CASE REPORT FORM (CRF)
A Retrospective, Multinational Study of Patients with Leigh Syndrome

Site ID: __ __	Patient ID: __ __ __ __	Date of registration: __/__/_____

INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA		
1. Clinical features compatible with Leigh syndrome, i.e. psychomotor regression, brainstem dysfunction, ataxia, dystonia, optic atrophy	☐ **Yes**	☐ No
2. MRI or CT or neuropathological findings of Leigh syndrome, i.e. bilateral symmetrical lesions in the basal ganglia, and/or thalamus, and/or brainstem§.	☐ **Yes**	☐ No
All inclusion criteria must be answered **Yes**, to be included in the study.		
EXCLUSION CRITERIA		
1. Known syndromic mitochondrial phenotype other than Leigh syndrome.	☐ Yes	☐ **No**
All exclusion criteria must be answered **No**, to be included in the study. If any of the exclusion criteria is answered Yes, the patient must be excluded from the study and no data must be collected in the following fields of the present CRF.		

DEMOGRAPHICS

- **Date of birth** (mm/yyyy): __/_____
- **Gender**: ☐ male ☐ female
- **Race**: ☐ caucasian ☐ black ☐ asian ☐ other_____ ☐ Unknown

FAMILY HISTORY

- **Parental consanguinity**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify degree of relatedness: _____
- **Presence of Leigh (or Leigh-like) syndrome in a relative**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify a) gender: ☐ Male ☐ Female ☐ Unknown
  b) origin of relatedness: ☐ Maternal ☐ Paternal ☐ Unknown
  c) degree of relatedness: ☐ 1st-degree ☐ 2nd-degree ☐ 3rd-degree ☐ >3rd-degree ☐ Unknown

- **Presence of other mitochondrial disorder in a relative**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify a) Disorder_____,
  b) Origin of relatedness: ☐ Maternal ☐ Paternal ☐ Unknown
  c) Degree of relatedness: ☐ 1st-degree ☐ 2nd-degree ☐ 3rd-degree ☐ >3rd-degree ☐ Unknown

- **Presence of other neurological disorder in a relative**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify a) Disorder_____,
  b) Origin of relatedness: ☐ Maternal ☐ Paternal ☐ Unknown
  c) Degree of relatedness: ☐ 1st-degree ☐ 2nd-degree ☐ 3rd-degree ☐ >3rd-degree ☐ Unknown
- **Comments** _____

MEDICAL HISTORY

Perinatal History

- **Gestational age**: ☐ <35 weeks ☐ 35-37 weeks ☐ 38-41 weeks ☐ >41 weeks ☐ Unknown
- **Pregnancy**: ☐ uneventful ☐ complicated by _____ ☐ Unknown
- **Birth weight**§: ☐ AGA ☐ SGA ☐ LGA ☐ Unknown
- **Did the fetus present intra-uterine growth restriction (IUGR)**§: ☐ Yes ☐ No ☐ Unknown
- **Head circumference at birth**§: ☐ normal ☐ microcephaly ☐ macrocephaly ☐ Unknown
- **APGAR score at 1-5-10 minutes**: ☐ - ☐ - ☐ ☐ Unknown
- **Respiratory difficulties at birth necessitating interventions**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify: ☐ oxygen by mask ☐ nasal CPAP ☐ intubation/ventilation
- **Any pathological signs at birth**: ☐ No ☐ Yes ☐ Unknown
  If yes, specify: ☐ hypotonia/floppiness ☐ hypertonia ☐ respiratory complications ☐ seizures
  ☐ dysmorphic features ☐ cardiac complications ☐ congenital lactic acidosis
  ☐ other: _____
- **Prenatal onset of symptoms**: ☐ Yes ☐ No ☐ Unknown
  If no, date at onset of symptoms (mm/yyyy): __/_____
- **Date of diagnostic testing for suspected mitochondrial disease** (mm/yyyy): __/_____

§ *see Attachment I: Instructions for Investigator*

- **Specify type of diagnostic testing** (more than one answers may be selected):
☐ muscle biopsy ☐ liver biopsy ☐ fibroblasts ☐ genetic investigation ☐ other, specify_____

Clinical Features

Fill in any of the following clinical features presented either at onset or during the disease course and specify time at presentation (i.e. at onset or later).

Motor dysfunction ☐No ☐ Yes		*If yes, please specify all that are applicable:*		
☐Hypotonia		☐At onset	☐later	☐Unknown
☐Hypertonia		☐At onset	☐later	☐Unknown
☐Dystonia		☐At onset	☐later	☐Unknown
☐Ataxia				
	☐*Cerebellar*	☐At onset	☐later	☐Unknown
	☐*Sensory*	☐At onset	☐later	☐Unknown
	☐*Unknown*			
☐Spasticity		☐At onset	☐later	☐Unknown
☐Paresis/palsy				
	☐*Hemiparesis/plegia*	☐At onset	☐later	☐Unknown
	☐*Paraparesis/plegia*	☐At onset	☐later	☐Unknown
	☐*Quadriparesis/plegia*	☐At onset	☐later	☐Unknown
	☐*Monoparesis/plegia*	☐At onset	☐later	☐Unknown
☐Myoclonus		☐At onset	☐later	☐Unknown
☐Hypokinesia/ Bradykinesia		☐At onset	☐later	☐Unknown
☐Chorea/Athetosis		☐At onset	☐later	☐Unknown
☐Other dyskinetic disorder				
Specify: _____		☐At onset	☐later	☐Unknown
☐Muscle weakness		☐At onset	☐later	☐Unknown
☐Cavus feet		☐At onset	☐later	☐Unknown
☐Babinski sign		☐At onset	☐later	☐Unknown
☐Tendon reflexes				
Specify: _____		☐At onset	☐later	☐Unknown
Ophthalmological dysfunction ☐No ☐ Yes		*If yes, please specify all that are applicable:*		
☐Ptosis		☐At onset	☐later	☐Unknown
☐Reduced eye motility		☐At onset	☐later	☐Unknown
☐Strabismus		☐At onset	☐later	☐Unknown
☐Nystagmus		☐At onset	☐later	☐Unknown
☐Optic atrophy		☐At onset	☐later	☐Unknown
☐Retinopathy		☐At onset	☐later	☐Unknown
☐Visual impairment		☐At onset	☐later	☐Unknown
☐Other				
Specify: _____		☐At onset	☐later	☐Unknown

Other dysfunction ☐No ☐ Yes	*If yes, please specify all that are applicable:*		
☐Seizures			
☐*Partial seizures*	☐At onset	☐later	☐Unknown
☐*Generalized seizures*	☐At onset	☐later	☐Unknown
☐*Neonatal seizures*	☐At onset	☐later	☐Unknown
☐*Myoclonic seizures*	☐At onset	☐later	☐Unknown
☐*Epilepsy syndrome*_____	☐At onset	☐later	☐Unknown
☐*Other* _____	☐At onset	☐later	☐Unknown
Are seizures therapy-resistant?	☐ Yes	☐ No	
Has the patient received valproate treatment?	☐ Yes	☐ No	
☐Cardiac dysfunction			
☐*Conduction defects*	☐At onset	☐later	☐Unknown
☐*Dilated cardiomyopathy*	☐At onset	☐later	☐Unknown
☐*Hypertrophic cardiomyopathy*	☐At onset	☐later	☐Unknown
☐*Other* _____	☐At onset	☐later	☐Unknown
☐Hepatic dysfunction			
Specify: _____	☐At onset	☐later	☐Unknown
☐Renal dysfunction	☐At onset	☐later	☐Unknown
Specify: _____	☐At onset	☐later	☐Unknown
☐Failure to thrive§	☐At onset	☐later	☐Unknown
☐Feeding difficulties			
☐requiring gastrostomi	☐At onset	☐later	☐Unknown
☐requiring feeding tube	☐At onset	☐later	☐Unknown
☐Sucking dysfunction	☐At onset	☐later	☐Unknown
☐Mental retardation§			
☐*Mild*	☐At onset	☐later	☐Unknown
☐*Moderate*	☐At onset	☐later	☐Unknown
☐*Severe*	☐At onset	☐later	☐Unknown
☐*Profound*	☐At onset	☐later	☐Unknown
☐Microcephaly	☐At onset	☐later	☐Unknown
Progressive microcephaly§ ☐yes ☐no			
☐Hearing dysfunction			
☐Conductive	☐At onset	☐later	☐Unknown
☐Sensorineural	☐At onset	☐later	☐Unknown
☐Peripheral neuropathy			
☐Demyelinating	☐At onset	☐later	☐Unknown
☐Axonal	☐At onset	☐later	☐Unknown
☐Respiratory disturbance			
☐*Apnea*	☐At onset	☐later	☐Unknown
☐*Central hypoventilation*	☐At onset	☐later	☐Unknown
☐*Hyperventilation/Abnormal breathing pattern*	☐At onset	☐later	☐Unknown
☐*Respiratory complications (non-CNS induced)*	☐At onset	☐later	☐Unknown
☐Hematological dysfunction			
Specify: _____	☐At onset	☐later	☐Unknown
☐Other dysfunction			
Specify: _____	☐At onset	☐later	☐Unknown

§ see Attachment I: Instructions for Investigator

DISEASE COURSE

-**Has the patient experienced acute exacerbation(s)/relapse(s) during the disease course**§: ☐Yes ☐No ☐Unknown

If yes, specify **a) the frequency of acute exacerbations/relapses during the past year:**

☐ ≤ 2 times ☐ 3-5 times ☐ 6-10 times ☐ >10 times ☐ Unknown

b) the main cause of acute exacerbations/relapses during the past year:

☐ infection(s) ☐ other, specify:_____ ☐ Unknown

c) did any of the acute exacerbations/relapses require ICU: ☐ Yes ☐ No ☐ Unknown

SURVIVAL STATUS

- **Current status**§: ☐ Alive ☐ Deceased ☐ Unknown/Lost-to-follow-up

If lost-to-follow-up, please specify last date of follow-up (mm/yyyy): __/____

If deceased, please specify§: **a) Date of death**: __/____

b) Cause of death: _____

c) Has postmortem investigation been performed: ☐ Yes ☐ No ☐ Unknown

GROWTH§

- Date of latest examination (mm/yyyy): __/____	☐ Unknown
- Weight for age: ___ SD	☐ Unknown
- Weight for height: ___ SD	☐ Unknown
- Height for age: ___ SD	☐ Unknown
- Head circumference for age: ___ SD	☐ Unknown

LABORATORY FINDINGS

Respiratory chain enzyme activity ☐Compex I deficiency ☐Compex II deficiency
(more than one fields may be selected)
☐Compex III deficiency ☐Compex IV deficiency ☐Compex V deficiency

Absolute values in blood§ (units)

Lactate	_____	mmol/l	☐ Unknown
Pyruvate	_____	mmol/l	☐ Unknown
Albumin	_____	g/l	☐ Unknown

Absolute values in CSF§ (units)

Lactate	_____	mmol/l	☐ Unknown
Pyruvate	_____	mmol/l	☐ Unknown
Albumin	_____	mg/l	☐ Unknown

Lactate: pyruvate ratio in blood§ (units)

Lactate/Pyruvate _____ mmol/l / _____ mmol/l ☐ Unknown

Lactate: pyruvate ratio in CSF § (units)

Lactate/Pyruvate _____ mmol/l / _____ mmol/l ☐ Unknown

CSF/serum albumin ratio§ _____ ☐ Unknown

Pathological aminoacids in plasma ☐Yes ☐No ☐Unknown, If yes Specify:

1._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
2._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
3._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological aminoacids in urin ☐Yes ☐No ☐Unknown, If yes Specify:

1._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
2._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
3._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological aminoacids in CSF ☐Yes ☐No ☐Unknown, If yes Specify:

1._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
2._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
3._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological organic acids in urin ☐Yes ☐No ☐Unknown, If yes Specify:

1._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
2._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____
3._____ Type:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

LABORATORY FINDINGS (continued)

Pathological total or free carnitine ☐Yes ☐No ☐Unknown, If yes Specify:

Type:_____ Tissue:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological acylcarnitine ☐Yes ☐No ☐Unknown, If yes Specify:

Type:_____ Tissue:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological Q10 ☐Yes ☐No ☐Unknown, If yes Specify:

Type:_____ Tissue:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pathological a-fetoprotein ☐Yes ☐No ☐Unknown, If yes Specify:

Type:_____ Tissue:_____ Absolute value: _____ Units: _____ Reference range: ____ - _____

Pyruvate dehydrogenase complex deficiency ☐Yes ☐No ☐Unknown

Pyruvate carboxylase deficiency ☐Yes ☐No ☐Unknown

Krebs cycle enzyme deficiency ☐Yes Specify:_____ ☐No ☐Unknown

Other enzyme deficiency ☐Yes Specify:_____ ☐No ☐Unknown

Blue native gel performed: ☐ Yes ☐ No ☐ Unknown

If yes, specify tissue and findings: _____

Comments:

MUSCLE PATHOLOGY

☐ Normal ☐ Abnormal

If abnormal, specify: ☐ COX deficiency ☐ SDH deficiency ☐ Ragged Red Fibers
☐ Mitochondrial proliferation ☐ Other, specify: _____

- **Electron microscopy performed**: ☐ Yes ☐ No ☐ Unknown

If yes, specify findings: _____

LIVER PATHOLOGY

☐ Normal ☐ Abnormal ☐ Unknown

If abnormal, specify: ☐ Inflammation ☐ Steatosis ☐ Fibrosis ☐ Other, specify: _____

GENETIC INVESTIGATIONS

- **Has the patient undergone genetic investigation(s)?** ☐Yes ☐No ☐Unknown, If yes Specify:

a) the type of genetic investigation(s) performed:_____

b) the genetic findings herebelow:

- **Does the patient harbor a pathogenic mutation?** ☐ Yes ☐ No ☐ Unknown

If yes specify below, including the locus, grade of heteroplasmy and tissue where applicable:

☐MTND1	☐ Not Performed	_____
☐MTND3	☐ Not Performed	_____
☐MTND4	☐ Not Performed	_____
☐MTND5	☐ Not Performed	_____
☐MTND6	☐ Not Performed	_____
☐MTATP6	☐ Not Performed	_____
☐MTTL1	☐ Not Performed	_____
☐MTTK	☐ Not Performed	_____
☐MTCO3	☐ Not Performed	_____
☐Other mitochondrial gene: _____		_____
☐SURF1	☐ Not Performed	_____
☐NDUFV1	☐ Not Performed	_____
☐NDUFS	☐ Not Performed	_____
☐SUCLA2	☐ Not Performed	_____
☐SUCLG1	☐ Not Performed	_____
☐PDHA1	☐ Not Performed	_____
☐Other nuclear gene: _____		_____

- **Does the patient harbor a mtDNA depletion?** ☐ Yes ☐ No ☐ Unknown

If yes, specify: a) the method used:_____

b) the percentage of abnormal mtDNA:_____%

c) the corresponding tissue:_____

MRI FINDINGS

1st MRI: Has MRI been done: ☐ Done ☐ Unknown/Not done

If Done, a) Date of 1st MRI§: __/_____

b) ☐ Normal ☐ Abnormal

If abnormal, specify the anatomical region(s) and type(s) of abnormalities:

Region	Signal abnormality		Atrophy	Comments
☐ Putamen	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Caudate nucleus	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Globus pallidus	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Thalamus	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ N subthalamicus	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Midbrain	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Pons	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Medulla	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Cerebellum				
☐ *grey matter*	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ *white matter*	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ *vermis*	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ *peduncles*	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ *dentate nucleus*	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Cerebral cortex	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Supratentorial white matter	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Bilateral ☐ Unilateral ☐ No Atrophy	
☐ Corpus callosum	☐ Increased T1 ☐ Increased T2 ☐ Decreased T1 ☐ Decreased T2	☐ Bilateral ☐ Unilateral	☐ Atrophy/hypoplasia ☐ Agenesis ☐ No Atrophy	

☐ Additional/other MRI findings: _____

- **Diffusion-weighted imaging (DWI)**: ☐ Normal ☐ Abnormal ☐ Unknown/Not done

If Normal, specify timepoint after acute episode (in days): ____ days

If abnormal, specify: timepoint after acute episode (in days): ____ days

a) type of abnormalities: _____ b) region of abnormalities: _____

- **Apparent diffusion coefficient (ADC):** ☐ Normal ☐ Abnormal ☐ Unknown/Not done

If abnormal, specify a) type of abnormalities: _____

b) region of abnormalities: _____

- **Magnetic Resonance Spectroscopy (MRS)**: ☐ Normal ☐ Abnormal ☐ Unknown/Not done

If abnormal, specify type and region of abnormalities

☐ Elevated lactate Region: _____ ☐ Decreased NAA Region: _____

☐ Elevated choline Region: _____ ☐ Other, specify _____ Region: _____

☐ Elevated succinate Region: _____

§ *see Attachment I: Instructions for Investigator*

2nd MRI: Has 2nd MRI been done: ☐ Done ☐ Unknown/Not done
If Done, specify Date of 2nd MRI§: __/_____
If 2nd MRI available, specify the progress of MRI findings in relation to the previous MRI:
☐ Progression, specify: _____
☐ Regression, specify: _____
☐ No change

3rd MRI: Has 3rd MRI been done: ☐ Done ☐ Unknown/Not done
If Done, specify Date of 3rd MRI§: __/_____
If 3rd MRI available, specify the progress of MRI findings in relation to the previous MRI:
☐ Progression, specify: _____
☐ Regression, specify: _____
☐ No change

- Do you wish to provide illustrative MRI image: ☐ Yes ☐ No ☐ NA

CT FINDINGS

Has CT been done: ☐ Done ☐ Unknown/Not done
If Done, specify Date of 1st CT§: __/_____
If 1st CT available, specify CT findings: ☐ Normal ☐ Abnormal
If abnormal, specify the anatomical region(s) and type(s) of abnormalities:
☐ Calcification(s) Specify region: _____
☐ High attenuation Specify region: _____
☐ Low attenuation Specify region: _____
☐ Other, specify a) type_____
b) region: _____

TREATMENT

Does the patient receive or has the patient received any of the following treatments? ☐No ☐Yes
If Yes, specify type and status (on-going or discontinued).

☐ **Antiepileptic treatment**
☐Single antiepileptic drug ☐Combination of antiepileptic drugs ☐Valproate either alone or in combination
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

☐ **Ketogenic diet**
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

☐ **Coenzyme Q1**
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

☐ **Thiamine/Vitamine B1**
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

☐ **Riboflavin**
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

☐ **Idebenone**
☐On-going *specify effect of this treatment*: ☐No apparent ☐Positive effect ☐Unknown
☐Discontinued *specify reason(s) for discontinuation*: ☐Lack of efficacy ☐Non-compliance
☐Lack of safety ☐ Other: _____
☐Unknown

TREATMENT (CONTINUED)

☐ **Arginine**
☐ On-going *specify effect of this treatment*: ☐ No apparent ☐ Positive effect ☐ Unknown
☐ Discontinued *specify reason(s) for discontinuation*: ☐ Lack of efficacy ☐ Non-compliance
☐ Lack of safety ☐ Other: _____
☐ Unknown

☐ **Carnitine**
☐ On-going *specify effect of this treatment*: ☐ No apparent ☐ Positive effect ☐ Unknown
☐ Discontinued *specify reason(s) for discontinuation*: ☐ Lack of efficacy ☐ Non-compliance
☐ Lack of safety ☐ Other: _____
☐ Unknown

☐ **Other, specify** _____
☐ On-going *specify effect of this treatment*: ☐ No apparent ☐ Positive effect ☐ Unknown
☐ Discontinued *specify reason(s) for discontinuation*: ☐ Lack of efficacy ☐ Non-compliance
☐ Lack of safety ☐ Other: _____
☐ Unknown

☐ **Other, specify** _____
☐ On-going *specify effect of this treatment*: ☐ No apparent ☐ Positive effect ☐ Unknown
☐ Discontinued *specify reason(s) for discontinuation*: ☐ Lack of efficacy ☐ Non-compliance
☐ Lack of safety ☐ Other: _____
☐ Unknown

ELECTRONIC SIGNATURE

I have carefully checked all data recorded in the electronic Case Report Form and I confirm that they are true, complete and accurate to the best of my knowledge.

Please enter your password:

Attachment I: Instructions for Investigator

Table INCLUSION/EXCLUSION CRITERIA - Inclusion criteria, page 1
Inclusion criterion #2: Neuroimaging findings include increased T2 signal on MRI or low attenuation on CT.

Table MEDICAL HISTORY - Perinatal History, page 1
Perinatal History – Birth weight - IUGR AGA (appropriate for gestational age): between the 10th and 90th percentile for gestational age SGA (small for gestational age): below the 10th percentile for gestational age LGA (large for gestational age): above the 90th percentile for gestational age IUGR (intra-uterine growth restricted): diminished growth velocity of the fetus on serial ultrasonographic scans.

Table MEDICAL HISTORY - Perinatal History, page 1
Perinatal History – Head circumference at birth Normal: between –2SD and +2SD for gestational age Microcephaly: below –2SD for gestational age Macrocephaly: above +2SD for gestational age

Table MEDICAL HISTORY - Other dysfunction, page 3
Failure to thrive: weight for age that falls below the 5th percentile on multiple occasions or weight deceleration that crosses two or more major percentile lines on a growth chart over time

Table MEDICAL HISTORY - Other dysfunction, page 3
Mental retardation: categorization will be based on the DSM-IV and ICD 10 criteria for mental retardation. According to ICD 10: Mild mental retardation: IQ range 50-69 Moderate mental retardation: IQ range 35-49 Severe mental retardation: IQ range 20-34 Profound mental retardation: IQ below 20

Table MEDICAL HISTORY - Other dysfunction, page 3
Progressive microcephaly: deceleration of head circumference that crosses two or more major percentile lines on a growth chart over time

Table DISEASE COURSE, page 4
Disease course: Acute exacerbation/relapse is defined as a worsening of patient's condition lasting longer than 24h, accompanied by significant deterioration of patient's motor function, requiring hospitalization and acute intervention.

Table SURVIVAL STATUS, page 4
Survival status **Current status:** patient's status at the time of data registration on the present CRF **Lost-to-follow-up**: specify last date of follow-up either in your site or elsewhere, if applicable

Table GROWTH, page 4
Growth: measurements at last visit. This also applies in case of death or lost-to-follow-up. Example: weight for age -1.5 SD

Table LABORATORY FINDINGS, page 4
Laboratory findings: for lactate and pyruvate absolute values, please provide the maximum available values. For the lactate/pyruvate ratio, please provide the absolute value of lactate in CSF / the absolute value of pyruvate in CSF, taken at the same time. For the CSF/serum albumin ratio, the maximum available value will be provided.

Table MRI FINDINGS, page 7
Date of 3rd MRI: In case of more than three MRIs available, register data on the last MRI performed.