SOLNATIDE

Exploration of safety, tolerability and clinical efficacy of Solnatide IMP in patients infected with the 2019 new coronavirus

Deliverable 5.4

Report on the suitability of solnatide IMP for treatment of COVID-19

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1 Executive Summary

During the SOLNATIDE project "Exploration of safety, tolerability and clinical efficacy of solnatide IMP in patients infected with the 2019 new coronavirus" the suitability of solnatide IMP for the treatment of patients with moderate to severe COVID-19 has been assessed:

A in the clinical study:

- "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS - a randomised, placebo-controlled, double-blind trial" (EudraCT Number: 2017-003855-47)

  https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003855-47

  https://clinicaltrials.gov/ct2/show/NCT03567577?term=03567577&draw=2&rank=1

B during Compassionate Use Programs in Austria and Italy:

- „Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS"

C outside the SOLNATIDE project in the clinical study:

- „Treatment of COVID-19 Patient" (EUDRACT 2020-001244-26) by the Medical University Vienna with support by APEPTICO.

1) Preliminary data from the above studies show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.

2) Interim clinical data from the above studies show a positive trend towards improvements of mortality for the therapeutic use of solnatide.

3) The data support the continuous use of solnatide for the therapeutic treatment of patients with moderate-severe COVID-19.

Work performed by the beneficiary BCN proofed the chemical stability of the IMP solnatide peptide during the manufacturing process and for minimum 18 months after batch release. Stress stability studies and regular stability studies have been conducted by BCN.

In addition, product- and process derived impurities have been detected, analysed, and adequate analytical methods have been developed and validated.

During the project, the three-dimensional structure of the solnatide peptide in solution has been deduced from NMR experiments to further specify the Mode of Action of the solnatide peptide.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

2 Introduction

During the SOLNATIDE project "Exploration of safety, tolerability and clinical efficacy of solnatide IMP in patients infected with the 2019 new coronavirus" the suitability of solnatide IMP for the treatment of patients with moderate to severe COVID-19 has been assessed:

***** In the clinical study:

- "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS - a randomised, placebo-controlled, double-blind trial" (EudraCT Number: 2017-003855-47)

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***** During Compassionate Use Programs in Austria and Italy:

- „Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS"

***** Outside the SOLNATIDE project in the clinical study:

- „Treatment of COVID-19 Patient" (EUDRACT 2020-001244-26) by the Medical University Vienna with support by APEPTICO.

According to WP5 "WP5 - Solnatide IMP Formulation & Manufacture" following task is related to D5.4:

"Report on the suitability of solnatide IMP for treatment of COVID-19"

Accordingly clinical data related to experience of solnatide in corona patients are reported here and published elsewhere.

Data on the stability of solnatide peptide during and after manufacture have been generated, potential product- and process-related impurities have been identified to optimise analytical methods and the entire solnatide manufacturing process.

During the project, the three-dimensional structure of the solnatide peptide in solution has been deduced from NMR experiments to further specify the Mode of Action of the solnatide peptide.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

3 Results

During the SOLNATIDE project "Exploration of safety, tolerability and clinical efficacy of solnatide IMP in patients infected with the 2019 new coronavirus" the suitability of solnatide IMP for the treatment of patients with moderate to severe COVID-19

A Has been assessed in the clinical study:

- "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS - a randomised, placebo-controlled, double-blind trial" (EudraCT Number: 2017-003855-47)

  https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003855-47

  https://clinicaltrials.gov/ct2/show/NCT03567577?term=03567577&draw=2&rank=1

B Has been assessed during Compassionate Use Programs in Austria and Italy:

- „Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS"

C Has been assessed outside the SOLNATIDE project in the clinical study:

- „Treatment of COVID-19 Patient" (EUDRACT 2020-001244-26) by the Medical University Vienna with support by APEPTICO.

According to WP5 "WP5 - Solnatide IMP Formulation & Manufacture" following task is related to D5.4:

"Report on the suitability of solnatide IMP for treatment of COVID-19"

Accordingly, interim clinical results on the treatment of covid-19 patients within the clinical study "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS" have been published as follow:

- Schmid B, Kranke P, Lucas R, Meybohm P, Zwissler B, Frank S. sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate to severe ARDS in a randomized, placebo-controlled, double-blind trial: preliminary evaluation of safety and feasibility in light of the COVID- 19 pandemic. Trials (2022) 23:252.

  https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06182-3

Please find below a summary of available clinical data for the use of solnatide for treatment of patients with moderate to severe COVID-19:

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

3.1 Safety and preliminary efficacy of solnatide to treat patients with moderate-to-severe ARDS (EUDRACT 2017-003855-47)

The interventional RCT study "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS - a randomised, placebo-controlled, double-blind trial" (EudraCT Number: 2017-003855-47) https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003855-47 was conducted at following clinical sites:

- **LMU: Klinik für Anaesthesiologie, Klinikum der Universität München, Campus Großhadern, München, Bayern, Germany,**

and with following additional partners (not part of the consortium) :

- Univ.-klinik f. Herz-, Thorax-, Gefäßchirurgische Anästhesiologie und Intensivmedizin, Medizinische Universität Graz, Graz, Steiermark, Austria
- Univ. Klinik für Innere Medizin / Gem. Einrichtung für Intensiv- und Notfallmedizin / GE Medizinische Universität Innsbruck, Innsbruck, Austria
- Department of Anesthesia, General Intensive Care and Pain Control, Medical University of Vienna, Vienna, Austria
- Klinik für Anaesthesiologie, Klinikum der Universität München, Campus Großhadern, München, Bayern, Germany
- Klinik für Operative Intensivmedizin und Intermediate Care, Aachen, Nordrhein-Westfalen, Germany
- Universitätsklinikum Bonn, Operative Intensivmedizin, Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin, Bonn, Germany
- Klinik für Anästhesiologie und operative Intensivmedizin, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany
- Klinik für Anästhesiologie / Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany
- Universitätsklinikum Würzburg, Klinik und Poliklinik für Anästhesiologie, Würzburg, Germany

Patients were treated with „low dose solnatide" (Dosing Group A, DG-A, 5 mg solnatide), „middle dose solnatide" (Dosing Group B, DG-B, 60 mg solnatide), and „high dose solnatide" (Dosing Group C, DG-C, 125 mg solnatide). The solnatide was administered as liquid aerosol every 12 hours for a maximum of 7 days.

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From April 2018 until early 2022, 65 patients with moderate to severe ARDS were randomised into the study for DG-A and DG-B. Amon these patients, approx. 10 patients developed ARDS due to severe infection with the new corona virus (SARS-CoV-2), thus having symptoms of moderate to severe covid-19. These patients were randomised into the study during the DG-B.

The clinical study protocol for this interventional trial has been published by:

- Schmid B, Kredel M, Ullrich R, Krenn K, Lucas R, Markstaller K, Fischer B, Kranke P, Meybohm P, Zwißler B, Frank S. Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate-to-severe ARDS—a randomized, placebo-controlled, double-blind trial. Trials (2021) 22:643.
- https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05588-9

An overview of this study including interim data has been published by:

- Schmid B, Kranke P, Lucas R, Meybohm P, Zwissler B, Frank S. sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate to severe ARDS in a randomized, placebo-controlled, double-blind trial: preliminary evaluation of safety and feasibility in light of the COVID- 19 pandemic. Trials (2022) 23:252.
- https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06182-3

Detail from the Schmid et al (2022) publication and clinical results are presented by the beneficiary LMU in the Section 3.1 of Deliverable D3.2 “SOLANTIDE Draft Clinical Study Report of COVID-19 patients”.

- Preliminary data from the show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.
- Interim clinical data show a positive trend towards improvements of clinical parameter including mortality for the therapeutic use of solnatide.
- The data support the continuous use of solnatide for the therapeutic treatment of patients with moderate-severe COVID-19.

3.2 Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS

The use of solnatide for Compassionate Use was conducted in Austria and Italy.

Following hospitals in Austria used solnatide for the treatment of moderate to severe COVID-19 patients:

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- KABEG KLINIKUM Klagenfurt am Wörthersee
  Abteilung für Anästhesiologie und Intensivmedizin
  9020 Klagenfurt
- Steiermärkische Krankenanstaltengesellschaft m.b.H
  LKH Graz II, Standort West
  Abteilung für Anästhesiologie und Intensivmedizin
  8020 Graz
- Landesklinikum Wiener Neustadt
  Abteilung für Anästhesie, Notfall- und Allg. Intensivmedizin
  2700 Wiener Neustadt
- Landesklinikum Gmünd - Waidhofen/Thaya – Zwettl
  Standort Gmünd, Innere Medizin
  3950 Gmünd

Following hospitals in Italy used solnatide for the treatment of moderate to severe COVID-19 patients:

- Department of Anesthesiology and Intensive Care Unit
  University of Modena
  41100 Modena
- Anestesia e Rianimazione in urgenza
  San Salvatore Centrale – Pesaro
- Ospedale Magalini
  37069 Villafranca di Verona

In total:

- 660 vials of solnatide were distributed in Austria.
- 520 vials of solnatide were delivered to Italy.

All covid-19 patients were ventilated patients. All patients had a WHO score of 6 or higher. Solnatide was delivered to patients as an aerosol with a dose of 100 mg every 12 hours for maximum 7 days.

Clinical detail related to the Compassionate Use of solnatide are summarised in Section 3.2. “Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS” in the Deliverable D3.2 “SOLANTIDE Draft Clinical Study Report of COVID-19 patients” prepared by the beneficiary LMU.

- Preliminary data from the show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.

This project has received funding from the EC special H2020 program “Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

- Interim clinical data show a positive trend towards improvements of mortality for the therapeutic use of solnatide.
- The data support the continuous use of solnatide for the therapeutic treatment of patients with moderate-severe COVID-19.

3.3 Treatment of COVID-19 Patient Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS

The interventional RCT study "COVID-19: Efficacy of solnatide to treat pulmonary permeability oedema in SARS-Cov-2 positive patients with moderate-to-severe ARDS - a pilot-trial" (EUDRACT 2020-001244-26) https://www.clinicaltrialsregister.eu/ctr-search/search?query=2020-001244-26 was conducted by the Medical University Vienna under the supervision of the Department of Clinical Pharmacology, Medical University of Vienna. The trial made use of the IMP solnatide.

The study was conducted at the Medical University Vienna (AKH, General Hospital) and the Department of Internal Medicine and Pneumology of the Clinic Floridsdorf of the Wiener Gesundheitsverbund.

The data management was monitored on a high frequency by the "Koordinationszentrum für Klinische Studien" (KKS) of the Medical University Vienna.

In total, 30 patients have been recruited on a 1:1 basis (solnatide vs. placebo). The solnatide dose was 100 mg as liquid aerosol every 12 hours for a maximum of 7 days.

Clinical study details are summarised in Section 3.3 "Treatment of COVID-19 Patient (EUDRACT 2020-001244-26)" within the Deliverable D3.2 "SOLANTIDE Draft Clinical Study Report of COVID-19 patients" prepared by the beneficiary LMU.

- Preliminary data from the show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.
- Interim clinical data show a positive trend towards therapeutic use of solnatide.
- The data support the continuous use of solnatide for the therapeutic treatment of patients with moderate-severe COVID-19.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

3.4 Optimisation of technical parameters for the manufacture, structural characterization and stability of solnatide

The analytical methods initially developed to analyse Solnatide did not allow the detection of one of the main process impurities (D-Cys17-Solnatide), as observed previously. For this reason, the analytical method used for the determination of impurities has been modified to find the chromatographic conditions that allow the detection of all relevant process and degradation impurities.

For details, please revert to section 3.1 "Analytical Method Optimization" of the Deliverable D4.3 prepared by the beneficiary BCN.

3.5 Impurity Profile Characterization

Extensive experimental work has been conducted for the characterization of the impurity profile of the solnatide batch AP301-2001-1:

Structure:	Cyclo(1-17) H-Cys-Gly-Gln-Arg-Glu-Thr-Pro-Glu-Gly-Ala-Glu-Ala-Lys-Pro-Trp-Tyr-Cys-OH
Molecular Formula:	$C_{82}H_{119}N_{23}O_{27}S_2$
Molecular Weight:	1923.1 (as free base)
BCN Peptides code:	AP301
Batch Studied	AP301-2001-1

The identification of the related peptides that can be present in the Solnatide produced at BCN Peptides has been done in different ways:

- Synthesis of potential impurities.
- Identification of impurities present in batch AP301-2001-1 (process impurities).
- Identification of impurities present in a sample submitted to a temperature stress treatment (degradation impurities).

For details related to the process- and product-related impurities, the entire impurity profile and adaptation of analytical methods please revert to section 3.2 "Impurity Profile Characterisation" of Deliverable D4.3 prepared by the beneficiary BCN.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

3.6 Analytical method validation

The validation of the method used for the net peptide content analysis of Solnatide has been performed according to the guideline ICH Q2(R1) (Validation of analytical procedures: Text and Methodology).

With the validation process it was proved that the results of the validation performed meet the pre-established acceptance criteria and therefore, the method is considered validated and is applied for the net peptide content routine analysis of Solnatide.

For details, please revert to section 3.3 “Analytical Method Validation” of Deliverable D4.3 prepared by the beneficiary BCN.

3.7 Stability assessment

Analytical procedures and stability testing have been performed to characterise the physico-chemical properties of solnatide over time.

The general test conditions comply with ICH regulations in terms of temperature, relative humidity and light irradiation (stress testing). Two protocols were performed during the stability studies:

- a protocol for the stress stability studies, and
- a protocol for the long-term storage conditions and for the accelerated stability studies.

Current data do not indicate any instability of the drug substance solnatide at -20°C; Only minor instability was observed at 5°C.

For details on the stability of solnatide at 25°C, 5°C and -20°C, as well accelerated conditions, please revert to section 3.4 “Stability Data” of the Deliverable D4.3 prepared by the beneficiary BCN.

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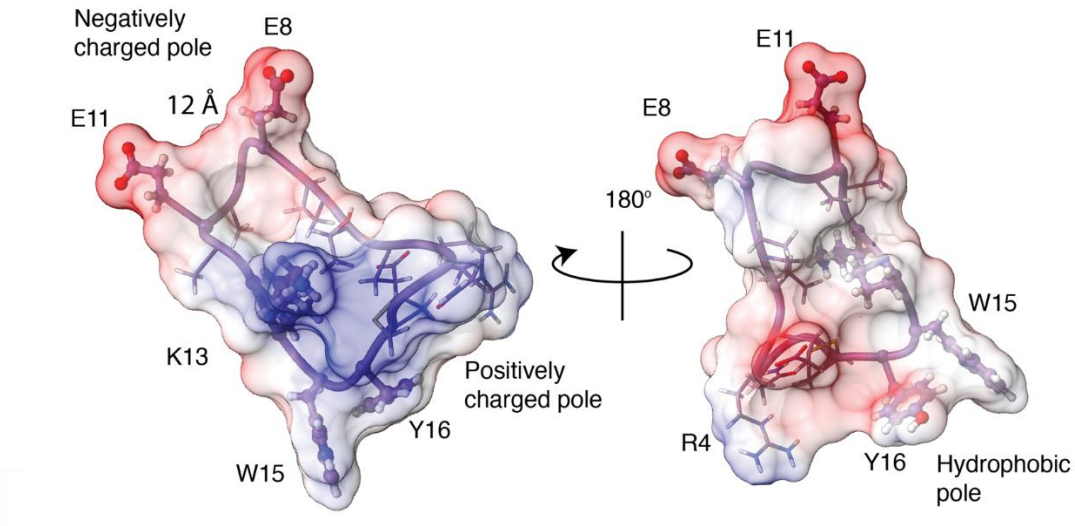
3.8 Three-dimensional structure of solnatide

To better understand the Mode of Action of solnatide, the three-dimensional structure of solnatide has been analysed by the beneficiaries BCN and APEP, and the external research group from the Barcelona Institute of Science and Technology.

The analysis of the conformational ensembles displayed by solnatide shows how the peptide recapitulates the main structural features as relevant for the ENaC-activating effect of the lectin-like domain of TNF, namely the critical role of the triad of residues in solnatide/hTNF: Thr6/105, Glu8/107 and Glu11/110, the hydrophobic region comprising three consecutive residues Pro14/113, Trp15/115 and Tyr16/115, and the presence of a charged dipole, all of which are observed in the peptide. The middle region of solnatide, represented by the sequence TPEGAEA, is ordered, shows H-bonding capacity, and adopts a backbone conformation similar to that of the native protein.

Based on the conformational studies and in the analysis of charge distribution of the peptide surface reported here, a model has been generated to describe how solnatide may interact with the cytoplasmic C-terminal domain of the ENaCα subunit via electrostatic complementarity.

Charge distribution of solnatide peptide.
Two views related by a 180 rotation are represented. The negatively and positively charged areas and the hydrophobic pole are labeled.



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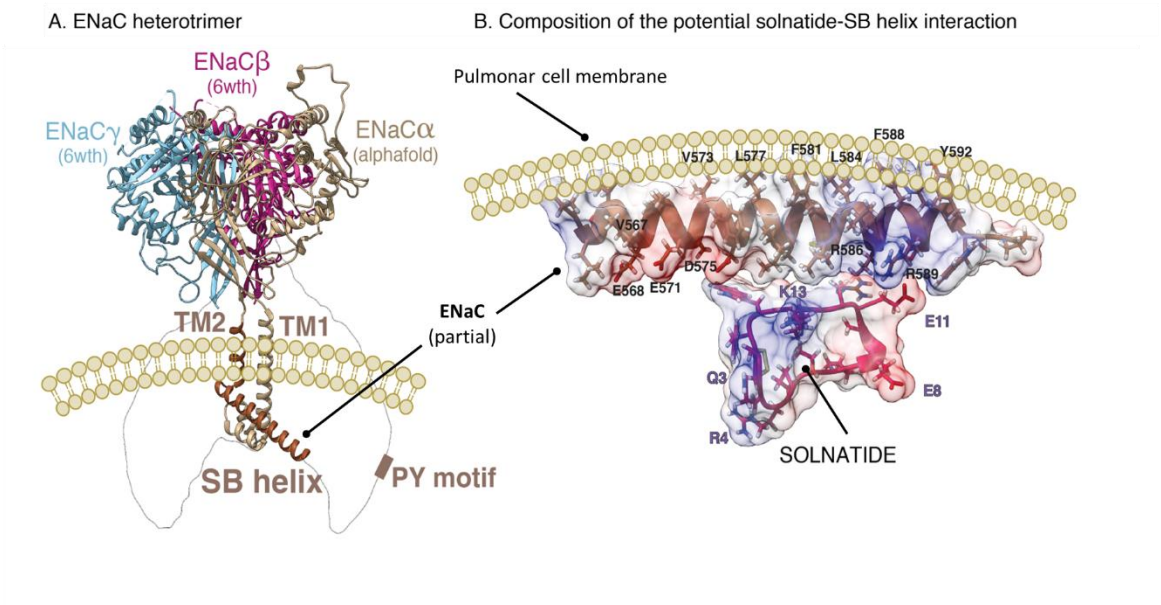
Proposed model of solnatide interaction with the C-terminal helix of the ENaCα.

A. ENaC heterotrimer as observed in the cryoEM structure. B. Expanded view of the cytoplasmic helical segment predicted by AlphaFold.



The study has been published as follow: Martin-Malpartida et al. Conformational ensemble of the TNF-derived peptide solnatide in solution. Computational and Structural Biotechnology Journal 20 (2022) 2082–2090. DOI: 10.1016/j.csbj.2022.04.031

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

4 Conclusions

During the SOLNATIDE project "Exploration of safety, tolerability and clinical efficacy of solnatide IMP in patients infected with the 2019 new coronavirus" the suitability of solnatide IMP for the treatment of patients with moderate to severe COVID-19 has been demonstrated:

A In the clinical study:

- "Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability oedema in patients with moderate-to-severe ARDS - a randomised, placebo-controlled, double-blind trial" (EudraCT Number: 2017-003855-47)

  https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003855-47

  https://clinicaltrials.gov/ct2/show/NCT03567577?term=03567577&draw=2&rank=1

B During Compassionate Use Programs in Austria and Italy:

- „Compassionate Use of solnatide for the treatment of COVID-19 patients with severe ARDS"

C Outside the SOLNATIDE project in the clinical study:

- „Treatment of COVID-19 Patient" (EUDRACT 2020-001244-26) by the Medical University Vienna with support by APEPTICO.

Preliminary data show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.

Interim clinical results on the treatment of covid-19 patients have been published as follow:

- Schmid B, Kranke P, Lucas R, Meybohm P, Zwissler B, Frank S. sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate to severe ARDS in a randomized, placebo-controlled, double-blind trial: preliminary evaluation of safety and feasibility in light of the COVID- 19 pandemic. Trials (2022) 23:252.

  https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06182-3

In the international publication "Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey" in Critical Care (2020) 24:516 Tzotzos et al demonstrate that the mortality of ventilated patients with covid-19 following infection with the new corona virus SARS-CoV-2 is 59%.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

However, preliminary clinical data from the above “solnatide studies” resulted in mortality rates far below 50% or even less. Preliminary clinical data also show that physiological parameter improved during the treatment period with solnatide. Preliminary clinical data also show that the WHO severity index of patients with covid-19 decreased from initially ≥6 to lower values.

1) Preliminary data from the above studies show that the solnatide IMP did not cause drug-related adverse events with covid-19 patients.

2) Interim clinical data from the above studies show a positive trend towards improvements of mortality for the therapeutic use of solnatide.

3) The data support the continuous use of solnatide for the therapeutic treatment of patients with moderate-severe COVID-19.

In addition, analytical work has demonstrated that the solnatide peptide manufactured by the beneficiary BCN is stable over many months, the impurity profile has been identified and characterised.

The three-dimensional structure of the solnatide peptide has been determined by NMR during the reporting period.

This project has received funding from the EC special H2020 program “Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.

5 Contact

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6 Attachment

EUDRACT 2020-001244-26: Approval Certificate by the Ethics Committee of the Medical University Vienna.

EUDRACT 2020-001244-26: Approval Certificate by the Austrian Competent Authority.

EUDRACT 2017-003855-47: Approval Certificate by the central Ethics Committee of the Medical University Vienna (for Austria) and of the University Munich (for Germany).

EUDRACT 2017-003855-47: Approval Certificate by the Austrian Competent Authority and the German Competent Authority.

Schmid B, Kredel M, Ullrich R, Krenn K, Lucas R, Markstaller K, Fischer B, Kranke P, Meybohm P, Zwißler B, Frank S. Safety and preliminary efficacy of sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate-to-severe ARDS—a randomized, placebo-controlled, double-blind trial. Trials (2021) 22:643.

Schmid B, Kranke P, Lucas R, Meybohm P, Zwissler B, Frank S. sequential multiple ascending doses of solnatide to treat pulmonary permeability edema in patients with moderate to severe ARDS in a randomized, placebo-controlled, double-blind trial: preliminary evaluation of safety and feasibility in light of the COVID- 19 pandemic. Trials (2022) 23:252.

Compassionate Use Program: Approval Certificate for Italy.

Compassionate Use Program: Approval Certificate for Austria.

Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. Critical Care (2020) 24:516.

Martin-Malpartida P, Arrastia-Casado S, Farrera-Sinfreu J, Lucas R, Fischer H, Fischer B, Eaton DC, Tzotzos S, Macias MJ. Conformational ensemble of the TNF-derived peptide solnatide in solution. Computational and Structural Biotechnology Journal 20 (2022) 2082–2090.

This project has received funding from the EC special H2020 program "Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic (call ID: SC1-PHE-CORONAVIRUS-2020)) under the grant no. 101003595.