21 May 2015
EMA/CHMP/288706/2015
Procedure Management and Committees Support Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Voncento

HUMAN COAGULATION FACTOR VIII / HUMAN VON WILLEBRAND FACTOR

Procedure no: EMEA/H/C/002493/P46/010.1

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Rapporteur's assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Voncento

Procedure no.: EMEA/H/C/002493

Marketing authorisation holder (MAH): CSL Behring

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|---|---|
| **Rapporteur:** | Prof. Dr. Pieter de Graeff |
| **Start of the procedure:** | 25 January 2015 |
| **Date of this report:** | 9 March 2015 |
| **Deadline for Rapporteur's AR:** | |
| **Deadline for CHMP member's comments:** | 12 March 2015 |
| **Date of the Rapporteur's final report:** | 16 March 2015 |
| **Responses to LoQ** | 10 April 2015 |
| **Rapporteur's Response-AR** | 20 April 2015 |
| **Deadline for CHMP member's comments:** | 12 May 2015 |
| **CHMP** | 21 May 2015 |

# Administrative information

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|---|---|
| Invented name of the medicinal product: | Voncento |
| INN (or common name) of the active substance(s): | Voncento contains human plasma derived coagulant FVIII/von Willebrand factor concentrate at a ratio of approximately 1:2.4 |
| MAH: | CSL Behring |
| Currently approved Indication(s) | the treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when DDAVP treatment alone is ineffective or contra-indicated, and for prophylaxis and treatment of bleeding events in patients with haemophilia A |
| Pharmaco-therapeutic group (ATC Code): | |
| Pharmaceutical form(s) and strength(s): | Powder and solvent for solution for injection (50 or 100 IU/ml FVIII) |
| Rapporteur:<br><br><br><br>Rapporteur's contact person:<br><br><br><br>Name of the Assessor: | **Name Prof. Dr. Pieter de Graeff**<br>Tel:<br>Fax:<br>Email:<br><br>**Name Willy Woldring**<br>Tel:<br>Fax:<br>Email: wh.woldring@cbg-meb.nl<br><br>**Name Dr. Babs O. Fabriek**<br>Tel:<br>Fax:<br>Email:bo.fabriek@cbg-meb.nl |
| Procedure Manager: | **Name: Antonio Cherchi**<br>Tel:<br>Fax:<br>Email: Antonio.Cherchi@ema.europa.eu |

# 1. Introduction

On 25 September 2014, the MAH submitted a final clinical study report CSLCT-BIO-09-64 for Voncento, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Voncento contains human coagulant FVIII/von Willebrand factor complex concentrate at a ratio of approximately 1:2.4 (100 IU/mL FVIII:C and approximately 240 IU/mL VWF:RCo).

Since 12 August 2013, Biostate has been licensed in the European Union under the trade name Voncento® for the treatment of hemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when DDAVP treatment alone is ineffective or contra-indicated, and for prophylaxis and treatment of bleeding events in patients with hemophilia A.

Regarding the paediatric use of Voncento in the paediatric population the SPC text (dd 12-08-2013) makes notice of the following:

- 4.2:
Paediatric population:
Dosing in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.
The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.
- 4.8:
Paediatric Population:
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

At the time of this Assessment, a procedure was ongoing in which data from pediatric study CSL-CT-08-52 was beingassessed, this involved 17 children with VWD. As part of this procedure an SPC update regarding the posology in children will becarried out.

This study was designed to comply with the CHMP guideline on the clinical investigation of human plasma-derived VWF products [CPMP/BPWG/220/02] the guideline on the Core SmPC for human plasma derived VWF [CPMP/BPWG/278/02] and Regulation (EC) no 1901/2006 of the European Parliament and of the council of 12/Dec/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, and Regulation (EC) No 726/2004. In addition, the study was designed to comply with the guideline on the role of PK in the development of medicinal products in the pediatric population EMEA/CHMP/EWP/147013/2004] and the note for guidance on clinical investigation of medicinal products in the paediatric population [CPMP/ICH/2711/99]. This study was subject to the Paediatric Investigational Plan (PIP) evaluation (EMEA-000312-PIP01-08).

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH has submitted a final clinical study report CSLCT-BIO-09-64 (an Open-Label, Multi-Centre Extension Study to Assess the Efficacy and Safety of Biostate® in Paediatric, Adolescent, and Adult Subjects with Von Willebrand Disease who Completed Clinical Studies CSLCT-BIO-08-52 or CSLCT-BIO-08-54).

**Assessor's comment**

This assessment report focusses on the extension of two pivotal studies carried out in VWD. Previously (November 2014) a request for extension of indication was submitted to the EMA (EMEA/H/C/002493/II/0008/G-EU/1/13/857/001-0044). In that report data from Studies CSLCT-BIO-08-52 or CSLCT-BIO-08-54 were discussed. In Study CSL-CT-08-52 17 children ≤12 years old with VWD were included, in study CSLCT-BIO-08-54, 3 adolescents (age 15-16 years) were included.

This assessment report solely focusses on the paediatric data from the extension study CSLCT-BIO-08-64 (extension of CSLCT-BIO-08-52 or CSLCT-BIO-08-54).

## *2.2. Information on the pharmaceutical formulation used in the study*

The MAH states that the formulation of the study drug administered was similar to that licensed for commercial use.

**Assessor's comment**

Some parts of the documentation submitted by the MAH the investigational medicinal product is addressed as 'Biostate'. Throughout this assessment report Biostate is referred to as Voncento, since in the EU the trade name Voncento is applicable.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- Clinical study CSLCT-BIO-09-64

Twenty subjects were enrolled in this study of which:

- 3 children (<12 years)

- 2 adolescents (12- <18 years)

- 15 adults (≥18years)

The study was a open-label study to investigate the long-term efficacy and safety of Voncento in children, adolescents and adults with Von Willebrand disease (VWD) in whom treatment with a VWF product is required for prophylactic therapy, haemostatic control during surgery, or control of a non-surgical, spontaneous, or traumatic bleeding event.

### 2.3.2. Clinical study

### Clinical study CSLCT-BIO-09-64

### Description

The MAH has submitted an appendix to module 2.5, a study narrative and a full study report as part of this art 46 submission.

Subjects admitted to the described study have completed study CSLCT BIO-08-52 ("Assessment of Efficacy and Safety of Voncento in Paediatric [aged <12 years] Subjects with VWD") or study CSLCT-

BIO-08-54 ("Assessment of Efficacy and Safety of Voncento in Adolescent or Adult Subjects with VWD"). Visit 1 (Day 1) of this study coincided with the Final Visit of study CSLCT-BIO-08-52 or study CSLCT-BIO-08-54.

## Methods

### *Objective(s)*

Primary objectives:

- To assess the effectiveness of a prophylaxis regimen as compared to on-demand therapy with Voncento in preventing non-surgical bleeding (NSB) events.
- To assess the haemostatic efficacy of Voncento in subjects with (VWD) who require a (VWF) product to control an NSB event.

Secondary objectives:

- To collect long-term data on the safety of Voncento both as on-demand therapy to treat NSB events and as prophylactic therapy.
- To collect long-term data on haemostatic efficacy of Voncento for subjects who undergo surgical procedures during the study period.

### *Study design*

Open-label study to investigate the long-term efficacy and safety of Voncento in children, adolescents, and adults with von Willebrand disease (VWD) in whom treatment with a von Willebrand factor (VWF) product is required for prophylactic therapy, haemostatic control during surgery, or control of a non-surgical, spontaneous, or traumatic bleeding event.

### *Study population /Sample size*

This is an open-label extension study without a comparator group and with enrolment restricted to subjects completing either of two prior studies (studies CSLCT-BIO-08-52 or CSLCT-BIO-08-54); therefore no sample size estimate is warranted. The MAH expected to include approximately 26 subjects in this extension study, 20 subjects actually enrolled.

### *Treatments*

Voncento was administered intravenously as a bolus dose at a maximum infusion rate of 6 mL/min as tolerated by the subject. The dosage and treatment rationale was based on the Core SmPC for haemophilia A and VWD [CPMP/BPWG/1619/1999; CPMP/BPWG/278/02], as well as the data collected from previous efficacy clinical studies which have been conducted with Voncento in both haemophilia A and VWD subjects. The doses for spontaneous bleeding events and for surgical events were similar to the recommendations of Mannucci [2004], and were in accordance with international practice. Each subject's individual dose was determined by the investigator, based on the reason for use (ie, as prophylaxis, to treat a major bleeding, provide prophylaxis for surgery, etc.) (

Table 1).

**Table 1 Guideline for dosage**

**Table 1: Guidelines for dosage**

| Indication | Dose (IU/kg) | | Dose Frequency | Target FVIII/VWF (% or IU/dL) |
|---|---|---|---|---|
| | FVIII:C | VWF:RCo | | |
| NSBs | 12.5-25 | 25-50 | Initial | VWF peak level >50%, FVIII >30% |
| | 12.5 | 25 | Subsequent (every 12-24 h) | VWF/FVIII trough levels of >30% until bleeding stops (usually 2-4 days) |
| Prophylaxis | 12.5-20 | 25-40 | 1-3 times weekly | Trough >1% |
| Prophylaxis for menorrhagia | 12.5-25 | 25-50 | On days 1, 1 & 2, or 1, 2 & 3 per cycle | VWF/FVIII peak levels >30%, |
| Minor surgery | 30 | 60 | Daily | VWF/FVIII trough levels of >30% until healing is complete (usually 2-4 days) |
| Major surgery | 30-40 | 60-80 | Initial | VWF peak level >100%, FVIII >60% |
| | 15-30 | 30-60 | Subsequent (every 12-24 h) | VWF/FVIII trough levels of >50% until healing is complete (usually 5-10 days) |

FVIII = Factor VIII; FVIII:C = Factor VIII: coagulant activity; IU = international units; NSB = non-surgical bleeding; VWF = von Willebrand factor; VWF:RCo = von Willebrand factor: ristocetin cofactor.

The study contained 3 study-arms:

• Prophylaxis arm (Arm 1): Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 and received Voncento as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a Final Visit at Month 12.

• On-demand arm (Arm 2): Subjects who were not being treated on a set prophylaxis regimen with a VWF product at the time of study entry, and who required a VWF product for the treatment of NSB events (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Voncento as on-demand therapy for the treatment of NSB events.

• Arm 3: Subjects, who completed on-demand treatment in Arm 2 and who qualified to be switched to a set prophylactic regimen according to the pre-specified criteria given below, entered Arm 3 and started Voncento treatment as prophylaxis therapy for an additional 12 months. The set prophylaxis regimen was only to be commenced if the investigator believed that it was clinically justifiable for the subject, and was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period.

Subjects were assigned to "Prophylaxis" or "On-demand" treatment by the investigator at each 3-monthly visit. Subjects were allowed to switch the treatment at any time during the study at the discretion of the investigator.

***Outcomes/endpoints***

Primary efficacy endpoints included:

• Hemostatic Efficacy: Assessment of hemostatic efficacy by the subject and investigator will use the grading scale of Excellent, Good, Moderate, None.

o At Time of NSB Event: Where applicable, subject and/or investigator assessment of hemostatic efficacy at the time of each NSB event.

o Retrospective Subject Review: Subjects will perform a monthly retrospective self-assessment of hemostatic efficacy.

o Retrospective Investigator Review: Investigator assessment of hemostatic efficacy will be performed retrospectively at the visit occurring every third month.

• Any blood product transfusion requirements, and the number of treatments/units required to resolve any bleeding event.

• VWF:RCo/FVIII:C concentrates usage: number of infusions, IU/kg per dose, per event, per month, and per year.

• Assessment of blood loss during any surgical procedure using the grading scale of Less, Equivalent, More.

• An assessment of the number of spontaneous or traumatic NSB events on a monthly basis and overall.

***Statistical Methods***

Efficacy: No formal statistical tests were performed. Efficacy variables were summarised by treatment arm and overall. Continuous variables were summarised using descriptive statistics (number of non-missing values, arithmetic mean, standard deviation, minimum, 1$^{st}$ quartile, median, 3$^{rd}$ quartile, and maximum). Numbers and percentages are presented in frequency tables for categorical variables.

Safety: Voncento doses were summarised using descriptive statistics

## Results

***Recruitment/ Number analysed***

First subject enrolled on 08-10-2010 and last subject completed 28-03-2014.

Twenty subjects were enrolled in this study of which:

- 3 children (<12 years)

- 2 adolescents (12- <18 years)

- 15 adults (≥ 18years)

Prophylaxis treatment: 10 subjects (including 3 children for study CSCT-BIO-08-52)

On demand arm: 8 subjects, of which 1 adolescent

Prophylaxis and on-demand: 2 subjects (1 adolescent).

One subject in the on-demand arm did not receive any Voncento during this extension study and was therefore excluded from analysis populations used for efficacy and safety analyses

***Baseline data***

Baseline characteristics were retrieved form the previous studies (CSCT-BIO-08-52 and CSCT-BIO-08-54) as these data were not captured in the extension study. The baseline was defined as either the assessment on the final visit of the previous study or the assessment made at day 1 of this extension study.

The majority of the subjects in the prophylaxis arm were male (8 subjects), while the majority in the on-demand arm were female (5 subjects).

All 3 participating children (2 age 6 years, 1 age 9 years) were in the prophylaxis arm, mean age of all subjects in this arm 35.8 years. In the on-demand arm the mean age was 29,7 years. 2 subjects in on-demand and prophylaxis arm were male, age 16 and 40. One additional adolescent was 17 years old in the on-demand arm. All subjects were Caucasian.

Overall, 2 subjects (10.5%) had VWD of Type 1, 4 (21.1%) of Type 2A, and the remaining 13 (68.4%) of Type 3, with similar distributions in prophylaxis and on-demand arms. The 2 subjects in the prophylaxis & on-demand arm both had VWD of Type 2A (of which one adolescent). Two out of the 3 children in this study had VWD type 3 and one had VWD type 2A.

## *Efficacy results*

- ***Prophylaxis arm:***

Hemostatic Efficacy:
Nine subjects (90.0%) of the prophylaxis arm reported a total of 118 NSB events during the study, 96 of which required treatment; 1 adult subject had no bleeding events on the prophylaxis regimen. The median number of NSB events per subject was 8.0 (range of 0-33). The majority of these events were spontaneous (79.7%), minor (89.8%), mucosal (88.1%), and treated at home (81.4%). Seven subjects experienced a total of 12 major NSB events, including 4 subjects with a total of 5 major mucosal NSB events.

Haemostatic efficacy was assessed by the investigator for all 96 events treated with Voncento, as excellent or good and as moderate for 2 events (2.1%). The haemostatic efficacy of major NSB events was assessed as excellent for 5 events (41.7%), including 3 major mucosal events, and as good for 7 events (58.3%), including 2 major mucosal events. The subject's assessment of haemostatic efficacy of bleeding days was in line with the investigator's assessment.

VWF:RCo/FVIII:C concentrates usage:
In the prophylaxis arm, the median number of infusions was 108.5 (range: 19-406). The median dose per infusion was 42.75 IU VWF:RCo/kg (range: 28.49-85.79 IU/kg). The majority of bleeding events either required no Voncento treatment (18.6% of events) or only 1 infusion of Voncento (71.2%).

**Paediatrics:**
Hemostatic Efficacy:
In the prophylaxis arm, 58 of the 96 treated NSB events occurred in the 3 children, who therefore had a higher NSB frequency than the 7 adults in the prophylaxis arm. 42 occurred spontaneously, 16 by trauma.

The hemostatic efficacy for all these events was assessed by the investigator as either excellent (91.4%) or good (8.6%), with a higher proportion of assessments of excellent than in the total prophylaxis arm. The distribution of NSB events in children across bleeding types was similar compared with the total prophylaxis arm.

The 3-monthly hemostatic efficacy assessment by the investigator for the 3 children was excellent throughout, except for 2 assessments of good at Months 6 and 27. Similarly, the monthly assessment by the subject (or legal guardian) was excellent for each month with the exception of 2 assessments of good at Months 26 and 27.

VWF:RCo/FVIII:C concentrates usage:
The children in the prophylaxis arm received a median number of infusions of 71 (range 67-379). The median dose per infusion was 57,76 IU VWF:RCo/kg (range: 47,9- 86,28 IU/kg).

**Assessor's comment:**
The median number of NSB bleeds of the prophylaxis treatment was lower then in the on-demand arm, however it is difficult to draw conclusions on this since the study groups are small and diverse. The prophylaxis treatment shows similar results as in CSCLT-BIO-08-54 where the prophylaxis treatment was proven efficacious. The children in study CSCLT-BIO-09-64 showed higher NSB frequency on prophylaxis than the 7 adults but the hemostatic efficacy throughout the study was similar to the adults.

When compared with studies CSLCT-BIO-08-52 and CSLCT-BIO-08-54, the median number of NSB events per year in the 3 children (22.2 events) and the 7 adults (0.6 events) of the prophylaxis arm in this study was similar to corresponding median numbers in the prophylaxis arm of study CSLCT-BIO-08-52 (23.5 events) and of the adult/adolescent study CSLCT-BIO-08-54 (1.0 event).

The median dose per infusion received during prophylaxis by the 3 pediatric patients (2 age 6 years, 1 age 9 years) was 57,76 IU VWF:RCo/kg (range: 47,9- 86,28 IU/kg), and is higher then the dose in the adults (42.75 IU VWF:RCo/kg (range: 28.49-85.79 IU/kg).

Similarly, (data from the CSR of studies CSL-CT-08-52 and CSL-CT-08-54), the median average dose in the 4 children (then aged 2 to 8 years) who had received prophylaxis in the preceding paediatric study CSLCT-BIO-08-52 was 62.6 IU VWF:RCo/kg per infusion. In adults (n = 8, all aged > 18 years) on prophylaxis in the preceding study CSL-CT-08-54, the median average dose was 28.8 IU VWF:RCo/kg per infusion.

Although it is generally considered that young pediatric patients may require higher doses or shorter dose intervals, the company is asked to discuss the considerably higher dose per infusion used by the patients <12 years while on a prophylaxis regimen in study CSL-CT-08-52 and CSL-T-BIO-09-64 compared to adults.

***On-demand arm***

- Haemostatic Efficacy:

One subject of the on-demand arm did not experience any bleeding events during the study and was therefore excluded from analyses. The 7 subjects (including 1 adolescent) experienced a total of 402 NSB events, resulting in a median number of NSB events per subject of 35.0 (range of 1-151). The majority of the NSB events were spontaneous ([98.8%), minor (97.8%), and mucosal (98.0%). Three subjects experienced a total of 9 major NSB events, including 1 major mucosal NSB.
For each 3-month interval, the haemostatic efficacy as excellent for 35 events (45.5%), as good for 41 events (53.2%), and as moderate for the 1 remaining event (1.3%). The haemostatic efficacy of major NSB events was assessed as excellent for 6 events (66.7%) and as good for 3 events (33.3%) including the single major mucosal event in the on-demand arm (post-surgical oral bleeding). The haemostatic efficacy was assessed by the subject / legal guardian as excellent for 34.6% of the 107 assessed bleeding days, as good for 21.5%, and as moderate for 43.9% (associated with menstrual bleedings).

- VWF:RCo/FVIII:C concentrates usage:

Subjects in the on-demand arm had a median number of 17.0 infusions (range: 1-67) at a median dose of 54.57 IU VWF:RCo/kg per infusion (range: 40.00-85.97 IU/kg). 80,8% of the bleedings required no Voncento treatment and 10,7% only 1 infusion of Voncento (10.7%).

The haemostatic efficacy for the 1 adolescent subject in the on-demand arm was similar to that seen in the total on-demand arm. The adolescent in the on-demand arm had 34.0 infusions at a dose of 59.87 IU VWF:RCo/kg.

**Assessor's comment:**
The haemostatic efficacy of the adolescent in the on-demand arm was similar to the adults. In subjects treated on-demand, the median number of bleeding events per year in this study (11.1 events) was lower than in the on-demand arm of study CSLCT-BIO-08-54 (19.5 events). No children were included in the on-demand arm.

***Prophylaxis & on-demand arm***
Two subjects (1 adult and 1 adolescent) started with prophylaxis treatment, but were switched to on-demand treatment after 3 and 6 months. Hemostatic efficacy was assessed by the investigator for the 97 events treated with Voncento, as excellent (63.9%) or good (36.1%). The haemostatic efficacy of the 6 major NSB events was assessed as excellent (33.3%) or good (66.7%). The haemostatic efficacy assessed by the subjects was rated similarly. All treated NSB events resolved within 1 day.

The 2 subjects in the prophylaxis & on-demand arm received 62 and 65 infusions with an average Voncento dose per infusion of 23.89 and 31.99 IU VWF:RCo/kg. Both subjects received 15 infusions each as prophylaxis treatment, with an average doses n of 22.00 and 30.14 IU VWF:RCo/kg. The remaining number of on-demand infusions had an average doses of 24.50 and 32.54 IU VWF:RCo/kg.

**Assessor's comment:**
The haemostatic efficacy of the 2 subjects in the prophylaxis and on-demand treatment was considered as good or excellent. The dosage received by the 2 subjects for the prophylaxis as well as for the on-demand treatment is however much lower then the median administered to the groups.
However, as this concerns only one adult and one adolescent, it is not possible to attach significance to this observation.

***Surgical events***
During the study, 7 subjects, including 2 children, underwent a total of 13 surgeries, 4 subjects in the prophylaxis arm with 1 minor surgery each and 3 subjects in the on-demand arm with 9 surgeries, of which 3 were major. The investigator's assessment of haemostatic efficacy at discharge from the hospital was assessed as excellent for 11 surgical events (including the 3 major events) and as good for 2 events. Where available, the subject rated the haemostatic efficacy as either excellent or good for all days except for 3 of 8 days and 1 of 3 days for the 2 major surgeries (teeth extractions) in the same subject. Blood loss during surgery was assessed as equivalent to that expected in the 4 surgical events that occurred in 4 subjects of the prophylaxis arm and 7 of the 9 surgeries in the on demand arm, and less than expected in the remaining 2 surgeries in the on-demand arm.
No subject required blood product transfusions.

## *Safety results*

During this extension study, 16 subjects (84.2%) reported a total of 79 TEAEs: 7 subjects (70.0%) in the prophylaxis arm had 55 TEAEs, all 7 subjects (100.0%) in the on-demand arm had 21 TEAEs, and the 2 subjects in the prophylaxis & on-demand arm had 3 TEAEs. The most frequently reported TEAEs,

each reported by 3 subjects (15.8%), were anaemia, arthralgia, nasopharyngitis, and upper respiratory tract infection. Three subjects reported a total of 5 serious TEAEs: One subject with diabetes insipidus, gastric ulcer, and pneumonia, and 1 subject each with dysfunctional uterine bleeding and mild carcinoma of the cervix (stage 0; resolved with sequelae after 15 days following surgery), respectively. The gastric ulcer and pneumonia events led to death of the subject; the gastric ulcer was present prior to the first administration, and the pneumonia was not considered related to or study procedures by both the investigator and the sponsor. No ADRs, AEs leading to discontinuation of Voncento, or TEAEs of special interest (development of FVIII / VWF inhibitors, virus transmissions, hypersensitivity reactions, and embolic and thrombotic events) occurred during this study.

**Paediatric data**

Other than TEAEs that are typical childhood diseases, there were no major differences in the TEAE reporting profile between the 3 children, 2 adolescents, and 14 adults included in the safety population. The 3 children included in the study (all in the prophylaxis arm) reported a total of 42 TEAEs (respiratory infections, arthralgia, anemia, gastrointestinal complaints) . One subject (9 years old) had 4 TEAEs that were severe in intensity (acute tonsillitis, severe tonsillitis, upper abdominal pain, and severe post-traumatic pain). Other TEAEs reported for the children were mild or moderate.
Overall, the AE reporting profile was typical for children with higher incidences of infection-related diseases and symptoms as well as injuries and falls, compared with the adult population.

The 2 adolescents included in the study reported a total of 5 TEAEs. One subject (aged 17 years) in the on-demand arm reported 4 TEAEs (nasopharyngitis and 3 cases of anaemia) and one subject (aged 16 years) in the prophylaxis & on-demand arm had a moderate TEAE of bronchitis.

**Safety Conclusion**

The children included in this study showed similar TEAE as adults, apart from AE related to the age of population. In study CSCLT-BIO-08-52 (pivotal study) AEs associated with common cold such as pyrexia, nasopharyngitis, and rhinitis, but also injuries were more frequently observed in the paediatric subjects (age <12) then adults.

Importantly, no development of FVIII / VWF inhibitors, virus transmissions, hypersensitivity reactions, or embolic and thrombotic events were reported.

Therefore, results from study CSCLT-09-64 support the safety results from CSCLT_BIO-08-52 and it can be concluded that no apparent clinically relevant differences were found between adults and children regarding the safety of Voncento in VWD.

For the adolescents, the cases of anaemia have not been described in the SPC for adults, therefore the MAH is requested to discuss these findings in relation to the Voncento treatment and bleeding events/blood loss in these patients.

## 2.3.3. Discussion on clinical aspects

**Efficacy summary:**

Voncento showed a long/term efficacy of a prophylaxis regimen and on-demand therapy with Voncento in preventing non-surgical bleeding (NSB) events (median per subject of 8 in prophylaxis and 35 in on-demand arm) and haemostatic efficacy of Voncento in subjects with (VWD) who require a (VWF) product to control an NSB event. The assessment of the haemostatic efficacy as assessed by the investigator and the subjects was rated excellent or good at multiple time points (e.g. at discharge, at treatment days) for 13 surgical events (including the 3 major events). No subject required blood product transfusions.

Moreover, long-term data on haemostatic efficacy of Voncento for subjects who underwent surgical procedures during the study period was shown. This study however only provided data on a small group of subjects.

The 3 children (2 with Type 3 and 1 with Type 2A VWD) in the prophylaxis arm had a higher NSB frequency than the 7 adults in the prophylaxis arm. The haemostatic efficacy for the 3 children was similar to that for the adults.

The haemostatic efficacy for the 1 adolescent subject in the on-demand arm and in the prophylaxis and on-demand arm was similar to overall on-demand arm. No children were included in the on-demand arm.

When compared with studies CSLCT-BIO-08-52 and CSLCT-BIO-08-54, in which the subjects were treated prior to this extension study, the median number of NSB events per year in the 3 children (22.2 events) and the 7 adults (0.6 events) of the prophylaxis arm in this study was similar to corresponding median numbers in the prophylaxis arm of the 12-month children study CSLCT-BIO-08-52 (23.5 events) and the 12-month prophylaxis treatment period of the adult/adolescent study CSLCT-BIO-08-54 (1.0 event). In subjects treated on-demand, the median number of bleeding events per year in this study (11.1 events; all subjects previously participating in study CSLCT-BIO-08-54) was lower than in the on-demand arm of study CSLCT-BIO-08-54 (19.5 events).

It seems reasonable to conclude that efficacy has been reached in this extension study. For paediatric patients the comparison of prophylaxis versus on-demand arm in NSB events could not be made, however the data of the children and adolescents behaved similar to the adults, therefore a difference in efficacy is not likely to occur.

**Dosing in paediatric population:**

The posology which was approved for the Voncento SPC gives the same recommendations as in the Core SPC with the qualification that dosing in adolescents aged 12 to 18 years is based on body weight and is therefore generally based on the same guidelines as in adults. No recommendation is currently made for dosage in children <12 years due to lack of data.

**Safety summary:**

The population studied is very small, however it can be concluded that the AE profile is mild.

The children included in this study showed similar TEAE as adults, apart from AE related to the age of population. In study CSCLT-BIO-08-52 (pivotal study) AEs associated with common cold such as pyrexia, nasopharyngitis, and rhinitis, but also injuries were more frequently observed in the pediatric subjects (age <12) than adults. Importantly, no development of FVIII / VWF inhibitors, virus transmissions, hypersensitivity reactions, or embolic and thrombotic events were reported. Therefore results from study CSCLT-09-64 support the safety results from CSCLT-BIO-08-52 and it can be concluded that no apparent clinically relevant differences were found between adults and children regarding the safety of Voncento in VWD.

For the adolescents, the cases of anaemia have not been described in the SPC for adults, therefore the MAH is requested to discuss these findings in relation to the Voncento treatment and bleeding events/blood loss in these patients.

## Overall conclusion

This study shows long-term Voncento exposure in paediatric and adolescent subjects with VWD who require prophylaxis or on-demand treatment with a VWF. It is difficult to draw conclusions for the extension study CSLCT-BIO-09-64 on the paediatric population due to the small amount of children. The company is asked to answer the points of clarification before a definitive positive B/R can be given.

The MAH does not propose any changes in the product information. The SPC currently carries the statement that *"the safety and efficacy of Voncento in children < 12 years have not been established. No data are available."*. Currently a procedure is ongoing in which data from pediatric study CSL-CT-08-52 has been assessed, this involved 17 children with VWD. As part of this procedure an SPC update regarding the posology in children will be carried out. Based on the data from study CSLCT-BIO-09-64 it is not considered necessary to alter this statement.

### Recommendation (preliminary)

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure. (see section IV "Additional clarifications requested")

## Additional clarifications requested

Based on the data submitted, the MAH should provide description of the additional clarifications as part of this procedure. Comments on the preliminary AR were received from DE and FR.

The MAH is to clarify the following points :

1. Regarding Efficacy of Voncento in the Paediatric population the MAH might provide comparative numbers on product consumption. According to the respective Clinical Guideline, consumption of FVIII and vWF should be presented as IU/kg per event (for on-demand treatment and surgery) as well as IU/kg per (month or) year for prophylaxis-regimen. Although patient numbers are low, comparison of consumption in paediatric, adolescent and adult subjects may contribute exploratory information.
2. This study doesn't propose any justification about the choice of posology in children, as it was mentioned at the time of the variation II-08 at CHMP. Although it is generally considered that young paediatric patients may require higher doses or shorter dose intervals, the company is asked to discuss the dose per infusion used by the patients <12 years while on a prophylaxis regimen in study CSL-CT-08-52 and CSL-T-BIO-09-64 compared to adults.
3. Safety: For the adolescents, the MAH is requested to discuss the 3 episodes of anaemia in Subject 08-54-07001 in relation to the Voncento treatment and bleeding events/blood loss.

# Annex. 1 Updated assessment report of the MAH answer to the Request for Supplementary Information

## *2. Clinical Aspects*

## 2.1 Efficacy

***Other concerns***

**Question 1:**

Regarding Efficacy of Voncento in the Paediatric population the MAH might provide comparative numbers on product consumption. According to the respective Clinical Guideline, consumption of FVIII and vWF should be presented as IU/kg per event (for on-demand treatment and surgery) as well as IU/kg per (month or) year for prophylaxis-regimen. Although patient numbers are low, comparison of consumption in paediatric, adolescent and adult subjects may contribute exploratory information

***Summary of MAH answer***

There were 10 subjects in the extension study CSLCT-BIO-09-64, 3 paediatric (< 12 years, from CSLCT-BIO-08-52) and 7 adults (> 18 years, from study CSLCT-BIO-08-54) who received prophylactic treatment with Voncento. No adolescent subjects, between 12 and < 18 years of age, were on prophylactic treatment. The consumption, expressed as the mean prophylactic dose (VWF:RCo IU/kg) and the mean calculated prophylactic dose per year (VWF:RCo IU/kg), as well as the frequency of infusion and the doses administered per individual subject, by age group, are provided in Table 2.

**Table 2 Prophylactic frequency and doses in children <12 years old an adults ≥18 years old (CSLCT-BIO-09-64)**

| Subject ID | No of infusions / No of days in study | Frequency of infusions/ week | Mean dose IU/kg | Total dose VWF:RCo IU/kg | Dose VWF:RCo IU/kg per year |
|---|---|---|---|---|---|
| **Paediatric Subjects** | | | | | |
| | 379/848 | 3.1 | 86.3 | 32702 | 14076 |
| | 67/526 | 0.9 | 47.9 | 3210 | 2227 |
| | 71/211 | 2.4 | 57.8 | 4101 | 7094 |
| Mean (SD) | | | 64.0 (19.9) | | 7799 (5956) |
| **Adult Subjects** | | | | | |
| | 311/763 | 2.9 | 28.2 | 8765 | 4193 |
| | 199/630 | 2.2 | 31.4 | 6240 | 3615 |
| | 226/650 | 2.4 | 30.4 | 6875 | 3861 |
| | 105/725 | 1.0 | 31.6 | 3313 | 1668 |
| | 96/721 | 0.9 | 46.6 | 4473 | 2264 |
| | 97/696 | 1.0 | 52.9 | 5133 | 2692 |
| * | 19/595 | - | 38.7 | 736 | - |
| Mean (SD) | | | 37.1 (9.4) | | 3049 (994) |

Source: 5.3.5.2.7 (VWD), CSLCT-BIO-09-64 Listing 16.2.6.4, 16.2.5.1
*Subject 10008 was on prophylactic treatment once a month to prevent extensive menstrual bleeds

In the 3 children, the mean dose per infusion for prophylaxis was 64.0 IU/kg and the mean dose per year 7799 IU/kg VWF:RCo. The number of prophylaxis infusions given to children was between 0.9 and 3.1 infusions per week, excluding the infusions administered for bleeding. Seven adults continued their prophylaxis regimen in the extension study CSLCT-BIO-09-64. The frequency of administration was between 0.9 and 2.9 infusions per week and this was very similar to the frequency in the children. However, the mean prophylactic doses per infusion and per year were 58 and 39% lower in adults than in children, 37.1 IU/kg and 3049 IU/kg/year, respectively. This observation was expected due to a generally higher clearance in young paediatric patients of these products. These children may require higher doses or shorter dose intervals to obtain an optimal efficacy. No apparent clinically relevant differences were found between adults and children regarding the safety of Voncento in VWD.

**On-demand treatment**

There were 8 subjects in the extension study CSLCT-BIO-09-64 who received on-demand treatment, 1 adolescent and 7 adults from study CSLCT-BIO-08-54. However, 1 of the adults was not treated for a non-surgical bleed with Voncento and was therefore not included in the analysis. No children below the age of 12 received treatment on-demand. The total dose and mean dose administered per bleeding event in the 1 adolescent and 6 adult subjects are presented by the MAH.

The mean dose to stop a bleeding event in the adolescent was 60.5 IU/kg and the mean dose for the adult subjects was 55.0 IU/kg/event, over a range from 38.3 to 86.0 IU/kg/event. Therefore, Voncento consumption in the adult and adolescent subjects to induce haemostasis was similar.

**Surgery**

During the extension study, 7 subjects (2 children and 5 adults), underwent a total of 13 surgeries; no adolescent subjects required surgery during the study. Details on the number of surgical events and doses administered (CSLCT-BIO-09-64, Efficacy/PP population) have been supplied by the MAH. The doses administered during surgery in the 2 children (< 12 years) were 68 and 533.3 IU VWF:RCo /kg/event (1 event a single infusion the other 10 infusions in total). In the adult subjects, doses ranged from 29.7 and 110.8 IU VWF:RCo/kg per infusion, with doses from 29.7 to 442.6 IU/kg/event for minor surgery and from 352 to 939 IU/kg/event for major surgery.

The doses administered during minor surgery for the paediatric and adult subjects receiving prophylaxis treatment was similar (range 46.7–68.0 IU/kg/event) with no requirement for postsurgical infusions. The doses received by the on-demand subjects for minor surgery varied according to the surgery type, for example tooth extraction (in 2 subjects, 5 events) required a dose of 88.0–110.8 IU/kg, followed up with post-surgical doses in the range 56.7–73.8 IU/kg (although the total dose varied 148 – 851 IU/kg). For major surgery, a direct comparison of dosage (consumption) is not possible between adult and paediatric subjects as no paediatric patients required major surgery.

**Rapporteur's Assessment**

The MAH has supplied data on the consumption of vWF for the prophylaxis treatment, the on-demand treatment and during surgery. For the prophylaxis treatment the frequency of infusion was very similar between adults and children. The mean prophylactic doses per infusion and per year were, however, 58 and 39% lower in adults than in children, respectively. From the pharmacokinetic data submitted as part of procedure EMEA/H/C/002493/II/0008/G, it has been shown that dose/kg-normalised AUC and Cmax are somewhat lower in the population <12 years, as compared to the population > 12 years. It is acknowledged that the lower incremental recovery in VWF patients < 12 years supports the higher dose used in this population as compared to the > 12 years population.

For on-demand treatment the consumption of Voncento in the adult and adolescent subjects to induce haemostasis was similar, however only 1 adolescent was included in this study-arm.

The doses administered during minor surgery for the paediatric (n=2) and adult (n=5) subjects receiving prophylaxis treatment was similar. The doses received by the on-demand subjects for minor surgery varied according to the surgery type. For major surgery, a direct comparison of dosage (consumption) is not possible between adult and paediatric subjects as no paediatric patients required major surgery.

**Issue resolved**

**Question 2:**
This study doesn't propose any justification about the choice of posology in children, as it was mentioned at the time of the variation II-08 at CHMP. Although it is generally considered that young paediatric patients may require higher doses or shorter dose intervals, the company is asked to discuss the dose per infusion used by the patients <12 years while on a prophylaxis regimen in study CSL-CT-08-52 and CSL-T-BIO-09-64 compared to adults.

***Summary of MAH answer***

The paediatric study CSLCT-BIO-08-52 included 17 children <12 years old. Four subjects were allocated to the prophylaxis therapy (Arm 1) and 13 to on-demand therapy (Arm 2). At the completion of the study, 3 of the 4 prophylaxis subjects, continued treatment with Voncento in the extension study (CSLCT-BIO-09-64) for up to an additional 32 months of treatment. The fourth paediatric subject receiving prophylaxis treatment in CSLCT-BIO-08-52 had previously received on-demand treatment. This subject did not continue treatment in the extension study.

*Prophylaxis treatment*
The recommendation for prophylaxis dosing in the VWD clinical trial protocols was the same for both paediatric (CSLCT-BIO-08-52) and adult/adolescent subjects (CSLCT-BIO-08-54): 25-40 IU/kg, 1 to 3 times per week. However, the 3 paediatric subjects were noted to continue their previous prophylactic dose and regimen into the study. In the year before study enrolment 3 prophylactic subjects from the site in Bremen were treated with Haemate P with doses higher than indicated in the protocol (40-80 IU/kg, 1-3 times per week). Their doses were observed to increase during the course of the extension study. The investigator decided to continue the Haemate regimen and dose level in the study. While it is acknowledged that the actual doses used were higher than indicated in the protocol, a mean of 58.7 IU/kg in study CSLCT-BIO-08-52 and a mean of 64.0 IU/kg in study CSLCT-BIO-09-64, the haemostatic efficacy and safety results were very good, in spite of the increase in number of minor mucosal and superficial bleeds.

The prophylactic frequency and doses used in children and adults in CSLCT-BIO-09-64 are summarised in the response to Question 1, Table 2. In order to compare the prophylactic dosing regimen in adults and children from studies CSLCT-BIO-08-52, CSLCT-BIO-08-54 to the dosing regimen of the extension study (CSLCT-BIO-09-64) mean doses are presented in Table 3.

**Table 3 Prophylactic doses in children < 12 years old and adults 18 years old**

| | Mean (SD) dose IU/kg |
|---|---|
| **Paediatric Subjects** | **CSLCT-BIO-08-52** | **CSLCT-BIO-09-64** |
| | 58.7 (9.2) | 64.0 (19.9) |
| **Adult Subjects** | **CSLCT-BIO-08-54** | **CSLCT-BIO-09-64** |
| | 28.9 (4.1) | 37.1 (9.4) |

Source: 5.3.5.2.6 (VWD), CSLCT-BIO-08-52 Listing 16.2.6.4, 16.2.5.1; 5.3.5.2.2 (VWD), CSLCT-BIO-08-54 Listing 16.2.6.4; 5.3.5.2.7 (VWD), CSLCT-BIO-09-64 Listing 16.2.6.4

The actual doses administered to the adult subjects were a mean of 37.1 IU/kg in study CSLCTBIO-09-64 which were within the proposed prophylactic dose range of 25-40 IU/kg body weight. The actual doses administered to the paediatric subjects were a mean of 58.7 IU/kg in study CSLCT-BIO-08-52 and a mean of 64.0 IU/kg in study CSLCT-BIO-09-64. For subject 110101 the mean dose increased approximately 30% to 86.3 IU/kg VWF:RCo during the extension study. This subject received treatment for a further 848 treatment days. The mean doses of subjects 110102 and 110103 were similar, with a dose decrease of approximately 18 and 11%, respectively during the extension study. Although for these subjects the number of bleeds changed (a reduction for subjects 110101 and 110103, an increase for subject 110102; (predominantly minor mucosal bleeds with a few superficial trauma bleeds/bruises)) the majority of haemostatic efficacy ratings were excellent.

Based on the actual doses used in studies CSLCT-BIO-08-52 and CSLCT-BIO-09-64, the MAH is proposing to amend the prophylactic dose range to 40-80 IU/kg body weight 1 to 3 times per week for paediatrics under the age of 12 (part of procedure EMEA/H/C/002493/II/0008/G)

*On-demand treatment*
For on demand subjects in study CSLCT-BIO-08-52 the recommended doses were the same as those recommended for adults (in study CSLCT-BIO-08-54); i.e. for non-surgical bleeds 25–50 IU/kg. The actual on-demand doses (mean and median) administered by the 12 paediatric subjects in study CSLCT-BIO-08-52 are provided in Table 8. These subjects in the on demand arm who treated a NSB, had a mean number of 10.4 infusions at a mean Biostate dose of 47.6 IU VWF:RCo/kg per infusion (median 40.8 IU/kg, range 30.2-88.6, Table 8). Although the majority of the administered doses were within the proposed dose range of 25-50 IU/kg VWF:RCo, some were higher, with a maximum of 88.6 IU/kg to treat a NSB. The haemostatic efficacy and safety results were good, although not all were assessed as excellent by both the investigator and subjects.

For on-demand treatment, the MAH maintains that the dosing of the paediatric population below the age of 12 should be based on the same guidance as that for adults and adolescents, i.e. 40 – 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW).

Additionally, further analysis of the prophylactic dose used in children was recently conducted, and communicated to EMA as part of the Response to questions for the variation application EMEA/H/C/002493/II/0008/G Change to therapeutic indication (VWD).

**Rapporteur's Assessment**

A similar question regarding the posology in children was addressed as part of the ongoing procedure EMEA/H/C/002493/II/0008/G. In the response to questions the MAH refers to this procedure. For the sake of consistency a short summary of the assessor's comment is provided below. The presented answers by the MAH are in line with procedure II/08/G.

The data in Table 2 and 3 show that the 4 children <12 years received a higher mean dose then the adult patients. It is noted that 3 of the 4 patients in study CSLCT-BIO-08-52 who received routine prophylaxis were enrolled at the same site (site 110 in Bremen) which may imply a specific treatment preference, but also suggests that the approach to management of these patients would have been consistent. Three subjects continued into extension study CSLCT-BIO-09-64 and received prophylactic doses at the same frequency. While it is acknowledged that the actual doses used were higher than indicated in the protocol, a mean of 58.7 IU/kg in study CSLCT-BIO-08-52 and a mean of 64.0 IU/kg in study CSLCT-BIO-09-64, the haemostatic efficacy and safety results were very good, in spite of the increase in number of minor mucosal and superficial bleeds.

PK data provided in EMEA/H/C/002493/II/0008/G from 17 children <12 years show that exposure in this age group is lower than in adults and subjects ≥12 years of age. The lower incremental recovery in VWF patients < 12 years supports the higher doses used in this population. The level of efficacy can be considered clinically acceptable and taking the PK data into account, it seems reasonable to also apply the recommendation of dose range 40 to 80 IU/kg VWF:RiCo to patients <12 years. This is the dose range currently approved for Voncento for the treatment of bleeds in patients ≥12 years and is also the dose recommended in the Core SPC for VWF products and allows for dosages up to 80 IU VWF:RCo. In view of the similar PK data in patients aged from 12 to 18 years it can be agreed that prophylactic dosing in this age group can be based on the same guidelines as for adults.

A modification of the information on dosing in the paediatric population in SmPC Section 4.2 is recommended in procedure EMEA/H/C/002493/II/0008/G, and is suggested as follows:

*Paediatric VWD population*

*Treatment of bleeding:*

*Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended in paediatric patients to treat a bleed.*

*Prophylaxis treatment:*

*In patients aged 12 to 18 years old dosing is based on the same guidelines as for adults.*

*Based on results from a clinical trial in paediatric patients under 12 years of age to achieve haemostasis, in this age group a prophylactic dose range of 40 – 80 IU VWF:RCo/kg body weight 1 to 3 times a week should be considered.*

*The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.*

The Issue **was resolved** with the SPC adjustments carried out as part of procedure EMEA/H/C/002493/II/0008/G.

## 2.2 Safety

***Other concerns***

***Question 3***

For the adolescents, the MAH is requested to discuss the 3 episodes of anaemia in Subject 08-54-07001 in relation to the Voncento treatment and bleeding events/blood loss in this patient.

***Summary of MAH answer***

Subject 07001was a 17 year old female subject with type 3 VWD who entered the extension study from study CSLCT-BIO-08-54 and was assigned to the on-demand treatment arm. The subject stayed on study for 32 months. During the study she experienced 32 bleeding events (monthly menorrhagia except for 4 joint bleedings), all of which could be controlled by 1 infusion of Biostate with the exception of bleeding event # 2 (6 infusions) and #4 (3 infusions). The efficacy of Biostate was rated by the investigator as excellent at all study visits (3 monthly) except for month 15, month 18, month 21, month 30 and month 32 when efficacy was reported as good.

The subject entered the study with a low baseline hemoglobin level (7.137 mmol/L) which was assessed as not clinically significant. The subjects hemoglobin levels stayed low throughout the entire study, ranging between 5.275mmol/L and 7.633 mmol/L.
Anaemia was reported as an AE on 3 occasions from 15 March-15 June 2011, 14 Sep 2011-17 Sep 2012 and 13 Mar -06 June 2013. All AEs were assessed as not related to the study drug, and the dose of Biostate was not changed. Anaemia was treated with administration of iron (Tardyferon®, oral) and vitamin B 12. The AEs were not connected to any specific bleeding event.

**Rapporteur's Assessment**

The MAHs opinion that the adverse events of anaemia in subject 07001 were not related to the study drug can be supported. The subject had low haemoglobin at study entry and this remained low during the study. Moreover, Voncento efficacy was rated excellent or good by the investigator.

**Issue resolved**

## Recommendation (final)

Based on the data submitted, procedure P46 010 was approvable, in the light of the relevant SPC adjustment carried out as part of procedure EMEA/H/C/002493/II/0008/G .

# Annex. 2 Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

## Clinical studies

Product Name: Active substance:

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| An Open-Label, Multi-Centre Extension Study to Assess the Efficacy and Safety of Biostate in Paediatric, Adolescent, and Adult Subjects with Von Willebrand Disease who Completed Clinical Studies CSLCT-BIO-08-52 or CSLCT-BIO-08-54] is a stand alone study(ies). | CSLCT-BIO-08-64 | 28 Mar 2014 (last subject completed) | Date of the report: 18 September 2014 |
| | | | |
| | | | |