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BRIEF REPORT

Efficacy and Safety of ELOM-080 as Add-On Therapy in COVID-19 Patients with Acute Respiratory Insufficiency: Exploratory Data from the Prospective Placebo-Controlled COVARI Trial

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ABSTRACT

Introduction: Enhancement of mucociliary clearance (MCC) might be a potential target in treating COVID-19. The phytomedicine ELOM-080 is an MCC enhancer that is used to treat inflammatory respiratory diseases.

Patients/Methods: This randomised, double-blind exploratory study (EudraCT number 2020-003779-17) evaluated 14 days' add-on therapy with ELOM-080 versus placebo in patients with COVID-19 hospitalised with acute respiratory insufficiency.

Results: The trial was terminated early after enrolment of 47 patients as a result of poor recruitment. Twelve patients discontinued pre-

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maturely, leaving 35 in the per-protocol set (PPS). Treatment with ELOM-080 had no significant effect on overall clinical status versus placebo ($p = 0.49$). However, compared with the placebo group, patients treated with ELOM-080 had less dyspnoea in the second week of hospitalisation ($p = 0.0035$), required less supplemental oxygen ($p = 0.0229$), and were more often without dyspnoea when climbing stairs at home ($p < 0.0001$).
Conclusion: These exploratory data suggest the potential for ELOM-080 to improve respiratory status during and after hospitalisation in patients with COVID-19.

Keywords: COVID-19; Dyspnoea; ELOM-080; MCC enhancement; Mucociliary clearance; Shortness of breath

Key Summary Points

The impairment of mucociliary clearance (MCC) has been demonstrated in particular for early stages of COVID-19.

The COVARI study investigated the potential of ELOM-080 (an MCC enhancer) as add-on therapy in hospitalised patients with moderate COVID-19-related acute respiratory insufficiency (ARI) requiring supplemental oxygen therapy.

The trial was stopped early because of lower rates of COVID-19 in summer 2021. Therefore, the overall clinical status did not differ significantly between both treatments.

However, exploratory data for ELOM-080 indicate an improvement of the respiratory status during (less dyspnoea and lower need of supplemental oxygen) and after hospitalisation (less dyspnoea on exertion) in patients with COVID-19.

INTRODUCTION

The rapid spread of the new severe acute respiratory syndrome inducing coronavirus type 2 (SARS-CoV-2) resulted in a global pandemic that started in 2019 and is still ongoing. The clinical manifestation of the resulting coronavirus disease (COVID-19) ranges from asymptomatic and mild upper respiratory tract infection to bilateral pneumonia with acute respiratory distress syndrome and multiple organ failure. Hypoxia seems to appear in the early stages of COVID-19, while excessive inflammation occurs at a later stage of the disease. Several research groups have demonstrated that SARS-CoV-2 infection induces a rapid loss of the ciliary layer in airway epithelium early in the disease pathogenesis, resulting in impaired mucociliary clearance (MCC) and decreased barrier function [1, 2].

COVID symptoms may persist for several weeks after infection [3] and include fatigue, breathlessness and cough [4]. The last two symptoms might at least partially be due to the loss of ciliary function during infection and the resulting impairment of MCC [1]. Drug substances that modulate ciliary beat frequency and/or enhance the mucociliary escalator might therefore be reasonable treatment options [5, 6].

ELOM-080 is a phytomedicine that has mucolytic, secretolytic, secretomotoric, anti-inflammatory, antioxidant, antimicrobial and bronchospasmolytic effects [6–8], and has demonstrated clinical efficacy, safety and tolerability in clinical trials [9–12].

The objective of the COVARI trial was to investigate the potential of ELOM-080 as add-on therapy in hospitalised patients with moderate COVID-19-related acute respiratory insufficiency (ARI) requiring supplemental oxygen therapy. The hypothesis was that adding an agent that improves MCC would provide passage for ventilation in the conducting zone supporting the supplemental oxygen therapy in patients with COVID-19 in order to improve their outcome.

METHODS

Trial Design

The exploratory phase II/III COVARI trial (EudraCT number 2020-003779-17) was designed to evaluate the efficacy of ELOM-080 as add-on therapy for the treatment of hospitalised patients with moderate COVID-19-associated ARI (WHO score 5) [13, 14] and a requirement for supplemental oxygen therapy. The study was conducted at 11 hospitals in Germany and was approved by the German Competent Authority (Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte]) and the relevant independent ethics committees (lead: Faculty of Medicine, RWTH Aachen, Germany; approved 15 December 2021, reference number EK 408/20). For a complete list of all ethic committees which approved the trial, see Table S1 in the electronic supplementary material. The trial was conducted in accordance with Good Clinical Practice guidelines and Declaration of Helsinki principles. All patients provided written informed consent.

Study Participants

Adult patients with laboratory-confirmed SARS-CoV-2 infection who had been admitted to an isolation ward with dyspnoea and/or tachypnoea, with a need for supplemental low-flow oxygen (up to 5 L/min) over the period January to July 2021 were eligible for enrolment. Key exclusion criteria were ARI needing high-flow oxygen, mechanical ventilation or support on intensive care units (ICU) at the time of inclusion, the presence of relevant laboratory abnormalities, and known hypersensitivity to trial medication or excipients (see Table S3 for all inclusion and exclusion criteria).

Treatment and Follow-up

After completion of a screening by the investigator, subjects were sequentially assigned to a randomisation number in ascending order based on a computer-generated randomisation schedule (performed by Staburo GmbH, Germany) with a fixed block size. Subjects were randomised (1:1) to double-blind treatment with orally administered ELOM-080 (GeloMyrtol® forte, G. Pohl-Boskamp GmbH & Co. KG, Germany) or matched placebo for 14 days. The ELOM-080 dosage was 2400 mg/day (4 × 2 capsules of 300 mg daily).

Patients were followed up for 29 days. If patients were discharged from hospital prior to either the interim visit on day 15 (± 2) or the follow-up visit on day 29 (± 2), follow-up was performed by telephone. In addition, discharged patients received a diary for daily documentation of symptom severity until the follow-up visit.

Outcomes

The primary endpoint was the sum of the daily 7-point Ordinal Status Score (OSS, from 1—death to 7—discharged) on days 2–15, defined as SOSS-14 (sum of OSS) [15].

Secondary endpoints included changes in respiratory status during hospitalisation (number of days with hypoxia and usage of supplemental oxygen; course of typical COVID-19 symptoms, i.e. shortness of breath or difficulty in breathing, cough, sore throat, and fatigue) and in the home environment (dyspnoea when walking, climbing stairs or speaking). Safety and tolerability were evaluated on the basis of the occurrence of adverse events, and changes in vital functions und laboratory parameters.

Assessments

The assessment of each patient's clinical status using the Ordinal Status Score was performed by the blinded investigator on a daily basis. The assessment of predefined COVID-19 symptoms was performed twice daily (morning and afternoon). The investigator asked the blinded patient for presence and severity (i.e. shortness of breath) using a verbal rating scale (VRS-4) ranging from 0 (none/absent) to 3 (severe). After discharge from hospital the subjects were asked to complete a diary once daily. Patients recorded the presence of their symptoms (yes/no)

plus interferences in daily activities (i.e. dyspnoea when climbing stairs).

Planned Sample Size and Statistical Analysis

This phase II/III trial was exploratory. The original plan was to enrol 75 patients per group, which would detect between-group differences of 3.0, 2.6 and 2.0 points on the SOSS-14 (standard deviation [SD] ± 7.5) at p values of 0.05, 0.10 and 0.20, respectively. Data sets were defined as:

Safety evaluable set (SES): All randomised subjects with post-baseline safety data.
Intent-to-treat (ITT): All randomised subjects with valid post-baseline efficacy data.
Per-protocol set (PPS): All ITT subjects without any major protocol deviation.

Between-group differences in the primary endpoint were tested using analysis of variance (ANOVA), with treatment and requirement for additional COVID medication as fixed effects and age as a covariate. Missing OSS data were imputed using the multiple imputation method. Secondary endpoints were analysed descriptively and a generalised linear model for categorical data was used to compare these outcomes between treatment groups. All statistical analyses were performed using Statistical Analysis Software SAS, version 9.4.

RESULTS

Study Participants

Low recruitment rates during the summer of 2021 meant that enrolment was stopped early, after the inclusion of 47 patients. Two patients withdrew consent on the day of randomisation, resulting in an ITT population of 45 patients. Ten further patients discontinued prematurely, leaving a PPS of 35 patients (15 treated with ELOM-080 and 20 treated with placebo; Fig. S1). In total, 12 patients, six in each treatment arm, discontinued prematurely: 8 (4/4) patients withdrew consent, 4 (2/2) discontinued for other reasons; a detailed description can be found in the supplementary material.

The mean age of participants in the ELOM-080 group was higher than that of those in the placebo group (Table S2). All outcome data are reported for the PPS.

Concomitant Medications and Comorbidities

ELOM-080 or placebo was given as add-on therapy to centre-specific COVID-19 treatment. This consisted predominantly of dexamethasone (15 and 18 patients in the ELOM-080 and placebo groups, respectively), remdesivir (2 and 10 patients), baricitinib (1 and 7 patients), and systemic antibiotics (6 and 10 patients). Apart from dexamethasone, all treatments were used in more patients in the placebo versus ELOM-080 groups (Table S2). Common comorbidities were coronary artery disease, chronic obstructive pulmonary disease, and chronic kidney failure, all of which were more prevalent in patients treated with ELOM-080 compared with placebo (Table S2).

Primary Endpoint

Overall, SOSS-14 did not differ significantly between the ELOM-080 and placebo groups (PPS; $p = 0.49$) (Fig. 1). Patients aged 70 years or older had lower SOSS-14 in general. However, patients in this age group showed a numerically higher SOSS-14 when treated with ELOM-080 versus placebo (Fig. 1).

Secondary Endpoints

Compared with the placebo group, patients treated with ELOM-080 reported less shortness of breath in the second week of hospitalisation ($p = 0.0035$; Fig. 2), required less supplemental oxygen ($p = 0.0229$), and had less shortness of breath when climbing stairs after discharge ($p < 0.0001$; Fig. 3). All other secondary endpoints did not differ between treatment groups.

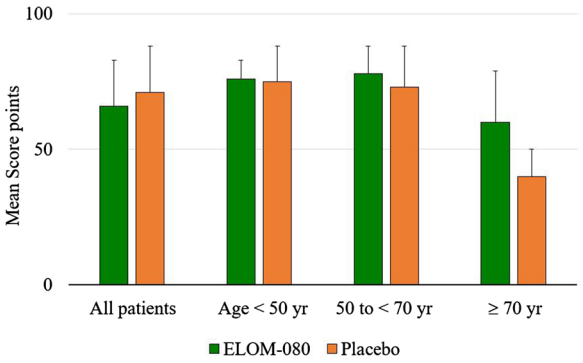

Fig. 1 Sum of the Ordinal Status Score over 14 days (SOSS-14) in the per-protocol set, overall and in patient subgroups based on age. Bars show mean values, and lines indicate standard deviation (overall $p = 0.49$; analysis of variance)

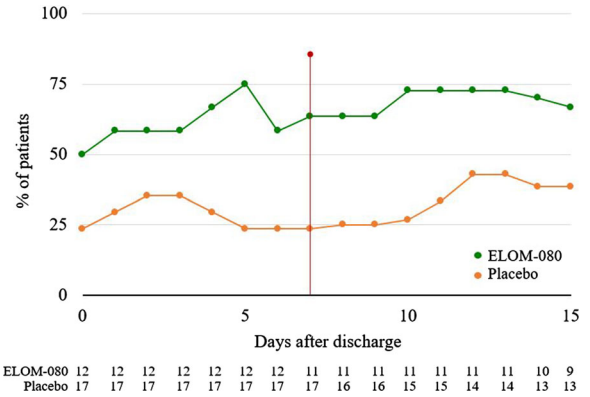

Fig. 3 Proportion of patients reporting no shortness of breath when climbing stairs after discharge (per-protocol set). Red line marks first week after discharge. Numbers below the graph are number of patients on each day of follow-up. $p < 0.0001$ for between-group comparison

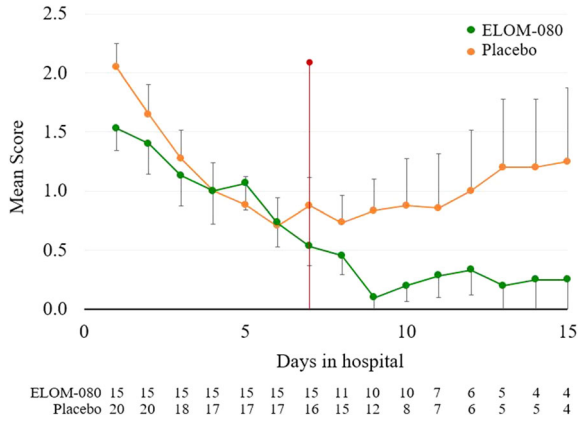

Fig. 2 Shortness of breath scores in hospitalised patients (per-protocol set). Red line marks the first week after randomisation. Numbers below the graph are number of patients on each day of follow-up. Dots show mean values and lines indicate standard error of the mean. $p = 0.0035$ for the comparison between scores in the ELOM-080 and placebo groups during the second week of hospitalisation

Worsening of Respiratory Status

Worsening of respiratory status could be identified by escalation in oxygen therapy (high-flow therapy, non-invasive or mechanical ventilation) with or without ICU admission. However, the incidences in the period of hospital attendance from day 1 to day 15 were reduced to a few isolated cases with two and three patients in the ELOM-080 and placebo group, respectively. A detailed description of those patients can be found in the supplementary material.

Safety

In the SES, 55 adverse events (AEs) were reported in 20/47 patients (42.6%). A total of 39 AEs occurred in 13/21 patients (61.9%) treated with ELOM-080, and 16 AEs occurred in 7/26 patients (26.9%) who received placebo. One AE (mild gastritis) was classified as possibly drug-related (ELOM-080 group). Eight serious adverse events (SAEs) were reported, none of which was related to ELOM-080. Two courses resulted in death due to COVID-19 (one in each group).

DISCUSSION

The aim of this study was to determine whether hospitalised patients with COVID-19-related moderate ARI who required supplemental oxygen would benefit from add-on therapy with ELOM-080. Although inclusion of 150 patients was planned, recruitment for the trial was stopped early because of lower rates of COVID-19 in summer 2021. Compared with other COVID-19 studies [16], the recruitment rate achieved in this trial (approximately 33%) was above average, but the difficulty in recruiting

sufficient patients also highlights the challenging circumstances for clinical trials during the pandemic.

Given that only a third of patients planned could be recruited, significant and evidence-generating results were not expected. The primary endpoint, reflecting overall clinical status, did not differ significantly between the ELOM-080 and placebo groups after correction for age. In addition, the study population was characterised by high heterogeneity in terms of age, which differed between treatment groups. As the recruitment period for the study progressed, the mean age of patients presenting to hospital with COVID-19 declined as vaccination commenced in more vulnerable, older age groups, which meant that it was predominantly younger patients being hospitalised. This, along with a coincidentally higher number of patients randomised to the placebo group during that period, contributed to the higher median age (and therefore more frequent comorbidities) in the ELOM-080 versus placebo group [17].

However, despite these limitations, this study did show potentially important differences in respiratory parameters between the two treatment groups, favouring ELOM-080. Patients treated with ELOM-080 showed a more pronounced improvement in dyspnoea during and after the hospitalisation phase. This is likely to be of clinical importance because dyspnoea is one major symptom of COVID-19, and has a negative impact on morbidity during and after the acute phase. Although these results must be interpreted with caution, they may indicate a conclusive signal for a COVID-19 lead symptom that was a trigger for hospitalisation in these patients and may also persist after discharge. Therefore, additional research into whether ELOM-080 is a useful supportive therapy during the early/outpatient phase of COVID-19 is warranted.

ELOM-080 is a potent enhancer of MCC [5, 6], and the findings of the current study support this mode of action, because of its beneficial effects on the passage for ventilation in the conducting zone. Additionally, ELOM-080 supports differentiation of ciliary epithelium in vitro and thereby may facilitate recovery of impaired MCC following viral infection [1, 18]. Furthermore, anti-inflammatory properties of ELOM-080 might be beneficial in early COVID-19-induced inflammation. However, as a result of early termination of the study, the data on which evaluation of patients' IL-6 and CRP levels was based was limited and available data did not show any relevant differences between placebo and ELOM-080. In this context, it would be useful to determine the value of treatments that restore airway lining mucus barrier function, especially in the early phase of COVID-19 disease. Readily available treatment options for outpatients become more and more important because the spread of highly transmissible variants will likely result in large numbers of patients being quarantined at home with on average younger age and a comparatively mild-to-moderate disease course. This population is not commonly expected to experience severe inflammatory conditions but effective early treatment could reduce and/or prevent morbidity, and future studies should assess whether treatment with ELOM-080 could contribute to preventing the development of long COVID symptoms [19].

As noted already, early termination of patient recruitment and mismatch between treatment groups in age and comorbidities despite the robust randomisation process were important limitations of this study. Therefore, the results should be considered as hypothesis generating rather than conclusive. In addition, the enrolment of patients with COVID-19 from a single country means that the results are only generalisable to similar patient populations in terms of ethnicity and demographics.

CONCLUSION

These hypothesis-generating data suggest a potential for benefit of treatment with ELOM-080 in patients with COVID-19-related ARI. However, additional research is needed to confirm the beneficial effects of ELOM-080 on dyspnoea in COVID-19 and define its role as a safe and potentially effective add-on therapy for both hospitalised and non-hospitalised patients.

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Author Contributions. All authors contributed to the design, conduct and evaluation of the study and were involved in planning, writing and review of the manuscript. Michael Dreher, Christian Grohè, Stephan Kanzler, Karin Kraft, Christoph Sarrazin, Michael Doll, Jens Spiesshöfer, Stephan Steiner, Jochen Wöhrle, Julia Seeger, and Stephan Eisenmann were involved as investigators, Michael Dreher also as co-ordinating investigator of the entire study.

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Compliance with Ethics Guidelines. The study was approved by the German Competent Authority (Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte]) and the relevant independent ethics committees (lead: Faculty of Medicine, RWTH Aachen, Germany; approved 15 December 2021, reference number EK 408/20; for a complete list of ethic committees, see Supplementary Table S1). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

Data Availability. The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality agreements.

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