A first-in-human clinical study of a new SP-B and SP-C enriched synthetic surfactant (CHF5633) in preterm babies with respiratory distress syndrome

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ABSTRACT
Objective CHF5633 (Chiesi Farmaceutici S.p.A., Parma, Italy) is the first fully synthetic surfactant enriched by peptide analogues of two human surfactant proteins. We planned to assess safety and tolerability of CHF5633 and explore preliminary efficacy.

Design Multicentre cohort study.

Patients Forty infants from 27+0 to 33+6 weeks gestation with respiratory distress syndrome requiring fraction of inspired oxygen (FiO2) ≥0.35 were treated with a single dose of CHF5633 within 48 hours after birth. The first 20 received 100 mg/kg and the second 20 received 200 mg/kg.

Outcome measures Adverse events (AEs) and adverse drug reactions (ADRs) were monitored with complications of prematurity considered AEs if occurring after dosing. Systemic absorption and immunogenicity were assessed. Efficacy was assessed by change in FiO2 after dosing and need for poractant-alfa rescue.

Results Rapid and sustained improvements in FiO2 were observed in 39 (98%) infants. One responded neither to CHF5633 nor two poractant-alfa doses. A total of 79 AEs were experienced by 19 infants in the 100 mg/kg cohort and 53 AEs by 20 infants in the 200 mg/kg cohort. Most AEs were expected complications of prematurity. Two unrelated serious AEs occurred in the second cohort. One infant died of necrotising enterocolitis and another developed RSV bronchiolitis after discharge. The single ADR was an episode of transient endotracheal tube obstruction following a 200 mg/kg dose. Neither systemic absorption, nor antibody development to either peptide was detected.

Conclusions Both CHF5633 doses were well tolerated and showed promising clinical efficacy profile. These encouraging data provide a basis for ongoing randomised controlled trials.

Trial registration number ClinicalTrials.gov NCT01651637.

INTRODUCTION
Respiratory distress syndrome (RDS) remains a leading cause of morbidity in preterm babies.1 Surfactant replacement therapy has become standard of care in RDS management.2,3 Comparative trials show superiority of natural, animal-derived surfactants over protein-free synthetic surfactants due to the presence of surfactant proteins SP-B and SP-C.4 A fully synthetic surfactant would have potential advantages such as no dependence on animal sources and less batch-to-batch variability.5 Animal experiments suggest that synthetic surfactants containing both peptides are superior to single peptide surfactants.6 CHF5633 is a new fully synthetic surfactant preparation consisting of the phosphatidylcholine and phosphatidylglycerol, enriched by peptide analogues of both human surfactant proteins SP-B and SP-C. When suspended in saline the final preparation consists only phospholipids.

What is already known on this topic?
► Randomised trials have confirmed superiority of natural, animal-derived surfactants containing proteins, over synthetic surfactants comprised only phospholipids.
► New generation surfactants that contain peptides mimicking effects of surfactant proteins have shown promise but are not yet widely accepted.

What this study adds?
► This first-in-human trial of synthetic surfactant CHF5633, containing peptide analogues of two surfactant proteins, shows that it was well tolerated without unexpected adverse effects.
► CHF5633 is similar in volume and appearance to poractan-tifa and appears to work as effectively.
Accordingly, following consultation with regulatory agencies and ethics committees, the study was designed to recruit premature neonates with ‘mild to moderate’ RDS who would be less likely to have other comorbidities and who would respond readily to rescue with other surfactants, if required.

This study aimed to investigate the safety and tolerability of intratracheal administration of CHF5633 in preterm babies. Two different doses (100 mg/kg and 200 mg/kg) were evaluated in terms of adverse events (AEs), adverse drug reactions (ADRs), haematology and biochemistry values, incidence of comorbidities, extent of systemic exposure to protein analogues and any potential immune response. Effects of CHF5633 on oxygenation, ventilatory requirements and need for rescue surfactant was assessed to explore efficacy.

**METHODS**
This was a first-in-human, single-escalating dose per-cohort study on administration of CHF5633. The trial was conducted in compliance with the Declaration of Helsinki and current guidelines for Good Clinical Practice after approval by regulatory authorities in each participating country and the ethical review boards for each institution and prior registration (ClinicalTrials.

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**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>100 mg/kg cohort (n=20)</th>
<th>200 mg/kg cohort (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>29.6 (2.0)</td>
<td>29.6 (1.9)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1274 (398)</td>
<td>1364 (416)</td>
</tr>
<tr>
<td>5 min Apgar</td>
<td>8.5 (8–9.5)</td>
<td>8 (7–8.5)</td>
</tr>
<tr>
<td>Gender male</td>
<td>11 (55%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>18 (90%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>Antenatal antibiotics</td>
<td>11 (55%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>FiO₂ predose</td>
<td>0.47 (0.16)</td>
<td>0.52 (0.13)</td>
</tr>
<tr>
<td>Time to treatment (hour)</td>
<td>7 (4–23)</td>
<td>5 (3–16.5)</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD) and n (%). Median (IQR) is reported for Apgar score and time to treatment. FiO₂, fraction of inspired oxygen.
Table 2 Patient sequence, individual characteristics, adverse events and outcomes

<table>
<thead>
<tr>
<th>Treatment date</th>
<th>Country</th>
<th>Age R (hours)</th>
<th>FiO</th>
<th>Sex</th>
<th>BW (g)</th>
<th>GA (week)</th>
<th>Laboratory abnormalities</th>
<th>Initial MV</th>
<th>CPAP</th>
<th>Adverse events</th>
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</tr>
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<td>6 days</td>
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<td>3 days</td>
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<td>3 days</td>
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1 ▌Na, hyponatraemia; ▌K, hypokalaemia; ▌SBR, hyperbilirubinaemia; ▌WCC, leucocytosis; ▌BG, leucopenia; ▌Na, hypoglycaemia; ▌CRP, elevated C reactive protein; ▌plats, thrombocytopenia; CPAP, continuous positive airways pressure; ET, endotracheal; INSURE, Intubation-SURfactant-Extubation; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PV1, periventricular leucomalacia; SVT, supraventricular tachycardia. Column 2 shows sequence of recruitment by country and site. GER-Germany; CZE-Czech Republic. Site number according to instutions of authors. Age R, treatment age; FiO, fraction of inspired oxygen required just prior to dosing. Airways pressure (CPAP) to maintain preductal pulse oximeter oxygen saturation (SpO₂) in the range 90%–95%. They required a normal cranial ultrasound scan and their clinician considered that surfactant was indicated. Infants were ineligible if they had already received surfactant, were already in another study, had a major congenital malformation, if there was a history of maternal drug/alcohol abuse, a clinical suspicion of pneumonia.

or sepsis, a 5 min Apgar score ≤3, a history of ruptured membranes of ≥3 weeks, or if seizures or pneumothoraces were detected before enrolment. The study was unusual in recruiting infants from whom, although for one dose, usual treatment was withheld. It was anticipated that a single-centre study would be prohibitively slow; therefore 40 babies were enrolled from 12 centres in three European countries, with careful coordination to control recruitment. The first infant was treated on 3 October 2012 and the last completed follow-up on 23 January 2015. Two groups of 20 infants were treated. The first cohort was given 100 mg/kg of CHF5633 (1.25 mL/kg) and the second cohort 200 mg/kg (2.5 mL/kg), administered by bolus via an endotracheal tube with a short period of manual/mechanical ventilation. No infant could receive more than one dose of CHF5633. Failure of response was defined as fall in FiO₂ <0.10 to maintain SpO₂ 90%-95% within an hour after treatment. Treatment failures were rescued with either 100 mg/kg or 200 mg/kg poractant-alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy). All infants could receive further doses of poractant-alfa as necessary. Decisions around premedication for intubation, positioning for surfactant administration, modes and duration of ventilatory support as well as weaning protocols were left to individual participating centres.

Safety and tolerability
A Safety Monitoring Board (SMB) was established comprising the principal investigator from each site and an independent neonatologist. The SMB reviewed the safety profile of CHF5633 in the week following administration and provided authorisation to continue. The first four babies in each cohort were recruited individually and recruitment stopped until progress to 7 days was reviewed. The subsequent 16 babies in each cohort were recruited in groups of four before SMB review. Safety and efficacy assessments were performed in the 24 hours following CHF5633 administration (at 0.5 hour, 1 hours, 3 hours, 6 hours, 12 hours and 24 hours), in the following 6 days (at days 2, 3 and 7) and in the follow-up period (at days 10 and 28, and at 36 weeks’ postmenstrual age). FiO₂, SpO₂, ventilator settings and blood pressure were monitored. Haematological and biochemical indices were collected at baseline, 24 hours and between 5 days and 10 days postdose. Data on all predefined expected neonatal comorbidities and deviations from expected normal values in haematological/biochemical indices were recorded as AEs and reviewed by the SMB for expectedness, severity and potential relatedness to study medication.

Evidence of systemic absorption and immunogenicity
Blood concentrations of SP-B and SP-C analogues were measured before, and 3 hours and 24 hours post-treatment using dried blood spots. SP-C concentrations were determined using validated HPLC-MS/MS methods (Accelera, Milan, Italy). Immunogenicity was assessed using 1 mL blood obtained 4–12 weeks after CHF5633 administration. IgG antibodies to peptides were assayed by titration versus positive control (SGS Life Science Services, Wavre, Belgium).

Efficacy
Efficacy was evaluated by examining response to CHF5633 in terms of changes in SpO₂, FiO₂, mean airway pressure (MAP), peak inspiratory pressure if ventilated and positive end-expiratory pressure at specified time points. Duration of mechanical ventilation was defined as time until first extubation lasting >24 hours. Durations of CPAP and supplemental oxygen were recorded. Bronchopulmonary dysplasia (BPD) was defined as need for supplemental oxygen to maintain SpO₂ ≥90% at 36 weeks’ postmenstrual age. The number of non-responders requiring rescue surfactant was recorded.

Statistical analysis
Because of the exploratory nature of this study, no formal power calculation was performed. Twenty babies in each cohort were deemed sufficient for reaching useful preliminary conclusions. Categorical variables are described using summary statistics, frequency count and percentages. Continuous variables are summarised using mean, SD, or median, IQR as appropriate.

RESULTS
A total of 75 babies were consented and 40 were dosed between October 2012 and November 2014 (figure 1). Baseline demographic data are shown in table 1. Date of patient recruitment, centre, AEs and outcomes for each participating infant is shown in table 2.
Treatment with either dose of CHF5633 resulted in a rapid improvement in oxygenation with corresponding decrease in the need for supplemental oxygen and a reduced MAP (figure 2). Ten babies were extubated to CPAP immediately following CHF5633 administration and never ventilated. A further four were ventilated for <30 min. The median (IQR) duration of mechanical ventilation was 0.70 (0.30–0.91) days in the 100 mg/kg cohort and 0.30 (0.02–0.95) days in the 200 mg/kg cohort. The median (range) duration of CPAP was 14.4 (4.9–29.9) days in the 100 mg/kg cohort and 6.7 (4.0–14.1) in the 200 mg/kg cohort. There was only one case of failure to respond to CHF5633, in the first cohort. This 32-week gestation 1490 g baby was treated at 37 hours of age, and had two further 200 mg/kg doses of poractant-alfa, but still without improvement in oxygenation. A pneumothorax was diagnosed 5 hours after study treatment; this was drained and the infant responded to high-frequency oscillation. In 2 of the 40 infants a repeat dose of poractant-alfa was required as part of ongoing management (table 2). Four babies developed BPD, two from each dosing cohort.

Systemic absorption/immunogenicity

No quantifiable concentrations of the SP-C analogue were detected in any blood sample at any time point. It was impossible to assess absorption of the SP-B analogue because in low quantities it is difficult to measure. No immune response antibodies were detected to either peptide from 36 available samples.

Adverse events

In total, 132 AEs were recorded, 79 experienced by 19 (95%) infants in the 100 mg/kg cohort and 53 by 20 (100%) infants in the 200 mg/kg cohort. Most events were expected clinical problems of preterm infants such as mild hyponatraemia. The investigators assessed and classified the laboratory values as normal, abnormal/not significant or abnormal/clinically significant. Most abnormalities were assessed as abnormal/not significant. Comorbidities before and after treatment are summarised in table 3 and are typical of issues in preterm babies.

Adverse drug reactions

Only one ADR was reported. Following administration of 200 mg/kg to a 27+2 week, 1075 g infant there was temporary obstruction of the endotracheal tube for 10–15 s, which resolved quickly with no clinical consequences. The baby was extubated after 4 min, with a transient rise in FiO2 to 80% but reducing over the following 3 hours on CPAP, and had echocardiographic evidence of transient pulmonary hypertension. Neither allergic reactions, nor any other events potentially caused by the drug, were reported.

Serious adverse events

Two SAEs were reported, both occurring in the 200 mg/kg cohort: an episode of fulminant necrotising enterocolitis occurring 13 days after CHF5633 in an infant of 28 weeks’ gestation who died at 21 days, and an episode of postdischarge viral bronchiolitis considered as serious due to need for rehospitalisation. Neither SAE was considered related to the study drug.

DISCUSSION

This first-in-human study shows that a CHF5633 dose of either 100 mg/kg or 200 mg/kg was well tolerated, without detectable systemic absorption, and resulted in prompt and sustained improvements in respiratory function. CHF5633 is the first synthetic surfactant to contain analogues of both SP-B and SP-C. It was developed to be similar to poractant-alfa (Curosurf) in terms of its low dose volume, appearance and simple handling requirements. It requires refrigeration, and only a short period of warming in the hand prior to administration, and the volume to deliver a 200 mg/kg dose is 2.5 mL/kg. Following a single intratracheal dose the brisk response allowed rapid

<table>
<thead>
<tr>
<th>Table 3 Comorbidities and complications of prematurity</th>
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<tbody>
<tr>
<td>100 mg/kg cohort (n=20)</td>
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<tr>
<td>Before n (%)</td>
</tr>
<tr>
<td>Any comorbidity</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
</tr>
<tr>
<td>Sepsis unspecified</td>
</tr>
<tr>
<td>Low fibrinogen</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Hypoaalbuminaemia</td>
</tr>
<tr>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
</tr>
<tr>
<td>Intraobserver haemorrhage</td>
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<tr>
<td>Cerebral haemorrhage</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Pneumothorax</td>
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<tr>
<td>Pulmonary interstitial emphysema</td>
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</tbody>
</table>

NA, not applicable.
extubation, including the use of the INtubation-SURfactant-Ex
tubation (INSURE) approach that is widely used with animal-de
derived surfactants. Apart from one patient, all infants showed an
immediate clinical response with a single dose.

The population selected for this study was reasonably stable
babies with RDS, deliberately chosen because of the relatively
low risk of complications to allow an informative safety and
tolerability assessment. They required surfactant, but were not
so unwell that there was insufficient time to obtain consent and
baseline investigations. Most were stable on CPAP, but with
increasing oxygen requirements. Such babies are scarce, there-
fore recruitment at multiple sites was needed to achieve the
required study population, even though this would be consid-
ered unusual for a phase I trial. The initial requirement to halt
after each enrolled subject made recruitment slow.

Despite careful selection of subjects, the majority still devel-
oped a range of comorbidities that needed to be analysed within
the context of what would normally be expected in a preterm
baby requiring surfactant. Only one death occurred; a case of
NEC considered a consequence of prematurity and unrelated
to CHF5633 treatment. The single episode of transient tube
obstruction was also considered a well recognised complication
of surfactant therapy. Neither allergic reactions nor other events
likely caused by the drug were reported. Lack of systemic expo-
sure and of specific immune response was also reassuring. The
overall rate of mortality, BPD, and their combination was low as
would be expected with this selected, relatively low-risk, preterm
population. These data are promising and randomised controlled
trials should now determine how CHF5633 performs in a larger
population including less mature and sicker infants (ClinTrials.gov
NCT02452476).

Baseline characteristics were similar in the two dosing cohorts,
although the predose FiO2 and MAP were slightly higher in the
second cohort, perhaps reflecting increasing confidence at
recruiting sicker babies. Statistical comparisons were not made
between dosing cohorts for this reason. Both doses were effica-
cious, resulting in sustained improvements in oxygenation that
occurred immediately after instillation. A median FiO2 of 0.21
was achieved within the first 24 hours of treatment. In terms of
respiratory support, a shorter duration of non-invasive venti-
lation was found in the 200mg/kg cohort despite them being
slightly worse at baseline. This might reflect a greater improve-
ment of lung mechanics with higher doses of CHF5633, although
this needs to be tested in randomised trials.

Only one other protein-containing synthetic surfactant, luci-
nactant had reached the stage of being used in comparative
clinical trials in preterm neonates. Lucinactant contains a high
concentration of the synthetic peptide sipatustide (KL-4),
designed to have similar activity to SP-B, but no SP-C peptide.
Lucinactant is a viscous fluid requiring warming to 44°C then
vigorous shaking until it becomes a free-flowing suspension.
The approved treatment dose volume is 5.8 mL/kg. In contrast,
CHF5633 is more akin to poractant-alfa in terms of its handling
requirements and the observed clinical response parallels in trials
of existing animal-derived surfactants.

Current thinking about optimal management of RDS is to aim
where possible to avoid mechanical ventilation. Administering
surfactant without mechanical ventilation is gaining acceptance
as a strategy to minimise lung injury. Fourteen babies in this
study were extubated within 30 min of CHF5633 administration,
including 10 where clinicians employed the INSURE technique.
Future comparative trials of CHF5633 should therefore explore
all potential modes of administration including minimally invasive
methods.

Animal-derived surfactants require pooling of material from
multiple animals. Quality control is stringent, but many stake-
holders would be reassured if the theoretical risks of infection
could be avoided. There is a drive towards ensuring that children of
all ages have access to age-appropriate formulations. This involves
tailoring administration to the needs of the child and optimising
pharmaceutical quality of the product. By ensuring that the volume
to be administered is small and avoiding use of animal products, the
development of CHF5633 addresses these needs. Ideally it would
also prove to be more efficacious in some circumstances. Studies in
a sheep model of acute lung injury suggest that CHF5633 may
be more resistant to inactivation than poractant-alfa. This raises
the possibility that it may have advantages in severe disease, or in
other causes of respiratory failure associated with surfactant inhibi-

In conclusion, CHF5633 is the first synthetic surfactant to
contain analogues to both surfactant proteins, SP-B and SP-C.
This first-in-human study shows that it was well tolerated by
preterm babies with moderate RDS and raised no safety
concerns, with a promising clinical efficacy profile. Larger trials
are warranted and if these produce similar results it is likely that
this will herald a new era of synthetic surfactant treatment.

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Contributors S recruited patients, helped with data analysis, drafted the initial
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helped with manuscript editing and approved the final manuscript and was part of
the safety monitoring board. S, P, S, G recruited the most patients and approved the
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preparation and approved the final manuscript. S recruited patients, was on the safety monitoring board, helped with manuscript
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the study, assisted with data analysis and approved the final manuscript. F and V
helped with data presentation and analysis and approved the final manuscript.
F conceptualised and designed the study, assisted with data analysis and approved the final manuscript.
F and V conceptualised and designed the study, assisted with data analysis and approved the final manuscript.

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S.p.A., sponsor of the study. DGS has previously acted in an advisory capacity for
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MAT serves as a consultant to Chiesi Farmaceutici S.p.A. (Italy) with respect to the

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