EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report May 2014

Central Study Coordinator
Dr Dina Battino
Fondazione I.R.C.C.S. Istituto Neurologico "Carlo Besta"
Via Celoria 11
20 133 Milano, Italy
Tel: + 39 (0)2 23 94 22 30
Fax: + 39 (0)2 700 42 91 60
E-mail: dbattino@istituto-besta.it

Chairman Central Project Commission
Dr Torbjörn Tomson
Department of Neurology
Karolinska University Hospital
S-171 76 Stockholm
Sweden
Tel: + 46 (0)8 51773705
Fax: + 46 (0)8 51773757
E-mail: torbjorn.tomson@karolinska.se

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, Latin America and Africa.

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.

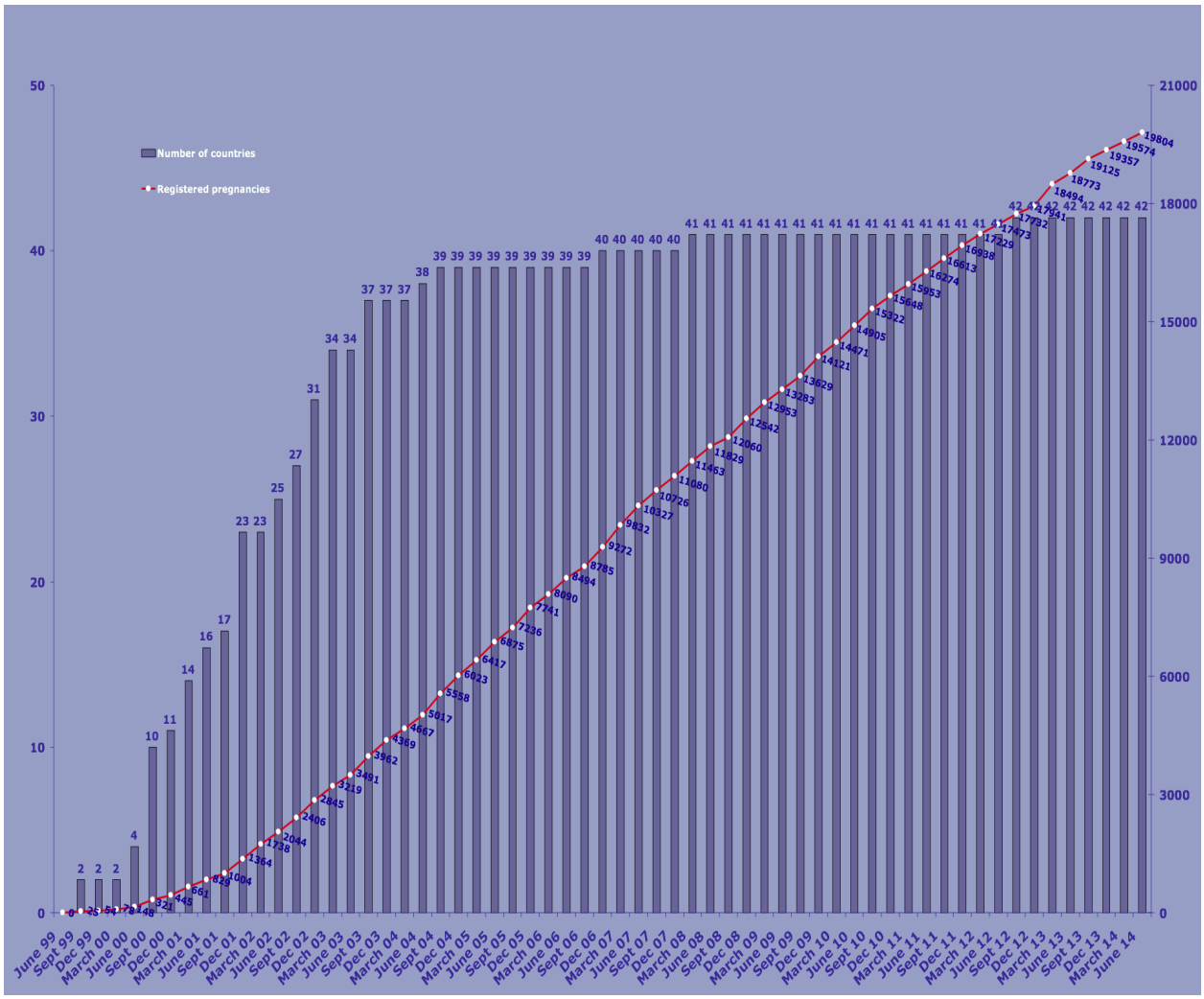
EVALUATION OF OUTCOME

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.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown rapidly with countries participating from Europe, Australia, Asia, South America and Africa. This development is 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 by June 2014.



The present report is **based on data available in the Central Registry by July 14th, 2014**. At that time more than 900 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).

COUNTRY	National Coordinator (or referring physician*)	Date of joining the Registry
Albania	Jera Kruja*	2002
Argentina	Silvia Kochen	2002
Australia	Frank Vajda	2000
Austria	Gerhard Luef	2000
Belarus	Halina Navumava*	2008
Belgium	Dick Lindhout & Eugène van Puijenbroek	2002
Chile	Alejandro De Marinis	2002
China	Weiping Liao	2006
Croatia	Dinko Vitezic	2002
Czech Republic	Jana Zarubova & Robert Kuba	2001
Denmark	Anne Sabers	2000
Emirates	Istvan Ferencz *	2008
Finland	Reetta Kälviäinen	2003
France	Michel Baulac	2000
Georgia	Sofia Kasradze & Otar Toidze	2000
Germany	Bettina Schmitz	2000
Guatemala	Henry Stokes*	2003
Hong-kong	Patrick Kwan	2002
Hungary	Gábor Barcs	2001
India	Sanjeev Thomas	2001
Israel	Miri Neufeld	2000
Italy	Luigi M. Specchio	2000
Japan	Hideyuki Ohtani	2001
Lithuania	Ruta Mameniskiene	2002
Macedonia	Gordana Kiteva Trencevska	2001
Netherlands	Dick Lindhout & Eugène van Puijenbroek	2002
Namibia	Herbie Burmeister*	2012
Norway	Karl-Otto Nakken	2000
Philippines	Leonor Cabral-Lim	2003
Poland	Joanna Jedrzejczak	2001
Portugal	Isabel Pires* & Luis Isidoro* & Elia Baeta*	2001
Russia	Alla Guekht & Oksana Lokshina	2004
Serbia & Montenegro	Maja Milovanovic	2002
Slovakia	Vladimír Safcák	2002
Slovenia	Boštjan Čebular	2002
Spain	Meritxell Martinez Ferri	2001
Sweden	Torbjörn Tomson	2000
Switzerland	Barbara Tettenborn & Martin Kurthen	2001
Taiwan	Chi Wan Lai & Alice Yu	2004
Turkey	Demet Kinay & Dilek Atakli	2000
Ukraine	Dmitriy Kovalenko*	2006
United Kingdom	John Craig & Aline Russell	2001

* referring physicians

By the cut-off date for this report (July 14, 2014), 19,848 pregnancies had been entered into the central database. Of these, **9,156 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n= 113).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n= 2,257).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n= 1,043).
4. Ongoing pregnancies, updated and corrected (n= 783).
5. Retrospective, but completed and corrected (n=3,550). Among these, there are true retrospective pregnancies i.e enrolled after 16th week of pregnancy (n=3,343) and a further two hundred and eight pregnancies (n=208) that otherwise met our criteria for prospective pregnancies since they were recruited within 16th week, but which patients had an ultrasound examination performed before enrolment.
6. Retrospective, i.e. initially classified as prospective pregnancies but re-classified as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=327).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=40). This includes 1 stillbirth with unknown fetal status, induced abortion with insufficient information on fetus (n=7), anomalies in livebirths where the information was insufficient to determine if qualifying for malformation diagnosis (n=28), 1 incomplete spontaneous abortion with unclear results of biopsy and 3 perinatal deaths in premature births (<35 gestational weeks) with anomalies difficult to classify as congenital or due to prematurity.
8. Not yet classified, i.e pregnancies which classification is pending as well as pregnancies which became completed after the last time we sent the database to the OCC, regardless if they contained some malformations or not (n=199).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=844).

Thus in total **10,692 prospective pregnancies** (enrolled at the latest during the 16th gestational week and before outcome is known) **are included** in this report.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 92 (1%) of the pregnant women.

Table 2. **Classification of the Epilepsy in 10,692 Prospective Pregnancies.**

Epilepsy	**N**	**%**
Localisation-related	5,703	53.3
Generalized	4,361	40.8
Undetermined	338	3.2
Missing information	198	1.8
No epilepsy	92	0.9
Total	**10,692**	**100**

The **maternal age** among prospective cases was 29.8 ±5.1 years (mean±SD), ranging from 14 to 46 years.

The women were of Caucasian **ethnicity** in 88% and of Asian in 8%.

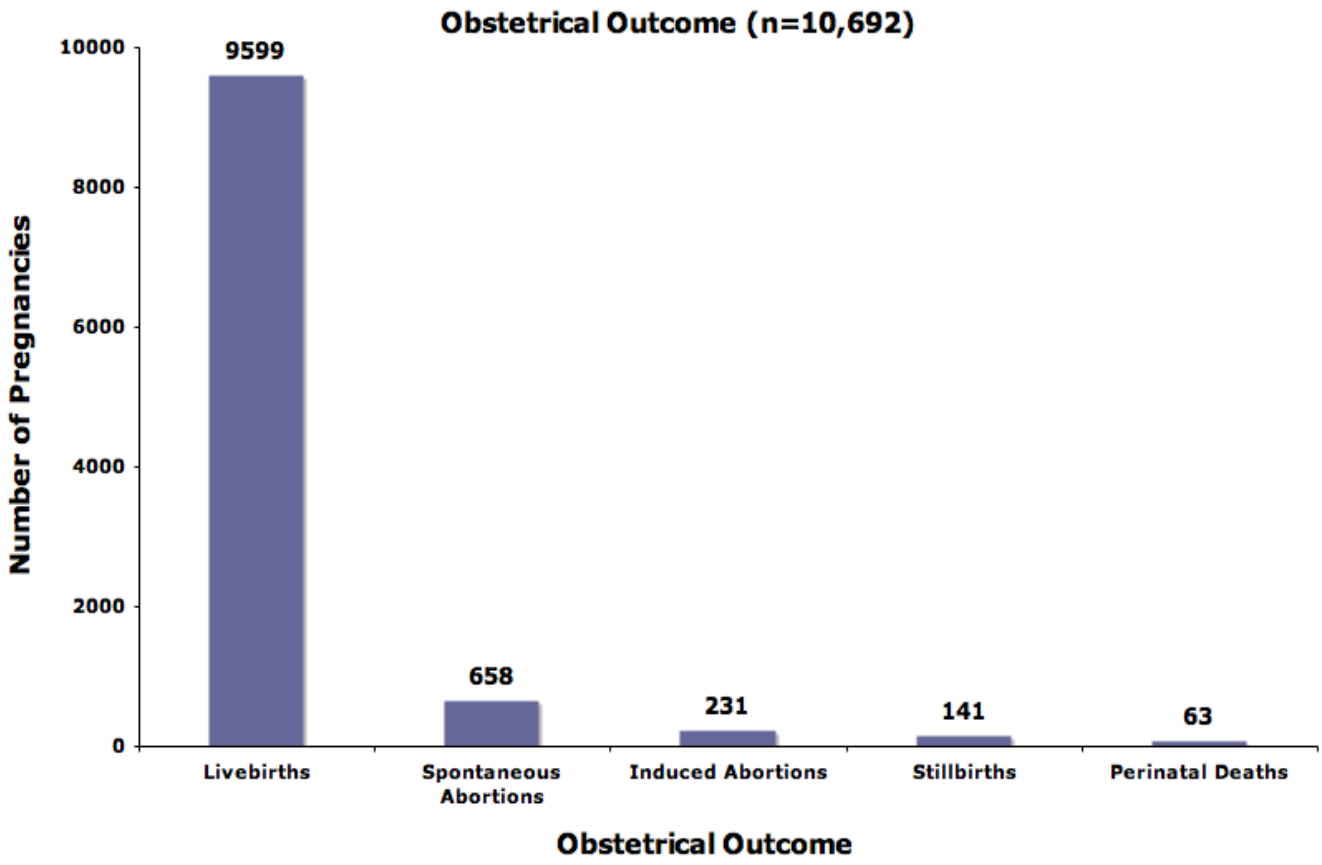
Gravida for each pregnancy is presented in Table 3.

Table 3. **Number of the Pregnancy in Prospective Cases.**

Gravida	**N**	**%**
1st pregnancy	4,898	45.8
2nd pregnancy	3,303	30.9
3rd pregnancy	1,459	13.7
4th pregnancy	646	6.0
5th pregnancy	233	2.2
> 5th pregnancy	152	1.4
Not ascertained	1	0.0
Total	**10,692**	**100**

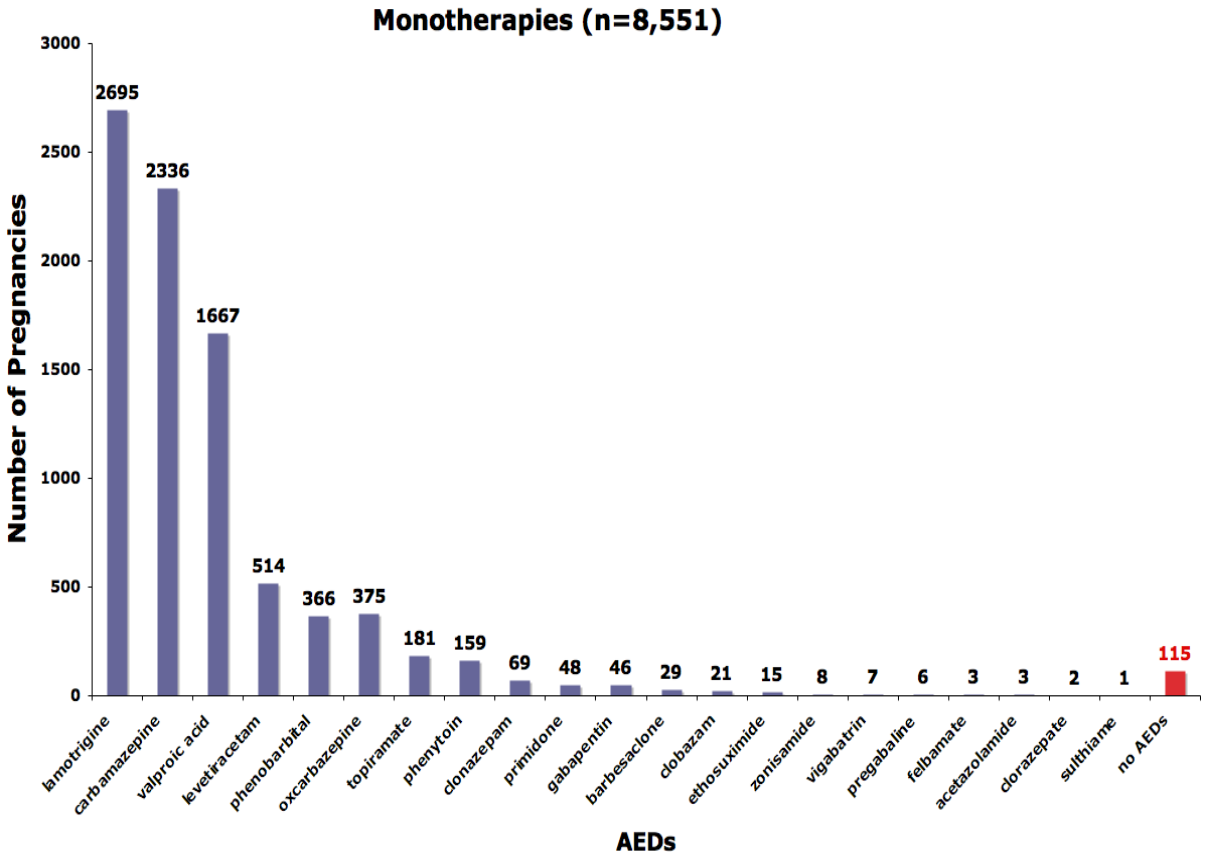
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 231 induced abortions, 34 were for chromosomal abnormalities and/or syndromes and 62 were for fetal indication detected by prenatal screening (out of these, 50 cases were confirmed major malformations and 12 cases were definitively classified as other abnormalities such as hydrops fetalis, molar pregnancies, blighted ovum, fetal placental transfusion syndromes, fetal growth retardation, fetus papyraceus, fetal death for unspecified causes, balanced translocation and insertion in normal individual,…etc).

Figure 2. Obstetrical Outcome of Prospective Pregnancies.



Of the pregnancies, 8,551 (80%) involved women on a single AED, 1,723 (16.1%) were on two AEDs whereas 303 (2.8%) took three AEDs or more. One hundred and fifteen women (1.1 %) 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 259 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=225), lamotrigine and levetiracetam (n=154), carbamazepine and levetiracetam (n=114), carbamazepine and lamotrigine (n=108), carbamazepine and valproic acid (n=77), carbamazepine and phenobarbital (n=73), lamotrigine and topiramate (n=68), carbamazepine and clobazam (n=65), clobazam and lamotrigine (n=48) and carbamazepine and topiramate (n=43) (Table 4).

Table 4. The Most Common AED Combinations.

lamotrigine + valproic acid	225
lamotrigine + levetiracetam	154
carbamazepine + levetiracetam	114
carbamazepine + lamotrigine	108
carbamazepine + valproic acid	77
carbamazepine + phenobarbital	73
lamotrigine + topiramate	68
carbamazepine + clobazam	65
clobazam + lamotrigine	48
carbamazepine + topiramate	43
clonazepam + lamotrigine	42
topiramate + valproic acid	37
levetiracetam + oxcarbazepine	35
levetiracetam + valproic acid	34
lamotrigine + oxcarbazepine	32
clonazepam + valproic acid	32
phenobarbital + valproic acid	32
phenobarbital + phenytoin	28
carbamazepine + clonazepam	26
lamotrigine + phenobarbital	22
lamotrigine + phenytoin	18
carbamazepine + vigabatrin	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.**

Lamotrigine	916
Levetiracetam	499
Topiramate	290
Oxcarbazepine	178
Gabapentin	56
Zonisamide	39
Vigabatrin	37
Pregabalin	18
Tiagabine	8

TERATOGENIC OUTCOME

There were 520 major congenital malformations (MCM), 19 syndromic and/or monogenic cases and 60 chromosomal abnormalities (CHR) in the prospective cohort of 10,034 pregnancies as shown in Table 6 (658 spontaneous abortions are excluded).

Table 6. Pathological Outcomes.

Outcome	Outcome Classification	N
MCM	Multiple major	48
	Isolated major	472
MCM		**520**
SYNDROMES or MONOGENIC CONDITIONS		**19**
CHR		**60**
Total		**599**

The 19 syndromic cases are Marfan's syndrome (2), Noonan syndrome (2), inherited tuberous sclerosis (3), Goldenhar syndrome (1), incontinentia pigmenti (2), inherited congenital glaucoma (1), inherited congenital cataract (1), inherited craniosynostosis (1), Di George's syndrome (1), bilateral hearing loss (1), X-linked lissencephaly (1), Skeletal dysplasia/Dwarfism (1), X-linked ichthyosis (1) and Freeman Sheldon syndrome (1).

In this report we will confine our analysis to the 520 MCM including 50 induced abortions, five stillbirths and 14 neonatal deaths. Of the 451 live births, 46 cases of malformations were ascertained prenatally, 287 were first reported at birth and 118 within one year after birth.

Among the 520 cases with MCM, 98 were detected by ultrasound examination. Out of these 98, there were 45 induced abortions, four stillbirths, three perinatal deaths and 46 live births.

The 520 cases represent a **malformation rate of 5.2%** of all prospective pregnancies for which follow-up has been completed (520/10,034).

The type of malformations is described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	**48**
	Nervous system	
MCM	Spina Bifida	40
MCM	Anencephalus and similar	2
MCM	Hydrocephaly	4
MCM	Microcephaly	1
MCM	Nervous system (other malformations)	10
MCM	all	**57**
	Heart	
	Atrial septal defect	36
MCM	Ventricular septal defect	40
MCM	Atrioventricular septal defect	2
MCM	Congenital heart disease	36
MCM	Tetralogy of Fallot	4
MCM	Transposition of great vessels (complete)	3
MCM	Pulmonary valve stenosis	7
MCM	Hypoplastic left heart	6
	all	**134**
	Urinary system	
MCM	Urinary system (other malformations)	29
MCM	Renal Dysplasia	3
	all	**32**
	Digestive system	
MCM	Diaphragmatic hernia	8
MCM	Ano-rectal atresia and stenosis	2
MCM	Digestive system (other malformations)	6
MCM	Duodenal atresia or stenosis	1
MCM	Gastroschisis	2
	Omphalocele	2
	all	**21**
	Limbs	
MCM	Upper limb reduction	6
MCM	Syndactyly	5
MCM	Polydactyly	22
MCM	Club foot - talipes equinovarus	17
	all	**50**
	Musculoskeletal	
MCM	Musculo-skeletal (other malformations)	8
MCM	Hip dislocation and/or dysplasia	54
	all	**62**
	Genital system	
MCM	Genital (developmental ovarian cyst)	3
MCM	Hypospadias	60
	all	**63**
	Eye, ear, face and neck	
MCM	Congenital cataract	4
MCM	Eye (other malformations)	3
MCM	Ear, face and neck	5
MCM	Choanal atresia	1
MCM	all	**13**
	Oro facial clefts	
MCM	Cleft lip with or without palate	12
MCM	Cleft palate	14
	all	**26**
MCM	**Other specified malformations** (including sacral teratoma, cystic hygroma, haemangiomas, accessory skin tags, aberrant subclavian artery, sequences, genetic syndromes)	**14**
MCM	**all**	**520**
	Chromosomal	
CHR	Chromosomal	14
CHR	Down's syndrome	30
CHR	Edward syndrome/trisomy 18	6
CHR	Klinefelter's syndrome	1
CHR	Patau syndrome/trisomy 13	4
CHR	Turner's syndrome	4
CHR	Wolff-Hirschorn syndrome	1
CHR	**all**	**60**
	Syndromes or monogenic conditions	
Syndrome	Marfan syndrome	2
Syndrome	Incontinentia pigmenti	2
Syndrome	Noonan's syndrome	2
Syndrome	Oculo-auriculo-vertebral syndrome	1
Syndrome	Di George's syndrome	1
Syndrome	Tuberous sclerosis	3
Syndrome	Craniosynostosis, inherited	1
Syndrome	Congenital cataract, inherited	1
Syndrome	Congenital glaucoma, inherited	1
Syndrome	X-linked Ichthyosis	1
Syndrome	X-linked Lissencephaly	1
Syndrome	Hearing loss, bilateral, inherited	1
Syndrome	Skeletal dysplasia	1
Syndrome	Freeman Sheldon Syndrome (distal arthrogryposis type 2A	1
Syndromes or Monogenic Conditions	**all**	**19**
Total		**599**

In 382 out of 8,056 pregnancies with AED monotherapy one or more birth defects were observed (4.7 %), as opposed to 135 out of 1,868 pregnancies with AED polytherapy (7.2 %) as shown in Table 8.

Table 8. *In this table, 658 spontaneous abortions have been excluded from the denominator.*

	No AED	%	Monotherapy	%	Polytherapy	%	Total
MCM	**3**	2.7	**382**	4.7	**135**	7.2	**520 (**5.2%**)**
CHR	**0**	0.0	**48**	0.6	**12**	0.7	**60 (**0.6%**)**
Syndromes	**0**	0.0	**15**	0.2	**4**	0.2	**19 (**0.2%**)**
No malformation	**107**	97.3	**7,611**	94.4	**1,717**	91.9	**9,435 (**94.0%**)**
Total	**110**	100	**8,056**	100	**1,868**	100	**10,034 (**100%**)**

Outcome regarding the four most common monotherapies has been published in Lancet Neurology, June 6, 2011. Outcome in relation to exposure to individual drugs or specific drug combinations is not included in the present 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, Bial, Sanofi-Synthelabo and UCB Pharma. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

APPENDIX

Central Project Commission

Dina Battino, Milano

Erminio Bonizzoni, Pavia

John Craig, Belfast

Dick Lindhout, Utrecht

Emilio Perucca, Pavia

Anne Sabers, Copenhagen

Sanjeev V Thomas, Trivandrum

Torbjörn Tomson, Stockholm, (chair)

Frank Vajda, Melbourne

Central Study Coordinator

Dina Battino, Milan

Scientific Advisory Board

Bernd Schmidt, Freiburg

Martin J Brodie, Glasgow

Outcome Assessment Committee

Elisabeth Robert-Gnansia, Lyon, France

Richard Finnell, Houston, Texas

Francesca Faravelli, Genoa, Italy

Chiara Pantaleoni, Milan, Italy