

Approved by: 
JSC Olpha Chairman of the Board
Juris Bundulis
Olaime. 17. 02. 2025

Approved by: 
JSC Olpha Scientific Office Director
Ēriks Ivanovskis
Olaime. 17. 02. 2025



Technical specification for the tender:

API Technology Transfer and Advanced Intermediate supply (ID No. 2025/02/01)

1. General information about the study sponsor:

Company name: JSC Olpha
Registration No.: 40003007246
Address: Rūpnīcu iela 5, Olaine LV-2114. Latvia

Contact persons:

Mārtiņš Kopeika, Project Manager, phone +371 27207950, Martins.Kopeika@olpha.eu
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2. Technical specification of the procurement object:
Technology Transfer of API including Advanced Intermediate supply.

Job assignment	Technology Transfer of API including Advanced Intermediate supply
Expected deadline for the execution of the Tasks 1 - 4.	Q1 2026
Task 1. Development of Technology for API (Optional task)	Development of technology for API in accordance with general principles described in ICH Q11 guideline, and with patent freedom to operate from the dates defined by the sponsor. 1) Feasibility Study: - Route of Synthesis scouting; - Small scale development of API synthesis; - Establishment of in process controls; - Gap analyses before Optimization; 2) Development of stability indicating Quality Control methods (Analytical Methods): - Development of Purity, Assay, Impurity analyses methods; - Assessment of genotoxic impurities; - Assessment of Related Substances and synthesis of Related Substances; - Assessment of possible sources of formation of nitrosamines; 3) Characterization of Raw Materials, Intermediates and final API - Identification of intermediates and API (NMR, IR, XRPD etc.); - Setting up critical quality attributes for intermediates and API; - Selection of Regulatory Starting Materials (RSMs); - Draft specifications and requirements for Raw Materials, intermediates and API 4) Preliminary Risk Assessment - Nitrosamines and genotoxic impurities according to ICH M7 guideline; - Elemental impurities according to ICH Q3D guideline; 5) Deliverables: - Feasibility Report including description of synthesis process (detailed procedures); - Description of preliminary analytical methods for quality control and in-process control; - Report on possible related substances and genotoxic impurities;

Task 2. Technology optimization and scale-up (<i>Optional task</i>)	1) Optimization of used quality control methods, determine the main sources of material loss (such as removal with mother liquors, decomposition or the formation of byproducts during synthesis); 2) Validation of control methods according to Ph. Eur. and ICH Q2R guidelines for stages starting from RSMs and to the API; 3) Defining Quality Specification (QS) of Raw Materials, Intermediates and API; 4) Justification for selection of RSMs; 5) Selection of manufacturers / supplier of raw materials; 6) Optimization of technology and in process controls; 7) Scale-up from small scale to target size batch production; 8) Manufacturing process validation for stages starting from the first use of RSMs and till the API preparation; 9) Pre-Stability test; 10) Deliverables: - Validated stability indicated analytical methods for quality control and in-process control; - Detailed description of optimized route of synthesis including critical parameters and in-process controls. batch records for scale-up batches; - Raw material, intermediate and API quality specifications; - Process validation report
Task 3. Technology Transfer (TT) of API	Technology transfer to the sponsor's production site, the production stages starting from the first use of the selected commercially supplied key intermediate to the final API. 1) Before the start of the TT, ensure the supply of the selected Key Intermediate produced under the GMP in the quantities required for the TT, and also provide information on manufacturers/suppliers of other necessary raw materials for TT for a timely order. 2) Documentation requirements for Technology Transfer: - The entire process must comply with current Good Manufacturing Practices (GMP), FDA, EMA, and ICH guidelines, as well as any other applicable regulatory standards or have documentation according to GMP, FDA, EMA, and ICH guidelines. - Provide a detailed report of the API synthesis route, including chemical reactions, reagents, solvents, intermediates, and process flow - Provide a comprehensive description of the manufacturing process, including detailed step-by-step procedures, key parameters (e.g., temperature, time, pH, solvents), and critical control points. - Detail the materials, chemicals, reagents, solvents, and equipment required for the process. Include supplier/vendor specifications - Provide comprehensive Safety Data Sheets (SDS) for all raw materials and intermediates, highlighting any hazardous materials, and safety risk assessments related to the synthesis production route.

	3) Quality Control, In-Process Control: - Transfer protocols for in-process testing, defining critical quality attributes (CQAs), and setting limits for acceptable performance. - Analytical methods and their validation (verification) report for Raw Material/ Reagent testing, including potency, identity, impurities, and any other relevant tests to ensure the quality of the API. - Analytical methods and their validation (verification) report for intermediate testing, including potency, identity, impurities, and any other relevant tests to ensure the quality of the API. - Analytical methods and their validation (verification) report for final API testing, including potency, identity, impurities, and any other relevant tests to confirm the quality of the API. - Provide typical CoAs for Starting materials, used reagents and final API. - Verify purity of all intermediates and the final product by HPLC (UV detection). Provide all chromatographic data to the study sponsor. Purity of API samples have to be in compliance with ICH Q3A and Q3C guideline requirements. 4) Analytical Method Transfer: - Define the performance metrics to evaluate the success of the Analytical Method Transfer, including method repeatability, variance and other parameters critical for successful method employment; - Provide Analytical Method Transfer protocol; - Provide the standards necessary for Analytical Method Transfer and control of TT batches production 5) Equipment requirements: - Provide specifications for any new or modified equipment required for the synthesis route. This should include reactor types, filtration systems, drying units, etc. - Detail requirements for control systems, including automation, monitoring, and data logging systems necessary to control and optimize the process. - Detail the requirements for the receiving facility. 6) Technology Transfer: - Define the performance metrics to evaluate the success of the technology transfer, including batch consistency, yield, purity, and compliance with regulatory requirements. - Clearly outline the acceptance criteria for process validation, scale-up batches, and final product quality; - Provide Technology Transfer protocol; - Review and correct production protocols / batch records for TT at sponsor's site; - Provide on-site support in the process of TT to adapt the production process to the sponsor's production equipment 7) Payment and Contract Terms: - Define the payment structure based on milestones, with payment due upon successful completion of each phase. 8) The deliverable result of Task 3:
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	- Technology Transfer report in English. - Analytical Method Transfer reports in English.
Task 4. Key Intermediate commercial supply	1) Documentation of Key Intermediate: - Ensure that specifications for intermediate/-s are well-defined, including purity, identity, and content. These specifications should be derived from validated analytical methods and in compliance with pharmacopoeia standards or internal specifications as well as in line with ICH and GMP requirements. - Document the required specifications and control methods for all starting materials used in the manufacture of the API, including intermediates, excipients, and raw materials. - Documentation must outline the QC testing requirements for all raw materials and intermediates, including any in-process controls. - Documentation on QC testing of intermediate/-s and raw materials including Analytical Methods, validations, Quality Specifications. - Risk Assessment Reports of intermediate and starting materials for – nitrosamine presence, genotoxic impurities according to ICH M7 and elemental impurities according to ICH Q3D. - Provide Certificate of Analyses of intermediate and starting materials (3 batches). - Documentation of the storage conditions (temperature, humidity, etc.) required for intermediates to maintain their quality and stability. - Readiness to undergo GMP audits as the site for the production of the first stages of the API. 2) Commercial price offer (should be provided within this offer): - Price should be expressed in EUR/ kg (or USD/ kg); - Price should be given at least for two levels (50 kg, 100 kg) and optimal amount; 3) Lead time (should be provided within this offer): - Lead time should be expressed in weeks; - Incoterm should be clearly indicated; 4) The Deliverable for Task 4 - Supply conditions and clearly defined pricing of Key Intermediate for API synthesis. - Supporting documentation for Key Intermediate for API dossier (e.g. documentary package in a form of secondary ASMF including all information necessary for creation of Applicant Part and Restricted Part of API dossier)

Other requirements	The contract organization performing the task must follow the methods and quality requirements defined by the study sponsor. It is required that: - The synthesis of API must not rely on the use of temperatures below -5°C for the TT stages from Key Intermediate to the API; - All starting materials, reagents and materials used for TT must be commercially available; - The use of ICH Class 1 solvents is prohibited (benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, 1,1,1-trichloroethane). The use of ICH Class 2 solvents and especially chlorinated solvents have to be avoided. - Avoid the use of highly toxic or explosive compounds for TT stages. - No column chromatography should be used in the main process for the synthesis/purification of the API and intermediates. Detailed description of pharmaceutically acceptable methods and quality requirements is available from the study sponsor upon e-mail request to the contact persons indicated above. All reports must be submitted electronically, in the form of MS Office documents written in English.
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3. Requirements to the Applicant:

1.	The legal status of the Applicant	The Applicant must be an organization engaged in chemical or pharmaceutical research.
2.	Track record of the Applicant	Not less than 3 (three) years experience in the development of synthetic methods suitable for large scale use in the pharmaceutical industry.
3.	The resources of the Applicant	1. The Applicant has sufficient research staff of suitable qualifications in the field of chemistry. 2. The Applicant must have at its disposal the necessary equipment for performing the work described in this Technical Specification (e.g. laboratory jacketed reactors equipped with adjustable thermostats).
4.	Validity term of offer	Until at least 31.03.2025.
5.	Deadline for performing the work	The expected deadline for performing the work is not later than Q1, 2026 . The deadline may be extended if additional and justified research becomes necessary (justification should be officially provided). The detailed conditions will be specified in Contract.
6.	Scope of work	The Applicant is expected to make an Offer covering the full scope of the Procurement Object. Task 1 and/or Task 2 are optional and price offer can be omitted significantly reduced for this Tasks if the relevant activities are completed by the Applicant, and the Applicant is ready to start the sponsored work from the later Tasks (e.g. Task 2 or Task 3). In this situation, the offer must contain relevant explanations from the Applicant for completing corresponding activities within Tasks 1 and/or Task 2.
8.	Equivalent offers	In case if an equivalent is possible to the requirements listed in this Technical Specification, which has not been anticipated by the Study Sponsor, the Applicant may submit an offer meeting the equivalent requirements.
9.	Offer price	The overall contract price and the price for each item listed in the "Work to be performed" section must be indicated in EUR (without VAT). The offer must contain separated information on the cost of purchasing additional raw materials, if not included in the total cost of Tasks 1-4. All Costs in offer must contain fixed price for each items in offer (Task 1, Task 2, Task 3, Task 4 including Key Intermediate commercial price offer, Raw materials and other costs) and overall price for all offer.
10.	Payment schedule	The Applicant agrees that the payment schedule and conditions will be defined in the Contract.
11.	Requirements for the formatting of Offer	- The Offer must be submitted in 1 copy prepared in digital format in English; - The date and place of the document preparation must be indicated, along with the name and signature of the responsible person, the legal address and registration number of the Applicant; The Offer must be mailed or delivered to the following address: Mārtiņš Kopeika, Project Manager, phone +371 27207950, Martins.Kopeika@olpha.eu and Kristīne Krūmiņa, Project Manager, phone +371 27201531, Kristine.Krumina@olpha.eu

4. Documents to be submitted:

Description of the work to be performed in accordance with the Technical Specification of the Procurement Object (Technical and Financial Offer – Annex No.1).

5. Additional conditions

This procurement is organized within the framework of Project No. 1.2.1.2.i.2/1/24/A/CFLA/005.

6. Annexes:

1. Technical and financial offer.

Technical and financial offer

Item	Work to be performed	Offer from the Applicant	Price without VAT (EUR)
1.	Task 1. Development of Technology for API (<i>Optional</i>): 1) Feasibility Study: - Route of Synthesis scouting; - Small scale development of API synthesis; - Establishment of in process controls; - Gap analyses before Optimization; 2) Development of stability indicating Quality Control methods (Analytical Methods): - Development of Purity, Assay, Impurity analyses methods; - Assessment of genotoxic impurities; - Assessment of Related Substances and synthesis of Related Substances; - Assessment of possible sources of formation of nitrosoamines; 3) Characterization of Raw Materials, Intermediates and final API - Identification of intermediates and API (NMR, IR, XRPD etc.); - Setting up critical quality attributes for intermediates and API; - Draft specifications and requirements for Raw Materials, intermediates and API. 4) Preliminary Risk Assessment - Nitrosoamines and genotoxic impurities according to ICH M7 guideline; - Elemental impurities according to ICH Q3D guideline; 5) Deliverables: - Feasibility Report including description of RoS; - Initial development of analytical methods for quality control; - Report on possible related substances and genotoxic impurities;		
2.	Task 2. Technology optimization and scale-up (<i>Optional</i>): 1) Optimization of used quality control methods, determine the main sources of material loss (such as removal with mother liquors, decomposition or the formation of byproducts during synthesis); 2) Validation of control methods according to PH. Eur. and ICH Q2R guidelines;		

	3) Defining Quality Specification (QS) of Raw Materials, Intermediates and API; 4) Optimization of technology and in process controls; 5) Scale-up from small scale to target size batch production; 6) Pre-Stability test; 7) Deliverables: - Validated stability indicated analytical methods for quality control; - Optimized route of synthesis description including critical parameters and in-process controls; - Raw material, intermediate and API quality specifications;		
3.	Task 3. Technology Transfer of API 1) Documentation requirements for Technology Transfer: - The entire process must comply with current Good Manufacturing Practices (GMP), FDA, EMA, and ICH guidelines, as well as any other applicable regulatory standards or have documentation according to GMP, FDA, EMA, and ICH guidelines. - Provide a detailed report of the API synthesis route, including chemical reactions, reagents, solvents, intermediates, and process flow. - Provide a comprehensive description of the manufacturing process, including detailed step-by-step procedures, key parameters (e.g., temperature, time, pH, solvents), and critical control points. - Detail the materials, chemicals, reagents, solvents, and equipment required for the process. - Include supplier/vendor specifications. - Provide comprehensive Safety Data Sheets (SDS) for all raw materials and intermediates, highlighting any hazardous materials, and risk assessments related to the synthesis route. 2) Quality Control: - Develop and transfer protocols for in-process testing, defining critical quality attributes (CQAs), and setting limits for acceptable performance. - Provide analytical methods and their validation (verification) report for Raw Material/ Reagent testing, including potency, identity, impurities, and any other relevant tests to confirm the quality of the API. - Provide analytical methods and their validation (verification) report for intermediate testing, including potency, identity, impurities, and any other relevant tests to confirm the quality of the API. - Provide analytical methods and their validation (verification) report for final API testing, including potency, identity, impurities, and any other relevant tests to confirm the quality of the API. - Provide examples of CoA for Starting materials, used reagents and final API.		

	- Verify purity of all intermediates and the final product by HPLC (UV detection). Provide all chromatographic data to the study sponsor. Purity of API samples have to be in compliance with ICH Q3A and Q3C guideline requirements. - Determine the main sources of material loss (such as removal with mother liquors, decomposition or the formation of byproducts during synthesis). 3) Analytical Method Transfer: - Provide Analytical Method Transfer protocol; 4) Define the performance metrics to evaluate the success of the Analytical Method Transfer, including method repeatability, variance and other parameters critical for successful method employment. 5) Equipment requirements: - Provide specifications for any new or modified equipment required for the synthesis route. This should include reactor types, filtration systems, drying units, etc. - Detail requirements for control systems, including automation, monitoring, and data logging systems necessary to control and optimize the process. - Detail the requirements for the receiving facility. 6) Performance Metrics and Acceptance Criteria: - Define the performance metrics to evaluate the success of the technology transfer, including batch consistency, yield, purity, and compliance with regulatory requirements. - Clearly outline the acceptance criteria for process validation, scale-up batches, and final product quality. 7) Payment and Contract Terms: - Define the payment structure based on milestones, with payment due upon successful completion of each phase. 8) The deliverable result of Task 1 - Technology Transfer report in English. - Analytical Method Transfer report in English.	
4.	Task 4. Key Intermediate commercial supply 1) Documentation of Key Intermediate: - Ensure that specifications for intermediate/-s are well-defined, including purity, identity, and content. These specifications should be derived from validated analytical methods and in compliance with pharmacopoeia standards or internal specifications as well as in line with ICH and GMP requirements. - Document the required specifications and control methods for all starting materials used in the manufacture of the API, including intermediates, excipients, and raw materials.	

	- Documentation must outline the QC testing requirements for all raw materials and intermediates, including any in-process controls. - Documentation on QC testing of intermediate/-s and raw materials including Analytical Methods, validations, Quality Specifications. - Risk Assessment Reports of intermediate and starting materials for – nitrosamine presence, genotoxic impurities according to ICH M7 and elemental impurities according to ICH Q3D. - Provide Certificate of Analyses of intermediate and starting materials (3 batches). - Documentation of the storage conditions (temperature, humidity, etc.) required for intermediates to maintain their quality and stability.	
	2) Commercial price offer: - Price should be expressed in EUR/ kg (or USD/ kg); - Price should be given at least for two levels (50 kg, 100 kg) and optimal amount; 3) Lead time: - Lead time should be expressed in weeks; - Incoterm should be clearly indicated; 4) The Deliverable for Task 2 - Supply conditions and clearly defined pricing of Key Starting Intermediate for API synthesis. - Supporting documentation for Key Starting Material for API dossier.	
3.	Costs of raw materials and other	
Overall price without VAT (EUR)		

Validity term of the Offer - _____.

Deadline for performing the work - _____.

Name, Surname
Position
Date
Signature