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ORIGINAL RESEARCH

A Phase II, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of HEX17, a Novel Broad-Spectrum Antiviral Drug, in a Controlled Human Infection Model of Influenza Challenge

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ABSTRACT

***Introduction*:** Viral respiratory tract infections are of global concern, with an unmet need for a broad-spectrum antiviral prophylactic. HEX17, a multivalent carbohydrate-binding module, binds to sialic acid, a cell surface glycan used by many viruses for host cell entry. HEX17 represents a potential broad-spectrum antiviral prophylactic therapy.

***Methods*:** This phase II randomised double-blind, placebo-controlled study was conducted in a UK centre. Healthy adults (18–55 years) were randomised (3:3:4) to daily HEX17 for 3 days (2.8 mg HEX17 from day −3 to −1); single-dose HEX17 (2.8 mg HEX17 on day −3; placebo on day −2 and −1); or daily placebo (day −3 to −1). Participants were challenged with influenza virus on day 0 and assessed from days 1 to 8. Primary outcomes were incidence and severity of symptomatic influenza in the pooled HEX17 arms versus placebo, in the per protocol population (PPP). Safety analysis included all participants receiving at least one dose of HEX17/placebo.

***Results*:** Of 104 participants enrolled between August 2022 and March 2023, 99 were included in the PPP (single-dose HEX17, $n=29$; daily HEX17, $n=30$; placebo, $n=40$). Symptomatic influenza occurred in 16/40 (40.0%) participants in the placebo arm versus 12/59 (20.3%) in the pooled HEX17 arms (−19.7% decrease; 95% confidence interval [CI] −38.0, −1.3; $p=0.0331$). The median peak total symptoms score was 3.00 in the placebo arm and 2.00 in the pooled HEX17 arms (versus placebo: 95% CI −2.00, 0.00; $p=0.1427$). Unsolicited adverse events (AEs) occurred in 17/41 (41.5%), 10/32 (31.3%), and 9/31 (29.0%) participants in placebo, daily HEX17, and single-dose HEX17 arms, respectively (safety population). No deaths or serious AEs occurred.

***Conclusion*:** Prophylactic HEX17 reduced the incidence of symptomatic influenza infection and may protect at-risk patients against influenza infection.

***Trial Registrations*:** EudraCT 2022-001853-22, Clinicaltrials.gov NCT05507567.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-025-01179-2.

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Key Summary Points

Why carry out this study?

Viral respiratory tract infections (RTIs) remain a great global concern. A well-tolerated, broad-spectrum prophylactic antiviral therapy, with a low risk of inducing viral resistance, would benefit the clinical management of viral RTIs.

HEX17 is a multivalent carbohydrate-binding module that targets sialic acid, with promising results available in preclinical models.

We conducted a phase II, randomised, double-blind, placebo-controlled study in healthy adults to assess the efficacy of intranasal prophylactic HEX17, in protecting against an influenza virus challenge.

What was learned from the study?

Occurrence and severity of symptomatic influenza were significantly reduced in participants who received HEX17 compared to those who received placebo.

HEX17 may represent an exciting and important prophylactic agent to prevent viral respiratory infections in patients at risk of complications due to underlying conditions.

INTRODUCTION

Viral respiratory tract infections (RTIs) are of great global concern. Viruses accounted for the majority of the estimated 17.2 billion incidences of upper RTIs in 2019 [1]. Although many viral RTIs are self-limiting, they still pose a major burden on patients and healthcare resources. Viral RTIs can represent a significant threat to vulnerable populations such as the elderly [2], people who are immunocompromised [3] and patients with underlying pulmonary disease [4, 5]. Pathogenic viruses that cause RTIs have also caused significant pandemics. These have included numerous pandemics caused by influenza viruses this century and last [6], as well as the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which has had a devastating global impact in terms of mortality, morbidity and disruption to everyday life [7, 8].

Despite the availability of vaccines for some viral RTIs, there remains an unmet need for effective antiviral therapies. Vaccines have limitations. A new vaccine is usually necessary for each new strain of a virus, requiring a lengthy development process [9]. Vaccine effectiveness can also be limited; for example, depending on the population and circulating strains, influenza vaccine effectiveness can range from 27% to 44% [10, 11]. A universal vaccine with greater efficacy, broader protection, and longer duration of protection could be transformative for influenza prevention and treatment. Unfortunately, development of such a universal vaccine is complicated by the variety of influenza reservoirs and the antigenic variation of the influenza virus [12]. Improved adjuvants may yield improved influenza vaccines [13].

In addition to vaccines, antiviral drugs are also available to treat some viral RTIs, including influenza [14, 15]. However, antiviral drug efficacy can be limited by toxicity [16] or viruses acquiring drug resistance [14, 16–19]. Therefore, a well-tolerated, broad-spectrum prophylactic antiviral therapy, with a low risk of inducing viral resistance, would benefit the clinical management of viral RTIs.

Sialic acid is a cell surface glycan expressed in the nasal epithelia which is used by many respiratory viruses to gain host cell entry [20]. Targeting sialic acid could represent a mechanism of protecting against multiple viruses with the same drug: both against those viruses that directly bind to sialic acid, such as influenza [20], as well as viruses such as human rhinoviruses A and B that recognise other proteins but whose binding and endocytosis require interactions with receptors that carry sialic acid [21]. In addition, blockade of a host ligand for viral entry is expected to reduce the risk of drug-resistant variants emerging [22].

The potential of sialic acid as a target in virus protection has been explored using engineered multivalent carbohydrate-binding modules (mCBMs) in vitro and in vivo. *Sp*2CBMTD is a hexavalent mCBM, consisting of the homologous domain from *Streptococcus pneumoniae* NanA sialidase fused to an oligomerisation domain from *Pseudomonas aeruginosa* sialidase. *Sp*2CBMTD administration up to 7 days prior to infection protected mice against lethal doses of A/WSN/1933 (H1N1) and the mouse-adapted A/California/04/2009 (H1N1) influenza viruses [20]. In other mouse studies, a high level of protection was conferred against lethal influenza virus by treatment with *Sp2*CBMTD 7 days before challenge [22]. HEX17 (Neumifil) is an mCBM that has been derived from *Sp*2CBMTD, with modifications made to reduce potential unwanted immunogenicity in humans. HEX17 significantly reduced the clinical disease severity and histopathological changes in the nasal cavity in a SARS-CoV-2 Syrian golden hamster model [23]. HEX17 has also demonstrated in vivo efficacy against respiratory syncytial virus and in vitro efficacy against human rhinovirus [24]. Together, these preclinical findings suggest HEX17 has the potential to protect against multiple respiratory viruses.

The aim of this phase II, proof-of-concept study was to evaluate the efficacy of prophylactic HEX17 in reducing the incidence and severity of symptomatic influenza virus challenge in healthy participants.

METHODS

Study Design

This was a phase II, randomised, double-blind, placebo-controlled study. The study was conducted at a single site in the United Kingdom (hVIVO Services Limited, Queen Mary BioEnterprises Innovation Centre, London, UK). The study was initiated on August 12, 2022, and was completed on May 03, 2023. This study was approved by the South Central-Berkshire B Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki, the principles of the International Council for Harmonisation Good Clinical Practice, and applicable local regulatory requirements.

Participants

The inclusion criteria were adults aged between 18 and 55 years (inclusive) with a body weight ≥ 50 kg, body mass index ≥ 18 kg/m^2; no medical history of clinically significant medical conditions; a negative pregnancy test (female participants) and use of an effective contraceptive method; and who were serosuitable (haemagglutination inhibition titre ≤ 1:10) for infection with the influenza A/Perth/16/2009 (H3N2) challenge virus at generic screening. The exclusion criteria were symptoms or signs of upper or lower RTI within 4 weeks prior to the first study visit; any history or evidence of any clinically significant or currently active condition that may have interfered with completion of the study; females who were breast-feeding or had been pregnant within 6 months prior to the study; history of anaphylaxis or history of severe allergic reactions; and nasal surgery or any significant abnormality affecting the nose or nasopharynx that may have interfered with the study within 3 months of the study. At the generic screening, participants were asked what biological sex they were assigned at birth (male or female). All participants provided informed written consent.

Randomisation and Masking

Participants were randomised to one of three study arms (daily HEX17 doses for 3 days, single-dose HEX17 on day −3 and placebo on day −2 and day −1, or daily placebo on day −3 to day −1) in a 3:3:4 ratio. An independent statistician provided a computer-generated randomisation code to determine which study medication regimen participants received. Randomisation was by block, with a block size of 10. Participants were dispensed blinded investigational medicinal product (HEX17/placebo) labelled with their randomisation number. The principal investigator/investigator, all clinical and nonclinical staff (excluding the unblinded

pharmacist, unblinded statistician and quality assurance auditors where necessary) and participants were blinded until after the database was locked and unblinding was approved.

Procedures

Participants were resident within the quarantine unit for the inpatient phase of 13 days (day −4 to day 8). Baseline assessments and randomisation were performed up to day −3, ahead of the first study dose.

HEX17 and placebo were provided by Pneumagen (Fife, Scotland, UK) and formulated as liquid sprays for intranasal administration. HEX17 was administered as a 10 mg/mL solution, at a dose of 2.8 mg in 0.28 mL (1.4 mg [0.14 mL] per nostril). The HEX17 dose in each treatment arm was determined based on the tolerability profile observed in the first-in-human study. HEX17 was delivered intranasally, from an Aptar Cartridge Pump System (CPS) Spray Pump. Matching placebo was administered at a volume of 0.28 mL (0.14 mL per nostril). Participants in the daily HEX17 arm received HEX17 once daily for 3 days (day −3 to day −1). Participants in the single-dose HEX17 arm received HEX17 on day −3, and placebo once daily on day −2 and day −1. Participants in the placebo arm received placebo once daily for 3 days (day −3 to day −1). Influenza A/Perth/16/2009 (H3N2) was provided by hVIVO (London, UK) and formulated as a liquid for intranasal drop administration in a capped vial. The virus was administered at an approximate dose of $10^{5.5}$ $TCID_{50}$ (50% tissue culture infectious dose). Participants were closely monitored for 24 h following challenge virus inoculation.

Nasal samples were collected by nasopharyngeal swabs on day 1 (once; PM), twice daily on day 2–7 (taken approximately 12 h apart), and on day 8 (once; AM). These samples were used to determine the incidence of influenza infection and viral load by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) and viral culture (for detailed methodology, see Supplementary Information).

Symptomatic influenza infection was defined as two detectable RT-qPCR measurements on two or more independent nasal samples over 2 days, or one quantifiable cell culture measurement, from day 1 to 8, and any symptoms of grade ≥ 2 at a single time point.

The severity of influenza symptoms was assessed using the total symptoms score (TSS). The TSS was based on diary cards that were completed by participants three times a day, from day 1 (AM) to day 8 (AM). Participants provided a grade from 0 to 3 for the following 11 symptoms: runny nose, stuffy nose, sneezing, sore throat, earache, malaise/tiredness, headache, muscle and/or joint ache, chilliness/feverishness, cough, and shortness of breath. The grading scale was as follows: grade 0—no symptoms; grade 1—just noticeable; grade 2—clearly bothersome from time to time but does not interfere with me doing my normal daily activities; grade 3—quite bothersome most or all of the time, and it stops me participating in activities. Shortness of breath had an additional grade, grade 4—symptoms at rest. An individual TSS was derived for each assessment as a sum of the symptom scores (with possible values ranging from 0 to 33). The peak TSS was defined as the maximum observed value for TSS from day 1 to 8. Area under the curve (AUC) of viral load and TSS was calculated using the trapezium rule:

With $n+1$ measurements y_i at times t_i, ($i=0$, n), the AUC is calculated as:

$$\mathrm{AUC} = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1})$$

The actual time of each assessment will be used in the calculation.

For viral load–area under the curve (VL-AUC), 14 measurements are used for the computation (1 on day 1, 2 on each day from day 2 to day 7 and 1 on day 8). For TSS-AUC, 24 measurements are used for the computation (3 on each day from day 1 to day 8).

Participants were discharged from the quarantine unit on day 8, having tested negative for the influenza virus by rapid viral antigen test and had no clinically significant symptoms. The final follow-up visit was conducted on day 28 (±3 days).

Outcomes

The co-primary outcomes for this study were the effect of HEX17 in reducing the incidence of symptomatic influenza infection and/or the severity of symptoms after influenza viral challenge, compared with placebo. The co-primary endpoint was chosen to allow determination of both symptomology as well as viral load, rather than viral load alone. Secondary outcomes included the effect of HEX17 compared with placebo on the following: reducing the incidence of influenza infection; the number of participants with grade 2 or higher symptoms; and reducing the influenza viral shedding/load. The safety of HEX17 and the challenge virus were also assessed. Adverse events (AEs; including serious AEs [SAEs]) and AEs of special interest (for HEX17, namely a clinically significant reduction in forced expiratory volume in 1 s and forced vital capacity) were recorded up to the follow-up visit. For the challenge virus, AEs and SAEs were recorded from day 0 to the planned discharge from quarantine (day 8). AEs were classified as solicited or unsolicited, and reported using descriptive statistics. Solicited AEs included bleeding, burning sensation, pain or irritation of the nose, loss of taste or smell, sensation of needing to sneeze, sneezing and unpleasant taste. Unsolicited AEs were reported by patients, assessed for relatedness to HEX17 prophylaxis and graded 1–4 for severity. Exploratory pharmacokinetic assessment of HEX17 plasma concentrations was also performed. Blood samples for this analysis were collected on days −3, −2 and −1; these were collected pre-dose (within 2 h before study medication administration), and 1, 2 and 3 h post-dose. Immunogenic response to HEX17 was not analysed in this study.

Statistical Analysis

The sample size was based on the primary comparison between the placebo arm and the two HEX17 dose arms pooled together. The number of participants in the placebo arm (40) and in the pooled HEX17 arm (60; 30 in each dose arm) had a power of at least 80% to detect a significant reduction in the following primary outcomes:

- A 70% reduction in symptomatic influenza infection rate compared with placebo assuming a symptomatic infection rate of 27.8% in the placebo arm
- A 65% reduction in peak TSS compared with the placebo arm, assuming a coefficient of variation of 125%, using a one-sided 0.05 type I error rate without adjustment for multiple testing

All analyses were prespecified. For the co-primary outcomes, pairwise comparisons of qRT-PCR confirmed symptomatic influenza infection and mean peak TSS were performed between the pooled HEX17 and placebo arms. Exploratory endpoints included comparisons between each HEX17 dose arm and the placebo arm. The incidence of symptomatic influenza infection was summarised for each arm using counts and percentages with comparisons between arms using the Pearson chi-square test. Peak TSS was summarised for each arm using means and medians, while the differences between arms were summarised using Hodges–Lehmann estimation and tested using the Wilcoxon rank-sum test. Tests for both primary outcomes used a nominal one-sided error of 0.05 without adjustment for multiplicity, because this was not assumed to be a requisite for a phase 2 aiming to provide proof of concept for the efficacy of HEX17. The primary efficacy analysis was conducted on the per protocol population data, defined as participants who had received all doses of the study medication and the challenge virus, completed the quarantine period, and presented with no major protocol deviation likely to impact data evaluation. Safety analysis was conducted on the safety analysis dataset, defined as participants who had received at least one dose of HEX17 or placebo. Statistical analysis conducted for the secondary outcomes was performed on the per protocol dataset as follows: incidence of RT-qPCR confirmed influenza infection was assessed by Pearson chi-square test; and viral shedding (as determined by viral load and peak viral load from RT-qPCR and viral culture) was assessed by Wilcoxon rank-sum test.

Statistical analysis was performed using SAS version 9.04.01M6P11072018. No data monitoring committee was used. This study was registered with EudraCT, 2022-001853-22 (and on ClinicalTrials.gov, NCT05507567).

RESULTS

From April 2022 to April 2023, 137 participants were invited to quarantine for admission. Of these, 104 participants were enrolled and randomised in the study and received at least one dose of HEX17 or placebo: 41 participants were in the placebo arm, 31 participants were in the single-dose HEX17 arm, and 32 participants were in the daily HEX17 arm (Fig. 1). Five participants were discontinued: one participant in the placebo arm was lost to follow-up before receiving the challenge virus; two participants in the single-dose HEX17 arm chose to withdraw after receiving challenge virus for personal reasons; and two participants were discontinued in the daily HEX17 arm before receiving challenge virus—one due to a decision by the investigator, and one did not complete the quarantine period. The participant demographic characteristics at baseline were generally similar between the treatment arms (Table 1).

Following virus challenge, detectable influenza by RT-qPCR was reported in 25 (62.5%) participants in the placebo arm (data not shown). This infectivity rate was comparable with historical data using influenza virus challenge [25].

The primary endpoint of symptomatic influenza infection incidence (as determined by RT-qPCR) was significantly reduced in the pooled HEX17 arm versus placebo; symptomatic influenza was detected in 16/40 (40.0%) and 12/59

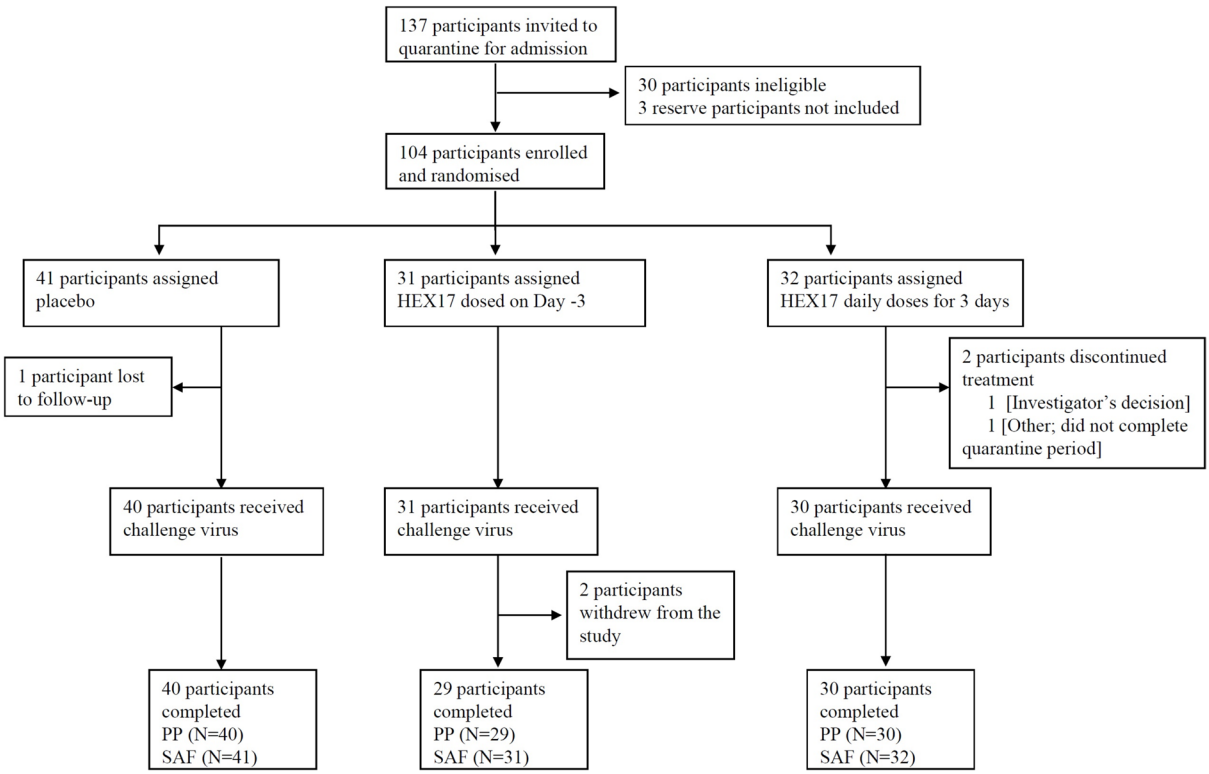


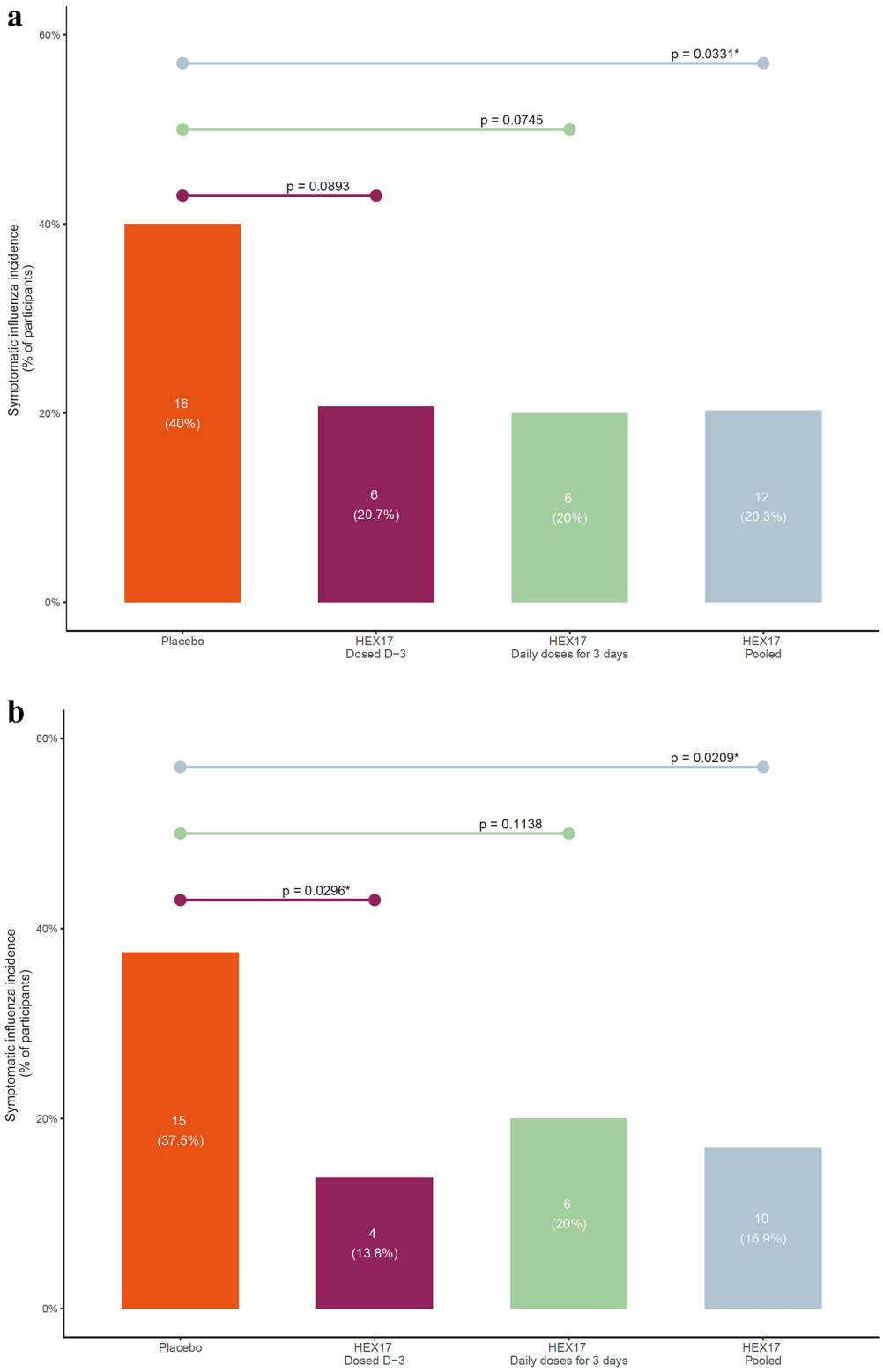
Fig. 1 Trial profile. One participant had reported headaches which started pretreatment and continued until the day of challenge with the influenza virus. Headache appears on the symptom questionnaire; including this participant would have distorted the result, so this participant was withdrawn from the study. *PP* per protocol set, *SAF* safety analysis set

Table 1 Demographic characteristics (safety analysis set)

	Treatment arm				
	Placebo (*N* = 41)	**Single-dose HEX17 (*N* = 31)**	**Daily HEX17 (*N* = 32)**	**Pooled HEX17 (*N* = 63)**	**All (*N* = 104)**
Sex, *n* (%)					
Male	27 (65.9)	22 (71.0)	23 (71.9)	45 (71.4)	72 (69.2)
Female	14 (34.1)	9 (29.0)	9 (28.1)	18 (28.6)	32 (30.8)
Age (years)					
Mean (SD)	31.05 (8.82)	30.32 (7.06)	31.22 (6.79)	30.78 (6.88)	30.88 (7.67)
Median (Q1, Q3)	27.0 (24.0, 37.0)	29.0 (26.0, 34.0)	28.5 (27.5, 35.0)	29.0 (26.0, 34.0)	28.0 (25.0, 36.0)
Min, max	20.0, 51.0	21.0, 48.0	22.0, 48.0	21.0, 48.0	20.0, 51.0
Ethnicity, *n* (%)					
Hispanic/Latino	2 (4.9)	2 (6.5)	1 (3.1)	3 (4.8)	5 (4.8)
Not Hispanic/Latino	39 (95.1)	29 (93.5)	31 (96.9)	60 (95.2)	99 (95.2)
Race, *n* (%)					
White	33 (80.5)	22 (71.0)	21 (65.6)	43 (68.3)	76 (73.1)
Black or African American	4 (9.8)	5 (16.1)	0	5 (7.9)	9 (8.7)
Asian	1 (2.4)	1 (3.2)	3 (9.4)	4 (6.3)	5 (4.8)
Other	3 (7.3)	3 (9.7)	6 (18.8)	9 (14.3)	12 (11.5)
Multiple	0	0	2 (6.3)	2 (3.2)	2 (1.9)

Max maximum, *min* minimum, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

(20.3%) participants in the placebo and pooled HEX17 arms, respectively (− 19.7% absolute decrease; 95% confidence interval [CI] − 38.0 to − 1.3; $p = 0.0331$) (Fig. 2a). The symptomatic influenza infection incidence (as determined by RT-qPCR) was similar between the single-dose HEX17 (6/29 [20.7%] participants) and daily HEX17 (6/30 [20.0%] participants) arms, but did not individually reach statistical significance in comparison to placebo, (single-dose HEX17 versus placebo: − 19.3% absolute decrease; 95% CI − 40.5 to 1.9; $p = 0.0893$; daily HEX17 versus placebo: − 20.0% absolute decrease; 95% CI − 40.9 to 0.9; $p = 0.0745$). The incidence of symptomatic influenza infection, as determined by viral culture, was significantly reduced in the pooled HEX17 arm compared with placebo; infection was reported in 15/40 (37.5%) participants in the placebo arm and 10/59 (16.9%) participants in the pooled HEX17 arm (− 20.6%; 95% CI − 35.5% to − 5.6%; $p = 0.0209$). Symptomatic influenza infection determined by viral culture was reported in 4/29 (13.8%) and 6/30 (20.0%) participants from the single-dose and daily HEX17 arms, respectively. Notably, the decrease in symptomatic influenza infection determined


a
60%
40%
20%
0%
Symptomatic influenza incidence
(% of participants)
p = 0.0331*
p = 0.0745
p = 0.0893
16
(40%)
6
(20.7%)
6
(20%)
12
(20.3%)
Placebo
HEX17
Dosed D−3
HEX17
Daily doses for 3 days
HEX17
Pooled
b
60%
40%
20%
0%
Symptomatic influenza incidence
(% of participants)
p = 0.0209*
p = 0.1138
p = 0.0296*
15
(37.5%)
4
(13.8%)
6
(20%)
10
(16.9%)
Placebo
HEX17
Dosed D−3
HEX17
Daily doses for 3 days
HEX17
Pooled

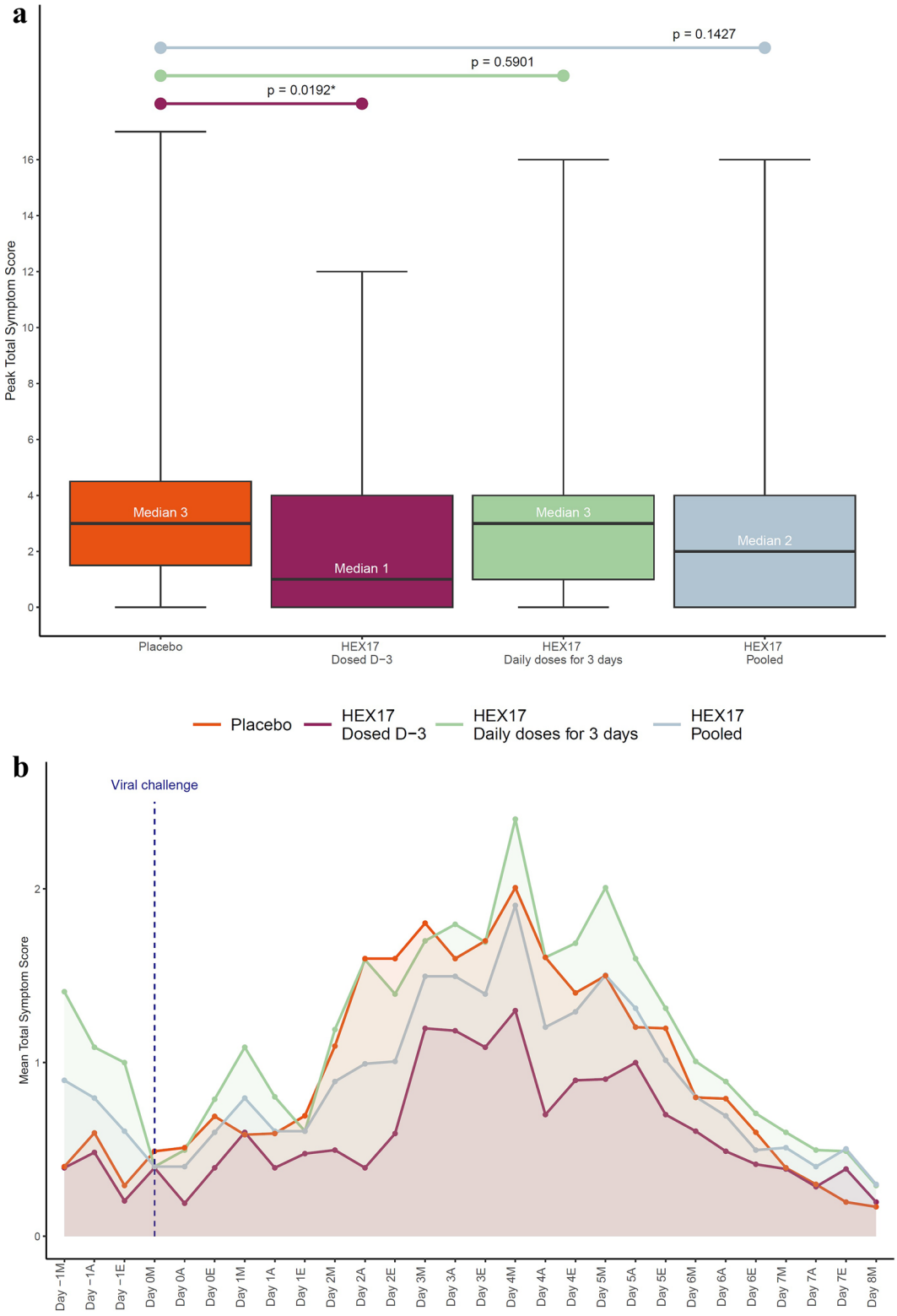
◂**Fig. 2** Symptomatic and detectable/quantifiable influenza incidence (per protocol set). **a** The incidence of symptomatic influenza infection as detected by RT-qPCR on nasal samples. Symptomatic influenza infection was defined as 2 detectable RT-qPCR measurements on 2 or more independent nasal samples over 2 days from day 1 up to the planned discharge from quarantine (day 8), and any symptoms of grade ≥ 2 at a single time point. **b** The incidence of symptomatic influenza infection as detected by viral culture on nasal samples. Symptomatic influenza infection was defined as 1 laboratory-confirmed culturable influenza infection starting from day 1 up to the planned discharge from quarantine (day 8, am), and any symptoms of grade ≥ 2 at a single time point. The numbers in the bars in both graphs are number of participants (% of participants in dose arm). Chi-square *p* values are presented for both graphs. **p* < 0.05. *D-3* day − 3, *RT-qPCR* reverse transcriptase quantitative polymerase chain reaction

by viral culture in the single-dose HEX17 arm was statistically significant versus placebo (− 23.7%; 95% CI − 43.3 to − 4.1; $p = 0.0296$) (Fig. 2b). Therefore, these results indicate that HEX17 can reduce the incidence of symptomatic influenza infection.

The other primary outcome of this study was to evaluate if HEX17 reduced the severity of influenza infection symptoms, using the participant-reported TSS. Although the median peak TSS in the pooled HEX17 arm was lower compared with the placebo, this difference was not statistically significant (2.00 [Q1 0.00, Q3 4.00] versus 3.00 [Q1 1.50, Q3 4.50], respectively; $p = 0.1427$) (Fig. 3a). The median peak TSS in the single-dose HEX17 arm was significantly lower than the placebo (1.00 [Q1 0.00, Q3 4.00]; $p = 0.0192$), while the daily HEX17 arm had a similar median peak TSS to the placebo (3.00 [Q1 1.00, Q3 4.00]; $p = 0.5901$]. Similar trends were observed with the secondary outcome severity measures. The mean TSS over time curves are shown in Fig. 3b. The median TSS-AUC was not statistically significantly different between the pooled HEX17 and placebo arms (2.44 [Q1 0.00, Q3 11.29] versus 3.73 [Q1 1.23, Q3 8.88], respectively; $p = 0.1307$). However, the median TSS-AUC in the single-dose HEX17 arm (0.11 [Q1 0.00, Q3 7.05]) was significantly lower than placebo ($p = 0.0124$). The daily HEX17 arm had a similar median TSS-AUC to the placebo (4.05 [Q1 1.32, Q3 12.03]; $p = 0.6190$) (Table 2). Grade 2 or higher symptoms were reported in 21/40 (52.5%) participants in the placebo arm; this incidence was significantly lower in the pooled HEX17 arm (19/59 [32.2%] participants; $p = 0.0434$) and the single-dose HEX17 arm (8/29 [27.6%] participants; $p = 0.0385$). Median duration of grade 2 symptoms was low in both placebo (1.00 h, [Q1 0.00, Q3 9.09]) and pooled HEX17 arms (0.00 h, [Q1 0.00, Q3 25.17]) (Table 3). Together, these findings suggest that prophylactic HEX17 therapy can reduce the severity of influenza symptoms.

The mean viral load curves from day 1 to day 8 as measured by RT-qPCR and viral culture are presented in Fig. 4a and b, respectively. The median VL-AUC, measured by RT-qPCR, was significantly decreased in the pooled HEX17 arm versus placebo (9.39 [Q1 6.38, Q3 26.38] versus 17.24 [Q1 6.39, Q3 34.03] $\log_{10}$ copies/mL × day, respectively; $p = 0.0382$). The median VL-AUC assessed by viral culture was significantly decreased in all HEX17 dose arms versus the placebo. For placebo, this was 4.79 (Q1 3.28, Q3 13.32) $\log_{10}$ $TCID_{50}$/mL × day, compared to 3.30 (Q1 3.28, Q3 6.31) for the pooled HEX17 arm ($p = 0.0110$), 3.30 (Q1 3.28, Q3 6.31) for the single-dose HEX17 arm ($p = 0.0429$), and 3.29 (Q1 3.28, Q3 6.57) for the daily HEX17 arm ($p = 0.0163$). The median peak viral load was significantly decreased in the pooled HEX17 arm and the single-dose HEX17 arm versus placebo. For placebo this was 2.40 (Q1 0.5, Q3 4.63) $\log_{10}$ $TCID_{50}$/mL × day compared to 0.50 (Q1 0.5, Q3 3.27) for the pooled HEX17 arm ($p = 0.0336$), 0.50 (Q1 0.5, Q3 3.25) for the single-dose HEX17 arm ($p = 0.0453$), and 0.50 (Q1 0.5, Q3 3.50) for the daily HEX17 arm ($p = 0.0884$) (Table 4). Together, these data show that HEX17 administration may be associated with a reduction in influenza viral load.

HEX17 had an acceptable safety profile and was generally well tolerated by participants. There were no treatment-emergent SAEs, AEs leading to study discontinuation, or deaths (Table 5). Of the participants that received HEX17 in the period prior to viral challenge, there were four transitory, unsolicited treatment-emergent AEs, occurring in three patients (C-reactive protein increase, anosmia, forced


a
p = 0.1427
p = 0.5901
p = 0.0192*
Peak Total Symptom Score
Median 3
Median 1
Median 3
Median 2
Placebo
HEX17 Dosed D−3
HEX17 Daily doses for 3 days
HEX17 Pooled
Placebo
HEX17 Dosed D−3
HEX17 Daily doses for 3 days
HEX17 Pooled
b
Viral challenge
Mean Total Symptom Score
Day −1M
Day −1A
Day −1E
Day 0M
Day 0A
Day 0E
Day 1M
Day 1A
Day 1E
Day 2M
Day 2A
Day 2E
Day 3M
Day 3A
Day 3E
Day 4M
Day 4A
Day 4E
Day 5M
Day 5A
Day 5E
Day 6M
Day 6A
Day 6E
Day 7M
Day 7A
Day 7E
Day 8M

◂**Fig. 3** Severity of influenza symptoms by total clinical symptoms score (per protocol set). Influenza symptom severity was measured by TSS, a graded symptom scoring system, ranging from 0 (no symptoms) to 3 (quite bothersome most or all of the time, and it stops me participating in activities). TSS was completed by participants 3 times a day from day 1 up to the planned discharge from quarantine (day 8). **a** Median peak TSS scores. Error bars show minimum and maximum values. **b** Mean TSS scores recorded from day − 1 to the planned discharge from quarantine (day 8). One-sided Wilcoxon rank-sum *p* values are presented for both figures. **p* < 0.05. *A* afternoon, *AUC* area under the curve, *D-3* day − 3, *E* evening, *M* morning, *TSS* total symptoms score

expiratory volume decrease, myalgia), all of which were mild. There was no evidence of systemic exposure of HEX17, with all plasma concentrations of HEX17 below the limit of quantification.

DISCUSSION

Results from this phase II, proof-of-concept study demonstrate that prophylactic HEX17 can reduce the incidence of symptomatic influenza infection and the severity of influenza symptoms in healthy participants following viral challenge. HEX17 also reduced the influenza viral load. HEX17 had an acceptable safety profile and was well tolerated by participants.

Detectable influenza by RT-qPCR was reported in 25/40 (62.5%) participants in the placebo arm following viral challenge. This infectivity rate was consistent with historical data using the same influenza challenge [25] and indicates that the virus performed as expected. Symptomatic influenza infection was reported in 16/40 (40.0%) participants in the placebo arm.

HEX17 has previously been shown to confer protection against viral challenge in animal models [20, 22, 23]. This study has shown that HEX17 confers protection against the influenza virus in humans; therefore, these data support that the animal findings are translatable into humans. Notably, it was observed that prophylactic therapy with HEX17 resulted in an approximately 50% relative reduction in the incidence of symptomatic influenza in the pooled HEX17 arm compared with placebo as assessed by RT-qPCR; this relative reduction was even greater when infection incidence was assessed by viral culture. Although the PCR-based method is more rapid and sensitive than culture-based methods, it does not differentiate between active replicating and non-viable viruses, making live culture more suitable for identifying infectivity [26]. Such a decrease in the incidence of symptomatic influenza caused by natural infection, particularly in at-risk populations, could lead to a clinically significant reduction in the morbidity, mortality and costs associated with the viral infection. As well as reducing symptomatic influenza incidence, prophylactic HEX17 also had beneficial effects on the symptom severity associated with influenza infection; both the pooled HEX17 and single-dose HEX17 arms had significantly fewer participants with symptoms scored grade 2 or higher compared with placebo.

Both dosing regimens used in this study (single-dose and daily HEX17) demonstrated a beneficial effect and indicate that dosing less frequently than daily may be effective in protecting against influenza. Despite the trends observed, this study was not adequately powered to compare the HEX17 arms independently, or address detailed differences in pharmacodynamics, but future studies investigating different dosing regimens are warranted.

There are limitations to this proof-of-concept study, including the relatively small sample sizes in each arm, which means that variability in baseline characteristics may have impacted results. The study was powered to compare the pooled HEX17 arms to the placebo arm, so any comparisons of the single or daily dose HEX17 and placebo, or between each of the HEX17 treatment arms, were exploratory only. In addition, only one influenza strain was tested. Some symptoms recorded in the TSS (e.g. sneezing, sore throat, malaise/tiredness, headache) are not specific to influenza infection, meaning this measure may have lacked sensitivity in this study. The exploratory analysis of the cytokines and/or chemokines produced in response to HEX17 dosing was inconclusive, owing to the timing of nasal sample collection. Each of these aspects can be addressed in subsequent studies,

Table 2 Area under the curve over time of total symptoms score (per protocol set)

	Treatment arm			
	Placebo (*N* = 40)	**Single-dose HEX17 (*N* = 29)**	**Daily HEX17 (*N* = 30)**	**Pooled HEX17 (*N* = 59)**
TSS-AUC				
Mean (SD)	7.72 (10.62)	4.85 (7.80)	8.83 (11.37)	6.88 (9.90)
Median (Q1, Q3)	3.73 (1.23, 8.88)	0.11 (0.00, 7.05)	4.05 (1.32, 12.03)	2.44 (0.00, 11.29)
HEX17 vs. placebo				
Between-mean comparison	NA	− 2.87	1.11	− 0.85
95% CI	NA	− 7.51, 1.78	− 4.17, 6.39	− 4.99, 3.30
H–L estimation of the location shift: median of differences	NA	− 1.58	0.29	− 0.86
95% CI	NA	− 3.76, 0.00	− 2.01, 2.92	− 2.79, 0.58
One-sided Wilcoxon rank-sum *p* value	NA	0.0124	0.6190	0.1307

CI confidence interval, *H–L* Hodges–Lehmann, *NA* not applicable, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation, *TSS-AUC* total symptoms score–area under the curve

Table 3 Participants with grade 2 or higher symptoms (per protocol set)

	Treatment arm			
	Placebo (*N* = 40)	**Single-dose HEX17 (*N* = 29)**	**Daily HEX17 (*N* = 30)**	**Pooled HEX17 (*N* = 59)**
Participants with symptoms scored grade 2 or higher				
n (%)	21 (52.5)	8 (27.6)	11 (36.7)	19 (32.2)
95% CI	37.5, 67.1	14.7, 45.7	21.9, 54.5	21.7, 44.9
Difference in incidence of symptoms scored grade 2 or higher (HEX17 vs. placebo)				
Difference (%)	NA	− 24.9	− 15.8	− 20.3
95% CI	NA	− 47.4, − 2.5	− 39.0, 7.3	− 39.8, − 0.8
Chi-square *p* value	NA	0.0385	0.1882	0.0434
Duration of grade 2 or higher clinical symptoms (h)				
Mean (SD)	14.17 (28.93)	17.03 (34.16)	23.07 (41.90)	20.10 (38.08)
Median (Q1, Q3)	1.00 (0.00, 9.09)	0.00 (0.00, 1.00)	0.00 (0.00, 30.67)	0.00 (0.00, 25.17)
Duration of TSS of 2 or more clinical symptoms, with at least 2 body systems (h)				
Mean (SD)	30.69 (43.99)	26.93 (48.01)	41.72 (51.84)	34.45 (50.12)
Median (Q1, Q3)	0.50 (0.00, 65.35)	0.00 (0.00, 24.67)	13.60 (0.00, 84.32)	1.00 (0.00, 73.70)

CI confidence interval, *NA* not applicable

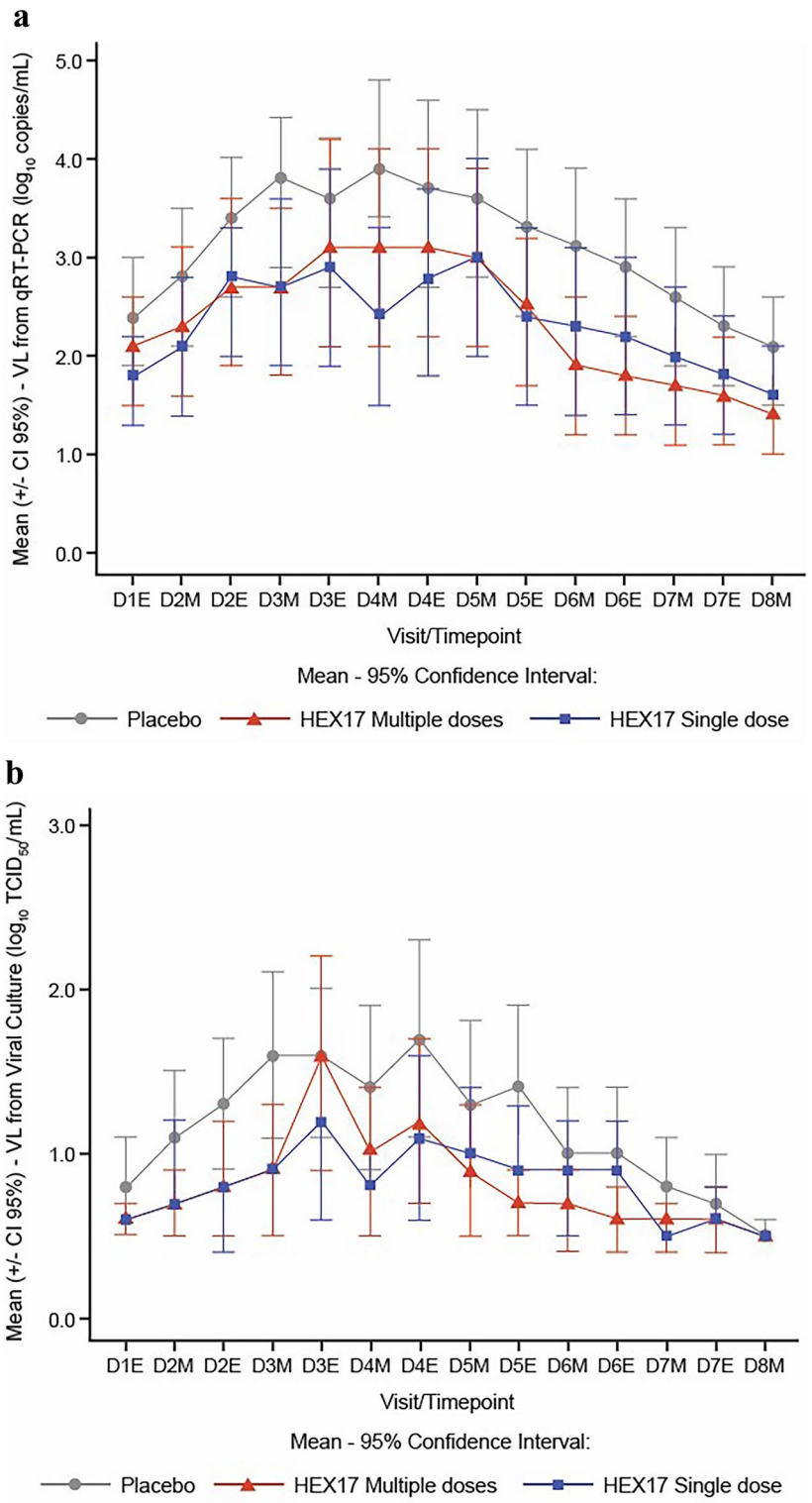


Fig. 4 Mean influenza viral load (per protocol set). **a** Mean (±95% CI) VL as detected by qRT-PCR. **b** Mean (±95% CI) VL as detected by VC. *CI* confidence interval, *D-3* day −3, *E* evening, *M* morning, *qRT-PCR* quantitative reverse transcriptase polymerase chain reaction, $TCID_{50}$ tissue culture infective dose (50%), *VC* viral culture, *VL* viral load

Table 4 Median viral load and peak viral load (per protocol set)

	Treatment arm			
	Placebo (*N* = 40)	**Single-dose HEX17 (*N* = 29)**	**Daily HEX17 (*N* = 30)**	**Pooled HEX17 (*N* = 59)**
VL-AUC by RT-qPCR (log_{10} copies/mL × day)				
Median (Q1, Q3)	17.24 (6.39, 34.03)	8.60 (6.40, 26.28)	9.96 (6.37, 26.38)	9.39 (6.38, 26.38)
H–L estimation of the location shift: median of difference (vs placebo)	NA	− 1.61	− 1.85	− 1.79
95% CI	NA	− 10.03, 0.37	− 10.04, 0.01	− 9.33, 0.01
One-sided Wilcoxon rank-sum *p* value	NA	0.1369	0.0304	0.0382
VL-AUC by viral culture (log_{10} $TCID_{50}$/mL × day)				
Median (Q1, Q3)	4.79 (3.28, 13.32)	3.30 (3.28, 6.31)	3.29 (3.28, 6.57)	3.30 (3.28, 6.31)
H–L estimation of the location shift: median of difference (vs placebo)	NA	− 0.04	− 0.04	− 0.04
95% CI	NA	− 4.30, 0.00	− 4.35, 0.00	− 2.50, 0.00
One-sided Wilcoxon rank-sum *p* value	NA	0.0429	0.0163	0.0110
VLPEAK by RT-qPCR (log_{10} copies/mL)				
Median (Q1, Q3)	6.04 (0.97, 7.79)	3.42 (0.97, 6.86)	4.04 (0.97, 7.21)	3.65 (0.97, 6.94)
H–L estimation of the location shift: median of difference (vs placebo)	NA	− 0.73	− 0.49	− 0.60
95% CI	NA	− 2.64, 0.00	− 2.18, 0.00	− 2.00, 0.00
One-sided Wilcoxon rank-sum *p* value	NA	0.0767	0.0716	0.0423
VLPEAK by viral culture (log_{10} $TCID_{50}$/mL)				
Median (Q1, Q3)	2.40 (0.50, 4.63)	0.50 (0.50, 3.25)	0.50 (0.50, 3.50)	0.50 (0.50, 3.27)
H–L estimation of the location shift: median of difference (vs placebo)	NA	0.00	0.00	0.00
95% CI	NA	− 1.54, 0.00	− 1.25, 0.00	− 1.04, 0.00
One-sided Wilcoxon rank-sum *p* value	NA	0.0453	0.0884	0.0336

CI confidence interval, *H–L* Hodges–Lehmann, *NA* not applicable, *Q1* first quartile, *Q3* third quartile, *RT-qPCR* reverse transcriptase quantitative polymerase chain reaction, *$TCID_{50}$* tissue culture infective dose (50%), *VL-AUC* area under the viral load–time curve, *VLPEAK* peak viral load

Table 5 Overall summary of adverse events (safety analysis set)

	Treatment arm		
	Placebo ($N = 41$)	Single-dose HEX17 ($N = 31$)	Daily HEX17 ($N = 32$)
Any solicited AEs[a]	29 (70.7) [137]	22 (71.0) [106]	29 (90.6) [200]
Any unsolicited AEs	17 (41.5) [25]	9 (29.0) [14]	10 (31.3) [13]
Any unsolicited TEAEs	17 (41.5) [25]	8 (25.8) [13]	9 (28.1) [12]
Mild–grade 1	14 (34.1) [20]	7 (22.6) [11]	9 (28.1) [12]
Moderate–grade 2	4 (9.8) [4][b]	2 (6.5) [2][c]	0
Severe–grade 3	1 (2.4) [1][b]	0	0
Treatment-related unsolicited TEAEs	2 (4.9) [3][d]	1 (3.2) [1][e]	1 (3.1) [2][f]
Challenge virus-related TEAEs	6 (14.6) [7]	4 (12.9) [4]	2 (6.3) [2]
Any unsolicited TEAE leading to study discontinuation	0	0	0
Any unsolicited TESAEs	0	0	0
Any unsolicited AE leading to death	0	0	0
TEAEs by system organ class preferred term			
Infections and infestations[g]	5 (12.2) [5]	3 (9.7) [4]	3 (9.4) [3]
Investigations[h]	2 (4.9) [2]	3 (9.7) [5][h]	3 (9.4) [4]
Blood and lymphatic system disorders[i]	3 (7.3) [4]	2 (6.5) [2]	1 (3.1) [1]
Musculoskeletal and connective tissue disorders[j]	3 (7.3) [3]	1 (3.2) [1]	2 (6.3) [2]
General disorders and administration site conditions[g]	3 (7.3) [3]	0	0
Eye disorders[g]	1 (2.4) [1]	1 (3.2) [1]	0
Gastrointestinal disorders[k]	2 (4.9) [2]	0	0
Injury, poisoning and procedural complications[g]	2 (4.9) [2]	0	0
Nervous system disorders[g]	1 (2.4) [1]	0	1 (3.1) [1]
Respiratory, thoracic and mediastinal disorders[g]	2 (4.9) [2]	0	0
Skin and subcutaneous tissue disorders[g]	0	0	1 (3.1) [1]

Data are presented as number of participants (percentage of participants) [number of events]. TEAEs were classified as treatment-related if they were deemed at least possibly related to HEX17/placebo

AE adverse event, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event

[a]List of solicited AEs: bleeding nose, burning sensation, pain or irritation of the nose, loss of taste or smell, sensation of needing to sneeze, sneezing and unpleasant taste

[b]In the placebo arm, there were four grade 2 TEAEs (lymphadenopathy, pain in extremity, diarrhoea and rhabdomylosis; in one patient each), and one grade 3 TEAE (toothache)

[c]In the single-dose HEX17 arm, two participants had grade 2 TEAEs (aspartate aminotransferase increased and neutropenia)

[d]Possibly related: electrocardiogram t-wave biphasic, headache, sinus pain

[e]Probably related: forced expiratory volume decreased

[f]Possibly related: C-reactive protein increased. Probably related: anosmia

[g]All AEs classified as mild–grade 1

[h]All AEs classified as mild–grade 1, aside from one moderate–grade 2 incidence of aspartate aminotransferase increase in the single-dose HEX17 arm

Table 5 continued

[i]All AEs classified as mild–grade 1, aside from one moderate–grade 2 incidence of lymphadenopathy in the placebo arm, and one incidence of moderate–grade 2 neutropenia in the single-dose HEX17 arm

[j]All AEs classified as mild–grade 1, aside from one moderate–grade 2 incidence of rhabdomylosis in the placebo arm

[k]All AEs classified as mild–grade 1, aside from one moderate–grade 2 incidence of diarrhoea and one grade 3 incidence of toothache in the placebo arm

now that proof-of-concept efficacy data are available.

Despite the availability of vaccines and antiviral drugs, viral RTIs continue to have a devastating impact. The HEX17 mechanism of action should mean that limitations associated with vaccines and antiviral drugs—namely their specificity to a particular virus strain [8] or the emergence of viral resistance [18, 19]—are largely avoided. Therefore, HEX17 may provide effective prophylactic treatment for vulnerable populations, such as individuals at risk of infection-induced exacerbations of conditions including chronic obstructive pulmonary disease (COPD), bronchiectasis and asthma [4] or in immune-suppressed patients in whom respiratory viral infections may lead to complications [3]. The broad-spectrum nature of HEX17 means it could be efficacious for prevention of various viral infections.

CONCLUSION

Given the promising efficacy and safety data from this study, HEX17 represents a viable candidate to progress into further clinical studies. Although this study focused on influenza virus, HEX17 is anticipated to have broad-spectrum antiviral effects based on its interaction with sialic acid. This is supported by work in animal models, where in addition to various influenza strains [20, 22], HEX17 also protected against SARS-CoV-2 [22] and respiratory syncytial virus [24]. Therefore, future clinical studies exploring the efficacy of HEX17 against a broader panel of viruses will be of great interest.

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Data Availability. Data will be shared in accordance with applicable guidelines. The data are not publicly available to share, but Pneumagen Ltd can provide descriptive data in table form. Requests should be made to the corresponding author.

Declarations

Conflict of Interest. Geoff Kitson, Lindsey Cass, Douglas Thomson, Brigitte Köhn are contracted by Pneumagen Ltd. Alessandra Bisquera, Marion Byford, Andrew Catchpole, David Howat, Nicholas Noulin were previously contracted to Pneumagen Ltd.

Ethical Approval. The protocol for this study was approved by South Central—Berkshire B Research Ethics Committee (REC reference 22/SC/0223), and the study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent to voluntarily participate in the investigation was obtained from all participants, and investigators were responsible for ensuring all participants understood the informed consent form (ICF). Participants were aware that they could withdraw from the study at any time, for any reason, and without prejudice to their future medical care. Participants consented to dissemination and publication of data from the study, with the assurance that all data would be handled in accordance with local data protection law.

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