Warsaw, March 13, 2024
place and date

PRICE INQUARY No. RIA/6/PR52746/2024
conducted in the market research mode

In connection with the implementation of the project entitled "Design and development of an innovative solution - a complex, three-component medicinal product targeting the treatment of hypertension" financed from the state budget by the Medical Research Agency, Zakłady Farmaceutyczne Polpharma S. A. is asking for offers to conduct a pharmacokinetic study.

I. NAME AND ADDRESS OF THE ORDERING PARTY

Zakłady Farmaceutyczne Polpharma S. A.
Pelplinska str. 19
83-200 Starogard Gdanski
website:https://www.polpharma.pl/

II. PROCEDURE OF AWARDING THE ORDER

1. This order is not subject to the provisions of the Act of September 11, 2019, Public Procurement Law (consolidated text: Journal of Laws of 2019, item 2019).
2. The proceedings are conducted in a market research manner, in a purposeful and economical manner, in compliance with the principles of:
   1) obtaining the best results from given inputs;
   2) optimal selection of methods and means to achieve the assumed goals;
   3) transparency, fair competition and equal treatment of contractors.

III. DESCRIPTION OF THE SUBJECT OF THE PRICE INQUIRY

III.1. The subject of the price inquiry is service of conducting one pharmacokinetic study for solid oral formulations with the participation of healthy volunteers. The aim of the study is to compare the pharmacokinetic parameters between the developed test formulation containing a combination of indapamide, amlodipine and ramipril and the combination of reference products containing indapamide, amlodipine and ramipril.

III.2. **CPV CODE: 73120000-9 - Research and development services**

III.3. Scope of the price inquiry:

III.3.1 Type: Investigational medicinal products

1. Tested product – Ramipril/Amlodipine/Indapamide 10 mg + 10 mg + 2.5 mg hard capsules (Zakłady Farmaceutyczne Polpharma SA)

2. Reference products:

- Tritace® 10 mg capsules (Sanofi), containing ramipril, used to treat cardiovascular diseases.

- Norvasc 10 mg capsules (Sanofi), containing amlodipine, used to treat cardiovascular diseases.

- Natrilix 2.5 mg film-coated tablets, containing indapamide, used in the treatment of cardiovascular diseases.

The Ordering Party reserves the right to change the trade name and pharmaceutical form of the reference products depending on the availability of the products on the market.

III.4 Description of the study

- Randomized, 2-arm, 2-period, crossover study in healthy, non-smoking volunteers, following a single administration under fasting conditions.
- The study is planned as a two-arm study in which one batch of the tested product and a combination of three reference products (one batch) will be used. Study design: open-label, single-administration, 2-period
- Sampling: 25 sampling points (including 23 for ramipril, 20 for ramiprilat, 16 for amlodipine, 19 for indapamide), up to 72 hours after dosing. For ramipril and ramiprilat, an individual sampling scheme was planned for each of the two analytes (i.e. some time points only for ramipril and some only for ramiprilat). If the Bidder does not have the technical possibility to use the above-mentioned approach, then the quote should include the collection and analysis of ramipril and ramiprilat samples at all 25 time points
- Confinement: at least 12 hours before and 24 hours after dosing
- Washout period: at least 21 days (the exact length of the washout period will be determined at the stage of protocol preparation)
- ECG examination during screening and after each dosing of each volunteer (approximately 4 to 6 hours after dosing)
- Blood pressure and heart rate measurement during screening, before dosing and after each dosing of each volunteer
- Sample size: 72 healthy volunteers, of which:
    1. Ramipril and ramiprilat will be tested in all 72 volunteers
    2. Amlodipine will be tested in the first 36 volunteers (no. 1 to 36)
    3. Indapamide will be tested in another 36 volunteers (no. 37 to 72)
- Analytes: ramipril, ramiprilat and amlodipine - in blood plasma, indapamide - in whole blood (an already developed and validated analytical method is required for all analytes at the moment of starting the dosage of the test products, in accordance with the guideline EMA/CHMP/ICH/172948/2019), with lower limit of quantification:
    1. not greater than 0.4 ng/mL for ramipril
    2. not greater than 0.2 ng/mL for ramiprilat
    3. not greater than 0.1 ng/mL for amlodipine
    4. not greater than 0.5 ng/mL for indapamide

III.5. The contractor is responsible for providing the complete service of conducting the study: the clinical part (including the preparation of full documentation specified in the detailed description of the order), the bioanalytical, pharmacokinetic and statistical part of the study along with the preparation of reports, as well as data management and study management. In particular, he is responsible for:

- Recruitment and screening of an appropriate number of volunteers for the study (including reserve subjects),

- Clinical assessment of volunteers during screening, during the course of the study and at the post-study visit (in accordance with local requirements, relevant European guidelines and regulations and contractor procedures),
- Preparation of full study documentation – including: study protocol with amendments (if applicable), ICF, CRF, submission of a clinical trial application to the regulatory body and bioethics committee (including fees), EudraCT management (if applicable), as well as data management and study management,
- Management of the investigational product (including relabeling and preparation for administration, as well as destruction and reconciliation of products) in accordance with Annex 13 of GMP,
- Administration of investigational products to healthy volunteers and then collection of blood samples at precise time points to determine the concentration of active substances in plasma and whole blood,
- Conducting analysis of drug concentration in blood samples using a validated method (including ISR), followed by pharmacokinetic and statistical calculations,
- Preparation of clinical and bioanalytical reports, including the results of pharmacokinetic parameters and statistical analysis in accordance with the requirements of the European Medicines Agency (EMA), as well as archiving of the study documentation for 25 years,

III.6. The contractor is responsible for providing the complete service of conducting the study: the clinical part (including the preparation of full documentation specified in the detailed description of the order), the bioanalytical, pharmacokinetic and statistical part of the study along with the preparation of reports, as well as data management and study management,

III.7. The study must be designed, conducted and documented in accordance with the principles of ICH-GCP, GLP, Directives 2001/20/EC, 2001/83/EC, 2005/28/EC, the Declaration of Helsinki and applicable European guidelines, in particular the guideline on bioequivalence studies (CPMP/EWP/QWP/1401/98 Rev.1/Corr**),

III.8. The analytical method must be developed and validated in accordance with applicable regulations, in particular ICH M10 guideline on the validation of bioanalytical methods and sample analysis (EMA/CHMP/ICH/172948/2019),

III.9. The documentation (including the Protocol, ICF, CRF and Final Study Report) must be prepared in accordance with guideline CPMP/ICH/137/95 and written in English and in the local language if required by local law; the final report from the study (including the bioanalytical report and the report on the validation of bioanalytical methods) should be prepared in the eCTD format,

III.10. The Contractor will represent the Ordering Party before the relevant authorities and the bioethics committee in the process of obtaining consent to conduct the study, as well as respond to inquiries from regulatory agencies in the procedure of marketing authorization application and potential documentation auditors.

III.11. Conducting internal audits of documentation and processes by the contractor during the study,

III.12. The order does not include study monitoring.

III.13. The Ordering Party does not allow the submission of partial or variant offers.

IV. PLACE AND DATE FOR COMPLETION OF THE PRICE INQUIRY

IV.1. Deadline for completing the subject of the order:

1. **Estimated date of signing the contract: May 2024.**
2. **Planned start of the study (first dosage): July 2024 (no later than 2 months from signing the contract)**

3. The contract implementation period must be completed no later than 120 calendar days from the date of commencement of the study.
4. The study results and necessary documents (in electronic and paper form) obtained in connection with the provision of the service must be delivered at the Contractor's expense to the Ordering Party's headquarters.
5. Deadline is a criterion for evaluating the offer and will be counted as the time from the beginning of the study to the moment of submitting all final audit reports to the Ordering Party.

V. REQUIREMENTS FROM CONTRACTORS

V.1. Contractors who meet the following conditions may apply for the contract:

1.The contractor is in an economic and financial situation ensuring timely and consistent performance of the order in question, is not in bankruptcy and is not subject to liquidation or restructuring proceedings.
How to evaluate the condition:
*The Ordering Party will consider that the Contractor meets this condition if the Contractor submits a declaration of meeting the conditions for participation in the procedure (**Appendix No. 2** to the Request for Quotation).*

2.The contractor will demonstrate that it has the appropriate potential to perform the contract:

The contractor is able to carry out the clinical, bioanalytical, pharmacokinetic and statistical part, in accordance with the principles of ICH-GCP, GLP, Directive 2001/20/EC, 2001/83/EC, 2005/28/EC, the Declaration of Helsinki and applicable European guidelines, in particular with the guideline on bioequivalence testing (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

How to evaluate the condition:
*Condition verification will be based on a declaration of meeting the conditions for participation in the procedure (**Appendix No. 2** to the Request for Quotation).*

The Ordering Party reserves the right to verify the compliance of the content of the Contractor's declaration with the actual situation and to conduct an audit of the Contractor.

3. The Contractor will demonstrate that it has appropriate staff, including qualified medical and nursing staff (with secondary or higher medical education), as well as key personnel necessary to perform the order, including at least one person in the position of: Principal Investigator, Head of the Bioanalytical Laboratory, Statistician or in an equivalent position.

Each of the above-mentioned persons, depending on their function, must:

a) have experience in conducting clinical trials (for the Chief Investigator, at least 5 years of experience and at least 10 years of experience as a doctor, for a Statistician, at least 5 years of experience, for the Head of Bioanalytical Laboratory min. 10 years of experience).
b) have specialized education (for the Chief Investigator: medicine, for the Head of Bioanalytical Laboratory and Statistics: medicine, biotechnology, pharmacy, biology, chemistry, mathematics, physics or related),

c) have the ability to analyze the results obtained in a clinical trial and correctly report trial data in accordance with appropriate procedures and standards.

The qualification criteria for key personnel should be included in the Contractor's appropriate procedures in accordance with the principles of ICH GCP.

How to evaluate the condition:
*The contractor must meet all conditions together. Verification of AC points will be based on the declaration of fulfillment of the conditions for participation in the procedure (**Appendix No. 2** to the Request for Quotation).*

4.The contractor will demonstrate that he has experience and appropriate potential to perform the contract:

a) The Contractor has a developed and validated analytical method for all analytes (ramipril, ramiprilat, amlodipine, indapamide) with an appropriate quantification limit in accordance with the requirements of the EMA/CHMP/ICH/172948/2019 or CHMP/EWP/192217/2009 Rev. guidelines. 1 Corr.2**.

*The Ordering Party will consider the condition to be met based on the Contractor's declaration (**Appendix 2**) and the presentation of a **list of validated analytical methods along with the LLOQ value.***

b) The contractor has an experience in conducting pharmacokinetic studies for fixed-dose combination medicinal products.

*The Ordering Party will consider the condition to be met based on the Contractor's declaration (**Appendix 2**) that it has performed at least 10 pharmacokinetic tests (including the clinical part) for oral fixed dose combination medicinal products over the last 10 years (if the Contractor's period of operation is shorter, during its period of operation). **and provide a list of at least 10 pharmacokinetic studies over the last 10 years***

c) The contractor of the clinical, bioanalytical and pharmacokinetic-statistical parts will present a list of inspections for the last 10 years (if the period of the Contractor's operation is shorter - during the period of its operation) with a summary of the inspection results. At least 1 inspection must be carried out by an appropriate authorities of one of the European Union countries in the field of GCP (Good Clinical Practice) and GLP (Good Laboratory Practice), and the results of all inspections during the given period cannot contain critical non-compliances. Inspections of tests carried out by the Contractor before 2014 will not be taken into account.

*The Ordering Party will consider the condition to be met based on the Contractor's declaration (**Appendix 2**) and the **presentation of the above-mentioned inspection list**.*

How to evaluate the condition:

*The contractor must meet all required requirements together. The Ordering Party will consider the condition to be met on the basis of the Contractor's declaration (**Appendix No. 2** to the Request for Proposal), the list of validated analytical methods referred to in **point 4a**, list of*

pharmacokinetic studies referred to in ***point 4b*** *and the inspection list referred to in* ***point. 4c*** .

V.2. The offers of Contractors who demonstrate compliance with the required conditions will be accepted for examination and evaluation. The assessment of the fulfillment of the conditions presented above will be made according to the formula: "meets - does not meet". A contractor who fails to meet any of the conditions will be rejected from the proceedings.

V.3. Entities in relation to which the following circumstances occur are also excluded from participation in the proceedings:

a) described in art. 7 section 1 of the Act of April 13, 2022 on special solutions for counteracting support for aggression against Ukraine and for protecting national security;

b) described in art. 5k of Council Regulation (EU) No. 833/2014 of 31 July 2014 concerning restrictive measures in connection with Russia's actions destabilizing the situation in Ukraine.

Method of verifying the grounds/lack of grounds for exclusion:

Verification will be based on the Bidder's declaration.

VI. PLACE AND DATE FOR SUBMITTING OFFERS

VI.1. Offers must be submitted **no later than March 27, 2024.**

- in electronic form (in the form of electronically signed documents or a scan of a signed document) to the following address:barbara.wendolowska@polpharma.com

VI.2. The submission of an offer will be considered effective if the complete offer reaches the e-mail address provided above within the deadline specified in this point.

VI.3. Offers submitted after the deadline will not be considered.

VII. DESCRIPTION OF CRITERIA WHICH THE ORDERING AUTHORITY WILL FOLLOW WHEN SELECTING AN OFFER

VII.1 When evaluating offers, the Ordering Party will be guided by given criteria:

- total net price for the service – 60%,
- service delivery time (working days) – 40%

VII.2 The offer will be scored according to the formula:

$$O_P = P_C + P_M$$

Where:

OP	point evaluation of the offer
P_C	number of points obtained in the "Total net price" criterion
P_M	number of points obtained in the "Service delivery time" criterion

VII.3 The number of points (PC) in the "Total net price" criterion will be calculated according to the formula:

$$P_C = \frac{C_N}{C_B} * 60\ pkt$$

Where:

PC - number of points for the "Total net price" criterion
CN - among the non-rejected offers, the lowest total net price of the offer
CB - total net price of the examined offer

Offers submitted in a currency other than PLN will be converted into PLN at the average NBP exchange rate as of the closing date for the submission of offers.

VII.4 Number points in the criterion P_T "Service delivery time" will be awarded as follows:

$$P_M = \frac{M_N}{M_B} * 40\ pkt$$

Where:

PM - number of points for the "service delivery time" criterion
MN - among the offers that were not rejected, the shortest delivery time for the subject of the price inquiry
MB - delivery time of the subject of the price inquiry declared in the offer

The service delivery time for the subject of a price inquiry should be given in full calendar days. Offers with a lead time longer than 120 calendar days will be rejected.

VII.5 The Bidder can obtain a maximum of 100 points. Calculations will be made with an accuracy of two decimal places.

VIII. DESCRIPTION OF THE METHOD OF PREPARING THE OFFER

VIII.1 The tenderer should prepare one offer in accordance with the template form attached as Annex 1 to the inquiry.
VIII.2 The Ordering Party does not allow the submission of partial or variant offers.
VIII.3 The bidder may change or withdraw his offer before the deadline for submitting offers.
VIII.4 Bidders are obliged to carefully read the information contained in the Request for Proposal.
VIII.5 The costs of preparing and delivering the offer are borne by the Contractor.
VIII.6 In matters related to this inquiry, please contact the Ordering Party, e-mail:barbara.wendolowska@polpharma.com

IX. GENERAL PROVISIONS AND CONDITIONS OF THE AGREEMENT

IX.1 The Ordering Party reserves the right to make significant changes to the provisions of the Agreement for the offered services in relation to the content of the offer on the basis of which the Contractor was selected, in the following scope and situations:
IX.1.1. changes in legal provisions to the extent affecting the implementation of the Agreement (in particular changes in VAT rates);
IX.1.2. improving the technical parameters of the subject of the Agreement, resulting from updating solutions due to technological progress, without affecting the gross lump sum price
IX.1.3. extending the deadline for the implementation of the Agreement due to the need to perform additional works, the execution of which is necessary for the proper performance of the Agreement and

the execution of which the Ordering Party, acting with due diligence, could not have predicted in advance, subject to subpoint. IX.1.6 below;

IX.1.4. extension of the deadline for the implementation of the Agreement as a result of force majeure, along with all the consequences arising in connection with the extension of this deadline;

IX.1.5. changes in the parameters of the subject of the Agreement, not leading to a change in the nature of the Agreement - technological changes, in particular: the need to implement the Agreement using other technical/technological and material solutions than those indicated in the Request for Quotation, in a situation where the use of the provided solutions would pose a risk of non-performance or defective performance of the Agreement, with reservation subpoint. IX.1.7. below;

IX.1.6. the changes concern the provision of additional deliveries or services of the Contractor not covered by the Agreement, provided that they have become necessary and the following conditions have been met:

- the change of the Contractor cannot be made for economic or technical reasons, in particular regarding the interchangeability or interoperability of equipment, services or installations ordered under the basic subject of the Agreement,
- a change of the Contractor would cause significant inconvenience or a significant increase in costs for the Ordering Party,
- the value of each subsequent change does not exceed 50% of the net value of the original subject of the Agreement;

IX.1.7. the change does not lead to a change in the nature of the Agreement and the following conditions have been met:

- the need to change the Agreement is caused by circumstances that the Ordering Party, acting with due diligence, could not have predicted,
- the value of the change does not exceed 50% of the net value of the original subject of the Agreement;

IX.1.8. The contractor is to be replaced by a new contractor:

- as a result of a merger, division, transformation, bankruptcy, restructuring or acquisition of the Contractor or his enterprise, provided that the new contractor meets the conditions for participation in the proceedings, there are no grounds for exclusion against him and it does not result in other significant changes to the Agreement,
- as a result of the Ordering Party taking over the Contractor's obligations towards its subcontractors.

IX.2. The Ordering Party also provides for the possibility of making insignificant changes to the provisions of the concluded Agreement in relation to the content of the offer on the basis of which the Contractor was selected.

IX.3. Changes to the Agreement will be introduced in the form of annexes signed by both Parties, and the possibility of their introduction depends on the acceptance by the Ordering Party.

IX.4. The ordering party requires other important offer parameters to be met:

- Payment term: minimum 30 days;
- Offer validity: 90 days;

IX.5. Important terms of the contract:

IX.5.1. Inconsistencies or defects - In the event of significant inconsistencies or defects in the performance of the Services due to the sole fault of the Supplier, the Supplier is obliged to perform the Services again at its own expense. Objections to the results should be reported to the Supplier by the Ordering Party within fourteen (14) business days. The Ordering Party will justify in detail significant inconsistencies and defects. This work should be completed promptly and the date for receipt of services or materials specified in the relevant Project Order will be extended accordingly. If the Supplier is unable to resupply the Materials or perform the Services without such inconsistencies or defects, the Supplier will refund amounts paid for such services in the event of any inconsistencies or defects being detected.

IX.5.2. Audit - the Ordering Party reserves the right to conduct an audit of the Supplier before concluding the contract or during its implementation.

IX.5.3. Contractual penalties - The Supplier is obliged to pay contractual penalties for:

- postponing the order completion date for each day of delay, if the delay is not the fault of the Ordering Party;
- improper performance of the contract;
- incomplete performance of the contract.

The Supplier agrees to deduct the amount of contractual penalties directly from the payment of the VAT invoice at the time of delivery.

IX.6. The Ordering Party reserves the right to cancel the procedure without giving a reason.

IX.7. If the procurement procedure is canceled, suppliers are not entitled to a claim for reimbursement of the costs of participation in the procedure.

IX.8. The Ordering Party's withdrawal from concluding the contract in the event of notifying the contractor of the selection of its offer cannot constitute the basis for claims for the costs of participation in the proceedings.

IX.9. In the course of assessing the submitted offers, the Ordering Party may request that the contractors provide explanations regarding the content of the documents they submitted.

IX.10. If the offer does not contain all the required elements, the Ordering Party may, in justified cases, call on the Contractor to supplement it.

IX.11. The Ordering Party reserves the right to negotiate offers with the Contractor whose offer has the highest number of points, especially when the price offered by the Contractor exceeds the budget allocated by the contracting authority for the execution of the contract. Negotiations may have several subsequent rounds, with the possibility of inviting the bidder to submit an updated offer after each round of negotiations.

IX.12 If the supplier's income obtained in connection with the implementation of the project is subject to withholding tax in Poland, then the Ordering Party (ZF Polpharma SA) is obliged by law to deduct withholding tax from the supplier's remuneration and pay it to the Polish tax **authorities (the remuneration presented in the offer includes withholding tax).**

X. OTHER INFORMATION

X.1. The bidder bears all costs related to the preparation and submission of the offer.

X.2. Until the deadline for submitting offers, the Ordering Party reserves the right to change or supplement the content of this price inquiry.

XI. LIST OF ANNEXES

The following documents are attached to this Quotation Request:

Attachment designation	Attachment name
Appendix 1	Pricing form template
Annex No. 2	Sample declaration on meeting the conditions for participation in a price inquiry

Annex No. 1 to the Price Inquiry No. RIA/6/PR52746/2024

PRICE FORM

Bidder:

Full name (company) or name and surname	
Registered office/place of residence/address of main place of business	
E-mail address to which the Ordering Party should send correspondence	
Tax Identification Number	
Statistical numer (if aplicable)	
Telephone	
Contact person with the Ordering Party	

We offer the execution of the subject of the order in the scope of services related to conducting a pharmacokinetic study in accordance with the requirements of the price inquiry, for the price of:

net amount: ……PLN / EUR/ USD

VAT rate: ……%, VAT amount: PLN / EUR / USD

gross amount: ……PLN / EUR / USD* *select the appropriate currency

Individual costs:

Study part	**Cost**	**Currency**	**Time** (working days)
Clinical part preparation		PLN/EUR/USD	
Clinical part / Clinical part		PLN/EUR/USD	
Analytical part		PLN/EUR/USD	
Statistical part / Pharmacokinetic and statistical analysis		PLN/EUR/USD	
Report / Report		PLN/EUR/USD	
Additional costs		PLN/EUR/USD	

Order processing time: ……..calendar days from the date of delivery of test samples for the order.

The payment deadline for invoices is ..... days.

The bidder has the status of - SME / Large Entrepreneur * (delete as appropriate)

At the same time, we declare that: :

a. we have read the Price Request with attachments and have no objections and have obtained the necessary information to prepare the offer,

b. the price includes a lump sum remuneration for all the obligations of the future Contractor necessary to complete the subject of the Quotation Request,

c. By submitting this offer, we declare that we meet the conditions for participation specified in point. V price inquiry.

d. By submitting this offer, we are bound by it for a period of 90 days from the deadline for submitting offers,

e. The following circumstances do not apply to us:

1. described in art. 7 section 1 of the Act of April 13, 2022 on special solutions for counteracting support for aggression against Ukraine and for protecting national security;
2. described in art. 5k of Council Regulation (EU) No. 833/2014 of 31 July 2014 concerning restrictive measures in connection with Russia's actions destabilizing the situation in Ukraine.

…… ……

(place and date)

(signature of the person(s) authorized to submit a declaration of will on behalf of the Bidder)

Annex No. 2 to the Price Inquiry No. RIA/6/PR52746/2024

STATEMENT OF MEETING THE CONDITIONS OF PARTICIPATION IN THE PRICE REQUEST

…… *(name of the tenderer)*

I/we declare that we meet the conditions for participation in the proceedings specified by the Ordering Party in Part V of the Request for Quotation, regarding:

1) economic and financial situation,

2) technical or professional capacity,

3) staff capacity,

4) experience.

Attachments to the declaration:

a) list of validated analytical methods with the LLOQ designation
b) a list of at least 10 pharmacokinetic studies for oral combination medicinal products
c) inspection list for the last 10 years

…… (place and date)

…… (signature of the person(s) authorized to submit a declaration of will on behalf of the Bidder)