Investigator Sponsored Research – Required Terms

Where Astellas agrees to provide support (funding or product or both) ("Support") an agreement will be entered into so that Support can be provided. This agreement must include, but not be limited to the following required terms. Astellas has limited resources to negotiate investigator sponsored research agreements so please ensure that your institution is able and willing to comply with these terms set out below before proceeding with your application.

1.
Research Design. The party seeking Support must initiate and design the research and create the protocol.

(Clause 2.2)

Regulatory Sponsor. Institution is the 'regulatory sponsor' of Research, as defined by Laws, is performing Research independently of Astellas and assumes full responsibility therefor. Institution is responsible for initiating and designing Research and creating Protocol. Astellas has not determined or influenced the design of Protocol or other aspects of Research and is not responsible for its implementation. Institution will not represent to any third party, including Participants, any regulatory agency or health authority, that Astellas is the sponsor.

2.
Regulatory Approvals. The party seeking Support must obtain applicable regulatory approval or license(s) required to conduct the research.

Ethics Approvals. The party seeking Support must obtain approval from ethics committees or institutional animal care and use committee, if required and provide Astellas with a written confirmation of approval, amendment and/or renewal.

(Clause 3.1)

Approvals. Institution shall ensure Approvals and license(s) (as required by Laws) are obtained for the conduct of Research and shall not commence Research and shall ensure Research Site(s) shall not commence Research until all such Approvals and license(s) have been obtained. Institution shall provide Astellas with copies of such Approvals and license(s) and any amendments or renewals to them, upon request. Institution agrees that Support shall only be provided on the basis Approvals are obtained and maintained by Institution. Institution shall notify Astellas promptly in the event of a withdrawal or amendment of any Approvals relating to Research. Upon the occurrence of such event, Astellas may terminate this Agreement in accordance Clause 16.

Notes:
Astellas will not provide Support until Astellas has received a copy of relevant approvals and license(s) have been obtained, as applicable.

3.
Informed Consent/Waiver. The party seeking Support must obtain informed consent from patients, if required.

(Clause 3.8)

Informed Consent; Authorization; Waiver. Institution shall obtain from each Participant, prior to their participation in Research as applicable and as required by Laws: (i) a signed ICF; or (ii) a waiver of authorization from Ethics Committee/IRB; and (iii) an appropriate authorization form. Institution shall ensure that adequate and sufficient data protection measures are in place throughout Research to protect personal

data of all Participants, in accordance with Laws, and in particular, Territory, and will be responsible for obtaining consent (as required by Laws) in respect of any personal data processing or transfer and any de-identification and/or anonymisation of personal data as may be required in order to comply with the terms of this Agreement. Institution shall inform Participants that Astellas is providing Support for Research.

4.
Liability. The party seeking Support must assume liability for any health injuries and adverse events caused during the research.

(Clause 15.3)

Liability. Institution shall be liable and responsible for and shall not hold Astellas liable or responsible for, any losses, costs, damages, or other expenses arising out of or resulting from: (a) design, content, or implementation of Protocol; (b) any injury (whether or not Research-related) to persons, equipment or damage to property involved in Research; (c) adverse events caused during Research; and (d) any negligent, reckless or wilful act or omission in the performance of any of Institution's obligations under this Agreement.

5.
Protocol and Timelines. The party seeking Support must use Support provided by Astellas to conduct the research in accordance with the protocol uploaded onto Astellas' ISR Portal and within the timelines agreed in the portal / the agreement. In the event the protocol is amended, the party seeking Support must notify Astellas. Astellas is under no obligation to provide further Support other than what was agreed in the agreement.

Compliance with Laws. The party seeking Support must comply with all applicable laws, ethical considerations, existing legislation and regulations, including compliance with all pharmacovigilance requirements.

(Clause 4.1.1)

Institution represents and warrants that:

it shall perform Research in accordance with Agreement and it shall and shall ensure Institution Personnel and Research Site(s) perform Research: (a) in a timely manner; (b) in accordance with (i) the highest professional standards and quality; (ii) Protocol and Laws; (iii) requirements of Ethics Committee/IRB; (iv) timelines in Milestone Table and Astellas ISR Portal; and (c) in a manner that shall not infringe, misappropriate, or violate the rights of any third party;

"Laws" means all applicable laws, rules and regulations, directives, statutes, orders, codes of practice and guidance relevant to the conduct of Research and/or governing the performance of Research in Territory; and/or where a regulatory filing is intended to be filed, as they may be amended or re-enacted from time to time, including: (a) ICH-GCP together with such other generally accepted good clinical practice standards or associated guidance on ICH-GCP as are specified in local law where Research is being performed and ethical considerations; (b) Corrupt Practices Laws; (c) Data Protection and Privacy Laws; (d) the Declaration of Helsinki, (e) pharmacovigilance requirements; (f) the advertising and promotion of medicinal products; (g) GMP; and (h) GDP. **"Laws"** shall include any additional local legal provisions, referred to in **Appendix 3**

6.
Records and Analysis. The party seeking Support must maintain adequate records and management of all analysis of research data in accordance with laws.

(Clause 9)

Institution shall and shall ensure Research Site(s) maintain and retain Research records in accordance with Laws. This **Clause** shall survive the termination or expiration of this Agreement.

7.

Final Study Report. The party seeking Support must prepare a final study report and/or manuscript which includes results related to key endpoints/objects.

The final study report must be suitable for submission for publication, include disclosure of Astellas' support and shall be delivered to Astellas at the completion of research or early termination of research in accordance with the timelines set out in the agreement or Astellas ISR portal.

(Clause 7)

Institution shall provide Astellas with Final Report: (a) in accordance with Milestone Table or Astellas ISR Portal; (b) in English language; and (c) which shall include Research results related to key endpoints and objectives, and if requested by Astellas a summary of any Serious Adverse Events and efficacy. Final Report shall be submitted to Astellas in the form of a manuscript suitable for submission for publication or in such other form as agreed with Astellas. If Final Report shall be disclosed publicly, Institution shall include a disclosure that Support was provided by Astellas**.** This **Clause** shall survive the termination or expiration of this Agreement.

8.

Safety Reporting. The party seeking Support must inform Astellas of any safety reporting, safety issue, periodic safety reports or summaries submitted by party seeking Support (or investigator) to a regulatory authority and/or ethics committee relating to an Astellas product.

(Appendix 4)

Where Product is used for an approved indication in accordance with the SmPC, the Institution shall use the SmPC as the source for reference safety information for the Research. Where Product is to be used outside of an approved indication, Astellas will provide support to Institution in identifying relevant reference safety information, in order to support Institution with its reporting obligations to any Regulatory Authority in accordance with Laws.

Parties understand and agree that responsibility for compliance with any Laws relating to the reporting of Adverse Events or Adverse Drug Reactions lies with Institution. However, Institution understands that Astellas wishes to be notified as quickly as possible of safety information in relation to Product. Institution therefore agrees that it shall immediately, and in any event within three (3) days, notify Astellas with regards to Product of any Adverse Event, Adverse Drug Reaction or follow up information that has been reported to any Regulatory Authority and any safety issue identified in the course of Research or otherwise, which may have a material impact on the safety, quality or efficacy of Product. Any such information should be provided to Astellas using the e-mail address provided under Appendix 1.

Institution will respond to queries from Astellas on reported Serious Adverse Events and provide such information and supporting documentation as Astellas may reasonably require.

Institution will ensure that Astellas immediately, and in any event within five (5) days of filing, receives a copy of any periodic safety report or summary (including clinical study report) filed with a Regulatory Authority and/or Ethics Committee/IRB.

"Adverse Drug Reaction" means a response to a medicinal product which is noxious and unintended.

"Adverse Event" means any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with such product. An Adverse Event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease

temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

"Serious Adverse Event" means any Adverse Event which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.
Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or results in death or hospitalisation but might jeopardise subject or might require intervention to prevent one of the other outcomes listed above.

9.
Publications. Publications related to the results of research must be developed independently from Astellas, however Astellas shall have the right to review the publication for facts relating to Astellas products, intellectual property, safety/pharmacovigilance and proper disclosure of Astellas' support.

(Clause 13)

Scope. Institution and Investigator shall be free to publish or present Research Results in the form of, including but not limited to a manuscript, abstract, oral presentation or poster ("**Publication**") subject to this **Clause 13**.

Review Period. At least sixty (60) days prior to submission of Publication in the form of a manuscript and at least thirty (30) days prior to submission of Publication in the form of an abstract, oral presentation or poster (collectively, "Review Period"), Institution and/or Investigator shall submit Publication to Astellas for review and comment.

Astellas Review. Astellas' review of a Publication shall be limited to the following: (a) facts related to Astellas products, (b) intellectual property, (c) safety/pharmacovigilance; and (d) disclosure of Support. Astellas shall not comment on methodology, data analysis, scientific/research rigor or author conclusions nor provide an editorial input. Astellas shall have the right to require Institution and/or Investigator to remove specifically identified Astellas Confidential Information and to request modification of any Publication if, in Astellas' reasonable opinion, such Publication will jeopardize a patent application or patent in relation to an Invention.

Disclosure of Support. Institution shall include and shall ensure Investigator includes, in all Publications, a disclosure of Support provided.

10.
Milestone Table. Astellas' support will be provided in accordance with completed milestones in accordance with the milestone table set out in the agreement and timelines referred to in the agreement or Astellas ISR Portal where research was submitted for Astellas' consideration for support.

Financial Reconciliation. The agreement will contain provisions for a financial reconciliation to be performed upon completion or early expiration of research, where support was provided by way of funding.

(Clause 3.7, 5.2 and 5.8)

Timelines. Institution shall and shall ensure Research Site(s) perform Research in accordance with timelines in Milestone Table and/or Astellas ISR Portal.

Invoicing and Payment. Payment of Research Grant shall be made in accordance with Milestone Table and Astellas ISR Portal. Institution shall invoice Astellas for each instalment of Research Grant falling due upon completion of the corresponding milestone in accordance with Milestone Table.

Effect of Termination for Research Grant. In the event of termination of this Agreement:

5.7.1 Institution shall be compensated only for those milestones achieved prior to notice of termination in accordance with Milestone Table;

5.7.2 by Astellas for no cause **(Clause 16.3(a))** or by Institution for the health or safety of Participants or for regulatory reasons **(Clause 16.5)**, Parties shall mutually agree on a payment based on actual work performed for any milestone(s) partially completed and reasonable non-cancelable material items included in **Appendix 1,** as of the date of notice of termination. Notwithstanding the foregoing, Astellas is under no obligation to pay Institution for activities undertaken following notice of termination unless mutually agreed by Parties in advance;

5.7.3 if payment of any sum has been made by Astellas to Institution in advance, any part of such sum not reasonably utilised in accordance with **Clause 5.7.2** shall be repaid to Astellas within thirty (30) days of Astellas' request;

5.7.4 the final invoice shall be issued to Astellas following Astellas' acceptance of the Final Report;

5.7.5 payment of the final invoice by Astellas shall be on the basis that there shall be no additional payments or expenses of any kind whatsoever due or that may become due to Institution.

11.
Intellectual Property. Where research involves an Astellas product, the agreement shall contain intellectual property language securing Astellas' rights.

(Clause 12)

Pre-Existing Property**.** Nothing contained in this Agreement shall affect the ownership of any Background Intellectual Property which one Party agrees to make available to the other from Effective Date. All such Background Intellectual Property shall remain the property of its owner. For the avoidance of doubt, nothing in this Agreement shall grant any right to Institution or Research Site(s) in Product and/or any Intellectual Property owned by or licensed to Astellas prior to or from Effective Date and it shall remain the property of Astellas. Institution has no ownership rights in Product.

Ownership. Final Report and Research Data shall be owned by Institution.

License(s). Astellas shall have unlimited and unrestricted rights to use Final Report free of charge as follows; (a) for internal purposes, which shall include use between Astellas and its Affiliates; (b) for any other purpose following the Non-Disclosure Period.

Inventions. Institution shall immediately report an Invention to Astellas within ten (10) days following its creation, but in any event prior to public disclosure. Astellas shall own all Inventions that arise out of the conduct of the Research and Institution hereby assigns any such Inventions to Astellas.

12.
Data Privacy. The agreement will contain data privacy language.

(Clause 3.10)

Personnel Consent. Institution shall ensure that the processing of any personal data of Research Personnel which may be necessary within the framework of Research, shall be undertaken in a lawful manner consistent with the terms herein. Such processing shall include the transfer of the personal data of Research Personnel to Astellas for Research-related purposes (e.g. ensuring compliance with data protection legislation; assessing Research Personnel's qualifications to perform Research and future projects; management and control of Research; or disclosing to the national or foreign regulatory authorities the details of any of Research Personnel's benefits under this Agreement, as required by Laws). Institution shall provide to Research Personnel the appropriate information for any data processing activities and particularly they will ensure that Research Personnel are fully informed that such transfer of their personal data may be to countries where the level of data protection may not be of the same level as offered by the law of their country. Parties shall undertake all required technical and organisational measures to ensure the security and integrity of Research Personnel's personal data processed within the framework of the present Research. Personnel shall be allowed to access their personal data that has been collected by Astellas, to update their personal data or to have any inaccurate personal data relating to them corrected, to request deletion or object to processing or to restrict processing of their personal data or request portability.

(Clause 14.2)

Privacy. Institution acknowledges that when reporting pharmacovigilance related reports and data, Astellas is a data controller for any such personal data received and shall provide to the relevant data subjects, Astellas' privacy notice (and consent forms where applicable) which can be found via the following link: www.astellas.com/en/privacy-notice-for-pharmacovigilance-and-medical-information-enquiries. Institution acknowledges that Astellas shall not have direct contact with data subjects of pharmacovigilance reports and shall therefore assist Astellas in complying with its legal obligations as data controller under Data Protection and Privacy Laws.

13.
Transparency. The agreement will contain provisions for the disclosure of transfers of value to enable Astellas to comply with applicable laws

(Clause 3.12)

Transparency. To enable Astellas to comply with Laws, Institution agrees that Astellas may report and/or disclose any payment or other transfer of value provided, directly or indirectly, to Institution pursuant to this Agreement. Institution agrees that information about payments or other value transferred to Institution by Astellas may be made publicly available. Institution shall promptly provide any information reasonably requested by Astellas, to facilitate such disclosures within thirty (30) days of such request. This Clause shall survive the termination or expiration of this Agreement.

14.
Termination by Astellas. The agreement contain a provision for Astellas to terminate the agreement in certain circumstances and a contract expiration date

(Clause 16.1, 16.3)

Term. This Agreement shall commence on Effective Date and shall remain in full force and effect, unless sooner terminated in accordance with this Agreement, until Institution's provision to Astellas and Astellas' acceptance of Final Report and where Support is provided as Research Grant, where Astellas made the last payment to Institution.

Astellas may terminate this Agreement: (a) upon giving thirty (30) days written notice to Institution for any reason; (b) immediately upon written notice to Institution for an incurable breach.

15.
Status Reporting. The party seeking Support must provide updates to Astellas every two (2) months on research progression in the form requested by Astellas. Where milestones are not likely to be met, the party seeking Support must provide Astellas with an explanation for the delays and possible corrective measures.

(Clause 6.1, 6.2)

Updates. Institution agrees to provide Astellas with an update of Research status through: (a) the Astellas ISR Portal (details to be separately provided by Astellas) every two (2) months; (b) another form or frequency reasonably requested by Astellas; and/or (c) as described under **Appendix 1**.

Delays. In the event a milestone in Milestone Table is at risk of not being met, Institution shall provide Astellas with the details as to why the milestone is at risk and how Institution plans to meet the agreed milestones. If there are justified reasons for a delay in the completion of a milestone, Parties shall first try to agree on new feasible dates before Parties or Astellas exercise its termination right as set out in **Clause 16.**

16.
Flow Down of Terms. In the event the research is multi-center or the party seeking Support engages with other research sites to perform the research or Institution wishes to subcontract a third party contract manufacturing organisation, the party seeking Support shall ensure that certain applicable terms of the agreement flow down into agreements with research sites and third party contract manufacturing organization.

(Clause 3.4, 3.5, 3.6, 4.1)

Institution Personnel. Institution shall ensure that Institution Personnel are made aware of and comply with the terms of this Agreement as applicable to them or are placed under contractual obligations that are consistent with this Agreement to enable Institution to meet its obligations under this Agreement. Institution shall at all times be liable for the performance of Institution Personnel.

Research Site(s). Institution may subcontract performance of Research to Research Site(s): provided, Institution: (a) has notified Astellas of such Research Site(s) on Astellas ISR Portal at the time of Astellas' evaluation of Institution's Research proposal or Astellas otherwise confirms in writing Support includes participation of Research Sites(s); and (b) remain liable for Research Site(s) performance of Research in accordance with this Agreement. Agreements with Research Site(s) shall not contain any terms and conditions which violate or contravene Astellas' rights under this Agreement. Institution shall provide Astellas with details of Research Site(s), as requested by Astellas.

Third-Party CMO. If Product is provided as Support, Institution may subcontract to a Third-Party CMO, the distribution of Product to Research Sites; *provided*: (a) Institution has notified Astellas of such Third-Party CMO on Astellas ISR Portal at the time of Astellas' evaluation of Institution's Research proposal; (b) the name and address of such Third-Party CMO is included under **Appendix 1**; and (b) Institution remains liable for Third-Party CMO's performance of its obligations in accordance with this Agreement and as required by Law. In the event Institution does not utilize a Third-Party CMO, then clauses referring to Third-Party CMO in this Agreement shall not be applicable.

Representations and Warranties. Institution represents and warrants that:

4.1.1 it shall perform Research in accordance with Agreement and it shall and shall ensure Institution Personnel and Research Site(s) perform Research: (a) in a timely manner; (b) in accordance with (i) the highest professional standards and quality; (ii) Protocol and Laws; (iii) requirements of Ethics Committee/IRB; (iv) timelines in Milestone Table and Astellas ISR Portal; and (c) in a manner that shall not infringe, misappropriate, or violate the rights of any third party;

4.1.2 it (a) shall enter into agreements with Research Site(s) for the performance of Research which cause Research Site(s) to be bound by and comply with those terms of this Agreement which pertain to Research Site(s) to enable Institution to meet its obligations under this Agreement and it shall notify Astellas upon execution of such agreement prior to Product being shipped to Research Site(s), if Product is provided as Support;

4.1.3 it shall and shall ensure Institution Personnel and Research Site(s) hold the necessary registration, as applicable, and have the necessary expertise and are qualified to perform Research;

4.1.4 if Product is provided as Support and Institution requires use of a Third-Party CMO to distribute Product to Research Site(s), Institution shall: (a) enter into an agreement with Third-Party CMO prior to Astellas shipping Product to Third-Party CMO causing Third-Party CMO to: (i) comply with Laws; (ii) be bound by and comply with those terms of this Agreement that pertain to Third-Party CMO to enable Institution to meet its obligations and under this Agreement; and (b) ensure Third-Party CMO holds and maintains certificates and licenses required by Laws;

4.1.5 if Product is provided as Support, Institution shall and shall ensure Institution Personnel, Research Site(s) and Third-Party CMO comply with Product Information and Astellas Instructions;

17.
Changes to Protocol. The Support provided is based on the version of the protocol uploaded into Astellas ISR portal and agreed by Astellas. Astellas may terminate the agreement in the event changes to the protocol means research can no longer be supported by Astellas.

(Clause 3.2)

Protocol. In the event that Institution determines changes to Protocol are required, Institution shall promptly notify Astellas in writing. Astellas shall not be obligated to provide any additional support other than as specified herein. Institution shall provide Astellas with a copy of any Protocol amendment. In the event such Protocol amendment requires additional support, Institution shall make a written request to Astellas for such additional support. Subject to Astellas' approval, Parties may execute a written amendment to this Agreement in accordance with **Clause 18.2**, evidencing Parties' agreement to the provision of such additional support. Astellas may terminate this Agreement in accordance with **Clause 16** in the event changes to the Protocol mean Research can no longer be supported by Astellas.

18.
Research Data. In the event a regulatory authority requests information about the research, the party seeking Support shall corporate with such authority. Astellas reserves the right to request anonymised research data at a later time if a regulatory authority requests it. Such request shall be subject a patients informed consent, as applicable and laws and will be agreed through a separate agreement between Astellas and the party seeking Support.

(Clause 8.1, 8.2)

Cooperation. Institution shall and shall ensure Research Site(s) cooperate with Regulatory Authority's request for further information in relation to Research to support any Astellas applications for changes to indications, strengths, dosages or dosage forms, routes of administration, or labelling changes in respect of Product, if Product is part of Research.

Request for Anonymized Research Data. Astellas shall not be provided with Research Data under this Agreement. Astellas reserves the right to request anonymized Research Data at a later time if a Regulatory Authority requests such data from Astellas. In such case and in accordance with the Participant's ICF or waiver and Laws, Institution and Astellas shall discuss in good faith a separate agreement regarding the provision of such Research Data to Astellas.

19.
Astellas Use of Final Report. Astellas shall have the right to use the final report for internal and external purposes following the party seeking Support's publication of research/research results or twelve (12) months following the provision of final report according to the milestones set out in the agreement.

(Clause 11.2, 12.3)

License(s). Astellas shall have unlimited and unrestricted rights to use Final Report free of charge as follows; (a) for internal purposes, which shall include use between Astellas and its Affiliates; (b) for any other purpose following the Non-Disclosure Period.

Non-Disclosure Period means Institution's publication of Research/Research Results or twelve (12) months following the provision of Final Report according to Milestone Table.

20.
Indemnity for Product. Astellas will not provide an indemnity for an Astellas product where provided as part of Support.

21.
Length of Negotiations. The agreement must be negotiated within the timelines set out by Astellas in writing as part of the Support approval letter. Where there are delays, Astellas may withdraw its offer of Support.