Opsoclonus Myoclonus Syndrome/Dancing Eye Syndrome (OMS/DES) in Children With and Without Neuroblastoma (NBpos and NBneg)

Inclusion Criteria:

Children with newly diagnosed OMS/DES either NB-pos or NB-neg.

Three out of the following four components are necessary for the diagnosis of OMS/DES:

- Opsoclonus or ocular flutter (but not nystagmus)
- Ataxia and/or myoclonus
- Behavioural change and/or sleep disturbance
- Neuroblastoma The diagnosis of OMS/DES may be difficult in some patients. Opsoclonus, in particular, may be intermittent or late in onset. A video example will be available at www.dancingeyes.org.uk. If uncertain, please contact the national coordinator for support in interpreting clinical features.

- Age 6 months or over up to less than 8 years (< 8th birthday) The date of diagnosis of OMS/DES is the date on which a doctor confirms the condition to be OMS/DES. The date of symptom onset needs also to be documented.
Treatment start with the standard corticosteroid treatment with dexamethasone pulses as proposed by the guidelines given in this trial protocol (see 11.10, page 71).

- In patients with presumed NB-neg OMS/DES, neuroblastoma must be excluded according the guidelines of this trial (see chapter 4.4.1.4, page 30, and appendix 11.9, page 70)
- Documented informed consent for treatment and enrolment in the trial by parents / legal representatives.

**Exclusion Criteria:**

Patients with opsoclonus, myoclonus or ataxia caused by other identified disease (e.g. current active CNS infection, neurometabolic disorder or demyelination).

An identified viral precursor is not an exclusion criterion.

- prior or parallel use of chemotherapy (other than required for treatment of the neuroblastoma)
- Corticoid steroid for OMS/DES or other reasons lasting 14 days or more immediately before treatment start according the standard treatment proposed (treatment with corticosteroids for less than 14 days will be allowed)
- contraindication of use of one of the experimental study drug (cf Summary of Product Characteristics used in this study)
11.10. Treatment guidelines and treatment plans

11.10.1. Guidelines for the standard corticoid treatment (Dexamethasone pulse therapy)

A corticosteroid standard treatment starting with dexamethasone pulse therapy is recommended for all patients with OMS/DES. Prompt treatment is generally regarded as important. Therefore, treatment should start as soon as the diagnosis of OMS/DES is established. In case of OMS/DES with Neuroblastoma, treatment start may, if it is felt to be clinically appropriate, be delayed until after resection of the tumour (but not for more than 14 days from diagnosis).

This dexamethasone standard treatment with 12 (– 14) scheduled pulses of dexamethasone (approximately one year of treatment) should be completed even if complete remission of OMS/DES symptoms is achieved during treatment. In patients not responding to dexamethasone alone, therapy will be intensified according to the guidelines of this trial (see 4.5, page 39ff).

Hospitals, where the trial has not officially been opened, will undertake the necessary activities to open the trial in their center during that initial treatment phase. In that case, the trial should be opened officially at the latest at the time-point for the first treatment escalation (see 4.5.3, page 39).

Dexamethasone pulse therapy:

20 mg/m² dexamethasone on 3 consecutive days every month for a total of 12 pulses (one year of treatment).

Administration modality:
- i.v., for
  - to be given as 2 hr infusion
  (for practical issues: e.g. in severely ill or very irritable children)
  - or

  orally, if possible,
  When given orally, the total daily dose of 20 mg/m² is split into
  2 doses of 10 mg/m²

In patients who show no improvement of symptoms or who show worsening of symptoms in the first 2 weeks after the first pulse of dexamethasone, an additional dexamethasone pulse may be added after two weeks in between the first and the scheduled second dexamethasone pulse. In the same way, an additional dexamethasone pulse may be added in the interval between the scheduled second and the scheduled third dexamethasone pulse (i.e. the total number of pulses in 12 months may be 12 - 14).

The interval between the scheduled dexamethasone pulses may be shortened by up to one week in patients showing improvement after dexamethasone, but worsening of symptoms prior to the schedule date of the next dexamethasone pulse.

The scheduled doses (12 (– 14) pulses of dexamethasone; approximately one year of treatment) should be completed even if complete remission of OMS/DES symptoms is achieved during treatment.

Patients scheduled to receive chemotherapy for Neuroblastoma according to the appropriate European or national trial will receive dexamethasone therapy in parallel with the chemotherapy required by the trial. As most current neuroblastoma trials schedule chemotherapy pulses in 3 week intervals, the interval of the dexamethasone pulses may be adapted.
In case the intervals between the pulses have been shortened, the time-points of scoring of OMS/DES symptoms (see 4.4.2.2, page 33) will be adapted to 3 weeks intervals (=prior to the scheduled pulses). The decision for escalation to dexamethasone/CP will be made after 3 scheduled dexamethasone pulses and immediately before the 4th scheduled dexamethasone pulse (see below), even if the interval has been shortened. In patients with one or two additional dexamethasone pulses (see above), the decision for escalation will be made after 3 scheduled + 1 – 2 additional dexamethasone pulses.

**Monitoring of therapy and side effects and supportive care:**
- gastritis prophylaxis during dexamethasone administration with H2-blockers and/or antacids is strongly recommended (according to the local use).
- during administration of intravenous dexamethasone, blood pressure and urine for glucose should be monitored according to local guidelines
- during therapy with dexamethasone, blood count, electrolytes, and blood glucose (or urine stick for glucose) should be monitored at regular intervals according to the use of the local hospital or as clinically indicated. These investigations should be extended to include liver enzymes, c-reactive-protein, total protein, clotting studies (INR and PTT) at longer intervals.
11.9. Guidelines for imaging at diagnosis

The following investigations are required:

- **MRI of the head**
  - including at least the following sequences:
    - transversal:
      - T1-weighted (T1w), T1-w contrast enhanced, T2-w, FLAIR
    - coronal:
      - T1-w, T1-w contrast enhanced
    - sagittal:
      - T2-w, FLAIR

**First line imaging to search for neuroblastoma:**

- **X-ray of the chest:**
  - AP, optional lateral

- **ultrasound**
  - of neck with particular attention to the sympathetic chain; of abdomen and pelvis with special attention to the adrenal and paravertebral regions

- **mIBG scintigraphy**
  - with 123I-MIBG in sufficient dose according to the current recommendations of EANM (80 – 370 MBq according body weight)
  - to be done in nuclear medicine institutes experienced in diagnosis and follow up of neuroblastoma as recommended by national or international neuroblastoma trials
  - single photon emission computed tomography (SPECT) is recommended
  - after appropriate blocking of the thyroid
    - (e.g. as recommended by the European guidelines (Ollivier, Colaninha et al. 2003; van Santen, de Kraker et al. 2003))

If a neuroblastoma is found in first line imaging, follow the imaging guidelines of the appropriate current national or European protocols for neuroblastoma.

If no neuroblastoma is found in first line imaging, second line imaging is required:

**Second line imaging to search for neuroblastoma:**

- **MRI**
  - in 4 mm sections of regions typically affected by neuroblastoma
    - paraspinal regions (cervical, thoracic, abdominal and pelvic)
    - adrenal regions
  - including at least the following sequences:
    - abdomen/pelvis:
      - transversal T1-w, T2-w sequence, T2-w fat suppression
      - coronal: T2-w
    - sagittal (spine) transversal T1-w, T2-w sequence, T2-w fat suppression
    - chest:
      - transversal T1-w, T2-w sequence
      - coronal: T2-w
    - sagittal (spine) transversal T1-w, T2-w sequence, T2-w fat suppression
    - neck:
      - transversal T1-w, T2-w sequence
      - sagittal (spine) transversal T1-w, T2-w sequence, T2-w fat suppression

If a tumour is suspected in one of the native investigations, T1-w contrast enhanced sequence of that investigation (abdomen, chest, or neck) should be added.

To guaranty sufficient quality of MRI and mIBG-scintigraphy, general anesthesia will be necessary for most of the children.
<table>
<thead>
<tr>
<th>Date:</th>
<th>at Diagnosis</th>
<th>prior to therapy</th>
<th>week 1</th>
<th>week 2</th>
<th>week 3</th>
<th>week 4</th>
<th>week 6</th>
<th>week 8</th>
<th>week 12</th>
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<tbody>
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<td><strong>Stance</strong></td>
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<td>Standing and sitting balance normal for age</td>
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<td>Mildly unstable standing for age, slightly wide-based</td>
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<td>Unable to stand without support but can sit without support</td>
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<td>Unable to sit without using hands to prop or other support</td>
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<td><strong>Gait</strong></td>
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<td>Mildly wide-based gait for age but able to walk indoors and outdoors independently</td>
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<td>Walks only or predominantly with support from person or equipment</td>
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<td>Unable to walk even with support from person or equipment</td>
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<td><strong>Arm and hand function</strong></td>
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<td>Normal for age</td>
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<td>1</td>
<td>Mild infrequent tremor or jerkiness without functional impairment</td>
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<td>2</td>
<td>Fine motor function (e.g. pinprick grip of small object, pencil use) persistently impaired for age but less precise manipulative tasks (e.g. playing with larger toys loading, dressing) normal or almost normal,</td>
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<td>Major difficulty with all age-appropriate manipulative tasks,</td>
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<td><strong>Opsoclonus</strong></td>
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<td>Rare or only when elicited by change in fixation.</td>
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<td>Frequent, interfering frequently with fixation and/or tracking</td>
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<td>Persistent, interfering continuously with fixation and tracking</td>
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<td><strong>Mood/behaviour</strong></td>
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<td>Mild increase in irritability but consolable and/or mild sleep disturbance but easily settled</td>
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<td>Irritability and sleep disturbance, interfering substantially with child and family life.</td>
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<td>Persistent severe distress.</td>
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In addition please record for all children aged 18 months or less:

- Able to hold head consistently erect when trunk vertical?
- Able to reach and grasp object with each hand?
- Able to roll back to front and front to back?
- Able to finger-feed self?

Please document also parents’ overview of symptoms for previous two weeks (compared to last assessment): worse, same, mild improvement, marked improvement, normal (see page 33).

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