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Title: **Clinical trials protocol – "Lumena";** Safety and usability of the LUMENA non-invasive ventilation mask	Doc #: CL-003 **Confidential**	Revision: 04 Page 1 of 20

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Revision History

Date	Revision level	Change description
26-Dec-2021	01	Initial release
22-Mar-2022	02	Update: Typos corrections, addition of groups definitions, statistical analysis
24-July-2022	03	Editorial changes of document visibility Update of sequences of mask using times
01-Jan-2023	04	6.1 -Addition of 20 patients to recruitment upper limit.; 9.7 - Removal of Myocardial infraction or stroke from exclusion criteria 14.2 – extension of treatment duration. 15.3 - Addition of Tidal volume, oxygen saturation, Mode of ventilation, peak Inspiratory Pressure, Pressure Support, Ventilator type and model, Trigger sensitivity, Fio2% and PEEP to collected data. 15.4 – elaboration regarding historical ECG. 15.7; 15.8; 15.9; 15.10- rephrasing the questions asked during the treatment. 18- update of patient enrollment definition.

Study Protocol

Safety and usability of the LUMENA non-invasive ventilation mask

Primary Investigator: Dr. Nimrod Adi

Sponsor: InspirLabs, LTD.

Version and date: 4.0 , January 01, 2023

Confidentiality Statement

Contents

1. Study Design:

A first-in-human, prospective, randomized, non-blinded cross-over study

2. Background:

The COVID-19 pandemic has taken the lives of millions of persons worldwide and disrupted the lives of countless more[1]. Healthcare workers are considered to be at increased risk of contracting SARS-CoV-2, possibly due to increased and prolonged exposure to SARS-CoV-2 confirmed or suspected individuals[2].

Nosocomial spread of SARS-CoV-2 amongst patients and contagious spread to HealthCare Workers (HCWs) have posed a major challenge and risk for healthcare systems. In Italy, HCWs are have paid a heavy price in addition to their professional and humanitarian efforts, with 21,338 cases (more than 10,4% of total Italian cases and 154 deaths among physicians)[3]. Protecting healthcare workers from nosocomial infection is therefore of paramount importance in curbing the spread of the pandemic and in maintaining healthcare systems` capacity. To this aim, guidelines for protection of healthcare workers, including the use of Personal Protective Equipment (PPE) have been issued by several international[4,5].

SARS-CoV-2 is considered to spread via droplet distribution, however the presence of the virus in aerosols has been documented in experimental[6] and real-life conditions in crowded, poorly ventilated hospital areas unrelated to aerosol generating procedures[7]. Such infections have been reported to be associated with aerosol-generating procedures such as positive pressure ventilation[8]. Several events of nosocomial infection with SARS-CoV-2 following to the use of inhalation devices and/or non-invasive ventilation have occurred in the Tel Aviv Sourasky Medical Center (TASMC) [Internal TASMC data].

Patients presenting to the emergency department, or needing hospitalization, for a variety of medical conditions often require Non-Invasive Ventilation (NIV). These patients` condition often requires close and continuous support by a staff member, putting these staff members at increased exposure to respiratory aerosols which could possibly contain SARS-CoV-2 of other airborne pathogens.

The "Lumena" mask is a disposable, single-patient, adult Oro-nasal mask, intended to provide a patient interface for transmission of NIV while minimizing dispersion of bio-aerosols from and into the breathing surrounding. It makes use of a dual layered containment space being constantly depressurized into a filtration system, thus allowing safety of use with non-hermetically sealed devices.

The mask has been approved by the Israeli Ministry of Health ("AMAR" / אמ"ר) as a medical device based on its intrinsic properties. This mask has undergone pre-clinical testing and is approved for marketing in several authorities. Inspir Labs, the sponsor is ISO 13485 certified. The purpose of this study is to evaluate the safety, usability and effectiveness of the Lumena mask and its ability to prevent the spread of respiratory aerosols in a real-world clinical setting.

3. Study Objectives:

3.1. Primary objective:

To assess the safety of the Lumena mask, compared to commercially available, commonly used oro-nasal face masks.

3.2. Secondary objectives:

3.2.1. To assess the effectiveness of the Lumena mask in achieving pre-defined clinical endpoints (i.e. oxygenation and ventilation), compared to commercially available, commonly used oro-nasal face masks.

3.2.2. To assess the effectiveness of the Lumena mask in reducing the spread of respiratory aerosol in the patient's environment, compared to commercially available, commonly used Oro-nasal face masks.

3.2.3. To assess patient comfort and satisfaction while using the Lumena mask, compared to commercially available, commonly used Oro-nasal face masks.

3.2.4. To assess staff ease of use and overall satisfaction with using the Lumena mask, compared to commercially available, commonly used Oro-nasal masks.

3.2.5. To assess the effectiveness of the Lumena mask in prevention of spread of respiratory particles during positive-pressure non-invasive ventilation within the Intensive Care Unit.

4. Sex:

Study will include both females and males, with at least 20% of patients beeing females.

5. Ages:

18 years and over

6. Number of patients:

6.1. 40 patients will be included in the study, until reaching 5 patients for each group. Patients who drop out of the study for any reason will be replaced.

6.2. The study will be designed to contain 4 groups, each containing 5 patients.

6.3. The trial is designed as a crossover trial, as all patients will be required to use both Lumena mask and the control mask. The order of interventions is determined by the designated group. Prior to every inhalation and particle sampling, a baseline sample will be taken to filter possible carryovers from previous sampling.

Table 1 - Crossover Groups & Periods

Group	Period 1	Period 2	Period 3
A	Standard	Lumena No Suction	Lumena Suction
B	Standard	Lumena Suction	Lumena No Suction
C	Lumena No Suction	Lumena Suction	Standard
D	Lumena Suction	Lumena No Suction	Standard

7. Statistical analysis:

Statistical analysis will be conducted following conclusion of the trial. A pre-test for the assumption of negligible carryover will be conducted as specified below:

$$T = \sqrt{\frac{mn}{N}} \frac{\bar{C}(X) - \bar{C}(Y)}{\sqrt{(SQ_{CX} + SQ_{CY}) / (N - 2)}}$$

After which a test for differences between treatment effects will be carried, according to the same formula but applying it to within-subject differences[9]

8. Inclusion Criteria:

8.1. Adults males and females aged 18 years and over.

8.2. Suffering from hypoxemic and/or hypercarbic respiratory failure requiring non-invasive ventilation and selected by medical staff to use CPAP or BiPAP.

8.3. Fully conscious (Glasgow Coma Scale 14-15) and able to cooperate with non-invasive ventilation.

8.4. Able to provide informed consent to participate in the study.

8.5. Have an active arterial line in place for arterial blood sampling (arterial lines will not be placed for the sole purpose of the study). Alternatively, IV line can be used.

9. Exclusion Criteria:

9.1. Age < 18 years.

9.2. Pregnancy.

9.3. Respiratory failure due to non-pulmonary pathology.

9.4. Presence of a contraindication to the use of non-invasive ventilation or an absolute indication for invasive ventilation.

9.5. Presence of a facial deformity, heavy beard or moustache which prevents a good seal between the mask and the face.

9.6. Hemodynamic instability.

9.7. Severe upper gastrointestinal bleeding.

9.8. Chest trauma.

9.9. Claustrophobia

10. Possible device related Adverse Effects:

10.1. Device-Specific AE's:

10.1.1. Impaired patient ventilator synchrony

10.2. Non Device-Specific possible AE's include:

10.2.1. Barotrauma

10.2.2. Nausea

10.2.3. Feeling of claustrophobia

10.2.4. Facial and eye irritation

10.2.5. Facial pain due to pressure

11. Special Populations:

The study will not include special populations such as pregnant women, persons who are not able to provide informed consent or those under 18 years of age.

12. Study device (Lumena mask) description:

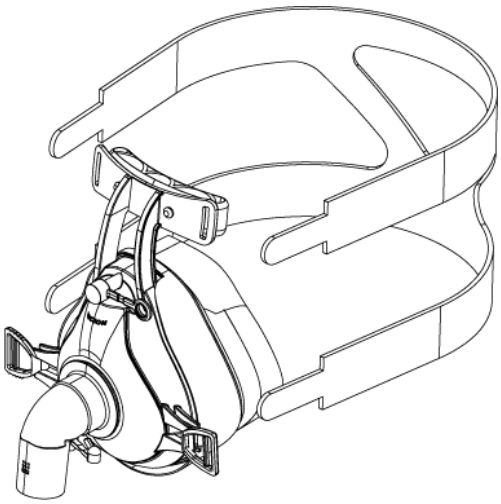


Figure 1: Lumena Mask

The Disposable Single-Patient-Use "Lumena" Oro-Nasal mask is a transparent mask for administration of non invasive ventilation (NIV) designed to minimize aerosolization into the surrounding environment. Each mask may be used for up to 14 days.

The mask is an interface accessory for use with a positive pressure ventilation device such as a BiPAP/CPAP machines or a mechanical ventilator. All of the mask components are able to be cleaned.

The face piece consists of an internal volume for providing patient ventilation by a positive pressure, "covered" with an external layer kept at a sub-atmospheric pressure by a suction source (either a dedicated vacuum generator or a hospital wall suction) in order to continuously capture any air escaping from the internal volume. A circumferential sealing cushion is positioned between the internal volume and the external layer to minimize any escape of potentially contaminated air into the external layer. The Mounting Head Gear has straps that are adjustable and hold the Face Piece against the patient's face while slightly squeezing the

aforementioned sealing cushion, thus minimizing any potential gas leakage from the internal volume.

The "Lumena" is a non-vented mask that does not incorporate an integrated CO_2 exhaust vent in its design, and as such must be used only as part of a dual limb circuit or a single limb circuit that contains auxiliary CO_2 exhaust features. The mask is designed to be used in positive pressures ranging from 4-30 cmH_2O.

The mask is connected via a standard suction tube to a vacuum source that can provide at least 30 liter/minute of flow as a safe, aerosol minimizing device, but can also be used as a regular, non-safe NIV mask when it is not connected to a vacuum source. The mask contains two separate spaces, an inner space positively pressurized to administer positive pressure ventilation, and a separate, negatively pressurized space that scavenges aerosol emitted during ventilation and prevents it from being released into the surrounding environment.

The mask has been approved by the Israeli Ministry of Health`s Medical Devices Department ("AMAR"/אמ"ר), approval #34860001.

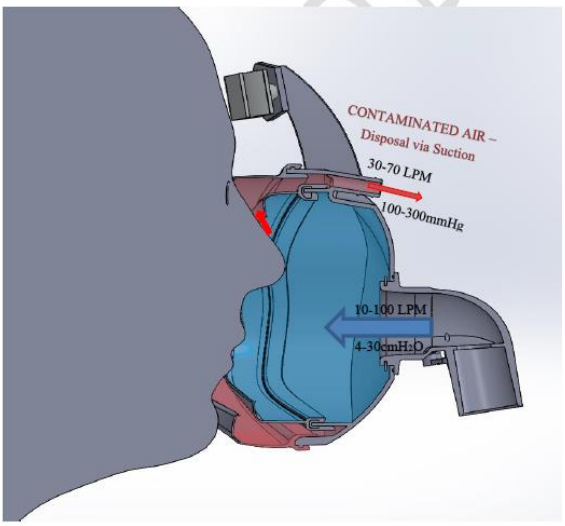
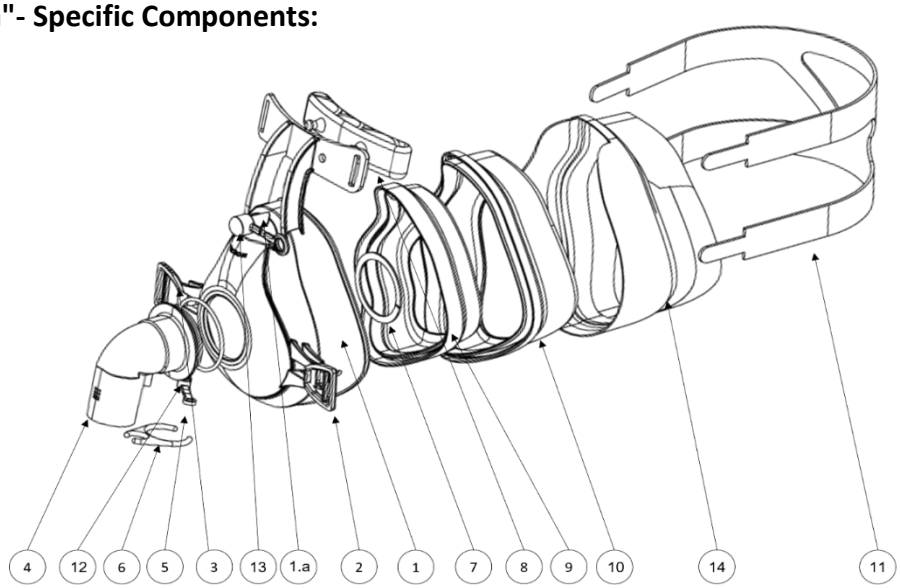


Figure 2: Lumena gap Pathway

13. "Lumena"- Specific Components:



The mask, which is available in 3 sizes (Small, Medium, Large), consists of the following basic components:

1. Mask Frame, containing:
   a. Suction port for connection to a vacuum source, either wall suction or a portable vacuum machine using via a 28Fr suction tube in order to maintain negative pressure in the mask's outer layer
2. Clip On
3. Quick-Release Clip
4. Elbow
5. Oxygen Port Cap
6. Suction & Inlet Tubes Gripper (*2 in kit)
7. Swivel lock Ring
8. Head Cushion
9. Inner Cushion
10. Outer Cushion
11. Headgear Strap
12. O-Ring
13. Suction Cap
14. Silicone Guard

14. Study Description:

14.1. Enrollment phase:

All patients at the relevant departments who require non-invasive mechanical ventilation according to treating physician's decision will be screened for eligibility, given an investigator is available. Study eligibility will be determined by the inclusion and exclusion criteria. All eligible patients who meet study eligibility will be offered to participate in the study. Signed informed consent will be performed by research staff.

The offer to enroll shall be presented only by the investigators and will be presented to all eligible patients.

Consented patients will be randomized to one of four groups. Each group has a unique sequence protocol:

A. 1) Standard NIV mask *[30-60 minutes]*; 2) Lumena mask without suction *[30-60 minutes]*; 3) Lumena mask with suction *[30-60 minutes]*.
B. 1) Standard NIV mask *[30-60 minutes]*; 2) Lumena mask with suction *[30-60 minutes]*; 3) Lumena mask without suction *[30-60 minutes]*.
C. 1) Lumena mask without suction *[30-60 minutes]*; 2) Lumena mask with suction *[30-60 minutes]*; 3) Standard NIV mask *[30-60 minutes]*.
D. 1) Lumena mask with suction *[30-60 minutes]*; 2) Lumena mask without suction *[30-60 minutes]*; 3) Standard NIV mask *[30-60 minutes]*.

Data required for study purposes (see below) will be collected at time of enrollment from the medical record and/or from direct questioning of the study patient.

14.2. Intervention phase:

Following randomization, each patient will be placed on BIPAP or a CPAP (per clinical need) using either the aerosol-reducing mask (Lumena) for approximately 1-2 hours, and then on the standard NIV mask used at the department for another 1-2 hours, or vice versa according to randomization scheme. In general, ventilation at each condition will be 30-60 minutes for each condition, with variation expected due to patient clinical need. Suction will be connected/disconnected from the Lumena mask according to the randomization schemes 30-60 minutes from placement of the mask. The patients will serve as their own control (cross over design).

During each of the three study phases (use of standard NIV mask, use of Lumina mask with suction and use of Lumina mask without suction), an inhalation of 5 ml 0.9% NaCl will be administered to the patient via the mask (using an in-line connector and a standard inhalation chamber) to enhance potential for environmental spread of small particles and thus enhance the ability to discriminate between the standard mask and the Lumina masks` ability to minimize aerosol spread.

Eligible patients will be enrolled into the study, perform trial activities and exit the study within a maximum of 1 day.

The study will be performed in a hospital intensive-care setting due to the nature of the device, and the required patients population.

14.3. Monitoring:

During all phases of the study (either using standard NIV mask or Lumina mask), a staff member will be present in the patient's room.

Vital signs during NIV will be recorded in real time by the staff member.

Before, during and after NIV, and electrocardiogram (ECG) will be monitored and arterial blood\ venous gas (ABG\VBG) samples will be drawn.

A particle-measuring device (Particle Plus 8303) will be placed at a distance of 1.5 meter from the patient`s face to record the level of aerosol spread.

Following each session of NIV, the patient as well as the staff member treating the patient will be asked to complete a short questionnaire regarding the comfort and ease of use of each of the masks used. Any adverse events will be captured in real time by the staff member.

15. Data Collected:

15.1. Demographics including as age, sex, DOB, height, weight and body mass index.

15.2. Past medical history including smoking status, co-morbid conditions and medication use.

15.3. Vital signs before, during and after non-invasive ventilation such as: heart rate, respiratory rate, Tidal volume, oxygen saturation, Mode of ventilation, peak Inspiratory Pressure, Pressure Support, Ventilator type and model, Trigger sensitivity,Fio2%, PEEP, blood pressure (invasive and/or non-invasive), and temperature.

15.4. Electrocardiogram (ECG) diagrams before use (historical ECG can be also use) and monitoring during use.

15.5. Arterial blood\ Venous blood gas analysis for O_2, CO_2, pH and HCO_3 as well as serum Lactate levels before, during and after non-invasive ventilation. A maximum of 20 ml of blood will be collected from each patient.

15.6. Symptoms and signs during use of non-invasive ventilation (e.g. diaphoresis, anxiety).

15.7. Estimation of patient preference of the mask- The question shall be phrased thusly: which mask do you prefer?

15.8. Estimation of staff comfort (an analog 1-5 scale as well as recording of verbal comments) – the question shall be phrased thusly: In a scale of 1-5, 1 being very uncomfortable and 5 being very comfortable, how would you rate the mask?

15.9. Estimation of staff use - The question shall be phrased thusly: which mask do you prefer?

15.10. Estimation of patient comfort – the question will be directed to the staff member. (an analog 1-5 scale as well as recording of verbal comments). – the question shall be phrased thusly: In a scale of 1-5, 1 being very uncomfortable and 5 being very comfortable ,how would you rate the patient's feeling with the experimental mask?

15.11. Device related adverse events will be reported by number, type, seriousness, severity , duration and attribution . All device and treatment related adverse events will be captured, regardless of severity.

16. Risk-Benefit Assessment

This is a feasibility proof of concept study, i.e. the nature and purpose of this study is to collect data to support research and development of the Lumena mask during noninvasive ventilation. The patients will have no direct health benefit from the use of the device.

Expected benefit for patients and staff will arise from the future creation a safer care environment, potentially minimizing the need for bulky personal protective equipment (PPE).

The Lumena mask is considered class II device in Europe. Risk assessment has been performed and no major or intolerable risks were found. All the mitigations were documented. The risk management summary in the company's IB demonstrates that the risks associated with the tested devices are well mitigated and are as low as reasonably practicable as defined by the applicable standards.

As for the Lumena mask usage, the protocol has been designed to decrease and minimize the risk to the patients by monitoring the respiratory parameters and using it for no more than an hour.

Expected adverse events like cough or bronchospasm may arise during inhalation study. Subjects will be monitored closely for safety and reporting of adverse events during the study including follow up until complete resolution of any adverse events.

17. Confidentiality and Information Security

Each patient will be assigned a unique identifying number and that number will be used throughout all data collection and analysis processes.

The mapping of study identifiers and patient details will be stored by the primary investigator in a locked cabinet or a password-protected hospital-issued computer. The mapping list will be deleted or physically destroyed after completion of data analysis, and a report of said deletion will be included in the study summary. This file will not be sent via unencrypted email nor will it be removed from hospital premises without written consent by the hospital's R&D division.

Only the primary and secondary investigators, who are hospital employees with permission to access medical records, will have access to the de-identified data. Specifically, the sponsor will not have access to de-identified patient data.

18. Study Duration:

18 months or until enrollment of 40 eligible patients (the first of both occurrences).

Each patient will be included for a maximum of one day, from enrollment and obtainment of informed consent until end of participation.

19. References:

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