EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report November 2013

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 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.

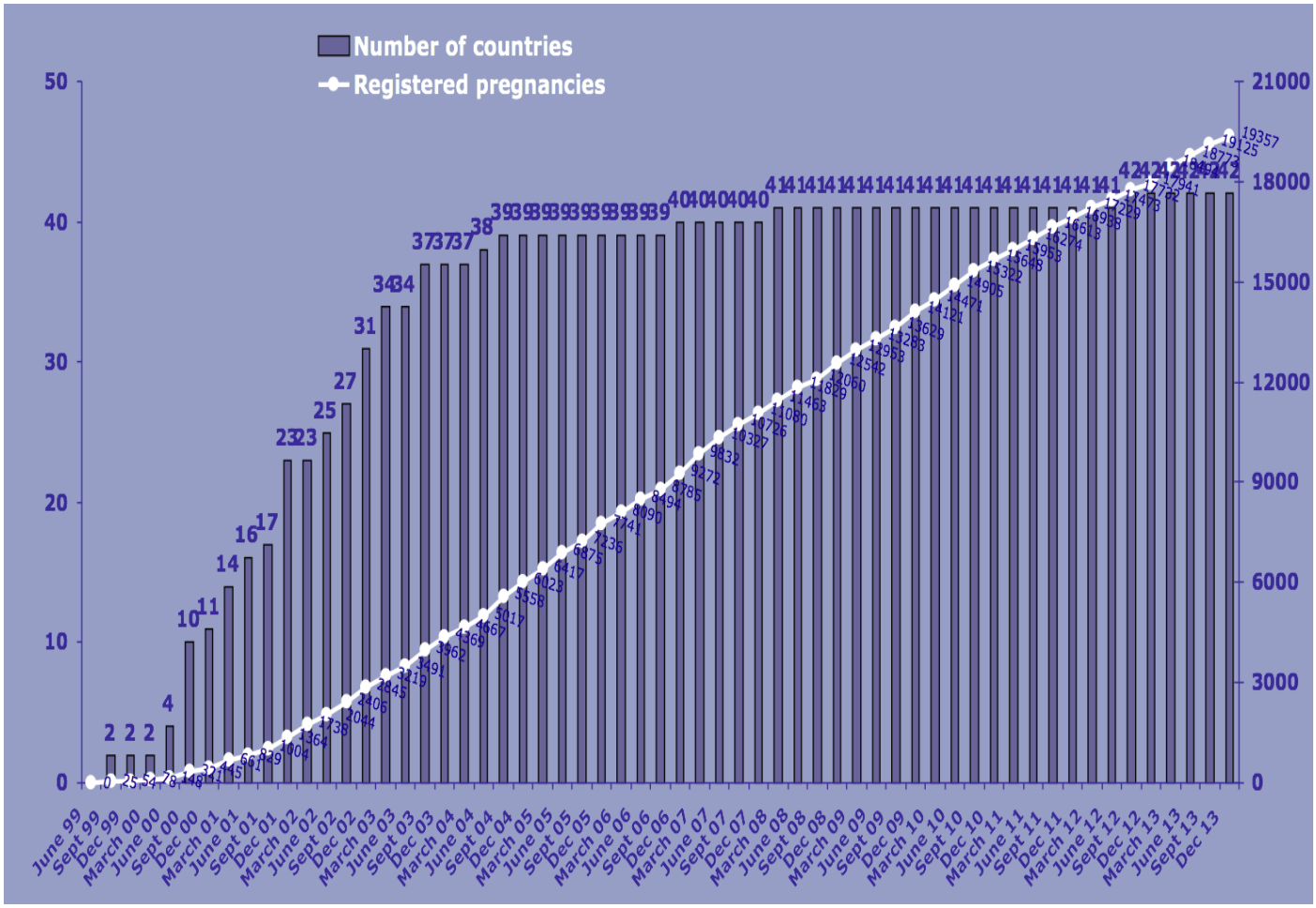
EVALUATION OF OUTCOME

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.

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 and South America. 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 December 2013.



The present report is **based on data available in the Central Registry by Jan 29, 2014**. At that time more than 800 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
Albania
Argentina
Australia
Austria
Belarus
Belgium
Chile
China
Croatia
Czech Republic
Denmark
Emirates
Finland
France
Georgia
Germany
Guatemala
Hong-kong
Hungary
India
Israel
Italy
Japan
Lithuania
Macedonia
Netherlands
Namibia
Norway
Philippines
Poland
Portugal
Russia
Serbia & Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Taiwan
Turkey
Ukraine
United Kingdom

By the cut-off date for this report (Jan 29, 2014), 19,420 pregnancies had been entered into the central database. Of these, **9,126 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n= 88).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n= 2,167).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n= 1,186).
4. Ongoing pregnancies, updated and corrected (n= 846).
5. Retrospective, but completed and corrected (n=3,475). Among these, there are true retrospective pregnancies i.e enrolled after 16th week of pregnancy (n=3,274) and a further two hundred and one pregnancies (n=201) 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 finally accepted as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=320).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=39). 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=27), 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=187).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=818).

Thus in total **10,294 prospective pregnancies** (enrolled at the latest during the 16th gestational week) **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 91 (1%) of the pregnant women.

Table 2. **Classification of the Epilepsy in 10,294 Prospective Pregnancies.**

Epilepsy	**N**	**%**
Localisation-related	5481	53.2
Generalized	4203	40.8
Undetermined	327	3.2
Missing information	192	1.9
No epilepsy	91	0.9
Total	**10,294**	**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%.

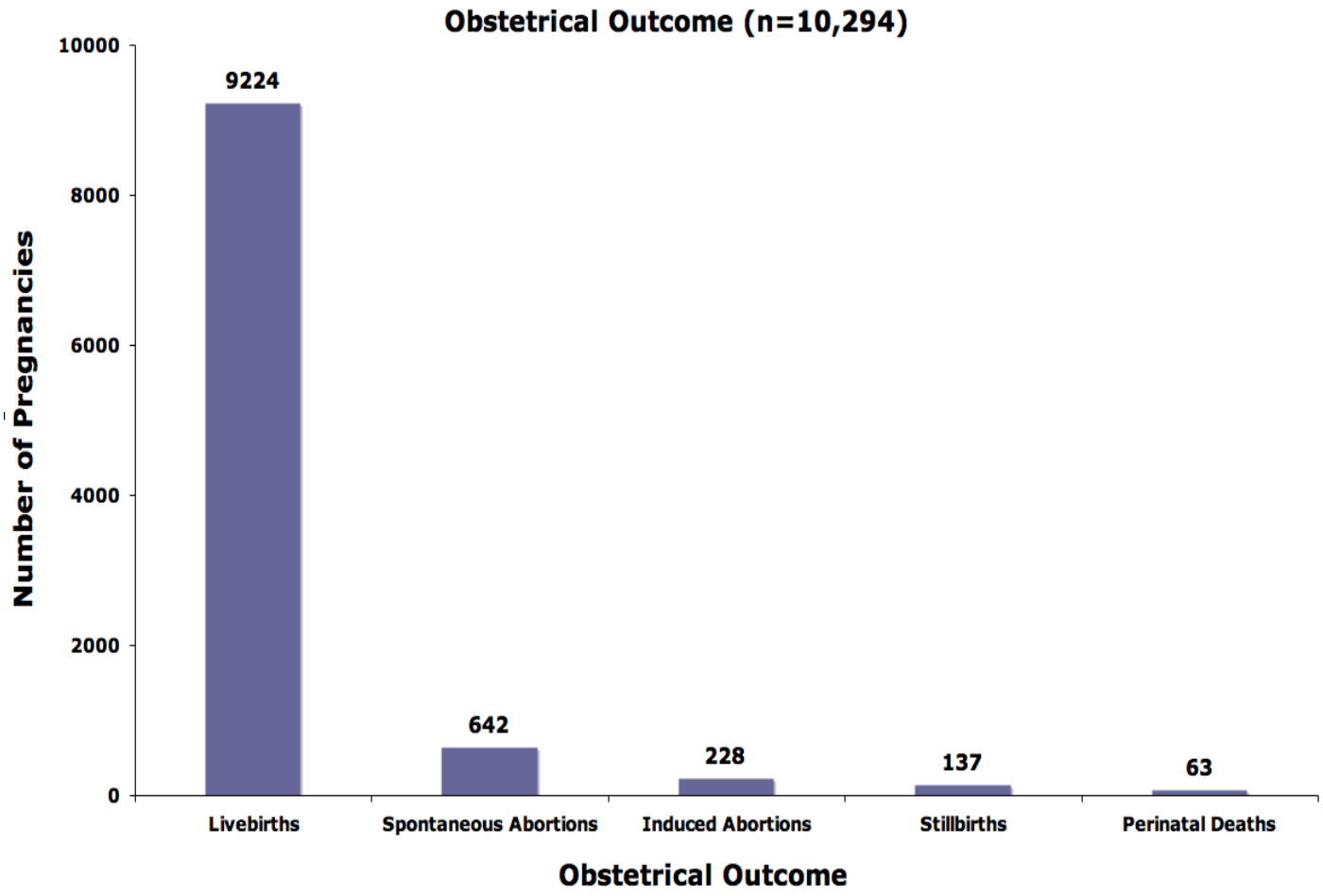
Gravida for each pregnancy is presented in Table 3.

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

Gravida	**N**	**%**
1st pregnancy	4718	45.8
2nd pregnancy	3166	30.8
3rd pregnancy	1409	13.7
4th pregnancy	628	6.1
5th pregnancy	225	2.2
> 5th pregnancy	147	1.4
Not ascertained	1	0.0
Total	**10,294**	**100**

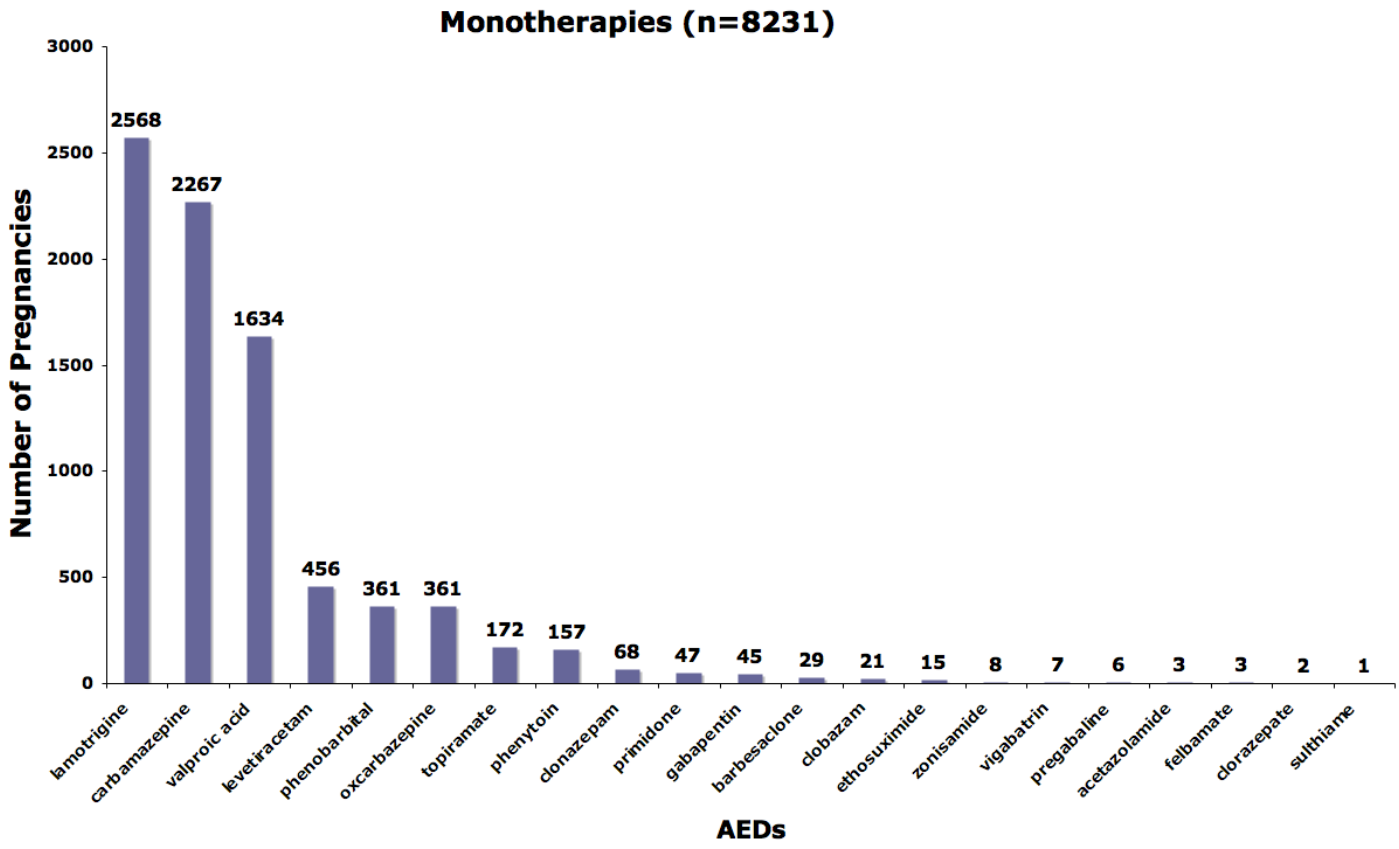
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 228 induced abortions, 33 were for chromosomal abnormalities and/or syndromes and 62 were for fetal indication detected by prenatal screening (out of these, 50 cases were confirmed major malformations and 12 cases 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, 8,231 (80%) involved women on a single AED, 1,664 (16.2%) were on two AEDs whereas 292 (2.8%) took three AEDs or more. One hundred and seven women (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 256 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=219), lamotrigine and levetiracetam (n=145), carbamazepine and levetiracetam (n=107), carbamazepine and lamotrigine (n=105), carbamazepine and valproic acid (n=75), carbamazepine and phenobarbital (n=73), lamotrigine and topiramate (n=64), carbamazepine and clobazam (n=63), clobazam and lamotrigine (n=45) and carbamazepine and topiramate (n=42) (Table 4).

Table 4. The Most Common AED Combinations.

lamotrigine + valproic acid	219
lamotrigine + levetiracetam	145
carbamazepine + levetiracetam	107
carbamazepine + lamotrigine	105
carbamazepine + valproic acid	75
carbamazepine + phenobarbital	73
lamotrigine + topiramate	64
carbamazepine + clobazam	63
clobazam + lamotrigine	45
carbamazepine + topiramate	42
clonazepam + lamotrigine	41
topiramate + valproic acid	36
levetiracetam + valproic acid	33
lamotrigine + oxcarbazepine	32
clonazepam + valproic acid	32
phenobarbital + valproic acid	32
levetiracetam + oxcarbazepine	31
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	879
Levetiracetam	460
Topiramate	278
Oxcarbazepine	171
Gabapentin	56
Vigabatrin	37
Zonisamide	35
Pregabalin	17
Tiagabine	8

TERATOGENIC OUTCOME

There were 502 major congenital malformations (MCM), 18 syndromic and/or monogenic cases and 59 chromosomal abnormalities (CHR) in the prospective cohort of 9,652 pregnancies as shown in Table 6 (642 spontaneous abortions are excluded).

Table 6. Pathological Outcomes.

Outcome	Outcome Classification	N
MCM	Multiple major	45
	Isolated major	457
MCM		**502**
SYNDROMES or MONOGENIC CONDITIONS		**18**
CHR		**59**
Total		**579**

The 18 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) and X-linked ichthyosis (1).

In this report we will confine our analysis to the 502 MCM including 50 induced abortions, five stillbirths and 14 neonatal deaths. Of the 433 live births, 42 cases of malformations were ascertained prenatally, 276 were first reported at birth and 115 within one year after birth.

Among the 502 cases with MCM, 94 were detected by ultrasound examination. Out of these 94, there were 45 induced abortions, four stillbirths, three perinatal deaths and 42 live births.

The 502 cases represent a **malformation rate of 5.2%** of all prospective pregnancies for which follow-up has been completed (502/9,652).

The type of malformations is described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	**45**
	Nervous system	
MCM	Spina Bifida	38
MCM	Anencephalus and similar	2
MCM	Hydrocephaly	4
MCM	Microcephaly	1
MCM	Nervous system (other malformations)	9
MCM	all	**54**
	Heart	
	Atrial septal defect	36
MCM	Ventricular septal defect	39
MCM	Atrioventricular septal defect	2
MCM	Congenital heart disease	35
MCM	Tetralogy of Fallot	4
MCM	Transposition of great vessels (complete)	3
MCM	Pulmonary valve stenosis	7
MCM	Hypoplastic left heart	6
	all	**132**
	Urinary system	
MCM	Urinary system (other malformations)	28
MCM	Renal Dysplasia	3
	all	**31**
	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	21
MCM	Club foot - talipes equinovarus	16
	all	**48**
	Musculoskeletal	
MCM	Musculo-skeletal (other malformations)	8
MCM	Hip dislocation and/or dysplasia	51
	all	**59**
	Genital system	
MCM	Genital (other malformations)	3
MCM	Hypospadias	59
	all	**62**
	Eye, ear, face and neck	
MCM	Congenital cataract	4
MCM	Ear, face and neck	5
MCM	Eye (other malformations)	2
MCM	Choanal atresia	1
MCM	all	**12**
	Oro facial clefts	
MCM	Cleft lip with or without palate	12
MCM	Cleft palate	12
	all	**24**
MCM	**Other specified malformations** (including sacral teratoma, cystic hygroma, haemangiomas, accessory skin tags, aberrant subclavian artery, sequences, genetic syndromes)	**14**
MCM	**all**	**502**
	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	3
CHR	Wolff-Hirschorn syndrome	1
CHR	**all**	**59**
	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	1
Syndrome	Congenital cataract	1
Syndrome	Congenital glaucoma	1
Syndrome	X-linked Ichthyosis	1
Syndrome	X-linked Lissencephaly	1
Syndrome	Hearing loss, bilateral	1
Syndrome	Skeletal dysplasia	1
Syndromes or Monogenic Conditions	**all**	**18**
Total		**579**

In 369 out of 7,749 pregnancies with AED monotherapy one or more birth defects were observed (4.8 %), as opposed to 130 out of 1,801 pregnancies with AED polytherapy (7.2 %) as shown in Table 8.

Table 8. *In this table, 642 spontaneous abortions have been excluded from the denominator.*

	No AED	%	Monotherapy	%	Polytherapy	%	Total
MCM	**3**	2.9	**369**	4.8	**130**	7.2	**502 (**5.2%**)**
CHR	**0**	0.0	**47**	0.6	**12**	0.7	**59 (**0.6%**)**
Syndromes	**0**	0.0	**14**	0.2	**4**	0.2	**18 (**0.2%**)**
No malformation	**99**	97.1	**7,319**	94.4	**1,655**	91.9	**9,073 (**94.0%**)**
Total	**102**	100	**7,749**	100	**1,801**	100	**9,652 (**100%**)**

Outcome in relation to exposure to individual drugs or specific drug combinations is not included in the present report.

Outcome regarding the four most common monotherapies has been published in Lancet Neurology, June 6, 2011.

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

National/Regional Coordinators

Silvia Kochen, Argentina

Frank Vajda, Australia

Gerhard Luef, Austria

Dick Lindhout and **Eugène van Puijenbroek,** BeNeLux

Alejandro de Marinis, Chile

Dinko Vitezic, Croatia

Jana Zarubova and **Robert Kuba**, Czech Republic

Anne Sabers, Denmark

Reetta Kälviäinen, Finland

Michel Beaulac, France

Otar Toidze and **Sofia Kasradze,** Georgia

Bettina Schmitz, Germany

Patrick Kwan, Hong Kong

Gábor Barcs, Hungary

Sanjeev V Thomas, India

Miri Neufeld, Israel

Luigi Maria Specchio, Italy

Hideyuki Ohtani, Japan

Ruta Mameniskiene, Lithuania

Gordana Kiteva-Trencevska, Macedonia

Karl-Otto Nakken, Norway

Weiping Liao, People's Republic of China

Leonor Cabral-Lim, Philippines

Joanna Jedrzejczak, Poland

Alla Guekht and **Oksana Lokshina,** Russia

Dragoslav Sokic, Serbia and Montenegro

Vladimir Safcak, Slovakia

Boštjan Čebular, Slovenia

Meritxell Martinez Ferri, Spain

Torbjörn Tomson, Sweden

Barbara Tettenborn and **Bernhard Oehl,** Switzerland

Chi-Wan Lai and **Alice Yu,** Taiwan

Demet Kinay and **Dilek Atakli,** Turkey

John Craig and **Aline Russell,** United Kingdom