**Phase-I trial of a new synthetic surfactant (CHF5633) in preterm babies with respiratory distress syndrome**

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**Clinical Trials Registry:** ClinicalTrials.gov [NCT01651637](https://clinicaltrials.gov/show/NCT01651637).

**Abstract**

**Objective**  CHF5633 (Chiesi Farmaceutici) 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/ setting** Multicentre cohort study

**Participants** 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 twenty received 100 and the second twenty 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 was assessed. Efficacy was assessed by change in FiO2 after dosing and need for poractant-alpha rescue.

**Results**  Rapid and sustained improvements in FiO2 were observed in 39 (98%) infants. One responded neither to CHF5633 nor two poractant-alpha 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 200mg/kg dose. There was no systemic absorption, nor antibody development to either peptide.

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

**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 upon 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 phospholipids phosphatidylcholine and phosphatidylglycerol, enriched by peptide analogues of both human surfactant proteins SP-B and SP-C. When suspended in saline the final phospholipid concentration is identical to that of poractant alfa (Curosurf®), at 80 mg/mL and a similar small dosing volume can be used. Intra-tracheal administration of CHF5633 to preterm newborn rabbits results in a marked improvement in lung expansion which is no different from that of poractant alfa.7 The structure of the peptide analogues has been modified to be resistant to oxidative injury and may improve resistance to inactivation.8,9 Preterm lambs with RDS treated with CHF5633 have better lung and brain injury scores than those treated with poractant alfa. 10 Based on these results it was anticipated that CHF5633 would be at least as effective as natural surfactants in the treatment of babies with RDS.

Surfactant treatment is normally administered as an endotracheal fluid bolus to infants. Conducting a phase-I study in adult volunteers was not appropriate. Accordingly, following consultation with regulatory agencies and ethics committees, the study was designed to recruit premature neonates with “moderate” RDS who would be less likely to have other comorbidities and who would respond readily to rescue treatment with other surfactants, if required.

This study aimed to investigate the safety and tolerability of intra-tracheal administration of CHF5633 in preterm babies. Two different doses (100 and 200 mg/kg) were evaluated in terms of adverse events (AEs), adverse drug reactions (ADRs), haematology and biochemistry values, incidence of co-morbidities, extent of systemic exposure to SP-B and SP-C analogues, and any potential immune response. Furthermore, effects of CHF5633 on oxygenation, ventilatory requirements, and the need for rescue surfactant were 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.gov [NCT01651637](https://clinicaltrials.gov/show/NCT01651637)). Written consent was sought before birth, or soon after, giving parents the maximum time to make an informed decision before enrollment.

Infants were eligible in the first 48 hours after birth if born between 27+0 and 33+6 weeks’ gestation, having clinical and radiological findings of RDS, and needing a fraction of inspired oxygen concentration (FiO2) ≥0·35 on continuous positive airways pressure (CPAP) to maintain pre-ductal 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-minute 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, albeit 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 co-ordination to control recruitment. The first infant was treated on October 3rd, 2012 and the last completed follow up on January 23rd, 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 as a bolus via an endotracheal tube with a short period of manual or mechanical ventilation. No infant could receive more than one dose of CH5633. 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 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 and weaning protocols were left to individual centres.

**Safety and Tolerability**

A Safety Monitoring Board (SMB) was established comprising an 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 seven 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, 1, 3, 6, 12, 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). Data were collected on FiO2, SpO2, ventilator settings, and blood pressure. Haematological and biochemical indices were collected at baseline, 24 hours, and between 5 and 10 days post dose. Data on all pre-defined expected neonatal co-morbidities 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 at 3 and 24 hours post treatment using dried blood spots. SP-C protein concentrations were determined using validated HPLC-MS/MS methods (Accelera, Milan, Italy). Immunogenicity was assessed using 1mL blood obtained 4-12 weeks after CHF5633 administration. IgG antibodies to peptides were assayed by titration versus positive control serum (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 (PIP) if ventilated and positive end-expiratory pressure (PEEP) at specified time-points. Duration of mechanical ventilation was defined as time until first extubation lasting more than 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’ post-menstrual 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, standard deviations, or median, interquartile range (IQR) as appropriate.

**RESULTS**

A total of 75 babies were consented and 40 were dosed between October 2012 and November 2014 (Fig 1). Baseline demographic data are shown in Table 1. Date of patient recruitment, centre, adverse events, 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 (Fig 2). Ten babies were extubated to CPAP immediately following CHF5633 administration and never ventilated. A further four were ventilated for <30 minutes. 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 a period of high-frequency oscillation. In two of the forty infants a repeat dose of poractant alfa was required as part of on-going management (Table 2). Four babies developed BPD, two from each dosing cohort.

**Systemic Absorption/ Immunogenicity:** No quantifiable concentrations of SP-C analogue were detected in any blood sample at any time point. It was impossible to assess absorption of 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 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. Co-morbidities before and after treatment are summarised in Table 3 and are typical of issues in preterm babies.

**Adverse Drug Reactions:** Only 1 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 seconds, which resolved quickly with no clinical consequences. The baby was extubated after 4 minutes, 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 post-discharge viral bronchiolitis considered as serious due to the need for re-hospitalization. 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 intra-tracheal dose the brisk response allowed rapid extubation, including the use of the IN-SUR-E approach (Intubate-Surfactant-Extubate) that is widely used with animal-derived surfactants.11 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 therefore recruitment at multiple sites was needed to achieve the required study population, even though this would be considered 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 developed a range of co-morbidities 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 with a 200mg/kg dose 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 exposure 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.12 These data are promising and a planned phase-II trial should now determine how CHF5633 performs in a larger population including less mature and sicker infants (ClinTrials.gov [NCT02452476](https://clinicaltrials.gov/show/NCT02452476)).

Baseline characteristics were similar in the two dosing cohorts, although the pre-dose 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 efficacious, 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 ventilation was found in the 200 mg/kg cohort despite them being slightly worse at baseline. This might reflect a greater improvement of lung mechanics with higher doses of CHF5633, although this needs to be tested in randomised trials.

Only one other protein-containing synthetic surfactant, Lucinactant had reached the stage of being used in comparative clinical trials in preterm neonates.13,14 Lucinactant contains a high concentration of the synthetic peptide sinapultide (KL-4), designed to have similar activity to SP-B, but no SP-C peptide. Lucinactant is a viscous fluid requiring warming to 44ºC 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 that observed in trials of existing animal-derived surfactants.15,16

Current thinking about optimal management of RDS is to aim where possible to avoid mechanical ventilation.17 Administering surfactant without mechanical ventilation is gaining acceptance as a strategy to minimise lung injury.18,19 Fourteen babies in this study were extubated within 30 minutes of CHF5633 administration, including 10 where clinicians employed the IN-SUR-E technique. Future comparative trials of CHF5633 should therefore explore all potential modes of administration including minimally invasive techniques.

Animal-derived surfactants require pooling of material from multiple animals. Quality control is stringent, but many stakeholders 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.20 This raises the possibility that it may have advantages in severe disease, or in other causes of respiratory failure associated with surfactant inhibition.21-24

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**.**

**What is already known on this topic:**

1. Randomised trials have confirmed superiority of natural, animal-derived surfactants containing proteins, over synthetic surfactants comprised only of phospholipids.
2. New generation surfactants that contain peptides mimicking effects of surfactant proteins have shown promise but are not yet widely accepted.

**What this study adds?**

1. This phase-1 trial of synthetic surfactant CHF5633, containing peptide analogues of two surfactant proteins, shows that it was well tolerated without unexpected adverse effects.
2. CHF5633 is similar in volume and appearance to poractant alfa and appears to work as effectively.

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**Contributors Statement:**

Dr Sweet recruited patients, helped with data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Prof Turner recruited patients, helped with manuscript editing and approved the final manuscript and was part of the safety monitoring board. Professors Straňák, Plavka, Singer, Goelz recruited the most patients and approved the final manuscript and were on the safety monitoring board. Dr Clarke recruited patients and helped with manuscript preparation and approved the final manuscript. Prof Stenson recruited patients, was on the safety monitoring board, helped with manuscript editing and approved the final manuscript. Drs Fabbri and Varoli conceptualised and designed the study, assisted with data analysis and approved the final manuscript. Dr Piccino and Santoro helped with data presentation and analysis and approved the final manuscript. Prof Speer conceptualised and designed the study, recruited patients, assisted with data analysis and approved the final manuscript.

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**Conflict of interest statement:** Laura Fabbri, Debora Santoro, Annalisa Piccinno and Guido Varoli are full employees of Chiesi Farmaceutici S.p.A., sponsor of the study. The remaining authors have no conflict of interest to declare. Dr Sweet has previously acted in an advisory capacity for Chiesi Pharmaceuticals UK. Mark Turner serves as a consultant to Chiesi Farmaceutici S.p.A. (Italy) with respect to the development of CHF5633 on behalf of the University of Liverpool without deriving any personal benefit from this consultancy. All authors received clinical research funds from Chiesi Farmaceutici S.p.A. as site investigators for this study.

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**Table 1: Baseline characteristics**

|  |  |  |
| --- | --- | --- |
|  | **100 mg/kg cohort** **(n=20)** | **200 mg/kg cohort** **(n=20)** |
| Gestational age (wks)  | 29·6 (2·0) | 29·6 (1·9) |
| Birthweight (g) | 1274 (398) | 1364 (416) |
| 5 min Apgar | 8·5 (8– 9·5) | 8 (7–8·5) |
| Gender male | 11 (55%) | 10 (50%) |
| Antenatal steroids | 18 (90%) | 19 (95%) |
| Antenatal antibiotics | 11 (55%) | 9 (45%) |
| FiO2 pre-dose  | 0.47 (0.16) | 0.52 (0.13) |
| Time to treatment (h) | 7 (4–23) | 5 (3–16·5) |

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, adverse events and outcomes**

| **Treatment Date** | **Country** | **Age Rx (hrs)** | **FiO2** | **Sex** | **BW (g)** | **GA (wk)** | **Laboratory abnormalites** | **Initial MV** | **CPAP** | **Adverse events** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **100mg/kg cohort** |  |  |  |  |  |  |  |  |  |  |
| 2012-10-03 | UK2 | 2 | 0.42 | M | 1505 | 30 | ↓Na ↑SBR | 22 hrs | 6 days |  |
| 2013-01-24 | UK 2 | 24 | 0.57 | M | 1160 | 31 | ↑SBR | 5 hrs | 5 days |  |
| 2013-02-16 | UK 1 | 5 | 0.38 | F | 900 | 27 | ↓Na ↑WCC | 3 hrs | 39 days |  |
| 2013-03-01 | UK 1 | 4 | 0.70 | M | 1660 | 31 | ↑Na ↓K | 17 hrs | 3 days |  |
| 2013-04-19 | UK 1 | 4 | 0.40 | F | 1010 | 28 | ↓Na | INSURE | 11 days |  |
| 2013-04-26 | UK 1 | 24 | 0.45 | F | 1270 | 30 | None | 21 hrs | none |  |
| 2013-05-21 | GER8 | 8 | 0.44 | M | 805 | 28 | ↓WCC ↑SBR ↑BG | 18 hrs | 47 days |  |
| 2013-06-11 | UK 1 | 6 | 0.40 | F | 1243 | 31 | ↓Na ↓K | INSURE | 9 days |  |
| 2013-06-27 | GER 7 | 15 | 0.45 | F | 988 | 28 | ↑SBR | 1 day | 29 days | PDA |
| 2013-06-29 | UK 6 | 4 | 0.36 | M | 1100 | 27 | None | 6 hrs | 6 days | IVH d5 PVL d28. |
| 2013-07-08 | GER 10 | 4 | 0.40 | M | 2250 | 33 | ↑SBR | 14 hrs | 2 days |  |
| 2013-07-31 | UK 2 | 5 | 0.44 | F | 1995 | 32 | ↑CRP | 17 hrs | none |  |
| 2013-09-20 | UK 1 | 9 | 0.36 | F | 832 | 28 | ↓Na | INSURE | 36 days |  |
| 2013-09-22 | GER 10 | 1 | 0.35 | M | 1490 | 32 | None | 16 hrs | 3 days | Non Responder, PTX Rescue Poractant x 2 |
| 2013-10-18 | GER 8 | 37 | 0.45 | F | 1490 | 33 | ↑HR | 4 days | 6 days | SVT day 20 |
| 2013-11-06 | UK 1 | 3 | 0.68 | M | 1140 | 28 | ↓Na | 8 hrs | 23 days | PDA |
| 2013-11-22 | UK 1 | 41 | 0.40 | M | 843 | 28 | ↓Na ↑SBR | 3 hrs | 55 days |  |
| 2013-12-15 | GER 7 | 24 | 1.0 | M | 1371 | 29 | ↑SBR | 21 hrs | 19 days | PDA |
| 2014-01-08 | UK 1 | 10 | 0.36 | M | 1580 | 31 | ↓Na ↑SBR ↓plats  | INSURE | 8 days |  |
| 2014-01-30 | UK 5 | 22 | 0.36 | F | 850 | 27 | None | 10 days | 53 days | PDA2nd dose Poractant day 5 |
| **200mg/kg cohort** |  |  |  |  |  |  |  |  |  |  |
| 2014-02-21 | GER 7 | 2 | 0.50 | F | 1050 | 30 | ↑SBR | 12 hrs | 3 days | Apnoeic episode |
| 2014-03-23 | CZE3 | 4 | 0.80 | M | 1100 | 27 | ↑SBR | 10 hrs | 48 days | PDA |
| 2014-04-12 | UK 6 | 4 | 0.75 | M | 1685 | 30 | ↓plats | 19 hrs | 13 days |  |
| 2014-05-09 | CZE4 | 3 | 0.50 | M | 1070 | 28 | ↑SBR | INSURE | 4 days | Apnoeic episode |
| 2014-05-26 | CZE4 | 26 | 0.38 | F | 1800 | 32 | None | INSURE | 4 days |  |
| 2014-05-27 | CZE4 | 20 | 0.38 | F | 1075 | 27 | None | INSURE | 16 days | Episode of ET tube blockage, PDA |
| 2014-06-01 | CZE3 | 2 | 0.60 | F | 1590 | 30 | ↑SBR | INSURE | 5 days |  |
| 2014-06-01 | CZE3 | 3 | 0.40 | F | 1490 | 30 | ↑SBR | INSURE | 4 days |  |
| 2014-06-25 | CZE3 | 2 | 0.45 | M | 1130 | 28 | ↑SBR ↓Na | 40 mins | 26 days |  |
| 2014-06-26 | CZE3 | 25 | 0.51 | M | 1060 | 28 | ↑SBR↓Na | INSURE | 26 days |  |
| 2014-06-27 | GER 10 | 5 | 0.60 | M | 975 | 28 | None | 14 hrs | 12 days | PDA, PTX,2nd dose Poractant day 2, NEC day 13 - DIED  |
| 2014-07-28 | UK e | 5 | 0.63 | M | 1690 | 33 | None | 20 hrs | 1 day |  |
| 2014-08-29 | UK 5 | 5 | 0.55 | F | 870 | 27 | None | INSURE | 33 days |  |
| 2014-09-15 | CZE4 | 33 | 0.70 | F | 2080 | 32 | ↑SBR | INSURE | 4 days |  |
| 2014-09-26 | UK 1 | 13 | 0.36 | F | 876 | 31 | ↑SBR, ↓Na | INSURE | 8 days |  |
| 2014-09-26 | CZE3 | 10 | 0.50 | M | 1306 | 30 | None | 1 hr | 12 days |  |
| 2014-10-21 | CZE3 | 2 | 0.55 | M | 1720 | 31 | ↑SBR | 1 hr | 7 days |  |
| 2014-11-11 | UK 1 | 29 | 0.41 | M | 1688 | 30 | None | 23 hrs | 7 days |  |
| 2014-11-18 | UK 6 | 5 | 0.48 | F | 2190 | 32 | None | 5 hrs | 2 days |  |
| 2014-11-21 | UK 5 | 6 | 0.41 | F | 840 | 28 | None | 3 days | 41 days |  |

Glossary of terms: ↓Na – Hyponatraemia; ↓K – Hypokalaemia; ↑SBR – Hyperbilirubinaemia; ↑WCC – Leucocytosis; ↓WCC – leucopenia; ↑BG – Hyperglycaemia; ↑CRP – Elevated C-reactive Protein; ↓plats – thrombocytopenia. PDA – Patent Ductus Arteriousus; IVH – Intraventricular Haemorrhage; PVL- Periventricular Leucomalacia; SVT-Supraventricular tachycardia; ET- endotracheal; INSURE – Intubate-SURfactant-Extubate; NEC- Necrotising enterocolitis. Column 2 shows sequence of recruitment by country and site. UK-United Kingdom; GER-Germany; CZE-Czech Republic. Site number according to instutions of authors. Age Rx- Treatment age FiO2 – Fraction of inspired oxygen required just prior to dosing

**Table 3: Co-morbidities and complications of prematurity**

|  |  |  |
| --- | --- | --- |
|  | **100mg/kg cohort (n=20)** | **200mg/kg cohort (n=20)** |
|  | **Before n (%)** | **After n (%)** | **Before n (%)** | **After n (%)** |
| Any co-morbidity | 5 (25%) | 15 (75%) | 2 (10%) | 13 (65%) |
| Anaemia | 0 | 0 | 1 (5%) | 0 |
| Tachycardia | 1 (5%) | 0 | 0 | 0 |
| Patent Ductus Arteriosus | 1 (5%) | 4 (20%) | 0 | 2 (10%) |
| Bacterial Sepsis | 1 (5%) | 1 (5%) | 0 | 0 |
| Sepsis unspecified | 0 | 1 (5%) | 0 | 2 (10%) |
| Low fibrinogen | 0 | 0 | 1 (5%) | 0 |
| Hyperglycaemia | 1 (5%) | 2 (10%) | 0 | 0 |
| Hypoglycaemia | 1 (5%) | 1 (5%) | 1 (5%) | 0 |
| Hypoalbuminaemia | 0 | 0 | 1 (5%) | 0 |
| Hyponatraemia | 1 (5%) | 8 (40%) | 0 | 3 (15%) |
| Necrotising Enterocolitis | 0 | 1 (5%) | 0 | 1 (5%) |
| Hyperbilirubinaemia | 0 | 5 (25%) | 0 | 10 (50%) |
| Intraventricular haemorrhage | 0 | 1 (5%) | 0 | 0 |
| Cerebral haemorrhage | 0 | 1 (5%) | 0 | 0 |
| Periventricular leukomalacia | 0 | 1 (5%) | 0 | 0 |
| Bronchopulmonary Dysplasia | NA | 2 (10%) | NA | 2 (10%) |
| Pneumothorax | 0 | 1 (5%) | 0 | 1 (5%) |
| Pulmonary Interstitial Emphysema | 0 | 0 | 0 | 1 (5%) |

**Abbreviations:** AE – Adverse event; ADR – Adverse Drug Reaction; FiO2 – Fraction of inspired oxygen; MAP – mean airway pressure; NA – not applicable; RDS – Respiratory distress syndrome; SPO2 – oxygen saturation by pulse oxymetry; SMB- Safety Monitoring Board; SP-B – Surfactant protein B; SP-C – Surfactant protein C.

Figure 1 legend

Fig 1. Patients’ Disposition

Figure 2 legend

Fig 2. Fraction of inspired oxygen in all babies and corresponding Mean Airway Pressure in those undergoing mechanical ventilation the 24 hours after CHF5633 in the two dosing cohorts. Bars represent SD. Data offset slightly to improve clarity. Inset shows same data over first 3 hours to illustrate speed of onset of action of effect

Figure 1. Patients’ disposition

75 consented neonates

Screening failure (n=35) (All occurred before dosing)

Reason for failure:

* parents’ consent withdrawn (n=1)
* condition placing the neonate at undue risk (investigator decision) (n=1)
* eligibility criteria not met (n=33):

1 gestational age out of range

12 no clinical and radiological signs of RDS

7 out of initial 48-hour treatment period

11 surfactant treatment not needed

19 FiO2 <0.35

3 cranial ultrasound not normal

3 surfactant treatment prior to study entry

1 maternal drug/alcohol abuse

\* 10 neonates with more than 1 eligibility criteria not met

40 treated neonates

1 neonate died (NEC)

20 neonates survived to discharge

19 neonates survived to discharge

Cohort B:

20 neonates treated with 200mg/kg

Cohort A:

20 neonates treated with 100 mg/kg

Figure 2.



