Warsaw, 27/05/2017

REQUEST FOR THE OFFER NO 30/2017 - ARG

I. THE ORDERING PARTY:

OncoArendi Therapeutics SA ul. Żwirki i Wigury 101 02-089 Warszawa VAT No. 728 27 89 248	**Contact person:** **Joanna Lipner** j.lipner@oncoarendi.com **+48 512 974 496**

II. OBJECT OF THE REQUEST:

Elaboration and execution of the preclinical research program for the Arginase inhibitor developed as an innovative treatment for cancer

The request for offers is carried out with the reference to the application process for the grant titled: ARG - PRE-CLINICAL AND CLINICAL DEVELOPMENT OF AN ARGINASE INHIBITOR FOR CANCER IMMUNOTHERAPY which would be co-financed by the National and European Union Funds and because of the competitiveness principle.

III. THE FORM OF THE ORDER:

III.1 The Request is not made under The Public Procurement Law (29/01/2004 i.e. Dz. U. z 2013 r., poz. 907 z późn. zm.).

III.2 This order is carried out in accordance with the principle of competitiveness, openness, transparency and equal access.

III.3 The Ordering Party reserves the right to cancel this procedure without providing reasons, and also to complete the procedure without choosing the winning tender.

III.4 In the course of examination and evaluation of the offers the Ordering Party may require Contractors to present explanations concerning the content of submitted bids.

III.5 The Ordering Party reserves the right to change the content of this request. If the changes can affect the content of tenders submitted in the procedure, the Ordering Party shall extend the tender submission deadline. Any changes made shall be provided promptly to all tenderers to which the request was sent and shall be binding on them.

III.6 This procedure does not set the obligation for OncoArendi Therapeutics SA to sign any formal contracts.

III.7 It is not possible to make an offer for a part of an order.

III.8 The offer submission is considered as acceptance of the content of the "Request for the Offer".

III.9 The Ordering Party will call the Contractor to conclude a conditional contract for the future project for which the Ordering Party is applying. After receiving the Grant the Ordering Party will call the Contractor to sign the Annex to the Conditional Contract.

IV. CONDITIONS FOR PARTICIPATION IN THE PROCEEDING AND MANNER OF EVALUATION OF MEETING THESE CONDITIONS

IV.1 The Request for offers relates to potential Service Providers whose scope of business activity is in full compliance with the subject of this Request.

IV.2 The offer may be issued by parties who:

- have the necessary qualifications to execute the project,
- are licensed to carry out the activity in question, if this is required by law,
- have the appropriate technical potential and personnel capable of performing the contract,
- are in a good economic and financial standing, which assures proper execution of the project in the declared time,

- will sign a confidentiality agreement which is available as an Appendix 4 to this Request

IV.3 Regarding knowledge and experience, the Ordering Party requires that the Service Provider:

1. has at least 15 years of experience in providing research service, including: toxicology studies (GLP), safety pharmacology studies (GLP), genotoxicity studies (GLP) and ADME studies, performed in compliance with the guidelines: OECD (*Organisation for Economic Co-operation and Development*), ICH (*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*), EMA (*European Medicines Agency*), FDA (*Food and Drug Administration*).
2. performed at least 100 preclinical 'First in Human' enabling projects, for innovative, low-molecular weight organic compounds, for third parties, within the last 5 years.
3. has at least 10 years of experience in performing toxicology study in rodents (mouse, rat) and non-rodents (dog, mini-pig, monkey).
4. has at least 10 years of experience in providing the bioanalytical service, including development and validation of bioanalytical methods for the determination of the test item concentration in rodents' and non-rodents' blood plasma.
5. has at least 10 years of experience in providing analytical service, including development and validation of analytical methods for testing dose formulations.
6. guarantees that any inspections that were carried out within the last five years didn't reveal any major negative findings and provides their 5 years' regulatory inspection history.
   * The Ordering Party reserves the right to enquire copies of selected certificates/documents issued by regulatory agency after inspections which took place between January 2012 and May 2017. If the documents are not disclosed within two days, the tender application may be considered as invalid.

The fulfillment of the above conditions will be evaluated on the basis of the statement of the Service Provider, a model statement is attached as Appendix 2 to the Request for the Offer.

IV.4 Regarding human resources, the Ordering Party requires the Service Provider to engage:

1. **Project Manager** who would be responsible for coordinating all project activities as well as communication with studies' directors and the Ordering Party. At least 2 years of experience in coordinating projects for third parties is required.
2. **Regulatory specialist /or specialists/**, who would be responsible for elaboration (in collaboration with the Ordering Party) of the detailed preclinical toxicology program (detailed study design, tox species selection, dose selection), safety pharm studies (detailed study design, tox species selection, dose selection), genotoxicity studies, ADME studies. At least 10 years of experience in designing time and cost efficient preclinical programs (compliant with ICH, EMA, FDA guidelines) for innovative, low-molecular weight organic compounds, including compounds developed for cancer, is required.
3. **Bioanalytical Specialist** who will be responsible for development and validation of bioanalytical methods. At least 10 years of experience in developing and validating bioanalytical methods for determination of the test item concentration in rodents' and non-rodents' blood plasma is required.

Fulfillment of the above conditions will be evaluated on the basis of:
a) statement of the Service Provider, a model statement is attached as Appendix 2 to the Request for the Offer,
b) CV's of above mentioned specialists.

IV.5 Regarding certificates, the Ordering Party requires the Service Provider to have valid:

1. GLP certificate
2. GMP certificate

Fulfillment of the above conditions will be evaluated on the basis of:
a) statement of the Service Provider, a model statement is attached as Appendix 2 to the Request for the Offer,

b) copies of GMP and GLP certificates.

VI.6 Excluded from the proceedings shall be those contractors who are personally or equity related to the Ordering Party.

Personal / capital connections between the Service Provider and the Ordering Party (or any person authorized to take on commitments or any person responsible for the preparation and the execution of the process of selecting the contractor) are understood to occur in situations such as:

a) participation in the company, in a civil or limited partnership,
b) holding at least 10 % shares or interests,
c) serving a function of a member of the supervisory organ, a member of the management organ or proxy,
d) having family ties, such as by marriage, by lineage at first or second degree, by adoption, guardianship or custody,

In order to prove the lack of basis for exclusion, the Service Provider will attach to the Offer a statement concerning personal / capital connections between the Service Provider and the Ordering Party, a model statement is attached as Appendix 3 to the Request for the Offer.

V. DETAILED DESCRIPTION OF THE SUBJECT OF THE REQUEST:

CPV code: 73111000

V.I General Information

The subject of the order is elaboration and execution of the preclinical research program for the Arginase inhibitor, including: toxicology studies (4-week and 13-week studies in rodents and non-rodents, GLP), safety pharmacology studies (respiratory system, cardiovascular system, central nervous system, GLP), genotoxicity studies (GLP) and ADME studies. The test item is an innovative, low-molecular weight organic compound, which is being developed as an innovative cancer treatment.
The preliminary design of the specific studies, which shall be used as a basis for preparing a pricing offer is presented in the Appendix No. 5. The Appendix No. 5 will be disclosed on the Contractor's demand only after signing the confidentiality agreement available as Appendix No. 4. The scan of filled and signed confidentiality agreement should be send by email to j.lipner@oncoarendi.com. The Appendix No. 5 will be provided within 48 hours from receiving a scan of the signed confidentiality agreement.

V.2 The contract includes:

1. Elaboration of the preclinical research program.
2. Project management.
3. Organization and execution of planned studies in compliance with OECD (*Organisation for Economic Co-operation and Development*), ICH (*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*), EMA (*European Medicines Agency*), FDA (*Food and Drug Administration*) guidelines.
4. Transfer and validation of dosing formulation procedure and method validation for the analysis of the test item in dose formulations
5. Development and validation of bioanalytical methods for determination the test item concentration in rodent and non-rodent plasma.
6. PK studies in rodents (mice and rats) and non-rodents (dogs and monkeys).
7. Toxicology studies in rodents (mouse, rat):
   - Dose Range Finding Study of the test item by oral administration, non-GLP.
   - 4-week toxicology study of the test item by oral administration with a 4-week recovery period, GLP.
   - 13-week toxicology study of the test item by oral administration with a 4-week recovery period, GLP.
8. Toxicology study in dog:
   - Maximum Tolerated Dose Study of the test item by oral administration, non-GLP.
   - 4-week toxicology study of the test item by oral administration with a 4-week recovery period, GLP.
   - 13-week toxicology study of the test item by oral administration with a 4-week recovery period, GLP.

9. Genotox studies:
   - AMES test, GLP.
   - *In vitro* micronucleus test, GLP.
   - *In vivo* micronucleus test, GLP.
10. Safety pharmacology studies:
   - Effects of the test item on hERG Tail Currents Recorded from Stably Transferred CHO Cells, GLP.
   - Effect in the Irwin Screen after single oral administration of the test item, (including formulation analysis, plasma samples analysis, preparation of PK profiles), GLP.
   - Respiratory effect following oral administration of the test item, (including formulation analysis, plasma samples analysis, preparation of PK profiles), GLP.
   - Effect of the test item by oral administration on cardiovascular parameters in conscious telemetered beagle dogs, (including formulation analysis, plasma samples analysis, preparation of PK profiles), GLP.
11. ADME studies:
   - Stability of test item in plasma.
   - Metabolic stability, microsomes (mouse, rat, dog, human).
   - *In vitro* comparative metabolism study with cryopreserved hepatocytes (mouse, rat, dog, mini-pig, monkey, human; both sexes) + *in vitro* metabolic ID.
   - Plasma Protein Binding, Whole Blood Binding, Blood to Plasma Ratio.
   - Mass-Balance Study (study with the radiolabelled test item).

V.3 The project execution timeline:

The Ordering Party expects the project to be executed within 18 months. The project execution time is defined as time form placing the formal order to filling the summary program report.

The Ordering Party expects the detailed schedule to be prepared within 2 weeks from placing the formal order.

The Ordering Party expects audited draft reports for 4-week toxicology studies to be issued within 3 months from the last day of the in-life phase.

V.4 The Ordering Party requires the Service Provider to:

1. conduct a preclinical research program as a comprehensive service. The general scope of the Order is listed in paragraph V.2.
2. engage, for the purpose of the project execution, the team having proven knowledge and experience in performing studies listed in the paragraph V.2, among others: toxicologist, veterinary scientist, veterinary technicians, pathologist etc.
3. engage, for the purpose of the project execution, the team having proven experience in developing and validating bioanalytical methods for determination the test item concentration in plasma samples.
4. ensure animal welfare in compliance with EU Directive 2010/63/EU or equivalent regulations.
5. ensure commitment to the humane care of the research animals they produce and work with in all of activities.
6. agree that the Sponsor audit their site/sites prior to signing the contract.
7. organize regular teleconferences to discuss the project progress.
8. prepare written project progress summaries.
9. organize project meetings at the Service Provider facility at the request of the Ordering Party.

V.5 The Ordering Party will provide:

1. Results of performed PK and preliminary toxicology studies.
2. Sufficient amount of the test item along with its analytical report.
3. Sufficient amount the test item standard along with its analytical report.
4. Sufficient amount of the internal standard along with its analytical report.
5. Dosing formulation procedure.
6. Bioanalytical method procedure.
7. Material Safety Data Sheet for the test item.

VI. EVALUATION OF THE OFFERS:

VI.1 Price – weight: 80% (80 pts.)

In this criterion point, will be calculated according to the formula below:

Points received = $Pc = \frac{C_{min}}{C_{evaluated}} \times 80$

where:

Pc – points received
C_{min}– the smallest Net price
$C_{evaluated}$ – Net price of the offer being evaluated
80 – weight of the criterion (80%)

The total contract value is a sum of costs for all individual studies. The studies were priced based on the information specified in the Request for the Offer as well as in the Appendix No 5.
The table no. 2 provides fix unit prices for individual study related services, that will serve the Parties to determine the content of amendments to the agreement if the initial study plan is changed

VI.2 Project execution time – weight: 20% (20 pts.)
20 points – up to 16 months from placing the formal order,
10 points – up to 17 months from placing the formal order,
0 points – up to 18 months from placing the formal order,
20 – weight of the criterion (20 %)

The project execution time is defined as time form placing the formal order to filling the summary program report.

VI.3 In the case of two or more tenders with equal number of points awarded, to guarantee performance of the contract in a manner favorable to the environment, by ensuring minimal consumption of materials, raw materials, energy, etc. Environmental certifications (eg. ISO), if available, will be taken into consideration.

If the abovementioned conditions do not allow to choose the best offer, the Ordering Party shall call Contractors who submitted equally evaluated offers to submit, within the period specified, additional offers. Contractors cannot offer higher prices than those offered in the tenders.

VII. HOW TO PREPARE AND SUBMIT THE OFFER:

VII.1. The offer should be signed by the person authorized to represent the Service Provider.
VII.2. Each service party may submit only one offer.
VII.3. The Service Provider should make the offer in Polish or English.
VII.4. The costs of the offer preparation shall be incurred by the offering party.
VII.5. The offer should be valid for at least 6 months from its submission.
VII.6. Offers must be submitted no later than: 26/06/2017 till 11:59 pm (UTC+01:00).
VII.7. The offer shall be submitted via email to: j.lipner@oncoarendi.com as a scan of a document signed by the person authorized to represent the Service Provider.
VII.8. The offer submission date is the date of its issuing on e-mail address indicated in Section VII.7.
VII.9. Offers that do not meet the deadline will not be taken evaluated.
VII.10. Any questions concerning the Object of the tender should be addressed to Joanna Lipner by e-mail j.lipner@oncoarendi.com or by phone +48 512 974 496 no later than 23/06/2017 till 4 pm (UTC+01:00).
VII.11. The offer should include:

1. Proposal prepared according to the template available as Appendix 1 to the Request for the Offer.
2. Fixed price (both Net and Gross) for the order execution in Polish Zloty, Euro or USD.

For the purpose of comparing submitted pricing offers, the offer prices will be convert in to PLN according to the average exchange rate of National Polish Bank on the day of the Request for the Offer publication.

3. The unit prices specified in Tables 2 and 3 of the Offer Form, attached as Appendix 1 to this Request, will be applied to determine the content of amendments to the agreement in the event of a necessity of the study plan modification.
4. Statement confirming fulfillment of the conditions described in the point IV of the Request for the Offers (Appendix 2 to the Request).
5. CVs of the project team members, as described in point IV.4.
6. Contact data to at least two persons, who would provide, upon request of The Ordering Party, a written assessment of The Contractor's work or a letter of reference.
7. Statement of the lack of personal and capital connections between the Ordering Party and the Service Provider (Appendix 3 to the Request).
8. Copies of valid GLP and GMP certificates.
9. Copies of the environmental certificates certified by the Service Provider - if applicable.
10. Documents confirming the authorization of the person/persons signing the offer to represent the Service Provider, such as an extract from the relevant register, power of attorney to represent the Service Provider, including the signing of the offer (certified as a true copy).
11. Detailed project schedule presented as a Gantt chart
    The following assumptions shall be made:
    a. The formal order will be placed on 01/11/2017.
    b. The test item (as well as necessary standards) for *in vitro* work, analytical and bioanalytical work will be delivered on 01/11/2017.
    c. Sufficient amount of the test item for tox studies will be delivered on 01/01/2018.
    d. Project completion date (this date should be in line with the declared project execution time).
12. Information about the research site/s address.
13. Signed confidentiality agreement (Appendix 4 to the Request)
14. The Service Provider's template of the Master Service Agreement.

VII.12. Description of the pricing methodology

1. The fixed price must cover all costs of the order execution.
2. The fixed, tender price has to include all costs of the Order execution. The fixed price shall be calculated based on the current studies' design, available as the Appendix 5. The fixed price has to include all services listed in this Request.
3. The net and gross prices should be given rounded to two decimal places, according to the mathematical principle of round up of figures.
4. The gross price should include the VAT. The correct determination of VAT is the responsibility of the Service Provider.
5. The Ordering Party does not allow to present the offer price in several variants.
6. Settlements between the Ordering Party and the Service Provider will be paid in Polish Zloty (PLN), Euro (EUR) or US Dollars (USD, according to the offer submitted by the Service Provider.

VIII. TENDER RESULTS

The winner will be informed via e-mail address. Formal results will be also published on the Ordering Party's website (www.oncoarendi.com).

IX. MOST IMPORTANT PROVISIONS OF THE AGREEMENT

IX.1 Supplier will be obligated to enter into the agreement including all conditions presented in the Request for the Offer.

IX.2 It is not possible to introduce significant changes to the content of the agreement in relation to the content of the offer, which was the base for the Service Provider selection, unless:

a) the amendments concern performing additional services by the Service Provider, not covered by the basic contract, provided they are necessary and the following conditions are met:

i. the change of the Service Provider cannot be made due to economic or technical reasons, in particular concerning the interchangeability and interoperability of equipment, services or installations, ordered as part of the basic contract,
ii. the change of the Service Provider would cause significant inconvenience or substantial cost increase to the Ordering Party,
iii. the value of any subsequent changes do not exceed 50% of the basic contract value,
b) the amendment does not lead to a change in the nature of the contract and the following conditions are met:
i. the need for the contract change is brought about by circumstances which the Ordering Party, acting with due diligence, could not foresee,
ii. the value of a change does not exceed 50% of the basic contract value,
c) the amendment does not lead to a change in the nature of the contract and the total value of changes is less than 209 000 EUR, and at the same time is less than 10% of the basic value
d) If the modification of clinical study plan become a matter of necessity, the order description and the studies' plans will be adjusted. The current studies' plans will be reviewed and validated after analyzing all preliminary toxicology data.
If the studies' plans change, the contract value will be amended. The amendment will be based on fixed unit prices included in the table no. 2 of the Offer Form (the Appendix 1).
The amendments will not cause introduction of a contract change.

Any contract amendment must be done in writing, otherwise will not be valid.

IX.3 Information regarding contractual penalties:
a) If the offered project execution time (as defined in Section VI.2.) extends for at least 30 days, the Service Provider shall pay the Ordering Party a contractual penalty of 1% of the net offer price for exceeding the time limit, and then another 2% of net offer price for each additional 30 days of delay. Moreover, the Ordering Party will gain a right to withdraw from the contract if the project execution time is exceeded by at least 60 days.
b) Due to the termination or withdrawal from the Agreement by either Party for reasons caused by the Service Provider, the Ordering Party will charge a contractual penalty of 10% of net offer price.
c) The formal basis for charging contractual penalties will be a debit note the Ordering Party delivers to the Service Provider. The Ordering Party shall be entitled to deduct contractual penalties from payments due to the Service Provider.
d) The Ordering Party has the right to claim damages in the amount exceeding contractual penalties based on general principles.
e) Contractual penalties will be paid within 7 days form the debit note receipt date.

APPENDICES TO THE REQUEST FOR THE OFFER:

1. The offer form.
2. Statement concerning fulfillment of all the requirements set out in part IV of the Request for Offer.
3. Statement concerning personal or/and capital connections between the Service Provider and the Ordering Party.
4. The confidentiality agreement form template.
5. The technical information package.
6. The conditional contract for the performance of the research services template.