Call for proposals (CfP-3iii) CHIKVACCINE Late-stage clinical development and equitable access of Chikungunya vaccines in endemic countries

Call for Proposals: CEPI-CfP-3iii CHIKVACCINE

CEPI is pleased to announce its call for proposals (CfP-3iii CHIKVACCINE) for the development of human vaccines against Chikungunya virus (CHIKV), with co-funding from the European Union. This document describes the scope, requirements, and processes for the submission of the proposal, and the process for review, and selection for funding. Further details can be found on our website here.

CfP-3iii CHIKVACCINE is a continuation of CEPI's advancing human vaccine late-stage development against CHIKV. We are pleased to announce this call which will make funding for studies to assess the long-term safety, durability of protection and a measurement of vaccine effectiveness in CHIKV endemic countries for advanced and/or licensed CHIKV vaccine candidates. Importantly, prior funding for this effort is not a precondition for applying for funding in this call.

CEPI invites applicants (i.e. relevant vaccine development organizations and/or consortia) to submit proposals for funding. Applicants should submit detailed plans for product development, manufacturing, and related activities as described in this document, including a clear development plan that describes milestones, timelines and criteria for success, and an assessment of risks and proposed mitigation measures to ensure their resolution. Emphasis on plans for equitable access and supporting affordable and on-time vaccine availability to low-resource settings consistent with CEPI's mission is a requirement for this CfP.

The budget of CfP-3iii CHIKVACCINE is EUR 50 million and is expected to fund 2 to 3 awards. Please note those applicants who can provide co-funding, complementary funding, or in-kind support to extend the impact of CEPI's funding will be considered favourably. CfP-3iii CHIKVACCINE projects must be completed within 3-4 years from signature with timeline to 1st marketing authorisation and initiation of Phase IV studies preferably within 12-18 months of project initiation.

Introduction

1.1. The Coalition for Epidemic Preparedness Innovations (CEPI)

The Coalition for Epidemic Preparedness Innovations (CEPI) is an international coalition of governments, academic, philanthropic, private, public, and intergovernmental institutions whose vision is to create a world in which epidemics and pandemics are no longer a threat to humanity. Our mission is to accelerate the development of vaccines and other biologic countermeasures against

epidemic and pandemic threats so they can be accessible to all people in need. CEPI operates under the laws of Norway as a non-profit international association and has offices in Oslo (HQ), London, and Washington, DC. More details about CEPI and our mission can be found on our website: www.cepi.net.

1.2. About this call for proposals

CEPI has undertaken the mission to develop vaccines against CHIKV infection and disease. Chikungunya fever is caused by the chikungunya virus (CHIKV) which is an RNA virus in the family Togaviridae, genus alphavirus. It is spread by the urban mosquitoes *Aedes aegypti* and *Aedes albopictus* which are abundant in the subtropical and tropical regions of the world and responsible for the rapid spread and large burden of CHIKV infection and disease globally. Acute CHIKV infection in humans results in an acute febrile illness that can cause a high degree of morbidity and loss of work-days due to associated joint pains, fever and fatigue but fortunately associated with a low case fatality. Morbidity can be prolonged for those recovering from acute infection leading to chronic debilitating joint pains (arthralgia) and joint damage (arthritis) which can last up to a year or more. A recent systematic literature review of the global epidemiology of CHIKV from 1999 to 2020, confirmed the large global burden of CHIKV with well described large outbreaks in the human populations in Africa, South and Central America, Caribbean, and Southeast Asia. [1]

This new call for proposals builds on CEPI's previous investment in vaccine candidates for Chikungunya. Whilst a human vaccine is nearing registration, there remains a key need to facilitate access to licensed products to all populations including the generation of effectiveness data, long term safety and durability of immunity and data to support additional indications such as in pregnant women, paediatric and immunocompromised populations.

The focus of this call for proposals will be to complete Phase III clinical testing for those developers/vaccine in late-stage development and support post-licensure needs for developers/vaccines with market authorization given the need for Phase IV effectiveness studies, long-term safety and durability of protection studies and additional data to support expanded indications as noted previously. Applicants should have a well- defined licensure strategy to include resource limited regions/setting and WHO pre-qualification when published and possess significant existing Phase II/III data and nearing licensure in order to be eligible for this call.

1.3. European Union support

This is the second jointly funded call for proposals resulting from the collaboration between CEPI and the European Union's Horizon programmes [2], [3]. Thanks to co-funding from the European Union, CEPI is now able to present this second funding opportunity in 2023 (CfP-3iii CHIKVACCINE). Whilst successful CfP3i applicants could be granted further funding through the current CfP-3iii CHIKVACCINE call, a successful prior CfP3i award is not a precondition for funding for this grant.

1.4. Funding opportunity

Allocated funding: total funds allocated for CfP-3iii CHIKVACCINE is EUR 50 million which will likely support 2-3 projects. Applicants who can access co-funding, complementary funding, or in-kind support will be considered favourably.
Project duration: Projects of 3-4 years are anticipated which should include a first Marketing Authorisation Application (FDA/EMA/ML3-4 NRA) and at least one clinical trial to support post marketing effectiveness and/or expansion of target population.

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[1] Bettis AA, , et al. (2022) The global epidemiology of chikungunya from 1999 to 2020: A systematic literature review to inform the development and introduction of vaccines.

[2] https://ec.europa.eu/research/participants/data/ref/h2020/wp/2018-2020/main/h2020-wp1820-health_en.pdf

[3] https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2021-2022/wp-4-health_horizon-2021-2022_en.pdf

2. Objectives of CfP-3iii CHIKVACCINE

Proposals must present their plans for late-stage clinical vaccine development of their CHIKV candidate. This may, or may not, build on data gathered from a previous CEPI supported project. Previous funding from CEPI is *not* a precondition for support. CEPI aims to achieve the following objectives:

a) Complete or completed Phase III clinical testing in a primary target population and additional studies in an endemic region using a viable vaccine candidate with a measurement of efficacy using a surrogate biomarker of protection, which has existing Preclinical, Non-clinical and Phase I-II clinical data, supported by manufacturing data supportive of licensure.

b) Study plans including specific sites for conducting phase IV studies of 3-year duration or more in an endemic country to assess long-term safety, durability of protection using a biomarker of protection and a measurement of vaccine effectiveness.

c) Study plans, phase II or III, on expanding the indication of the vaccine into the pregnant population (if appropriate to the vaccine platform), paediatric and immunosuppressed populations.

d) Clinical development phase appropriate GMP manufacture and release of CTM for proposed studies, supported by process and analytical validation at scale and long-term stability of the Drug Product at 2-8°C (preferred) or -20°C.

e) Technology Transfer of a commercial process to a geo diversified manufacturing organisation can be supported or established via a supply agreement.

f) Pursue licensure for the candidate via established stringent and/or local regulatory authorities with a focus on regulatory approval that will ensure use in the Global South i.e. endemic CHIKV areas- using clinical immunological data with an established surrogate of protection in lieu of Phase III efficacy studies to support licensure.

g) Plans for regulatory interactions, including those with a view to ultimate vaccine licensure and/or emergency use with a national regulatory agency and regulators in endemic countries.

h) Plans for maintaining a rolling stock of vaccine (Pre- and Post-licensure) which could be deployed in an emergency.

3. Scope and call for proposals structure.

3.1. CHIK Phase III/IV clinical vaccine development

Disease scope: human vaccines to protect against CHIKV disease.

Indicative work package (WP): funding will be targeted towards WPs that will result in advancing of vaccine candidates suitable for prophylactic and/or reactive use in target populations in countries affected by CHIKV disease, as described in Table 1 below.

Project eligibility criteria:

- *Key criterion:* Vaccine candidate programs currently in or having completed Phase III clinical trials nearing licensure in a target market. *Specific additional criteria are listed in Table 1*

- Activities not considered eligible for CfP-3iii CHIKVACCINE:
    - Early stage CHIKV vaccine programs with only PhI/II data
    - Non-vaccine platforms i.e. Gene encoded antibodies, therapeutics.
    - Manufacturing and scale up activities post licensure, not related to technology transfer.

Table 1: CHIKVACCINE vaccine development Work Packages and eligibility criteria

Work Packages	Eligibility criteria by Work package
Work Package 1 Clinical & effectiveness studies	Applicants must propose: 1. A Phase IV post-licensure clinical development plan including testing in countries with documented burden of disease in humans. 2. Additional studies, randomized control trials, to expand the indication to paediatric, immunocompromised and pregnant populations for safety and efficacy as measured to a biomarker of protection. 3. An outbreak response outline for clinical deployment and scale up of manufacturing to enable use of the vaccine candidate in a CHIK outbreak before and after licensure.
Work Package 2 CMC & Tech transfer activity	Applicants must have: 1. Validated commercial manufacturing process to be capable of supplying primary licensed regions with a readily available stock of vaccine for outbreak use. 2. Demonstrated experience in developing a validated vaccine process at scale that is suitable for licensure through a stringent regulatory agency. 3. Track record and evidence of manufacturing capacity for GMP material suitable for clinical studies and commercial supply. 4. Manufacturing plans supportive of technology transfer to LMICs.
Work package 3 Regulatory engagement and licensure	Applicants should have: 1. A detailed regulatory and licensure strategy and plan that describes pathway to licensure/emergency use, and post licensure activity considering the overall project development plan. 2. An engagement plan with LMIC and stringent regulatory authorities to seek relevant advice in connection with the proposed Ph III/IV clinical trials.
Work Package 4 Enabling science and assays	Applicants must have: 1. Validated assays where possible, such that they will facilitate vaccine licensure and/or emergency use. 2. A plan to incorporate the WHO endorsed International Chikungunya reference standard[4] into clinical testing.
Work Package 5 (optional) Non-clinical studies	For this optional work package, applicants must have: 1- Plans and rationale for additional non-clinical/animal testing if deemed necessary for licensure, or expansion of indications.

[4] https://www.pei.de/SharedDocs/Downloads/EN/regulation-en/referencematerial/1502-19-ifu.pdf?__blob=publicationFile&v=2

	NOTE: To support this WP, applicants are expected to have: a. Completed studies to establish of a correlate of protection. These data should contribute to the identification, testing, evaluation, and prioritization of surrogate-endpoints of protection in CHIK disease (e.g., immunobridging between human survivor studies and/or testing of clinical samples). b. Suitable pre-existing data on animal challenge studies or human survivor studies/clinical trials that could inform the development of a correlate of protection. c. Completed DART and neonatal studies to support vaccine deployment in vulnerable populations, or a documented regulatory waiver from a licensing authority
Work Package 6 Project management	Applicant project management plans must include: 1. Defined milestones and regular project meeting cadence 2. Clear Go/no-go decision points 3. Stage gates (where relevant) 4. High level Gantt chart

4. Applicant eligibility criteria

The funding opportunity through this CfP is open worldwide to all types of non-profit research organisations, for-profit companies, international organisations and foundations, joint R&D ventures, government research organisations, and academic institutions. Applicants must be legal entities, or consortia comprised of legal entities. At least one of the partners in the applicant organisations or consortia of partnering organisations should have significant experience in human vaccine development, clinical development, manufacturing and have a track record of bringing vaccine candidates through to licensure. Applicants unable to demonstrate this experience will not be considered eligible for funding.

Proposals will be eligible for funding only if they are:

- Coherent with the CfP objectives described in section 2
- Relevant to the CfP disease scope, as described in section 3
- Consistent with the CfP timeline and award conditions as described in sections 1.4 and 8
- Complete in terms of required content in the proposal templates described in section 5.1.

5. Applicant guidelines

5.1. Application steps and templates

Step 1:

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To respond to this CfP, you may express your intent to submit a proposal by emailing the CfP-CHIKVACCINE@cepi.net mailbox by 20 July 2023, 1600 CET. The CHIKVACCINE submission template application will be provided along with instructions for submission to CEPI secure portal by unique customized link to ensure a secure submission process. We encourage applicants to submit their proposals well in advance of the deadline.

The submission should be uploaded in PDF format. No additional documentation other than those specified in the template should be submitted.

Additional needs for technical support/clarification must be requested by email to: CfP-CHIKVACCINE@cepi.net.

The CEPI Secretariat will address any questions within the shortest possible timeframe. Any

questions submitted, along with answers, will be anonymised and made public if relevant to the preparation of this application. Summary of frequently asked questions (FAQ) will be uploaded to the CEPI website.

All applications will be stored in a restricted access repository. Personal data included in proposals will be handled according to CEPI's Privacy Notice on www.cepi.net/terms/. CEPI will not cover any costs incurred for the development and submission of the application. Furthermore, CEPI will not provide funding retrospectively for activities carried out prior to an award.

Step 2:

Entities that have submitted a notified CEPI of Intent to apply, **must** submit their completed proposal to CEPI by secure portal website by 20 August 2023, 16:00 CET. All associated documents must be uploaded in the file formats specified below:

- Completed application template including a product development plan (in English, PDF format, 30 pages)
- Project plan/GANTT (MS-Project format)
- Completed budget and narrative templates
- A maximum of 10 CVs or bio sketches *(max. 2 pages per CV/bio sketch for applicants, partners, and key experts)* (PDF file) Personal data included in proposals will be handled according to CEPI's Privacy Notice.
- Signed letters of support for all partners confirming their agreement to participate in the proposed projects and agreeing with the content of the proposals (PDF file)

5.2. Submission overview

For the submissions to be accepted and registered, applications must fulfil the following norms:

- Submission of applications **must** be completed by 20 August 2023 16:00 CET
- All communication of information and documents must be conducted/translated in English
- All budget proposals should be submitted in US Dollars

5.3 Timeline overview

- Call publication date: 20 June 2023
- Email notification of intent to apply: 1600hrs CET, 20 July 2023*
- Final Submission deadline for applications: 1600hrs CET, 20 August 2023*
- Peer review and selection: August through September 2023*
- Target dates for Due diligence, contract signatures, project launch: end-October 2023*
- CEPI Grant duration: 60 months

*NOTE: CEPI reserves the right to modify open Call for Proposal timelines in accordance with European Commission funding requirements for CfPs published on the EC Horizon Cascade Funding Calls

6. Review criteria

Proposals will be assessed against the criteria listed in Table 2 below. Performance of proposals will be evaluated through the evidence provided on all aspects listed under each criterion. Therefore, the quality of the information provided by applicants is crucial to CEPI's funding decision. The basis for selecting proposals for funding will be technical performance, the total costs, and timeframes for completing the projects, and the realism and reasonableness of the proposed project plans. Information requirements to address the criteria are provided in the documents listed in section 5.1.

Table 2 Review criteria for eligible CHIKVACCINE proposals

Criterion	Assessment levels	Definition
		CHIKV Vaccine
1. Immunogen	• Immunogen selection • Immunogen design • Immune response in Phase II/III efficacy studies	• Relevance of immunogen and selection according to the Target Product Profile intended indication. • Scientific rationale and the technologies to justify immunogen. • Immunological strategy (such as virus panels, cross-neutralization) that will allow the demonstration of breadth of immune response
2. Vaccine technology	• Candidate safety and proven efficacy per TPP • Dosing regimen • Delivery system • Clinical database • Non-clinical data such as NHP active and passive immunization studies to establish protection from CHIK infection/disease • Regulatory experience • Results from Phase II-III clinical studies.	• Documentation or plans for access to proven and/or licensed vaccine technology platform. • Understanding of platform safety and immunogenicity potential based early-stage clinical data on safety and immunity • Demonstration of the vaccine's protective potential in Non-Human Primates/ animal models relevant to disease • Potential need of adjuvant and the complexity this adds to development / supply. • Description and characterisation of the proposed route of delivery and/or system. • Feasibility of securing licensure. • Estimated probability of technical and regulatory success (PTRS). • Objectives to secure licensure or if licensed -regulatory path and label claims.
3. Safety potential	• Non-clinical • Clinical	• Safety profile of the platform in animal models • Safety profile in humans • Profile of Reproductive Toxicology studies
4. Speed of development	• Manufacturing strategy • Infrastructure	• Potential for manufacturing scale up • Plans for manufacturing scale-up and/or scale-out during clinical development. • Complexity of technology transfer plans. • Infrastructure, internally or through partnerships, to rapidly advance development. • Path to licensure (overarching regulatory strategy & late development expedited plans to licensure) and fulfilment of post licensure commitments. • Experience in engaging with national regulatory authorities and regional regulatory authorities in LMICs. • Existing partnerships in LMICs
5. Technical/ Manufacturing scalability	• Formulation • Speed of production and scale • Scale of production • Quality standards	• Extent to which the technology and plans are expected to enable fast production in large volumes. • Adjuvant access and supply (if applicable) • Likelihood of lower costs. • Commitment to tech transfer manufacturing and analytical process to LMIC manufacturer, including process and analytical validation.
6. Equitable access	• Storage and delivery • Sustainability of supply • Access	• Possibility of formulations and presentations with suitable storage conditions and stability. • Extent to which the technology can be delivered easily in a way that facilitates equitable access e.g. liquid presentation that is stable at refrigerated temperature, lyophilized and if needed, multi-dose vials. • Extent of vaccine to enable global equitable access by making vaccine timely available to populations when and where they are needed regardless of ability to pay.
7. Partnership	• Competency, experience, and track-record • Willingness to collaborate with other partners to enable global scale out and affordable manufacturing	• Extent to which the partnership, its plans and procedures are viable and of sufficient quality to deliver on the proposed activities of the project. The potential involvement of Developing Country Vaccine Manufacturer(s). • Partnerships that will secure access to data, samples, and reagents necessary to demonstrate preclinical and clinical Proof of Concept.

7. Review and due diligence process timeline

The Secretariat will assess whether received applications fulfil the published eligibility criteria of the call and may send the eligible proposals to internal and independent external experts for review. All reviewers who participate in the review process will be evaluated for any potential conflicts of interest and will be required to sign non-disclosure agreements.

Applicants may be invited to clarify any outstanding questions, further details prior to concluding the full review. Proposals and budgets will be subject to a cost challenge undertaken in the context of the applicant's projects and CEPI's policies and cost guidance.

Contract arrangements will be initiated along with technical and financial due diligence and pursued to recommendations for funding to the Board. For the candidates not proceeding to due diligence the Secretariat will seek to communicate this as early as possible.

The CEPI Secretariat will publicly announce each award when the partnering agreement has been signed. Applicants whose proposals do not advance to contract will be notified confidentially of the outcome of the process.

NOTE: CEPI reserves the right to modify timelines subject to programmatic and review requirements

8. Technical and administrative questions

Technical and administrative questions about CfP-3iii CHIKVACCINE should be directed to CEPI Secretariat by email to CfP-CHIKVACCINE@cepi.net. A summary of frequently asked questions and answers (FAQs) may be posted on CEPI's website.

9. Award conditions from funders

Funding must reflect the proposed activities and agreed conditions of the award decision made by CEPI. CEPI reserves the right to terminate agreements according to mutually agreed "go/no-go" decision criteria.

CEPI is committed to achieving equitable access to all CEPI-supported programmes including vaccines, platforms, data, results, and materials. Specifically, equitable access to epidemic vaccines in the context of an outbreak means that appropriate vaccines are first available to populations when and where they are needed to end an outbreak or curtail an epidemic, regardless of ability to pay. To ensure that CEPI delivers on its commitment to equitable access, CEPI must include access considerations as a component of any agreement with an awardee. If you have specific questions regarding the equitable access policy, please contact CEPI at CfP-CHIKVACCINE@cepi.net.

CEPI maintains the following research-related policies to provide further guidance to its research partners on:

- Animal research
- Clinical trials (including transparency requirements)
- Equitable access policy
- Scientific integrity/Open Access policy

Other policies/guidance designed to support CEPI partners on general administrative issues and ensure investor requirements and industry best practices include:

- Anti-corruption
- International sanctions
- Managing conflict of interest
- Procurement
- Travel
- Transparency and confidentiality
- Cost guidance
- European Union regulatory bodies rights of review and audit plus acknowledgement of EU funding

10. Animal Welfare and Well-being

The National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) is collaborating with CEPI to embed the 3Rs into CEPI funded projects. The collaboration focuses on reviewing proposals to ensure that animal welfare standards are genuinely high and exceed the legal minima, local issues relating to poor practice are addressed, and overseas work is conducted to standards equivalent to those in the UK (https://www.nc3rs.org.uk/integrating-3rs-publicly-funded-research).

In CEPI's call for vaccine development, the NC3Rs will only evaluate proposals entering due diligence/negotiation processes and that include projects involving the use of animals highlighted by NC3R (i.e., non-human primates (NHPs), cattle, dogs, cats, pigs, and equines). Based on the review, the NC3Rs will provide recommendations to CEPI, including advice on opportunities to implement the 3Rs, raise specific animal welfare concerns, highlight where good practice is not being adopted, and monitor the implementation of specific policies and guidance. This advice will be used during decisions on funding and when drafting the terms and conditions of grant awards.

To prepare your proposal for this review process, please consider the following guidelines:

- NC3Rs Guidelines: Non-human primate accommodation, care and use
- Responsibility in the Use of Animals in Bioscience Research, which applies to use of any vertebrate species
- ARRIVE Guidelines on the reporting of *in vivo* studies

Implementation of the principles in these guidelines is a condition of receiving funds from CEPI.

Other information that will be considered during the review can be found on the NC3Rs website:

- Directive 2010/63/EU
- Scientific literature on applying the 3Rs in drug development
- NC3Rs resources on best practice – including those on improving non-human primate welfare (such as the Macaque Website)

In addition, the NC3Rs has produced a PDF presentation to remind applicants of the required animal welfare standards and to provide advice on choosing appropriate contractors. Applicants contracting out animal research or collaborating with other laboratories (regardless of species) are advised to view the presentation well in advance of submitting their application.