molecure

Warsaw, 16/05/2023

REQUEST FOR THE PROPOSAL No 16/2023 - DUBs

I. ORDERING PARTY

Molecure S.A. ul. Żwirki i Wigury 101 02-089 Warsaw VAT ID: 728 27 89 248	**Contact person:** Jacek Chrzanowski **e-mail:** j.chrzanowski@molecure.com

II. OBJECT FOR THE REQUEST

In vitro safety studies for pharmaceutical safety and determination of ADME parameters (Absorption, Distribution, Metabolism and Excretion) for small molecule compounds within 7 months from the validation of the agreement.

The order is carried out as a part of the project titled:

— **DUBs: „**RESEARCH AND DEVELOPMENT OF DEUBIQUITINASE INHIBITORS IN ANTITUMOR IMMUNOTHERAPY" (POIR.01.01.01-00-0615/19)

co-financed by the European Union Funds and because of the competitiveness principle.

III. THE FORM OF THE ORDER

III.1 The request is not made under the Act of 11 September 2019 - Public Procurement Law (Journal of laws of 2019, item 2019 as mentioned).

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 winner 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 In justified cases, at any time, before the deadline for the submission of tenders, the Ordering Party reserves the right to change the content of this request. If the changes can affect the content of tenders, the Ordering Party shall extend the tender submission deadline. The Ordering Party shall inform potential Contractors about the changes made by publishing relevant information on its website, on Competitiveness Database website and by e-mail to all Contractors to which the request was sent or to all Contractors who submitted bids.

III.6 This procedure (also referred to in the text as "Request for the proposal") does not set the obligation for the Ordering Party to sign any formal contracts.

III.7 It is a **possible** to make and offer for part of order. Partial offers may be submitted for what is called Part in point V.

III.8 For the avoidance of doubt, the selection of an offer as the best in the procedure does not constitute a

contract or an order to perform any services or perform any deliveries. The contract will be concluded in writing form.

IV. CONDITIONS FOR PARTICIPATION IN THE PROCEEDINGS AND A DESCRIPTION OF THE MANNER OF ASSESSING THE FULFILMENT OF THOSE CONDITIONS

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

IV.2 The offers may be issued by Contractors who:

A) have the necessary qualifications to carry out the described activity and have the appropriate technical potential and personnel capable of performing the contract;
B) are in a good economic and financial standing, which assures proper execution of the order;
C) will pursue the contract in a way that is beneficial to the environment by minimizing the consumption of materials, raw materials, energy, etc.

As a proof of the above, the Ordering Party requires that the Contractor submit, along with the tender, a statement about fulfilling conditions for participation in the proceedings. The model statement is attached as Appendix 2 to this request for proposal.

IV.3 Excluded from the proceedings shall be those Contractors who are personally or equity related to the Ordering Party. Equity or personal relationship is understood as relations between the Ordering Party or individuals authorized to take commitments on behalf of the Ordering Party or those acting on behalf of the Ordering Party in order to prepare and implement the Contractor selection procedure and the Contractor, including in particular:

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.

As a proof of the above, the Ordering Party requires that the Contractor submit, along with the tender, a statement about not being related to the Ordering Party. The model statement is attached as Appendix 3 to this request for proposal.

IV.4 Submitting the offer represent the full acceptance of the rules set in this Request and in particular the essential terms of the contract.

V. DETAILED DESCRIPTION OF THE OBJECT OF THE REQUEST

CPV Code: 73111000-3 – Research laboratory services

Part 1: In vitro safety

No	Assay	Assay description	Amount of Assay
1	AMES fluctuation assay – utilizing 4 strains of Salmonella: TA98, TA100, TA1535, TA1537 with or without rat liver S9 fraction (with cytotoxicity assay)	1 compound, 4 concentrations (48 repetitions)	2
2	hERG Human Potassium Ion Channel cell based automated patch clamp assay	IC50 determination, 1 compound, minimum 5 concentrations in duplicate	5
3	Interaction with ion channel acccording to CiPA initiative – minimum 6 different assays, automated patch clamp	1 compound, 3 concentrations in duplicate	2
4	Kinase inhibition panel (minimum 50 different kinases) for example: SAPK2A (p38alpha), Akt1, GSK3beta, c-Raf (Raf-1), MEK1, PKA, Fyn, PKC, CDK2/CyclinA, CDK1 /CyclinB, IKKalpha, PDGFRbeta, IGF1R, LYN, Aurora-A, CDK6 /CyclinD3, Abl, EGFR, EphB4, ALK, PI3Kgamma, Plk3, Pim1, IRAK4, TAK1, ROCK1, PI3Kalpha, PI3Kbeta, PI3Kdelta, ASK1, KDR (VEGFR2), JAK2, eEF-2K, MNK2, LOK, MLK1, mTOR, AMPKalpha1	Screening 1 compound at 1 concentration in duplicate	1
5	Off-targets interaction panel (safety/diversity panel) for minimum 87 off-targets, for example: NK1 receptor, NK2 receptor, NK3 receptor, Rat Neuropeptide Y receptor, alpha2 Rat Adrenoceptor, Rat Opioid receptor, B1 Bradykinin receptor, H2 Histamine receptor, Glutamate Rat Ion Channel, Rat P2X Ion Channel, Rat P2Y receptor, H3 Histamine receptor, CRF1 receptor, ER NHR, MT1 receptor, CHT1, V1A Human Vasopressin / Oxytocin receptor, Cav1.2 (L-type) Rat Calcium Ion, TRH receptor, Cav1.2 (L-type) Rat Ion Channel, KWP Rat Ion Channel, KV rat Ion Channel, SKCa Rat Ion Channel, Rat Sodium Ion Channel, Rat GABAA Ion Channel, beta1 Adrenoceptor receptor, MAO-A, EP2 Prostanoid receptor, A1 Adenosine receptor, beta2 Adrenoceptor receptor, ATPase (Na+/K+), Brain, Pig, PDE5, HDAC3, Tyrosine Hydroxylase, CENPE, EG5 Human Kinesin, IP Human Prostanoid receptor, PR Human Progesterone NHR, W1 receptor, HDAC4, HDAC6, Sirtuin 1, Sirtuin 2, PTP1B, W2 receptor, HDAC11, 5-HT1, Rat GABAA Ion Channel, Adenylyl Cyclase, Guanylyl Cyclase, nAChR (alpha4/beta2) Ion Channel, B2 Bradykinin receptor, MAO-B, sigma, NET, NOP (ORL1) Opioid receptor, Acetylcholinesterase, CB2 receptor, CCK1 receptor, A2A Adenosine receptor, PDE1B, PDE2A1, PDE3A, PDE4D2, CCK2 receptor, COX1, MC4 receptor, SET, D1 receptor, CDC25A, D2S receptor, GABA transaminase, PKCalpha, GR, CB1 receptor, D3 receptor, D4.4 receptor, V2 Human Vasopressin / Oxytocin receptor, DW, ETA receptor, ETB receptor, Rat GABAA Ion Channel, A3 Adenosine receptor, GABA Rat Transporter, PPARgamma, Glutamate Rat Ion Channel, 5-LOX, alpha1 (Non-Selective) Rat Adrenoceptor, Imidazoline I2, CysLT1 receptor, H1 Histamine receptor, Rat Acetylcholine receptor, AR Androgen NHR	Screening 1 compound at 1 concentration in duplicate	2
6	Safety/off-targets panel (minimum 40 off-targets), for example: Delta DOP, mu MOP, H2 histamine receptor, alpha2A Adrenoceptor, 5-HT1A, D2S Dopamine, 5-HT2B, V1A Human Vasopressin/Oxytocin receptor, Cav1.2 (L-type) Rat Calcium Ion Channel, KV (Non-Selective) Rat Potassium Ion Channel, Rat Sodium Ion Channel, beta1 Adrenoceptor, beta2 Adrenoceptor, alpha1A adrenoceptor, Rat GABAA Ion Channel, Lck,	Screening 1 compound at 1 concentration in duplicate	2

	nAChR (alpha4/beta2), NET, acetylcholinesterase, CB2, CCK1 (CCKA), A2A Adenosine receptor, PDE3A, PDE4D2, hERG, 5-HT3, COX1, COX2, 5-HT1B, SET, D1, MAO-A, kappa (KOP) receptor, GR, CB1 receptor, 5-HT2A, DW, ETA receptor, NMDA Rat Ion Channel, H1 Histamine receptor, M1 Acetylcholine receptor, M2 Acetylcholine receptor		

Part 2: ADME I

No	Assay	Assay description	Amount of Assay
1	Determination of Caco-2 bidirectional permeability (pH 6.5/7.4)	1 compound, 1 concentration	10
2	Determination of MDCKII-MDR1 bidirectional permeability	1 compound, 1 concentration	10
3	Determination of intrinsic clearance (CLint) using liver microsomes (Human or Rat or Mouse)	1 compound, 1 concentration	10
4	Determination of intrinsic clearance (CLint) using liver microsomes (Monkey or Dog or Minipig)	1 compound, 1 concentration	3
5	Determination of intrinsic clearance (CLint) using intestinal microsomes (Human or Rat or Mouse)	1 compound, 1 concentration	3
6	Determination of intrinsic clearance (CLint) using intestinal microsomes (Dog)	1 compound, 1 concentration	3
7	Determination of intrinsic clearance (CLint) using cryopreserved hepatocytes (Rat or Mouse)	1 compound, 1 concentration	3
8	Determination of intrinsic clearance (CLint) using cryopreserved hepatocytes (Monkey or Minipig or Human or Dog)	1 compound, 1 concentration	3
9	Determination of plasma stability (Human or Rat or Mouse)	1 compound, 1 concentration	3
10	Determination of plasma stability (Monkey or Dog)	1 compound, 1 concentration	3
11	Determination of plasma protein binding (Human or Rat or Mouse)	1 compound, 1 concentration	10
12	Determination of plasma protein binding (Monkey or Dog or Minipig)	1 compound, 1 concentration	3
13	Microsomal protein binding (Human or Minipig or Rat or Mouse)	1 compound, 1 concentration	4
14	Microsomal protein binding (Dog)	1 compound, 1 concentration	3
15	Tissue homogenate protein binding (mice or rat; e.g, brain)	1 compound, 1 concentration	3
16	Evaluation of cytochromes inhibition including: CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A (midazolam and testosterone as probe substrates) (HLM, 1 TA concentration), package of 8 assays	1 compound, 1 concentration	3
17	Evaluation of cytochromes inhibition for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A (midazolam and testosterone as probe substrates) (HLM, IC50 determination), non-package	1 compound, 8 concentrations	6
18	Blood stability (mouse or rat)	1 compound, 1 concentration	3
19	Blood stability (human)	1 compound, 1 concentration	3

Part 3: ADME II

No	Assay	Assay description	Amount of Assay
1	Blood to plasma ratio (Human or Mouse)	1 compound, 1 concentration	3
2	Blood to plasma ratio (Rat)	1 compound, 1 concentration	3
3	Blood to plasma ratio (Monkey or Dog)	1 compound, 1 concentration	3
4	Metabolite identification in vitro (liver microsomes) cold compound; Human or Monkey or Dog or Rat or Mouse)	1 compound, 1 concentration	2
5	Metabolite identification in vitro (cryopreserved hepatocytes); cold compound; Human or Monkey or Dog or Rat or Mouse)	1 compound, 1 concentration	2

6	Reactive metabolite assessment (glutathione trapping) (1 compound, HLM in the presence and absence of NADPH)	1 compound, 1 concentration	3
7	CYP reaction phenotyping (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4; recombinant enzymes)	1 compound, 1 concentration	3
8	UGT reaction phenotyping (UGT2B7, UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT2B15, UGT1A4) (recombinant enzymes)	1 compound, 1 concentration	1
9	Evaluation of cytochromes inhibition for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A (midazolam and testosterone as probe substrates) (HLM, time-dependent inhibition (IC50 shift))	1 compound, 5 concentrations	2
10	Evaluation of cytochromes induction (CYP1A2, CYP2B6, CYP3A4; 3 donors; 3 concentrations; mRNA endpoint)	1 compound, 3 concentrations	2
11	Inhibition of drug transporters including: P-gp, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K (1 concentration)	1 compound, 1 concentration	1
12	Inhibition of drug transporters including: BSEP (1 concentration)	1 compound, 1 concentration	1
13	Inhibition of drug transporters for P-gp, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1 or MATE2-K (IC50 determination)	1 compound, 5 concentrations	1
14	Inhibition of drug transporters for BSEP (IC50 determination)	1 compound, 5 concentrations	1
15	Half-life (blood; dog or monkey)	1 compound, 1 concentration	3
16	Glutathione conjugate detection (liver S9; mouse or rat or human)	1 compound, 1 concentration	1
17	Glutathione conjugate detection (liver S9; dog or monkey)	1 compound, 1 concentration	1

Each commissioned study (applies to Part 1, 2 and 3) should end with a report containing the results of the analysis. The data obtained during the test should be available online or sent upon request.

The Ordering Party reserves the right not to order the services in the specified quantities (applies to Part 1, 2 and 3). The ordered quantities of assays may change as a result of the project implementation and the Contractor shall have no claim to any payment or compensation. The Contractor will receive remuneration for the work already performed.

VI. EVALUATION OF THE OFFERS

VI.1 Price – weight: 80% (80 pts.)

In this criterion points will be calculated (to two decimal places) according to the formula below:

$$Pc = \frac{C_{min}}{C_{evaluated}} x80$$

Pc – points received in the price criterion

C_{min} – the smallest Net price out of the submitted offers that are not subject to rejection

$C_{evaluated}$ – Net price of the offer being evaluated

For evaluation purposes only, the offers submitted in currency other than polish zloty (PLN) will be converted into PLN using the NBP (central bank of the Republic of Poland) average rate of exchange (Table A) in effect on the publication date of the Request For Proposal.

VI.2 **Payment deadline– weight: 20% (20 pts.)**

The number of points for the criterion payment deadline will be awarded according to the following scheme:

20 points – when the payment deadline is >= 30 days from the date of delivery of a correctly issued invoice

10 points - when the payment deadline is set between 20-29 days from the date of delivery of a correctly issued invoice

0 points – when the payment deadline is 19 days or less from the date of delivery of a correctly issued invoice

VI.3 In the case of two or more tenders with equal number of points awarded, the Ordering Party shall call Contractors who submitted equally evaluated offers to submit, within the period specified, additional offers. For any of the evaluation criteria, the additional offer may not be less favorable than the one submitted in response to the Request for offers (i.e. in the first offer).

VII. HOW TO PREPARE AND SUBMIT THE OFFER

VII.1 The offer should be signed by the person authorized to represent the Contractor. If the offer is signed by an attorney, a power of attorney must be attached to the offer.

VII.2 Each contractor may submit only one offer.

VII.3 Costs of the offer preparation shall be incurred by the offering party.

VII.4 Offers must be submitted no later than: **24/05/2023 23:59:59 CET** and must be written on the form as in Appendix 1 to the request for proposals.

VII.5 Offers shall be issued (a scan of the offer is allowed) via email to: **p.chmielewska@molecure.com** or by Competitiveness Database website available at **https://bazakonkurencyjnosci.funduszeeuropejskie.gov.pl/** (In case of submitting offers via the Competitiveness Database, the Ordering Party requires the value of the offer to be indicated in Net values).

VII.6 The receipt of the offer via electronic means indicated in point VII.5 shall be considered as a date of submitting the offer.

VII.7 Offers that do not meet the deadline, are incomplete (despite a request for supplementation, if such a request was possible and in accordance with the regulations) or sent to the wrong email address will not be taken into consideration.

VII.8 Any questions concerning the Object of the tender should be addressed to **j.chrzanowski@molecure.com** no later than 22/05/2023 14:00 (CET). Contact person is: Jacek Chrzanowski.

VII.9 Any questions concerning the formal issues of the tender should be addressed to k.kazimierczak@molecure.com no later than 22/05/2023 14:00 (CET). Contact person is: Kinga Kazimierczak.

VII.10 The offer should include the validity date (at least 30 days from the submission deadline).

VII.11 The price should be set in both Net and Gross.

VII.12 The values in the offer (Net and Gross) should be rounded to two decimals with the mathematical rule of rounding the numbers.

VII.13 The offer price should include VAT. The correct determination of VAT is responsibility of the contractor – in accordance with the provisions of the Act of 11 March 2004 on Goods and Services Tax (Journal of Laws of 2021 item. 685 as mentioned) if applicable or other applicable laws.

VII.14 The offer shall not be prepared in price variants.

VII.15 The financial settlements between the Ordering Party and the Contractor may be made in PLN, EUR, GBP or USD.

VIII. TENDER RESULTS

Bidder will be informed about choosing his offer via email. Formal results will be also published on the Ordering Party's website (www.molecure.com) and on Competitiveness Database website.

IX. MOST IMPORTANT PROVISIONS OF THE AGREEMENT

IX.1 Contractor will be obligated to enter into the agreement including all conditions presented in this Request and in 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 Contractor selection, unless:

A) The amendments concern performing additional supplies or services by the Contractor, not covered by the basic contract, provided they are necessary and the following conditions are met:

i. The change of the Contractor cannot be made due to the economic or technical reasons, in particular concerning the interchangeability and interoperability of equipment, services or installations, ordered as part of basic contract,

ii. The change of the Contractor 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 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 change in the nature of the contract and the total value changes is less than 215 000 EUR, and at the same time is less than 10% of the basic contract value.

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

IX.3 Ordering Party reserves that the contract that will be concluded with the Bidder will include the provisions on the transfer of the entirety of intellectual property generated or developed in the course of and in connection with the execution of the Project.

X. APPENDENCIES TO REQUEST FOR PROPOSAL

A) Appendix No. 1 - The offer form

B) Appendix No. 2 - Statement concerning fulfillment of all the requirements set out in part IV of the Request for offers

C) Appendix No. 3 - Statement regarding personal and capital connections with the Ordering Party

D) Appendix No. 4 - Declaration of compliance with the information obligations provided for in Article 13 or Article 14 of the GDPR