related to this Agreement will be addressed in writing, in English, and (i) mailed posted repaid by certified or registered mail, return receipt re-· quested, or (ii) personally delivered to the appropriate party via electronic delivery or reputable overnight service with written verification of receipt, or (iii) emailed, in each case to the appropriate addresses indicated below:

Grupo Español de Investigación en Sarcomas
C/ Diego de León 47
28006 Madrid, Spain
Email: secretaria@grupogeis.org

Lixte Biotechnology Holdings, Inc.
248 Route 25A No. 2
East Setauket, New York 11733, USA
Email: [jkovach@lixte.com

Notices shall be deemed to have been received at the earlier of receipt or five (5) days from the date of mailing (in the case of a letter).

14.2 Law and Jurisdiction. This Agreement and its appendices shall be governed by Spanish law. In order to resolve any discrepancy that may occur in the application or interpretation of the provisions of this Agreement, the parties submit, expressly waiving any jurisdiction that may correspond to them, to the jurisdiction of the Courts of Madrid, Spain.

14.3 Compliance with Law. Any provisions of law that invalidate, or otherwise are inconsistent with, the terms of this Agreement, or that would cause any of the parties to be in violation of the law, shall be deemed to supersede the terms of this Agreement; provided, however, that the parties shall use their best efforts to amend this Agreement to accommodate any such changes that most closely approximate the intent and economic effect of the invalid provision. In the event that this Agreement cannot be so amended, this Agreement shall terminate, and the provisions of Section 13.4 shall apply.

14.4 Assignment. Neither party may assign this Agreement without the prior written consent of the other party, which consent will not be unreasonably withheld; provided, however, that either party may assign this Agreement without consent to a successor-in-interest to substantially all of the business of that party to which the subject matter of this Agreement relates upon delivery to the other party of notice of such assignment, provided that the successor agrees to assume all responsibilities and obligations under this Agreement. This Agreement, including the indemnification obligations under Section 7.3, shall be binding upon and inure to the benefit of the ·parties hereto, their respective permitted successors, assigns, legal representatives and heirs.

14.5 Independent Contractors. For purposes of this Agreement, LIXTE shall not be deemed an agent, servant, partner, joint venturer or employee of Sponsor. Thus it does not have the authority to take action on Sponsor's behalf or to bind Sponsor without Sponsor's prior written consent. Lixte is acting in the capacity of an independent contractor of Sponsor.

14.6 No Waiver. Either party's failure to require the other party to comply with any provision of this Agreement shall not be deemed a waiver of such provision or any other provision of this Agreement.

14.7 Entire Agreement. This Agreement represents the entire understanding of the parties with respect to the subject matter hereof, and supersedes all prior and contemporaneous agreements between the parties, whether written or oral. Any modification, amendment or supplement to this Agreement or Appendices attached hereto shall be in a writing signed by an authorized representative of each party.

14.8 Severability. If any clause, section or paragraph of this Agreement is determined by a court of competent jurisdiction to be illegal, invalid or unenforceable, it will be deemed severed from the remainder of this Agreement and will have no effect on the legality, validity or enforceability of the remaining provisions of this Agreement. The parties shall negotiate in good faith to replace any illegal, invalid or unenforceable provision with a legal, valid and enforceable one such that the objectives contemplated by the parties when entering this Agreement may be realized.

14.9 Rules of Construction and Interpretation. Unless the context otherwise requires: (i) references in this Agreement to any gender include references to all genders, and references to the singular include references to the plural and vice versa; (ii) the words "include", "includes" and "including" when used in this Agreement shall be deemed to be followed by the phrase "without limitation"; (iii) references in this Agreement to Articles, Sections, Appendices and Schedules shall be deemed references to Articles and Sections of, and Appendices and Schedules to, this Agreement, as applicable; (iv) the words "hereof", "hereby" and "herein" and words of similar meaning when used in this Agreement refer to this Agreement in its entirety and not to any particular Article,. Section or provision of this Agreement; (v) where either party's "consent" or "approval" is required hereunder, except as otherwise specified herein, such party's consent or approval may be granted or withheld in such party's sole discretion; (vi) the words "shall," "will," or "agrees" are mandatory and "may" is permissive; (vii) the word "or" is not exclusive; (viii) any definition or reference to any agreement, instrument or other document herein shall be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein or therein); (ix) all references to contracts, agreements, leases or other arrangements shall refer to oral as well as written matters; (x) any reference to any laws herein shall be construed as referring to such laws as from time to time enacted, repealed or amended and (xi) any reference herein to any person shall be construed to include the person's successors and permitted assigns.

14.10 Representations and Warranties. Sponsor and LIXTE each represent and warrant that: (i) it is a corporation or other legal entity duly incorporated or established, validly existing and in good standing, (ii) such party has the legal authority and right to enter into this Agreement, (iii) it has taken all necessary actions on its part to authorize the execution, delivery and performance of the obligations undertaken in this Agreement, and no other corporate actions are necessary with respect thereto, (iv) it has no obligation to any other party which is in conflict with its obligations under this Agreement, and (v) it is duly licensed, authorized or qualified to do business and is in good standing in every jurisdiction in which a license, authorization or qualification is required for it to perform its obligations under this Agreement.

14.11 Further Assurances. Each party hereto agrees to duly execute and deliver, or cause to be duly executed and delivered such further instruments and do and cause to be done such further acts and things, including without limitation, the filing of such additional assignments, agreements, documents and instruments, that may be necessary or as the other party hereto may at any time and from time to time reasonably request in connection with this Agreement or to carry out more effectively the provisions and purposes hereof or to better assure and confirm unto such other party its rights and remedies under this Agreement.

14.12 Counterparts. This Agreement may be executed in several counterparts, each of which shall be deemed an original but all of which shall constitute one and the same instrument. This Agreement may be executed electronically. Each counterpart shall be considered an original whether or not such counterpart is executed electronically.

In proof of conformity, the parties sign this Agreement in duplicate as of the Effective Date.

| Grupo Español de Investigación en Sarcomas | | Lixte Biotechnology Holdings, Inc. | |
|---|---|---|---|
| By: | | By: | |
| Name: | Claudia Valverde Morales | Name: | John S. Kovach, M.D. |
| Title: | President | Title: | President & CEO |
| Date: | | Date: | |

**Appendix 1: Budget & Payment Schedule**

Protocol reviewed by FDA and delivery of required documentation/permits

| Payment No. | Total*** | Milestone | Estimated Date |
|---|---|---|---|
| 1 | | Upon CTA signature | Q3 2019 |
| 2 | | Protocol reviewed by FDA and delivery of required documentation/permits for LB-100 import and use in the EU | Q3 2019 |
| 3 | | EC and RA approvals in Spain | Q4 2019 |
| 4 | | Phase 1: First patient in | Q4 2019 |
| 5 | | Phase 1: Final clinical report | Q2 2020 |
| 6 | | EC and RA approval in Country 2 | Q1 2020 |
| 7 | | Phase 2: First patient in | Q2 2020 |
| 8 | | Phase 2: 20% of patients enrolled (30) | Q3 2020 |
| 9 | | Phase 2: 40% of patients enrolled (60) | Q4 2020 |
| 10 | | Phase 2: Interim analysis report | Q1 2021 |
| 11 | | Phase 2: 60% of patients enrolled (90) | Q2 2021 |
| 12 | | Phase 2: 80% of patients enrolled (120) | Q3 2021 |
| 13 | | Phase 2: 100% of patients enrolled (150) | Q4 2021 |
| 14 | | Phase 2: Final clinical report | Q1 2022 |
| 15 | | Phase 2: First publication in congress | Q2 2022 |
| 16 | | Phase 2: All sites closed-out | Q3 2022 |
| 17 | | Phase 2: Manuscript published in journal | Q4 2022 |

**Appendix 2: Drug Supply**

Samples provided for protocol:

**"Randomized phase I/II trial of LB-100 plus doxorubicin vs. doxorubicin alone in first line of advanced soft tissue sarcoma"**

LIXTE will provide the Sponsor with the samples described below for use in the Trial only.

| Name of the product: | LB-100 for intravenous injection |
|---|---|
| Product code: | |
| Item Code: | |
| Type of sample: | Glass vials each containing 10 mL of 1.0 mg/mL LB100 |
| Presentation/Content: | |
| Quantity: | |
| Technical storage conditions: | Frozen at minus 10° C to minus 25° C or lower |
| Period of technical validity: | To March 30, 2020 |
| Packaging components: | Frozen vials |
| Reference documents: | |

**Reception and Storage**

Upon receipt of the product, check that the seal is intact and contents are frozen. Ensure that the material is. stored in a -20° C freezer or colder in accordance with Good Manufacturing Practice (GMP) or local regulations in force. If there is any sign of deterioration, contact LIXTE immediately.

**Postprocessing**

Any further processing must be carried out in accordance with GMP standards or local regulations in force.

The Sponsor will be responsible for ensuring that the packaging/labeling complies with local regulations, product separation and appropriate controls to prevent product mixing.

Subsequent delivery, monitoring and other rearrangement activities will also be under the responsibility of the Trial Sponsor.

**Notifications and Complaints**

If during the Trial LIXTE becomes aware of any problem that may affect the quality of the samples, LIXTE will promptly notify the Sponsor. The responsibility for claiming any investigational medication rests with the Sponsor, after consultation with LIXTE and/or any other company that supplied the products.

The Sponsor must notify LIXTE of protocol changes that may affect the use of the samples provided for the clinical trial.

**Destruction**

The destruction will be performed by the Sponsor in accordance with Good Manufacturing Practice, Good Clinical Practice and national legal requirements.

**Appendix 3: Notifications of Safety Data**

**Definition of Adverse Event and Serious Adverse Event**

For the purposes of this Agreement, an adverse event .(AB) means any harmful incident to a clinical trial subject's health, whether or not causally related to the drugs (or other materials) used in the Trial, and a serious adverse event (SAE) means any adverse event that results in death, life threatening, disabling or incapacitating, requiring hospitalization or prolongation of hospitalization.

**Serious Adverse Events**

The Sponsor shall notify LIXTE and Theradex Oncology of all SAEs that occur during the Trial in subjects exposed to the LIXTE drug(s) (in accordance with the protocol) by sending a copy of the original pages of the SAE forms, completed in English within 24 hours of becoming aware of the event, regardless of the causal assessment established by the Sponsor/Investigator.

PDF's of SAE are emailed to:

TBD
TBD
Theradex Oncology
4365 Route 1 South
Suite 101
Princeton, NJ 08540 USA

John S. Kovach
jkovach@lixte.com
Lixte Biotechnology
248 Rout 25A No. 2
East Setauket, NY 11733 USA

**Pregnancy Notification**

The Sponsor will notify LIXTE of the pregnancy status of any patient who becomes pregnant while participating in the Trial and has been exposed to a LIXTE medication under the Trial by sending copies of the original pregnancy notification form to LIXTE within two weeks of becoming aware of the pregnancy. It will also follow up to determine the outcome of the pregnancy, including premature pregnancy termination.

**How Safety Clinical Data Will Be Submitted to LIXTE**

The above notices and information, shall be communicated to LIXTE in English to the following address:

248 Route 25A No. 2
East Setauket, New York 11733, United States
Attention: CEO

**Reporting Period**

AEs that are subject to the above provisions are those that occur after the first dose of the LIXTE Trial drug(s) up to 28 days after discontinuation of the LIXTE Trial drug(s).

**Request for Follow-Up Information**

The Sponsor will provide LIXTE with details of to whom LIXTE should address requests for followup information regarding the AEs cases reported in this Trial, and undertakes to update these details as appropriate.

**Appendix 4: Anti-Corruption Clauses**

These anti-corruption clauses form part of the terms and conditions of the Agreement between the Sponsor and LIXTE. Any supply of product and services to Veolia incorporates these terms by reference.

1. In carrying out the Trial, the Sponsor hereby undertakes to strictly comply with applicable laws prohibiting the bribery of public officials and private persons, ·influence peddling, money laundering that may in particular entail a public contract debarment. The Sponsor undertakes to put in place and implement all necessary and reasonable policies and measures to prevent corruption.

2. The Sponsor declares that to its knowledge, its legal representatives, directors, employees, agents, and anyone providing services do not and will not directly or indirectly offer, give, agree to give, authorize, solicit, or accept the giving of money or anything else of value or grant any advantage or gift to any person, company or undertaking whatsoever including any government official or employee, political party official, candidate. for political office, person holding a legislative, administrative or judicial position of any kind for or on behalf of any country, public agency or state owned company, official of a public international organization, for the purpose of corruptly influencing such person in their official capacity, or for the purpose of rewarding or inducing the improper performance of a relevant function or activity by any person in order to obtain or retain any business or to gain any advantage in the conduct of business.

3. The Sponsor further undertakes to ensure that neither the Sponsor nor any of its legal representatives, directors, employees, agents, sub-contractors and anyone performing services under this Agreement has been, or is listed ·by any government agency as being debarred, suspended, proposed for suspension or debarment.

4. The·Sponsor agrees to notify any breach of any term of these clauses, to LIXTE within a reasonable time.

5. If LIXTE notifies the Sponsor that it has reasonable grounds to believe that the Sponsor has breached any term of these clauses:

(a) LIXTE is entitled to suspend performance of this Agreement without notice for as long as LIXTE considers necessary to investigate the relevant conduct without incurring any liability or obligation to the Sponsor for such suspension;

(b) The Sponsor is obliged to take all reasonable steps to prevent the loss or destruction of any evidence in relation to the relevant conduct.

**Appendix 5: Protocol Synopsis**

**CLINICAL TRIAL SUMMARY**

| | |
|---|---|
| **Trial Title** | Randomized phase I/II trial of LB-100 plus doxorubicin vs. doxorubicin alone in first line of advanced soft tissue sarcomas |
| **Study Type** | Phase I-II, two-arm, randomized, open-label, multicenter, international clinical trial |
| **Sponsor** | Grupo Español de Investigación en Sarcomas (GEIS)<br>C/ Diego de León, 47<br>28006, Madrid, Spain<br>www.grupogeis.org |
| **CRO** | Sofpromed Investigación Clinica, SLU<br>C/ del Ter, 27 - 2nd Floor - Office 8D<br>07009 Palma de Mallorca, Spain<br>Tel: +34 648 414 261<br>Fax: +34 971 570 222<br>E-mail: ensayos@sofpromed.com |
| **Study Indentifiers** | Study Acronym:<br>Sponsor Protocol Number: GEIS-74<br>EudraCT Number: 2019-003034-16 |
| **Coordinating Investigators** | Clinical Coordinating Investigator:<br>● Dr. Javier Martin - Hospital Universitario Virgen del Rocío (Seville)<br>Translational Coordinating Investigator:<br>● Dr. David da Silva Moura - Hospital Universitario Virgen del Rocío (Seville) |
| **Planned Calendar** | ● Administrative start-up: 4 months<br>● First subject first visit (FSFV): Q4 2019<br>● Total recruitment period duration: 24 months<br>● Treatment: 6 months<br>● Follow-up period: 6 months<br>● Close-out: 4 months<br>● Estimated end of study date: Q3 2022 |
| **Estimated Accrual Rate** | 6-7 cases per month (at international level) |

**Clinical Study Objectives**

***PHASE I***

***Primary clinical study objective***

- To determine the maximum tolerated dose (MTD) of LB-100 in combination with doxorubicin (to be used as recommended dose for the phase II part).

***Secondary clinical study objectives***

- To evaluate the safety profile according to CTCAE 4.03.
- To assess the activity of this combination (ORR, median PFS, median OS)
- To assess pharmacodynamic parameters in tumor tissue

***PHASE II***

***Primary clinical study objective***

- T o comparatively evaluate the efficacy of the LB-100 plus doxorubicin combination vs. doxorubicin alone as measured by median progression-free survival (PFS) in patients with advanced soft tissue sarcomas.

***Secondary clinical study objectives***

- To determine the objective response rate (ORR).
- To evaluate overall survival (OS).
- To evaluate the safety profile.
- To evaluate quality of life.
- To correlate translational parameters (biomarkers) with clinical outcome.

**Analytical Endpoints**

***PHASE I***

***Primary clinical study objective***

- The MTD of LB- I 00 in combination with doxorubicin will be determined by assessing adverse events according to CTCAE 4.03 and they will be used as a rule for escalating or diminishing dose levels regarding the dose-limiting toxicities detailed in the protocol.

***Secondary clinic.al study objectives***

- Safety profile of the trial treatments, through assessment of adverse event type, incidence, severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be grad- ed and tabulated by using CTCAE 4.03.

- Activity will be measured as ORR, median PFS and media OS.

- Pharmacodynamic changes will be checked in order to analyze the impact of combination of these compounds in cell-cycle control and apoptosis signaling.

***PHASE II***

***Primary clinical study endpoint***

- Progression-free survival (PFS): Efficacy measured by median PFS according to RECIST 1.1. PFS for each patient is defined as the time measured in months from registry to progression or to death due to any cause, whatever occurs first.

***Secondary clinical study endpoints***

- Objective Response Rate (ORR): ORR is defined as the number of subjects with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) divided by the number of response evaluable subjects (according to RECIST 1.1 criteria).

- Overall survival (OS): OS is defined as the time between the date of first dose and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. Median of OS

- Safety profile of the trial treatments, through assessment of adverse event type, incidence , severity, time of appearance, related causes, as well as physical explorations and laboratory tests. Toxicity will be graded and tabulated by using CTCAE 4.03.

- Quality of life measured by QLQ-C30 EORTC questionnaire.

| | |
|---|---|
| **Population** | Adult patients with confirmed diagnosis of advanced undifferentiated pleomorphic sarcoma, leiomyosarcoma, myxoid/and hypercellular myxoid liposarcoma, myxofibrosarcoma, NOS sarcoma, synovial sarcoma, fibrosarcoma and malignant peripheral nerve sheath tumors (MPNST). |
| **Number of Patients** | Phase I: 9-18 patients<br><br>Phase II: 150 patients<br><br>Total study: 168 (including 14% of losses) |
| **Sample Size Calculation** | A n enrollment of 150 patients is planned (75 per arm), of whom at least 130 are expected to be considered eligible (including external pathological review), recruited during 24 months. A maximum of 14% patients is assumed not reaching progression or death during the study because of follow-up losses, protocol violations, and patient refusal or not having progressed at the time of the statistical analysis of study endpoints.<br><br>The primary endpoint, progression free survival (PFS) will be measured from the date of randomization until there is radiological evidence of disease progression or death of any cause. The main analysis will be conducted when 102 events occur. Assuming a control group median PFS of 4.5 months (HO) and an alternative mPFS of 7.5 months for the experimental arm (Hl ), this design will allow for the demonstration of a statistically significant decrease in the relative risk of progression or death with a Hazard Ratio of 0.72 in the experimental arm (alpha=0.05, beta=0.2). |

**Treatment**

***Phase I: Dose-finding stage***

A dose-finding stage is planned for an initial set of 9-18 patients (21-day cycles):

- Starting at Dose Level 1: LB-100 1.75 mg/m2/d dl-3 followed on day 1 by Doxorubicin 60 mg/$m^2$ /d (d1 only)
- Dose Level 2: LB-100 1.75 mg/m2/d dl-3 followed on day 1 by Doxorubicin 75 mg/$m^2$ /d (d1 only)
- Dose Level 3: LB-100 2.33 g/$m^2$/d dl-3 followed on day 1 by Doxorubicin 75 mg/$m^2$ /d (dl only)
- Dose Level -1: LB-100 1.25 mg/$m^2$ /d d1-3 followed on day 1 by Doxorubicin 60 mg/$m^2$ /d (dl only)
- (If Dose Level -1 needs to be tested, a new scalation dose level would be LB-100 1.25 mg/$m^2$/d dl-3 followed on day 1 by Doxorubicin 75 mg/$m^2$/d (d1 only)

After 6 cycles (in absence of progression or intolerance), LB-100 will be administered as maintenance phase, until disease progression or intolerance, in cycles every 3 weeks.

The procedure in the Phase I part is the classical 3+3 design. The dose escalation rules are as follows: escalating in cohorts of 3-6 patients per dose level. Three patients are treated at a given dose level. If at least 2 patients are observed to have dose-limiting toxicity (DLT), the prior dose level is defined as the maximum tolerable dosage (MTD) (unless only 3 patients have been treated at that level, in which case it is the tentative MTD). If 0 of the 3 patients are observed to have DLT, the dose level is escalated one step for the next cohort of 3 patients, and the process continues as above. If exactly 1 of the 3 patients treated show DLT, 3 additional patients are treated at the current dose level. If none of these additional 3 patients show DLT, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD.

***Phase II***

In the phase II part, the dose of doxorubicin in the control arm will be 75 mg/$m^2$/d dl intravenously by 20 minute infusion every 3 weeks and in the experimental arm, doxorubicin, at recommended dose derived from phase I part, will be administered intravenously by 20 minute infusion after completion of the administration of LB-100 by 2-hour intravenous infusion at the recommended dose derived from phase I part. LB-100 is administered during each of the first 3 days of each cycle and doxorubicin is administered on day 1 only of each 3-week cycle.

After 6 cycles (in absence of progression or intolerance), LB-100 will be administered as maintenance phase, until disease progression or intolerance, in cycles every 3 weeks.

Treatment will continue until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient or investigator decision.

**Drug Information**

***LB-100***

Pharmaceutical form: Sterile solution for injection.

Route of administration: Intravenous use.

***Doxorubicin***

Pharmaceutical form: Powder for injection.

Route of administration: Intravenous use.

**Inclusion Criteria**

1. Patients must provide written informed consent prior to performance of study-specific procedures and must be willing to comply with treatment and follow-up. Informed consent must be obtained prior to start of the screening process. Procedures conducted as part of the patient's routine clinical management (e.g. blood count, imaging tests, etc.) and obtained prior to signature of informed consent may be used for screening or baseline purposes as long as these procedures are conducted as specified in the protocol.
2. Age ≥ 18 years
3. Histologic diagnosis of soft tissue sarcoma (undifferentiated plea- morphic sarcoma, leiomyosarcoma, myxoid and hypercellular myxoid liposarcoma, myxofibrosarcoma, NOS sarcoma, synovial sarcoma, fibrosarcoma, and malignant nerve sheath tumor) confirmed by central pathology review.
4. Mandatory pre-treatment formalin-fixed paraffin embedded (FFPE) tumor tissue must be provided for all subjects without exception for central pathology review and translational research. If archive biopsy is not available or this achived tuor sample is older than 3 months, the patient must be willing to have a pre-treatment re-biopsy of primary or meta- static tumor (baseline biopsy). In the phase I part, there will be a second mandatory biopsy just before the 3rd cycle.
5. Metastatic/advanced disease in progression in the last 6 months, and not suitable for metastasectomy or surgical resection.

6. Measurable disease according to RECIST 1.1 criteria.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
8. The patient is naive of any previous treatment with anthracyclines.
9. Adequate organ, hepatic, renal, cardiac, and hematologic function.
10. Laboratory tests as follows:

Absolute neutrophil count ≥ 1,200/$mm^3$

Platelet count ≥ 100,000/mm3

Hg > 9 g/dl

Bilirubin ≤ 1.5 mg/dL

PT and INR ≤ 1.5

AST and ALT ≤ 2.5 times ULN

Creatinine ≤ 1.5 mg/dL or estimated C1Creatinine ≥ 90 ml/min

Calcium ≤ 12 mg/dL

Blood glucose < 150 mg/dL

11. Left ventricular ejection fraction ≥ 50% by echocardiogram or MUGA scan assessed within 28 days before randomization.

12. Females of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to study treatment initiation and agree to use birth control measures during study treatment and for 7 months after its completion. Patients must not be pregnant or nursing at study entry. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

13. Men or women of child bearing potential should be using an effective method of contraception before entry into the study and throughout the same and for 6 months after ending the study. Women of childbearing potential must have a negative urine pregnancy test before study treatment initiation.

14. Patient must have a Central Venous Catheter for treatment.

**Exclusion Criteria**

1. Previous treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines or any other systemic therapy.
2. Uncontrolled intercurrent illness including (not limited to): symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] III/IV), unstable angina pectoris or coronary angioplasty, or stenting within 24 weeks prior to registration, unstable cardiac arrhythmia (ongoing cardiac dysrhythmias of NCI CTCAE version 4.03 Grade >= 2), known psychiatric illness that would limit study compliance, intra- cardiac defibrillators, known cardiac metastases, or abnormal cardiac valve morphology(>= Grade 3).
3. It should be performed HBV and HCV serologies prior to inclusion. If HbsAg is positive it is recommended to reject the existence of replicative phase ($HbaAg^{+}$, DNA $VHB^{+}$). If these were positives the inclusion is not recommended, remaining at investigators' discretion the preventive treatment with lamivudine. If a potential patient is positive for antiHCV antibodies, presence of the virus should be ruled out with a qualitative PCR, or the patient should NOT be included in the study (if a qualitative PCR cannot be performed then patient will not be able to enter the study)
4. Other disease or illness within the past 6 months, including any of the following:

    - Myocardial infarction
    - Severe or unstable angina
    - Coronary or peripheral artery bypass graft
    - Symptomatic congestive heart failure
    - Cerebrovascular accident or transient ischemic attack
    - Pulmonary embolism

5. Plasma bilirubin > ULN.
6. Creatinine > 1.6 mg/dL.
7. Evidence of a bleeding diathesis.
8. Ongoing cardiac dysrhythmias > Grade 2.
9. Prolonged QTc interval (i.e., QTc > 450 msec for males or QTc > 470 msec for females) on baseline ECG.
10. History of allergy to study drug components.
11. History of another cancer with the exception of adequately treated basal cell carcinoma or in situ cervical cancer, or with a relapse-free interval longer than 5 years after treatment of the primary cancer with no substantial risk of recurrence.
12. Presence of brain or central nervous system metastases at the time of randomization .
13. Patient is unwilling to provide translational tumor sample/s or biopsies (if required) are not easy to be taken.

**Translational Study Objectives**

1. To determine predictive biomarkers, or predictive gene signatures, of LB-100 plus doxorubicin, in formalin-fixed paraffin-embedded (FFPE) tumor samples collected before treatment.
2. To study the cell signaling pathways relevant in the potential clinical benefit induced by the combination of LB-100 plus doxorubicin.
3. To evaluate the immune-phenotype induced by LB-100 plus doxorubicin, in peripheral blood samples collected at several time points during patient treatment.
4. To assess potential soluble predictive biomarkers of LB-100 plus doxorubicin in plasma samples collected during patient treatment.

**The Spanish Sarcoma Group Will Lead a European Consortium to Evaluate the Ability of Lixte Biotechnology Holding's LB-100 to Improve First Line Therapy for Advanced Soft Tissue Sarcomas.**

EAST SETAUKET, NY -- (August 6, 2019) - Lixte Biotechnology Holdings, Inc. (OTCQB: LIXT) announced that it signed a clinical trial agreement with the *Spanish Sarcoma Group (Grupo Español de Investigación en Sarcomas, GEIS)* to support a Phase 1b/randomized Phase 2 study of doxorubicin, the global standard for initial treatment of advanced soft tissue sarcomas (ASTS), versus doxorubicin plus LB-100.

Dr. John S. Kovach, CEO of Lixte, said, "We are pleased to support this investigator-initiated trial proposed by GEIS, a leader for many years in seeking improved therapies for ASTS. GEIS has a network of referral centers in Spain and across Europe that has an impressive track record of efficiently conducting innovative studies in ASTS. We believe GEIS and their EU collaborators are an excellent team to evaluate the potential benefit of adding Lixte's non-cytotoxic inhibitor of DNA damage repair to standard treatment for this challenging disease. The goal is to enter the first patient in the last quarter of this year and to complete enrollment of approximately 170 patients over two years."

Dr. Kovach continued, "Doxorubicin alone has been the mainstay of first line treatment of ASTS for over 40 years with little therapeutic gain from adding cytotoxic compounds to or substituting other cytotoxic compounds for doxorubicin. In animal models, LB-100, an inhibitor of protein phosphatase2A (PP2A), consistently enhances the antitumor activity of doxorubicin without apparent increases in toxicity and, in a Phase 1 clinical trial, LB-100 alone was associated with stabilization of an advanced chondrosarcoma and fibrosarcoma for 6 and 9 months, respectively, without toxicity. LB-100 potentiates the effectiveness of agents like doxorubicin by inhibiting multiple steps required to repair chemotherapy induced DNA damage. We are excited to learn if the combination of LB-100 and doxorubicin will finally advance the effectiveness of ASTS therapy."

Dr. Javier Martin-Broto, Coordinating Investigator of the trial and medical oncologist at Virgen del Rocío University Hospital (Seville) commented, "Although there has been an increase in overall survival in advanced sarcoma in recent years, this gain has not been accompanied by advances in first line therapy. Anthracyclines, and specifically doxorubicin, is still the standard initial treatment. The growing list of negative phase III trials indicates to us that sarcoma therapy is in crisis. It is true that sarcoma encompasses more than 60 different subtypes and, for some of them, substantial advances have emerged. But it is also true that the most frequent sarcoma subtypes desperately need a turning point. One promising topic of research is the combination of doxorubicin with drugs that are able to impair the mechanisms of DNA repair. LB-100 has demonstrated synergistic action in *in vivo* preclinical mesenchymal tumors. GEIS will lead a European initiative to conduct a phase I/randomized II trial exploring the combination of doxorubicin plus LB-100 in first line of advanced soft tissue sarcomas".

**About Lixte Biotechnology Holdings, Inc.**

Lixte is a biotech company that identifies enzyme targets associated with serious common diseases and then designs novel compounds to attack those targets. Lixte's product pipeline is primarily focused on inhibitors of protein phosphatases, used alone and in combination with cytotoxic agents and/or X-ray and immune checkpoint blockers.

**About GEIS (Grupo Español de Investigación en Sarcomas)**

GEIS is a non-profit organization in Spain engaged in the research, development and management of studies and clinical trials for sarcomas. GEIS has a mission to ensure the best healthcare to sarcoma patients by helping bring new treatments to them through clinical research. GEIS has successfully partnered with various institutions and companies to help bring new treatments to patients with sarcomas. Through the group's many research projects it has created or participated in over the years, it has made a significant impact in the global research effort to better treat patients with sarcomas. For more information:http://www.grupogeis.org.

**Forward-Looking Statements**

This announcement contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, and Section 21E of the Securities Exchange Act of 1934. For example, statements regarding the Company's financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about future product demand, supply, manufacturing, costs, marketing and pricing factors are all forward-looking statements. These statements are generally accompanied by words such as "intend," anticipate," "believe," "estimate," "potential(ly)," "continue," "forecast," "predict," "plan," "may," "will," "could," "would," "should," "expect" or the negative of such terms or other comparable terminology. The Company believes that the assumptions and expectations reflected in such forward-looking statements are reasonable, based on information available to it on the date hereof, but the Company cannot provide assurances that these assumptions and expectations will prove to have been correct or that the Company will take any action that the Company may presently be planning. However, these forward-looking statements are inherently subject to known and unknown risks and uncertainties. Actual results or experience may differ materially from those expected or anticipated in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, regulatory policies, available cash, research results, competition from other similar businesses, and market and general economic factors. This discussion should be read in conjunction with the Company's filings with the United States Securities and Exchange Commission at http://www.sec.gov/edgar.shtml.

**Additional information on the Company is available at** www.lixte.com**.**

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