GA 101003666 Start date: 01/04/20 End Date: 31/03/22	
Project Title	OPENCORONA
WP number, deliverable number, and Title	WP4 D4.1: A locked Cliniporator with pulse pattern for plasmid DNA delivery
Responsible partner name and contact	Partner number: 4 Organisation: IGEA Name: Matteo Cadossi Email: m.cadossi@igeamedical.com
Nature R-Report P-Prototype D-Demonstrator O=-Other	Report
Dissemination level **PU**-public **PP**-restricted to otherprogramme participants RE-restricted to a group of partners **CO**-only for consortium members	Public
Delivery Month Planned	12 (31/3/21)
Actual delivery date (dd/mm/yy)	31/3/21

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003666

Description of deliverable

- **COMPLETED**

The electrical pulse protocol chosen is the following: 1 High-voltage pulse 600V/cm, 1ms length, 1s pause length, 1 Low-voltage pulse 60V/cm 400ms length. This pulse protocol has been tested for efficacy in DNA vaccination setting by KI and it is currently used in all the DNA vaccination experiments carried out by the partners of the OPENCORONA consortium. The identified pulse protocol will be used for the OPENCORONA clinical trial. To make sure that the pulse pattern cannot be accidentally modified by the operator during the clinical trial, the "OPENCORONA" pulse pattern has been loaded and saved into the software of the Cliniporator.

When starting the Cliniporator, the main menu window appears. From the main menu, the operator will be instructed to choose the GENE button to access the section that allows delivering treatments with personal settings and gene transfer (EGT). In the screen dedicated to the treatment parameter definition, the "OPENCORONA" pulse protocol has been loaded and then saved with the Filename "OPENCORONA". The OPENCORONA pulse protocol will be the only file available in the Cliniporator and selectable by the operator. When pressing the file name, the combination of parameters is automatically loaded into the electrical parameter window. At this point, by pressing the confirmation button, the operator will proceed to the treatment screen to deliver the electrical pulses. If any change is applied to the electrical parameters after loading the protocol the operator must confirm the process to avoid any inadvertently changes to pulse protocol. This system guarantees that the pulse protocol cannot be accidentally modified by the operator during the clinical trial.

To ensure the functionality of the "OPENCORONA" pulse protocol, the following tests have been carried out:

- Code coverage testing: software code coverage of Graphical User Interface (GUI), server and Field Programmable Gate Array (FPGA) was performed to detect code coverage during the use of the device with the intended use of the OPENCORONA clinical trial on Cliniporator EPS02 FULL version. The result of the code coverage test is the following: PASSED.
- Software functional testing: Protocol testing has been carried out to assess the step related to: protocol loading procedure, protocol access procedure, and functionality of the "OPENCORONA" pulse protocol: PASSED.
- Software system testing: System testing was performed to assess the correct functioning of the device with the "OPENCORONA" pulse protocol loaded: PASSED.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003666

GA 101003666 **Start date: 01/04/20** **End Date: 31/03/22**	
Project Title	OPENCORONA
WP number, deliverable number, and Title	WP4 D4.2: Documentation for EMA
Responsible partner name and contact	Partner number: 4 Organisation: IGEA Name: Matteo Cadossi Email: m.cadossi@igeamedical.com
Nature R-Report P-Prototype D-Demonstrator O=-Other	Report
Dissemination level **PU**-public **PP**-restricted to otherprogramme participants RE-restricted to a group of partners **CO**-only for consortium members	Public
Delivery Month Planned	15 (30/6/21)
Actual delivery date (dd/mm/yy)	24/6/21

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003666

Description of deliverable

- **COMPLETED**

To ensure clinical trial approval, the following documents will be provided to the EMA:

1. CE certificate for the electroporation device Cliniporator EPS02 (EC Certificate No 1289/MDD, date 02.06.2020).
2. Declaration of conformity for the electroporation device Cliniporator EPS02 serial number 00281011, stating that the above mentioned device is manufactured in conformance with the Medical Device Directive 93/42/EEC and 2007/47/EEC Annex II section 3 (certificate number 1289/MDD issued by the notified body n.0051 IMQ S.p.A.).
3. Technical file “System Essential Performance Requirements” stating that the energy delivered by the OPENCORONA protocol is safe and cannot create unacceptable risk for the patient. To ensure the safety of the procedure, an essential performance analysis has been carried out. In accordance with EN 60601-1, "essential performance" is defined as the performance of a clinical function for which loss or degradation beyond the limits specified by the manufacturer is deemed to pose an unacceptable risk ". The essential performances of Cliniporator EPS02, identified by the manufacturer according to this definition, are the control of the energy delivered during the treatment. It has been estimated that uncontrolled energy delivery above 60 Joules per single HV pulse (64.3 Joules considering the tolerances) would expose the patient to a risk deemed unacceptable. The verification of the essential performances has been carried out through the measurements of the amplitude (V) of the supplied pulses and of the duration (L) of the pulses. For the OPENCORONA pulse protocol applied to the muscle tissue we expect a total energy delivered of 2.6 J. This energy delivery is considered safe and cannot create unacceptable risks for the patient.

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101003666

GA 101003666 **Start date: 01/04/20** **End Date: 31/03/22**	
Project Title	OPENCORONA
WP number, deliverable number, and Title	WP4 D4.3: A single step delivery procedure
Responsible partner name and contact	Partner number: 4 Organisation: IGEA Name: Matteo Cadossi Email: m.cadossi@igeamedical.com
Nature R-Report P-Prototype D-Demonstrator O=-Other	Report
Dissemination level **PU**-public **PP**-restricted to otherprogramme participants RE-restricted to a group of partners **CO**-only for consortium members	Public
Delivery Month Planned	15 (30/6/21)
Actual delivery date (dd/mm/yy)	24/6/21

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003666

Description of deliverable

- **COMPLETED**

The activities of this task consist in the study and identification of the necessary technical solutions for the development of a device that enables injection of DNA and in vivo electroporation in a single step. Currently, the effectiveness of ElectroGeneTransfer (EGT) might be undermined by the low reproducibility of the procedure in use especially when injecting in deep tissue (such as muscle). The insertion of the electrode needles in the area of DNA injection might not be precisely centred thus limiting the efficiency of EGT.

IGEA designed a new device dedicated to DNA vaccination that enables the injection of the DNA vaccine and the delivery of the electrical pulses within one simple and fast procedure.

First of all, analysis and identification of design solutions and concepts for the realization of the new device have been performed. A technical analysis of the materials deemed most appropriate for the intended use (medical field) has been carried out. The technical analysis was aimed at verifying biocompatibility, mechanical functionality and electrical performance.

Then number, diameter and length of the needle electrodes, geometry of the electrode and the electrode introduction system have been evaluated. The electrode geometry has been optimize to: 1) reduce the number of the needles (to minimize pain); 2) guarantee a homogenous distribution of the electrical field; 3) provide a volume of electroporation sufficient to cover the volume of the injected DNA vaccine. Modelling of the electric field distribution for different electrode configurations has been performed using COMSOL software. The modelling results have been verified in laboratory on experimental models for a qualitative and quantitative analysis of the electroporation volume.

The new guided device must also provide for the DNA injection system. The concept for the guided device foresees a site to accommodate the syringe containing the DNA vaccine. COMSOL modelling showed that the DNA injection needle significantly interferes with the electric field distribution, therefore a system to retract the DNA syringe after the injection and before the delivery of the electric pulses has been implemented in the design of the new guided device.

The final design of the one-step delivery device (E-Gun) has been identified and prototypes have been produced to assess usability and functionality. Finally, E-Gun has been granted CE approval for the passive transmission of electrical pulses to body tissues (EC Certificate No 1673/MDD, date 01.02.2021).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101003666