Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Sativex delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

UK/W/0107/pdWS/001

Marketing Authorisation Holder: GW Pharmaceuticals

Rapporteur:	UK
Finalisation procedure (day 120):	16/07/2018

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Sativex Oromucosal Spray
INN (or common name) of the active substance(s):	delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).
MAH:	GW Pharma Ltd
Currently approved Indication(s)	Treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication
Pharmaco-therapeutic group (ATC Code):	Other Analgesics and Antipyretics (N02BG10)
Pharmaceutical form(s) and strength(s):	Oromucosal spray 2.7 mg THC and 2.5 mg CBD

I. EXECUTIVE SUMMARY

The MAH has submitted a report of paediatric study GWSP08258, conducted as part of the Paediatric Investigation Plan (PIP - EMA-000181-PIP01 08-M03) for Sativex in children with spasticity associated with existing neurological condition. Sativex oromucosal spray is a product containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The drug is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.
The aim of the paediatric study was to evaluate the efficacy, safety and tolerability of Sativex in children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic central nervous system injury who have not responded adequately to their existing anti-spasticity medications. The study had 2 phases, a 12-week randomised phase which was followed by a 24-week open-label extension (OLE) phase.
Based on the inclusion criteria for spasticity severity, as assessed by the spasticity numerical rating scale (NRS) scores and Modified Ashworth Scale (MAS) scores at baseline, patients in the trial had moderate to severe spasticity.

A total of 72 participants were randomised; 47 participants received Sativex and 25 participants received placebo. 67 participants entered the OLE phase.
The primary endpoint for analysis was the change in spasticity severity 0–10 NRS score from baseline (mean of the last 7 days of baseline period) on Sativex compared with placebo at the end of the randomised phase (mean of last 7 days prior to completion/withdrawal). This is a primary caregiver reported outcome, was agreed in the PIP and was the same as in the pivotal trials in adults with spasticity due to MS. Clinician-rated outcome measures of spasticity [Modified Tardieu Scale (MTS) of the most affected limb and Modified Ashworth Scale (MAS) of the main muscle groups of the upper and lower limb of the most affected limb] were included in the secondary efficacy endpoints. Other secondary endpoints evaluated included sleep quality, pain, quality of life (QOL), comfort, depression, caregiver QOL and caregiver global impression of change.

The two treatment groups were overall comparable at baseline. Most patients had severe impairment of motor function (GMFCS level IV or V). The baseline spasticity severity 0–10 NRS score for Sativex participants was 6.958 (range 4.43 10.00; SD 1.3875) and for placebo participants was 6.680 (range 4.43–9.00; SD 1.3939).

After 12 weeks of treatment, there was no statistically significant change for Sativex treated patients' spasticity severity scores compared to placebo patients. The least square mean (LSM) difference between the Sativex and the placebo treatment group for change in spasticity severity 0–10 NRS score from baseline to the end of treatment (EOT) for the ITT analysis set was −0.166 (95% CI −1.119, 0.787); this was not statistically significant (p=0.7291).
Additionally, there was no statistically significant change for Sativex-treated patients compared with placebo patients for all secondary endpoints tested in this trial. The overall safety results were consistent with the known safety profile of Sativex as observed in adults, with the exception of retching.

Based on the submitted study, the benefit risk ratio of Sativex treatment remains unchanged.

The MAH has proposed SmPC changes in section 4.2 and 5.1 to add the results of this study. At day 89 the MAH was requested to provide supplementary information. Specifically, the MAH was

requested to provide a responder analysis, more information on a case of a patient presenting with attempted suicide and a review of cases of patients presenting with seizure related AEs.

The rapporteur concludes that, based on the results of this study, the SmPC should be updated. SmPC changes are proposed in sections 4.2, 4.4 and 5.1.

Summary of outcome

☐ No change

☐ Change

☐ New study data

☐ New safety information

☒ Paediatric information clarified: 4.2, 4.4 and 5.1

☐ New indication

II. RECOMMENDATION

The SmPC should be updated as follows.

Section 4.2
[…]
Paediatric population
Sativex is not recommended for use in children or adolescents below 18 years of age. A randomised placebo-controlled trial was performed in children and adolescents with cerebral palsy or traumatic central nervous system injury and its results regarding efficacy were negative. These data are described in section 5.1.

~~**Children**~~
~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Section 4.4

~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Section 5.1

[…]
Paediatric population
The efficacy and safety of Sativex was evaluated in a 12-week randomised, double-blind, placebo-controlled study involving 72 children and adolescents aged from 8–18 years with cerebral palsy or traumatic central nervous system injury. The placebo controlled phase was followed by a 24-week open label extension phase. The maximum permitted daily dose in this trial was 12 sprays and was titrated for 9 weeks. At baseline, most patients had

severe impairment of motor function (Gross Motor Function Classification Scale level IV or V). The primary efficacy endpoint was the change in spasticity severity 0–10 numerical rating scale (NRS) score from baseline which is a carer reported outcome measure.
The baseline spasticity severity 0–10 NRS score for Sativex-treated participants was 6.958 (range 4.43–10.00;SD 1.3875) and for placebo participants was 6.680 (range 4.43–9.00; SD 1.3939). After 12 weeks of treatment, the NRS was 5.107 (range 0.43-10.00; SD 2.0978) for Sativex-treated participants and 5.107 (range 1.86-9.86; SD 2.0468) for placebo participants. The least square mean difference between the two groups (−0.166, 95% CI −1.119, 0.787) was not statistically significant (p=0.7291).
Safety findings were in general the same as in the adult studies, with exception of retching. No data are available in children below 8 years (see section 4.2 for information on paediatric use).

III. INTRODUCTION

In December 2017, the MAH submitted a completed paediatric study for Sativex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Sativex. The MAH proposed SmPC wording for section 4.2 and 5.1 to include the results of this study.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

The same formulation as the product licensed for adults was used in this study and administered to the sub-lingual or oral mucosa. The placebo group received investigational medicinal product (IMP) with similar presentation and packaging (see further details below under "treatments").

IV.2 Clinical study

The MAH submitted a final report for study GWSP08258.

- **Description**

Study title: The efficacy, safety and tolerability of Sativex as an adjunctive treatment to existing anti-spasticity medications in children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic central nervous system injury who have not responded adequately to their existing anti-spasticity medications: a parallel group randomised, double-blind, placebo-controlled study followed by a 24-week open-label extension phase.

The study was conducted as part of the Paediatric Investigation Plan (PIP - EMA-000181-PIP01-08-M03) commitment for the Sativex product. Another study in children less than 8 years of age with intractable spasticity due to cerebral palsy or traumatic CNS injury is also part of this PIP.

Assessor's comments:
The study title is not accurate as, based on the inclusion criteria, patients were required to have inadequate response to previous anti-spasticity medications but were not required to be taking such medications at the time of enrolment. Therefore, Sativex was not investigated in all patients as adjunctive treatment to other anti-spasticity medications.

- **Methods**

  - Objectives

Primary Objective:
To assess the efficacy of Sativex on spasticity in a population of children and adolescents aged from 8–18 years with cerebral palsy (CP) or traumatic central nervous system (CNS) injury.

Secondary Objectives:
To assess the efficacy of Sativex compared with placebo in terms of spasticity, sleep quality, pain, quality of life (of both the participant and the caregiver) and the caregiver's global impression of change using:

• Modified Tardieu Scale (MTS) of the most affected limb.
• Modified Ashworth Scale (MAS) of the main muscle groups of the upper and lower limb of the most affected limb.
• Sleep quality 0–10 numerical rating scale (NRS).
• Pain measured using the paediatric pain profile (PPP).
• Participant quality of life (QOL) using the CP QOL-child/teen questionnaire.
• Comfort questionnaire.
• Children's Depression Inventory 2 (CDI 2).
• Caregiver QOL using the 36-Item Short-Form Health Survey Version II (SF-36-II).
• Caregiver global impression of change (CGIC) questionnaire.

To evaluate the safety and tolerability of Sativex compared with placebo through the following assessments:
• Adverse events (AEs).
• Clinical laboratory tests.
• Vital signs.

- Study design

This was a 2-part phase 3 trial that consisted of a 12-week randomised, double-blind, placebo-controlled, parallel group phase followed by a 24-week open-label extension (OLE) phase. After informed consent (and if applicable assent) was given by the participant or the participant's authorised representative, the participant was screened for entry into the trial.
At baseline (Visit 1) the primary caregiver was instructed on how to complete the paper diary where the spasticity severity 0–10 NRS, sleep quality 0–10 NRS, and the daily comfort questionnaire were to be recorded each day. All those participants who met the entry criteria were randomised 1 week later, at Visit 2 (Day 0) and received either Sativex or placebo (2:1), in identical containers. Following the final assessment of the randomised phase of the trial on Day 84 (Visit 9), all participants were invited to enter the OLE phase during which they received Sativex for a maximum period of 24 weeks. During the OLE, participants were assessed at 56-day intervals, on Day 140, Day 196, and Day 252. Trial-related observations also took place at each clinic visit and included: physical examination, vital signs, weight, AEs, laboratory tests (at EOT visit only), and concomitant medications. For participants who decided not to participate in the OLE phase there was a safety follow-up telephone contact visit on Day 98 (Visit 10), 14 days after Visit 9.
All concomitant anti-spasticity medications were to be continued at the same dose throughout the trial, or could be reduced in the event of AEs that were attributed to the concomitant medication.
For the randomised phase, clinic visits took place on Day −7, 0, 28, 56, and 84. Telephone contact visits took place on Day 7, 14, 42, and 70 (and Day 98 if the participant did not participate in the OLE phase).

Trial Diaries:
• At Visit 1 (Day −7) each participant's caregiver was given a paper diary and asked to complete the participant's sleep quality 0–10 NRS, spasticity 0–10 NRS, the comfort questionnaire and anti-spasticity medication used on a daily basis (the sleep quality 0–10 NRS was to be completed in the morning after waking up and the other questions were to be completed before bed at the same time each evening). At each visit, the diary was collected and a new diary was given to the caregiver to complete until the following visit.

• After Visit 2 (Day 0), following randomisation, the caregiver was also to record the daily dose of the IMP in the diary each evening.
During the OLE phase (Visit 9–13) the caregiver was only to record the participant's spasticity 0–10 NRS, anti-spasticity medication, and Sativex usage in the trial diary on a weekly basis noting down the average weekly scores.

Assessor's comments:
The study design is adequately described and in line with what has been agreed in the Sativex PIP. This was a randomised placebo controlled parallel study with an allocation ratio of 2:1.

- Study population

Inclusion criteria:

1. Males and females aged between 8 and 18 years and suffering from spasticity due to CP or traumatic CNS injury.
2. Willing and able to give informed consent for participation in the trial (participant and/or authorised representative consent/assent).
3. Had been under treatment for their spasticity for at least 1 year and reached a stage of non-progressive spasticity.
4. Able and willing to comply with all trial requirements.
5. Had received inadequate efficacy and/or experienced unacceptable side effects from previous or current treatment with at least 1 of the following medications for spasticity: baclofen, diazepam (or another benzodiazepine), dantrolene, tizanidine, gabapentin, trihexyphenidyl.
6. Gross Motor Function Classification Scale (GMFCS) level III–V.
7. MAS of 2 or higher in at least 1 muscle group.
8. Minimum average spasticity 0–10 NRS of > 4 (the sum of the last 6 days of the spasticity 0–10 NRS prior to randomisation had to be greater than 24).
9. Willing (participant and/or authorised representative consent/assent) for the responsible authorities to be notified of their name for participation in this trial, as applicable in individual countries.
10. Willing (participant and/or authorised representative consent/assent) to allow their primary care practitioner and consultant, if appropriate, to be notified of participation in the trial.

Exclusion criteria:

1. Known or suspected history of:
• Schizophrenia or other psychotic illness, or diagnosis of schizophrenia in a first-degree relative.
• Alcohol or substance abuse.
2. Any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP(s).
3. Use of *Cannabis* or cannabinoid based medications (including within 30 days or 60 days of trial entry, respectively).
4. Weighed less than 15 kg.
5. Females of child bearing potential and male participants whose partner was of child bearing potential, unless willing to ensure that they or their partner used effective contraception during the trial and for 3 months thereafter.
6. Females who were pregnant, lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
7. Received an IMP within 12 weeks prior to the screening visit.
8. Treated with botulinum toxin within 12 weeks prior to the screening visit.
9. Concomitant use of botulinum toxin.
10. Any cardiac disorder that, in the opinion of the investigator, would cause the risk of a clinically significant arrhythmia or myocardial infarction.

11. Significantly impaired hepatic function (ALT > 5 × upper limit of normal [ULN] or total bilirubin [TBL] > 2 × ULN). If the ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5, the participant should not enter the trial. *This criterion could only be confirmed once laboratory results were available.*
12. Any other significant disease or disorder, which, in the opinion of the investigator, would either put the participant at risk because of participation in the trial, influence the result of the trial, or the participant's ability to participate in the trial.
13. Following a physical examination any abnormalities that, in the opinion of the investigator, would prevent the participant from safe participation in the trial.
14. Any planned surgical procedure during the 12-week randomised phase of the trial.
15. Planned travel outside the country of residence planned during the trial.
16. Previously randomised into this trial.
17. Unwilling to abstain from donation of blood during the trial.

Assessor's comments:
Patients recruited had to be Gross Motor Function Classification Scale (GMFCS) level III–V. In terms of spasticity at baseline, patients needed to have a MAS score of 2 or higher (scale of 0, 1, 1+, 2, 3, 4) and had a baseline score of spasticity NRS>4 (ranges from 0-10). Therefore, a population with moderate to severe spasticity was included, reflecting the population with the greatest medical need for such a treatment as agreed in the PIP. In addition, patients needed to be under treatment for their spasticity for at least 1 year and needed to have reached a stage of non-progressive spasticity.
It can be argued that a population with milder disease and naïve to other anti-spasticity medication could have also benefited from treatment with Sativex and could have been included in the study. However, it may not be feasible to identify a population naïve to treatment or carers agreeing to use a new drug alone (or placebo) as first line therapy and not the current standard of care. In addition, it may have been difficult to demonstrate an effect in patients with low spasticity scores.

- Sample size

In order to achieve 80% power to detect a difference between treatments of 1.5 NRS points, with a common standard deviation (SD) of 2.1, using a 2-tailed test at a 5% significance level, and with a 2:1 randomisation, the trial required 48 participants in the Sativex group and 24 in the placebo group.
In practice 85 participants were screened, of those 13 participants were classified as screen failures and a total of 72 participants were randomised; 47 participants received Sativex and 25 participants received placebo. 67 participants entered the OLE phase.

- Treatments

Active IMP was Sativex. Sativex contained THC (27 mg/mL): CBD (25 mg/mL), in ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavouring. Each actuation delivered 100 µL (2.7 mg THC and 2.5 mg CBD) and was administered to the sub-lingual or oral mucosa.
Comparator: Placebo IMP was presented as an oromucosal spray, containing ethanol: propylene glycol (50:50) excipients, with peppermint oil (0.05%) flavouring and colourings FD&C Yellow No.5 (E102 tartrazine) (0.0260%), FD&C Yellow No.6 (E110 sunset yellow) (0.0038%), FD&C Red No. 40 E129 Allura red AC) (0.00330%) and FD&C Blue No.1 (E133 Brilliant blue FCF) (0.00058%).
Active IMP and placebo IMP were both presented as an oromucosal spray in an amber plastic-coated glass vial and packaged in cartons.

Dosing: The dose was titrated for 9 weeks. The maximum permitted daily dose in this trial was 12 sprays. Titration could stop at any tolerable dose that was within the range of the guided number of sprays for each week of the first 9 weeks.

Treatment assignment: An independent statistician produced a treatment allocation schedule using balanced randomly permuted blocks using a computer-based algorithm. Randomisation numbers were listed as unique numbers. The randomisation was balanced within trial sites.

Blinding: During the trial, the treatment assignment code list was available only to the trial statistician and the clinical trials supplies operations group. Except in cases of emergency unblinding, participants, investigational site personnel, GW employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every participant had completed trial treatment and the database had been locked. Once the blind was broken for a given participant, that participant was not permitted to reinitiate treatment with the IMP.

Duration of treatment: The 12-week randomised, double-blind, placebo-controlled, parallel-group phase comprised a 9-week titration period and a 3-week treatment period.

Prior and concomitant therapy: Wherever possible, all medications prescribed for spasticity were to be continued during the trial at a stable dose. It is possible that cannabinoids may modify the metabolism of other drugs administered concurrently. Throughout the trial any concomitant medications that may have affected the primary endpoint (in the opinion of the investigator) were not to be prescribed or altered in dose, except when the medical situation demanded.

Assessor's comments:
Treatment allocation, randomisation schedule and blinding are well described. Blinding is particularly important for this study with a subjective caregiver rated outcome. The blinding, as described in detail in the study report, seems satisfactory. 2 cases of unblinding are mentioned, one for a patient after having completed the randomised and OLE phase and another for a patient prior to enrolling in the OLE phase. Taken into consideration the timing of the unblinding and the measures taken to maintain blinding of other patients in the same centre, it is concluded that these cases probably did not impact on the trial integrity.
A difference of 1.27 in spasticity NRS was found to be the minimal clinically important difference in a study to validate NRS in adult patients with spasticity associated to multiple sclerosis (MS) (Farrar JT et al, 2008). Based on this study and without similar data for children with spasticity, the minimal difference between treatments of 1.5 NRS points that was used for the sample size calculation is acceptable.

- Outcomes/endpoints

Efficacy:
Primary Efficacy Endpoint:
The primary endpoint for analysis was the change in spasticity severity 0–10 NRS score from baseline (mean of the last 7 days of baseline period) on Sativex compared with placebo at the end of the randomised phase (mean of last 7 days prior to completion/withdrawal).

Secondary Efficacy Endpoints:
The efficacy of Sativex compared with placebo (randomised phase of the trial) or Sativex (OLE) for:
• MTS (of the most affected limb).
• MAS (of the main muscle groups of the upper and lower limb).
• Sleep quality.
• PPP.

• CP QOL-child/teen questionnaire.
• CDI 2.
• Comfort questionnaire.
• Caregiver QOL questionnaire (SF-36-II).
• CGIC.

No pharmacokinetic (PK) measurements were conducted in the trial.

Assessor's comments:
The primary and secondary endpoints are as in the agreed PIP. In addition, the primary efficacy endpoint is the same as the one measured in the adult trials of Sativex in patients with spasticity due to MS. The primary caregiver was explained the difference between spasticity and spasm and was asked the question: "*This question is about your child's muscles and how soft or tight/hard they have felt today. Think carefully about how your child's muscles have felt today and circle a number from 0–10 that best describes this" With the anchors ranged:*
0 = 'my child's muscles have felt totally relaxed'.
10 = 'my child's muscles have felt the tightest/hardest they have ever felt'.
Other measures of spasticity, such as MAS and MTS are measured as secondary endpoints.

There is not much evidence for the validity of this outcome measure for evaluating spasticity in children. However, it is a patient/carer reported outcome allowing for an assessment of clinical relevance and it is measured over a specified period (7 days) to account for day to day fluctuations. One study that investigated the validity of spasticity NRS in 50 children with CP, concluded this scale may be useful in evaluating certain properties of spasticity but may be inaccurate as a specific spasticity measure because it measures the patient and caregiver perception of spasticity which may differ from the clinicians' assessment. The validity and reliability of this measure as a primary outcome in the adult studies of Sativex in patients with MS was extensively discussed during the licensing procedure and this score was accepted as a primary efficacy endpoint. Moreover, the spasticity NRS scale was agreed as the primary outcome measure in the PIP.
Although this is a carer reported outcome with questionable validity for evaluating changes in spasticity in children, the fact that this was a double-blind placebo controlled trial means that any effect in either direction could most probably be discriminated from the placebo effect. Importantly, more objective clinician rated outcome measures (MAS and MTS) were added as secondary endpoints and any treatment effect in the primary outcome should have been supported by similar effects in these secondary outcomes.

Based on adult data, there is a high degree of intra- and inter-subject variability in PK parameters, difficulty to establish a dose-response relationship and the dose is titrated according to clinical response. Therefore, it was concluded in the PIP that PK data generation in children would not be of benefit to clinical practice.

Safety:
The safety and tolerability of Sativex compared with placebo (randomised phase) or Sativex (OLE) assessed through:
• AEs
• Laboratory parameters (haematology, biochemistry, urinalysis, THC(urine), pregnancy (serum).
• Vital signs, physical examination, oral examination, 12-lead EEG

- Statistical Methods

The intention to treat (ITT) was the primary analysis set of interest in all efficacy analyses for the randomised phase of the trial.

The spasticity severity 0–10 NRS score and change from baseline score were summarised across treatment groups and for each week and EOT, presenting the number of participants, mean, SD, median, minimum and maximum values. Change from baseline was compared between groups using analysis of covariance (ANCOVA) with baseline score as a covariate and treatment as a fixed effect. A 2-sided significance test was used in all comparisons at the 5% level of significance. The mean difference in change from baseline in spasticity severity 0–10 NRS score between treatment groups and the 95% confidence interval (CI) were presented. Analyses were performed on both the ITT and per protocol analysis sets.
For each continuous secondary efficacy endpoint (sleep 0–10 NRS scores, MTS score, MAS score, CP QOL-child/teen, CDI 2, PPP, SF-36-II, and comfort questionnaire), an ANCOVA model was fitted for the change from baseline score at EOT with the baseline value of the corresponding measurement as a covariate and treatment as a fixed effect. A 2-sided significance test was used in all comparisons at a 5% level of significance.
All the secondary measures/endpoints were summarised across treatment group and visit (or for each diary week and EOT) by presenting appropriate summary statistics. Analyses were performed on the ITT analysis set only. All OLE phase efficacy endpoints and change from baseline in these endpoints were summarised by treatment group (placebo–Sativex, Sativex–Sativex and overall) and visit for the safety-extension population. No statistical comparisons were made using the data from the OLE phase.

- **Results**

  - Recruitment/ Number analysed/baseline data

<u>Randomised Phase:</u>

A total of 85 participants were screened; 13 (15.3%) participants were classed as screen failures and 72 (84.7%) participants were randomised within the UK (11 trial sites), Israel (2 trial sites), and the Czech Republic (1 trial site). In summary, 44 (61.1%) participants were male and the ratio of male:female participants was similar within each treatment group. The majority of participants were White/Caucasian (63 [87.5%] participants). The mean age was 12.34 years, mean height was 1.342 m, mean weight was 33.08 kg, and mean body mass index was 17.832 kg/m2; all of which showed little variation between treatment groups. A greater number of participants were diagnosed with CP compared with traumatic CNS injury (64 [88.9%] participants vs. 8 [11.1%] participants), and the mean time since diagnosis of CP or traumatic CNS injury was 10.39 years (range 0.8–16.9 years). According to the Gross Motor Function Classification Scale only 1 participant was classed as level III the majority of participants were classed as level V (51 [70.8%] participants), and all other participants were classed as level IV (20 [27.8%] participants). The majority of participants had previously taken at least 1 anti-spasticity medication (65 [90.3%] participants), of which botulinum toxin was the most frequently used (57 [79.2%] participants) followed by diazepam (21 [29.2%] participants), baclofen and trihexyphenidyl (20 [27.8%] participants each), and benzodiazepine (16 [22.2] participants). The majority of participants had not previously used *Cannabis* (71 [98.6%] participants). The majority of participants were taking at least 1 anti-spasticity medication during the trial (65 [90.3%] participants), of which baclofen (49 [68.1%] participants) was the most frequently used, followed by diazepam and trihexyphenidyl (20 [27.8%] participants), and midazolam (13 [18.1%] participants).

Table 8.2.1-1 Demographics and Baseline Characteristics, Randomised Phase Safety Analysis Set			
	Sativex N=47	**Placebo N=25**	**Overall N=72**
Sex			
Male	29 (61.7)	15 (60.0)	44 (61.1)
Female	18 (38.3)	10 (40.0)	28 (38.9)
Race			
White/Caucasian	42 (89.4)	21 (84.0)	63 (87.5)
Black/African American	1 (2.1)	1 (4.0)	2 (2.8)
Hispanic/Latino[#]	0	0	0
Asian	1 (2.1)	2 (8.0)	3 (4.2)
Other	3 (6.4)	1 (4.0)	4 (5.6)
Prior Use of Cannabis			
Yes	0	1 (4.0)	1 (1.4)
No	47 (100.0)	24 (96.0)	71 (98.6)
Nature of Diagnosis			
CP	43 (91.5)	21 (84.0)	64 (88.9)
Traumatic CNS injury	4 (8.5)	4 (16.0)	8 (11.1)
Gross Motor Function Classification Scale			
Level 1	0	0	0
Level 2	0	0	0
Level 3	1 (2.1)	0	1 (1.4)
Level 4	10 (21.3)	10 (40.0)	20 (27.8)
Level 5	36 (76.6)	15 (60.0)	51 (70.8)
Previously Taken Anti-spasticity Medication			
Taken at least 1	42 (89.4)	23 (92.0)	65 (90.3)
Botulinum toxin	36 (76.6)	21 (84.0)	57 (79.2)
Diazepam	14 (29.8)	7 (28.0)	21 (29.2)
Baclofen	13 (27.7)	7 (28.0)	20 (27.8)
Trihexyphenidyl	15 (31.9)	5 (20.0)	20 (27.8)
Benzodiazapine	11 (23.4)	5 (20.0)	16 (22.2)
Others	4 (8.5)	2 (8.0)	6 (8.3)
Gabapentin	4 (8.5)	0	4 (5.6)
Dantrolene	2 (4.3)	1 (4.0)	3 (4.2)

Table 8.2.1-1 Demographics and Baseline Characteristics, Randomised Phase Safety Analysis Set			
	Sativex N=47	**Placebo N=25**	**Overall N=72**
Tizanidine	1 (2.1)	1 (4.0)	2 (2.8)
Concomitant Anti-spasticity Medication			
Taking at least 1	45 (95.7)	20 (80.0)	65 (90.3)
Baclofen	33 (70.2)	16 (64.0)	49 (68.1)
Diazepam	15 (31.9)	5 (20.0)	20 (27.8)
Trihexyphenidyl/ Trihexyphenidyl hydrochloride	13 (27.7)	10 (40.0)	23 (31.9)
Midazolam	12 (25.5)	1 (4.0)	13 (18.1)
Gabapentin	4 (8.5)	2 (8.0)	6 (8.3)
Clobazam	3 (6.4)	1 (4.0)	4 (5.6)
Clonazepam	3 (6.4)	1 (4.0)	4 (5.6)
Tizanidine	4 (8.5)	0	4 (5.6)
Nitrazepam	1 (2.1)	0	1 (1.4)
Dantrolene	1 (2.1)	0	1 (1.4)
Oxazepam	1 (2.1)	0	1 (1.4)
	Mean (SD) [Range]		
Age (years)	12.58 (3.340) [8.0–18.0]	11.90 (2.390) [8.2–16.6]	12.34 (3.044) [8.0–18.0]
Height* (m)	1.344 (0.1852) [1.05–1.75]	1.339 (0.1599) [1.06–1.59]	1.342 (0.1757) [1.05–1.75]
Weight* (kg)	34.04 (14.560) [17.0–79.4]	31.26 (10.219) [16.1–52.8]	33.08 (13.207) [16.1–79.4]
BMI* (kg/m^2)	18.222 (4.7776) [12.35–33.68]	17.101 (3.5501) [12.17–27.33]	17.832 (4.3974) [12.17–33.68]
Time Since Diagnosis (years)	10.32 (4.217) [0.8–16.9]	10.53 (3.595) [1.5–15.6]	10.39 (3.988) [0.8–16.9]

Hispanic/Latino refers to participant ethnicity rather than race.

* Measured at Visit 1 (Day −7).

Concomitant medications were classified in accordance with the WHO-drug dictionary, Version June 2014 and the table shows the ATC fourth level subgroup within the corresponding ATC first level subgroup. Percentages were based on the number of participants in each treatment group in the safety analysis set.

Concomitant medications included all medications that a participant used at any stage during the trial.

Open-label Extension Phase:

Of the 68 participants who completed the randomised phase, 67 entered the OLE phase; comprising 43 participants who were previously exposed to Sativex and 24 participants who had taken placebo during the randomised phase of the trial. Since the majority of participants continued to the OLE phase of the trial, the demography and baseline characteristics mirrored almost exactly that of the randomised phase.

Assessor's comments:

The treatment groups were comparable at baseline in terms of age, sex, somatic measures, prior use of cannabis, GMFCS level and previous use of anti-spasticity medication. The aetiology of spasticity was due to CP in a higher proportion of participants randomised to Sativex compared to placebo (91.5% vs 84%); at least one concomitant anti-spasticity medication was taken by more patients in the Sativex group compared to the placebo group (95.7% vs 80%). For both groups, most patients had severe impairment of motor function (GMFCS level IV or V).

- Efficacy results

Randomised Phase:

All 72 (100.0%) randomised participants were included in the safety analysis set and the ITT analysis set. Overall 63 (87.5%) participants were included in the PP analysis set; 9 (12.5%) participants were excluded. Five (10.6%) participants from the Sativex treatment group were excluded from the PP analysis set and 4 (16.0%) participants were excluded from the placebo treatment group. The majority of exclusions were due to insufficient time on established dose (5 [6.9%] participants), followed by changes in anti-spasticity medications for 3 (4.2%) participants, and surgery during treatment for 1 (1.4%) participant.
After 12 weeks of treatment there was no statistically significant change for Sativex-treated participants' spasticity severity 0–10 NRS score compared with placebo participants.
The baseline spasticity severity 0–10 NRS score for Sativex participants was 6.958 (range 4.43 10.00; SD 1.3875) and for placebo participants was 6.680 (range 4.43–9.00; SD 1.3939).
Overall the mean change from baseline to the EOT in spasticity severity 0–10 NRS score for the ITT analysis set of this trial for those participants taking Sativex was −1.850 (range −6.37–+2.62; SD 1.9275). The mean change from baseline for those participants taking placebo was −1.573 (range −5.17–2.86; SD 2.0976). The least square mean (LSM) difference between the Sativex and the placebo treatment group for change in spasticity severity 0–10 NRS score from baseline to the EOT for the ITT analysis set was −0.166 (95% CI −1.119, 0.787); this was not statistically significant (p=0.7291).
Sensitivity analysis of the primary endpoint showed that the change in spasticity severity 0–10 NRS score from baseline to any weekly time period with observed data or with worst observation carried forward was not statistically significant when the Sativex treatment group was compared with the placebo group. Using the PP analysis set, again both treatment group participants had a baseline spasticity NRS score of greater than 5 and showed an improvement greater than 1.5 points which equates to an approximate 26.6% and 26.1% reduction from baseline in spasticity severity 0–10 NRS scores for Sativex and placebo participants, respectively.
Additionally, there was no statistically significant change for Sativex-treated participants compared with placebo participants for all secondary endpoints tested in this trial.

Subgroup analysis
The following subgroup analyses were performed for the primary endpoint only:
• Participants with no concomitant anti-spasticity medications taken during the trial.
• Participants with at least 1 concomitant anti-spasticity medication taken during the trial.
• CP participants.
• Traumatic CNS injury participants.
No statistically significant difference between the placebo and Sativex was found for any of these analyses. However, for both the traumatic CNS injury participant subgroup analysis and participants not taking concomitant anti-spasticity medications subgroup analysis it should be noted the sample size was small and the results should be interpreted with caution.

Open-label Extension Phase:
No statistical comparisons were made using data from the OLE phase.
The spasticity severity 0–10 NRS score for OLE participants at baseline was 6.830 (range 4.43–10.00; SD 1.4303) and the overall mean change in spasticity severity 0–10 NRS score from baseline to the last month of the OLE phase was −2.098 (range −6.47–+5.57; SD 2.4243). As a negative score is indicative of improvement, those participants who were exposed to Sativex during the randomised phase and during the OLE phase showed a slightly greater improvement compared with placebo–Sativex participants. Placebo–Sativex participants in the last month of the OLE compared with the EOT of the randomised phase showed a slight improvement in their spasticity severity 0–10 NRS scores (−6.17 vs. −5.17 ITT and PP analysis set). Longer exposure

to Sativex showed a marginal improvement in participants' mean spasticity severity 0–10 NRS scores compared with the shorter exposure time to Sativex during the randomised phase (−2.098 change from baseline to last month of OLE vs. −1.850 [change from baseline to EOT randomised phase; ITT analysis set] and −1.827 [change from baseline to EOT randomised phase; PP analysis set]).

MAH's efficacy discussion

The primary endpoint for this trial was the change in the validated 0–10 NRS spasticity severity score from baseline where a reduction from baseline is indicative of improvement. It was assumed that the average participants' spasticity 0–10 NRS score at baseline would be 5 and that the average improvement in spasticity with Sativex treatment would be 30% versus no improvement for the placebo participants. It has been shown that approximately a 20% reduction in spasticity NRS is minimally clinically relevant and this equates to a 1.5 point difference on the 0–10 NRS between active and placebo following treatment (30% is a clinically important difference). Although both the Sativex and placebo group participants had a baseline score greater than 5, they showed a spasticity NRS improvement of greater than 1.5 points at the EOT. Whilst the improvement in the Sativex group was greater than in the placebo group, the difference was not statistically significant.

It is postulated the higher than expected placebo response observed during the trial for the primary endpoint could be due to carer assessment (i.e., parents often desperate for their child's health and QOL to improve) rather than self-reported as had been done in previous Sativex trials, but given the patient population of this trial, carer-assessment was a necessity. Furthermore, the additional clinical visits and assessments compared with typically limited number of clinic visits may have provided a feeling of wellbeing. Even though participants were exposed to a stable Sativex dose for a relatively short time period during the randomised phase (due to a very cautious titration period) this is unlikely to have contributed to the lack of Sativex efficacy compared with placebo with respect to spasticity severity 0–10 NRS scores as a similar response was noted for longer exposure during the OLE phase (an approximate 26.6% reduction at the EOT of the randomised phase compared with an approximate 30.7% reduction in the last month of the OLE).

The MAH concluded that, given the outcome of this trial, perhaps a greater active: placebo ratio would have been beneficial in addition, an enriched trial design as per the adult pivotal trial may also have been more meaningful.

Assessor's comments:

The study did not meet its primary endpoint. The least square mean (LSM) difference between the Sativex and the placebo treatment group for change from baseline in spasticity severity 0–10 NRS score was −0.166 which is not clinically nor statistically significant (p=0.7291).

In PP analysis both groups showed a similar improvement in spasticity NRS score, in the range of 26%. This improvement may be clinically meaningful but may be attributed to the subjective nature of the outcome measure and to the treatment response expectancy, as hypothesised by the MAH.

The same primary efficacy endpoint was assessed in the pivotal trials in patients with moderate to severe spasticity due to multiple sclerosis (MS). Two phase 3 randomised placebo controlled trials, a 6-week Study (0106) and a 14-week Study (0403), showed weak evidence of efficacy and no efficacy respectively in the primary analysis. However, a meta-analysis of these 2 trials showed that responder rates for Sativex in comparison to placebo were more encouraging with mean response rate (30% improvement) of 35% for Sativex compared with 24% for placebo. Following these findings, the MAH performed a third trial with an enriched enrolment randomized withdrawal trial design (Study 0604). In this study patients who failed to respond in an initial 4-week therapeutic trial, were excluded.

The rationale behind the additional design is explained in the Public assessment report for Sativex: "The notion of a dichotomy of patients some of whom will show no response and some

of whom may show a good response seems plausible as does the argument that an important effect in some patients might be masked by the data "noise" from a large number of non-responders in an analysis of mean changes. It was agreed that in a situation where only a minority of patients might be expected to respond to a treatment, a therapeutic trail to identify the responders could in principle be justified provided that non-responders can be identified quickly and the risk to them of the therapeutic trial is low."
This study showed that patients who achieve a 20% response in the first 4 weeks derived benefit from continued treatment with Sativex as measured on the NRS. Subsequently Sativex received an indication in adults for the "treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy."

It should be noted that the mean difference found in the paediatric trial (-0.166) is even smaller than what was found in study 0106 in adults (around -0.5) or from that was found in the meta-analysis of the 2 adult trials (-0.34). A reduction of 0.166 points in an 11 point scale (NRS 0-10) is very small to be considered clinically relevant.
However, the MAH states that an enriched trial design as per the adult pivotal trial may also have been more meaningful for the paediatric study. The MAH is requested to provide a responder analysis similar to the one performed in adults. Although this analysis cannot change the negative results in the primary variable, it is requested to explore whether an alternative study design, i.e. an enrichment design, would be more meaningful in terms of demonstrating an effect.

The MAH has performed subgroup analysis with subgroups based on aetiology of spasticity and use or not of concomitant anti-spasticity medications. The results of this analysis were consistent with the primary analysis. The Sativex and placebo groups were overall comparable at baseline. Considering that the primary endpoint has not been achieved and the sample size is small to detect subgroup effects, no further subgroup analysis is recommended.

The results for the secondary endpoints were consistent with the results of the primary efficacy endpoint.

- Safety results

Randomised Phase:
Sativex was generally well tolerated. The incidence of all-causality treatment-emergent adverse events (TEAEs) was slightly higher in participants exposed to placebo compared with those exposed to Sativex (92.0% vs. 83.0%). Nearly all TEAEs by maximal severity were mild (53.2% Sativex and 60.0% placebo) or moderate (25.5% Sativex and 28.0% placebo) in severity and the most commonly reported within the Sativex group (i.e., reported in > 10% of participants) were vomiting (12.8% Sativex vs 16.0% placebo), retching (12.8% Sativex vs. 0% placebo), and somnolence (12.8% Sativex vs. 8.0% placebo).
Treatment-related TEAEs occurred at a higher incidence in those participants exposed to Sativex compared with those exposed to placebo (53.2% vs. 32.0%). Overall, the most common treatment-related TEAEs within the Sativex group (i.e., reported in > 10% of participants) were somnolence (12.8% Sativex vs. 4.0% placebo), and retching (10.6% Sativex vs. 0% placebo).
Only 2 (4.3%) participants experienced TEAEs that led to discontinuation of IMP; both participants were exposed to Sativex; 1 participant experienced stomatitis and oropharyngeal pain and the other participant experienced retching that were considered to be treatment-related. Both participants recovered shortly thereafter.

There were no serious adverse events (SAEs) with a fatal outcome during the trial and treatment-emergent serious adverse events (TESAEs) occurred at a slightly greater incidence in the placebo group (8.5% Sativex vs. 12.0% placebo). Only 1 participant had TESAEs that were considered to be Sativex-related by the investigator; a case of retching and food aversion from which the participant recovered following a reduction in Sativex dose.
AEs of special interest during the randomised phase of the trial included 1 participant with hallucination (participant recovered without intervention) and seizures experienced by 7 participants. All 7 participants had an ongoing medical history of epilepsy, however 2 participants experienced seizure-related TEAEs that were considered to be treatment-related.
There were no treatment-associated abnormalities of laboratory results, vital signs or electrocardiogram.

Open-label Extension Phase:
All 67 (100.0%) OLE participants were included in the OLE safety analysis set.
Sativex was generally well tolerated in this population of participants with CP or traumatic CNS injury during the extended time period of the OLE. The majority of TEAEs by maximal severity were mild (38.8%) or moderate severity (29.9%). The incidence of TEAEs during the OLE mirrored that of the Sativex group within the randomised phase (83.6% vs. 83.0%), and the incidence of treatment-related TEAEs was slightly lower during the OLE (44.8% vs. 53.2%).
The only notable difference in TEAEs by system organ class (SOC) was the greater incidence of AEs within Metabolism and nutritional disorders in the OLE phase compared with the Sativex group of the randomised phase (10.4% vs. 0%), and for treatment-related TEAEs by SOC the greatest difference was a lower incidence of AEs within Nervous system disorders during the OLE (17.9% vs. 25.5%). The greatest difference in TEAEs by preferred term (PT) in the OLE compared with the Sativex group of the randomised phase was a lower incidence of retching (4.5% vs 12.8%) and for treatment-related AEs by PT there was a lower incidence of somnolence (4.5% vs. 12.8%).
During the OLE phase of the trial, TEAEs of upper respiratory tract infection (16.4%), convulsion (14.9%), vomiting (13.4%), and lower respiratory tract infection (10.4%) were the most commonly reported (i.e., reported in > 10% of OLE participants). No treatment-related TEAEs were reported at an incidence of > 10%, however, vomiting (7.5%), convulsion (6.0%), somnolence (4.5%), and retching (4.5%) were the most frequently reported.
In total, 9 (13.4%) OLE participants developed all-causality TEAEs that led to discontinuation of IMP (compared with 4.3% Sativex participants during the randomised phase); of these 8 (11.9%) OLE participants developed AEs that were considered to be treatment-related. All but 2 participants recovered; 1 had hallucination auditory and 1 had hallucination, both events were reported as ongoing. The greater incidence of discontinuation was not considered an unexpected finding given the longer duration of the OLE.
There were no fatal SAEs during the OLE and TESAEs occurred at an incidence of 28.4% which was greater than that observed within the Sativex group during the randomised phase (8.5%).
The greater incidence of SAEs was not considered an unexpected finding given the longer duration of the OLE. Treatment-related TESAEs were reported for 8 (11.9%) participants; vomiting and convulsion were the most frequently reported (4.5% and 3.0%). AEs of special interest during the OLE phase included 1 participant who experienced a fall (unrelated to Sativex treatment), 1 participant who attempted suicide (unrelated to Sativex treatment), 1 participant who experienced hallucination auditory (treatment-related and ongoing), 1 participant who experienced hallucinations (treatment-related and ongoing), 1 participant who experienced a potential drug withdrawal syndrome, and seizure-related TEAEs in 13 participants (6 treatment-related), 12 of whom had an ongoing history of epilepsy or seizures. The seizure-related TEAEs resolved in all but 2 participants. Laboratory results and vital signs mirrored that noted during the randomised phase of the trial and no clinically significant trends were evident.

Due to this being the first trial to use Sativex in a paediatric population, this trial utilised a data safety monitoring committee. The committee assessed at intervals (25%, 50%, 75%, and 100%

participant recruitment) the progress of the trial and the safety data (primarily SAEs). Based on their findings the data safety monitoring committee recommended whether to continue, modify, or stop the trial.

MAH's safety discussion

Sativex was well tolerated at doses up to 12 sprays per day in participants with CP or traumatic CNS injury during the randomised phase as well as the longer exposure period (24 weeks) of the OLE; there was a particularly cautious titration period that need not be followed in future trials in a paediatric population. It is postulated that the doses tolerated may be due to the positive expectations participants and their carers had, which may have increased tolerance and reduced side effects reported.

The incidence of treatment-related TEAEs during this trial (randomised phase and OLE) was lower than that previously recorded for several Sativex spasticity/MS phase 3 trials.

There were no findings of note on laboratory analyses, vital signs or ECG during the randomised phase. Similarly, during the OLE there were no findings of note on laboratory analyses or vital signs and there were no new safety concerns identified in this paediatric participant population after 24 weeks of Sativex exposure. The below normal reference range creatinine levels observed in the majority of participants throughout the conduct of the trials (randomised and OLE phase) are likely related to the reduced muscle mass seen in participants with CP and traumatic CNS injury. Likewise abnormal electrolyte levels, as observed in some participants in both the placebo and Sativex arms of the trial, are common in these patient populations, therefore little clinical significance can be attributed to them.

Many of the AEs noted during the trial are typical of a paediatric population and also typical of the underlying condition as CP patients are prone to pulmonary aspiration and pneumonia, accidents, musculoskeletal spasticity and prevalent bowel and urinary issues include incontinence, urinary tract infections, and constipation.

The MAH concluded that there were no safety concerns identified in this paediatric participant population during the course of the trial.

Assessor's comments:

Treatment related TEAEs occurred at a higher incidence in participants exposed to Sativex compared with those exposed to placebo; the most common TEAEs in the placebo controlled phase were somnolence and retching. These were also observed in the open label phase but with a lower incidence.

Somnolence is mentioned as a common adverse event under nervous system disorders in section 4.8 of the Sativex SmPC. Retching is not mentioned; however, vomiting is mentioned under common adverse events of the GI system.

In the randomised phase, 2 (4.3%) participants experienced TEAEs (stomatitis and oropharyngeal pain and the other participant experienced retching) that led to discontinuation of IMP; both participants were exposed to Sativex. In total, 9 (13.4%) OLE participants developed all-causality TEAEs that led to discontinuation of IMP (compared with 4.3% Sativex participants during the randomised phase); of these 8 (11.9%) OLE participants developed AEs that were considered to be treatment-related. All but 2 participants recovered; 1 had hallucination auditory and 1 had hallucination, both events were reported as ongoing. One more patient had hallucination in the randomised phase but recovered without intervention.

Information relevant to hallucinations and other psychiatric symptoms is found in the SmPC in the following sections:

Section 4.3:

"The product is contraindicated in patients:

- with any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition."

Section 4.4:
- “Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with Sativex. These are likely to be the result of transient CNS effects and are generally mild to moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of Sativex medication.”
- “Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In any of these circumstances, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved.”

Psychiatric disorders (depressed mood, anxiety, hallucinations, food aversion) were frequent AEs leading to discontinuation in the open label phase.
Importantly it is mentioned that one patient attempted suicide which was unrelated to treatment. It is stated that the patient did not have a previous medical history of suicidal ideation. The IMP was stopped for this participant and they were withdrawn from the trial. The MAH is requested to provide more information about this case to understand how causality was assessed.

A patient presented with fall. This is captured in the SmPC in section 4.4 as:
“There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait.”

Potential drug withdrawal syndrome was noted in one patient. The SmPC mentions in section 4.4:
“The abrupt withdrawal of long-term Sativex treatment has not resulted in a consistent pattern or time-profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients.”

It is mentioned that seizure-related TEAEs were observed in 13 participants (6 treatment-related), 12 of whom had an ongoing history of epilepsy or seizures. The seizure-related TEAEs resolved in all but 2 participants. The MAH provides further details (within the study report) on the cases presenting with seizures:

Randomised phase: Seven (9.7%) participants experienced 14 seizure-related TEAEs (defined as TEAEs with a PT, lower level term or verbatim term containing ‘seizures’) during the randomised phase of the trial; 4 (8.5%) participants in the Sativex group and 3 (12.0%) participants in the placebo group. All participants had an ongoing medical history of epilepsy. Two participants experienced seizure-related TEAEs (PT: convulsion[s]) that were considered treatment-related; 1 (2.1%) in the Sativex group experienced 5 events (3 mild and 2 moderate in severity) whilst 1 (4.0%) in the placebo group experienced 2 events of mild severity. No action was taken with the IMP for any of the treatment-related events. The remaining TEAEs were not considered to be related to the IMP; all were mild in severity however 3 were TESAEs (in 1 placebo participant with serious partial seizures, 1 Sativex participant with serious grand mal convulsion and 1 Sativex participant with convulsion). The dose was temporarily reduced for the Sativex participant experiencing the serious grand mal convulsion.

OLE: Thirteen (19.4%) participants experienced 24 all-causality TEAEs (defined as TEAEs with a PT, lower level term or verbatim term containing ‘seizures’ or ‘convulsion’) during the OLE phase of the trial; 6 (25.0%) participants in the placebo–Sativex group and 7 (16.3%) participants in the Sativex–Sativex group. All but 1 participant had an ongoing medical history of epilepsy or seizures. The TEAE occurring in the participant without a medical history of epilepsy was reported using the PT convulsion (verbatim term: 3 seizures -evolving epilepsy).

The convulsion which began on Day 240 and resolved without intervention, on Day 255 was moderate and not considered to be treatment-related. Six (9.0%) participants experienced treatment-related seizure-related TEAEs, 4 (9.3%) in the Sativex–Sativex group and 2 (8.3%) in the placebo–Sativex group. Three (7.0%) participants in the Sativex–Sativex group and 3 (12.5%) participants in the placebo–Sativex group experienced TESAEs. IMP was interrupted for 2 participants experiencing moderate TESAEs of convulsion; both participants were in the Sativex– Sativex group. Sativex was interrupted for 1 participant in the placebo–Sativex group experiencing a mild TESAE of grand mal convulsion. The dose was reduced for 1 participant (in the placebo–Sativex group) with a moderate treatment-related TESAE. One (4.2%) participant in the placebo–Sativex group experienced seizures whilst hospitalised due to a TESAE. All but 2 participants were documented as recovered; both participants were in the Sativex–Sativex group.

The effect of Sativex in patients with epilepsy is unknown. The SmPC does not provide specific information on the effects of Sativex in epileptic patients but states in section 4.4: "Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures." Of note, seizures are not mentioned in section 4.8.
The applicant provided a summary of the cases but no narratives of these cases to further understand how causality was attributed to treatment or not and whether treatment with Sativex exacerbated seizures (or certain seizure types) in patients with a history of epilepsy. It is also not mentioned what percentage of the overall population had an epilepsy history to put the incidence of seizure related TEAEs in context. The MAH is requested to provide more details on these cases. Based on the review of these cases, the MAH should conclude on whether treatment-related seizures were more frequent in children compared to adults, if Sativex exacerbated seizures and what type of seizures. If needed, the MAH should propose relevant information for inclusion in the SmPC.

Overall, adverse events documented in this trial were consistent with what is already known for adults except for seizures for which further information is requested.

MAH's proposal for updating the SmPC
Based on the results of the paediatric study GWSP08258, the MAH proposed the following SmPC updates:

Section 4.2:
Paediatric population
Experience with Sativex in patients under the age of 18 years is limited.
Currently available data are described in section 5.1 but no recommendation on a posology can be made.
The safety and efficacy of Sativex in children aged 0 to 8 years have not yet been established.
~~**Children**~~
~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Section 5.1
Paediatric population
A Phase 3 trial to assess the efficacy of Sativex on spasticity in a population of children and adolescents aged from 8–18 years with cerebral palsy (CP) or traumatic central nervous system (CNS) injury has been completed. After 12 weeks of treatment, there was no statistically significant change for Sativex-treated participants' spasticity severity 0–10 NRS scores compared with placebo participants. No safety concerns were identified during the trial; the safety profile was considered acceptable for the participant population.

Currently no studies have been performed on children aged from 0–8 years.

Assessor's comments:
The assessor agrees that results of this paediatric study should be added in the SmPC as per the SmPC guideline:
For section 4.2, the results of this study justify the inclusion of the following:

Paediatric population
The safety and efficacy of Sativex in children 0-18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

For section 5.1, per the SmPC guideline: "The results of the main endpoints (using absolute figures), the doses used, and the main characteristics of the patients (age and number of patients) should be given. The results of the study should be provided whether positive or negative and if data are considered inconclusive, this should be stated. In presenting the results, it should be clear why an indication has not been granted, with a cross reference to section 4.2"

To include a more comprehensive description of study GWSP08258, the wording proposed by the MAH is proposed to be changed as follows:

Paediatric population
The efficacy and safety of Sativex was evaluated in a 12-week randomised, double-blind, placebo-controlled study involving 72 children and adolescents aged from 8–18 years with cerebral palsy or traumatic central nervous system injury. The placebo controlled phase was followed by a 24-week open label extension phase. The maximum permitted daily dose in this trial was 12 sprays and was titrated for 9 weeks. At baseline, most patients had severe impairment of motor function (Gross Motor Function Classification Scale level IV or V). The primary efficacy endpoint was the change in spasticity severity 0–10 numerical rating scale (NRS) score from baseline which is a carer reported outcome measure.
After 12 weeks of treatment, the mean change from baseline for Sativex-treated participants' spasticity severity 0–10 numerical rating scale (NRS) scores was −1.850 (SD 1.9275) and for placebo participants −1.573 (SD 2.0976). The least square mean difference between the two groups (−0.166, 95% CI −1.119, 0.787) was not statistically significant (p=0.7291).
No new safety findings were identified in this study.
No data are available in children below 8 years (see section 4.2 for information on paediatric use).

Information on paediatric population is already included in section 4.4 of the SmPC: "Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data." As new more specific wording on use of Sativex in the paediatric population is proposed, this sentence can be deleted from section 4.4.

Member states' comments (day 70)
Comments were received from 3 member states. The MSs endorsed the rapporteur's assessment but had additional comments:

MS1 comments:

Section 4.2

To date safety and efficacy of Sativex in children have not been established and it cannot be foreseen if they will ever be established. Therefore we propose to delete the word “yet”:

MS2 comments:

The Rapp’s proposal for SmPC 4.2 update is supported, but we suggest to delete the word ”yet”.

Regarding the rapporteur’s recommendation to remove the following sentence in SmPC 4.4:

~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

It is suggested to keep this warning as efficacy has not been demonstrated. In addition, the paediatric population studied are patients with cerebral palsy or traumatic central nervous system injury which is not same as the approved indication for MS patients in adults. Paediatric data for MS patients are still lacking.
Therefore, we suggest to modify the wording as follows:

Sativex is not recommended for use in children or adolescents 8-18 years of age due to limited safety and efficacy data. No data are available in children below 8 years of age.

MS3 comments:
For section 4.2 of the SmPC, the statement suggested by the MAH could be kept with the following minor modification:
Paediatric population
Experience with Sativex in patients under the age of 18 years is limited.
Currently available data are described in section 5.1 but no recommendation on a posology can be made.
The safety and efficacy of Sativex in children aged 0 to 8 years have not ~~yet~~ been established.

Assessor’s comments:
The proposal of all three MSs to delete the word “yet” from section 4.2 paediatric information is acceptable. The wording proposed by the MAH for section 4.2 has been modified by the rapporteur, in order to use one of the standard statements of the SmPC guideline to indicate that there is no indication for a subset of the paediatric population. We therefore maintain our initial proposal to keep this wording in section 4.2: “The safety and efficacy of Sativex in children 0-18 years of age have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.”

MS2 has proposed to keep the sentence in section 4.4 with a minor change, as efficacy in children 8-18 years has not been demonstrated.

The rapporteur agrees with MS2 that, based on the submitted study, there are concerns about the efficacy of Sativex in children with spasticity due to CP/CNS injury. Because of these concerns, it was initially considered to include in section 4.2 a different standard statement, i.e. “Sativex should not be used in children 8-18 years because of efficacy concerns (see section 5.1)”. However, we considered the following:
- The submitted study had potential limitations (in terms of study population and validity of the primary efficacy outcome) to evaluate robustly the efficacy of Sativex in children with spasticity.
- As MS2 mentions, there are available data only for a specific patient population in terms of disease and age group and therefore no data for children below 8 years of age or with spasticity due to MS.

We therefore concluded that the more general statement in section 4.2 that safety and efficacy have not been established/no posology recommendation, without specifying any indication and covering the whole paediatric age group, was more appropriate. The prescriber is then referred to section 5.1 to find further information on the specific patient population for which data are available.
Moreover, regarding safety and pending the MAH's responses on seizure related AEs, a specific safety concern/risk has not been identified in the paediatric population to justify this sentence in section 4.4. As this sentence does not offer additional paediatric information to the proposed wording in section 4.2 and 5.1, we propose to delete it from section 4.4.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AT DAY 89

List of questions:

1. The MAH is requested to provide a responder analysis as the one performed in adults. Although this analysis cannot change the negative results in the primary variable, it is requested to explore whether an alternative study design, i.e. an enrichment design, would be more meaningful in terms of demonstrating an effect.
2. The MAH is requested to provide information about the case of a patient presenting with attempted suicide during the open label phase to better understand how causality was assessed.
3. The MAH is requested to provide details on the cases of patients presenting with seizure related AEs as well as the percentage of the overall study population that had a history of epilepsy to put the incidence of seizure related TEAEs in context. Based on the review of these cases, the MAH should conclude on whether treatment-related seizures were more frequent in children compared to adults, if Sativex exacerbated seizures and what type of seizures. If needed, the MAH should propose relevant information for inclusion in the SmPC.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1:
The MAH is requested to provide a responder analysis as the one performed in adults. Although this analysis cannot change the negative results in the primary variable, it is requested to explore whether an alternative study design, i.e. an enrichment design, would be more meaningful in terms of demonstrating an effect.

MAH's response:
A responder analysis has been conducted as requested using cut-offs of 30% and 50% improvement in spasticity NRS score. This compares the end of treatment to baseline using the same definitions as for the primary endpoint. At both responder cut-offs there is no difference between Sativex and placebo in the percentage of patients meeting the improvement level.

The table below presents a summary of the statistics where it can be seen that the percentages are the same for active vs. placebo.

Responder Table 1: Summary of Spasticity Severity NRS Score Responders
Baseline to End of Treatment
(ITT Analysis Set)

Variable		Randomised Treatment Sativex (N=47)	Placebo (N=25)
30% Improvement in Spasticity	Yes	17 (36.2%)	9 (36.0%)
	No	30 (63.8%)	16 (64.0%)
50% Improvement in Spasticity	Yes	10 (21.3%)	5 (20.0%)
	No	37 (78.7%)	20 (80.0%)

ITT: Intent-to-treat. Baseline is defined as the average of Day -7 to Day -1.
End of Treatment is the average of the last 7 days of diary data up to the earliest of Day 84, the last dose of IMP (as stated on the study outcome CRF page) and the last day with relevant efficacy data.
The summary is based on the question "…Think carefully about how your child's muscles have felt today and circle a number from 0 to 10 that best describes this" collected in the Diary.

Assessor's comments:

A responder analysis was submitted which shows that there are no differences between the placebo and Sativex group both for 30% and 50% improvement in spasticity scores. Issue resolved.

Question 2
The MAH is requested to provide information about the case of a patient presenting with attempted suicide during the open label phase to better understand how causality was assessed.

MAH's response:
The MAH provided the detailed SAE case summary for the patient presenting with attempted suicide. This case is summarised in the public assessment report for confidentiality reasons.

This clinical trial case concerned a 9-year-old boy with a history of spasticity and dystonia due to cerebral palsy (GMFCS level IV and was dependent on family for all personal care), seizures due to epilepsy, gastro-oesophageal reflux disease and other associated comorbidities. The boy has no individual or family history of any psychological or psychiatric events prior to participating in the study. He was not receiving any medications concomitantly.

The patient was allocated to the placebo group in the randomised controlled phase and received Sativex only in the open label phase for approximately 4-4.5 months. The dose was reduced after he experienced drowsiness, dry mouth and nausea and stopped temporarily after the patient developed auditory hallucinations. Within 10 days from treatment cessation, Sativex was recommenced, subsequently the dose was reduced, and treatment stopped again as the patient had persisting hallucinations, worsening anxiety and depressive symptoms and presented with a medically significant SAE of suicidal ideation and attempted suicide.

Investigator's comment: The Investigator considered the event of suicidal ideation and attempted suicide to be unrelated to open-label study medication (Sativex).

MAH's comment: Suicidal ideation is listed in the Investigator Brochure (DCSI dated 30 November 2015) for Sativex. The MAH considered the event to be unrelated to the open-label study medication (Sativex). Confounding factors include increasing levels of anxiety secondary to his functional disability.

Assessor's comments:
The boy was tested with the children's depression inventory (CDI) at various timepoints. At screening he provided answers that indicate some depressive symptomatology which carries on at subsequent visits. It is not reported what was the overall score in the CDI, if there was a predetermined cut off score for referring the patient, and if needed, whether this patient has been appropriately and timely referred to a mental health professional.
Based on the narrative provided, it cannot be determined whether there was a causal association between treatment and the event or if the drug exacerbated previous symptomatology as the patient may have had depressive symptoms even before start of treatment. According to the psychiatrist, investigator and MAH, the event seems not to be related to study medication and according to the psychiatrist " ..associated with increasing levels of anxiety secondary to little improvement in functional disability..".
The SmPC already mentions psychotic illness as a contraindication and in section 4.4 mentions that psychiatric symptoms have been reported and a causal association with treatment cannot be ruled out. In such cases, the SmPC advises that the drug should be stopped immediately, and the patient monitored until symptoms have resolved.
No further SmPC updates are warranted based on this event.

Question 3:
The MAH is requested to provide details on the cases of patients presenting with seizure related AEs as well as the percentage of the overall study population that had a history of epilepsy to put the incidence of seizure related TEAEs in context. Based on the review of these cases, the MAH should conclude on whether treatment-related seizures were more frequent in children compared to adults, if Sativex exacerbated seizures and what type of seizures. If needed, the MAH should propose relevant information for inclusion in the SmPC.

MAH's response:
Specific details of the reported seizure events during the blinded and open label phases of the GWSP0258 study were provided, summarized from the study report (these are already mentioned in the safety section under assessor's comments). The MAH concluded:

The incidence of seizures was equivalent in the active treatment arm (3 patients (8.5%) and placebo treatment arms (3 patients (12%) during the randomized phase of the GWSP08258 study. During the open label study, 13 patients (19.4%) reported a convulsion TEAE, which was not an unexpected finding in consideration of the longer duration of the open label study
21 patients (44.7%) in the Sativex treatment group and 9 patients (36%) in the placebo group of the GWSP08258 study had a documented medical history of epilepsy; 30 patients (41.7%) overall. With the exception of 1 patient, all seizure terms reported during the GWSP08258 study were in patients with a documented history of epilepsy.
4 of the seizures in the blinded randomized phase referenced an increased seizures component and 5 seizure terms in the open label phase referenced an increased / prolonged seizure component. There was no evident pattern in relation to the time to onset for these seizure types.
The MAH does not consider the specific study population to be representative for assessing a potential increased exacerbation of seizures in children, in consideration of the underlying background incidence of epilepsy in the patient population (predominantly cerebral palsy) and as the seizure episodes were (with the exception of 1 patient) in patients with a documented history of epilepsy.
The MAH is not proposing additional wording to be referenced in the SmPC in relation to seizures in the paediatric population.

Assessor's comments:

The MAH's explanation is satisfactory. Based on the study results, it cannot be concluded that Sativex exacerbated seizures in patients with epilepsy. Issue resolved.

Member states' comments at day 89

Following the circulation of day89 PdAR, comments from MS4 were received:

The following changes of the text is proposed as indicated:

Section 4.2

Paediatric population

Sativex is not recommended for use in children or adolescents below 18 years of age. T~~t~~he safety and efficacy of Sativex in children 0-18 years of age **is not** ~~have not yet been~~ established. **A RCT was performed in children and its results regarding efficacy was negative. These data are described in section 5.1.** ~~Currently available data are described in section 5.1 but no recommendation on a posology can be made.~~

Section 4.4

~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Argumentation

Efficacy was not shown in randomised control clinical trial. The study was clearly negative not inconclusive (p=0.7291). The statement that no recommendation on a posology can be made, suggests Sativex still may be used. Therefore, CMS suggests emphasising the lack of efficacy for children in SmPC.

For section 5.1, the CMS agrees with the overall conclusion of the RMS, however recommends instead of mean change scores for NRS, absolute values for the baseline and result in two groups be mentioned.

CMS recommends changes in following statement from section 5.1:

Safety findings were in general the same as in the adult studies, with exception of retching. ~~No new safety findings were identified in this study.~~

Argumentation

In the study retching was one of the most commonly reported treatment-emergent adverse events (TEAEs) in those participants exposed to Sativex compared with those exposed to placebo (10.6% Sativex vs. 0% placebo). As this side effect is not mentioned in the current SmPC, CMS proposes to also name this safety finding.

Assessor's comments:

The MS4 comments are endorsed. According to the SmPC guideline, when there is no paediatric indication, one of standard statements should be used. We agree to add the sentence "Sativex is not recommended for use in children or adolescents below 18 years of age" and thus the sentence "The safety and efficacy of Sativex in children 0-18 years of age is not established" is not further needed and we propose to delete it. In conclusion, the following is proposed for section 4.2:

Sativex is not recommended for use in children or adolescents below 18 years of age. A randomised placebo-controlled trial was performed in children and its results regarding efficacy were negative. These data are described in section 5.1.

We agree with the rest of MS4 proposals for section 5.1 wording and the text will be changed to:

Paediatric population
The efficacy and safety of Sativex was evaluated in a 12-week randomised, double-blind, placebo-controlled study involving 72 children and adolescents aged from 8–18 years with cerebral palsy or traumatic central nervous system injury. The placebo-controlled phase was followed by a 24-week open label extension phase. The maximum permitted daily dose in this trial was 12 sprays and was titrated for 9 weeks. At baseline, most patients had severe impairment of motor function (Gross Motor Function Classification Scale level IV or V). The primary efficacy endpoint was the change in spasticity severity 0–10 numerical rating scale (NRS) score from baseline which is a carer reported outcome measure.
The baseline spasticity severity 0–10 NRS score for Sativex-treated participants was 6.958 (range 4.43–10.00;SD 1.3875) and for placebo participants was 6.680 (range 4.43–9.00; SD 1.3939). After 12 weeks of treatment, the NRS was 5.107 (range 0.43-10.00; SD 2.0978) for Sativex-treated participants and 5.107 (range 1.86-9.86; SD 2.0468) for placebo participants. The least square mean difference between the two groups (−0.166, 95% CI −1.119, 0.787) was not statistically significant (p=0.7291).
Safety findings were in general the same as in the adult studies, with exception of retching. No data are available in children below 8 years (see section 4.2 for information on paediatric use).

Member states' comments at day 115:
Following the circulation of day90 PdAR, comments were received from 2 MSs who endorsed the rapporteur's conclusion and had no further comments.
MS1 endorsed the rapporteur's assessment, but also had additional comments:

1. Section 4.2 of the SmPC:

The indication in the trial performed in children and adolescents differs from the authorised indication and therefore we recommend rephrasing the new wording proposal as follows:
"Paediatric population
Sativex is not recommended for use in children or adolescents below 18 years of age. A randomised placebo-controlled trial was performed in children and adolescents with cerebral palsy or traumatic central nervous system injury and its results regarding efficacy were negative. These data are described in section 5.1."

2. MS1 comments concerning MAH's response to Question 3:

There is an inconsistency concerning the incidence of seizures: page 21 of the PdAR (assessor's comments): " Seven (9.7%) participants experienced 14 seizure-related TEAEs (defined as TEAEs with a PT, lower level term or verbatim term containing 'seizures') during the randomised phase of the trial; **4 (8.5%) participants in the Sativex group** and 3 (12.0%) participants in the placebo group."
Page 29 of the PdAR (MAH's response):
" The incidence of seizures was equivalent in the **active treatment arm (3 patients (8.5%**) and placebo treatment arms (3 patients (12%) during the randomized phase of the GWSP08258 study."
Concerning a possible aggravation of a known seizure disorder by intake of Sativex the MAH's response is not satisfactory for excluding such an aggravation: " 4 of the seizures in the blinded

randomized phase referenced an increased seizures component and 5 seizure terms in the open label phase referenced an increased / prolonged seizure component."
More information is needed. How many of the 4 seizures in the blinded randomized phase referencing an increased seizure component occurred in the Sativex group? And how has been excluded that the 5 seizure terms in the open label phase referencing an increased/prolonged seizure component have been induced by the intake of Sativex? It still has not been excluded that the intake of Sativex can exacerbate seizures in patients with a history of epilepsy.

Assessor's comments:
The MS1 comment regarding specifying the study population in the paediatric study is endorsed as is the proposed wording for section 4.2.

With regards to the number of patients experiencing seizure-related TEAEs in the two arms during the randomised period, the MAH's response does not reflect the numbers in the study report; according to the report the number of patients is 4 and 3 in the Sativex and placebo group respectively.

We acknowledge that the MAH has not provided many details on these events. However, considering the low number of patients, almost equal seizure frequency in Sativex and placebo arms and the fact that these patients have epilepsy with natural fluctuation in seizure frequency, it will be challenging to receive any more meaningful information with an aim of updating the SmPC. There is already a warning in the SmPC: "Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures." and therefore no further SmPC amendments should be proposed at this stage.
The MAH should continue monitoring, via the appropriate PV regulatory procedures, seizure-related AEs in patients receiving Sativex to ensure identification of this potential safety signal and, if needed, further regulatory actions should be taken.

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH submitted the final report for study GWSP08258. This was a 12-week parallel group randomised, double-blind, placebo-controlled study in 72 children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic central nervous system injury who have not responded adequately to their existing anti-spasticity medications. The randomised phase was followed by a 24-week open-label extension (OLE) phase.
The study did not meet its primary endpoint. Additionally, there was no statistically significant change for Sativex-treated participants compared with placebo participants for all secondary endpoints tested in this trial.
Safety findings in this study were in general the same as in the adult studies, with the exception of retching. The MAH was asked to review cases of patients presenting with seizure-related AEs. Based on the submitted data, no SmPC wording is proposed to be added further to the existing one relating to seizures. However, the MAH should continue monitoring seizure-related AEs in patients receiving Sativex to ensure identification of this potential safety signal and, if needed, further regulatory actions should be taken.
Based on the data provided as part of this paediatric work-sharing procedure under Article 46, the benefit-risk balance of Sativex remains unchanged.

- **Recommendation**

The following SmPC changes are proposed:

Section 4.2
[…]
Paediatric population
Sativex is not recommended for use in children or adolescents below 18 years of age. A randomised placebo-controlled trial was performed in children and adolescents with cerebral palsy or traumatic central nervous system injury and its results regarding efficacy were negative. These data are described in section 5.1.

~~**Children**~~
~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Section 4.4
[…]
~~Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.~~

Section 5.1
[…]
Paediatric population
The efficacy and safety of Sativex was evaluated in a 12-week randomised, double-blind, placebo-controlled study involving 72 children and adolescents aged from 8–18 years with cerebral palsy or traumatic central nervous system injury. The placebo-controlled phase was followed by a 24-week open label extension phase. The maximum permitted daily dose in this trial was 12 sprays and was titrated for 9 weeks. At baseline, most patients had severe impairment of motor function (Gross Motor Function Classification Scale level IV or V). The primary efficacy endpoint was the change in spasticity severity 0–10 numerical rating scale (NRS) score from baseline which is a carer reported outcome measure.
The baseline spasticity severity 0–10 NRS score for Sativex-treated participants was 6.958 (range 4.43–10.00;SD 1.3875) and for placebo participants was 6.680 (range 4.43–9.00; SD 1.3939). After 12 weeks of treatment, the NRS was 5.107 (range 0.43-10.00; SD 2.0978) for Sativex-treated participants and 5.107 (range 1.86-9.86; SD 2.0468) for placebo participants. The least square mean difference between the two groups (−0.166, 95% CI −1.119, 0.787) was not statistically significant (p=0.7291).
Safety findings were in general the same as in the adult studies, with exception of retching. No data are available in children below 8 years (see section 4.2 for information on paediatric use).

A Type IB procedure shall be submitted within 30 days by the concerned MAH after the end of the procedure in order to update the product information.