PRESENTATION OF THE FINAL RESULTS OF DELIBERATE RELEASE INTO THE ENVIRONMENT OF GENETICALLY MODIFIED ORGANISMS

IN ACCORDANCE WITH ARTICLE 10 OF DIRECTIVE 2001/18/EC

The final report format shall be completed by the notifier.

- The notifier shall fill in the report format according to the proposed form.
- The notifier shall illustrate as much as possible the reported data by means of diagrams, figures and tables.
- Statistical data could also be provided where relevant.
- In the case of multi-sites and/or multi-events release(s) the notifier shall provide a general overview of the measures taken and effects observed for the full duration of the consent.
- The space provided after each item is not indicative of the depth of the information required for the purposes of this report.
- The information provided in this report is not considered confidential in accordance with Article 25 of Directive 2001/18/EC.

1. General information

1.1. European notification number: *Number can be found on the corresponding SNIF form (i.e. year and number, B/NL/xx/xxx)*	**B/NL/16-010**
1.2. Member State of notification:	**The Netherlands**
1.3. Date of consent: *Date of issue of permit*	24 Januari 2017
1.4. Title of the project:	Safety and protective efficacy of genetically modified Plasmodium berghei (*Pb(PfCS@UIS4)*) malaria parasites in healthy volunteers [monitoring and sampling of volunteers]
1.5. Name of institution or company: *i.e. legal entity = notifier*	Havenziekenhuis and institute for tropical diseases, Rotterdam, The Netherlands
1.6. Duration of release:	Monitoring and sampling of volunteers started after first administration on 6 June 2017 and ended on 19 April 2018
1.7. Period of release:	Monitoring and sampling of volunteers started after first administration on 6 June 2017 and ended on 19 April 2018

2. Characteristics of the release

2.1. Scientific name of the recipient organism:	Homo sapiens
2.2. Transformation event(s) (acronym(s)) or vectors used: *Describe the GMO(s) and/or vector(s) and insert(s) used for the modification*	The vector is *Plasmodium berghei* malaria parasite; a rodent-infective Plasmodium species that is not pathogenic to humans. The genetic modification is performed by insertion via homologous recombination of the *Plasmodium falciparum* circumsporozoite protein gene in the 230p neutral locus of P. berghei, under the control of the *P. berghei* UIS4 promoter.
2.3. Unique identifier, if available: *i.e. product name or GMO name*	*Pb(PfCS@UIS4)*
2.4. Geographical location(s) (administrative region):	Rotterdam, The Netherlands
2.5. Number of test subjects:	24 volunteers (18 in phase 1 and 18 in phase 2, 12 volunteers participated in both groups)
2.6. Amount of GMO administered to each test subject:	Administration is no part of this notification, but took place under the notification of Radboud UMC and was 5 to 75 mosquito bites per administration.
2.7. Number of administrations per test subject:	Administration is no part of this notification, but took place under the notification of Radboud UMC and was 1 to 4 administrations per volunteer.

3. Risk management measure(s)

Please report the risk-management measures used to avoid or minimize the spread of the GMO(s) outside the site(s) of release, and in particular those measures

- *not originally notified in the application,* N.A.
- *applied in addition to the conditions in the consent.* N.A.
- *required by the consent only under certain conditions,* see below
- *that the consent allowed the notifier a choice of measures.* N.A.

Answer: When blood samples test positive for malaria parasites between administration and 28 days after the last administration the volunteer is treated with anti-malaria medicines.

4. Post-release monitoring measures

Please describe here any monitoring strategies.

Answer: Volunteers were followed on an out-patient basis. All blood samples taken after exposure and before anti-malarial treatment were tested for the presence of parasites by thick smear analysis or PCR.

5. Results of the foreseen and unforeseen release(s)

Consider in the following questions 5.1 through 5.4 all results of the foreseen and unforeseen release(s) in respect of any risk for human health or the environment, without prejudice to whether the results indicate that any risk is increased, reduced or remains unchanged.

5.1. Results of the study

Provide a summary of the study results in respect of any risk for human health or the environment. Include also the results of the monitoring measures (if applicable).

Answer: Phase 1 – Objective: evaluate safety and tolerability of *Pb(PfCS@UIS4)* administration
A total of 18 healthy adult volunteers was recruited over 3 groups and received bites of 5, 25 or 75 *Pb(PfCS@UIS4)*-infected mosquito. The volunteers were closely monitored. No unexpected adverse events were observed and no *Pb(PfCS@UIS4)* parasites were found in the blood as assessed by thick smear or PCR.

Phase 2 - Objective: evaluate the safety and protective efficacy of repeated exposure to *Pb(PfCS@UIS4)*-infected mosquito bites by subsequent controlled human malaria infection of test subjects.
The same volunteers of group 3 were exposed three more times to bites of 75 mosquitoes infected with *Pb(PfCS@UIS4)*, with a four to eight week interval. No unexpected adverse events were observed and no *Pb(PfCS@UIS4)* was found in the blood as assessed by thick smear or PCR.
For testing the protective effect during phase 2, no GMO was administered.

5.2. Unexpected effect(s) and adverse effects

'Unexpected effects' refer to effects on human health or the environment, which were not foreseen or identified in the environmental risk assessment of the notification. This part of the report should contain any information with regard to unexpected effects or observations relevant for the initial environmental risk assessment. In case of any observed unexpected effects or observations, this section should be as detailed as possible to allow a proper interpretation of the data.

Answer: No unexpected effects or unexpected adverse effects were observed.

5.3. Unintended release of the GMO

'Unintended releases' refer to any incidents or spills with regard to the GMO that occurred during the study, where possible effect(s) on human health and/or the environment cannot be excluded. Describe these effects, including actions taken to manage the risks.

Answer: No unintended release occurred during the trial.

5.4. Other information

Notifiers are encouraged to supply information, which is outside the scope of the notification but which might be relevant to the trial(s) in question. This may also include observations of beneficial effects.

Answer: N.A.

6. Assessment of risk following completion of release

Please provide a reflection of the risk assessment and risk management strategies carried out prior to the release in relation to the obtained results and findings of for instance monitoring and samples taken from the test subjects. Do the results of the study justify the performed environmental risk assessment and conclusion?

Answer: The product *Pb(PfCS@UIS4)* was administered in the Radboud UMC and volunteers visited the Havenziekenhuis frequently for follow-up afterwards. During these visits, blood and urine samples were taken according to standard laboratory procedures and laboratory materials (e.g. needles) were discarded according to standard procedures. Presence of *Pb(PfCS@UIS4)* was not observed in the blood of the volunteers, as expected. Measures taken to avoid spread of the product were sufficient.

7. Conclusion

Here the notifier should elaborate on the efficacy and efficiency of all measures taken, and elaborate on the insights gained during this release. Also, specify how the gain in experience can benefit further (future) releases with respect to risk management.

Answer: As the measures taken were sufficient, no additional measures are needed.