EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report Germany – November 2025

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BACKGROUND

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal use of antiseizure medications (ASMs) have agreed on a prospective international multi-centre study of pregnancies with ASMs. 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 ASMs and their combinations during pregnancy.

METHODS

EURAP is an observational study. Women taking ASMs 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 Central EURAP Registry in Milan, Italy.

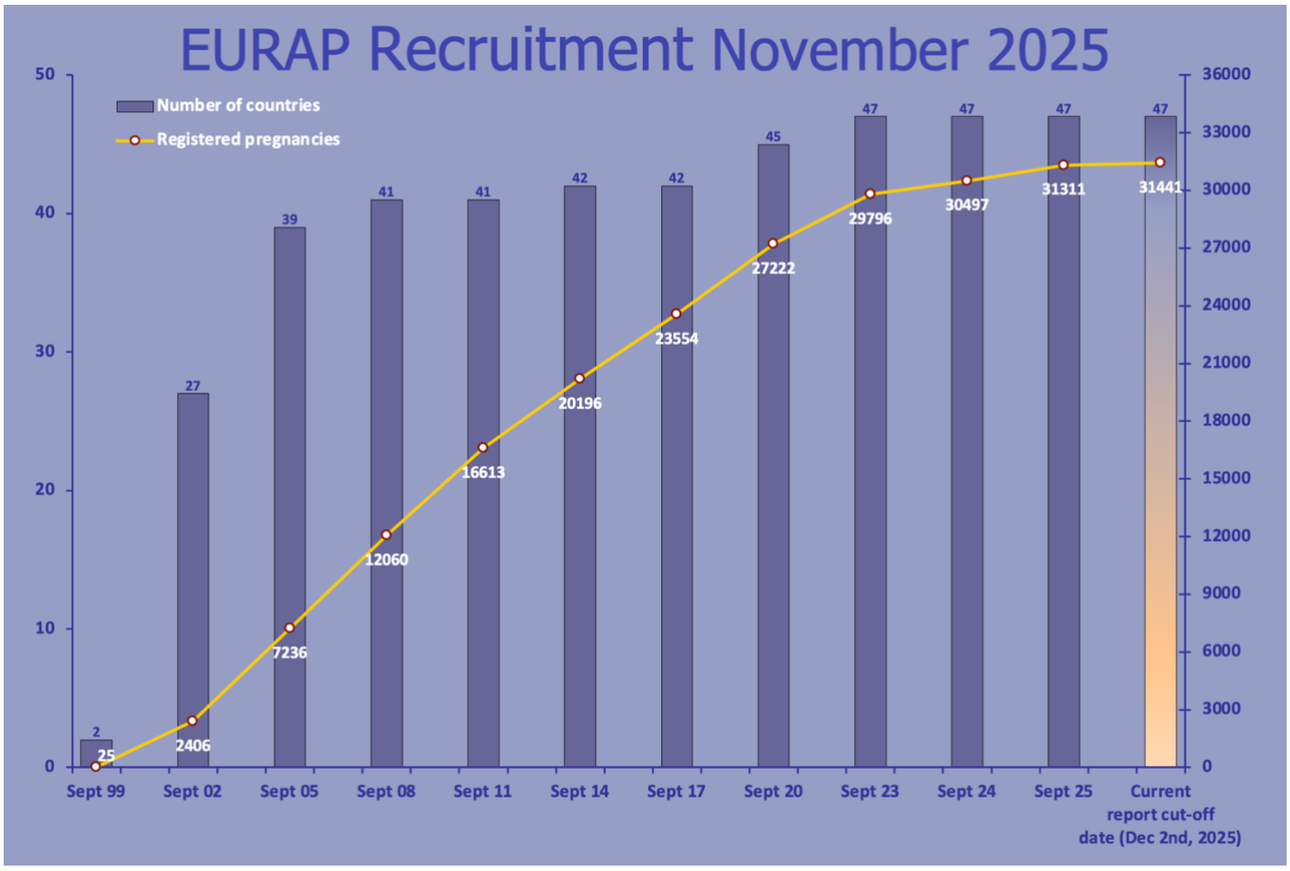
EVALUATION OF OUTCOME

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 Figure 1.

Figure 1. Number of Participating Countries and Pregnancies Reported to the Central Registry by December 2nd, 2025.



The present report is **based on data available in the Central Registry by December 2nd, 2025**. At that time more than 1,500 reporting physicians from 47 countries had contributed cases to the Central Registry.
Table 1 shows the number of cases included in the May 2025 interim report, for each country, with Germany highlighted.

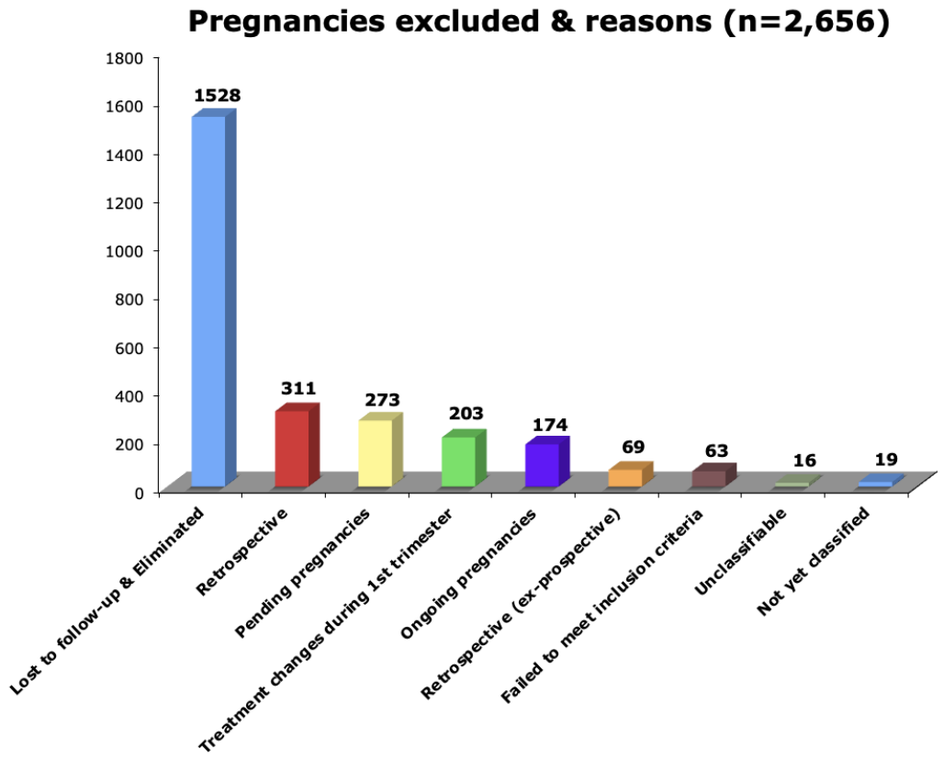
Table 1. Countries with pregnancies included in the current report (n=43).

COUNTRY	INCLUDED CASES
Italy	2,726
Germany	**2,381**
Denmark	1,578
Norway	1,572
Sweden	1,468
Netherlands	1,465
India	839
Australia	808
Spain	772
Czech Republic	757
Japan	628
Finland	498
Austria	466
United Kingdom	366
Serbia & Montenegro	364
Switzerland	230
Taiwan	192
Chile	188
Slovakia	180
Israel	129
Turkey	120
Slovenia	99
Belgium	97
Macedonia	93
Georgia	89
Lithuania	84
Iran	76
Argentina	75
Portugal	67
Philippines	47
France	36
Estonia	35
Croatia	27
Poland	26
China	19
El Salvador	18
Belarus	17
Hong-kong	12
Hungary	6
Russia	2
Albania	1
Algeria	1
Ukraine	1
TOTAL	**18,655**

By the cut-off date for this report (**December 2nd, 2025**), **5,037 pregnancies from Germany had been entered into the central database**. Of these, **2,656 pregnancies are excluded** from the present interim report for reasons explained in Graphic 1 and here below:

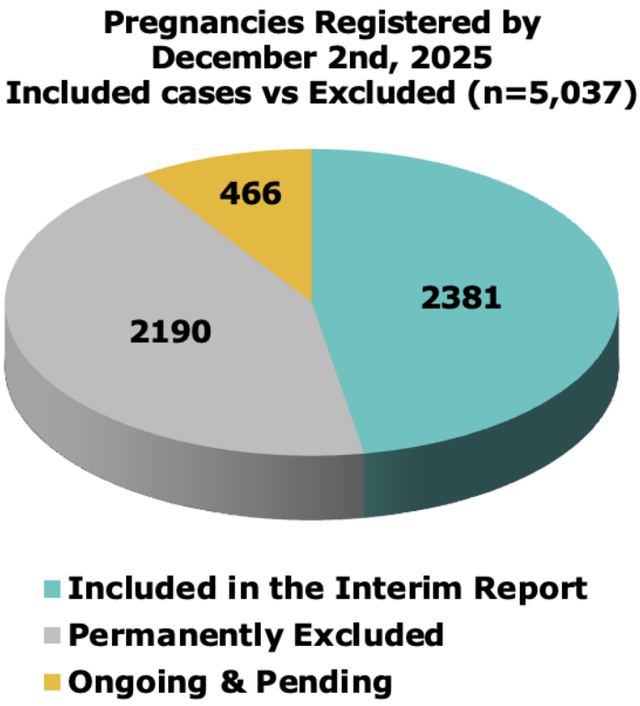
1. Pregnancies that **failed to meet inclusion criteria** (**n=63**).
2. Lost to follow-up, including cases **eliminated** by the central registry as failing to submit sub-forms within preset deadlines (**n=1,528**).
3. **Pending pregnancies**, awaiting updates or corrections of different sub-forms (**n=273**).
4. **Ongoing pregnancies**, updated and corrected (**n=174**).
5. **Retrospective**, but completed and corrected (**n=311**). Among these, there are true retrospective pregnancies (n=281) and a further thirty pregnancies (n=30) 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=69**).
7. **Unclassifiable** i.e. cases for which it was impossible to determine if there was a malformation or not (**n=16**). This includes 1 induced abortion with insufficient information on fetus, and anomalies in 15 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, 4 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 where classification is pending as well as pregnancies which became completed after the database was last sent to the Outcome Assessment Committee (OAC) (**n=19**).
9. **Treatment was changed** from one ASM monotherapy to another, or from mono- to polytherapy or vice versa during the first trimester (**n=203**).

Graphic 1: Reasons of pregnancies' exclusions from the current interim report.



Thus, in total **2,381 prospective pregnancies** (enrolled at the latest during the 16th gestational week and before outcome was known) **are included** in this report. The registration status of all pregnancies included in the central database by the cut-off date for this report (December 2nd, 2025) is illustrated in Graphic 2

Graphic 2: Pregnancies registered in the central database at the interim report.



The indication for treatment and the classification of the epilepsy among the prospective pregnancies are reported in table 2. Epilepsy was the indication for treatment in all but 11 (0.5%) of the pregnancies.

Table 2. Classification of the epilepsy in 2,381 prospective pregnancies.

Epilepsy	N	%
Localisation-related*	1,157	48.6
Generalized	1,054	44.3
Undetermined	84	3.5
Missing information	75	3.1
No epilepsy	11	0.5
Total	**2,381**	**100**

**Focal, according to current ILAE terminology.*

The women were of Caucasian **ethnicity** in 93.6% and other but unspecified ethnicity in 2.6%.

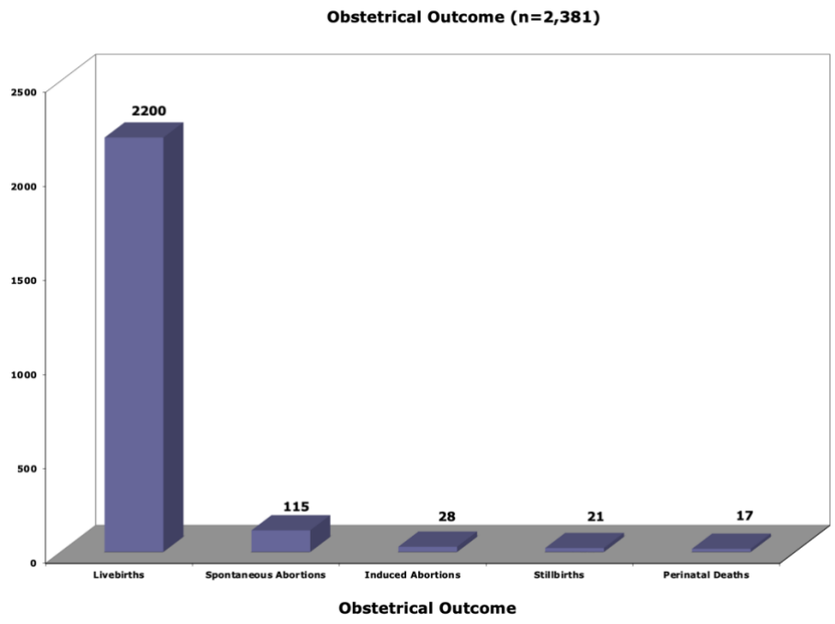
Gravida for each pregnancy is reported in Table 3.

Table 3. Number of the pregnancy in 2,381 prospective cases.

Gravida	N	%
1st pregnancy	1,249	52.5
2nd pregnancy	712	29.9
3rd pregnancy	272	11.4
4th pregnancy	98	4.1
5th pregnancy	34	1.4
> 5th pregnancy	15	0.6
Missing information	1	0.1
Total	**2,381**	**100**

The outcomes of the prospective completed pregnancies are illustrated in Figure 2. Out of the **28 induced abortions**, 14 cases were due to maternal reasons (either social or medical), 9 cases were for chromosomal abnormalities and/or syndromes and 5 cases were due to other fetal indications detected by prenatal screening Of the latter 5 cases, 3 were confirmed as major malformations and the remaining 2 were classified as other abnormalities such as fetal growth retardation and unverifiable foetus.

Figure 2. Obstetrical outcome of prospective pregnancies.



Of the 2,381 pregnancies, **1,950 (81.9%) involved women on a single ASM**, 361 (15.2%) women on two ASMs, whereas 41 (1.7%) occurred in women who took three ASMs or more. Twenty-nine women (1.2%) were not on ASM treatment during the 1st trimester. The type of ASM treatment is described in Graphic 3, while the exposure to the different ASMs in monotherapy among the prospective pregnancies is illustrated in Figure 3.

Graphic 3: **Type of ASM treatment in 2,381 prospective pregnancies.**

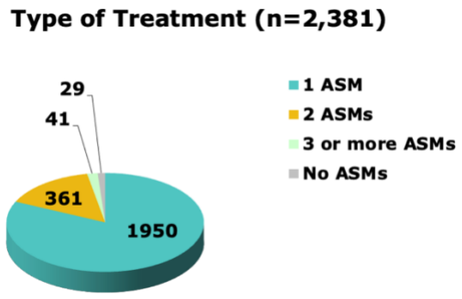
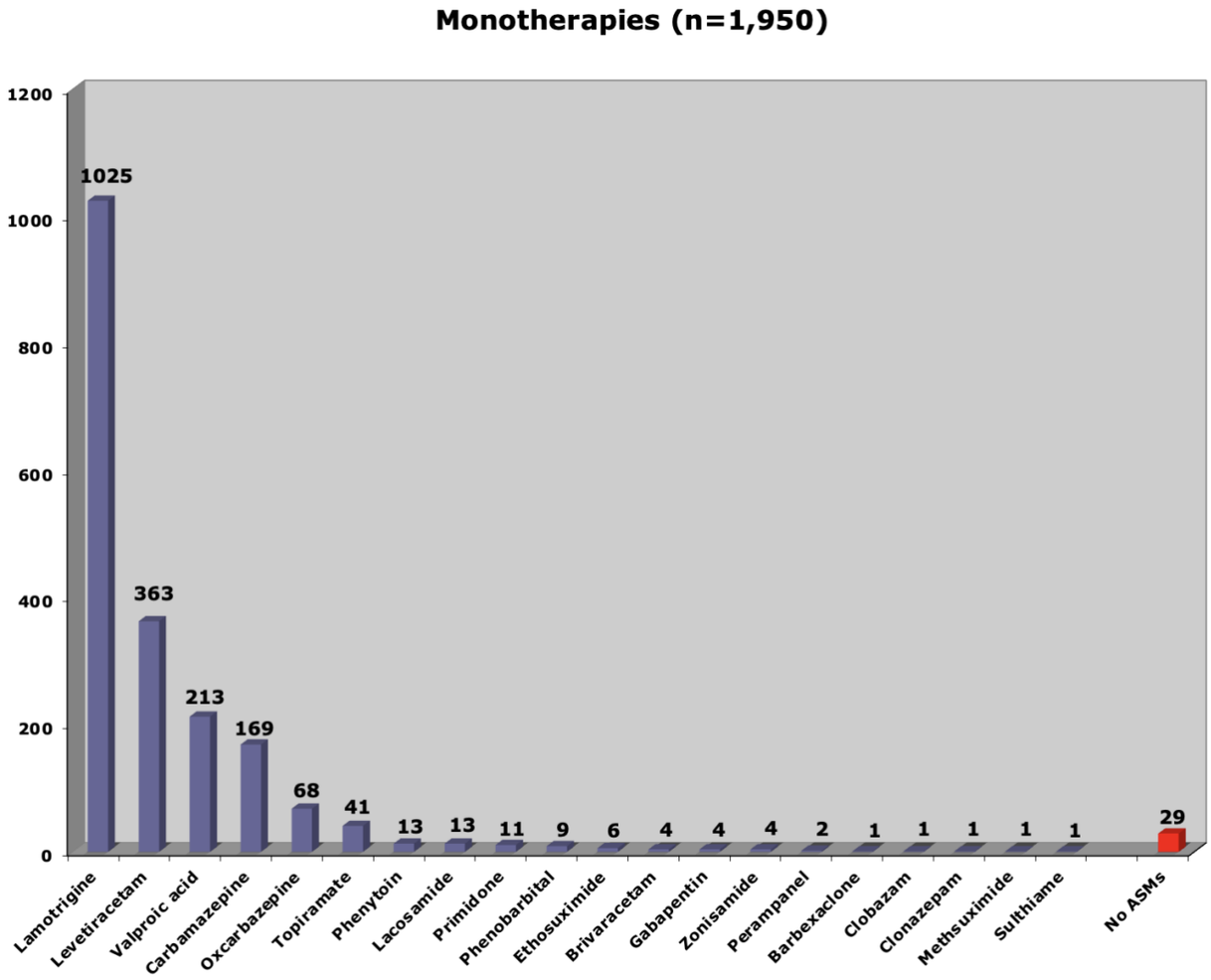


Figure 3. **Number of prospective pregnancies exposed to different ASMs in monotherapy during the first trimester of pregnancy.**

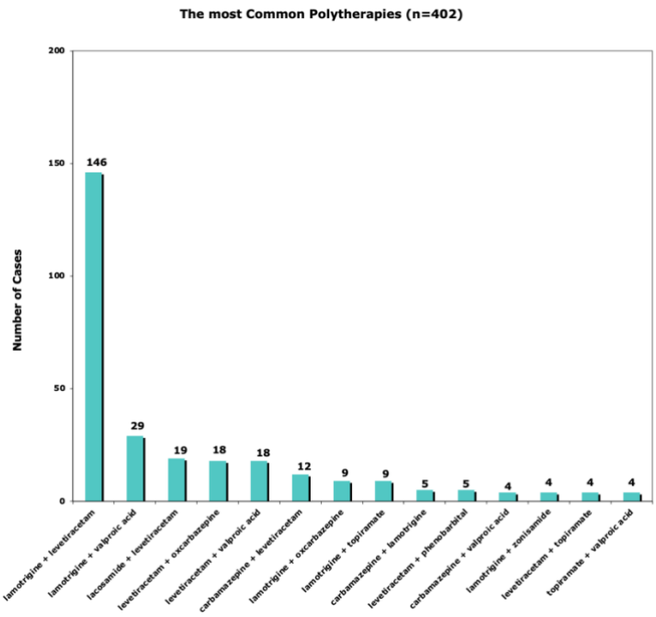


There were 97 different ASM combinations. The most frequently used combinations were lamotrigine and levetiracetam (n=146), lamotrigine and valproic acid (n=29), lacosamide and levetiracetam (n=19), levetiracetam and valproic acid (n=18), levetiracetam and oxcarbazepine (n=18), carbamazepine and levetiracetam (n=12), lamotrigine and topiramate (n=9), lamotrigine and oxcarbazepine (9), carbamazepine and lamotrigine (n=5), levetiracetam and phenobarbital (n=5), lamotrigine and zonisamide (n=4), topiramate and valproic acid (n=4), carbamazepine and valproic acid (n=4) and levetiracetam and topiramate (n=4) (Table 4 and Graphic 4).

Table 4. Most common ASM combinations recorded in prospective pregnancies.

Most common polytherapies during the first trimester of pregnancy	N
Lamotrigine + levetiracetam	146
Lamotrigine + valproic acid	29
Lacosamide + levetiracetam	19
Levetiracetam + valproic acid	18
Levetiracetam + oxcarbazepine	18
Carbamazepine + levetiracetam	12
Lamotrigine + topiramate	9
Lamotrigine + oxcarbazepine	9
Carbamazepine + lamotrigine	5
Levetiracetam + phenobarbital	5
Lamotrigine + zonisamide	4
Topiramate + valproic acid	4
Carbamazepine + valproic acid	4
Levetiracetam + topiramate	4

Graphic 4: Most common ASM combinations recorded in prospective pregnancies.

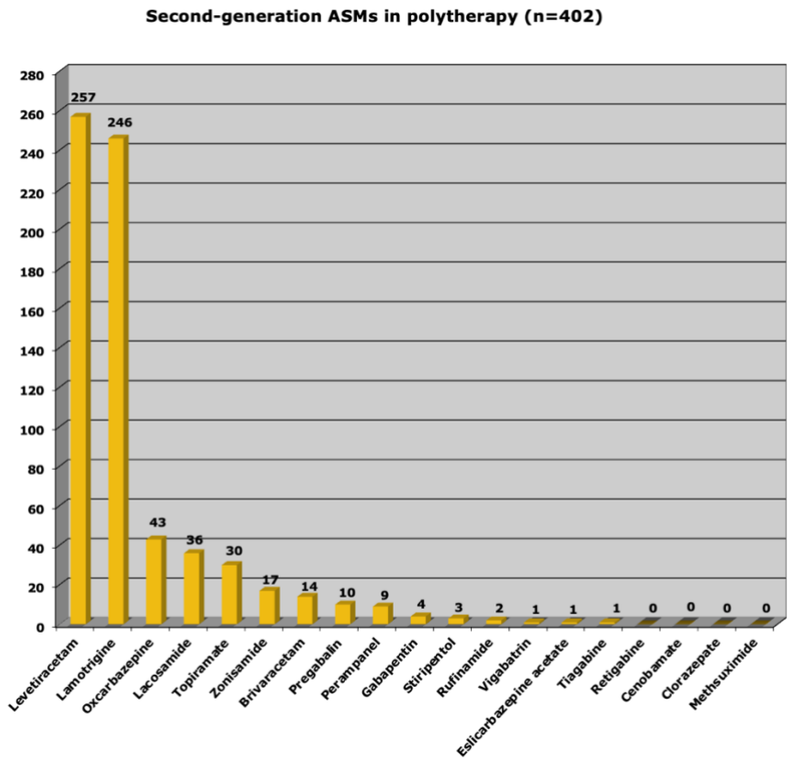


The number of pregnancies exposed to different second-generation ASMs taken in combination with other ASMs are listed in Table 5 and Graphic 5.

Table 5. **Number of pregnancies exposed to second-generation ASMs in a polytherapy regimen.**

Levetiracetam	257
Lamotrigine	246
Oxcarbazepine	43
Lacosamide	36
Topiramate	30
Zonisamide	17
Brivaracetam	14
Pregabalin	10
Perampanel	9
Gabapentin	4
Stiripentol	3
Rufinamide	2
Vigabatrin	1
Eslicarbazepine acetate	1
Tiagabine	1

Graphic 5: **Number of pregnancies exposed to second-generation ASMs in a polytherapy regimen.**



TERATOGENIC OUTCOME

There were 103 cases of major congenital malformations (MCMs), 6 syndromic and/or genetic cases and 12 chromosomal abnormalities (CHR) in the prospective cohort of 2,266 pregnancies for which follow-up has been completed, as shown in Table 6 (*115 spontaneous abortions are excluded*).

Table 6. Pathological outcomes.

Outcome	Outcome Classification	N
MCMs	Multiple major	8
	Isolated major	95
	Total MCMs	**103**
Syndromes or genetic conditions		**6**
CHR		**12**
Total		**121**

The 6 syndromic and/or genetic cases include inherited tuberous sclerosis (1), incontinentia pigmenti (Bloch-Sulzberger syndrome) (1), inherited congenital cataract (1), Zellweger syndrome (1) and achondroplasia (2).

In this report we confine our analysis to the 103 MCMs, including those identified in 3 induced abortions, 3 neonatal deaths and 97 live births. Of the 97 live births, 12 cases of malformations were ascertained prenatally, 63 were first reported at birth, and a further 22 not detected at birth were identified within one year after birth.

Among the 103 cases with MCMs, 17 were detected by ultrasound examination. Out of these 17 cases, there were 3 induced abortions, two perinatal deaths and 12 live births.

The 103 cases represent a **MCM prevalence of 4.5%** of all prospective pregnancies for which follow-up has been completed (103/2,266).

The type of MCMs, CHR, genetic conditions, and other syndromes are described in Table 7.

Table 7

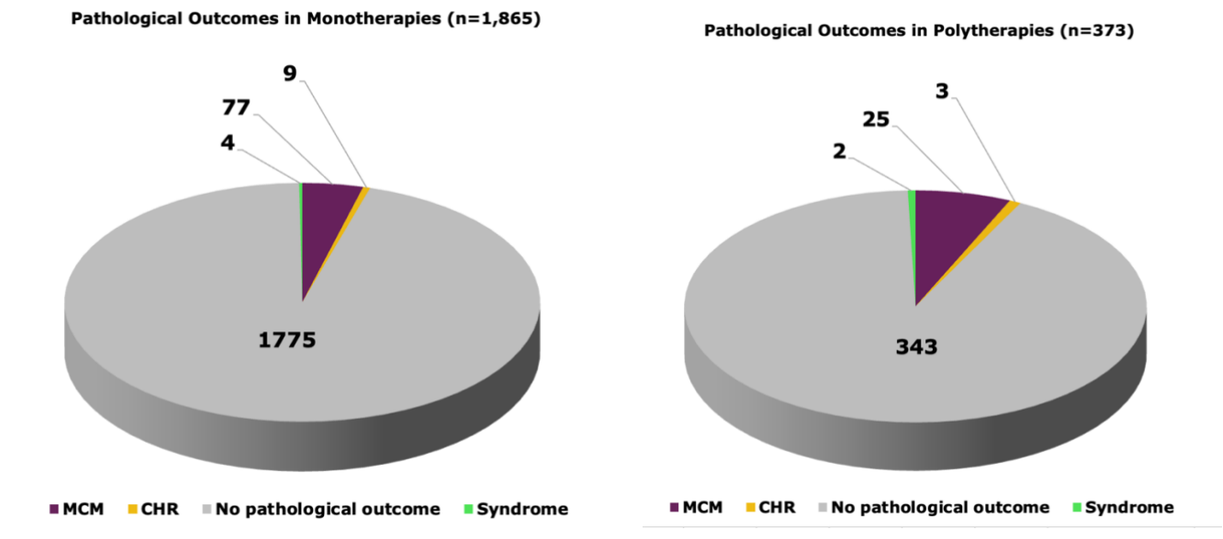
PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	8
	Cardiovascular system	
MCM	Atrial septal defect	2
MCM	Patent ductus arteriosus	3
MCM	Congenital pulmonary valve stenosis	2
MCM	Pulmonary valve atresia	1
MCM	Hypoplastic left heart syndrome	1
MCM	Ventricular septal defect	12
MCM	Congenital malformations of the heart, unspecified	1
MCM	Other congenital malformations of aorta; Atrial septal defect	1
	all	23
	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	4
	all	8
	Musculoskeletal	
MCM	Hip dislocation and/or dysplasia	17
	all	17
	Urinary system	
MCM	Atresia and stenosis of ureter	1
MCM	Accessory kidney	1
MCM	Congenital deformity of urinary system, NOS	1
MCM	Congenital megaloureter	2
MCM	Congenital pelviureteric junction obstruction, unilateral	1
MCM	Patent urachus	1
MCM	Impervious urethra (Megacystis-megaureter syndrome)	1
MCM	Double or triple kidney	2
MCM	Congenital hydronephrosis; Congenital posterior urethral valves	1
MCM	Other cystic kidney disease	1
MCM	Potter's syndrome	1
	all	13
	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	2
	all	2
	Limbs	
MCM	Polydactyly	5
	all	5
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**	**103**
	Chromosomal	
CHR	Chromosomal abnormality (defective chromosomes 4 and 16)	1
CHR	Other specified chromosome abnormalities (n.16, proximal 16p11.2 duplication syndrome, including TBX6 gene)	2
CHR	Down's syndrome	3
CHR	Edward syndrome	1
CHR	Klinefelter's syndrome	1
CHR	Patau's syndrome	2
CHR	Turner's syndrome	2
CHR	**all CHR**	**12**
	Syndromes or genetic conditions	
Syndrome	achondroplasia	2
Syndrome	congenital cataract, inherited	1
Syndrome	tuberous sclerosis, inherited	1
Syndrome	incontinentia pigmenti (Bloch-Sulzberger syndrome)	1
Syndrome	Zellweger syndrome	1
Syndromes	**all syndromes or genetic conditions**	**6**
Total		**121**

One or more MCMs were recorded in 77 out of 1,865 (4.1%) pregnancies exposed to ASM monotherapy, as opposed to 25 out of 373 (6.7%) pregnancies exposed to ASM polytherapy (Table 8 and Graphic 6).

Table 8. Pathological outcomes by ASM treatment categories.
(In this table, 115 spontaneous abortions have been excluded from the denominator).

	No ASM	%	Monotherapy	%	Polytherapy	%	Total
MCM	**1**	3.6	**77**	4.1	**25**	6.7	**103** (4.5%)
CHR	**0**	0.0	**9**	0.5	**3**	0.8	**12** (0.5%)
Syndromes	**0**	0.0	**4**	0.2	**2**	0.6	**6** (0.3%)
No pathological outcome	**27**	96.4	**1,775**	95.2	**343**	91.9	**2,145** (94.7%)
Total	**28**	100	**1,865**	100	**373**	100	**2,266** (100%)

Graphic 6: Pathological outcomes by type of ASM treatment (monotherapy vs polytherapy).
(In this figure, 115 spontaneous abortions have been excluded from the denominator).



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

ORGANISATION, FUNDING AND SUPPORT

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APPENDIX

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