

**COLLABORATIVE RESEARCH AGREEMENT BETWEEN IVI FOUNDATION AND CHEMO  
RESEARCH, S.L.  
IN RELATION TO THE RESEARCH PROJECT ENTITLED:  
“Effect of cupric sulphate on sperm functionality.”  
(the “Agreement”)**

This Agreement is entered this 31 January 2023 (“Effective Date”) into **BY AND BETWEEN:**

**On the one part,**

- **MR NICOLAS GARRIDO PUCHALT**, holder of Spanish ID Card No. 29183060Q, acting for and behalf of **FUNDACIÓN IVI**, with registered office in Avenida Fernando Abril Martorell, 106 - Torre A, 1<sup>st</sup> floor, 46026 Valencia, and with Tax ID No. G96699566.

Hereinafter referred to as “**FIVI**”

- **MR JUAN ANTONIO GARCÍA VELASCO**, holder of the Spanish ID Card No. 1823265-D, acting for and behalf of **IVI MADRID S.L.**, with registered office in Avenida del Talgo 68, CP 28034 and Tax ID B-81368623. Hereinafter referred to as “**IVI MADRID**”.

- **MR. ALBERTO PACHECO CASTRO**, of legal age, holder of ID No 00827760J acting as Principal Researcher. Hereinafter referred to as “**Principal Researcher**”

- **On the other part, CHEMO RESEARCH, S.L.**, , a company duly incorporated under the laws of Spain, with corporate domicile at Manuel Pombo Angulo, 28, 3<sup>rd</sup> floor, Madrid, Spain Hereinafter referred to as “**CHEMO**”.

FIVI, IVI MADRID and the Principal Researcher shall together be referred to as the “**Site**”.

FIVI, IVI MADRID, the Principal Researcher and CHEMO shall be jointly referred to as the “**Parties**” and each of them, individually, as a “**Party**”.

The Parties have sufficient legal capacity to execute this Agreement.

**WHEREAS**

- I. FIVI is fully devoted to basic research applied to the field of Human Reproduction.
- II. IVI MADRID is a medical institution of the IVI Group whose purpose is to provide services for the treatment of infertility, research and patient care in the field of gynaecology and assisted reproduction, with extensive and proven experience in carrying out and providing

all types of services, analyses, examinations, diagnosis, treatment and services on the problems of human reproduction and sterility, both for men and women.

- III. CHEMO is a company belonging to a large international chemical-pharmaceutical group focused on the research, development, manufacturing, and commercialization of active ingredients and pharmaceutical products, committed to the principles of sustainable development, and focusing its business strategy on the research and innovation.
- IV. Both Parties wish to collaborate to conduct a preclinical study entitled “Effect of cupric sulphate on sperm functionality” (Hereinafter referred to as the “**Study**”).
- V. NOW, THEREFORE, in consideration of the foregoing, the mutual covenants hereinafter set forth, the Parties agree as follows:

## **CLAUSES**

### **ONE. – Purpose of the Agreement**

The purpose of this Agreement is to set forth the terms and conditions under which the Study is to be developed and carried out by the Site in accordance with the protocol of the Study described in Appendix A attached hereto, as amended from time to time (the “Protocol”).

### **TWO. – Acceptance**

The Site hereby agree to conduct the aforementioned Study in accordance with the terms and conditions defined herein and the applicable laws, and with due care, skill and diligence of an orderly entity and loyal businessperson, and, where necessary, in accordance with other specifications included in the most recent version approved by the relevant CEI (Research Ethics Committee).

### **THREE. – Description of the Work**

The work description, responsibilities, and timeline for the performance of the Study by the Site are described in the Protocol.

The Site agree that conduct the Study within the timelines described in the Protocol attached is of the essence of this Agreement. Notwithstanding the foregoing, as soon as the Site become aware of any unforeseen delay that may occur during the Term of this Agreement, the Site shall give CHEMO written notice and shall provide CHEMO with a plan to minimize such delay and the new timings for the performance of the conduct of the Study.

The Site shall be solely and fully responsible for ensuring compliance with all applicable Laws, regulations, applicable guidelines and standards, and shall obtain and maintain all authorizations

or consents required by applicable Laws, regulations, applicable guidelines and standards for the performance of the Study.

#### **FOUR. – Term**

This Agreement shall come into effect on the Effective Date and shall remain in force until the earliest of (i) the completion of the Study as indicated by CHEMO in the protocol; (ii) the 1<sup>st</sup> of November 2024

#### **FIVE. – Compensation**

CHEMO will pay FIVI a lump sum of 12.636€ for the performance of the Study (“Compensation”), as set forth in Appendix B (“Budget”).

The payment of the Compensation shall be performed in one sole instalment at the time of the signature of the present agreement under the conditions established below.

All the invoices shall be payable by CHEMO within sixty (60) calendar days from the date of the invoice to the following bank account:

**BANK ACCOUNT DETAILS FOR PAYMENT TO IVI MADRID:**

Account holder: FIVI

Bank Name: CAIXABANK, S.A

Bank Adress: c/ Pintor Sorolla nº 2, 46002 Valencia

IBAN Number: ES68-2100-3835-5302-0005-0157

SWIFT CODE: CAIXESBBXXX

Contact person: Carmen.Rodriguez@ivirma.com

For the avoidance of doubt, upon the signature of the present Agreement and once FIVI issues the relevant invoice, CHEMO shall pay the Compensation within sixty (60) days after the reception of the invoice, provided that, and upon to, sixty (60) calendar days have been elapsed from the date of receipt by CHEMO of such invoice.

Taxes levied on the transactions provided for in this Agreement shall be borne by the Parties, as the case may be, in accordance with the applicable law.

#### **SIX. – Confidentiality and Data Protection**

##### **6.1. Confidentiality**

a. Confidential Information. The Parties agree to maintain the confidentiality of any type of scientific and technical information provided by any Party and/or its Affiliates (“Disclosing Party”) to the other Party and/or its Affiliates (“Receiving Party”). “Confidential Information” means all information (whether economic, financial, technical, commercial, pharmaceutical,

chemical, strategic or any other kind of information), which is exchanged by the Parties during the term of Agreement by any means, including written, electronic, and verbal, whether identified or not as "Confidential". In particular, the information and documentation related to the Results, and the Results themselves, shall be considered as Confidential Information.

"Affiliate" shall mean, with respect to a Party, any corporation or other legal entity, directly or indirectly, controlled by, controlling or under common control with a Party; and the term "control" shall mean direct or indirect ownership of the voting stock or securities (or other comparable ownership interest) of more than fifty percent (50%) of such corporation or legal entity, or the power to direct or cause the direction of the management and policies of such corporation or legal entity, directly or indirectly, through ownership of stock, by contract or otherwise.

b. Exclusions. Confidential Information does not include information that:

(1) becomes public information or is generally available to the public other than by an unauthorized act or omission of the Receiving Party;

(2) is received by the Receiving Party from third parties who rightfully possess the information and have the legal right to make a disclosure;

(3) the Receiving Party can show by written records its possession of the information before the time of the disclosure and that the information was acquired legally and not directly or indirectly from the Disclosing Party;

(4) is generated by employees or Affiliates of the Receiving Party who did not have access to the Confidential Information as evidenced by written records.

c. Obligation. Except as required by law, the Receiving Party shall maintain in strict confidence, and shall not use or disclose, except as expressly permitted under this Agreement, any Confidential Information received from the Disclosing Party. In the event the Recipient Party is required by law to disclose the Confidential Information, the Recipient Party shall notify the Disclosing Party, as soon as legally possible, of such circumstance.

Each Party further agrees to use the same degree of care to maintain the confidentiality of all Confidential Information received from the other Party that it uses to maintain the confidentiality of its own information of similar importance, but in no event will it use less than reasonable care.

d. These confidentiality obligations shall be applicable to the workers, employees, staff, self-employees, legal and financial and professional advisors, auditors and personnel of the Parties ("Representatives"), who shall be identified and shall execute a confidentiality agreement that warrants the confidentiality and secrecy of the Confidential Information in the terms and conditions of this Agreement. In all cases, each Party shall be liable, at any moment

and under any circumstance, of any breach of the obligations resulting from this Agreement, including in the event that such breach is attributed to one or several Representatives.

- e. The obligations of confidentiality shall remain in force for as long as the Confidential Information remains confidential and does not fall in the public domain due to infringement of this Agreement by any of the Parties.

## **6.2. Data protection**

In the performance of this Agreement, the Parties may have to collect, use and/or disclose personal data in compliance with all currently applicable laws and regulations, in particular relating to protection of personal data, including without limitation Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (General Data Protection Regulation, “**GDPR**”) and Organic Law 3/2018 of December 5, on the Protection of Personal Data (“**LOPDGDD**”), as amended from time to time, and/or any subsequent legislation in relation to the protection of personal data (all together referred to as “**Data Protection Laws**”).

The Parties declare that they are aware of, comply with and expressly submit to Data Protection Laws, undertaking to make correct use of the personal data obtained within the framework of this Agreement although personal data are duly pseudonymized.

The Parties agree that the Site is responsible and data controller of medical records and patients health data files (source data) collected within the Study, being responsible for the processing of participant’s personal data for healthcare purposes and assistance and, as the case may be, its research purposes in accordance herewith. Chemo, as sponsor of the Study, is responsible for designing the protocol and monitoring the Study, being considered data controller with regard to research data obtained during the Study. In any case, personal data submitted to Chemo shall be prior pseudonymized and coded by the Site so as not to be possible to identify the participants.

In compliance with the Data Protection Laws, each Party undertakes to comply with all the legal obligations that may apply to it, and, in particular, to comply with the following:

6.2.1 To carry out the processing activities for which each Party is responsible in accordance with the provisions of the Study and the present Agreement, and with the applicable legislation.

6.2.2 The Parties will respectively provide the information concerning the processing of data of the parties individually as indicated in articles 13 and 14 of the GDPR, to those data subjects or natural persons that are relevant and necessary for the execution of the agreement.

6.2.3 The Parties shall attend any request for the exercise of personal rights that may arise in the performance of the specific processing activities. During the Study, the Site should serve as the only contact for participants and for the exercise of their data protection rights. To the extent that a participant directly contact the Site and its request is transferred to Chemo, the Site ensures that no identifying data of the participant will be attached and communicated to Chemo.

In any case, the Party who receives a request for the exercise of rights must inform the other Party, especially in view of the possibility that the data subject or interested party may, in any case, exercise the rights recognised by the applicable regulations against each of the Parties.

6.2.4 In addition, the Parties and, in particular, the Site when processing personal data according to the Protocol, shall ensure that:

- The principles of personal data processing referred to in Article 5 of the GDPR, included the privacy by design and by default principle are observed. Transparent, clear and simple information is provided on the data processing envisaged, as well as on the rest of the legal provisions to that effect.
- The personal data collected from participants is processed for the sole purposes of the Study and, in particular, the Site undertakes to process personal data according to the instructions and research purposes of the protocol of the Study.
- Personal data of participant is not communicated or processed by third parties nor transferred to third parties located outside the EU territory unless prior authorized and foreseen in the protocol of the Study. In case of being necessary such data transfer outside the European Economic Area ("EEA") (i.e. Member States of the European Union in addition to Norway, Iceland & Liechtenstein), the Party conducting the data transfer shall ensure the appropriate legitimation for such processing and apply the safety measures needed to ensure data protection compliance in accordance with the GDPR.
- The legal basis necessary for the legitimate processing of the personal information concerned in each case is met. When such legal basis is based on the data subject's consent, it shall also be ensured that the necessary conditions for its validity are met in accordance with the provisions of Articles 7 and 8 of the GDPR and the applicable state regulations. In particular, the Site shall be responsible for informing and ensuring that all participants have reviewed and signed the required informed consent before participating in the Study, drafted and provided by Chemo.
- The necessary technical, organisational and security measures are adopted at all times according to Article 32 of the GDPR in order to address the risks of varying likelihood and severity to the rights and freedoms of natural persons. This takes into account the nature, scope, context and purposes of the processing, as well as such risks, especially the unintentional or illegal destruction, loss, alteration, unauthorized disclosures or access to personal data. When submitting personal data to Chemo, the Site shall adopt appropriate measures to ensure that personal data of participants are duly coded and pseudonymized so they do not include any personal information that may identify individuals.
- The notification obligations referred to in Articles 33 and 34 of the GDPR are complied with and the other Party is informed in advance, providing each other with mutual assistance to investigate, remediate and notify any data breach within the Study. This notification must be accompanied, when available, by all documents and information that may enable the Party to report the data breach to the competent supervisory authority.

- Due assistance and support is provided to the other Party in the possible performance of Personal Data Protection Impact Assessments (PDIA) when appropriate or when it is agreed by the parties with regard to the processing activities in question.
- They comply at all times with all legal obligations regarding the protection of personal data and that documentation which serves as proof of proper data processing activities is duly retained by each of the Parties.

6.2.5 The Parties shall observe the strictest confidentiality and duty of secrecy with respect to the information or data that may be provided within the Study, including the codes, user identifications and/or passwords of the systems that may be provided. The obligations of confidentiality and secrecy established in this document shall have an indefinite duration, remaining in force after the termination, for any reason, of the relationship between the Parties. Likewise, the Parties declare that all persons entrusted with data processing have been obliged to maintain confidentiality and they are subject to a contractual/ legal obligation of confidentiality.

6.2.6. The Site agrees to make available to Chemo any information or documents expressly requested to enable the Sponsor to demonstrate, monitor and supervise compliance with obligations and instructions set out herein and in the protocol for research purposes of the Study.

6.2.7. In case the Site needs to outsource the provision of services to comply with its obligations under this Agreement, the Site shall inform Chemo before the contract with the processor is concluded. The Site shall enter into a data processing agreement in accordance with Article 28 of the GDPR and impose the same data protection obligations as the ones set out herein.

6.2.8. Upon termination of this Agreement and the Study, the Site shall return to Chemo all coded research data collected during the Study for the sole research purposes of the protocol, and destroy its copies unless there is a legal requirement to be kept by the Site.

In addition, each Party shall process Personal Data of the other Party in order to manage its relationship as required to execute this Agreement (mainly employees' and representatives' contact details). The legal representatives / signatories of the parties to this Agreement as well as any other individuals whose personal data is processed to execute this Agreement shall have the rights pertaining to data subjects in terms of the GPDR, namely, the right to obtain confirmation whether the other party is processing their personal data, to access their personal data, to request rectification and request deletion when the data is no longer necessary. These rights can be exercised through the following email address:

- CHEMO: data.protection@insudpharma.com
- IVI MADRID: DPO@ivirma.com

The obligations contained in this section shall survive the termination or expiry of the Agreement for as long as personal data collected for the Study remains in the possession of the Site.

Each Party shall be liable for the damage caused by the processing not in compliance with the GDPR and shall indemnify the other Party against claims for damages by third parties or fines. The Party contracting a processor shall be liable to the other Parties for any fault of its processor

as for its own fault to the extent the other Parties suffers a damage as a result of such faults. In addition, the Site shall be liable to Chemo for any damage, fine or claim arising as a consequence of the data processing carried out not in compliance with instructions provided in the protocol with regard to the Study purposes.

#### **SEVEN. – Industrial and Intellectual Property Rights and Publication of Results**

For the purposes of this Agreement, “**Intellectual Property Rights**” shall mean (i) patents, patent applications, provisional patents, divisional patents, continuations in part, utility models, designs and design inventions (whether registered or unregistered), any other intellectual property right in connection with any type of invention of whatever nature, trade secrets, know-how, copyright and related rights, database rights, trademarks and related goodwill, trade names (whether registered or unregistered), and rights to apply for registration; (ii) domain names, applications, extensions and renewals in relation to any of these rights; and/or (iii) all other rights of a similar nature or having an equivalent effect (anywhere in the world), including, but not limited to, any and all rights under the regulations on intellectual, industrial and/or copyright property rights.

Any Intellectual Property Rights relating to the activities that have been acquired and/or developed by the Parties, prior to the conduct of the Study, shall belong to its owner, as evidenced by written records (“**Background IPR**”).

For the purposes of this Agreement, (i) all the data, results, discoveries, inventions, information, and reports resulting from the Study and this Agreement (“**Results**”), and (ii) the potential Intellectual Property Rights thereof, whether or not patentable, shall be the exclusive and absolute property of CHEMO or its Affiliates, and the Site shall refrain from claiming any ownership rights or trying to acquire protection over the Results or potential Intellectual Property Rights thereof. Assignment and transfer to CHEMO. The Site hereby assigns and transfers, and shall ensure that its Affiliates and employees assign and transfer, to CHEMO, or CHEMO’s designee, all Intellectual Property Rights over the Results (and all materials embodying these rights) to the fullest extent permitted by Law, without reservations or limitations, and without any additional compensation. The Site expressly waives any claim, whether present or future, under the Results and the Intellectual Property Rights mentioned herein and acknowledges that CHEMO, or its designee as the case may be, is entitled to assign and/or license the Intellectual Property Rights and the Results.

The Site undertakes to execute, and shall ensure that its Affiliates and employees execute, all documents, make all applications, give all assistance and do all acts and things, at the expense of CHEMO and, at any time either during or after the Agreement, as may, in the opinion of CHEMO, be necessary or desirable to vest the Intellectual Property Rights in, register, obtain or



maintain any and all Intellectual Property Rights or register the Results in the name and on behalf of CHEMO or its Affiliates; and to defend CHEMO against claims embodying the Intellectual Property Rights or the Results infringe third party rights, and otherwise to protect, enforce and maintain such Intellectual Property Rights and Results.

Site's representations, warranties, and undertakings.

(a) The Site undertakes that its directors, employees, subcontractors, agents, representatives, and the Site have given, and shall give, written undertakings in the same terms applicable to the Site.

(b) The Site represents and warrants to CHEMO and undertakes to:

- i. notify CHEMO in writing full details of all Results promptly;
- ii. keep and treat any potential or actual Intellectual Property Rights, and the Results as Confidential Information;
- iii. whenever requested to do so by CHEMO and, in any event, on the termination of the Agreement (for any reason whatsoever), promptly to deliver to CHEMO all correspondence, documents, papers and records on all media (and all copies or abstracts of them), recording or relating to any part of the Results and the process of their creation using the necessary resources to keep such information secret and confidential;
- iv. not to acquire, register, nor attempt to do so, any of the Intellectual Property Rights in the Results, unless requested in writing to do so by CHEMO; and
- v. not proceed, neither its employees, with any publication, submission for publication or presentation of the Services, the Results, or other information related to the Services without having obtained the prior written approval from CHEMO.

(c) The Site represents and warrants to CHEMO that the Site has not given and will not give permission or authorization to the Site or to any third party to use the Results, nor any of the Intellectual Property Rights in the Results. No terms or Clauses of this Agreement shall be construed as a concession, assignment or granting of any rights or licenses to the Site or to any third party, whether implied or express, of any of the Results or Intellectual Property Rights (neither prior to nor after the date of this Agreement).

No further remuneration. The Site agrees and acknowledges that no further remuneration or compensation other than that provided for in this Agreement is or may become due to the Site in respect of the provisions of this Clause SEVEN.

**Use and Publication of Results**

As required by the applicable laws, the Parties undertake to publish the Results of the Study (both positive and negative results). Members of the Parties shall contribute to the publication of the Results, especially those individuals who had actively participated in the Study, as evidenced by

Site's written records. Each Party will choose the individuals who will participate in the Study and when it comes to the publication of Results, both the first and last author, shall be members of each Party.

Notwithstanding the foregoing, the Site shall obtain prior written consent and approval from CHEMO in order to publish any Results, data, and/or information from the Project, CHEMO shall have 45 days from receipt of such manuscripts and materials to review and comment. In absence of a response within the period specified, the authorization for publication shall be deemed to have been granted. CHEMO shall have the right to delay the publication and/or use of the Results up to four (4) months and amend any proposed publication or presentation on reasonable grounds prior to submission to (i) ensure the accuracy of the presentation or publication, (ii) ensure that proprietary information is not inadvertently divulged, (iii) enable Intellectual Property Rights to be secured, and/or (iv) enable relevant supplementary information to be provided.

Any scientific communication made by CHEMO, which may use the data generated during the Study, shall include an express reference to the Site with the explicit statement that the data were obtained from IVI in the framework of the Study's execution and the date of obtention.

Any communication made by the Site, which may use the data generated during the Study, shall include an express reference to CHEMO with an explicit statement that the data were obtained from CHEMO in the framework of the Study's execution and the date of obtention.

#### **EIGHT. – Independent Contractors**

Each of the Parties is an independent contractor and nothing herein contained shall be deemed to constitute the relationship of partners, joint ventures, nor of principal and agent between the Parties. Neither Party shall at any time enter into, incur, or hold itself out to Third Parties as having authority to enter into or incur, on behalf of the other Party, any commitment, expense, or liability whatsoever.

#### **NINE. - Termination**

If any of the Parties breaches the terms of this Agreement, the offended Party shall notify the other Party of the breach. In the event a breach is not cured or remedied by the breaching Party within thirty (30) calendar days after the offended Party's notice, the offended Party shall have the right to terminate this Agreement immediately without penalty.

If at any time and with no cause CHEMO decides to unilaterally terminate the Agreement, IVI MADRID must be notified with at least thirty (30) calendar-days to the effective termination date, in which case (i) all payments already performed by CHEMO in favor of FIVI shall not be refundable in any case, regardless the date of termination; and (ii) CHEMO will be responsible for the non-cancellable, non-refundable or irrevocable incurred costs, expenses and pass-through

costs (as expressly established in Appendix BI, if any) due until such termination date; and in both cases FIVI being obliged to provide CHEMO with the required documentation evidencing proper performance of services and such costs, expense and pass-through costs.

For clarity, in the event of early termination of this Agreement (for any reason whatsoever) the Site shall (i) use all reasonable efforts to conclude the uncompleted services related to the Study as directed by CHEMO, as expeditiously as possible; and/or (ii) transfer within thirty (30) calendar days after the termination all the information and Results of the Study; and (iii) return to CHEMO all its Confidential Information within thirty (30) calendar days after the expiration or termination of this Agreement, with the exception of retention of one archival copy which shall be kept confidential and may be used solely for the purpose of monitoring compliance with the confidentiality and non-use provisions of this Agreement.

CHEMO shall return to the Site all its Confidential Information disclosed under this Agreement within thirty (30) calendar days after the expiration or termination of this Agreement, with the exception of retention of one archival copy which shall be kept confidential and may be used solely for the purpose of monitoring compliance with the confidentiality and non-use provisions of this Agreement.

#### **TEN. – Liability and Reciprocal Indemnity**

##### **A) Liability**

In no event shall either Party be liable for any special, incidental, consequential, punitive, or indirect losses or damages (including, without limitation loss, modification and/or unavailability of data, revenue, profits, use, or other economic advantage) arising out of, or in any way connected with the purpose of this Agreement.

##### **B) Reciprocal Indemnity**

To the extent not caused by (a) the gross negligence or wilful misconduct of the other Party, or and/or (b) failure of the other Party to comply with the terms of this Agreement, each Party shall indemnify, defend and hold the other Party, its Affiliates, and their respective directors, officers, and employees harmless against any and all claims, liabilities, damages, losses, costs, expenses (including, but not limited to settlements, judgments, court costs and reasonable attorneys' fees) and any loss or damage arising out of or relating to (i) the breach of its obligations under this Agreement; and/or (ii) wilful misconduct and/or negligence of the Party in the performance of its obligations under this Agreement.

#### **ELEVEN. – Insurance**

Each Party undertakes to have in force an appropriate liability insurance policy with sufficient level of cover and with other terms of insurance in accordance with the purposes of this Agreement. All Parties undertake to maintain such insurance policy during the term of this Agreement.

The Site shall comply with all terms and conditions of the insurance policies at all times. If cover under the insurance policies shall lapse or not be renewed or be changed in any material way or if the Site is aware of any reason why the cover under the insurance policies may elapse or not be renewed or be changed in any material way, the Site shall notify CHEMO without delay.

**TWELVE. – Assignment and Subcontracting**

The Site shall not assign or transfer the Agreement of any interest therein, in whole or in part, without the prior written consent of CHEMO. Any such assignment or transfer shall be null and void. In the event of an assignment or subcontracting authorized by CHEMO, the Site shall be, in all cases, jointly and severally liable in front of CHEMO and its Affiliates for the compliance of all Clauses, rights, and obligations under this Agreement assumed by the assignee or subcontractor.

Notwithstanding the foregoing, CHEMO shall be entitled to assign, at any time, its contractual position, and its rights and obligations arising from the Agreement, in whole or in part, to any third party, in which case CHEMO shall be obliged to inform the Site about such circumstance with, at least, fifteen (15) calendar day prior notice.

**THIRTEEN. – Notices**

Any notices or other communications to be served or sent to either Party shall be in writing and shall be sufficiently sent if delivered in person or by registered prepaid airmail. The Parties expressly designate by means of this Agreement that the address for any communications is the address established in the heading of this Agreement or such other address as may from time to time be notified in writing by that Party to the other.

**FOURTEEN. – Amendments**

This agreement may not be amended, altered, or complemented except by a written document duly signed by all Parties.

**FIFTEEN. – Force Majeure**

In the event of a delay caused by, without limitation, inclement weather, fire, flood, strike or other labour dispute, acts of God, acts of Governmental officials or agencies, or any other cause that were are not reasonable foreseeable by the affected Party, and beyond the control of the Site and/or CHEMO, either or both Parties shall be excused from performance hereunder for the period or periods of time attributable to such delay, which may extend beyond the time lost due to one or more of the causes mentioned above. In the event that any such delay fundamentally changes the circumstances, causing the unenforceability of this Agreement, then this Agreement may be revised by changing the maximum amount, performance period, and other provisions, as appropriate, by mutual agreement of the Parties.

**SIXTEEN. – Waivers and Rights**

Neither Party may waive any right or provision of this Agreement, grant its consent or approval as required by this Agreement or grant its consent or approval for the other Party to desist, in whole or in part, from the execution or performance thereof, unless it is in writing and signed by the Party against whom the application of such waiver, consent or approval is sought. Such waiver, consent or approval shall be effective only for the specific instance and for the purposes for which it was given. In no event shall the failure or delay of either Party to exercise or enforce any condition, provision, remedy, measure, right or part of this Agreement be construed as (i) a waiver of the condition, provision, remedy, measure, right or part thereof or (ii) a loss of the right to enforce it in the future.

Except as otherwise provided, the rights of each Party shall be deemed to be cumulative in nature and the exercise of any one of them shall not be deemed to restrict the exercise of any other right granted under this Agreement or under applicable Law.

**SEVENTEEN. – Partial Nullity or Supervening Illegality**

If any provision of this Agreement is or becomes void, illegal, or ineffective, the validity, legality and effectiveness of the remaining provisions shall in no event be affected or impaired. In such event, the Parties shall negotiate in good faith the new terms of the void, illegal or ineffective provision in such a way that its effects are as close as possible to those of the void, illegal or ineffective provision.

**EIGHTEEN. – Warranties**

Without prejudice to any other representation or warranty established under this Agreement, the Site represents and warrants that:

- (i) The Site has read and understood CHEMO's ABC Book (available at <https://www.insudpharma.com/en/transparency/>), and that has been in compliance with the principles of the ABC Book.
- (ii) The Site hereby also warrants CHEMO that it is not debarred by any relevant regulatory authority, including, but not limited to, the European Medicines Agency (EMA) and the Federal Drug Administration (FDA), and that it will not carry out the Services through any employee and/or permitted contractor (if applicable) that are debarred by a Regulatory Authority. The Company shall notify immediately in the event the Site or any of its employees or permitted contractors (if applicable) (i) is under investigation by any relevant Regulatory Authority for debarment action or is presently debarred pursuant to any relevant regulations, or (ii) has a disqualification hearing pending, or (iii) has been disqualified or debarred by any relevant Regulatory Authority.

The Site and CHEMO make no warranties for any purpose whatsoever, express, or implied, as to the Study or the results of the Study, including the merchantability or fitness for a particular purpose of the Study or the Results of the Site under this Agreement.

### NINETEEN.- Governing Law and Jurisdiction

The validity, construction and performance of this Agreement shall be governed by the Spanish common laws.

All disputes arising out of or in connection with this Agreement shall be finally settled under the Courts of the city of Madrid (Spain). Both Parties expressly waive their own jurisdiction.

IN WITNESS whereof the Parties hereto have signed this Agreement in triplicate for one unique effect. This Agreement has been executed on the date first above written.

#### IVI FOUNDATION

DocuSigned by:  
*Nicolás Garrido Puchalt*  
Nombre del firmante: Nicolás Garrido Puchalt  
Motivo de la firma: Apruebo este documento  
Hora de firma: 31-Jan-2023 | 02:31 PST  
B3D77C8A355542FB8CB22D3014426767

Dr. Nicolas Garrido Puchalt

#### IVI MADRID

DocuSigned by:  
*Juan Antonio García Velasco*  
Nombre del firmante: Juan Antonio García Velasco  
Motivo de la firma: Apruebo este documento  
Hora de firma: 31-ene.-2023 | 03:25 EST  
96C94CA1CCD646688FBB40B960C837CB

Dr. Juan Antonio García Velasco

#### PRINCIPAL RESEARCHER

DocuSigned by:  
*Alberto Pacheco Castro*  
Nombre del firmante: Alberto Pacheco Castro  
Motivo de la firma: Apruebo este documento  
Hora de firma: 06-feb.-2023 | 12:40 CET  
87AF373FD9F7468FA0834426DE1FCD14

Dr. Alberto Pacheco Castro

#### CHEMO RESEARCH, S.L.

DocuSigned by:  
*Enrico Colli*  
Signer Name: Enrico Colli  
Signing Reason: I approve this document  
Signing Time: 31-Jan-2023 | 09:22 CET  
7A024DD0DC2A4F9EB54889670EC54350

Dr. Enrico Colli

Appendix A

# Protocolo de Investigación Biomédica

2208-MAD-107-AP

[Subject]

## Project Title

## Título del Proyecto

Efecto del sulfato de cobre sobre la funcionalidad espermática

**Código de Proyecto:** 2208-MAD-107-AP

**Línea de investigación:** Male fertility, testicular and sperm biology, diagnosis and selection

**Fecha de Alta:** 01/09/2022

**Palabras clave:**

[Keywords]

## Datos del Promotor

**Nombre** IVI Madrid

**Dirección** Avda. del Talgo 68

**Correo electrónico** [ivimadrid@ivirma.com](mailto:ivimadrid@ivirma.com)

**Teléfono / Fax** 911802900

## Datos de los investigadores principales

**Nombre y Apellidos** Alberto Pacheco

**Filiación** IVI Madrid

**Correo electrónico** [Alberto.Pacheco@ivirma.com](mailto:Alberto.Pacheco@ivirma.com)

**Teléfono / Fax** 911802900

## Datos del responsable de la gestión administrativa del estudio

**Nombre y Apellidos** Alberto Pacheco

**Filiación** IVI Madrid

**Correo electrónico** [Alberto.Pacheco@ivirma.com](mailto:Alberto.Pacheco@ivirma.com)

**Teléfono / Fax** 911802900



## Investigadores colaboradores

---

Nombre y Apellidos	Patricia Aspiazu
Filiación	IVI Madrid
Correo electrónico	Patricia.aspiazu@ivirma.com
Teléfono / Fax	911802900

---

Nombre y Apellidos	Nuria García
Filiación	IVI Madrid
Correo electrónico	Nuria.Garcia@ivirma.com
Teléfono / Fax	911802900

---

Nombre y Apellidos	Rubén Salvanés
Filiación	IVI Madrid
Correo electrónico	Ruben.salvanes@ivirma.com
Teléfono / Fax	911802900

---

## Responsabilidades y firmas

Al firmar este protocolo del proyecto titulado:

Los abajo firmantes afirman que:

- El estudio respeta las normas éticas y legales aplicables a este tipo de estudios y seguirá las normas de buena práctica clínica en su realización.
- Cuenta con los recursos materiales y humanos necesarios para llevar a cabo el estudio, sin que ello interfiera en la realización de otro tipo de estudios ni en otras tareas clínicas que tiene habitualmente encomendadas.
- Se comprometen a que cada sujeto sea tratado y controlado siguiendo lo establecido en el protocolo con dictamen favorable por el Comité Ético de Investigación Clínica y resto de comités y autoridades implicadas.
- Los colaboradores que se incluyen en el estudio están adecuadamente formados para su realización, tendrán una participación activa y consienten la misma.

### Director/a de laboratorio y/o Clínica



---


Dr/a. Alberto Pacheco Castro

---

Fecha 01/09/2022

Director/a de laboratorio/Clínica IVIRMA Madrid

### Investigador principal



---

Dr/a. Alberto Pacheco Castro

---

Fecha 1/09/2022

Director/a de laboratorio/Clínica IVIRMA Madrid

---

## Contenido

• Project Title .....	16
• Título del Proyecto .....	16
Datos del Promotor .....	16
Datos de los investigadores principales .....	16
Datos del responsable de la gestión administrativa del estudio .....	16
Investigadores colaboradores .....	17
Responsabilidades y firmas .....	18
Contenido .....	19
• Abstract .....	20
• Resumen.....	20
Lista de acrónimos .....	20
• AIM: main objective/research question.....	21
• Objetivo Principal .....	21
Introducción .....	21
A. Antecedentes: .....	21
B. Justificación: .....	22
Metodología.....	22
A. Diseño del Estudio.....	22
B. Periodo del estudio y contexto .....	22
C. Población de referencia .....	22
D. Criterios de selección .....	23
Metodología estadística.....	24
A. Base de datos .....	24
B. Variables de estudio.....	25
C. Tamaño muestral y potencia del estudio.....	25
D. Análisis estadístico de datos .....	26
Plan de Trabajo.....	26
Consideraciones éticas.....	28
Financiación.....	28
ANEXO 1. Estimación de los costes marginales del proyecto de investigación. .. <b>Error! Bookmark not defined.</b>	
Publicación y Difusión .....	29
Bibliografía .....	29

## Abstract

In order to perform their function physiologically, spermatozoa must be able to pass through the female reproductive tract and simultaneously acquire the fertilizing capacity through the process of sperm capacitation. These processes are highly dependent on the ion flux inside the cell and the extracellular pH/ions content and conductivity. For that reason, alterations in the ion content of the extracellular media can favor or, on the contrary, inhibit sperm function. The aim of the present experimental pilot study is to test the effect of copper sulfate on the impairment of sperm functionality (sperm motility and vitality) in semen samples, to determine whether this compound could potentially be used in the future as the basis of a non-hormonal contraceptive, thus presenting fewer adverse effects.

## Resumen

Para realizar su función de forma fisiológica, los espermatozoides deben ser capaces de atravesar el tracto reproductivo femenino y, al mismo tiempo, adquirir la capacidad fecundante mediante el proceso de capacitación espermática. Estos procesos dependen en gran medida del flujo de iones en el interior de la célula y del contenido de pH/iones extracelulares y de la conductividad. Por ello, las alteraciones en el contenido iónico del medio extracelular pueden favorecer o, por el contrario, inhibir la función espermática. El objetivo del presente estudio piloto experimental es comprobar el efecto del sulfato de cobre sobre la alteración de la funcionalidad espermática (movilidad y vitalidad de los espermatozoides) en muestras de semen, para determinar si este compuesto podría utilizarse en el futuro como base de un anticonceptivo no hormonal, presentando así menos efectos adversos que los actuales.

## Lista de acrónimos

SC	Sulfato de cobre
SIVIS	Plataforma digital de gestión de la información de IVI

## AIM: main objective/research question

The main objective of the study is to determine the efficacy of copper sulphate as a sperm motility inhibitor for potential use as a non-hormonal contraceptive.

## Objetivo Principal

El objetivo principal del estudio es determinar la eficacia del sulfato de cobre como inhibidor de la movilidad espermática para su potencial uso como anticonceptivo no hormonal.

## Introducción

### A. ANTECEDENTES:

El espermatozoide es la única célula del cuerpo que debe realizar su función, la fecundación del óvulo, fuera del organismo que la generó y además principalmente en un entorno hostil. Esta capacidad fecundante la va adquiriendo a medida que atraviesa el tracto reproductor femenino (1). En este sentido, cuando los espermatozoides son depositados en la vagina y entran en contacto con las secreciones del tracto genital femenino, deben realizar dos procesos íntimamente conectados: a) deben llegar a la proximidad del óvulo, y para ello, gracias a la movilidad espermática, deben realizar un trayecto hasta las trompas a través del moco cervical, guiados por un gradiente de moléculas liberadas en el fluido folicular por componentes celulares del tracto reproductor femenino, que servirá para seleccionar los más adecuados, y b) adquirir la capacidad fecundante en un proceso, denominado globalmente capacitación espermática, en el que se incluyen un gran número de reacciones bioquímicas mediadas a menudo por un flujo de iones en el exterior e interior celular (2-3). Cerca ya del ovocito, se producirán los últimos procesos como la activación de la reacción acrosómica e hiperactivación, la cual es indispensable para la unión del espermatozoide al óvulo y su posterior fecundación (4). Por ello, en todos estos procesos es fundamental tanto la adecuada movilidad espermática, como el flujo de iones y equilibrio electrostático en el entorno del aparato reproductor femenino donde se produce la activación espermática. En este sentido, se han descrito numerosos estudios donde se utilizan compuestos que mejoran la movilidad espermática o la capacidad funcional (5).

Pero también hay algunos estudios publicados donde, basándose en estos requerimientos funcionales de los espermatozoides, están estudiando determinados compuestos que producen una acción inhibitoria de la movilidad espermática o de la capacidad funcional (6-9), lo cual puede ser de gran interés para el desarrollo de métodos anticonceptivos alternativos a los hormonales, que produzcan menos efectos secundarios para la mujer.

## **B. JUSTIFICACIÓN:**

La modificación de la movilidad espermática y/o la capacidad fecundante mediante la utilización de determinados compuestos que alteren el flujo de iones entre el exterior y el interior celular puede ser muy relevante tanto para aumentar la capacidad fecundante, como para inhibir la actividad espermática. En este último caso, ya hay trabajos publicados que emplean diferentes compuestos que inhiben o bloquean total o parcialmente la movilidad espermática. Estos compuestos podrían ser utilizados como principio activo de dispositivos anticonceptivos que, a diferencia de los métodos basados en el bloqueo hormonal, no produzcan efectos secundarios, lo cual sería de gran utilidad e impacto en la mejora de los métodos anticonceptivos.

En este sentido, el objetivo del presente estudio piloto es evaluar el impacto del sulfato de cobre (SC) como inhibidor de la funcionalidad espermática, analizando el efecto de diferentes dosis y a diferentes tiempos del sulfato de cobre sobre muestras de semen de una población de individuos candidatos a donantes masculinos de IVI.

## **Metodología**

### **A. DISEÑO DEL ESTUDIO**

Análisis prospectivo experimental para evaluar el efecto del sulfato de cobre (SC) sobre la movilidad y vitalidad espermática en 40 muestras de semen procedentes de una población masculina de edad fértil.

Para la realización del estudio, se partirá de una solución stock de sulfato de cobre (a 1,9 mM de concentración), de la que se prepararán 5 soluciones de trabajo de SC: 0,75 mM, 0,6 mM, 0,45 mM, 0,30 mM y 0,15 mM con buffer de dilución.

### **B. PERIODO DEL ESTUDIO Y CONTEXTO**

El periodo del estudio se llevará a cabo en la clínica IVI Madrid y tendrá una duración aproximada de 3 meses en total: un periodo estimado de inclusión de pacientes de 2 meses, más 2 meses posteriores para la evaluación y análisis de los resultados, y redacción de la publicación.

### **C. POBLACIÓN DE REFERENCIA**

Varones de entre 18 y 35 años de edad, candidatos a donantes de semen del Banco de Semen de IVI Madrid.

## D. CRITERIOS DE SELECCIÓN

Se incluirán a todos aquellos individuos que acudan a la clínica IVI Madrid para hacerse las pruebas de calidad espermática dentro del proceso de selección de candidatos a donantes de semen, y que acepten voluntariamente la participación en el estudio.

Se excluirán del estudio aquellos individuos que no presenten espermatozoides en el eyaculado, que tengan una movilidad espermática inferior al 10%, o que presenten alguna patología infecciosa que pueda interferir con la calidad seminal.

## E. INTERVENCIÓN Y SEGUIMIENTO

Los pacientes no requerirán intervenciones y seguimientos más allá de los establecidos por la práctica clínica habitual de la donación de semen.

## F. RECOGIDA DE MUESTRAS BIOLÓGICAS E INFORMACIÓN

### Método de obtención de las muestras y objetivo de su recolección

Tanto para la obtención como para la utilización de las muestras, se recabará el consentimiento informado de aquellos que deseen participar. Las muestras de eyaculado se recogerán por masturbación, siguiendo la práctica clínica habitual. La calidad seminal será evaluada (seminograma) siguiendo también la práctica habitual en el programa de donación de semen. El resto de la muestra seminal será empleada para alcanzar el objetivo de este estudio que, como se ha mencionado anteriormente, es evaluar el efecto del sulfato de cobre (SC) sobre la movilidad y vitalidad espermática.

En cada muestra de semen de los individuos incluidos en el estudio, se realizará el siguiente protocolo:

- Tras realizar el análisis de calidad seminal (seminograma) incluido en el proceso de selección de donantes, se separará la muestra en dos alícuotas: 1 ml de semen fresco y resto para realizar la capacitación por el método de *swimup*, siguiendo el siguiente protocolo:
  - Añadir a la muestra de semen, 2 mL de medio de cultivo
  - Centrifugar la muestra a 2000 rpm durante 10 minutos
  - Eliminar el sobrenadante y añadir lentamente 1 mL medio de cultivo fresco
  - Incubar la muestra durante 45 mins a 37°C
  - Aspirar y separar 1 mL de medio y pasar a un tubo nuevo

- Una vez obtenida la muestra capacitada, dividir cada tipo de muestra (fresco y capacitado) en 6 tubos, añadiendo 160  $\mu$ L en cada tubo
  - Añadir en los tubos los siguientes preparados:
    - o Tubo 1: 40  $\mu$ L de buffer de dilución (tubo control)
    - o Tubo 2: 40  $\mu$ L de concentración 0,15 mM de SC
    - o Tubo 3: 40  $\mu$ L de concentración 0.30 mM de SC
    - o Tubo 4: 40  $\mu$ L de concentración 0.45 mM de SC
    - o Tubo 5: 40  $\mu$ L de concentración 0.60 mM de SC
    - o Tubo 6: 40  $\mu$ L de concentración 0.75 mM de SC
  - Incubar a 37°C
  - Analizar movilidad y vitalidad espermática de cada tubo a tiempo 1h y 2h, manteniendo la muestra entre los dos tiempos a 37°C
- Anotar datos obtenidos en cuaderno de recogida de datos

#### Método de identificación de las muestras

Tras la obtención de las muestras se les asignará un código que será su única identificación. El código asignado no debe permitir extraer ningún tipo de información sobre la identidad o patología del paciente.

#### Conservación

Las muestras recogidas para el estudio se utilizarán inmediatamente tras el análisis de calidad seminal en el Laboratorio de Andrología del centro IVI Madrid, lugar de obtención de las muestras, cuyo responsable será el director de laboratorio participante en el estudio. La muestra sobrante será destruida a causa del análisis, o con posterioridad a su uso.

## Metodología estadística

### A. BASE DE DATOS

La base de datos se definirá rigurosamente con las variables destinadas a ser analizadas en función de los objetivos planteados. La información necesaria se recogerá en un cuaderno de recogida de datos (CRD) diseñado en formato Excel protegido con contraseña.

Los datos recogidos quedarán debidamente codificados con el objeto de proteger la información clínica y personal de las donantes según dispone la ley aplicable.



Finalmente, y previo paso al estudio estadístico, se llevará a cabo un análisis exploratorio de datos para revisar la calidad de la información extraída.

## **B. VARIABLES DE ESTUDIO**

### VARIABLES RESPUESTA (DEPENDIENTES)

Se estudiarán los siguientes parámetros de calidad seminal, tanto en la muestra en fresco como en la muestra capacitada:

1. Volumen
2. Concentración
3. Movilidad progresiva
4. Movilidad no progresiva
5. Nº total de espermatozoides móviles progresivos (TMP)
6. Vitalidad espermática

Asimismo, en cada muestra de estudio, y a los diferentes tiempos de análisis, se estudiarán las siguientes variables:

1. Concentración
2. Movilidad progresiva
3. Movilidad no progresiva
4. Nº total de espermatozoides móviles progresivos (TMP)
5. Vitalidad espermática

### VARIABLES DE CONTROL

1. Edad (años) del varón
2. Abstinencia sexual previa a la donación
3. IMC (kg/m<sup>2</sup>)
4. ID\_Paciente (pseudoanonimizado)

## **C. TAMAÑO MUESTRAL Y POTENCIA DEL ESTUDIO.**

Como se trata de un estudio piloto, no existe un cálculo real del tamaño de la muestra. De acuerdo con los criterios de selección de pacientes y el tiempo de estudio, se prevé la inclusión de 40 individuos, en los que se analizará tanto la muestra en fresco como tras su capacitación, por lo que el número total será de 80 muestras analizadas. Sin embargo, considerando los

criterios de selección y el período de estudio, esperamos tener un poder estadístico suficiente para encontrar diferencias clínicamente relevantes que puedan ser confirmadas estadísticamente.

## D. ANÁLISIS ESTADÍSTICO DE DATOS

### análisis descriptivo

Se representarán las características descriptivas de la muestra de estudio del siguiente modo:

- Las variables cualitativas mediante tablas de frecuencia y representación en gráficas de barras.
- Las variables cuantitativas con la media, desviación típica, y descriptivos básicos de localización (mínimo, máximo y cuartiles). Se representarán mediante histogramas y diagramas de cajas.

### Análisis de homogeneidad

Aunque los criterios de inclusión y el diseño del estudio tienden a preservar la homogeneidad de los grupos de estudios, conviene asegurarse que no existen efectos poblacionales ajenos. Por tanto, las variables control antes mencionadas serán contrastadas con el objeto de valorar la comparabilidad de los grupos.

Previo al análisis, se comprobarán las condiciones de aplicabilidad necesarias y en caso de no cumplirse estas, se realizará el correspondiente test no paramétrico. En cualquier caso, todas las pruebas de significancia con p-valores, se compararán con 0,05.

### Evaluación de los objetivos

Para la evaluación del objetivo principal, las variables cuantitativas se analizarán mediante el test de ANOVA y el análisis de la varianza según los habituales criterios de aplicabilidad.

## Plan de Trabajo

---

- Fase I. Redacción del protocolo y aprobación por Comité Ético (Septiembre 2022)
- Fase II. Selección de candidatos y realización del estudio (Septiembre-Octubre 2022)
- Fase III: Exportación y análisis de datos (Octubre 2022)
- Fase III. Redacción de publicaciones (Octubre-Noviembre 2022)

### Tareas de los investigadores

- Dr Alberto Pacheco participará en la generación del protocolo, elaboración del proyecto exportación de los datos de la plataforma SIVIS, análisis de resultados, y redacción de informe y publicación
- Nuria García participará en la selección y reclutamiento de candidatos, realización estudio y recogida de datos
- Rubén Salvanés participará en la selección y reclutamiento de candidatos, realización estudio y recogida de datos
- Patricia Aspiazu participará en la selección y reclutamiento de candidatos, realización estudio y recogida de datos,

		2022											
		Ene	Feb	Mar	Abr	May	Jun	Jul	Ago	Sep	Oct	Nov	Dic
Fase I													
Fase II													
Fase III													
Fase IV													

## Consideraciones éticas

El proyecto de investigación respetará los principios fundamentales establecidos en la Declaración de Helsinki, en el Convenio del Consejo de Europa relativo a los derechos humanos y la biomedicina, en la Declaración Universal de la UNESCO sobre el genoma humano y los derechos humanos, así como cumplir los requisitos establecidos en la legislación española en el ámbito de la investigación biomédica 14/2007 tal y como exige la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales y la bioética y las Normas Buenas de Práctica Clínicas.

Los datos de carácter personal se tratarán según el Reglamento UE 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de esos datos.

## Financiación

---

Necesita financiación	Sí	
Proyecto financiado externamente	Sí	Institución financiadora Exeltis
Plan de financiación externa (Si no dispone de financiación aún)	No aplica	
Financiación solicitada a IVIRMA	No	
Proyecto financiado internamente	No	
Periodo de financiación	No aplica	
Presupuesto	No aplica	

## Seguro

La Clínica IVIRMA Madrid, dispone de una Póliza de Seguros de Responsabilidad Civil en vigor que se ajusta a la legislación vigente y con cobertura para compensar e indemnizar supuestos de menoscabo de la salud o lesiones de los sujetos, que pudieran producirse en relación con su participación en el Estudio, dentro de la práctica clínica habitual.

## Publicación y Difusión

Se prevé al menos una publicación en una revista internacional del campo de la Medicina Reproductiva:

- Reproductive Biomedicine Online (FI 2.682)
- Assian Journal of Andrology (FI 2.213)

## Bibliografía

1. Hoang HD, Miller MA.. Sperm Navigation Mechanisms in the Female Reproductive Tract. *Results Probl Cell Differ*. 2017;59:241-267. doi: 10.1007/978-3-319-44820-6\_9.
2. Carrasquel Martínez G, Aldana A, Carneiro J, Treviño CL, Darszon A. Acrosomal alkalization occurs during human sperm capacitation. *Mol Hum Reprod*. 2022 Mar 8;28(3): doi: 10.1093/molehr/gaac005.
3. Vaughan DA, Sakkas D. Sperm selection methods in the 21st century. *Biol Reprod*. 2019 Dec 24;101(6):1076-1082. doi: 10.1093/biolre/ioz032.
4. Matamoros-Volante A, Treviño CL. Capacitation-associated alkalization in human sperm is differentially controlled at the subcellular level. *J Cell Sci*. 2020 Jan 30;133(2):jcs238816. doi: 10.1242/jcs.238816.
5. Allouche-Fitoussi D, Breitbart H The Role of Zinc in Male Fertility. . *Int J Mol Sci*. 2020 Oct 21;21(20):7796. doi: 10.3390/ijms21207796.
6. Calle-Guisado V, Hurtado de Llera A, González-Fernández L, Bragado MJ, Garcia-Marin L. Human sperm motility is downregulated by the AMPK activator A769662. *J. Andrology*. 2017 Nov;5(6):1131-1140. doi: 10.1111/andr.12423. Epub 2017 Oct 5.
7. Holland MK, White IG. Heavy metals and human spermatozoa: II. The effect of seminal plasma on the toxicity of copper metal for spermatozoa. *Int J Fertil*. 1982;27(2):95-9.
8. Skandhan KP. . Review on copper in male reproduction and contraception. *Rev Fr Gynecol Obstet*. 1992 Dec;87(12):594-8

9. Kaneshiro B, Aeby T. . Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010 Aug 9;2:211-20. doi: 10.2147/ijwh.s6914

**Appendix B**

<b>BUDGET PARA 40 INDIVIDUOS (80 MUESTRAS)</b>		
<b>CONCEPTO</b>	<b>COSTE (€)</b>	<b>TOTAL (€)</b>
Elaboración de proyecto científico + C.I. para presentación a UAGI y envío a CEI		608
Pago al CEI		300
Procesamiento de muestras (40 en fresco + 40 capacitadas **)	90€ /Muestra	6,800
Recogida de datos*** (1920 datos total)		960
Análisis de datos, elaboración informe y presentación resultados		3,840
Nonoxynol-9		128
<b>TOTAL</b>		<b>12,636</b>

\* = Este importe se añadirá al procesamiento por muestra en el presupuesto presentado al CEI

\*\* = Incluye material fungible (plástico desechable, medios de cultivo, reactivos de tinción...) y tiempo de procesamiento muestras. Las sales de cobre serán suministradas por Exeltis

\*\*\* = Incluye analisis 5 concentraciones + 1 control y 2 tiempos estudio para cada concentración = 12 datos/muestra. De cada muestra, se analizará movilidad y vitalidad espermática

**Certificat de réalisation**

Identifiant d'enveloppe: 09E604220BDD4B9C87478DC978FFE3D7 État: Complétée  
 Objet: Complete with DocuSign: Research collaboration agreement Exceltis\_IVIRMA 2208-MAD-107-AP\_Clearv...  
 Enveloppe source:  
 Nombre de pages du document: 31 Signatures: 4 Émetteur de l'enveloppe:  
 Nombre de pages du certificat: 6 Paraphe: 0 SILVIA VILLAR  
 Signature dirigée: Activé Silvia.Villar@chemogroup.com  
 Horodatage de l'enveloppe: Activé Adresse IP: 80.169.75.50  
 Fuseau horaire: (UTC+01:00) Bruxelles, Copenhague, Madrid, Paris

**Suivi du dossier**

État: Original Titulaire: SILVIA VILLAR Emplacement: DocuSign  
 31/01/2023 09:15:44 Silvia.Villar@chemogroup.com

**Événements de signataire**

Alberto Pacheco Castro  
 alberto.pacheco@ivirma.com  
 Niveau de sécurité: E-mail, Authentification de compte (obligatoire)

*Alberto Pacheco Castro*

Envoyée: 31/01/2023 09:20:18  
 Consultée: 06/02/2023 12:39:36  
 Signée: 06/02/2023 12:40:52

**Signature**

Sélection d'une signature : Style présélectionné  
 ID de signature:  
 87AF373F-D9F7-468F-A083-4426DE1FCD14  
 En utilisant l'adresse IP: 195.235.53.177

**Horodatage**

Avec authentification de signature via mot de passe  
 DocuSign  
 Avec motifs de signature (sur chaque onglet):  
 Apruebo este documento

**Divulgence relative aux Signatures et aux Dossiers électroniques:**

Accepté: 06/02/2023 12:39:36  
 ID: 31499014-3d2c-404a-b835-6924d26e6a1e

Enrico Colli  
 enrico.colli@exeltis.com  
 CSO  
 Exeltis

Niveau de sécurité: E-mail, Authentification de compte (obligatoire)

*Enrico Colli*

Sélection d'une signature : Écrit sur un appareil  
 ID de signature:  
 7A024DD0-DC2A-4F9E-B548-89670EC54350  
 En utilisant l'adresse IP: 165.225.93.25

Envoyée: 31/01/2023 09:20:15  
 Consultée: 31/01/2023 09:21:30  
 Signée: 31/01/2023 09:22:16

Avec authentification de signature via mot de passe  
 DocuSign  
 Avec motifs de signature (sur chaque onglet):  
 I approve this document

**Divulgence relative aux Signatures et aux Dossiers électroniques:**

Accepté: 20/03/2020 17:42:34  
 ID: 2ed94454-7936-47bc-b72a-8ef74b7b0bcb



Événements de signataire	Signature	Horodatage
--------------------------	-----------	------------

Juan Antonio García Velasco  
Juan.Garcia.Velasco@ivirma.com  
Niveau de sécurité: E-mail, Authentification de compte (obligatoire)

DocuSigned by:  
*Juan Antonio García Velasco*  
Nombre del firmante: Juan Antonio García Velasco  
Motivo de la firma: Apruebo este documento  
Hora de firma: 31-ene.-2023 | 03:25 EST  
96C94CA1CCD646688FBB40B960C837CB

Envoyée: 31/01/2023 09:20:17  
Consultée: 31/01/2023 09:21:58  
Signée: 31/01/2023 09:25:40

Sélection d'une signature : Style présélectionné  
ID de signature:  
96C94CA1-CCD6-4668-8FBB-40B960C837CB  
En utilisant l'adresse IP: 195.235.53.177

Avec authentification de signature via mot de passe  
DocuSign  
Avec motifs de signature (sur chaque onglet):  
Apruebo este documento

**Divulgateion relative aux Signatures et aux Dossiers électroniques:**

Accepté: 31/01/2023 09:21:58  
ID: 8cf629eb-254e-4b67-aa32-f4e060b69929

Nicolás Garrido Puchalt  
Nicolas.Garrido@ivirma.com  
Niveau de sécurité: E-mail, Authentification de compte (obligatoire)

DocuSigned by:  
*Nicolás Garrido Puchalt*  
Nombre del firmante: Nicolás Garrido Puchalt  
Motivo de la firma: Apruebo este documento  
Hora de firma: 31-Jan-2023 | 02:31 PST  
B3D77C8A355542FB8CB22D3014426767

Envoyée: 31/01/2023 09:20:18  
Consultée: 31/01/2023 11:31:24  
Signée: 31/01/2023 11:31:48

Sélection d'une signature : Style présélectionné  
ID de signature:  
B3D77C8A-3555-42FB-8CB2-2D3014426767  
En utilisant l'adresse IP: 195.235.53.177

Avec authentification de signature via mot de passe  
DocuSign  
Avec motifs de signature (sur chaque onglet):  
Apruebo este documento

**Divulgateion relative aux Signatures et aux Dossiers électroniques:**

Accepté: 31/01/2023 11:31:24  
ID: dab66f6d-a380-44cb-bb70-8bfb81884099

Événements de signataire en personne	Signature	Horodatage
--------------------------------------	-----------	------------

Événements de livraison à l'éditeur	État	Horodatage
-------------------------------------	------	------------

Événements de livraison à l'agent	État	Horodatage
-----------------------------------	------	------------

Événements de livraison intermédiaire	État	Horodatage
---------------------------------------	------	------------

Événements de livraison certifiée	État	Horodatage
-----------------------------------	------	------------

Événements de copie carbone	État	Horodatage
-----------------------------	------	------------

Elza Daoud  
elza.daoud@exeltis.com  
Niveau de sécurité: E-mail, Authentification de compte (obligatoire)

**Copie**

Envoyée: 31/01/2023 09:20:19  
Consultée: 01/02/2023 12:21:23

Événements de copie carbone	État	Horodatage
-----------------------------	------	------------

**Divulgence relative aux Signatures et aux Dossiers électroniques:**

Accepté: 28/04/2022 09:05:07

ID: d6706428-a7b5-4900-b3e2-5d86c72defb3

Événements de témoins	Signature	Horodatage
-----------------------	-----------	------------

Événements notariaux	Signature	Horodatage
----------------------	-----------	------------

Récapitulatif des événements de l'enveloppe	État	Horodatages
---	------	-------------

Enveloppe envoyée	Haché/crypté	31/01/2023 09:20:19
Livraison certifiée	Sécurité vérifiée	31/01/2023 11:31:24
Signature complétée	Sécurité vérifiée	31/01/2023 11:31:48
Complétée	Sécurité vérifiée	06/02/2023 12:40:52

Événements de paiement	État	Horodatages
------------------------	------	-------------

**Divulgence relative aux Signatures et aux Dossiers électroniques**

## **ELECTRONIC RECORD AND SIGNATURE DISCLOSURE**

From time to time, Insud Pharma S.L.U. - 21 CFR Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

### **Getting paper copies**

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a \$0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

### **Withdrawing your consent**

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

### **Consequences of changing your mind**

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

### **All notices and disclosures will be sent to you electronically**

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

### **How to contact Insud Pharma S.L.U. - 21 CFR Part 11:**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To contact us by email send messages to: [jose.salvador@insudpharma.com](mailto:jose.salvador@insudpharma.com)

### **To advise Insud Pharma S.L.U. - 21 CFR Part 11 of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [jose.salvador@insudpharma.com](mailto:jose.salvador@insudpharma.com) and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

### **To request paper copies from Insud Pharma S.L.U. - 21 CFR Part 11**

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [jose.salvador@insudpharma.com](mailto:jose.salvador@insudpharma.com) and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

### **To withdraw your consent with Insud Pharma S.L.U. - 21 CFR Part 11**

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

- i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
- ii. send us an email to jose.salvador@insudpharma.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

### **Required hardware and software**

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: <https://support.docusign.com/guides/signer-guide-signing-system-requirements>.

### **Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to ‘I agree to use electronic records and signatures’ before clicking ‘CONTINUE’ within the DocuSign system.

By selecting the check-box next to ‘I agree to use electronic records and signatures’, you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Insud Pharma S.L.U. - 21 CFR Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Insud Pharma S.L.U. - 21 CFR Part 11 during the course of your relationship with Insud Pharma S.L.U. - 21 CFR Part 11.