



EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report

May 2009

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BACKGROUND

All old-generation antiepileptic drugs (AEDs) are considered to be teratogenic and AEDs are among the most common causes of adverse effects to the foetus. The risks associated with the treatment of epilepsy during pregnancy is therefore of major concern to all women of childbearing potential with epilepsy. The information on the comparative teratogenicity of these AEDs in humans is, however, conflicting, mainly due to inadequate sample size and methodological differences between previous studies. The teratogenic potential of newer AEDs is even less known, a situation that prevents a rational approach to AED treatment in women of childbearing potential.

To address this problem, it is necessary to compile more information on outcome of pregnancies following maternal exposure to AEDs. Such information is needed to provide pre-pregnancy counselling concerning teratogenic risks, and possibilities for specific prenatal monitoring, including prenatal diagnosis of foetal disorders associated with specific medications. Given the current number of available AEDs and combinations, very large numbers of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of the main endpoint of outcome, major congenital malformations.

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal AED use have agreed on a prospective international multi-centre study of pregnancies with AEDs. Data from all participating groups are shared in a Central Registry of Antiepileptic Drugs and Pregnancy (EURAP). EURAP was established in the first centres in some European countries and has since then gradually expanded to include more centres and countries now involving also Asia, Oceania and Latin America.

OBJECTIVE OF EURAP

The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of AEDs (old and new) and their combinations during pregnancy.

METHODS

EURAP is a prospective and retrospective observational study. Women taking AEDs at the time of conception, irrespective of the indication, may be included. To avoid selection bias, only pregnancies recorded before foetal outcome is known and within week 16 of gestation are included in the prospective risk assessment. Cases ascertained later in pregnancy are recorded as retrospective cases, as they may provide signals, but are not included in the comparative risk evaluation.

Information on patient's demographics, type of epilepsy, seizure frequency, family history of malformations, drug therapy and of other potential risk factors is obtained, and follow-up data are collected once at each trimester, at birth and at one year after delivery.

Networks of reporting physicians have been established in countries taking part in the collaboration. During the course of the pregnancy, and the follow-up time after delivery, the participating physician enters data into five Subforms (Subforms A-E) for each patient.

Subform A is completed on enrolment of the patient, Subform B after the first trimester, Subform C after the second trimester, Subform D within three months after delivery, and Subform E within 14 months after birth. Immediately after completion, each Subform is submitted to the national coordinator for review. The national coordinator transfers the reviewed and accepted Subform to the Central EURAP Registry in Milan, Italy.

EVALUATION OF OUTCOME

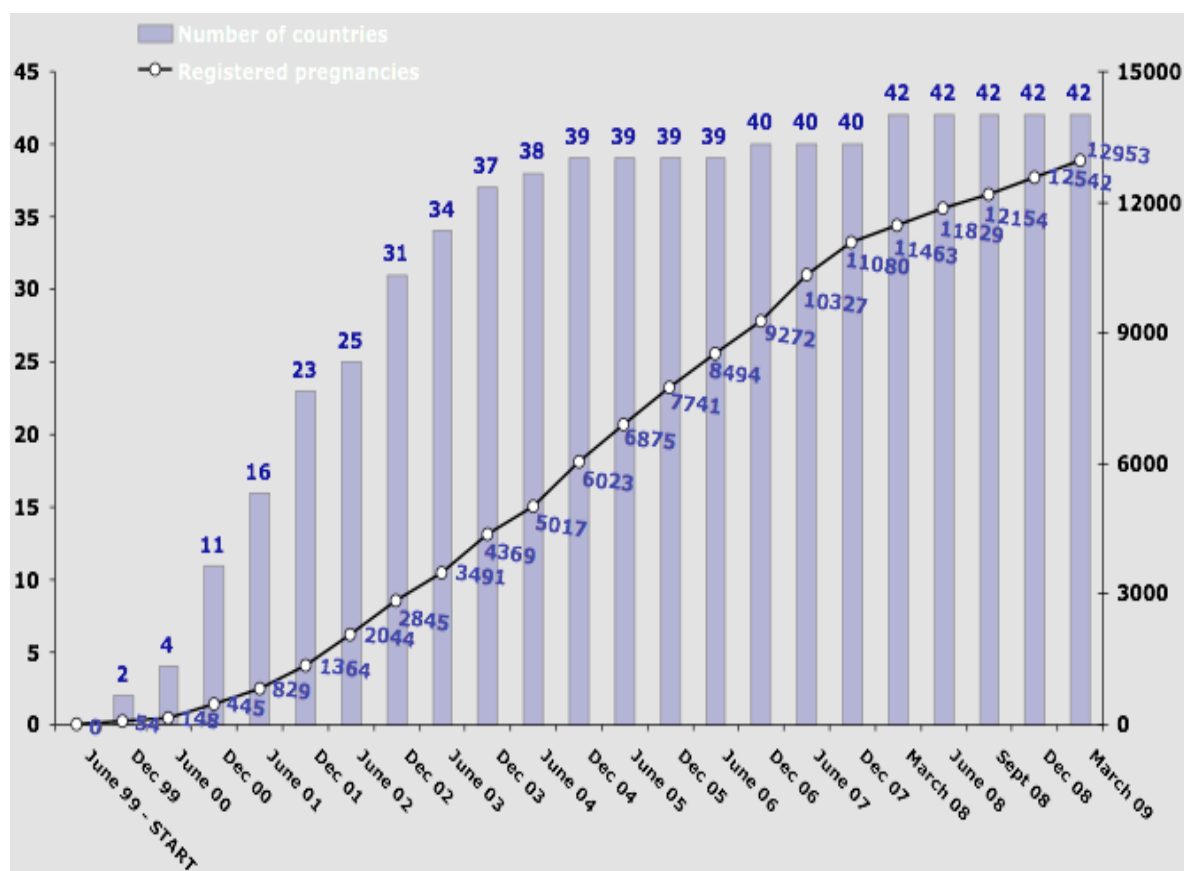
The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed regularly by an outcome assessment committee, which is kept blinded with respect to the type of exposure.

Outcome in relation to exposure to individual drugs or drug combinations will be assessed only after sufficient data is available for a meaningful statistical analysis. Determination of the sample size needed is complicated by lack of reliable information about the distribution of individual drugs and their combinations and about the prevalence of the teratogenic event. Applying the general empirical rule that the ratio between the overall number of events (teratogenic events) and the number of explanatory variables (predictors) should be at least equal to 10, a total sample size of at least 5,000 prospectively ascertained pregnancies would be needed to allow analysis of 25 predictors (different AEDs and other relevant risk factors) assuming a prevalence of malformations in the order of 5%. Such analysis is now underway.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown rapidly with increasing numbers of participating countries from Europe, Australia, Asia and South America. This development is also reflected by increasing numbers of enrolled pregnancies. The development since 1999 is illustrated in Fig. 1.

Fig 1. Number of participating countries and pregnancies reported to the Central Registry May 2009



The present report is based on data available in the Central Registry by May 29, 2009. At that time more than 750 reporting physicians from 42 countries had contributed cases to the Central Registry. Countries that had been active are listed in Table 1.

Table 1
Countries that have contributed with pregnancies reported to the Central Registry of EURAP (n=42)

- Albania
- Argentina
- Australia
- Austria
- Belgium
- Belarus
- Chile
- China
- Croatia
- Czech Republic
- Denmark
- Emirates
- Finland
- France
- Georgia
- Germany
- Guatemala
- Hong Kong
- Hungary
- India
- Israel

Italy
Japan
Lithuania
Macedonia
The Netherlands
Norway
Philippines
Poland
Portugal
Russia
Scotland
Serbia and Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Taiwan
Turkey
Ukraine
United Kingdom

By the cut-off date for this report (29 May 2009), 13,205 pregnancies had been entered into the central database. Of these, 2,810 were retrospective, a further 1,511 are excluded for reasons specified below (point 1 and 2), 1230 are pending (awaiting updates or corrections of different sub-forms), 964 are ongoing pregnancies and 6,443 are prospective which have completed the study including the one-year follow-up after birth. Reasons for not including pregnancies in the present interim report were:

1. Pregnancies that failed to meet inclusion criteria (n=53).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,458).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=1230).
4. Ongoing pregnancies, updated and corrected (n=964).
5. Retrospective, but completed and corrected (n=2,296).
6. Retrospective, i.e. initially classified as prospective pregnancies but finally accepted as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=201).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=21). This includes 1 stillbirth with unknown fetal status, induced abortion with insufficient information on fetus (n=3), and anomalies in livebirths where the information was insufficient to determine if qualifying for malformation diagnosis (n=17).
8. Pregnancies completed by the cut-off date (May 29, 2009), but too recent for having their classification of outcome completed in time for this report (n=17).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=522).

Thus in total 6,443 prospective pregnancies (enrolled at the latest during the 16th gestational week) are included in this report. One hundred and four of these pregnancies (1.6%), that otherwise met our criteria for prospective pregnancies, had an ultrasound examination performed before enrolment.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 59 (1%) of the pregnant women.

Table 2

Classification of the epilepsy in 6,443 prospective pregnancies.

Epilepsy	N	%
Generalized	2,676	41.5
Localisation-related	3,373	52.3
Undetermined	226	3.5
Missing information	109	1.7
No epilepsy	59	1.0
Total	6,443	100.0

The maternal age among prospective cases was 29.6±5.1 years (mean±SD), ranging from 14 to 46 years.

The women were of Caucasian ethnicity in 89.5% and of Asian in 6.7%.

The number of the current pregnancy in individual women is presented in Table 3.

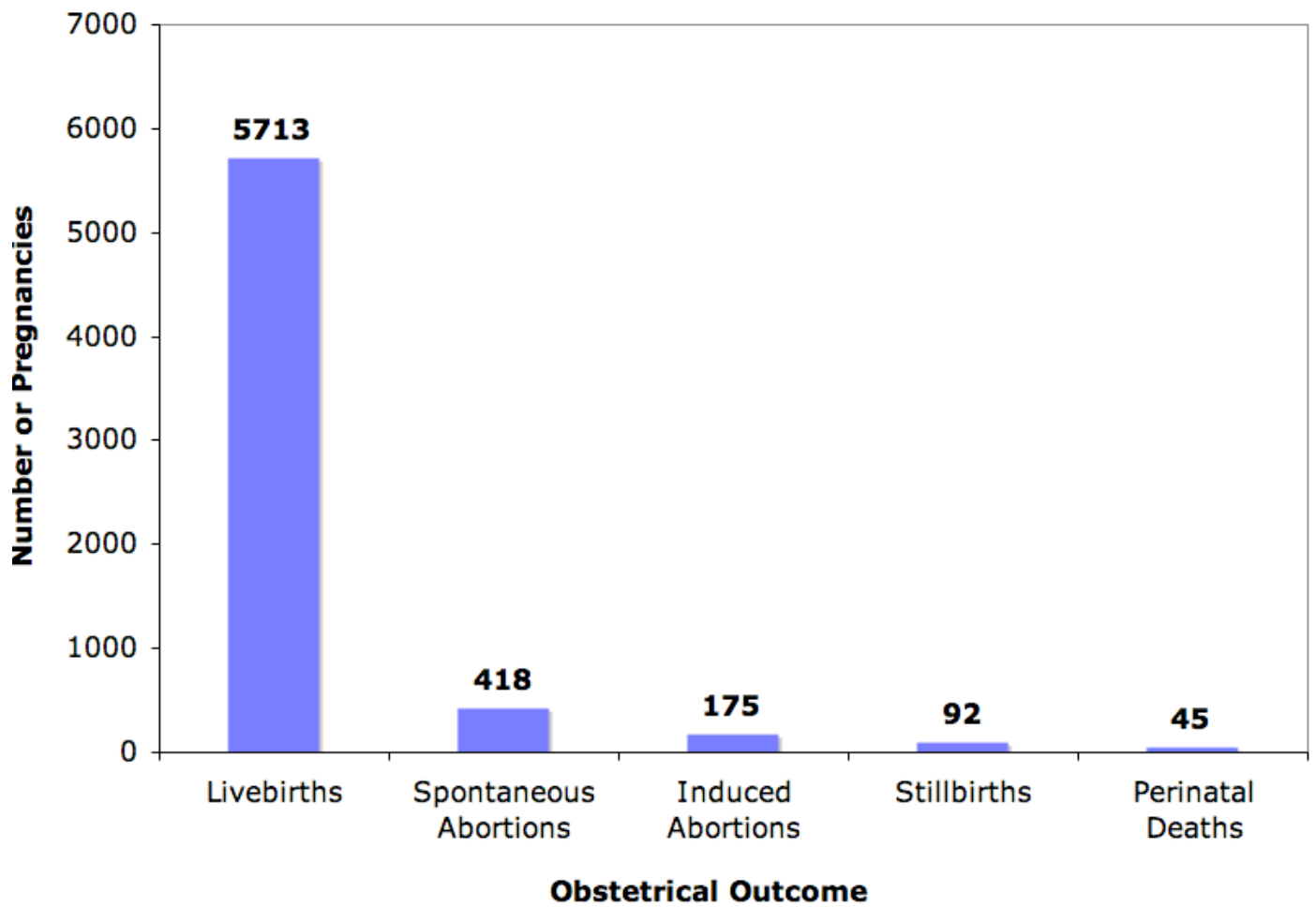
Table 3

Number of the pregnancy in prospective cases

Gravida	N	%
1st pregnancy	2,984	46.3
2nd pregnancy	1,938	30.1
3rd pregnancy	889	13.8
4th pregnancy	371	5.8
5th pregnancy	157	2.4
> 5th pregnancy	103	1.6
Not ascertained	1	
Total	6,443	100.0

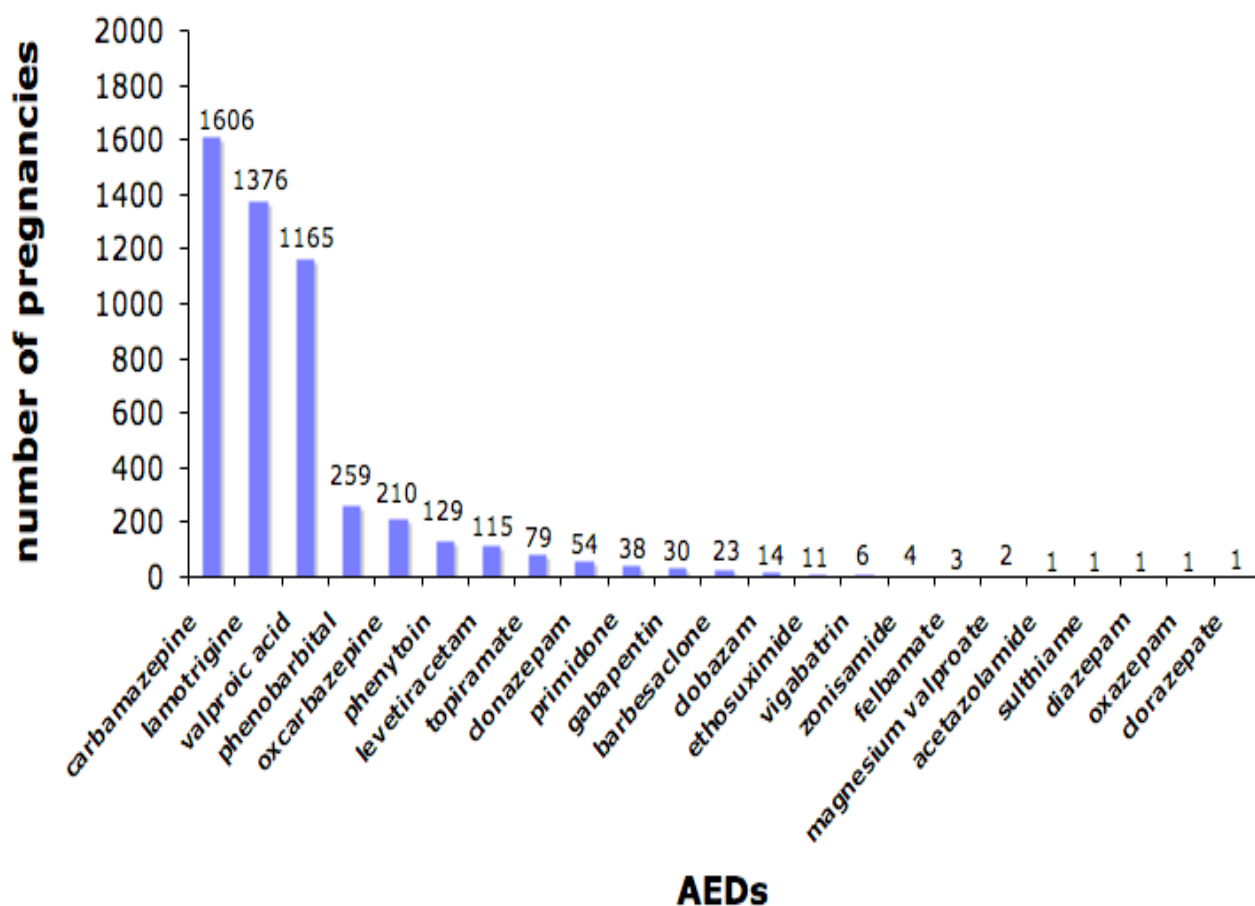
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 175 induced abortions, 38 were for fetal indication (major malformation or other abnormalities detected by prenatal screening) and 20 for chromosomal abnormalities.

Figure 2. Obstetric Outcome of prospective pregnancies



Of the pregnancies, 5129 (79.6%) involved women on a single AED, 1056 (16.4%) were on two AEDs whereas 183 (2.8%) took three AEDs or more. seventy-five women (1.2%) were not on AED treatment during the 1st trimester. The exposure to the different AEDs in monotherapy among the prospective pregnancies is presented in Figure 3.

Figure 3. Number of prospective pregnancies with exposure to different AEDs in monotherapy



There were 192 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=157), carbamazepine and lamotrigine (n=87), carbamazepine and phenobarbital (n=60) and carbamazepine and valproic acid (n=59) (Table 4).

Table 4. The most common AED combinations

lamotrigine + valproic acid	157
carbamazepine + lamotrigine	87
carbamazepine + phenobarbital	60
carbamazepine + valproic acid	59
lamotrigine + levetiracetam	53
carbamazepine + levetiracetam	48
lamotrigine + topiramate	37
carbamazepine + clobazam	33
carbamazepine + topiramate	31
phenobarbital + valproic acid	28
clonazepam + valproic acid	27
topiramate + valproic acid	23
carbamazepine + clonazepam	22
lamotrigine + clonazepam	22
clobazam + lamotrigine	20
lamotrigine + oxcarbazepine	20
lamotrigine + phenobarbital	18
phenobarbital + phenytoin	18

The number of pregnancies with exposure to different new generation AEDs taken in combination with other AEDs are listed in Table 5.

Table 5. Number of pregnancies with different new generation AEDs in combination therapy

AED	N
Lamotrigine	543
Levetiracetam	188
Topiramate	179
Oxcarbazepine	96
Gabapentin	44
Vigabatrin	32
Zonisamide	9
Tiagabine	7
Pregabalin	5

TERATOGENIC OUTCOME

There were 344 major congenital malformations (MCM), 5 syndromic cases and 37 chromosomal abnormalities in the prospective cohort of 6,025 pregnancies (excluded spontaneous abortions) as shown in Table 6.

Table 6. Pathological outcomes

Outcome	Outcome classification	N
MCM	Multiple major	32
	Isolated major	312
		344
SYNDROMES		5
CHR		37
Total		386

The 5 syndromic cases are respectively 2 Marfan syndrome, 1 Incontinentia pigmenti, 1 Goldenhar syndrome and 1 Vacterl syndrome.

In this report we will confine our analysis to the 344 MCM including 38 induced abortions, five stillbirths and fourteen neonatal deaths. Of the 287 live births, 29 cases of malformations were ascertained prenatally, 182 were first reported at birth and 76 within one year after birth.

Among the 344 cases with MCM, 69 were detected by ultrasound examination. Out of these 69, there were 34 induced abortions, 3 stillbirths, 3 perinatal deaths and 29 live births.

The 344 cases represent a malformation rate of 5.7% of all prospective pregnancies for which follow-up has been completed (344/6,025) and the same rate of 5.7% is obtained if the 96 cases with ultrasound before enrolment are excluded (340/5,933). The type of malformations is described in Table 7.

Table 7

Pathological outcomes	Apparatus	N
MCM	Multiple major	32
	Urinary	20
	Diaphragmatic hernia	5
	Anencephalus and similar	3
	Ano-rectal atresia and stenosis	1
	Atrial septal defect	21
	Atrioventricular septal defect	1
	Cleft lip with or without palate	8
	Cleft palate	10
	Club foot – talipes equinovarus	5
	Congenital cataract	4
	Congenital glaucoma	1
	Congenital heart disease	24
	Congenital hydronephrosis	1
	Congenital megaloureter	1
	Coronal craniosynostosis	1
	Cystic hygroma	2
	Digestive system	4
	Duodenal atresia or stenosis	1
	Ear, face and neck	1
	Eye	1
	Gastroschisis	1
	Genetic syndromes + microdeletions	1
	Genital	1
	Haemangioma, any site	2
	Hip dislocation and/or dysplasia	29
	Hydrocephaly	5
	Hypoplastic left heart	5
	Hypospadias	41
	Microcephaly (Q02)	1
	Musculo-skeletal	8
	Nervous system	6
	Other malformations	7
	Polydactyly	14
	Pulmonary valve stenosis	3
	Renal Dysplasia	2
	Sacral teratoma	1
	Spina Bifida	26
	Syndactyly	5
	Talipes equinovarus (clubfoot)	1
	Tetralogy of Fallot	5
Transposition of great vessels (complete)	2	
Upper limb reduction	3	
Ventricular septal defect	28	
All	344	
CHR	Chromosomal	5
	Chromosomal abnormality, unspecified	1
	Down's syndrome	21
	Edward syndrome/trisomy 18	4
	Hypospadias, unspecified Wolff-Hirschorn syndrome	1
	Indeterminate sex	1
	Klinefelter's syndrome	1
	Patau syndrome/trisomy 13	1
	Turner's syndrome	2
	All	37
Syndrome	Anophthalmos/microphthalmos	1
	Genetic syndromes + microdeletions	1
	Other malformations	1
	Renal Dysplasia	1
	Syndactyly	1
All	5	
All		386

In 289 out of 4,819 pregnancies with AED monotherapy one or more birth defects were observed (6.0%), as opposed to 95 out of 1,136 pregnancies with AED polytherapy (8.4%) as shown in Table 8.

Table 8

	Monotherapy	%	Polytherapy	%	Total
MCM	255	5.3	87	7.7	342
CHR	31	0.6	6	0.5	37
Syndromes	3	0.1	2	0.2	5
No malformation	4530	94.0	1041	91.6	5571
Total	4819	100	1136	100	5955

Outcome in relation to exposure to individual drugs or specific drug combinations is presently being analyzed. This work has, however, not been completed in time to be included in the present interim report.

ORGANISATION, FUNDING AND SUPPORT

EURAP is a consortium of independent research groups working on a non-profit basis. The project is administratively organised by the Central Project Commission (CPC) with members representing different geographical areas and disciplines. The project has been supported by educational grants to the CPC from Eisai Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Pfizer, Sanofi-Synthelabo, UCB Pharma and. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

APPENDIX

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