**Annex 4**

**ADDITIONAL AGREEMENTS TO THE TEMPLATE AGREEMENT**

As one party, Mr.      , acting as Managing Director of the Centre      .

As another, Ms      , acting as Managing Director of the Managing Body.

On the other, Mr./Mrs.      , as      of       (hereinafter, the "Sponsor").

And on the other, Mr./Mrs.      , as the Study Principal Researcher, as confirmation of knowledge and acceptance.

**HEREBY DECLARE**

I.- Whereas the current template contract for the performance of observational studies was approved by the General Secretariat for Research, Development and Innovation in Health in its Resolution of 28 May 2019, and its update requires a procedure which is still being processed as the administrative services responsible have a very high workload due to the COVID-19 pandemic, especially those departments whose competencies are directly affected by this long-term situation.

II.- Whereas the agents responsible for carrying out these types of studies in the Andalusian Public Health System require the abovementioned contract to be updated in accordance with the applicable regulations that came into force in January 2021.

**HEREBY STATE**

**First:** Whereas the parties wish to state the following in the following terms:

A) The references included in the template contract for the performance of post-authorisation studies to Order SAS/3470/2009, of 16 December, which publishes the guidelines on post-authorisation observational studies for human medical products, published in Official State Gazette (BOE) no. 310, of 25 December 2009, shall be deemed to have been made with reference to observational studies in accordance with the provisions contained in Royal Decree 957/2020, of 3 November, which regulates observational studies with human medicinal products, published in Official State Gazette (BOE) no. 310, of 26 November 2020, which came into force on 2 January 2021, and therefore the classification of studies referred to in the aforementioned template contract shall not apply.

In this sense, it is expressly clarified that the articles referring in the aforementioned template contract to the previous regulation shall be replaced by those regulating the matter in question, namely:

* Clause Two, on obligations of the parties, section B) to Article 9 of the new regulation.
* Clause Three: section 3, relating to the compensation of the research team, to 7.3.
* Clause Ten, on publication of results, to Articles 6.3 and 9.j).

B) The references to Decree 439/2010, of 14 December, regulating healthcare ethics and biomedical research bodies in Andalusia, shall be deemed to refer to Decree 8/2020, of 30 January, which regulates healthcare ethics and biomedical research bodies in Andalusia.

C) References to Spanish data protection regulations shall be understood to refer expressly to Organic Law 3/2018, of 5 December, on the Protection of Personal Data and Guarantee of Digital Rights.

**Second:** That the parties wish to add to the following content related to Anti-corruption to Statement III:

1. The Centre, the Managing Body and the Principal Researcher declare and guarantee that they have not carried out any actions supposing a breach of local or international anti-corruption regulations applicable to this Agreement (hereinafter, “Anti-corruption Legislation”). In addition, they declare that they will ensure that their executives, employees or agents do not commit this type of behaviour. Furthermore, it is specified that neither the Centre, nor the Principal Researcher, nor the Managing Body will, directly or indirectly, make any payments, offers, promises of payment, or deliveries of economic value, and neither will they agree, promise to make payments, or offer or transfer anything of any economic value to any public officials or employees of the Public Administration, to any politicians, to any political parties, or to any candidates to occupy political or public positions, or to any third parties who may be related to the purpose of this Agreement, with the intention of having an influence over any decisions related to the Sponsor or its affiliates and/or its business activity in contravention of Anti-corruption Legislation.

In line with the foregoing, the Centre, the Managing Body and the Principal Researcher state that they have performed and will perform their activity in conformity with that established in Anti-corruption Legislation applicable for this purpose.

In addition, the Centre and the Managing Body will be responsible for keeping appropriate internal accounting control and ensuring that all accounting aspects of the Study are recorded in their books and records in a precise, complete and truthful manner, as well as for the principal aspects of the documents on which said books and records are based being precise, complete and truthful.

The Centre and the Managing Body are to maintain and provide access to the Sponsor and/or to its auditors or any other representatives the latter delegates, whenever this may be requested, to records (financial or of any other kind) as well as the supporting documentation related to the purpose of this Agreement, to document or verify their conformity with the provisions of this clause.

Without detriment to that established in the clauses of this Agreement in relation to Termination and Compensation, respectively, should the Centre, the Managing Body and/or the Principal Researcher breach any of the provisions established in this clause, said breach shall be considered a serious breach of this Agreement and shall entitle the Sponsor to terminate it with immediate effect by means of a written notification to the Centre, the Managing Body and/or the Principal Researcher, with this not causing the Sponsor to incur any kind of financial liability or to have to pay any compensation due to said termination.

2. The parties declare that they know and undertake to comply with Spanish legislation on corrupt practices and/or any against the interests of the Public Administration, including, but not limited to, articles 419 to 427 bis (section 2), related to bribery; articles 428 to 431, related to the exercise of undue influence; articles 432 to 435, related to misappropriation; articles 436 to 438, related to acts of fraud and illegal exaction; articles 439 to 444, related to dealings and activities prohibited for public officials; and article 445 bis (section 2), related to offences of corruption in international transactions, all these articles being of the Criminal Code; and any other related regulations applicable. In addition, the Sponsor declares that it knows and undertakes to comply with the United States Foreign Corrupt Practices Act, or FCPA.

**Third:** That the parties wish to add the following content in clause two, in relation to the Obligations of the Parties:

The Centre certifies that both itself and the Principal Researcher have the licence or authorization, or otherwise the qualification, necessary to perform the Clinical Trial and their corresponding activities, in conformity with any applicable laws, regulations, policies or administrative requirements, and that no applicable regulations or other obligations exist that prohibit the performance of the clinical trial and the conclusion of this agreement. The Centre also certifies that neither itself nor the Principal Researcher have been disqualified, that they have not been prohibited from performing clinical research in any jurisdictions in which they have worked; and that they will in no way request services from any persons disqualified by competent authorities in respect of the services to be performed by virtue of this agreement. During the period of validity of the agreement, and for a period of three years as from its termination, the Centre must inform the Sponsor / CRO immediately should any circumstances that may give rise to disqualification or prohibition on performing the aforementioned activities arise.

**Fourth**: That the parties wish to add the following content in clause three, relating to Economic Aspects:

The Centre, the Managing Body and the Principal Researcher declare that the fees to be paid by virtue of this Agreement represent fair compensation for the actions to be performed.

**Fifth:** That the parties wish to add the following content in clause seven, on Confidentiality and Access to Information:

The Centre undertakes to use all means it has available to guarantee the confidentiality of the information provided by the CRO or the Sponsor to perform the clinical trial, as well as that obtained during the performance of the same (including the Protocol, the Researcher Handbook, details of the clinical trial, details of the biological material analysis, and any other information related to the trial, the investigational drug, and the business plans and technology both of the CRO and of the Sponsor). The Sponsor and the CRO undertake to use all means available to them to guarantee the confidentiality of the information provided in relation to the business plans of the Centre, research or political activities and procedures shared with the Sponsor or the CRO, within the context of the clinical trial.

Each party shall process the confidential information of the other party in conformity with its confidential and secret nature, ensuring the restricted circulation of said information, taking appropriate measures for this and assuming responsibility for all persons having access thereto fulfilling this obligation, in accordance with that agreed in this agreement.

Specifically, the parties undertake the following:

1. To receive and store any confidential information of the other party respecting this nature.

2. To use any confidential information of the other party solely for the purposes and objectives set down in this agreement.

3. To reveal any confidential information of the other party to third parties only with the prior written consent of the owning party and provided that the third party is involved in the clinical trial and undertakes, in addition, to maintain the confidentiality demanded in this agreement.

The foregoing will not be applicable to information in the following cases:

I. Whenever it is or becomes of public domain by any means other than a breach of this confidentiality clause.

II. Whenever it is legitimately received by any third parties without a breach by the parties of this confidentiality clause.

III. Whenever it was known by the corresponding party previously and it was revealed free from any confidentiality obligations.

IV. Whenever it may be mandatory to reveal said information by virtue of law or at the requirement of the corresponding authority.

**Sixth:** That the parties wish to add the following content in clause eigth, relating to Personal Data Protection:

Obligations of the parties:

• The Centre:

1. The Centre, responsible for the processing of medical records and data for research, makes the information described in the research protocol available to the Sponsor responsible for processing the case report form of pseudonymized data.
2. The Centre, via the Principal Researcher, is to process the data of participants as indicated in the protocol. Only those persons indicated on the information and consent form used to formalize the participation of the data subjects may access their personal data.

• The Sponsor:

1. By means of the data management plan included in the protocol, monitoring and audit, the Sponsor must guarantee that the personal data appearing in the documentation related to the trial have been collected in accordance with applicable regulations, with the necessary information to be transmitted to the titleholders in conformity with articles 12 and 13 of the General Data Protection Regulations (GDPR).
2. The Sponsor acts as the data controller in respect of the case report form of pseudonymized data used in the research project and assumes all the functions and obligations imposed in data-protection regulations in this regard. In particular, the inclusion of this processing activity in a record containing the information required in articles 30.1 of the General Data Protection Regulations (GDPR) and 31 of Spanish Organic Act 3/2018, of 5 December, on Personal Data and the guarantee of digital rights (LOPDGDD under the Spanish initials).
3. Whenever the Sponsor is located outside the EU, it must designate a representative in the EU to comply with its obligations as data controller.
4. Should the Sponsor have subscribed to any Code of Conduct relating to data protection in clinical research, it must indicate this subscription and provide evidence of fulfilment of the same. The Sponsor must identify any obligations that such Code imposes on it and which may modify the fulfilment of any of the clauses of this agreement. In addition, it must provide a copy to the signing parties and provide training and appropriate coverage in order for the rest of the parties intervening to be able to know and apply that provided in said Code of Conduct.
5. The Sponsor must conclude the corresponding data processing agreements, in fulfilment of article 28 of the GDPR and article 33 of the LOPDGDD, in respect of any entities contracted or subcontracted that require access to the personal data of the subjects participating in the research project; such is the case of the Contract Research Organization (CRO), the Monitor or the Auditor. Should fulfilment of this requisite not be accredited, the Centre may not provide access to the processing activities for which it is responsible.
6. Access to identified personal data of participants shall be restricted to the study physician / collaborators, healthcare authorities (The Spanish Agency of Medicines and Medical Devices, and foreign healthcare authorities where applicable), to the Research Ethics Committee and/or the Drug Research Ethics Committee (CEIC /CEIm) and personnel authorized by the sponsor (study monitors and auditors), whenever they so require in order to verify the data and procedures of the study, but always maintaining the confidentiality of the same in accordance with legislation in force.
7. In any cases in which the Sponsor may require the consent of those participating in the research project (e.g. in a clinical trial) as a basis for legitimation to process their personal data, proof must be stored of this in the Centre in order to be able to provide evidence of the existence of guarantees that enable the exchange of information between the processing activity of the personal data that comprises the medical record intended for healthcare attention and the scientific research, for which the Centre is responsible, and the case report form of pseudonymized data for which the Sponsor is responsible.
8. The Sponsor knows and accepts that the healthcare institution shall provide instructions and sufficient information on the authorized mechanisms of access and collection of information on the data-processing activities for which it is responsible, from the Principal Researcher, from collaborating personnel, and also from all other professionals involved in the clinical research project (the CRO, the monitor and the auditor). All of the foregoing is in fulfilment of its information security policy and procedures developing the same.
9. Whenever pseudonymized data are worked with in the clinical research project, the Sponsor must adopt the pertinent measures to guarantee the protection of the privacy of the participants, not allowing for their data to be crossed with any other databases that may allow for them to be identified. Should the Sponsor not be able to confirm fulfilment of this requirement, the participants must be informed of the risk of re-identification derived from the reutilization of their data in future studies not presently defined.
10. The Sponsor must perform the corresponding assessment of risks and the impact on data protection prior to the determination of applicable security measures. To do so, it may request the collaboration of suitable personnel of the centre or healthcare institution. The assessment must expressly cover risks of reidentification,considering questions such as the technique applied and the requisites of the case report form, both documented in the data-processing plan of the protocol.
11. All information systems and technological infrastructures used in the clinical research project provided for by the Sponsor must guarantee compliance with the National Security System (in accordance with that provided in Royal Decree 3/2010, of 8 January, regulating the National Security System in the area of Electronic Administration) or equivalent international standard, paying particular attention to the catalogue of security measures applicable in conformity with the category of the system used. Unless otherwise reported, the category of the system by default shall be medium.
12. In any case, the Sponsor must:
13. Guarantee the permanent confidentiality, integrity, availability and resilience of the processing systems and services.
14. Restore the availability of and access to the personal data rapidly, in any cases of physical or technical incidents.
15. Verify, assess and evaluate, on a regular basis, the efficacy of the technical and organizational measures implemented in order to guarantee the security of the processing.
16. Define techniques and provide tools to enable the Centre to pseudonymize the source data derived from medical records.
17. Code the pseudonymized personal data, both for the storage thereof and whenever they are being transmitted (communications).
18. Implement any other measures which, taking into account the overall processing that it performs, may be necessary in order to guarantee a suitable level of security for the risk.
19. Where applicable, for international transfers of the data in the case report form of pseudonymized data to third countries or international organizations, that provided in chapter V of the GDPR and any recommendations or observations made to such effect by supervisory authorities must be taken into account, with national and regional regulations applicable also to be taken into consideration. The necessary

basis for this must be the legal transfer mechanisms admitted, such as suitability decisions, standard contractual clauses or binding corporate rules, which must be reviously authorized by all the parties affected. These mechanisms must be documented, signed and annexed to this agreement as an integral part of the same.

Whenever any one of the guarantees necessary is not provided, an authorization is to be requested from the competent supervisory authority on personal data protection in order to be able to perform the international transfer of data.

* + All parties:

1. Should any of the parties become aware of any breach of personal data (under articles 33 and 34 of the GDPR) in relation to the case report form of pseudonymized data, said party must notify this conveniently and immediately to the other. In such case, the parties are to cooperate fully between each other in order remediate the breach of personal data, comply with appropriate legal obligations of notification and repair any damages.
2. It is determined that the categories of data subjects, in their capacity as the titleholders of the personal data transferred, are [indicate as appropriate]:
3. Citizens  Workers  Patients  Disabled persons
4. Users of Information Systems  Minors  Researchers  Students
5. Others:

**Seventh:** That the parties wish to add the following content in clause nine, on Industrial and Intellectual Property Rights:

Should the performance of the Clinical Trial result in any of the inventions or discoveries referred to in clause eleven of the agreement, the Centre, via the Principal Researcher, must inform the CRO / Sponsor immediately. The Centre, via the researcher, must provide reasonable assistance to the Sponsor to present and process any applications for patents related to said inventions or discoveries, at the expense of the Sponsor.

**Eighth:** That the parties wish to add the following content in clause nine, related to Industrial and Intellectual Property Rights:

Should this matter not be specified in the Study Protocol, in which case that provided therein shall prevail, the parties involved in the performance of the same agree the following:

The Centre, via the Principal Researcher, must provide any publications related to the Study to the Sponsor at least sixty (60) working days before they are sent for publication or disseminated in any other manner. During this period, the publication will be retained in order for the Sponsor to be able to assess its impact. Should it be necessary to apply any measures to protect the intellectual or industrial property rights mentioned, the Sponsor must notify this to the Centre and to the Principal Researcher in writing as soon as possible. In this case, the Principal Researcher must delay the dissemination for an additional period that is not to exceed sixty (60) working days.

During this period of retention, the Sponsor may request the Principal Researcher to eliminate any type of confidential information that has not been published previously from the publication.

Should the Study form part of a multi-centre study, the parties recognize that the first publication will be a joint publication, covering all the centres, and that any subsequent publications must refer to said first publication.

Notwithstanding the foregoing, should a joint manuscription not be sent to all the centres participating within a term of eighteen (18) months following the conclusion of the Study in all participating Centres, the Principal Researcher may publish the results of the Study individually, provided that it fulfils the remaining requisites included in this Agreement.

**Ninth:** That the parties wish to add the following content in clause fifteen, on General Points:

The agreement will come into effect as from the data on which it is signed, or, should it be signed on different dates, on the date on which the last of the signatories signs, and it shall be valid until the finalization of the Clinical Trial, without detriment to any obligations assumed by the parties that may continue to remain in force following the finalization of the same or following the early termination of said agreement.

This agreement may be concluded in two or more copies, each one of which shall be considered an original, and all copies shall jointly constitute one same and single instrument. The parties may sign this agreement in the following manners:

1. All by hand, on paper.
2. All in an electronic form complying with that established in Act 6/2020, of 11 November, regulating certain aspects of electronic trust services, with such signature being valid and binding for all purposes in the same manner as a handwritten signature. For this purpose, it is a priority for it to be signed using the signature of an official electronic certification service provider entity. In this case, it must be possible for the authenticity of the status of the digital identification certificate (such as the Spanish Royal Mint) and the integrity of the signature document to be verified.
3. Exceptionally, should it not be possible for all parties to sign in conformity with that provided in the preceding sections, one party may do so by hand and the other electronically. Nevertheless, it is recommended for the Parties to sign this Agreement in the same manner, in order to reinforce the legal security of the signature.

**Tenth:** That the parties wish to introduce a new clause, seventeen, into the template agreement, and to add content in this related to Inspections by Regulatory Authorities:

The Centre must notify the Sponsor or the CRO, without delay, of any regulatory inspections of the Centre in conformity with this document, for their knowledge, and provide copies of inspection reports related to the clinical trials referred to in this agreement, with either of the two entities being able to make contributions to the answers that are going to be sent to the corresponding authorities. A copy of the final reply sent must be provided.

**Eleventh:** That the parties wish to introduce a new clause, eighteen, into the template agreement, and to add content in this related to Preservation of the Master File:

The documentation relating to the observational study with drugs constitutes the master file of the same, with those essential documents that enable the supervision of the performance thereof and of the quality of the data obtained having to appear recorded therein. Said documents must demonstrate fulfilment by the sponsor and of the researchers of the requisites established for this kind of studies, in accordance with that established in article 17.1 of Royal Decree 957/2020, of 3 November, regulating observational studies with drugs for human use.

The master file of the study shall provide the basis for any audits and for inspections by competent health care authorities, in conformity with that set down in article 17.2 of the mentioned regulation.

In accordance with article 9, section n) of the mentioned Royal Decree 957/2020, the Sponsor is responsible for preserving the content of the master file of the study in accordance with applicable regulations.

In this regard, the parties involved in the performance of the Study agree that the Centre and the Principal Researcher must collaborate in the preservation of the file of the Study in accordance with any instructions for the performance of observational studies published by the Spanish Agency of Medicines and Medical Devices in its web page, in conformity with that established in article 17.3 of said regulation. Medical records are to be stored and preserved in accordance with that provided in Act 41/2002, of 14 November, the basic regulation for the autonomy of patients and rights and obligations in the area of information and clinical documentation and in conformity with any instructions for the performance of observational studies published by the Spanish Agency of Medicines and Medical Devices.

Should, in addition to the Master File stored by the Sponsor, it be agreed for the Centre to preserve copies of the documentation that forms part of the File, and should it not be possible for the file of the Study to be stored during the period of preservation due to exceptional circumstances, the Centre or the Managing Body must contact the Sponsor to organize the transfer of the Study File to the person designated by the Sponsor.

The Researcher and/or the Centre may not destroy the documentation that forms part of the master file of the Study without prior instructions in writing from the Sponsor in this regard, unless they have requested these and the Sponsor has not sent them by a deadline of 30 working days as from the reception of such request, in which case the file of the Study may be destroyed, once the necessary term for it to be preserved has elapsed, in any case.

**Twelfth:** The Parties state that the content of this document does not contravene the content of the Template Agreement published in the Official Journal of the Government of Andalusia number 118, dated 21 June 2019, or legislation in force, and that it responds to the need to specify certain aspects on the part of the Sponsor.

And, in witness of conformity with the full content of this document, the parties intervening in the agreement hereby sign the same.

In Almería, on 31 January 2023

**On behalf of the Centre** **On behalf of the Managing Body**

Signed: Mr Pedro José Acosta Robles Signed: Ms. Sarah Eilis Biel Gleeson

**The CRO on behalf of the Sponsor**  **Read and understood by the Principal Researcher**



Signed: Ms Susana Fraile Fernández Signed: Mr Carlos Hernández Montoya