**INVESTIGATOR INITIATED RESEARCH AGREEMENT**

THIS INVESTIGATOR INITIATED RESEARCH AGREEMENT (this “**Agreement**”), is effective as of June 1st, 2021 (the “**Effective Date**”), by and between:

**Alfasigma S.p.A.,** a company organized and existing under the laws of Italy, having its registered offices at Via Ragazzi del ’99, n. 5, Bologna, Italy, registration number with the Company Register of Bologna 03432221202 (**“Alfasigma”**),

**Dr. Hugo Laparra Escareño from Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Department of Angiology and vascular surgery,** existing under the laws of the México, whose administrative offices are located atVasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan, 14080 Ciudad de México, CDMX, (the “**SPONSOR**”).

The SPONSOR and Alfasigma are hereinafter individually (or collectively) referred to as a “**Party**” (or the “**Parties**”).

# PREAMBLE

**Whereas**, Alfasigma owns certain rights relating to the product Sulodexide (trademark Vessel®) (the “**Product**”),

**Whereas**, the SPONSOR is interested in investigating the safety and the possible protective /restorative effect of the Product in the in convalescent COVID-19 patients and is willing to perform a clinical trial (the “**Study**”) in accordance with the protocol entitled **“*Endothelial protection in convalescent COVID-19 patients. The effect of Sulodexide on serum levels of biomarkers for endothelial dysfunction. A prospective, randomized, placebo-controlled, investigator-initiated trial*”**, attached hereto as synopsis in Exhibit 1 (the “**Protocol**”),

**Whereas**, in order to carry out the Study, the SPONSOR requires certain quantities of Product and significant financial resources,

**WHEREAS**, the SPONSOR has requested Alfasigma, and Alfasigma has accepted, to support the performance of the Study in accordance with the following terms.

**Now, therefore, the Parties have agreed as follows:**

**1. PURPOSE OF THIS AGREEMENT**

The purpose of this Agreement is to set forth the terms and conditions governing the support by Alfasigma to the SPONSOR with respect to the performance of the Study.

**2. OBLIGATIONS OF THE SPONSOR**

**2.1** The SPONSOR shall perform the Study in accordance with the Protocol and any subsequent amendments thereto. Any substantial changes in the Protocol shall be communicated to Alfasigma.

**2.2** The SPONSOR represents that it is the sole sponsor of the Study and warrants that the Study will be performed in compliance with all applicable local and international laws and regulations (including WHO and ICH guidelines for Good Clinical Practices), under its exclusive responsibility and at its own costs. Furthermore, the SPONSOR herewith warrants that: (i) the Protocol herein enclosed in Exhibit 1 has been approved, and any subsequent amendment thereto will be approved, by the Ethics Committee(s) of the site(s) participating in the Study, and (ii) the SPONSOR has already obtained the necessary certificates, licences and authorisations from the competent authorities to carry out the Study, including any necessary approvals to import the Product in the country(ies) (the “**Study country**”) where the Study shall be performed, so that Alfasigma is discharged from any responsibility.

**2.3** In accordance with all applicable laws and regulations, the SPONSOR shall notably be responsible for all required periodic updates to the health authorities of the Study country and reports of all Serious Adverse Events arising during the performance of the Study. For the purposes hereof, "Serious Adverse Event" means any event as defined in the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

In order to permit Alfasigma to comply with its own regulatory obligations or internal procedures, the SPONSOR will use reasonable efforts to send to Alfasigma all requested information and data relating to the conduction of the Study with special attention to the transmission of Serious Adverse Events, in accordance with the operating procedures of the Safety Management Plan (the “**Safety Management Plan**”) attached hereto in Exhibit 2.

**2.4** Study reporting

Alfasigma has designated **Dr. Nora Lecuona** to be the primary contact with the SPONSOR to receive all data, information or reports on the Study.

The SPONSOR has designated **Dr. Dr. Hugo Laparra Escareño** as Principal Investigator for the Study (the “**SPONSOR Representative**”). The SPONSOR Representative will maintain contacts with the designated Alfasigma primary contact and keep Alfasigmainformed of the progress and status of the Study on a bi-monthly basis, by providing Alfasigma in particular with the following information:

1. Study start date, first patient in
2. number of patients enrolled
3. number of patients completed
4. endpoints
5. Study end date, last patient completed

Furthermore, the SPONSOR Representative shall promptly report to Alfasigma any significant events or results occurring or found during the course of the Study which might affect its performance thereof. Serious Adverse Events occurring during treatment must be reported and managed as described in Exhibit 2 and must be sent by the SPONSOR by fax or e-mail within 24 (twenty-four) hours from their acknowledge by the SPONSOR Representative, to:

Alfasigma S.p.A.

e-mail: Corporate.Pharmacovigilance@alfasigma.com

fax: +39 06 9139.40.07

tel: +39 06 9139.33.39

**2.5** The final results of the Study shall be provided to Alfasigmaby the SPONSOR in the form of a statistical analysis and a clinical report.

**3. CONTRIBUTION OF Alfasigma; PRODUCT SUPPLY**

**3.1** Contribution. As global contribution for the performance of the Study, Alfasigma agrees to(i)provide the SPONSOR with the quantities of Product (and placebo) required for the performance of the Study, as set forth in Exhibit 3 hereto, as well as with any relevant information the SPONSOR may need for the use of the Product, and (ii) grant to the SPONSOR a lump sum equal to **€ 200.000,00** (the “**Grant**”), to be paid as detailed in Exhibit 4 hereto, upon receipt of the relevant invoice(s), ((i), and (ii), collectively, the “**Contribution**”).

**3.2** Supply of Product. (a) The terms and conditions of the supply of Product (and placebo) are detailed in Exhibit 3 hereto. If the shelf life of Product is not long enough to cover the whole duration of the Study, Alfasigma will to resupply it, and the SPONSOR shall promptly return, or have returned, to Alfasigma all quantities of unusable Product, or will document their proper on-site destruction, in accordance with the written instructions that Alfasigma will provide to the SPONSOR separately.

(b) Alfasigma shall ensure that all quantities of Product (and placebo) supplied by Alfasigma to the SPONSOR for the purposes of the Study shall be manufactured in compliance the current Good Manufacturing Practices*.* EXCEPT AS EXPRESSLY SET FORTH IN this paragraph (B), NO REPRESENTATION OR WARRANTY OF ANY KIND RELATING TO THE PRODUCT, EITHER EXPRESS OR IMPLIED, INCLUDING ANY EXPRESS OR IMPLIED WARRANTY OF non-infringement OR MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE IS MADE BY ALFASIGMA and IN NO EVENT SHALL ALFASIGMA BE LIABLE TO THE SPONSOR FOR ANY LOSSES (AS DEFINED BELOW) INCURRED OR SUFFERED BY THE SPONSOR AS A RESULT OF THE USE OF THE PRODUCT in the Study.

**3.3** The SPONSOR shall use (or have used) the Product and the Grant exclusively for the performance of the Study. Upon completion of the Study or termination of this Agreement, whichever occurs first, the SPONSOR shall either return to Alfasigma any unused quantities of Product or provide Alfasigma with a certificate of destruction of the unused quantities of Product, unless otherwise agreed by the Parties. In no case shall the remaining quantities of Product be used by the SPONSOR and/or the site(s) participating in the Study without the prior written consent of Alfasigma.

**3.4** For the sake of good order, the Parties hereby acknowledge and agree that except for the Contribution, no additional support, sum, compensation or reimbursement whatsoever shall be due by Alfasigma to the SPONSOR and/or the Study site(s) and/or the Investigator(s) and/or any third parties in connection with of the Study.

**3.5** The SPONSOR acknowledges that (i) the Contribution provided by Alfasigma hereunder does not imply any direct or indirect involvement or responsibility of any kind on Alfasigma in the performance of the Study, and (ii) Alfasigma is not sponsor or co-sponsor of the Study and shall not be referred to as such by the SPONSOR under any circumstances.

**4. OWNERSHIP AND USE OF DATA, DOCUMENTS AND RESULTS**

**4.1** Ownership of Product-related inventions

## The SPONSOR agrees that it has no proprietary rights to or property interest in or license in respect of the Product. Any analogues, derivatives, improvements, inventions, discoveries, suggestions, ideas or innovations related exclusively to the Product made or conceived by or on behalf of the SPONSOR during the performance of the Study shall be promptly disclosed by the SPONSOR to Alfasigma and shall be the exclusive property of Alfasigma. Except as expressly provided herein, nothing in this Agreement shall be construed as granting the SPONSOR any rights or licenses whatsoever in or to the Product and/or any associated intellectual property rights. The SPONSOR hereby declares and warrants that, notwithstanding the Study may be partially funded by non-profit organizations and the SPONSOR may have certain obligations regarding the administration of discoveries/inventions made using these funds, such obligations do not conflict with the provisions of this Article 4.1.

**4.2** Ownership of results

As sponsor of the Study, the SPONSOR shall be the owner of the results arising out of the Study.

**4.3** Use of results byAlfasigma

In consideration for its Contribution to the Study, the SPONSOR hereby grants to Alfasigma a non-exclusive licence to use and exploit, on a world-wide basis, and without making any additional contribution or royalty to the SPONSOR, Investigator(s), or any other third party taking part in the Study all Study results to improve the knowledge of the efficacy and safety of the Product.

**5. CONFIDENTIALITY, RESTRICTED USE AND PUBLICATION**

**5.1** Confidentiality and Restricted Use

Throughout the term of this Agreement, each Party (the “**Receiving Party**”) may be given information and other proprietary material from the other Party (the “**Disclosing Party**”) which the Disclosing Party declares being secret and confidential (the “**Confidential Information**”). In no event shall the Receiving Party use the Disclosing Party’s Confidential Information for any purpose other than as may be required for the performance of its obligations hereunder, or disclose or make available any of such Confidential Information to third parties other than those (e.g., Investigator(s), physicians, technicians, researchers, employees directly involved in conducting the Study) who have a need to know for the purposes of this Agreement and have undertaken to be bound by confidentiality and limited use obligations not less stringent than those established on the Receiving Party hereunder.

Upon any termination of this Agreement, the Receiving Party shall promptly return to the Disclosing Party or, at the Disclosing Party’s request, erase (providing to Disclosing Party written confirmation of such destruction) all such Confidential Information in written or recorded form and all copies thereof, and all forms, stationery and other office supplies of the Disclosing Party in Receiving Party’s possession, in any way pertaining to or arising out of or in connection with the Disclosing Party’s business. The term “written or recorded form” as used in this Agreement includes not only files and records furnished by the Disclosing Party for the purposes of this Agreement, but also all other files, records, notes, memoranda, correspondence or other papers, computer files and disks, video tapes, slides and films, or any other electronic media created or written by the Receiving Party or at the direction of the Receiving Party for the purposes of this Agreement.

The confidentiality and non-use obligations provided for herein shall survive the expiry or termination of this Agreement and remain in force for 10 (ten) years from the Effective Date.

However, no confidentiality obligations contained herein shall be construed so as to preclude use or disclosure of information:

1. which is known to the Receiving Party, as evidenced by its written records, before the disclosure of the Disclosing Party and was not otherwise acquired from the Disclosing Party directly or indirectly under a confidentiality obligation still in force;

(b) which is disclosed in good faith to the Receiving Party by a third person lawfully in possession of such information and not under an obligation of nondisclosure towards the Disclosing Party;

(c) which is or becomes part of the public knowledge or is publicly divulged through no fault of the Receiving Party;

1. which is disclosed by the Receiving Party as a result of applicable laws and regulations or pursuant to an order of a competent court or regulatory/administrative agency if, to the extent legally permissible, an immediate communication concerning this disclosure is made to the Disclosing Party;
2. which is, at any time, developed by employees of the Receiving Party and/or of its affiliates without any use of the Confidential Information received by the Disclosing Party hereunder.

 For the avoidance of any doubt, the provisions contained herein shall not apply to the results of the Study, which Alfasigma shall have the right to use as set forth in Article 4.3 above.

* 1. Publication

No publication or release pertaining to the Study shall be made by the SPONSOR or any other third parties involved in the performance of the Study without giving Alfasigma the opportunity to review any draft thereof. For this purpose, the SPONSOR hereby agrees to provide Alfasigma with the draft (i) of any abstract at least two (2) weeks and (ii) of any publication or release at least four (4) weeks prior to the date of submission. If, within the aforesaid periods, Alfasigma notifies the SPONSOR any reasonable changes to the proposed publication or presentation deemed necessary by Alfasigma solely to preserve its own Confidential Information and/or any intellectual property rights associated with the Product, the SPONSOR shall promptly implement or have implemented such changes. Notwithstanding anything else herein (specifically including Alfasigma’s right of review set forth in this paragraph 5.2) nothing in this Agreement shall prohibit the SPONSOR from the publication of all information necessary for the accurate interpretation and presentation of the Study results. The absence of any above mentioned notification by Alfasigma within the aforesaid periods, shall be deemed Alfasigma’s acceptance of the proposed publication or presentation.

Any publication or presentation shall, at Alfasigma’s request, mention Alfasigma’s support to the Study*.*

**6. AUDIT AND DIRECT ACCESS**

**6.1** If any state or local government authority conducts, or gives notice to the SPONSOR of its intent to conduct an inspection at the site(s), or takes any other regulatory action with respect to the Study, then the SPONSOR shall promptly give Alfasigma notice thereof and shall provide Alfasigma with any information reasonably required in connection therewith.

**6.2** If information concerning the Product is requested, notably by regulatory or health authorities, the SPONSOR shall give Alfasigma direct access to the Study site(s), source data/documents and reports at all times, as far as the terms and conditions of Article 5 of this Agreement are respected.

**7. TERM AND TERMINATION**

**7.1** Term

 This Agreement shall commence as of the Effective Date and shall remain in force and effect until the completion date of the Study, which date shall be promptly communicated by the SPONSOR to Alfasigma’s primary contact, as identified in Article 2.4 hereof, but with the Parties estimate being no later than December 31, 2022.

**7.2** Alfasigma’s right of early termination

Alfasigma reserves the right to terminate, at any time, this Agreement in the event any significant treatment related problems occur during the Study. Alfasigma shall notify the SPONSOR of its decision in writing and termination shall become effective forthwith.

**7.3** Rights of either Party to early termination

Without prejudice to the rights of either Party existing under the terms of this Agreement, either Party shall be entitled, by notification to the other Party of its decision by registered mail with return receipt requested, to terminate this Agreement with immediate effect in the following circumstances if it is proven by reasonable evidence that the other Party is in breach of its essential obligations hereunder by causes and reasons within its control and responsibility and has not cured such default within thirty (30) days after notice requesting the correction of the breach.

**7.4** Consequences of termination

Promptly after the termination of this Agreement, the SPONSOR shall use reasonable efforts, upon request of Alfasigma, to provide to Alfasigma a written interim report for that portion of the Study that has been completed and the results obtained up to the termination date. Furthermore, in case of termination of this Agreement, for whatever reason, the provisions of Articles 3.2 and 10.6 shall apply.

**8. INDEMNIFICATION AND INSURANCE**

**8.1** The SPONSOR shall defend, indemnify and hold harmless Alfasigma and its officers, directors, employees and agents, from and against any and all costs, liabilities, losses, damages and expenses (including reasonable attorneys’ fees and other expenses of legal proceedings) (the “**Losses**”) incurred or suffered by them or any of them in connection with any claim, demand, action or proceeding brought by a third party (each, a “**Claim**”) arising out of the performance of the Study. It is understood, however, that the SPONSOR shall not be liable for those Claims that result solely from the quality of the Product, as specified in Article 3.2(b) above, and provided that the SPONSOR has complied with (i) all terms of this Agreement including the Protocol, (ii) all dosage and other specifications, directions and recommendations furnished by Alfasigma for the use and administration of the Product and (iii) all applicable laws, rules and regulations.

**8.2** The SPONSOR hereby certifies that it is covered by an insurance policy in order to cover its responsibility as sponsor of the Study and the responsibility of all Investigator(s) and personnel involved in the Study. The SPONSOR shall, if requested by Alfasigma, produce a certificate of insurance or copy of the valid insurance agreement which shows that the necessary coverage is currently in force.

**9. FORCE MAJEURE**

**9.1** Neither Party hereto shall be liable in damages for any delay or default in such Party’s performance hereunder if such default or delay is caused by events beyond such Party's reasonable control including, but not limited to, acts of God, regulation or law or other action of any government or agency thereof, war or insurrection, civil commotion, destruction of production facilities or materials by earthquake, fire, flood or storm, labor disturbances, epidemic or pandemic, or failure of suppliers, public utilities or common carriers.

**9.2** A Party claiming to be unable to perform the obligations under this Agreement, shall promptly inform the other Party of the existence of such conditions of force majeure.

**9.3** In the event that such conditions of force majeure continue or are expected to continue for more than two (2) consecutive months as of the notification as mentioned hereabove in Article 9.2, the Parties shall consult together in order to find a mutually acceptable solution.

**9.4** In the event that no solution is acceptable by one of the Parties and if force majeure continue or are expected to continue for more than two (2) months as of the termination of the two (2) month period as mentioned hereabove in Article 9.3, then this Agreement shall be terminated by one (1) month’s prior written notice.

**10. MISCELLANEOUS**

**10.1** Notices

Any notices, which either Party may require or shall desire to give hereunder, shall be deemed to be duly given when delivered personally or if mailed by certified or registered mail, postage prepaid, upon receipt.

**10.2** Invalidity

If any of the provisions of this Agreement is considered to be or become invalid, illegal or unenforceable in any respect under any applicable law, the validity, legality and/or unenforceability of the remaining provisions shall not in any way be affected or impaired.

**10.3** Independent contractor

 It is understood and agreed that the SPONSOR is acting in the capacity of an independent contractor and shall not be considered an agent, servant, partner, joint venturer of Alfasigma or Alfasigma’s employee. Accordingly, the SPONSOR has no authority to take action on behalf or to bind Alfasigma without Alfasigma’s prior written consent.

**10.4** Modification of this Agreement

No amendments, changes, modifications or alterations of the terms of this Agreement shall be binding upon either Party hereto unless in writing and signed by the Parties.

* 1. Survival

The terms and conditions of Articles 2, 3.2, 4, 5, 6, 7.4, 8 and 11 of this Agreement shall survive the expiration or any termination (irrespective of the reason of such termination) hereof.

* 1. The SPONSOR will be responsible to Alfasigma for ensuring compliance with the obligations provided for in this Agreement by the Study site(s), the Investigator(s) and/or any third parties participating in the Study or otherwise involved in the performance of the Study.
	2. Privacy

Unless otherwise agreed in writing by the Parties, Alfasigma shall process SPONSOR’s personal data and/or the personal data of its employees, investigator(s) exclusively for the purposes of the execution and performance of this Agreement and in accordance with the information on the processing of personal data available at the website: https://it.alfasigma.com/informative-privacy/informativa-fornitori/.

SPONSOR shall notify to its employees the Alfasigma’s information on the processing of personal data and shall take any action required to ensure Alfasigma’s compliance to SPONSOR and/or to SPONSOR’s employees with the provisions of Articles 13 and 14 of EU Regulation 2016/679.

* 1. Code of Ethics.

The SPONSOR acknowledges the “Code of Ethics” of Alfasigma prepared by Alfasigma pursuant to the applicable law on the administrative liability of the legal entities arising out of crimes committed by its shareholders, employees and/or agents, and available on the Alfasigma’s website www.alfasigma.com, a copy of which the SPONSOR shall have the right to request at any time to Alfasigma.

**11. GOVERNING LAW/DISPUTE RESOLUTION**

The Parties’ relationship and this Agreement shall be governed by and construed according to the laws of Italy. The Parties agree that the venue for any dispute arising out of this Agreement will be in the ordinary courts of Bologna, Italy.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be duly executed on their behalf by their representatives.

**Alfasigma S.p.A. Dr. Dr. Hugo Laparra Escareño**

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Dr. Massimo Vanoli Name:

Proxy Title:

Date: Date:

**EXHIBIT 1**

**“Safety Management Plan”**

**EXHIBIT 2**

**“Conditions of Supply”**

1. Supply of Product

After the signature of this Agreement and subject to the receipt of the SPONSOR’s instructions furnished as per paragraph 3 below, Alfasigma will provide the SPONSOR with the following:

Vessel 13500 cps (540 blisters, 25 cps each)

Placebo 13500 cps (540 blisters, 25 cps each)

1. Package and labelling

All Product supplied for the purpose of the Study shall be packaged and labelled in English, in compliance with all applicable laws and regulations, including WHO and ICH guidelines for Good Clinical Practices. Alfasigma undertakes to label the Product in accordance with the instructions furnished in writing by the SPONSOR, which shall take responsibility for compliance of the labelling with the requirements of the local authorities.

Alfasigma will provide the SPONSOR with a copy of the certificate of analysis of each batch of supplied Product.

 3. Shipment

Alfasigma shall dispatch the required quantities of Product in blister, to the address(es), and in accordance with the instructions, to be furnished in writing by the SPONSOR promptly after the signature of this Agreement.

**EXHIBIT 3**

**“Economic Support”**

**Grant:**

## In support of the Study, Alfasigma will grant to the SPONSOR a lump sum of € 200.000,00, to be paid as follows, upon receipt of the relevant invoice:

(i) € 60.000,00 shall be paid following the signature of this Agreement by both Parties;

(ii) € 20.000,00 shall be paid upon the obtainment by SPONSOR the Study Registration as detailed in Protocol hereto;

(iii) € 50.000,00 shall be paid upon commencement of the enrolment phase, as properly documented by SPONSOR;

(iv) € 50.000,00 shall be paid upon completion of the enrolment phase, as properly documented by SPONSOR.

(v) € 20.000,00 shall be paid upon completion of the Study, payment shall be subject to Alfasigma’s receipt and acceptance of the a final written report, detailing the Study perfomed by SPONSOR hereunder and the results obtained.