EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report Germany – May 2022

National Coordinator
Prof. Dr. Bettina Schmitz
Chefärztin der Klinik für Neurologie
Stroke Unit und Zentrum für Epilepsie
Vivantes Humboldt-Klinikum
13509 Berlin, ***Germany***
Tel: + 49-30-130-12-22-45
Fax: + 49-30-130-12-22-47
E-mail: Bettina.Schmitz@vivantes.de

Central Study Coordinator
Dr. Dina Battino
Fondazione IRCCS Istituto Neurologico Carlo Besta
20 133 Milano, ***Italy***
Tel: + 39-02-23-94-22-30
Tel (other): + 39-02-23-94-26-36
E-mail: eurap@istituto-besta.it

Chairman Central Project Commission
Prof. Torbjörn Tomson
Department of Clinical Neuroscience
Karolinska Institutet
Department of Neurology
Hotellet, Plan 4
Karolinska University Hospital
SE 171 76 Stockholm, ***Sweden***
E-mail: torbjorn.tomson@regionstockholm.se

BACKGROUND

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal use of antiepileptic drugs (AEDs) 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. The EURAP Study protocol has been updated in June 2021 and can be found on www.eurapinternational.org

OBJECTIVE OF EURAP

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

METHODS

EURAP is an 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.

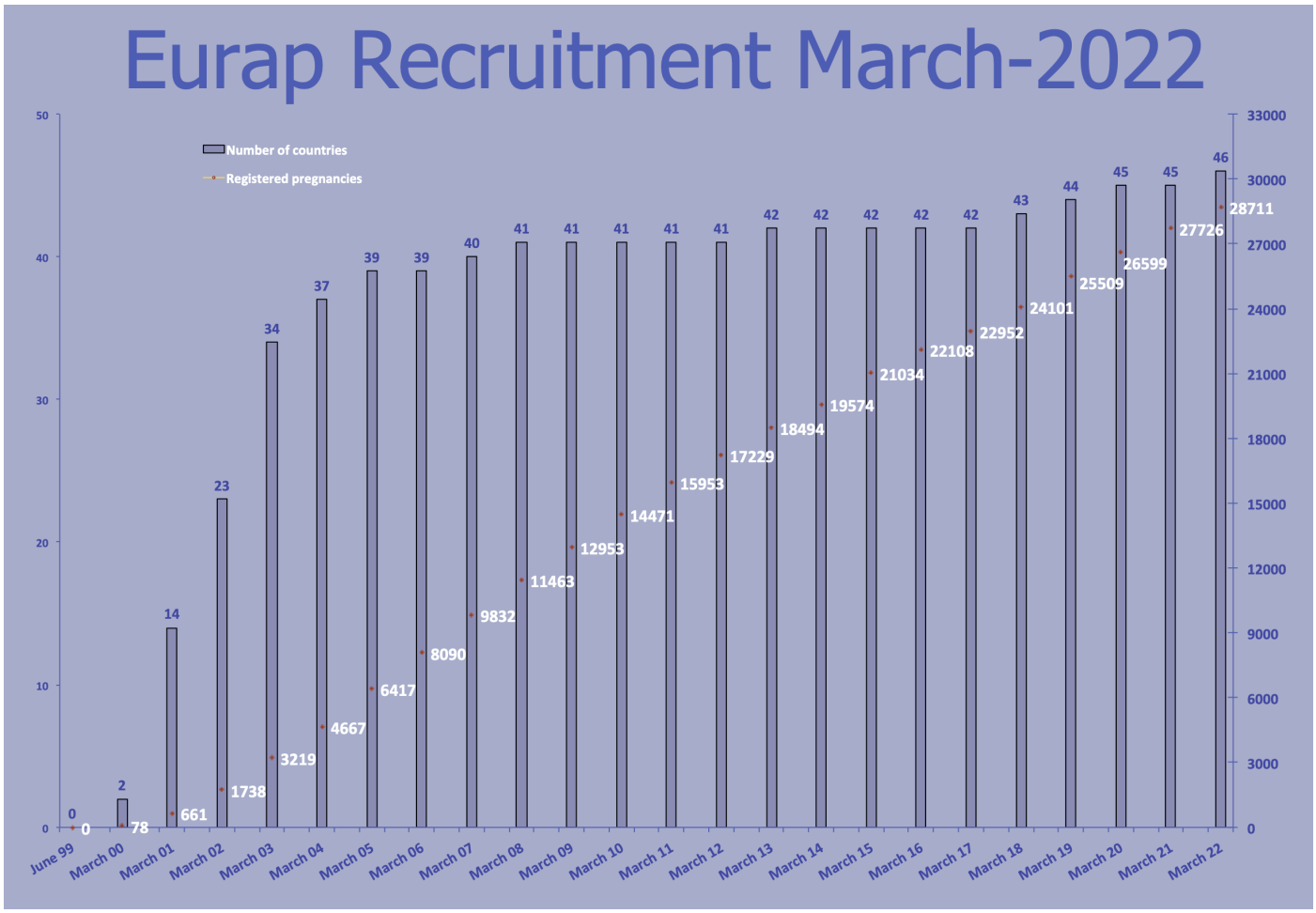
EVALUATION OF OUTCOME

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 to include countries from Europe, Oceania, Asia, Latin 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 March 2022.



The present report is **based on data available in the Central Registry by May 25th, 2022**.
At that time more than 1,500 reporting physicians from 46 countries had contributed cases to the Central Registry.
Table 1 shows the number of cases included in the May 2022 interim report, for each country.

Table 1. Countries with pregnancies included in the current report (n=42)

COUNTRY	INCLUDED CASES
Italy	2,483
Germany	**1,905**
Netherlands	1,446
Norway	1,381
Denmark	1,360
Sweden	1,358
Australia	808
India	779
Spain	690
Czech Republic	657
Finland	456
Japan	438
Austria	417
United Kingdom	366
Serbia & Montenegro	350
Switzerland	198
Slovakia	168
Taiwan	168
Chile	147
Turkey	118
Israel	102
Slovenia	99
Belgium	87
Lithuania	84
Macedonia	75
Argentina	74
Georgia	73
Portugal	59
Philippines	47
Iran	36
France	31
Croatia	27
Poland	26
China	18
El Salvador	18
Hong-kong	12
Estonia	8
Hungary	6
Belarus	5
Russia	1
Albania	1
Ukraine	1
TOTAL	**16,583**

By the cut-off date for this report (May 25th, 2022), **4,278 pregnancies from Germany had been entered into the central database**. Of these, **2,373 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n=62).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,302).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=292).
4. Ongoing pregnancies, updated and corrected (n=156).
5. Retrospective, but completed and corrected (n=270). Among these, there are true retrospective pregnancies (n=244) and a further twenty-six pregnancies (n=26) that otherwise met our criteria for prospective pregnancies since they were recruited within 16th week, but for 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=65).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=14). This includes 1 induced abortion with insufficient information on fetus, and anomalies in 13 live births where the information were insufficient to determine if qualifying for malformation diagnosis (*i.e. 1 case with suspected cornelia de lange syndrome, 1 case without a clear diagnosis, 2 cases with an unspecified congenital heart defect, 2 cases with an emangioma but missing information on size, 2 cases with dermal sinus, 1 case with ventricular brain asymmetry, 2 cases with atrial septal defect without follow-up after birth and 2 cases with pyelectasia but missing information about size of pelvic dilatation*).
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 Outcome Assessment Committee (OAC), regardless if they contained some malformations or not (n=38).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=174).

Thus in total **1,905 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 11 (0.6%) of the pregnant women.

Table 2. **Classification of the epilepsy in 1,905 prospective pregnancies.**

Epilepsy	**N**	**%**
Localisation-related*	928	48.7
Generalized	844	44.3
Undetermined	68	3.6
Missing information	54	2.8
No epilepsy	11	0.6
Total	**1,905**	**100**

**Focal, according to more current terminology.*

The **maternal age** among prospective cases was **30.2 ±5.1 years** (mean±SD), ranging from 14 to 45 years.

The women were of Caucasian **ethnicity** in 93.3% and of Asian in 1.4%.

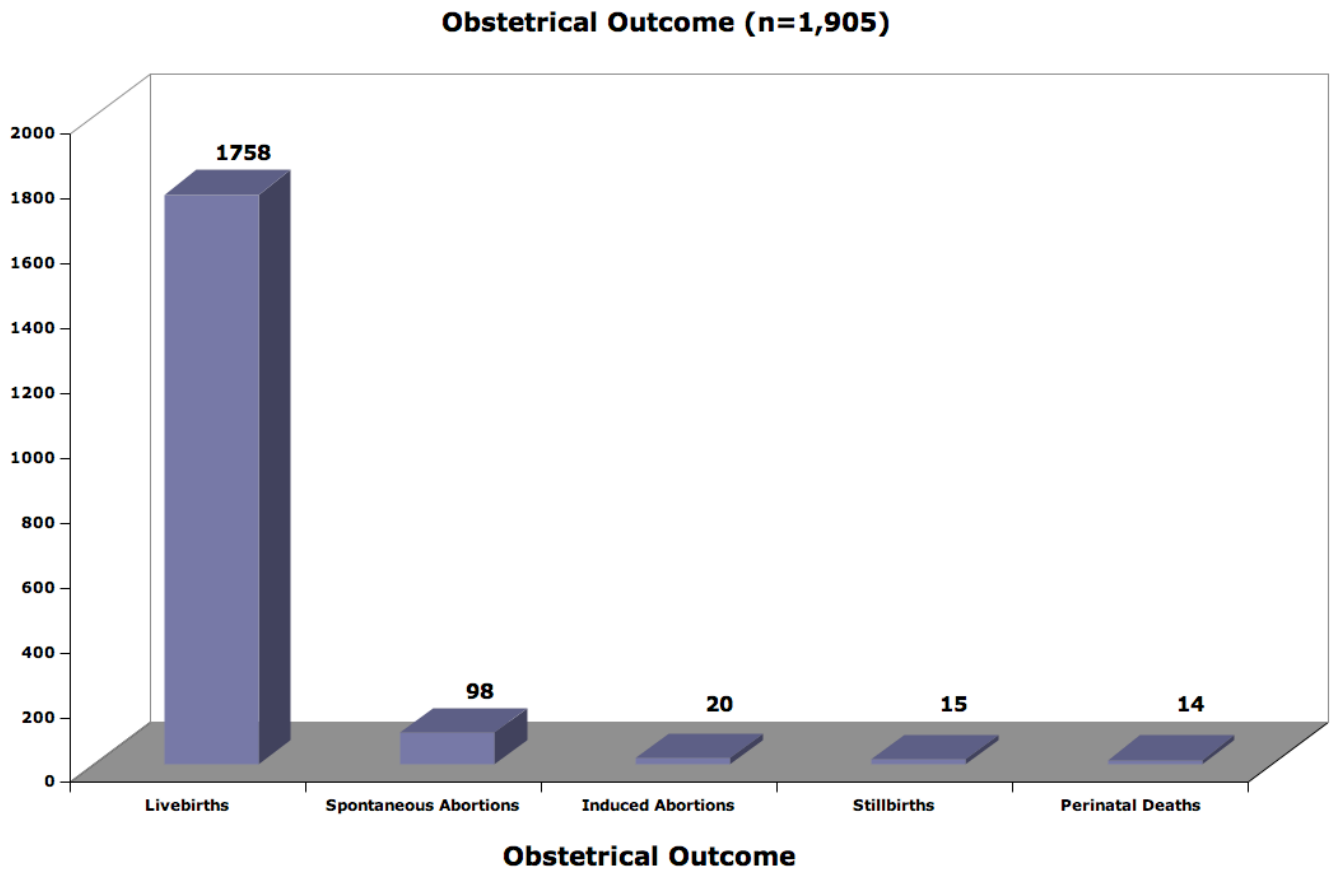
Gravida for each pregnancy is presented in Table 3.

Table 3. **Number of the pregnancy in 1,905 prospective cases.**

Gravida	**N**	**%**
1st pregnancy	998	52.4
2nd pregnancy	569	29.9
3rd pregnancy	214	11.2
4th pregnancy	78	4.1
5th pregnancy	32	1.7
> 5th pregnancy	13	0.7
Not ascertained	1	0.0
Total	**1,905**	**100**

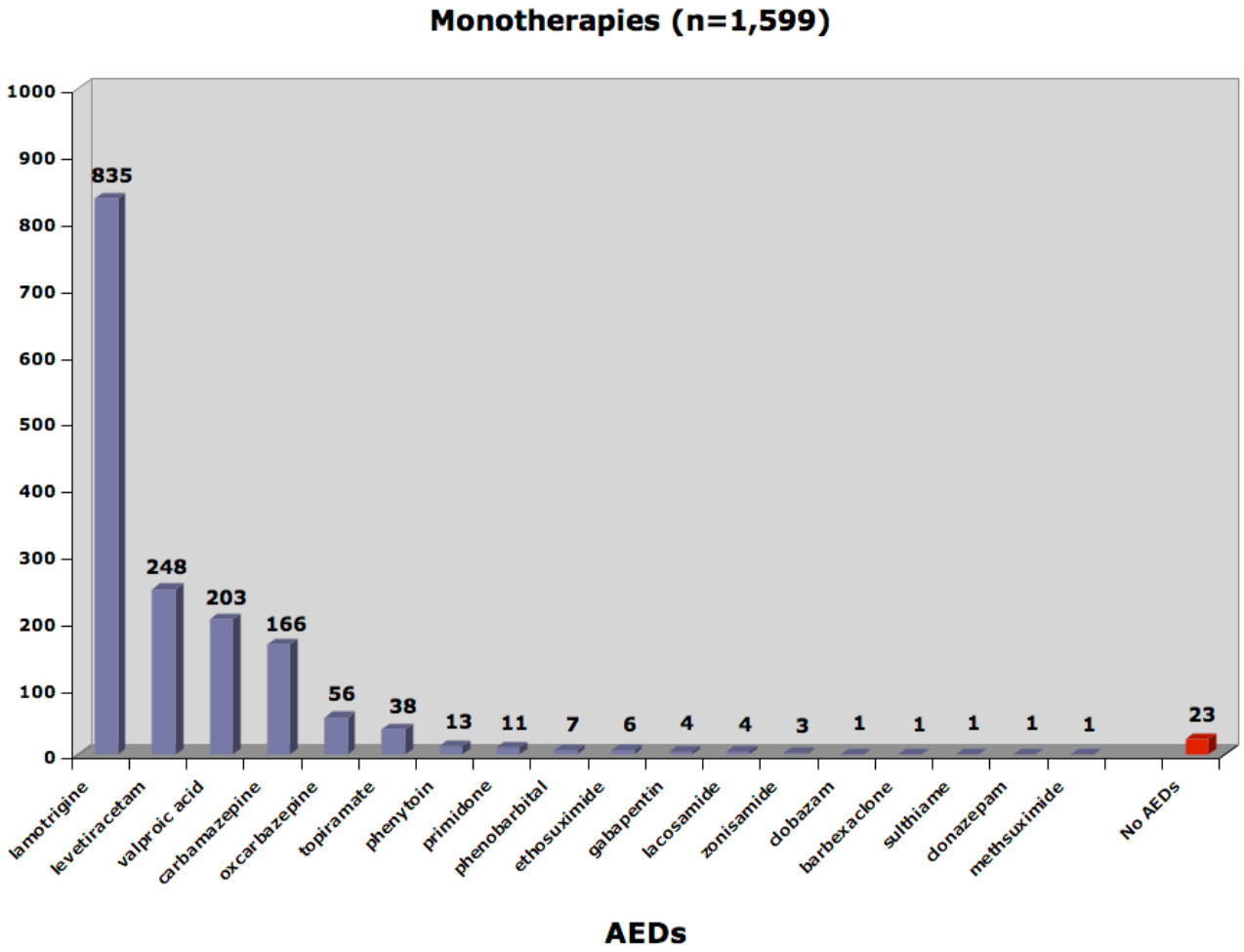
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 20 induced abortions cases, 10 cases were due to maternal reasons (either social or medical), 5 cases were for chromosomal abnormalities and/or syndromes and 5 cases were due to other fetal indication detected by prenatal screening (*out of these 5 cases, 3 were finally confirmed as major malformations and 2 cases were definitively classified as other abnormalities such as fetal growth retardation and unverifiable foetus*).

Figure 2. Obstetrical outcome of prospective pregnancies.



Of the pregnancies, **1,599 (83.9%) involved women on a single AED**, 254 (13.3%) were on two AEDs whereas 29 (1.6%) took three AEDs or more. Twenty-three 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 during the first trimester of pregnancy.**



There were 77 different AED combinations. The most frequently used combinations were lamotrigine and levetiracetam (n=94), lamotrigine and valproic acid (n=23), levetiracetam and valproic acid (n=16), levetiracetam and oxcarbazepine (n=13), carbamazepine and levetiracetam (n=12), lacosamide and levetiracetam (n=8), lamotrigine and topiramate (n=7), carbamazepine and lamotrigine (n=5), levetiracetam and phenobarbital (n=4), topiramate and valproic acid (n=4), carbamazepine and valproic acid (n=4), levetiracetam and topiramate (n=4) and lamotrigine and oxcarbazepine (4) (Table 4).

Table 4. The most common AED combinations.

The most common polytherapies during the first trimester of pregnancy	N
lamotrigine + levetiracetam	94
lamotrigine + valproic acid	23
levetiracetam + valproic acid	16
levetiracetam + oxcarbazepine	13
carbamazepine + levetiracetam	12
lacosamide + levetiracetam	8
lamotrigine + topiramate	7
carbamazepine + lamotrigine	5
levetiracetam + phenobarbital	4
topiramate + valproic acid	4
carbamazepine + valproic acid	4
levetiracetam + topiramate	4
lamotrigine + oxcarbazepine	4
lamotrigine + phenytoin	3
carbamazepine + phenobarbital	3
lamotrigine + levetiracetam + valproic acid	3
lamotrigine + levetiracetam + oxcarbazepine	3

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

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

Levetiracetam	175
Lamotrigine	168
Oxcarbazepine	30
Topiramate	24
Lacosamide	13
Zonisamide	8
Gabapentin	4
Perampanel	4
Pregabalin	3
Brivaracetam	3
Tiagabine	1
Vigabatrin	1
Eslicarbazepine acetate	1
Rufinamide	1
Retigabine	0

TERATOGENIC OUTCOME

There were 84 major congenital malformations (MCM), 5 syndromic and/or genetic cases and 8 chromosomal abnormalities (CHR) in the prospective cohort of 1,807 pregnancies as shown in Table 6 (*98 spontaneous abortions are excluded*).

Table 6. Pathological outcomes.

Outcome	Outcome Classification	N
MCM	Multiple major	7
	Isolated major	77
MCM		**84**
SYNDROMES or GENETIC conditions		**5**
CHR		**8**
Total		**97**

The 5 syndromic and/or genetic cases are referred to inherited tuberous sclerosis (1), incontinentia pigmenti (1), inherited congenital cataract (1), Zellweger syndrome (1) and Achondroplasia (1).

In this report we will confine our analysis to the 84 MCM including 3 induced abortions, 2 neonatal death and 79 live births. Of the 79 live births, 9 cases of malformations were ascertained prenatally, 51 were first reported at birth, and a further 19 cases not detected at birth but within one year after birth.

Among the 84 cases with MCM, 13 were detected by ultrasound examination. Out of these 13, there were 3 induced abortions, 1 neonatal death and 9 live births.

The 84 cases represent a **malformation prevalence of 4.7%** of all prospective pregnancies for which follow-up has been completed (84/1,807).

The type of malformations is described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	7
	Cardiovascular system	
MCM	Atrial septal defect	2
MCM	Patent ductus arteriosus	1
MCM	Congenital pulmonary valve stenosis	2
MCM	Hypoplastic left heart syndrome	1
MCM	Ventricular septal defect	9
MCM	Congenital malformations of the heart, unspecified	1
MCM	Other congenital malformations of aorta; Atrial septal defect	1
	all	**17**
	Genital system	
MCM	Developmental ovarian cyst, single	1
MCM	Developmental ovarian cyst, multiple	1
MCM	Hypospadias	9
MCM	Other specified congenital malformations of female genitalia	1
	all	**12**
	Nervous system	
MCM	Spina Bifida	3
MCM	Single congenital cerebral cyst	1
MCM	Congenital celebral cysts	3
	all	**7**
	Musculoskeletal	
MCM	Hip dislocation and/or dysplasia	15
	all	**15**
	Urinary system	
MCM	Atresia and stenosis of ureter	1
MCM	Accessory kidney	1
MCM	Congenital deformity of urinary system, NOS	1
MCM	Congenital megaloureter	1
MCM	Congenital pelviureteric junction obstruction, unilateral	1
MCM	Patent urachus	1
MCM	Impervious urethra (Megacystis-megaureter syndrome)	1
MCM	Double or triple kidney	1
	all	**8**
	Digestive system	
MCM	Imperforate anus	1
MCM	Congenital cardiospam	1
MCM	Congenital absence, atresia and stenosis of duodenum	1
MCM	Duplication of anus, appendix, caecum and intestine	1
MCM	Atresia of oesophagus without fistula	2
MCM	Hirschsprung's disease	2
	all	**8**
	Eye, Ear, Face and Neck	
MCM	Congenital absence, atresia and stricture of auditory canal (external)	1
MCM	Congenital cataract	1
	all	**2**
	Oro facial clefts	
MCM	Cleft palate	1
	all	**1**
	Limbs	
MCM	Polydactyly	2
	all	**2**
MCM	**Other specified malformations** (*including sacral teratoma, aberrant subclavian artery, congenital malformations of spleen, congenital malfomations of lung, congenital malformations of thyroid gland*)	5
MCM	**all MCMs**	**84**
	Chromosomal	
CHR	Chromosomal abnormality (defective chromosomes 4 and 16)	1
CHR	Down's syndrome	2
CHR	Edward syndrome	1
CHR	Klinefelter's syndrome	1
CHR	Patau's syndrome	2
CHR	Turner's syndrome	1
CHR	**all CHR**	**8**
	Syndromes or monogenic conditions	
Syndrome	Achondroplasia	1
Syndrome	Congenital cataract, inherited	1
Syndrome	Tuberous sclerosis, inherited	1
Syndrome	Incontinentia pigmenti	1
Syndrome	Zellweger syndrome	1
Syndromes	**all syndromes or monogenic conditions**	**5**
Total		**97**

In 67 out of 1,521 pregnancies with AED monotherapy, one or more MCMs were observed (4.4%) as opposed to 16 out of 263 pregnancies with AED polytherapy (6.1%), as shown in Table 8.

Table 8. Pathological outcomes by AED treatment categories.
(In this table, 98 spontaneous abortions have been excluded from the denominator).

	No AED	%	Monotherapy	%	Polytherapy	%	Total
MCM	**1**	4.3	**67**	4.4	**16**	6.1	**84 (**4.7%**)**
CHR	**0**	0.0	**5**	0.3	**3**	1.1	**8 (**0.4%**)**
Syndromes	**0**	0.0	**3**	0.2	**2**	0.8	**5 (**0.3%**)**
No malformation	**22**	95.7	**1,446**	95.1	**242**	92.0	**1,710 (**94.6%**)**
Total	**23**	100	**1,521**	100	**263**	100	**1,807 (**100%**)**

PUBLICATIONS

Changes in AED prescribing patterns and in rates of MCM over time in the EURAP cohort were published in *Neurology. 2019 Aug 27;93(9):e831-e840*.

Outcome regarding the eight most common monotherapies has been published in *Lancet Neurology, April 18, 2018*.

The dose-dependent risk of MCM with exposure to valproate in mono- and polytherapy has also been analysed and reported (*Neurology, Sept 8, 2015*) and so has the risk of intrauterine death in association with different treatments (*Neurology Aug 18, 2015*).

A manuscript on seizure control in pregnancies with withdrawal of or switch from valproate during 1st trimester as compared with maintained valproate treatment has been published in Epilepsia (*Epilepsia 2016; 57: e173-7*).

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 over the years by donations to EURAP from Angelini Pharma, Bial, Eisai Pharmaceuticals, GlaxoSmithKline, GW/Jazz Pharmaceuticals, Janssen-Cilag, Johnson & Johnson, Novartis, Pfizer, Sanofi, Teva UCB biopharma and Glenmark Pharmaceuticals. 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

(*The persons below have contributed to the work of the OAC during different time periods of the project*)

Chiara Pantaleoni, Milan, Italy

Claudia Ciaccio, Milan, Italy

Elisabeth Robert-Gnansia, Lyon, France

Francesca Faravelli, Genoa, Italy

Richard Finnell, Houston, Texas