EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on neurodevelopmental disorders with paternal exposure to valproate and related substances

EPITT no: 20191

Confirmation assessment report	26 June 2025
Adoption of first PRAC recommendation	10 July 2025
MAH submission	24 September 2025
Preliminary assessment report on additional data[1]	3 November 2025
Deadline for comments[4]	17 November 2025
Updated rapporteur assessment report[4]	20 November 2025
Adoption of second PRAC recommendation[4]	27 November 2025
Study authors' responses	11 March 2026
MAH submission	07 April 2026
Preliminary assessment report on additional data	12 May 2026
Deadline for comments	27 May 2026
Updated rapporteur assessment report	04 June 2026
Adoption of second PRAC recommendation	11 June 2026

Note

Assessment report as adopted by the PRAC with all information of a (commercially) confidential nature deleted and personal data anonymised.

Administrative information

Active substance(s) (invented name)	Valproate and related substances (sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium)
Indication(s)	Epilepsy Bipolar Disorder Migraine Disorders
Marketing authorisation holder(s)	Sanofi (for innovator)
Authorisation procedure *[Tick the appropriate box(es) below.]*	
☐	Centralised
☐	Mutual recognition or decentralised
☒	National

Adverse event/reaction:[2]	Neurodevelopmental disorders

Signal validated by:	NL
Date of circulation of signal validation report:	26 June 2025
Signal confirmed by:	NL
Date of confirmation:	26 June 2025
PRAC Rapporteur appointed for the assessment of the signal:	Liana Martirosyan (NL)

[2] Please use MedDRA terminology whenever possible

Table of contents

1. Background

In Europe valproate and related substances (valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide) are licensed since 1967 to treat epilepsy, since 1995 to treat bipolar disorders (BP) and, in some EU member states (MS), also indicated in the prophylaxis of migraine attacks. They have been authorised via national procedures in all EU Member States (MS), and in Norway and Iceland. Worldwide, these products are approved and marketed in more than 120 countries.

NDD disorders following paternal exposure in the periconception window is considered an important potential risk for valproate. In order to address this potential risk, a cat 1 PASS study (first paternal PASS study) has been imposed to the MAH's of medicinal product(s) containing valproate and related active substances in the European Union (EU), in the framework of the Article 31 referral completed in 2018. The final study results were submitted to EMA on 19 January 2023.

Results of first Paternal PASS

The aim of this PASS (reference number EUPAS34201), a retrospective cohort study using databases from Denmark (DK), Sweden (SE) and Norway (NO), was to examine the association between paternal exposure to valproate at conception and the risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), as well as congenital malformations (CM) in the offspring. Both descriptive and comparative cohorts were established. In the comparative cohorts, paternal exposure to valproate was compared to paternal exposure to lamotrigine or levetiracetam.

Having considered the results of the PASS final report, together with non-clinical, literature data to date, the input of external stakeholders (including representative of patients and HCP organisations) and clinical experts who attended at the SAG neurology (enriched with psychiatry expertise), as agreed during the plenary meeting held on 8-11 January 2024, the PRAC scientific conclusions were as follows.

The results of the population-based, retrospective cohort study using databases from three Nordic countries (DK, SE, NO), suggested an increased risk of NDD (including ASD), but no difference in the risk of CM in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine or levetiracetam. A trend for an increased risk of NDD (including ASD), although not significant in the three individual countries, was apparent in the data from NO, SE and DK, and the combined data from these three countries showed a borderline statistically significant increased risk. Meta-analysis of data from 3 Nordic countries resulted in a pooled aHR of 1.50 (95% CI: 1.09-2.07) for NDD in children of fathers treated with valproate in the 3 months prior to conception compared with lamotrigine or levetiracetam. The adjusted cumulative risk of NDD was estimated to be around 5% in the valproate group versus around 3% in the lamotrigine and levetiracetam group. However, taking into consideration the study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, together with (limited) information from other sources, and the input of external stakeholders and clinical experts, the risk was considered by PRAC as potential (i.e. causality has not been established). In addition, the study was not large enough to identify which types of NDDs children could be at increased risk of developing.

Considering the seriousness of the NDDs (including ASD) and their life-long impact on children and families, the PRAC also concluded that the study findings, including their uncertainties, should be communicated to patients and healthcare professionals (HCP) and confirmed that current available data were sufficient to justify applying precautionary, risk proportionate, measures, also in light of the confirmed and higher risk for children following in utero exposure to valproate. The input obtained from clinical experts and stakeholders also supported the PRAC's conclusion on the request to the MAH

to address the uncertainty of this potential risk, via (new) additional analyses (including subgroup analyses and stratification), as part of a new category 1 PASS with appropriate milestones.

In light of all the above, with regard to male patients, the PRAC recommended to update the product information of medicinal products containing valproate and related substances to include that / with:

- It was recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy, bipolar disorder or migraine.
- The need for a regular review by a specialist to evaluate whether valproate is (still) the most suitable treatment and to remind the male patient about the potential risk for NDD (including ASD) with valproate when used during conception and talk about whether the male patient wishes to conceive a child.
- Information on the potential risk of NDD in the offspring born to fathers using valproate around the conception period, including the recommendation for prescribers to inform patients on the potential risk, discuss the need to consider effective contraception in male patients using valproate (and their female partner), advice male patients to consult their specialist when they are planning to conceive a child and before discontinuing contraception, and to consider the possibility of treatment alternatives in case the male patient using valproate is planning to conceive a child. Male patients should also be advised to not donate sperm while on valproate treatment, and for at least 3 months after treatment discontinuation.
- Educational materials are made available for healthcare professionals and patients. A patient guide should be provided to male patients using valproate.

In addition, a DHPC was disseminated, the HCP guide was updated, the patient card was updated and a guide for male patients was introduced.

Christensen et al (2024)

Christensen et al (2024) conducted a study to evaluate the association between paternal use of valproate during spermatogenesis and offspring risk of congenital malformations and NDD using the Danish national registries. This study did not suggest an increased risk of NDD with paternal valproate exposure in the 3 months before conception compared to unexposed children (general population), with adjusted HR of NDD of 1.10 (0.88 - 1.37) and the aHR of autism spectrum disorder was 0.92 (95%CI, 0.65-1.30). In analyses addressing the robustness of the findings (i.e., dose-response analyses, sibling analyses, analyses restricted to children of fathers with epilepsy, analyses that used children with paternal lamotrigine exposure as active comparator, and analyses that used children with paternal exposure to valproate only before spermatogenesis as a negative control exposure), there still was no increased risk of any of the included end points.

The preliminary results of this study have been considered in the assessment of the results of the paternal PASS in procedure *[number redacted]*. The final publication of Christensen et al 2024 has been discussed in PSUSA/00003090/202401. PRAC considered that although there was overlap in data sources used and study period, the studies differed in study methodology with regard to inclusion/exclusion criteria, comparator cohorts, outcome definitions used, type of analysis applied and considerations of confounders and risk factors, and the paternal PASS included additional data sources, which could at least partly explain the different results observed in these studies.

2. Initial evidence

2.1. Signal validation

Christensen et al (2025)

In a new study, Christensen et al (2025) further aimed to replicate the first paternal PASS and to address the conflicting results between the paternal PASS and the published study by Christensen et al (2024). The authors presented additional analyses of their data with further alignments to the first paternal PASS based on the final study reports of the paternal PASS as published at the EMA webpage. Instead of the general population, a comparator group similar to the paternal PASS was used i.e. exposed to levetiracetam or lamotrigine. Also, only monotherapy of valproate, lamotrigine or levetiracetam was considered. A range of analyses were performed to explore the impact of methodological choices and definitions used in the first paternal PASS: excluding children of parents with NDDs or congenital malformations, excluding children of mothers with epilepsy; excluding children with epilepsy, rerunning analyses without adjustment for parental epilepsy and education, and stopping follow-up at age 12 years.

In the overall analysis, compared to lamotrigine/levetiracetam monotherapy, paternal valproate monotherapy exposure was not associated with an increased risk of NDDs (composite end point of all NDD aHR, 1.02; 95%CI, 0.67-1.54). No significant increased risks were observed across analyses of specific NDDs, analyses of valproate dose, analyses accounting for time trends, analyses allowing for polytherapy, analyses expanding the definition of NDDs, analyses restricted to fathers with epilepsy, and analyses with a restricted exposure window. In analyses restricted to fathers with epilepsy of unknown underlying cause, the aHR was 2.48 (95%CI, 1.13-5.44); however, the association was no longer significant in analyses matched on birth year (aHR, 2.33; 95%CI, 1.00-5.44). Analyses undertaken to further examine the definitions used in the paternal PASS revealed no increased risk of NND associated with valproate exposure.

Despite the further alignments to the first paternal PASS, in terms of study population and study definitions, this cohort study was unable to replicate the findings of the PASS conducted by the Consortium of MAHs regarding the potential increased risk for NDDs in children with paternal valproate exposure. Instead, the findings are in line with the findings of their previous study (Christensen et al 2024), which did not show an increased risk of NDD in offspring paternally exposed to valproate.

2.2. Signal confirmation

During procedure *[number redacted]* PRAC concluded that, having considered the results of the paternal PASS final report, together with non-clinical, literature data, the input of external stakeholders (including representative of patients and HCP organisations) and clinical experts who attended at the SAG neurology (enriched with psychiatry expertise), that the risk of NDD in children after paternal valproate exposure was considered a potential risk. Following the publication by Christensen et al (2024), PRAC considered the conclusions and recommendations regarding the potential risk of NDD in children of fathers that used VPA in the three months before conception remained valid, considering differences in study methodology and data sources used.

With the publication of Christensen et al 2025, a study with methodology more similar to the paternal PASS has been performed showing different results compared to the paternal PASS performed by the consortium. Although some methodological differences can still be identified between the paternal PASS and Christensen et al 2025, e.g. NDD definition and statistical methods used, important similarities include the data source, comparable study period, studying NDD in children after paternal

valproate monotherapy exposure compared to monotherapy of lamotrigine or levetiracetam. However, despite further alignment of the study methodology to that of the paternal PASS, no statistically significantly increased risk for NDD has been observed by Christensen et al 2025 (aHR for NDD composite 1.02 (0.67-1.54); this was the case also in the paternal PASS for DK [for DK aHR for NDD composite 1.34 (0.79, 2.25)]. Note: the paternal PASS showed statistically significantly increased risk for 3 countries combined (aHR of 1.50 (95% CI: 1.09-2.07).

The paternal PASS did not provide stratified results per indication of paternal antiepileptic drug use. Christensen et al 2025 provided several subgroup analyses. The only analysis with statistically significant increased risk for NDD included the analysis restricted to fathers with epilepsy, in particular those with epilepsy of unknown underlying cause, showing an aHR of 2.48 (95%CI, 1.13-5.44); however, the association was no longer significant in analyses matched on birth year (aHR, 2.33; 95%CI, 1.00-5.44). Further discussion of this finding and role of indication and type of AED and calendar year in relation to NDD diagnosis in the children is needed.

The results of Christensen et al 2025 are considered a new aspect for the potential risk of NDD in children with paternal valproate exposure. Therefore there is a need for better understanding and clarification of the observed differences in study results between the paternal PASS, in particular for DK and the study published by Christensen et al 2025.

Based on the evidence above, the signal is confirmed.

Further evidence expected to be generated

It is noted that at least the following evidence on NDD and paternal valproate exposure will become available in the future. At the moment we are aware of the following:

- Final results from the study about paternal valproate exposure and NDD in children using data from Taiwan and Norway were expected in May 2025 (date of final report: 31/05/2025), see: https://catalogues.ema.europa.eu/node/4318/administrative-details
- Further evidence may be generated via ADEPT: feasibility of estimating the risk of adverse pregnancy, neonatal and child outcomes following either in utero ASM exposure through the mother, or peri-conceptional ASM exposure through the father | HMA-EMA Catalogues of real-world data sources and studies. Final study report is expected in March 2026.
- The cat 1 PASS requested by PRAC following assessment of the final results of the first paternal PASS to address the uncertainty of the potential risk, via (new) additional analyses (including subgroup analyses and stratification). Assessment of the protocol is ongoing (TANGO study). According to study protocol version 3.0, final results are expected in Q1 2028.

2.3. Proposed recommendation

Having considered that the risk of NDD with valproate was considered a potential risk in previous assessments, the uncertainties of the paternal PASS results and the new data on the potential risk of NDD with paternal valproate that has become available, the LMS is of the opinion that a careful critical review of the new publication of Christensen et al 2025 is needed to further elucidate the risk of NDD in children with paternal valproate exposure. Therefore, the brand leader MAH Sanofi should respond to the following request for supplementary information:

- The MAH should provide a detailed discussion of the study results of Christensen et al 2025 including strengths and limitations of the study. Analyses that were performed by Christensen 2025 to explore the impact of methodological choices and definitions used in the paternal PASS study performed by the Consortium should also be addressed.

- The findings related to analyses restricted to fathers with epilepsy of unknown underlying cause, which showed a higher risk (aHR > 2) which was not observed in any other analysis performed by Christensen et al 2025, should be discussed. Further discussion of this finding and role of indication, type of AED and calendar year in relation to NDD diagnosis in the children is needed.
- The MAH should provide a clarification of the observed differences in NDD risk observed between the paternal PASS, in particular for Denmark, and the study published by Christensen et al 2025. This should include critical and in depth review and comparison of study methodology and study results, including (but not limited to) inclusion/exclusion criteria, study period, comparator cohorts, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, also for different NDD definitions (NDD composite, NDD composite narrow, NDD sub-types). Any other potential reasons for the observed differences should be provided and explained.
- Any new additional non-clinical data or literature data available should be discussed.

In addition, considering that final study report was planned 31 May 2025, the PRAC Rapporteur suggests to requests the researchers of the studies using data from Norway and Taiwan to share their study results with PRAC in a confidential manner to ensure these study results could be considered in current signal procedure.

A 60/60 timetable is proposed.

2.4. Adopted PRAC recommendation

Having considered the available evidence from the epidemiological study, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of the innovator products containing valproate and related substances (Sanofi) should submit by 27/08/2025, responses to the following:

- The MAH should provide a detailed discussion of the study results of Christensen et al 2025 including strengths and limitations of the study. Analyses that were performed by Christensen et al 2025 to explore the impact of methodological choices and definitions used in the paternal PASS study performed by the Consortium should also be addressed.
- The findings related to analyses restricted to fathers with epilepsy of unknown underlying cause, which showed a higher risk (aHR > 2) which was not observed in any other analysis performed by Christensen et al 2025, should be discussed. Further discussion of this finding and role of indication, type of AED and calendar year in relation to NDD diagnosis in the children should be provided.
- The MAH should provide a clarification on the observed differences in NDD risk observed between the paternal PASS, in particular for Denmark, and the study published by Christensen et al 2025. This should include critical and in depth review and comparison of study methodology and study results, including (but not limited to) inclusion/exclusion criteria, study period, comparator cohorts, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, also for different NDD definitions (NDD composite, NDD composite narrow, NDD sub-types). Any other potential reasons for the observed differences should be provided and explained.
- Any new additional non-clinical data or literature data available should be discussed.

In addition, the PRAC will request the researchers of the study using data from Norway and Taiwan to share their study results to ensure they can be considered in this assessment.

The PRAC will assess the provided data within a 60-day timetable.

3. Additional evidence

3.1. Assessment of additional data

3.1.1. MAH response to request for supplementary information in PRAC confirmation

Question 1

The MAH should provide a detailed discussion of the study results of Christensen et al 2025 including strengths and limitations of the study. Analyses that were performed by Christensen et al 2025 to explore the impact of methodological choices and definitions used in the paternal PASS study performed by the Consortium should also be addressed.

MAH response

The MAH provided the following overview of Christensen et al (2025), its strengths and limitations, including a discussion about the analyses performed to try to align with the PASS paternal (in *italic*):

Objective

To assess whether paternal exposure to valproate during spermatogenesis is associated with an increased risk of neurodevelopmental disorders (NDDs) in offspring. This study was conducted in response to a prior signal reported in the PASS PATERNAL (EUPAS34201) performed by the valproate Consortium of MAHs, which suggested such a potential risk.

Design and methods

This study was a nationwide population-based cohort study in Denmark. Singleton children born alive between 1997 and 2017, having a family linkage (mother-father-child) in the Danish registries were included.

The exposure of interest was defined as paternal monotherapy with valproate, during a window spanning from 120 days before to 14 days after the first day of the last menstrual period (LMP) of the child's mother; the comparative group consisted of paternal monotherapy with lamotrigine, or levetiracetam in the same window as the one of interest in the valproate group.

The primary outcome was the incidence of NDDs in offspring from age 1 to end of follow-up (2018). Specific NDDs including intellectual disability, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and disorders of psychological development were studied as secondary outcomes.

Relative risk of NDDs between the 2 groups was estimated using Cox proportional hazards models adjusted for multiple confounders: adjustment for child's sex, birth year, parental age, psychiatric history, epilepsy, education, and maternal valproate use.

Secondary and sensitivity analyses included variations in exposure windows, exclusion criteria (restricted to fathers with epilepsy, fathers with idiopathic epilepsy), and various adjustments, different from the main analysis.

MAH comment to design and methods *- The authors described their methods in detail and additionally performed analyses specifically aiming to try to align with / replicate the PASS Paternal (Table 2 of Christensen et al., see page 8): exclusion of children of parents with malformations or NDDs, exclusion of children with epilepsy or maternal epilepsy, and leaving out adjustments for*

parental education. Nevertheless, the methods used by Christensen et al. to produce these results, were not exactly the same as those used in the PASS Paternal, e.g. window used to define the parental exclusion criteria, (differences are discussed in detail in the answer to Question #3 below) and produced slightly different estimates of the HRs.

Key findings

A total of 961 children (501 male [52.1%]; median [IQR] age at the end of follow-up, 10.6 [5.4-15.0] years) exposed to valproate monotherapy and 1401 children (725 male [51.8%]; median [IQR] age at end of follow-up, 5.5 [2.7-9.3] years) exposed to lamotrigine or levetiracetam monotherapy were included in the main analysis.

In the main analysis, no increased risk of NDDs was found in children of fathers exposed to valproate compared to lamotrigine or levetiracetam (adjusted HR: 1.02; 95% CI: 0.67–1.54). Similarly, no increased risk was observed for any specific NDDs subtypes, Intellectual disability: aHR = 1.85 (95% CI: 0.72–4.76), ASD: aHR = 0.69 (0.37–1.28), ADHD: aHR = 0.60 (0.33–1.12).

Sensitivity analyses (adjusting for calendar trends or allowing polytherapy, excluding children with epilepsy, adjusting for education, stopping follow-up at age 12) consistently showed no significant association.

A notable exception though was the analyses restricted to fathers with epilepsy of unknown cause: a higher risk was observed in the subgroup of fathers with epilepsy of unknown cause (i.e. idiopathic epilepsy) treated with valproate monotherapy: aHR: 2.48 (1.13–5.44). It was attenuated when matched on birth year, aHR: 2.33 (1.00–5.44). This is discussed in more detail in answers to Question 2.

Strengths

This nationwide cohort included all singleton children from fathers exposed to valproate or lamotrigine/levetiracetam monotherapy and applied minimal criteria of exclusion (In Vitro Fecundation, missing paternal link, unrealistic gestational age), which enhances external validity. Nevertheless, some analyses were performed in small numbers of event (cf. Limitation section below).

The use of comprehensive Danish health and prescription registries provides reliable information on both exposure and outcomes, minimizing their misclassification and enabling robust longitudinal analyses.

The study employed a wide range of sensitivity analyses, including alternative exposure definitions with variations in exposure windows, different sets of adjustments, NDDs subtypes and subgroup stratifications. They provided consistent results, except for a notable exception when restricting to fathers with idiopathic epilepsy, aHR >2, discussed in detail in Question #2 of this RSI.

Limitations

As with all observational studies, the potential for residual confounding remains, despite extensive covariate adjustment. Unmeasured or inadequately measured variables may still bias the observed associations. This limitation was also acknowledged in the PASS Paternal, using similar design.

Some subgroup analyses (e.g., intellectual disability and analyses restricted to fathers with idiopathic epilepsy) were performed on small event numbers. Notably, in the analyses focusing only on fathers with epilepsy, numbers drastically dropped (~50%) and numbers of NDDs cases were very low.

The comparator group (lamotrigine/levetiracetam) had a shorter median follow-up period, which may have influenced the likelihood of outcome detection and introduced bias, as suggested by the estimate change after adjustment for the birth year suggest.

Despite the use of various and appropriate adjustments in the different sets of analyses, and similarly to the PASS Paternal, important unmeasured confounders such as genetic susceptibility, parental

lifestyle, parental cognitive traits, or environmental exposures were not captured in the registries. Their omission could lead to biased estimates if these factors are associated with both exposure and outcome, which can't be ruled out.

Results are based on one country only (Danish data) and should only be compared to the respective results in Denmark in PASS Paternal and not to the results of the meta-analysis of 3 countries (Denmark, Norway and Sweden).

Conclusion

The study by Christensen et al. 2025 found no significantly increased risk of NDDs in offspring from fathers exposed to valproate compared to those exposed to lamotrigine or levetiracetam, in monotherapy during spermatogenesis, from the registries data available in Denmark.

One exception is notable though: when restricting the analyses to fathers with idiopathic epilepsy and matching on birth year, the authors found a borderline increased risk (two-fold). This is, however, hardly interpretable as it is based on small number of events and may reflect a complex interplay of several contributing factors, explored in question #2 of this RSI.

As in the PASS Paternal, the marked difference in follow-up time between exposure groups is a limitation that could bias the estimation of the relative risk.

MAH discussion on impact of methodological differences and choices - *When putting in perspective with the PASS Paternal, except for the analyses restricted to fathers with idiopathic epilepsy which was not performed in the PASS Paternal, the estimates of the HR for NDD are slightly different from the two studies, with aHR: 1.02 (0.67–1.54) in Christensen, PSW-HR: 1.34 (0.79–2.25) in the PASS Paternal. The estimates of the incidence rate are very similar with 6.7 and 7.2 per 1000 person-year in the valproate group in the Christensen and PASS Paternal for Denmark respectively versus 5.6 per 1000 person-year in the lamotrigine/levetiracetam in both studies. Altogether the results from Christensen et al. and those from the Danish results of the PASS Paternal are aligned: both studies found* ***no statistically significant increased risk of NDDs*** *following paternal exposure to valproate in Denmark. Due to slight methodological differences, the PASS Paternal reported a slightly higher point estimate for NDD risk, but it was not statistically significant.*

In addition, results for ASD are interestingly similar too between the two studies: Christensen 2025, aHR=0.69 (0.37 - 1.28) and PASS Paternal for Denmark, PSW-HR=0.76 (0.30 - 1.89).

PRAC Rapporteur assessment

As requested, the MAH provided a discussion of the publication by Christensen et al (2025), including its strengths and limitations, as well as a discussion about the analyses performed to try to align with the paternal PASS.

The main study objective (to evaluate the risk of NDD in offspring paternally exposed to valproate) and overall study design (nationwide cohort study using population-based databases from DK) are comparable to the paternal PASS. However, there are differences regarding study methodology, such as differences in exclusion criteria, definitions of exposure and outcome, use of different statistical analysis methods and differences in covariates considered for adjustments. These methodological differences are further discussion in Q3 below.

In their main analysis, Christensen et al (2025) found no increased risk of NDDs in children of fathers exposed to valproate compared to lamotrigine or levetiracetam (aHR 1.02 [95% CI: 0.67-1.54).

Christensen et al (2025) did not find an increased risk for any specific NDD subtype. The results of various secondary and sensitivity analyses (e.g. dose effect, accounting for calendar trends, allowing polytherapy, excluding children of parents with CM or NDD or mothers with epilepsy, etc) generally showed similar risk estimates as observed in the main analysis, and no statistically significant increased risks were observed. Higher risk estimates were observed in analyses restricted to fathers with epilepsy (aHR 1.42 [95% CI: 0.82-2.46]) and restricted to fathers with epilepsy of unknown underlying cause (aHR 2.48 [95% CI: 1.13-5.44), but these risk estimates attenuated (and were no longer significant for epilepsy of unknown underlying cause) when matching on birth year (aHR 1.14 [95% CI 0.59-2.21] and aHR 2.33 [1.00-5.44], respectively. This is further discussed in Q2 below.

In the paternal PASS, the effect estimation for NDD included 1796 offspring; 678 from the valproate group (38 cases NDD) and 1118 from the lamotrigine/levetiracetam group (36 cases NDD). A total of 2362 offspring were included in the main analysis in Christensen et al (2025), including 961 from the valproate group (50 cases NDD) and 1401 from the lamotrigine/levetiracetam group (67 cases NDD). For the paternal PASS, minimum sample size to observe a HR of 2.00 with 5% significance and 80% power was calculated to be 1178, with 598 per exposure group. This sample size was reached in Denmark in both the paternal PASS and Christensen et al (2025). Both studies were insufficiently powered to study NDD subtypes.

Regarding strengths and limitations, the MAH notes the following strengths for the study of Christensen et al (2025): nationwide cohort with minimal exclusion criteria enhances external validity; reliable information on exposure and outcome due to use of comprehensive DK registries; wide range of sensitivity analyses, including alternative exposure definitions, different adjustment sets and stratifications generally provided consistent results to the main analysis. These strengths generally also apply to the paternal PASS (although there are differences in e.g. specific sensitivity analyses applied). The study by Christensen et al (2025) additionally provided analyses stratified by indication, which was not available in the paternal PASS. This is further discussed in Q2 below.

The main limitations include the potential for residual confounding due to unmeasured or inadequately/incomplete measured variables (e.g. environmental exposures, parental lifestyle, genetic susceptibility); the small number of events for some subgroup analyses; the shorter follow-up period in the comparator group; and results are based on one country only.

Overall, the study by Christensen et al (2025) is considered a well-conducted study using population-based Danish data. It is acknowledged that their results are based on one country only (Denmark) whereas the paternal PASS additionally considered results from Norway and Sweden. The minimum sample size to observe a HR of 2.00 with 5% significants and 80% power (pre-determined minimum sample size for paternal PASS) was reached in Denmark both in the paternal PASS and Christensen et al (2025). The pooled results of the paternal PASS showed an increased risk of NDD for offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam (aHR 1.50 [95%CI 1.09-2.08] main analysis; aHR 1.69 [95%CI 1.20-2.39] for narrow NDD composite), with HRs above 1 in the same direction (although not statistically significant) in the 3 individual countries. Further discussion regarding the methodological differences between the Christensen et al (2025) publication and paternal PASS is addressed under Q3 below.

Question 2

The findings related to analyses restricted to fathers with epilepsy of unknown underlying cause, which showed a higher risk (aHR > 2) which was not observed in any other analysis performed by

Christensen et al 2025, should be discussed. Further discussion of this finding and role of indication, type of AED and calendar year in relation to NDD diagnosis in the children should be provided.

MAH response

The MAH provided the following discussion about the two aHRs found in the analyses restricted to fathers with idiopathic epilepsy:

The finding of a significantly increased risk of NDDs in offspring of fathers with idiopathic epilepsy, with an aHR of 2.48 (1.13-5.44), and 2.33 (1.00-5.44) when matched on the child's birth year is indeed particularly noteworthy, as it is not found in any of other analyses by Christensen.

Although the results are interesting, the MAH would like to point out that, apart from the HRs themselves, there is no additional information, interpretation or discussion about these 2 analyses by the authors. Besides, rationale and objective of these analyses were not explicitly provided by Christensen and al.. Hence, it makes it challenging for the MAH to try to interpret them. For example, based on the limitations from the PASS Paternal, it was not possible to consider the type of epilepsy, e.g. focal or generalized. Here, the authors did not stratify on the type of epilepsy. One may assume that with these sub-group analyses the authors were trying to assess the role of the underlying cause of seizure: primary or secondary epilepsy. However, it remains an assumption.

We thoroughly examined the numbers presented for these restricted analyses (Table 2). The way the numbers of exposed fathers and numbers of cases decreased between the main and the restricted analyses was very different according to the exposure group: in the valproate group the number of exposed father and number of NDD cases decreased by 38.3% (from 961 to 593 fathers) and 25.4% (from 67 to 50 cases) respectively from the main to restricted analyses; in the comparator group, the respective percentages (and numbers) were -65.9% exposed fathers (from 1401 to 478) and -84.0% NDD cases (from 50 to 8).

This **asymmetry** shows that in this study, there are more fathers treated for idiopathic epilepsy in the valproate group. Consequently, the comparator group (lamotrigine/levetiracetam) may have included more fathers with secondary or structural epilepsy, who were excluded in this idiopathic epilepsy subgroup analysis. This introduces a **selection bias** and an **amplification of relative risk (HR)**, hence a bias: the relative risk becomes more pronounced in this idiopathic epilepsy subgroup, not because the number of cases in the valproate group increased, but because the comparator group shrank dramatically, especially in terms of NDD cases (from 50 to 8). This magnifies the contrast between groups and inflates the hazard ratio, even though the absolute number of cases in the valproate group decreased.

Altogether, the shrinkage in the comparator group makes the comparison **vulnerable to random variation and model overfitting.**

Besides, the small number of events in the comparator group (n = 8) introduces **instability** in the hazard ratio estimate, resulting in **statistical fragility and lack of precision**. The confidence interval (1.13–5.44) is wide, and in the birth-year matched analysis, the lower bound is exactly 1.00, indicating borderline statistical significance. This raises concerns about statistical fragility: small changes in case classification or censoring could shift the result from significant to non-significant or vice-versa.

The results from analysis matched on birth year in the restricted subgroup of fathers with idiopathic epilepsy demonstrate this fragility by showing the impact of the imbalanced follow-up between the two groups. The valproate group had a longer follow-up (median 10.6 years vs. 5.5 years), potentially increasing outcome detection. When matching on birth year, which allowed to control for difference of follow-up, the aHR slightly decreased, with the minimization of **detection bias**.

One final point to consider in the difficulty to interpret these results lies in the conflicting results of this analysis with a similar one done by Christensen et al. in the 2024 publication. In the 2024 paper, the restriction analysis 2, authors compared children of valproate-fathers with idiopathic epilepsy with children of unexposed-valproate fathers with idiopathic epilepsy. They found no higher risk with an adjusted HR of 1.13 (0.86-1.47). This raises questions on why this higher risk in children would exist when comparing against lamotrigine-exposed fathers and not when comparing against unexposed-valproate fathers (including therefore lamotrigine or levetiracetam-exposed fathers). This might suggest, as stated above, the importance of the dilution/concentration of the cases that can lead to amplification/diminution of relative risk (HR).

In conclusion, the elevated risk of NDDs in offspring of valproate-exposed fathers with idiopathic epilepsy is hardly interpretable as it may reflect a complex interplay of disease predisposition, treatment selection bias, residual confounding, and an eventual treatment effect. This subgroup analysis likely represents a population in which the multiple factors selection has mathematically led to an increased risk due the concentration of cases in only one group. Therefore, while the results are noteworthy, they should be interpreted with caution.

PRAC Rapporteur assessment

As requested, the MAH provided further discussion regarding the observed increased risk of NDD in offspring of fathers with idiopathic epilepsy (aHR 2.48 [95% CI: 1.13-5.44]) which was attenuated when matched on birth year (aHR 2.33 [1.00-5.44]).

A higher risk estimate as compared to the main analysis (although not statistically significant), attenuated after matching on birth year, was also observed in offspring of fathers with epilepsy (aHR 1.42 [95% CI: 0.82-2.46]; aHR 1.14 [95% CI 0.59-2.21], respectively).

The MAH notes asymmetry in the decrease in number of exposed fathers and cases between the valproate and comparator group: the number of exposed fathers and number of showed a stronger increase in the comparator group than in the valproate group (fathers: -38.4% and -65.9%; cases -25.8% and -84.0%, respectively), implying more fathers in the valproate group are treated for idiopathic epilepsy, whereas more fathers in the comparator group had secondary or structural epilepsy. When compared to the total number of fathers with epilepsy per exposure group, 65% of fathers in the comparator group had epilepsy of unknown underlying cause, and 80% of fathers in the valproate group had epilepsy of unknown underlying cause.

It is acknowledged that selection bias can occur with subgroup analyses. However, the publication by Christensen et al (2025) does not provide baseline characteristics of the overall population or populations included in subgroup analyses, thus it cannot be determined to what extent these groups differ in terms of baseline characteristics, e.g. differences in follow-up time and risk factors. In addition, it is acknowledged these analyses are limited by smaller number of events resulting in a wider confidence interval around the risk estimate. Also, the number of variables adjusted for in the analyses may have impacted the results i.e. overfitting the model.

The MAH further notes conflicting results between the Christensen et al publication from 2025 and the publication from 2024. The 2024 study does not report an increased risk of NDD in valproate-exposed offspring of fathers with epilepsy of unknown cause compared to unexposed offspring (aHR 1.13 [0.86-1.47]).

It is acknowledged that the results of these analyses among children of fathers with idiopathic epilepsy are not further discussed by Christensen et al (2025). The MAH assumes that these analyses were performed to further investigate the impact of underlying cause of seizures (primary or secondary epilepsy), which is acknowledged. Valproate and other AEDs may be prescribed for different types or

severity of epilepsy as well as other conditions such as bipolar disorder and migraine, and analyzing these in a restricted populations limits potential confounding by indication. Information on disease severity (and other baseline characteristics) of the fathers is not included in the publications by Christensen et al (2025).

The MAH concludes that these results should be interpreted with caution, due to concentration of cases in only one group and the potential impact of disease predisposition, treatment selection bias and residual confounding. This is agreed. In the PASS paternal, information on epilepsy subtype was not available and no analyses stratified by indication were performed. For the follow-up study (TANGO), stratified analyses by indication for treatment and sub-type of epilepsy are planned to assess confounding.

Considering the limitations of this subgroup analysis, these results cannot confirm an increased risk for NDD in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam.

Question 3

The MAH should provide a clarification on the observed differences in NDD risk observed between the paternal PASS, in particular for Denmark, and the study published by Christensen et al 2025. This should include critical and in depth review and comparison of study methodology and study results, including (but not limited to) inclusion/exclusion criteria, study period, comparator cohorts, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, also for different NDD definitions (NDD composite, NDD composite narrow, NDD sub-types). Any other potential reasons for the observed differences should be provided and explained.

MAH response

Main results from both studies are aligned. The PASS Paternal found a higher risk estimate of NDDs in valproate-exposed offspring (PS-weighted HR of 1.34 (0.79–2.25) in Denmark, vs. adjusted HR of 1.02 (0.67-1.54) in Christensen et al.). Thus, in both studies statistical significance was not reached for the risk estimate in Denmark, except for a concentrated subgroup of offspring from fathers with idiopathic epilepsy in Christensen study (Question #2). [Of note: only the pooled HR across countries in the PASS Paternal showed significance (HR = 1.50).]

The estimates of the incidence rate are also similar with 6.7 and 7.2 per 1000 person-year in the valproate group in the Christensen and PASS Paternal for Denmark respectively versus 5.6 per 1000 person-year in the lamotrigine/levetiracetam in both studies.

MAH comment *- In addition, results for ASD are interestingly similar too between the two studies: Christensen 2025, aHR=0.69 (0.37 - 1.28) and PASS Paternal for Denmark, PSW-HR=0.76 (0.30 - 1.89).*

Several methodological differences likely contribute to the differences between the two studies, among which the major ones are:

- Broader set of confounders included in the PASS Paternal
- Different adjustment strategies: the PASS Paternal used propensity score weighting (PSW) plus additional adjustment (for maternal affective disorder and psychiatric condition medication use), while Christensen used traditional multivariable Cox regression.
- Exclusion of the influential subjects in the PASS Paternal.

The methodological differences are detailed in the Table 1 below.

Table 1 Summary table of methods and differences discussions

Methods aspect	**Christensen et al. 2025**	**PASS Paternal** (EUPAS34201) **(Danish data)**	**MAH Discussion**
Data sources	Retrospective cohort using Danish national registries	Retrospective cohort using Danish national registries	Similar registry-based designs; comparability in data sources.
Study Period	1997–2017 (births), follow-up to 2018	1997–2018 (births), follow-up to 12 years	Similar periods; Longer follow-up in Christensen (not capped to 12y)
Inclusion Criteria	Singleton live births, with paternal linkage, gestational age known, no IVF (In Vitro Fertilization)	Singleton pregnancies ≥12 weeks, with linkage to both parents, father with ≥12 months data	Comparable, though PASS Paternal includes more detailed linkage and exposure history
Exclusion Criteria	IVF, missing gestational age, no paternal link additional exclusions in the sensitivity to try to align with the PASS exclusion criteria, but definitions were different	IVF, missing gestational age, adopted children, maternal ASM exposure, epilepsy in child or mother	PASS Paternal applied more extensive exclusions for confounding control
Exposure Definition	Prescription filled for valproate monotherapy 120 days before to 14 days after LMP Additional sensitivity analysis using 60-day window	Prescription filled for valproate monotherapy 3 months before conception (spermatogenic window) Additional sensitivity using 6 months prior LMP	Slightly different exposure windows; PASS Paternal main window aligns more closely with biological plausibility Additional sensitivity in both studies, with results similar to main ones
Comparator Group	Lamotrigine or levetiracetam monotherapy	Lamotrigine or levetiracetam monotherapy	Similar
Outcome Definition	Composite NDD (ICD-10 codes), subtypes: ASD, ADHD, ID, Psychological Disorders.	Composite NDD (ICD-10 codes), ASD subtypes, Sensitivity analyses for narrow NDD	Outcome definitions are aligned. Both includes same NDDs; Both analysed composite as main analysis; Christensen stratified on subtypes
Analysis Type, Adjustment/Matching	Cox regression, adjusted for parental characteristics Christensen used matched analyses to address follow-up bias.	Crude and PSW[#]-adjusted Cox regression, with additional covariate adjustment Birth year included in the PSW model	PASS Paternal uses more advanced confounding control (PSW + covariates added in the model)
Subgroups/ Stratified analyses	Fathers with epilepsy, epilepsy of unknown cause (i.e. idiopathic epilepsy)	Stratified by exposure clusters, indication, and follow-up duration	Different subgroups/stratified analyses
Follow-up	From age 1 to 2018; median follow-up: 10.6 years (valproate) vs. 5.5 years (comparator)	From age 1 to end of study (2018); mean follow-up: 9.2 years (valproate) vs. 6.6 years (comparator)	Imbalanced follow-up acknowledged and considered in both studies (matching on birth year in Christensen; birth year included in the PSW model in the PASS Paternal)
Confounders Considered	Parental age, psychiatric history, epilepsy, education, maternal ASM use	Extensive list[#], including psychiatric comorbidities, polypharmacy, smoking, year of conception	PASS Paternal includes broader and more granular confounder adjustment
Follow-up Duration	Median 10.6 years (valproate), 5.5 years (comparators)	Mean 9.2 years (valproate), 6.6 years (comparators)	Longer follow-up in valproate group in both studies may bias results upward. Considered in the PSW model in the PASS Paternal. Considered in matched sensitivity analysis in Christensen
Sensitivity Analyses	Multiple, including dose-response, polytherapy, epilepsy subgroups, follow-up truncation, additional exclusions to try to align with the PASS Paternal exclusion criteria	Multiple, narrow NDD, exposure trajectory clusters	PASS Paternal provides more extensive and nuanced sensitivity analyses. Christensen provides more granular subgroup analyses.

List of variables in the PSW model: Offspring risk factors/confounders: “Gender”; Maternal risk factors/confounders: “Mother's age”; “Affective disorder ”, “Diabetes”, “Gestational diabetes”, “Neurotic disorder”, “Obesity”, “Substance abuse during pregnancy”, “Smoking during pregnancy”, “Maternal polypharmacy index prior to LMP2, mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2”, “Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy”, “Concomitant medications associated with neuropsychiatric adverse events prior to LMP2”, “Concomitant medications associated with neuropsychiatric adverse events during pregnancy”; Paternal risk factors/confounders: “Affective disorder”, “Bipolar affective disorder”, “Mania”, “Neurotic disorder”, “Schizophrenia, schizotypal and delusional disorders”, fathers with at least one prescription of: “concomitant medications associated with neuropsychiatric adverse events prior to LMP2”, “year of offspring conception”

MAH discussion on implications of the methodological differences in the interpretation of the slightly different Danish relative risks estimates:

Confounding control

The PASS Paternal used a broader set of confounders. The PASS Paternal used PS weighting and double adjustment for maternal psychiatric conditions and medication use, which may explain the stronger signal in PASS Paternal. More broadly, the PASS Paternal adjusted for more covariates (e.g., maternal psychiatric medication use, paternal polypharmacy). This strategy likely reduced residual confounding more effectively than Christensen et al.'s approach, who used traditional multivariable adjustment, which may not fully balance covariates.

Exposure window:

Christensen used a broader window (120 days pre-LMP), while PASS Paternal used a biologically grounded 3-month window. This could lead to exposure misclassification in Christensen, diluting the effect. Dilution of the effect is also what the PASS Paternal observed in one of the sensitivity analyses, in which the window prior to conception was extended to six months instead of three.

The narrower exposure window in PASS Paternal (90 days) aligns more closely with the spermatogenic cycle, potentially improving exposure specificity.

Follow-up duration bias:

Longer follow-up in valproate-exposed children increases the likelihood of NDD detection. This could inflate risk estimates in valproate group due to increased opportunity for diagnosis. Christensen et al. addressed this via sensitivity analyses, by matching on the birth year which impacted the HR estimate. PASS Paternal acknowledged this limitation and possible bias; birth year was included in the PSW model, but this may not allow to fully adjust for it.

Outcome definitions and censoring; subgroup / sensitivity analyses:

PASS Paternal included sensitivity analyses with narrow NDD definitions and ASD-only outcomes, which showed higher point estimates.

Christensen's main analysis used a broader composite, potentially diluting specific signals.

Christensen et al.'s significant findings in fathers with idiopathic epilepsy suggest that complex interplay of several contributing factors may confound the association (cf. Question #2 above). PASS Paternal did not isolate this subgroup, possibly diluting the signal.

Statistical Power and Modelling:

Both studies have wide Cis (Confidence Interval), reflecting limited power due to small numbers of cases. Both studies are underpowered for rare outcomes like ASD. Small differences in case numbers can therefore shift HRs substantially. PASS Paternal larger sample and meta-analytic approach increased power and precision, revealing a significant pooled effect not seen in Christensen et al.

Residual Confounding:

The PASS Paternal acknowledges potential residual confounding from unmeasured variables, e.g. generalize (genetic) epilepsy syndromes. Christensen also noted limitations of registry-based data. The results in the subgroup of fathers with idiopathic epilepsy raise questions about residual confounding (cf. Question #2)

Additional Considerations

The K-means clustering used in the PASS Paternal, to identify exposure trajectories (e.g., constant high vs. low-to-high) may better reflect real-world treatment patterns.

In both studies, valproate-exposed children were more likely to be conceived earlier in the study period, leading to longer follow-up and potentially higher diagnosis rates. This temporal trend likely introduced a temporal bias.

Both studies rely on ICD-10 codes from national registries, which may vary overtime in sensitivity/specificity for NDDs; this can introduce a bias, given the temporal trend mentioned above.

MAH Conclusion

While both studies used Danish registry data and similar comparator groups, methodological differences - particularly in exposure definitions, confounder adjustments, and statistical modelling - resulted in slightly different estimates. Nevertheless, the conclusion in Denmark was consistent: no increased risk was observed in offspring of fathers exposed to valproate during the three months prior to conception, compared to those exposed to lamotrigine or levetiracetam.

PRAC Rapporteur assessment

The MAH notes that the results of both studies are aligned, as both studies do not report a statistically significant risk increase in DK data sources (except for the idiopathic epilepsy subgroup, see Q2 below). It is acknowledged that crude incidence rates were comparable between studies in the valproate group (6.7/1000 PTY for Christensen et al vs 7.2/1000 PTY for paternal PASS) and similar for both studies in the comparator group (5.6/1000 PTY), and that no statistically significant increased risk was observed in DK in both studies. However, it is not agreed that the risk estimates observed in both studies are comparable. The HR observed in the main analysis of the paternal PASS (aHR 1.34 [0.79-2.25]) was higher than the observed aHR in Christensen et al (aHR 1.02 [0.67-1.54]). In addition, the statement that the outcomes of the studies are aligned is not agreed: the composite NDD outcome used by Christensen et al concerns a narrower composite NDD outcome (including intellectual disability, disorders of psychological development, autism spectrum disorder and ADHD) than used in the primary analysis of the paternal PASS. In the paternal PASS, the risk estimates were higher (although not significant) in a sensitivity analysis using a more narrow composite NDD outcome (excluding disorders of psychological development, hyperkinetic disorders, tic disorders and movement disorders) (for DK aHR 1.59 [0.89-2.86]), which is more similar to the composite NDD outcome used by Christensen et al (2025) (aHR 1.02 [0.67-1.54]). In the PASS, results from DK were considered together with results from NO and SE, with the pooled HR showing an increased risk (aHR 1.50 [1.09-2.08] for broad composite endpoint in primary analysis and aHR 1.69 [1.20-2.39] for narrow NDD endpoint).

The MAH provided a further discussion on the methodological differences between the paternal PASS and the publication by Christensen et al (2025) (e.g. see Table 1 above).

Data sources, study period, comparator groups, and follow-up duration are mostly comparable for both studies. The study population is generally comparable, although there are some slight differences in inclusion and exclusion criteria applied. Additional inclusion criteria for the paternal PASS include paternal continuous enrolment for ≥12 months prior to conception date (father) or childbirth (mother) and adopted children. For the paternal PASS, exclusion criteria included offspring with parents with a history of CM or NDD, fathers unexposed to AED, offspring paternally exposed to AED polytherapy or any AED other than VPA or lamotrigine/levetiracetam in the 3 months prior to conception date, offspring maternally exposed to AEDs in utero in 3 months prior to conception date, mothers with

history of epilepsy and offspring exposed to AEDs and/or diagnosed with epilepsy after birth. Christensen et al (2025) excluded offspring where father did not fill prescription for valproate or lamotrigine/levetiracetam during the spermatogenesis window, and children that died or emigrated before year 1. In various secondary analyses, Christensen et al (2025) excluded children of parents with CM or NDD, children of mothers with epilepsy, children with epilepsy, leaving out adjustment for maternal and paternal epilepsy or parental education, and ending follow-up at 12 years. However, the study did not include a secondary or sensitivity analysis that applied all exclusion criteria as were applied in the paternal PASS. The results of the secondary analyses were in line with the main analysis and did not suggest an increased risk of NDD in the valproate group compared to the lamotrigine/levetiracetam group.

In the paternal PASS, the effect estimation for NDD included 1796 offspring; 678 from the valproate group (38 cases NDD) and 1118 from the lamotrigine/levetiracetam group (36 cases NDD). A total of 2362 offspring were included in the main analysis in Christensen et al (2025), including 961 from the valproate group (50 cases NDD) and 1401 from the lamotrigine/levetiracetam group (67 cases NDD). For the paternal PASS, minimum sample size to observe a HR of 2.00 with 5% significance and 80% power was calculated to be 1178, with 598 per exposure group. This sample size was reached in Denmark in both the paternal PASS and Christensen et al (2025). Both studies were insufficiently powered to study NDD subtypes.

Exposure definition differed: the exposure period chosen in the PASS (90 days) more closely aligns to the biological spermatogenesis window whereas the 120-day period chosen by Christensen et al (2025) included the time of spermatogenesis (3 months prior to conception) plus an additional 30 days to account for prescriptions filled just prior to spermatogenesis. However, a sensitivity analyses using an exposure window of 60 days prior to LMP was also included by Christensen. In addition, a sensitivity analysis in the paternal PASS extending the window to 6 months prior to conception (also including offspring of fathers exposed 3 months prior to conception) still suggested a borderline increased risk (aHR 1.37 [1.00 – 1.89]).

Both studies used a composite NDD outcome. In contrast to the comment made by the MAH, the paternal PASS used a broader NDD composite outcome in the primary analysis compared to Christensen 2025. As noted above, a more narrow NDD composite outcome comparable to the outcome used in the primary analysis of Christensen et al (2025) was used in a sensitivity analysis and showed a higher risk estimate both in individual countries and pooled HR in a meta-analysis compared to the main analysis of the paternal PASS. For the narrow NDD composite outcome, in Denmark the aHR was 1.59 (0.89-2.86) vs aHR 1.02 (0.67-1.54) in Christensen et al (2025).

The studies used different methods for data analyses: Christensen et al (2025) used a Cox regression model to estimate hazard ratios, adjusted for sex of the child, year of birth, paternal and maternal characteristics (age, psychiatric diagnoses, psychotropic medication use, epilepsy diagnoses and educational level) and maternal valproate use during pregnancy. The paternal PASS considered additional covariates, including maternal (gestational) diabetes, obesity, smoking, viral infections (CMV, Rubella), alcohol abuse, as well as parental substance abuse, concomitant medications and polypharmacy index. Offspring maternally exposed to AEDs in utero or in the 3 months prior to LMP2 were excluded in the paternal PASS, whereas maternal AED use was not considered in Christensen et al (2025). However, not all covariates were retained in the PS model, and questions regarding selection of covariates included in the PS model were raised during assessment of the results of the paternal PASS. In the paternal PASS, a Cox Proportional Hazard (PH) adjusted regression model was used and the meta-analysis showed a slightly lower and non-significant aHR 1.25 (0.95 -1.66) compared to the pooled aHR of the PS-weighted analysis (1.50 (1.09 -2.07)). This comparison showed that the results and observed aHRs depend on the type of model used and how confounding and risk

factors are considered. A PS-weighted model was preferred as more covariates were considered compared to the Cox Proportional Hazard (PH) adjusted regression model in which clearly less covariates were considered in all countries and the selection of covariates was quite strict (i.e. only when associated both with the exposure and the outcome).

Follow-up and follow-up duration was largely similar between the studies. Offspring were followed from birth in the paternal PASS and from age 1 in the study by Christensen et al (2025). Follow-up from year 1 excludes potential unreliable NDD diagnoses, as these are generally not diagnosed before age 1. In both studies, follow-duration was longer in the valproate exposed offspring compared to the lamotrigine/levetiracetam offspring, which affects likelihood of NDD diagnoses. Both studies address this difference in follow-up time, either by including calendar year of conception in the PS model or by analyses matched on birth year. In the study by Christensen et al (2025) the aHR was 1.09 (0.68-1.75) in the analysis matched on birth year (including 715 offspring in both groups).

To conclude, the MAH provided a further discussion on the observed differences in NDD risk observed between the paternal PASS (for DK) and the study by Christensen et al (2025). The MAH considers the broader set of covariates considered in the paternal PASS, the different adjustment strategies applied (propensity score weighting vs traditional multivariable Cox regression) and exclusion of influential subjects in the PASS paternal to be the main methodological differences that may contribute to the observed differences in study results. It is agreed that these aspects highlighted by the MAH are methodological differences that may be the main contributors the observed differences in risk estimates, e.g. in the paternal PASS the use of a multivariable regression model that considered less covariates also showed attenuated risk estimates compared to the PS-weighted analyses. However, the extent to which these differences can impact the observed differences in risk estimates is difficult to determine. In addition, the PRAC Rapporteur considers the use of different inclusion and exclusion criteria is an important aspect, as this may affect baseline risk and potential for confounding.

In the paternal PASS, the results of DK were considered together with results from NO and SE. The risk estimates observed were lowest in de DK data source; however, as a significantly increased risk was observed in the meta-analysis and a trend for an increased risk observed in data for all 3 individual countries, PRAC concluded that a potential risk of NDD in children of fathers that used valproate in the three months before conception cannot be ruled out, despite limitations in the study design of the paternal PASS.

Question 4

Any new additional non-clinical data or literature data available should be discussed.

MAH response

A cumulative literature search was done in Embase and Medline databases on 29 July 2025 using the key words "valproate and congenital malformations/teratogenicity/autism/ neuro developmental disorders after paternal exposure in humans". This search did not retrieve any new publication discussing non-clinical or clinical data regarding NDD risk in offspring following paternal use of valproate.

PRAC Rapporteur assessment

The MAH notes that no new publication discussing non-clinical or clinical data regarding NDD in offspring following paternal use of valproate was retrieved (search on 29 July 2025).

PRAC Rapporteur assessment

Meng et al confidentially shared a draft publication of a cross-national cohort study in Norway and Taiwan that aimed to evaluate the association between paternal valproate exposure use before conception and the risk of NDDs in offspring. The study used nationwide population-based databases in Norway and Taiwan and included all liveborn singletons with available paternal data born between 2010 and 2015 and followed up through 2021. The authors report no increased overall risk for NDDs in offspring whose fathers used valproate compared to children whose fathers were unexposed or whose father were exposed to lamotrigine/levetiracetam. In the active comparator analyses the risk estimates were NO aHR 1.02 (0.57-1.82), TW aHR 1.22 (0.64-2.33), and meta-analysis pooled HR was 1.10 (0.72-1.70). In the paternal PASS these were aHR 1.34 (0.79-2.25) for DK, aHR 1.54 (0.95-2.51) for SE and aHR 1.76 (0.83-3.71) for NO, and meta-analysis pooled aHR 1.50 (1.09-2.07).

For the Norwegian part of the study, the data sources used are comparable to the paternal PASS, with additional use of a reimbursement database used to obtain information on study covariates. The study included all live-born singletons born between 2010 and 2015. Exclusion criteria are comparable to those used in the PASS, but the PASS additionally excluded adopted children, children of fathers or mother without continuous enrolment in the 12 months prior to index date, offspring with parents with history of CM or NDD, offspring exposed to AEDs in utero or in 3 months prior to LMP and offspring or mother with epilepsy. Thus, due to use of different inclusions and exclusion criteria, the study populations differ. Sensitivity analyses applying some of the PASS exclusion criteria (e.g. restriction to fathers without NDDs, exclusion of mothers using VPA during pregnancy and exclusion of children conceived via artificial reproductive technology) were performed by Meng et al, and generally showed consistent results with the main analysis of the study.

In both studies, the primary outcome was NDD as a composite outcome. The NDD composite outcome used by Meng et al was broader than the NDD composite outcome used by Christensen et al (2025). Compared to the paternal PASS NDD composite outcome, this study did not include movement disorders, but did include behavioral and emotional disorders and disorders of social functioning with onset specific in childhood which were not included in the paternal PASS. The study used both ICD-9 and ICD-10 codes compared to only ICD-10 codes in the paternal PASS, and there are some differences in the specific ICD-10 codes used for the different outcomes (see Table 2 in Annex). Meng et al did perform stratified analyses by individual NDD subtypes, but did not include an analysis using a more narrow NDD composite outcome similar to Christensen et al (2025) or the narrow NDD composite outcome used in the paternal PASS. The study outcome is therefore not fully comparable between the studies.

Strengths of the study include use of population-based data sources with high linkage in both cohorts, use of a minimum follow-up time of 6 years, use of a validated outcome algorithm, use of an active comparator, and consideration of various covariates, including indication, paternal and maternal comorbidities, medication use, and substance abuse in a PS model.

Compared to the paternal PASS, one of the key strengths of this study is the use of a validated outcome algorithm (Straub et al, 2021), which limits outcome classification and improves validity. For the paternal PASS, the primary outcome was defined as a diagnosis of at least one ICD-10 code, whereas in the Meng et al study at least 2 diagnoses of the same NDD on a different date were required, as well as a minimum age for diagnosis. Meng et al performed a sensitivity analysis using 1 NDD code (active comparator analysis NO aHR 0.49 [0.21-1.13]).Based on the number of cases reported in this sensitivity analysis compared to the main analysis, the use of a single NDD code mainly resulted in an increased number of NDD cases reported in the comparator group but not in the valproate group (VPA 24/319 in main analysis and 25/319 in sensitivity analysis; comparator 59/730

versus 67/730). Use of at least 2 ICD-10 codes for the same NDD is planned to be used in the follow-up study to the paternal PASS (TANGO).

Another key strength is the use of a minimum follow-up time of 6 years for all offspring. Minimum follow-up time of 6 years is considered to be sufficient for at least early diagnoses of NDD. Mean age of ASD diagnosis is known to be around 4-5 years of age and may be higher for other NDDs (e.g. ADHD) but can also vary between countries. In the Meng et al study, median follow-up time was comparable in the valproate (NO 8.7 years, TW 7.7 years), ASM-indication unexposed (NO 8.4 years, TW 7.8 years), and lamotrigine/levetiracetam (NO 8.6 years, TW 8.1 years) cohorts in both NO and TW. A major limitation of the paternal PASS in general concerned differences in follow-up time in the valproate group compared to the lamotrigine/levetiracetam group. Due to longer follow-up time in the valproate group, offspring in the valproate group may have had a higher chance of being diagnosed with NDD due to longer follow-up. This may be particularly the case for NDD diagnosed later in childhood. For Norway; however, mean follow-up time in the paternal PASS was comparable in the valproate and lamotrigine/levetiracetam group (4.9 and 4.8 years, respectively), which could be sufficient to capture early diagnoses but not for NDD diagnosed later, although this impacted both exposure groups similarly. The study by Meng et al does not provide information on the age at which NDD were diagnosed, thus the impact of this difference in follow-up time cannot be fully determined.

The Meng study used a stepwise analysis to evaluate the impact of potential confounding, including both analyses versus a general population, as well as indication-restricted and an active comparator PS weighted analyses. The paternal PASS used an active comparator design to limit confounding by indication but did not provide analyses stratified by indication (foreseen for the follow-up study TANGO). Both the Meng study and the paternal PASS used a propensity score model to adjust for a wide range of covariates. Although the precise covariates considered and definitions used for both studies differed (see Table 2 in Annex), both studies considered calendar year of conception or birth, parental age, comorbidities and medication use, as well as lifestyle factors such as smoking. In both data sources of the Meng et al study (NO and TW), there are differences in baseline characteristics between the valproate and lamotrigine/levetiracetam group. However, these differences vary by country. In NO, epilepsy diagnosis is reported in 62.1% and 42.6% in the valproate and lamotrigine/levetiracetam group, respectively. In Taiwan, epilepsy diagnosis is reported in 30.1% of valproate group and 49.0% of lamotrigine/levetiracetam. Information on subtype or severity of epilepsy is not available. In Norway, paternal psychiatric indications, sleep disorders and NDD were less prevalent in the valproate compared to the lamotrigine/levetiracetam group. In Taiwan, paternal substance abuse/alcohol abuse and use of anxiolytics/hypnotics and sedatives were more prevalent in the valproate group, and use of other AEDs was more prevalence in the comparator group. Thus, baseline characteristics in valproate and comparator group differed between countries and the populations using valproate and lamotrigine/levetiracetam may not be fully comparable.

A limitation of the paternal PASS was the concern for confounding by indication, as valproate may be prescribed for different or more severe conditions than lamotrigine/levetiracetam. Although analyses stratified by indication were requested during assessment of the final study results, these analyses were not provided by the MAH but are planned for the follow-up study to the paternal PASS (TANGO). Analyses restricted by indication were provided by Meng et al. For the analysis restricted to fathers with epilepsy, the indication-restricted analysis had aHR 1.19 (0.65-2.19) and for the active comparator analysis the aHR was 1.00 (0.47-2.13). For the analyses restricted to fathers with psychiatric disorders and fathers with somatic indications, HRs generally did not differ from the main analysis. However, these analyses are limited by small sample size. The study did not distinguish between subtypes of epilepsy or severity of epilepsy.

Stratified analyses by NDD subtype should higher HRs compared to the main analysis, for ASD aHR 1.48 (0.82-2.68) in indication-restricted analysis, and aHR 1.66 (0.55-4.98) in active comparator analysis, for ADHD aHR 1.15 (0.60-2.19) and aHR 1.28 (0.64-2.56), for developmental speech/language disorder aHR 2.87 (0.99-8.34) and aHR 1.12 (0.37-3.35), for behavioral disorder aHR 1.41 (0.56-3.38) and aHR 0.58 (0.23-1.49). Based on these stratified analyses, increased risk for individual NDD subtypes cannot be excluded; however, these analyses are limited by (very) small sample size resulting in very imprecise risk estimates with wide confidence intervals.

A limitation of the Meng study is the relatively small sample size in the comparative analyses using an active comparator. Although the overall cohort in the study is large, the numbers of offspring included in the analyses using an active comparator are lower. For Norway, the active comparator analysis included 319 offspring exposed to valproate and 730 offspring exposed to lamotrigine/levetiracetam. For Taiwan, the active comparator analysis included 564 offspring exposed to valproate and only 96 offspring exposed to lamotrigine/levetiracetam. The analyses using an active comparator in the individual countries may be underpowered, as noted by the authors, and this is particularly relevant for the TW results. For the paternal PASS, minimum sample size to observe a HR of 2.00 for NDD as composite with 5% significance and 80% power was calculated to be 1178, with 598 per exposure group. For the Meng et al study, this sample size was not reached in the individual countries (NO and TW). Both the paternal PASS and Meng et al study were insufficiently powered to study NDD subtypes. The uneven use of lamotrigine/levetiracetam use across the two countries can affect precision of the risk estimate and could impact the ability to control for confounding. Indeed, the authors note that in TW not all covariates were balanced after propensity score weighting and although these covariates were later adjusted for, this could have resulted in less precision of the risk estimate in TW. Imbalanced use of the comparator drug across countries may impact generalizability of the study results. In the paternal PASS use of lamotrigine/levetiracetam was more comparable across the three countries included.

Further, the prevalence of NDD is notably different between the NO and TW cohorts in the Meng et al study. For NO, in the valproate group, rates range between 8.7-8.8/1000 PY for valproate, and between 5.3-9.4/1000 PY in the comparator group. For Taiwan, rates range between 29.7/1000 PY in the valproate group and 21.2-23.5/1000 PY in the comparator group. The article does not provide information on the type of NDDs reported in the different exposure group or on the age at which the NDD were diagnosed. The authors note that the difference in NDD prevalence between Norway and Taiwan may reflect variations in healthcare systems, including differences in diagnostic practices, service availability, and reporting standards, which is acknowledged. Based on the number of individual NDDs reported in the stratified analyses by NDD type, it seems there are differences in the types of NDDs reported in NO vs TW: for the active comparator analyses: ASD NO 7/319 (2.2%) TW 16/564 (2.8%), ADHD NO 14/319 (4.4%) TW 62/564 (11%), specific learning disorders NO <3/319 (≤0.63%) TW 5/564 (0.9%), developmental speech and language disorder NO 5/319 (1.6%) TW 69/564 (12.2%), developmental coordination disorder NO 0/319 TW 47/564 (8.3%), intellectual disability NO <3/319 (≤0.63%) TW 10/564 (1.8%), behavioral disorder NO 6/319 (1.9%) TW 15/564 (2.7%). Thus, most notable differences are relatively more diagnoses for ADHD (4.4% vs 11%), developmental speech and language disorders (1.6% vs 12.2%) and developmental coordination disorders (0 vs 8.3%) in Taiwan compared to Norway. The difference in prevalence of reported NDD overall as well as differences in specific subtypes of NDD reported may limited generalizability of the TW results to the EU population, although an increased risk for NDD due to VPA could still be identified in such a population.

As with all observational studies, residual confounding could be an issue in both the paternal PASS and the Meng et al study. Despite use of an active comparator design and use of propensity score weighting, incomplete or missing data on lifestyle or genetic factors, as well as type and severity of

underlying conditions could impact the study results, and exposure and outcomes may be subject to misclassification.

Overall, the Meng et al study is a well-conducted study that contains some key strengths compared to the paternal PASS, such as use of a validated outcome algorithm and comparable follow-up time across cohorts. In addition, the authors used an active comparator analysis and propensity score weighting to limit confounding, and provided subgroup analyses by indication, which provide further insight into potential for confounding by indication. These analyses by subgroup also did not suggest an increased risk for NDD in valproate group. Analyses stratified by NDD subtype showed higher HRs compared to the main analyses, but with low precision due to small numbers. The study is limited by small sample size in both the NO but especially the TW dataset in the comparative analyses. It is unclear whether the analyses in individual countries were sufficiently powered for the study outcome.

3.2. Rapporteur's discussion

The risk of NDD with valproate after paternal exposure during spermatogenic risk window was considered a potential risk in previous assessments. In current assessment round, the MAH provided an evaluation and discussion of the publication by Christensen et al (2025), including strengths and limitations. The study by Christensen et al (2025) is a well-conducted study using population-based Danish data sources. Despite aligning study methodology to that of the paternal PASS, the authors could not replicate the results of the PASS and did not find an increased risk of NDD in offspring whose fathers had used valproate prior to conception compared to offspring whose fathers had used lamotrigine/levetiracetam (aHR 1.02 [95% CI: 0.67-1.54).

Strengths of the Christensen et al (2025) study include use of a nationwide cohort with minimal exclusion criteria (enhancing external validity), reliable information on exposure and outcome due to use of comprehensive Danish registries, wide range of sensitivity analysis applied, including alternative exposure definitions, different adjustment sets and stratifications which generally showed the same results as the main analysis. These strengths also apply to the paternal PASS.

Main limitations include the potential for residual confounding due to unmeasured or inadequately/incomplete measured variables (e.g. environmental exposures, parental lifestyle, genetic susceptibility, severity of disease), the small number of events for some subgroup analyses, and the short follow-up period in the comparator group. These limitations are also similar to the paternal PASS. In addition, neither study used double coding to identify NDD outcomes which could lead to outcome misclassification.

The minimum sample size pre-determined for the paternal PASS (to observe a HR of 2.00 with 5% significant and 80% power) was reached in Denmark both in the paternal PASS and the Christensen et al (2025) study.

Despite further alignment to the methodology of the paternal PASS there are still some differences in study methodology of Christensen et al 2025, such as differences in exclusion criteria, definitions of exposure and outcome and use of statistical analysis methods and covariates considered for adjustment. It is agreed with the MAH that the broader set of confounders included in the paternal PASS, different adjustment strategies and exclusion of influential subjects in the paternal PASS may be the most important methodological differences that could explain the difference in study results. In general, it is agreed that these factors can impact study results. Christensen et al (2025) adjusted for sex of the child, year of birth, paternal and maternal characteristics (age, psychiatric diagnoses, psychotropic medication use, epilepsy diagnoses and educational level) and maternal valproate use during pregnancy. The paternal PASS considered additional covariates, including maternal (gestational) diabetes, obesity, smoking, viral infections (CMV, Rubella), alcohol abuse, as well as parental

substance abuse, concomitant medications and polypharmacy index. Offspring maternally exposed to AEDs in utero or in the 3 months prior to LMP2 were excluded in the paternal PASS, whereas maternal AED use was not considered in Christensen et al (2025). Thus, overall the PASS considered more confounders or risk factors for NDD in offspring. Regarding the difference in statistical model use, in the paternal PASS, a Cox Proportional Hazard (PH) adjusted regression model was used in a sensitivity analysis, and the meta-analysis showed a slightly lower and non-significant aHR 1.25 (0.95 -1.66) compared to the pooled aHR of the PS-weighted analysis (1.50 (1.09 -2.07)). This comparison showed that the results and observed aHRs depend on the type of model used and how confounding and risk factors are considered. A PS-weighted model is preferred as more covariates were considered compared to the Cox Proportional Hazard (PH) adjusted regression model in which less covariates were considered in all countries. It is agreed that these are methodological differences that may effect observed risk estimates. In addition, the PRAC Rapporteur considers the use of different inclusion and exclusion criteria is an important aspect, as this may affect baseline risk and potential for confounding. However, the extent to which these differences can impact the observed differences in risk estimates is difficult to determine.

In addition, Christensen et al (2025) only showed results from Denmark, whereas the paternal PASS also included results from Norway and Sweden. The risk estimates observed were lowest in de Danish data source and the data for Denmark only were not statistically significant also in the MAH funded paternal PASS. For the paternal PASS, the main analysis showed an aHR of 1.34 (95% CI 0.79-2.25) for DK alone, and an aHR of 1.50 [95%CI 1.09-2.08) after pooling with results from NO and SE. In addition, in the paternal PASS, use of a more narrow composite NDD outcome (more similar to the composite outcome used by Christensen et al, 2025) showed an aHR of 1.59 (95%CI 0.89-2.86). As significantly increased risk was observed in the meta-analysis based on 3 countries, and a trend for an increased risk observed in data for all 3 individual countries, PRAC concluded that a potential risk of NDD in children of fathers that used valproate in the three months before conception cannot be ruled out, despite limitations in the study design of the paternal PASS.

Final study results of another study evaluating the risk of NDD after paternal exposure to valproate using population-based data sources from Norway and Taiwan were confidentially shared by the authors. These authors also did not find an increased risk for NDD in the Norwegian and Taiwan cohorts separately, nor in a meta-analysis pooling the HRs of both countries. In active comparator PS-FSW analyses for valproate monotherapy and levetiracetam/lamotrigine monotherapy, aHRs were 1.02 (95% CI 0.57 to 1.82) in Norway and aHR 1.22 (95% CI 0.64 to 2.33) in Taiwan, with a pooled aHR of 1.10 (95% CI 0.72 to 1.70). In the paternal PASS these were aHR 1.34 (0.79-2.25) for DK, aHR 1.54 (0.95-2.51) for SE and aHR 1.76 (0.83-3.71) for NO, and meta-analysis pooled aHR 1.50 (1.09-2.07).

For the Norwegian part of the study, the data sources used are comparable to the paternal PASS, with additional use of a reimbursement database used to obtain information on study covariates. Due to use of different inclusion and exclusion criteria as well as inclusion period, the study populations differ.

In both studies, the primary outcome was NDD as a composite outcome, which was broader than the composite outcome used by Christensen et al (2025); however, the NDDs considered for the composite outcome differed and specific ICD-10 codes used for the different outcomes differ. The study outcome is therefore not fully comparable between the studies.

Strengths of this study that also apply to the paternal PASS include the use of population-based data sources with high linkage, consideration of various covariates including paternal comorbidities, medication use and substance abuse in a PS model, and long-follow-up time (up to 11 years). Meng et al additionally considered indication for valproate use, and also presented analyses restricted to fathers with epilepsy or bipolar disorder. Additional strengths compared to the PASS are the use of a validated outcome algorithm (included 2 or more of the same NDD code and age restriction), which limits

outcome misclassification and improves validity, and the use of a minimum follow-up time of 6 years for all offspring, which is considered sufficient at least for diagnoses of early NDD. Follow-up time was balanced across cohorts.

A major limitation of the paternal PASS in general concerned differences in follow-up time in the valproate group compared to the lamotrigine/levetiracetam group. Due to longer follow-up time in the valproate group, offspring in the valproate group may have had a higher chance of being diagnosed with NDD due to longer follow-up, particularly for NDD diagnosed later in childhood. For Norway; however, mean follow-up time in the paternal PASS was comparable in the valproate and lamotrigine/levetiracetam group (4.9 and 4.8 years, respectively), which could be sufficient to capture early diagnoses but not for NDD diagnosed later, although this impacted both exposure groups similarly.

The Meng study used a stepwise analysis to evaluate the impact of potential confounding, including both analyses versus a general population, as well as indication-restricted and an active comparator PS weighted analyses. The active comparator analysis (as also applied in the paternal PASS) is considered most informative due to differences in baseline characteristics between valproate users and unexposed. Both the Meng study and the paternal PASS used a propensity score model to adjust for a wide range of covariates, calendar year of conception or birth, parental age, comorbidities including substance abuse, medication use, as well as lifestyle factors such as smoking. Although most of these covariates were considered in both studies, there are some differences in e.g. specific co-medications or comorbidities considered, e.g. the Meng et al study considered use of other ASMs, triptans, triptans, antipsychotics, antidepressants, anxiolytics and sedatives and opioids whereas the paternal PASS considered a broad range of medications used for the indications that valproate is prescribed for, medications associated with neuropsychiatric adverse events, as well as a polypharmacy index. The Meng et al study considered comorbidities sleep disorders, substance abuse, NDDs, whereas parental history was an exclusion criterion in the paternal PASS, and sleep disorders was not considered in the paternal PASS. Both studies considered lifestyle factors such as smoking and obesity. The Meng et al study considered paternal epilepsy, which was not included in the paternal PASS. Thus, although the covariates considered in both studies are generally comparable, there are differences in the definitions of the covariates considered.

A limitation of the paternal PASS was the concern for confounding by indication, as valproate may be prescribed for different types of epilepsy or more severe conditions than lamotrigine/levetiracetam. Although analyses stratified by indication were requested during assessment of the final study results, these analyses were not provided by the MAH, but are planned for the follow-up study (TANGO). Meng et al study provided results of analyses restricted to fathers with epilepsy, and these analyses do not suggest an increased risk for NDD in the valproate group compared to the lamotrigine/levetiracetam group, similar to the results of the main analysis. However, these analyses are limited by small sample size. In addition, no information on epilepsy subtypes or severity of epilepsy was retrieved from the study by Meng et al.

Stratified analyses by NDD subtype showed higher HRs compared to the main analysis, thus an increased risk for individual NDD subtypes cannot be fully excluded; however, these analyses are limited by (very) small sample size resulting in very imprecise risk estimates with wide confidence intervals.

Key limitation of the Meng study include the relatively small sample size in the comparative analyses using an active comparator. The analyses are likely underpowered, as noted by the authors, and this is particularly applicable for the Taiwan results. For the analyses using an active comparator, the minimum sample size pre-determined for the paternal PASS (to observe a HR of 2.00 with 5% significant and 80% power) was not reached in both individual countries in the Meng et al study.

Imbalanced use of the comparator drug across countries may limit generalizability of the study results. In the paternal PASS use of lamotrigine/levetiracetam was more comparable across the three countries included. In addition, the difference in prevalence of reported NDD overall as well as differences in specific subtypes of NDD reported between Norway and Taiwan may limit generalizability of the Taiwan results to the EU population, although an increased risk for NDD following VPA could still be identified in such a population.

Overall, the Meng et al study is a well-conducted study that contains some key strengths compared to the paternal PASS. The authors used an active comparator analysis and propensity score weighting to limit confounding, and provided subgroup analyses by indication, which provide further insight into potential for confounding by indication. These analyses by subgroup also did not suggest an increased risk for NDD in valproate group. Analyses stratified by NDD subtype showed higher HRs compared to the main analyses, but with low precision due to small numbers. The study is limited by small sample size in both the NO but especially the TW dataset in the comparative analyses. The minimum sample size pre-determined for the paternal PASS (to observe a HR of 2.00 with 5% significant and 80% power) was not reached in NO or TW; however, results were also pooled in a meta-analysis which showed an aHR of 1.10 (95% CI 0.72 to 1.70) in the active comparator analysis.

3.3. Rapporteur's proposed recommendation

With the availability of the results of studies by Christensen et al (2025) and Meng et al (draft), there are now two studies using similar as well as additional data sources as the paternal PASS that did not show an increased risk of NDD following paternal exposure to valproate, in contrast to the results of the paternal PASS.

Both studies are well-conducted studies that contribute to the totality of evidence regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window. These studies had the same study aim and used comparable data sources that were also used in the paternal PASS, but there are several methodological differences between the studies that could impact study results. Compared to the paternal PASS, the Christensen et al (2025) study considered a smaller number of important risk factors that may be associated with the occurrence of NDD in children. The Meng et al study is methodologically strong and addresses several limitations of the paternal PASS, but is limited by small sample size, and the analyses using an active comparator may be underpowered.

Precautionary measures for male patients have been implemented following the final results of the paternal PASS, despite limitations of the study leading to uncertainties regarding the strength of evidence. The results of Christensen et al (2025) and Meng et al add to that uncertainty, as both studies did not show the increased risk that was observed in the PASS. However, both studies also have limitations, such as small sample size or less adjustment for confounders. Therefore, the results of these studies cannot fully outweigh the results of the paternal PASS. In addition, further evidence is expected in the (near) future from the ongoing MAH-sponsored TANGO PASS and non-clinical study program (both classified as Cat 1 PASS). The TANGO PASS will provide additional relevant data regarding the risk of NDD in offspring paternally exposed to valproate, including analyses restricted to former users of valproate (outside the spermatogenic window (before or after)), and if feasible, stratified analyses by indication, sub-type of epilepsy, calendar year of birth, and parental NDD/MCM, as well as analyses to further explore potential variations in risk of NDD over time. In addition, the TANGO PASS will include data from additional countries (DE, FI) increasing sample size and is therefore expected to be able to detect a smaller HR. Analyses in former users as well as variations in risk of NDD over follow-up time have not been performed by either Christensen et al (2025) or Meng et al. Similarly, both studies could not provide further information on the potential impact of subtype of epilepsy.

Taking into account the evidence reviewed in current assessment round, the PRAC Rapporteur considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk. The currently available information in the PI with advice for considering contraception in male patients using valproate and discussing potential alternative treatment options in case of a wish to father a child is considered proportional to this uncertainty. Further data regarding the risk of NDD is expected (see section 1). The PRAC rapporteur considers it important to evaluate all available data including the results from the ongoing MAH-sponsored PASS before decision making and therefore proposes to await the final study results of the follow-up study TANGO (expected in Q1 2028) for further re-evaluation of the measures implemented after the final study results of the paternal PASS.

3.4. Comments from other PRAC members and MAH(s)

MS 1 comments

We thank the Lead Member State for their thorough analysis of the Signal on neurodevelopmental disorders with paternal exposure to valproate and related substances and for reviewing/ summarising the Additional data relevant for the Signal that were available at the time this report, including the unpublished data shared by Meng et al.

On November 7th (after the circulation date of the LMS report), the French Regulatory Authorities published an important new epidemiological study based on the "EPI-MÈRES" Register and entitled "Paternal exposure to valproate during spermatogenesis and risk of neurodevelopmental disorders in children". This large study suggests an increased risk of neurodevelopmental disorders, and especially intellectual developmental disorders (risk more than doubled) in children born to fathers exposed to valproate during the 4-months period before conception (so within the spermatogenic window).

We believe that this large study should be considered in the context of the present Signal, before a final recommendation could be issued. Additionally, the potential need for updating/completing the product information and the risk minimization material (HCP Guide, Patient Leaflet) available for male patients exposed to valproate with information originating from this new study should be re-considered.

While we agree with the Lead Member State that the TANGO study will bring insightful information, results will only be available by 2028. An update of the safety documentation available for valproate-containing products before that date may be in the patients' best interests.

If the LMS agrees to pursue with the Signal analysis as suggested above, the very recent publication from Willoch-Olstad et al.1 may be considered as well, as it highlights how genetic confounders may impact this risk, and may help reconcile the apparent discrepancy between the different studies discussed within this Signal.

1. Olstad EW, Nordeng HME, Bjørk MH, Selmer K, Gervin K. Paternal valproate use and impact of shared genetic susceptibility on child neurodevelopment. Sci Rep. 2025 Nov 7;15(1):39033.

PRAC Rapporteur assessment

We thank the MS 1 colleagues for their input and suggestions. We fully agree that the newly published French epidemiological study based on the EPI-MÈRES registry should be considered in the context of current signal procedure. We therefore propose an additional round for current procedure in which the MAH will be requested to provide a thorough discussion of the results of this new study. We also agree that the totality of evidence currently available for the risk of neurodevelopmental disorders after paternal exposure should be reflected in the product information and available additional risk minimisation materials, and will request the MAH to propose such updates in the next round based on

the review of data that has become available in current procedure. We will additionally request the MAH to discuss the recent publication by Olstad et al (2025). The proposed recommendation has been updated accordingly (see section 3.5).

MS 2 comments

The MS 2 team thank the PRC Rapporteur for the thorough analysis of the Signal on neurodevelopmental disorders with paternal exposure to valproate and related substances (EPITT no: 20191) received on the 3rd of November. We have assessed the AR and preliminary we can agree. However, as the French study about paternal exposure with valproate published was not included in the pAR (it was published online on the 6th of November), we believe our comments will be of greater value if they assess the updated AR planned for November 20. We apologise for informing you of this only today.

PRAC Rapporteur assessment

We thank the MS 2 colleagues for their input. We also consider that the new French study provides important additional information and should be carefully discussed in context of current signal procedure. We therefore propose an additional round for current procedure in which the MAH will be requested to provide a thorough discussion of the results of this new French study. See updated recommendation below (section 3.5).

MS 3 comments

We appreciate the thorough assessment of the MAH's response regarding the study by Christensen et al. and paternal PASS studies, including differences, strengths and limitations. We were critical to the PRAC recommendations to include warnings for fathers using valproate including recommendations to use contraception. The paternal PASS showed a small increased risk of NDD (as a composite) of 1.50 (1.09 - 2.07) with the lower CI close to the null. The risk in the individual countries where all non-significant, and although this could be due to lack of power, it also indicates a degree of instability of the data where few cases in one or the other group would have changed the result. A small risk of 1.5 is also sensitive to unmeasured confounders like genetics and importantly social status. We therefore considered the data insufficient to recommend a strong warning to fathers including use of contraception to men using valproate. The warning is included in the patient information as part of the valproate PPP which in our opinion is not proportionate to the uncertainty of the risk.

Now to new studies using data sets partly overlapping with the data used in the paternal PASS, both demonstrates the absence of a NDD risk in children fostered by fathers taking valproate during spermatogenesis. We agree with the rapporteur that these studies are well conducted adjusting for most relevant and identifiable confounders. Neither Christensen et al. nor Meng et al. could identify an increased risk of NDD using either a traditional cox proportional regression or a PS-FSW method. As with all studies based on register data, they both have strengths and limitations as is the case with the paternal PASS. The rapporteur considers the PS methodology used in the paternal PASS preferable as it included more variables as compared to the regression analysis used by Christensen et al. While this is somewhat agreed, Meng et al. also used PS for adjustment, and they did not find an increased risk. Interestingly the paternal PASS did not find an increased risk when analysing the data using a cox proportional method for adjusting (a finding in line with the Christensen el al. study). Our interpretation is that the data seem sensitive to the methodology used, adding to the uncertainty.

Based on these recent findings we consider that there is much uncertainty with regard to any risk of NDD in children fostered by fathers taking valproate, and that the information now included in the product- and patient information should be removed as it is not considered sufficiently documented. In

our opinion the new set of data indicate the absence of a risk. We consider that the current information may cause more harm than benefit potentially leading patients to stop a necessary treatment.

PRAC Rapporteur assessment

We appreciate the comments from the MS 3 colleagues and acknowledge their different view on the necessity of reflecting the potential risk of neurodevelopmental disorders after paternal exposure in the product information and risk minimisation materials. It is also acknowledged that the choice of statistical model used to analyse study results can impact the risk estimate, as demonstrated by the sensitivity analyses included in the paternal PASS, and this adds to the uncertainty regarding the robustness of the study findings. These, and other important limitations of the paternal PASS have been considered by the Rapporteur and by PRAC during discussion of the final study results of the paternal PASS and preclude drawing final conclusions regarding causality for this risk. Nevertheless, also after consideration of input from various stakeholders, precautionary measures were implemented. Although we agree that the newly available studies increase uncertainty regarding the strength of evidence, we still consider the risk of neurodevelopmental disorders remains an important potential risk and therefore the previously implemented precautionary measures are still proportionate.

In addition, as communicated by the MS 9 colleagues to the network on Nov 7, another new study evaluating the risk of neurodevelopmental disorders after paternal exposure to valproate during spermatogenesis has become available. This study concerns the largest study to date and describes an increased risk of NDD in children paternally exposed to valproate compared to children paternally exposed to lamotrigine/levetiracetam. We consider that this newly published French epidemiological study provides additional relevant new information on the offspring risk of neurodevelopmental disorders after paternal valproate exposure and therefore propose an additional round of assessment for further discussion and assessment of these French study results. See updated recommendation in section 3.5.

MS 4 comments

We endorse the PRAC Rapporteur's conclusion and appreciate the thorough assessment.

The two new studies by Christensen et al. 2025 (DK) and Meng et al. 2025 (NO, Taiwan) show no significant increased risk of neurodevelopmental disorders with paternal use. Data from DK and NO was also included in the non-interventional imposed paternal PASS *[number redacted]*, and it is noted that the paternal PASS did not find a significantly increased risk of neurodevelopmental disorders for the individual countries included in the study (DK, NO and SE). Therefore, the results for DK and NO from the two new studies (Christensen et al. 2025 and Meng et al. 2025) are overall in line with the findings from the paternal PASS regarding the finding of a not significantly increased risk of neurodevelopmental disorders.

However, it is important to note, that none of the newly identified studies includes all three countries included in the paternal PASS (DK, NO and SE) and that the meta-analysis pooled aHR for the three countries have not yet been attempted to be replicated in other studies (to our knowledge).

Considering the conflicting data, we therefore agree with the PRAC Rapporteur's conclusion that it is important to evaluate all available data including the results from the TANGO PASS before decision making.

However, the current recommendation is not considered fully clear on how the different published study results will be incorporated in the discussion on this topic when the final study results from the TANGO study will be available. It is therefore proposed to request the MAH to include a cumulative review of literature in the TANGO PASS final study report. The review could be included in the

discussion section of the report as outlined in the Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies - EMA/48663/2013 section 11.3 Interpretation (See below).

11.3. Interpretation

[Overall interpretation of results considering objectives, limitations and findings from similar studies and other relevant evidence supporting or conflicting with the study results. Results should also be interpreted in relation to the safety issue leading the study to be imposed or initiated, their impact on the benefit-risk balance of the concerned product(s) and the information included in the summary of product characteristics and the risk management plan of the product(s).]

PRAC Rapporteur assessment

We thank the MS 4 colleagues for input and suggestion. We agree that at time of final discussion of the TANGO results, other relevant published studies should be considered and will include this in the final recommendation of current procedure. Following suggestions from other colleagues, we also consider that based on the information that has become available in current procedure (studies by Christensen et al, 2025; Meng et al; and new French EPI-MÈRES registry study to be discussed in next round of current procedure), a further discussion regarding the necessity of updating the currently reflected information regarding the risk of neurodevelopmental disorders in the product information and additional risk minimization materials is warranted, and have updated the Rapporteur's recommendation accordingly.

MS 5 comments #1

We thank the LMS for their very comprehensive assessment of MAH responses to request for supplementary information. We consider that given the recent publication of the additional study by EPI-Phare GIS ANSM-Cnam[3], which appears to provide analysis in terms of individual NDD subtypes, review of this study in the context of the current signal procedure (by way of another assessment round) would allow the opportunity to evaluate the relevance of this report in the context of overall evidence.

- In terms of adjustment for covariates, we note LMS comment on page 36

  "Both the Meng study and the paternal PASS used a propensity score model to adjust for a wide range of covariates, including epilepsy, calendar year of conception or birth, parental age, comorbidities including substance abuse, medication use, as well as lifestyle factors such as smoking".

  From Appendix 15.4 of the study report it does not appear that paternal epilepsy or paternal age were included in the propensity score models for EUPAS34201 (notwithstanding paternal age appears to have been balanced across exposure groups within countries after propensity score weighting).

  In contrast in the Christensen study, it appears that paternal epilepsy was included as a covariate in the Cox proportional hazards regression model for the main analysis.

  It is understood that the potential for confounding by indication in EUPAS34201 will be further explored in TANGO. However, at this stage, the MAH could consider further the potential for confounding by indication and how this was handled across the studies, and whether it may contribute to the differing results observed.

- We generally agree that the available data in the current assessment round do not provide sufficient basis to support updates to the precautionary measures for male patients at this time. Nonetheless, given that in addition to the PASS study there are now additional data available from the two well-conducted retrospective cohort studies evaluated within the signal procedure and the above EPI-Phare study, consideration should be given as to whether the PI and aRMMs should be updated to reflect this also.

PRAC Rapporteur assessment

We fully agree with the MS 5 colleagues that the newly available French study should be considered in current procedure, and therefore suggest an additional round of assessment for discussion of these study results as well as the necessity of updating current information on the risk of neurodevelopmental disorders after paternal exposure in the product information and additional risk minimisation materials based on all data that has become available in current procedure, see updated recommendation in section 3.5.

The MS 5 comment regarding the covariates adjusted for is appreciated and this has been corrected in the PRAC Rapporteur's discussion. The available studies indeed differ with respect to the consideration of paternal epilepsy as covariate in the statistical models, with Christensen et al (2025), Meng et al, and new EPI-MÈRES study including paternal epilepsy in their main analyses or in a sensitivity analysis, whereas the paternal PASS did not. In addition, analyses stratified by epilepsy were provided by these 3 studies, whereas the paternal PASS did not. As a further discussion regarding the results of the EPI-MÈRES study have been requested for the next round, including discussion of potential reasons for observed differences, such as impact of considering paternal epilepsy as covariate in the statistical models, between the available studies, see updated recommendation in section 3.5.

MS 5 comments #2

We thank the PRAC rapporteur for their assessment of the Ad Hoc Consortium Communication and updated AR, and have the following comments:

Further to our earlier comments, and in line with those of other MSs, we suggest that the Consortium should be asked to evaluate the EPI-Phare study and consider how it adds to the available data within this signal.

In addition, it might be useful for the EPI-Phare group to comment on aspects of the study which give rise to some uncertainty. Initial observations which might be considered are outlined below.

- While in the main analysis the overall incidence of NDDs was higher in children born to fathers exposed to VPA compared to children born to fathers exposed to levetiracetam/lamotrigine, the lower bound of the CI is close to the null (weighted HR 1.24, 95% CI 1.07-1.44) and for the difference in incidence per 1000 child years the CI is wide (rate difference 2.23, 95% CI 0.67; 4.03).
- Moreover, it is understood that the analysis above refers to combination therapy. When restricted to monotherapy in sensitivity analysis, the association with NDD is attenuated and no longer significant (weighted HR 1.17, 95% CI 0.98 – 1.40). Further of note, this sensitivity analysis (restricted to children whose fathers were exposed to monotherapy) does not appear to be adjusted for paternal epilepsy.
- Further, in terms of adjustment for parental NDD we note that according to Table S1, it appears that the study adjusted for parental autism spectrum disorder and attention deficit disorder

with or without hyperactivity, but not for parental diagnosis of intellectual disability which would be of particular relevance to the findings regarding IDD.

- In terms of the risk of IDD:
    - The confidence intervals are wide, noting the small number of cases (42 events among children born to fathers exposed to VPA and 11 events among those born to fathers exposed to levetiracetam/lamotrigine) and the lower bound for IDD close to the null in a number of analyses.
    - The main analysis (children born to exposed fathers v children born to fathers exposed to lamotrigine or levetiracetam incl weighted HR 2.12, 95 % CI 1.05 – 4.30 for IDD) appears to be for combination therapy (which was more prevalent in the comparator cohort). Although power may have been more limited and the point estimate is still above 2, when restricted to monotherapy as a sensitivity analysis, the association is not significant (weighted HR 2.07, 95% CI 0.78 – 5.53). Also of note, this analysis does not appear to have been adjusted for paternal epilepsy and the distribution of epilepsy across cohorts of children born to fathers who only received monotherapy is unclear.
    - Adjustment for paternal epilepsy appears to have been performed only as a sensitivity analysis for the main analysis involving combination therapy (i.e. children born to exposed fathers v children born to fathers exposed to lamotrigine or levetiracetam incl weighted HR 2.12, 95 % CI 1.05 – 4.30 for IDD), and after this adjustment the confidence interval is wide with lower bound even closer to the null (HR 2.20, 95% CI 1.01 – 4.77).
- It is also noted that the study mostly used robust standard errors to calculate confidence intervals following propensity score weighting. One sensitivity analysis (matching on birth year) involved bootstrapping. Other analyses, including the sensitivity analysis of association of combination therapy with IDD with adjustment for paternal epilepsy (where lower bound of 95% CI is 1.01), used robust standard errors. Considering the margins by which some findings such as this reach significance, literature suggesting that robust standard errors may not be valid and that other methods may be preferable in this setting is noted (Reifeis & Hudgens 2022).
- It is not fully clear whether the rate differences and their 95% confidence intervals were calculated by applying the weighted hazard ratios to the incidence rates of NDD in the comparator cohorts before or after weighting these cohorts. A further consideration may be the impact of the weighting on incidence rates in the comparator cohort and whether and how this might affect calculation of rate differences and their 95% confidence intervals.

PRAC Rapporteur assessment

We appreciate the additional comments from the MS 5 colleagues regarding the French EPI-MÈRES study. We agree that these new results warrant further discussion and evaluation, including discussion how these new data add to the available data regarding the risk of neurodevelopmental disorders after paternal exposure. Another round is proposed which allows the MAH to respond to and discuss these results in context of the other studies evaluated in current signal.

The MS 5 colleagues further note that it may be useful to request the EPI-Phare group who conducted the study to comment on several aspects of the study which give rise to uncertainty of the study results. We fully agree that there are several aspects of the study design as well as interpretation of the study results that warrant further assessment and discussion. The main points raised by the MS 5 colleagues, i.e. use of valproate not restricted to monotherapy, consideration of paternal epilepsy in the analyses, wide confidence intervals for some of the risk estimates, as well as other methodological issues such as the methodology to estimate confidence intervals are agreed by the PRAC Rapporteur. The suggestion to forward these points to the EPI-Phare group can be further discussed during PRAC plenary.

MS 6 comments

We agree with the assessment of the rapporteur regarding the uncertainty of the risk of NDD after paternal exposure to valproate during the spermatogenic risk window. At this point of time we have conflicting information, therefore this should remain an important potential risk.

Nevertheless, this signal should be monitored closely and new studies regarding this topic should be discussed as soon as possible. The french Epi-PHARe study (06.11.2025) with a large number of exposed children might help to clarify this potential risk earlier than the TANGO study.

PRAC Rapporteur assessment

We thank the MS 6 colleagues for their comments, and we suggest an additional round in current procedure to discuss the results of the French Epi-PHARe study, see updated recommendation in section 3.5

MS 7 comments

we fully agree with the PRAC Rapp's assessment and conclusions.

We support the Rapp's position that the results of the studies Christensen et al (2025) and Meng et al cannot outweigh the results of the paternal PASS, however, they bring more unclarity into the causal association between valproate used by men and the risk of NDD in offsprings.

We support the continuation of the established aRMMs implemented based on the outcome of the paternal PASS. The risk of NDD in children conceived by men treated with valproate remains the Important potential risk, the information implemented to PI after finalisation of paternal PASS remains still valid (it already states that the risk is possible, but the causal role of valproate is not confirmed).

Further evidence from the ongoing PASS studies is needed.

PRAC Rapporteur assessment

We appreciate the MS 7 support for the Rapporteur's position. Following other MS comments, and as the current product information and additional risk minimisation measures only describe results of the paternal PASS, whereas new data regarding the risk of neurodevelopmental disorders after paternal exposure to valproate has become available in current procedure, we have requested the MAH to provide a proposal to update the product information and additional risk minimisation measures based on all available data to date, see updated recommendation in section 3.5.

MS 8 comments

The MS 8 PRAC team thank the PRAC Rapporteur for the thorough analysis of the Signal on neurodevelopmental disorders with paternal exposure to valproate and related substances (EPITT no: 20191), and especially for the difficulties that this procedure entails.

After the review of the assessment, we still agree in that NDD after paternal exposure should currently be considered as an important potential risk for valproate, as concluded in previous PASS procedure assessment *[number redacted]*. The PASS study confirmed that combined data from DK, NO, SE countries showed a borderline but statistically significant increased risk: 1.50 (95% CI: 1.09-2.07) for NDD in children of fathers treated with valproate in the 3 months prior to conception compared with lamotrigine or levetiracetam (with an estimated cumulative risk of NDD of about 5% versus 3%, respectively). However, the study had limitations, as potential confounding by indication (and by disease severity), differences in follow-up time between exposure groups, and size limitations to provide results on specific types of NNDs. In spite to this, due to the seriousness of the issue and lifelong impact on NDD, updates on PI and aRMMs to adequately inform the risk were warranted; but

PASS (TANGO) was requested to address the mentioned uncertainties. Clinical experts and stakeholders also supported the PRAC's conclusion.

For the assessment of this signal procedure, results of 2 additional studies were taken into account: the Study of Christensen et al., utilizing DK databases, implementing also a second reanalysis with an approach more similar than the one performed in previous PASS; and a 2nd study, using NO and Taiwan population databases. These studies contradict the results provided in previous PASS conclusions, by showing no relatedness between NDD after paternal exposure with valproate use versus patients exposed to lamotrigine or levetiracetam.

As the rapporteur has concluded in their thorough and well detailed assessment, we consider all 3 studies as high quality, well performed studies, but with specific differences between them, as well as their own strengths and limitations, which should be taken into account. Based on this, assessment of these do not allow us to place more importance on the conclusions of one study beyond the others, or to clearly elucidate and solve the limitations from each of these. In this regard, we believe the integrated conclusion of these 3 studies add more uncertainty than the one already posed in previous PASS procedure assessment regarding the potential causal relationship of valproate and NDD with paternal exposure.

Based on this conclusion, we agree on the need of the results from the study PASS TANGO to address the limitations observed in previous PASS study and the other studies performed, to further elucidate whether a true causal association exist regarding this risk and which measures to take.

However, taking into account the concerns that pose the delay of the results of this final PASS study (to 2028), and, due to the impact the conclusion of this procedure could have, we suggest it is necessary to ensure the inclusion of all the evidence available at this moment in the assessment of this risk. So, in line with comments from other MSs, we support the inclusion of the assessment of the French study about paternal exposure with valproate (EPI-Phare study) in this signal procedure (i.e with an RSI), before closing it. It seems to be the largest study to date, and the study appears to be very robust to the numerous analyses performed. It is of relevance the HRs in NDD subgroups observed when the population was restricted to children whose father has an epilepsy diagnose (based on MS FR comments). Although it has an important limitation, the fact that father-child linkage is available for approximately 70% of all children. Nevertheless, we consider this study of relevance.

We expect the inclusion of this study in the signal assessment would help to provide a more comprehensive conclusion for this procedure and has the potential to shed light on current uncertainties this procedure is entailing.

PRAC Rapporteur assessment

We thank the MS 8 colleagues for their support and suggestions. As noted in comments to other MS above, we fully agree that the newly available French EPI-MÈRES study provides an important new source of information that should be considered in current signal procedure and therefore propose an additional round of assessment to further discuss this new French study. We also agree that further update of the current information regarding the risk of neurodevelopmental disorder after paternal exposure to valproate may be warranted as currently only results of the paternal PASS are reflected, whereas new well-performed studies have become available. The Rapporteur's recommendation has been updated accordingly, see section 3.5.

MS 9 comments

We would like to thank the rapporteur for the quality of their analysis and report.

Three studies focusing specifically on the association between paternal exposure to valproate and the risk of NDD have been published: one based on data from the Swedish National Register from 2006 to 2016 (Tomson et al. 2020), another one based on data from the Danish National Register from 1997 to 2017 (Christensen et al. 2024, 2025), and finally, a study from Sanofi and IQVIA gathering data from Sweden (2007-2019), Denmark (1997-2018) and Norway (2010-2019), initially reported in the PASS report and recently published in the JAMA Network Open (Colas et al. 2025). Limitations of these studies and the heterogeneity of their results have already been discussed. The main limitation is the size of the population and especially the small number of exposed cases.

Noteworthy, in the two studies reporting results by type of NDD, paternal exposure to valproate at conception was associated with an increased risk of IDD (Intellectual Development Disorders) - although the association did not reach statistical significance - by 60% (HR 1.6, IC95% 0.5 to 5.1) in the Swedish registry study and by 85% (HR 1.85, IC95% 0.72 to 4.76) in the Danish registry study.

As indicated in our previous comments, the EPI-PHARE group (a partnership between ANSM and Cnam) conducted a study based on data from the EPI-MERES register, which covers all pregnancies in France since 2010. The study report was published on November 6th, 2025. All children born alive between 2010 and 2015 and with an identified father and mother were included, except those with a brain malformation and those born from a pregnancy with medically assisted procreation or exposed to a medicine whose in utero exposure is associated with an increased risk of NDD (i.e., valproic acid, valpromide, carbamazepine or topiramate). Each child was followed from birth until the occurrence of NDD (including attention deficit disorders with or without hyperactivity, intellectual developmental disorders, autism spectrum disorders, communication disorders, and learning disorders), death, or until 30 September 2024. Children whose father had had at least one dispensation of valproic acid (or valproate) indicated in epilepsy within four months prior to conception (period of spermatogenesis) were considered to be exposed. The incidence of NDDs, considered overall or separately by type of NDD, was compared between exposed children and (1) those whose father had had a dispensation of lamotrigine or levetiracetam during spermatogenesis (main analysis); (2) those of fathers (i) who stopped valproate before spermatogenesis or (ii) with epilepsy not treated with valproate, lamotrigine or levetiracetam (complementary analyses). The comparisons were made using weighted Cox models using propensity scores accounting for sociodemographic and health characteristics of the children and their two parents and characteristics of the pregnancies from which they were born. Sensitivity analyses were carried out to test the robustness of the results across variations of the statistical methodology, the definition of exposure and the population considered.

Among a total of 2,832,850 children born between 2010 and 2015, 4,773 were born to fathers treated with valproate during spermatogenesis (exposed children, median duration of follow-up after birth 11.9 years), and 3,115 to fathers treated with lamotrigine or levetiracetam (main comparator group, median duration of follow-up after birth 11.2 years). A total of 583 (12.2%) NDD cases were observed among the exposed children and 310 (10.0%) in those of the comparator group: attention deficit disorders with or without hyperactivity for 149 (3.1%) and 77 (2.5%) respectively, intellectual development disorders for 42 (0.9%) and 11 (0.4%), autism spectrum disorders for 77 (1.6%) and 39 (1.3%), communication disorders for 294 (6.2%) and 157 (5.0%), learning disorders for 160 (3.4%) and 97 (3.1%).

Accounting for the confounders through a propensity score approach, the overall incidence of NDDs was significantly higher among exposed children than among children of fathers treated with lamotrigine or levetiracetam (Incidence rate per 1000 child-years, IR: 11.0 [95% CI: 10.1-11.9] versus 9.2 [8.1-10.2]; Hazard Ratio, HR: 1.24 [1.07-1.44]). Furthermore, in the analyses by type of NDD, the risk of intellectual developmental disorders (42 cases [0.9%] in exposed children versus 11 cases [0.4%] in the controls) was more than 2 times higher among exposed children than among

those of fathers treated with lamotrigine or levetiracetam (IR 0.7 [0.5-1.0] versus 0.3 [0.1-0.5]; HR 2.12 [1.02-4.30]), with a difference in incidence rate of 0.35 per 1000 child-years. The risk of the other types of NDD was higher among exposed children than among those of fathers treated with lamotrigine or levetiracetam, but with less marked differences than for intellectual developmental disorders.

The associations between paternal exposure to valproate during spermatogenesis and the risks of NDD were mostly unchanged in sensitivity analyses. However, they were reinforced when the population was restricted to children whose father had an epilepsy identified in the SNDS, with HR reaching 2.62 [1.07-6.41] for intellectual developmental disorders, 1.56 [1.05-2.30] for attention deficit disorders with or without hyperactivity, 1.95 [1.19-3.20] for autism spectrum disorders and 1.34 [1.04-1.72] for communication disorders. In addition, the association with intellectual developmental disorders was strengthened after excluding children with identified epilepsy (HR 2.50 [1.07-5.83]) or those of a father or mother with a mental health disorder or NDD (HR 2.64 [1.17-5.96]).

As in the main analysis, the risk of intellectual developmental disorders was more than 2 times higher in exposed children compared to children of fathers who discontinued valproate (HR 2.32 [0.94-5.76]) and children of fathers with epilepsy not treated with valproate, lamotrigine or levetiracetam (HR 2.10 [1.17-3.76]). By contrast, the incidence of other types of NDD did not differ between exposed children and those of fathers who discontinued valproate before spermatogenesis or who had epilepsy not treated with valproate, lamotrigine or levetiracetam.

This study is the largest to date on the association between paternal exposure to valproate during spermatogenesis and the risk of NDD in children. Indeed, the analyses included 4,773 exposed children, i.e. more than 8 times more than in the Tomson et al study (which included 576 exposed children), 5 times more than in the Christensen et al study (961 exposed children) and almost 3 times more than in the Sanofi/IQVIA study (2,024 exposed children). Thanks to this large population size and the wealth of information from the SNDS, the risks of five distinct types of NDDs could be studied specifically, including some particularly infrequent ones such as intellectual developmental disorders.

Several arguments are in favour of the plausibility of the association between paternal exposure to valproate during spermatogenesis and the risk of intellectual developmental disorders in children found in the EPI-PHARE study. First, associations of the same order of magnitude have been reported in previous studies on the subject. Indeed, paternal exposure to valproate at conception was associated with a risk of intellectual developmental disorders increased - although the association did not reach statistical significance - by 60% (HR 1.6, IC95% 0.5 to 5.1) in the Swedish registry study and by 85% (HR 1.85, IC95% 0.72 to 4.76) in the Danish registry study. The increase found in the EPI-PHARE study (HR 2.12, IC95% 1.02-4.30) is consistent with these previous results in terms of magnitude, and thanks to a greater statistical power this increase appears statistically significant, unlike previous studies whose limited numbers did not make it possible to detect significant differences in incidence for an event as rare as intellectual developmental disorders. Furthermore, in the Sanofi/IQVIA study, paternal exposure to valproate at conception was associated with an increase in the overall risk of NDD of the same order of magnitude as that reported in our study (HR 1.47, IC95% 1.10 to 1.96 versus HR 1.24, IC95% 1.07 to 1.44). Second, the association between paternal exposure to valproate at conception and the risk of intellectual developmental disorders identified in the EPI-PHARE study appears to be very robust to the numerous sensitivity analyses performed. In particular, when only children whose father had received at least 3 dispensations of valproate during the period of spermatogenesis (suggesting that they were definitely exposed) are considered as exposed, the HR value is close to or even slightly higher than in the main analysis (2.36 versus 2.12). Moreover, when the analyses are adjusted on co-occurring NDDs, when the risk exposure period is restricted to the 2 months prior to conception and when the study period is extended until 2018, the HR value for

intellectual developmental disorders remains unchanged while the associations with ADHD, ASD and communication disorders risks diminish. Third, the association between paternal exposure to valproate and the risk of intellectual developmental disorders is maintained or even strengthened in analyses taking into account the diagnosis of paternal epilepsy (either by adjustment or by restriction to children of fathers with epilepsy) as well as in those excluding children of mothers with epilepsy, children with epilepsy or children with one parent with mental health disorders or NDD, suggesting that the increased risk of intellectual developmental disorders is not explained by differences in paternal or maternal morbidity or child comorbidity.

The EPI-PHARE study has some limitations. First, while mother-child linkage is available for almost all children in EPI-MÈRES, father-child linkage is available for approximately 70% of all children. Among these children with an identified father, the established associations between paternal characteristics and those of the child, for example regarding asthma, are observed as expected, suggesting the validity of chaining and the absence of major selection bias. Second, temporal trends in the use of valproate and in the incidence of NDD are likely to lead to biases that cannot be taken into account by statistical modelling. To limit these biases, the main analysis was restricted to children born between 2010 and 2015, i.e. before the sharp decline in valproate use. In addition, the comparison groups were balanced over the year of birth of the children by weightings using the propensity score, and even more accurately in sensitivity analysis, by matching on the year of birth. Third, in the absence of clinical information available in the SNDS, the characteristics of paternal epilepsy could not be taken into account in the analyses. However, the robustness of the association between paternal exposure to valproate and the risk of intellectual developmental disorders across analyses with varying comparator groups (children of fathers treated with lamotrigine or levetiracetam in the main analysis; children of fathers who discontinued valproate before spermatogenesis or of fathers with epilepsy not treated with valproate, lamotrigine or levetiracetam in complementary analyses) makes it implausible that this association is explained by a specificity of paternal epilepsy. Fourth, although a sibling analysis was considered to allow residual confounding bias to be taken into account, it could not be implemented due to too limited case numbers (only 6 cases of IDD in total among siblings including at least one child with paternal exposure to valproate and one child without). However, the e-value, which informs about the strength of the association that would be needed between an unaccounted confounding factor and both the exposure and the event of interest to cancel the observed association, is equal to 4. This suggests that for a characteristic not considered in the analyses to explain the association identified in our study between paternal exposure to valproate and the risk of IDD, it would have to be associated with both a 4-fold increase in paternal exposure to valproate and a 4-fold increase in the risk of intellectual developmental disorders. The existence of such a characteristics seems unlikely.

In conclusion, this study, the largest to date on the subject, suggests that paternal exposure to valproate during spermatogenesis is associated with an increased risk of NDD in the offspring. The results are particularly strong for intellectual developmental disorders whose risk appears to be doubled among exposed children, resulting in an additional 3.5 cases per 1000 children born to a father treated with valproate at the time of conception. This result, robust to variations in comparator group, statistical methodology, exposure definition and population considered, confirms trends reported in previously published studies. For ADHD, ASD and communication disorders, a more moderate increase in risk (around 20-25%) cannot be excluded, but these less robust results need to be further confirmed.

These results were published on the EPIPHARE and ANSM websites. We presented these findings to stakeholders (including healthcare professionals, patient associations, and victims' organization). The results were met with significant interest and positive feedback.

We believe it is essential for these data to be discussed during the PRAC deliberations.

At this stage, and in light of these elements, we support the rapporteur's proposals to maintain the current risk minimization measures. Furthermore, given the data, particularly from the EPI-PHARE study, we no longer consider the evidence to be uncertain for IDD. Uncertainty may remain for other NDDs. As such, it is necessary to update the product information and the risk minimization material to reflect this new information.

PRAC Rapporteur assessment

We appreciate the detailed input from the MS 9 colleagues regarding the publication by the EPI-PHARE group, who published a study based on the EPI-MÈRES register on November 6th, and of which an English version which was kindly shared with the Rapporteur and network on November 7th. The study used a data source covering all French pregnancies since 2010, with linkage to father and mother, and concerns the largest study evaluating this risk to date, including 4,773 offspring exposed to valproate and 3,115 offspring exposed to lamotrigine/levetiracetam with long follow-up time that was balanced across cohorts (11.9 years for VPA and 11.2 years for lamotrigine/levetiracetam, respectively). The authors report an increased risk of neurodevelopmental disorders (composite) in offspring paternally exposed to valproate in the spermatogenic risk window compared to offspring exposed to lamotrigine/levetiracetam (aHR: 1.24 [95%CI 1.07-1.44]. Higher risk estimates were observed when adjusting for paternal epilepsy (aHR 1.32 (95%CI 1.13-1.55) and in an analysis restricted to fathers with epilepsy (aHR 1.38 (95% CI 1.15-1.65). This was observed both for the composite endpoint as well as individual NDD. The results were generally consistent across various sensitivity analyses, e.g. applying additional exclusion criteria, matching on birth year, or variations in definition of exposure. Results for individual NDD subtypes were generally consistent with the main results, although with less precision and generally with lower bound of the confidence interval below one (except for the analyses restricted to epilepsy). An exception is intellectual disability for which a consistently statistically significant increased risk was observed for the valproate exposed group compared to the lamotrigine/levetiracetam exposed group.

The French study has several strengths, including the large sample size from a data source covering all pregnancies in France since 2010, with high linkage (>99%) to mother and linkage of 70% to fathers; the availability of information on various covariates, including medication use, concomitant conditions, as well as some lifestyle factors and sociodemographic characteristics; the long follow-up time that is balanced between exposure groups; and the use of a validated outcome algorithm. This study also included analyses not provided in previous studies, such as a comparison with offspring of fathers who stopped valproate prior to spermatogenesis (former users) and a comparison with offspring of fathers with epilepsy who were not treated with valproate, lamotrigine or levetiracetam. The main limitations of the study are that in most analyses including the main analysis, valproate exposure included both monotherapy and polytherapy; the lower linkage to fathers compared to the Nordic data sources; unavailability of information on epilepsy subtype or severity. In addition, there are some concerns regarding the methodology used in the propensity score model, as several factors occurring after exposure were included in the model (e.g. child characteristics such as prematurity, weight for gestational age, and hypoxia at birth) which is generally not preferred and may impact reliability of the study results. The MS 5 colleagues also noted similar limitations/uncertainties that may require further clarification and discussion (see MS 5 comments #2 above).

The MS 9 colleagues consider the risk of ID should be reflected in the PI as they consider the results of the EPI-Phare study has lifted the uncertainty regarding this risk. As also noted by the MS 5 colleagues, the results for ID are based on a limited number of events, resulting in wide confidence intervals, and attenuated risk estimates in some of the sensitivity analyses. We consider an update at this stage premature, as we consider the strengths and limitations of the study including impact of choices for study methodology (see above) should be further discussed and assessed.

Overall, we consider this new study an important new source of information regarding the potential risk of neurodevelopmental disorders in offspring paternally exposed to valproate, and believe this study requires careful discussion and assessment. We therefore propose an additional round of assessment in current procedure to allow for sufficient time for proper discussion and analyses of these new results.

MS 10 comments

MS 10 acknowledges that the risk of neurodevelopmental disorders (NDD) associated with paternal valproate exposure cannot be established based on the currently available evidence, including the data published by Christensen (2024, 2025), the confidential findings from the Meng study, and the paternal PASS dataset. However, MS 10 proposes the findings of the French Epi-PHARe study, published after the pAR was circulated, to be evaluated and included in the assessment, as they provide further relevant evidence regarding this potential risk.

PRAC Rapporteur assessment

We appreciate the MS 10 endorsement and fully agree with the proposal to further discuss the results of the French EPI-MÈRES study in the current signal procedure and therefore have proposed an additional round of assessment.

3.5. Updated rapporteur's proposed recommendation

With the availability of the results of studies by Christensen et al (2025) and Meng et al (draft), there are now two studies using similar as well as additional data sources as the paternal PASS that did not show an increased risk of NDD following paternal exposure to valproate, in contrast to the results of the paternal PASS.

Both studies are well-conducted studies that contribute to the totality of evidence regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window. These studies had the same study aim and used comparable data sources that were also used in the paternal PASS, but there are several methodological differences between the studies that could impact study results. Compared to the paternal PASS, the Christensen et al (2025) study considered a smaller number of important risk factors that may be associated with the occurrence of NDD in children. The Meng et al study is methodologically strong and addresses several limitations of the paternal PASS, but is limited by small sample size, and the analyses using an active comparator may be underpowered.

Precautionary measures for male patients have been implemented following the final results of the paternal PASS, despite limitations of the study leading to uncertainties regarding the strength of evidence. The results of Christensen et al (2025) and Meng et al add to that uncertainty, as both studies did not show the increased risk that was observed in the PASS. However, both studies also have limitations, such as small sample size or less adjustment for confounders. Therefore, the results of these studies cannot fully outweigh the results of the paternal PASS. Taking into account the evidence reviewed in current assessment round, the PRAC Rapporteur considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk. The currently available information in the PI with an advice for considering contraception in male patients using valproate and discussing potential alternative treatment options in case of a wish to father a child is considered proportional to this uncertainty, thus based on the evidence reviewed in current round (studies by Christensen et al, 2025; Meng et al) no updates to these recommendations are proposed. In addition, further evidence is expected in the (near) future from the ongoing MAH-sponsored TANGO PASS and non-clinical study program (both classified as Cat 1 PASS), as well as other sources (see section 1 in this AR).

Following circulation of the preliminary assessment report, results of another new study evaluating the risk of neurodevelopmental disorders in offspring paternally exposed to valproate in the spermatogenic risk window have been published on the ANSM website (Botton et al, 2025). This study concerns the largest study evaluating this risk to date, using data sources (French EPI-MÈRES registry) not used in the previous studies. The authors report an increased risk for neurodevelopmental disorders (composite) in offspring paternally exposed to valproate in the spermatogenic risk window compared to offspring exposed to lamotrigine/levetiracetam. The increased risk was more pronounced in analyses restricted to fathers with epilepsy, and for intellectual disability as a specific NDD subtype. The study has several strengths, such as use of a data source covering all pregnancies in France since 2010, balanced follow-up time across cohorts, analyses restricted by indication and in former users (outside of spermatogenic window to adjust for confounding by indication). But the study also has limitations, such as the use of valproate not being restricted to monotherapy, lower linkage, and potential impact of considering infant factors as covariate in the statistical model.

We consider this new study an important new source of information regarding the potential risk of neurodevelopmental disorders in offspring paternally exposed to valproate, and believe this study requires further careful discussion and assessment. We therefore propose an additional round of assessment in current procedure to allow for sufficient time for proper discussion and analyses of these new results.

The MAH is requested to provide:

- A detailed discussion of the study results of the French EPI-MÈRES study (Botton et al, 2025), including strengths and limitations of the study, a review of study methodology (e.g. inclusion/exclusion criteria, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, etc) and study results, including discussion on the complementary analyses compared to fathers who had stopped valproate before spermatogenesis or who had epilepsy not treated with valproate, lamotrigine or levetiracetam, as well as a comparison with the paternal PASS and other available studies reviewed in current procedure. This should include a discussion on the potential impact of considering paternal epilepsy as covariate in the statistical models. Any other potential reasons for the observed differences between study results should be provided and explained.
- A discussion of the recently published article by Olstad et al (2025), as well as any other new relevant literature or non-clinical data, if available.
- An overall conclusion regarding the risk of NDD following paternal exposure in view of totality of all available evidence from all sources.
- A proposal for an update of the currently included information regarding the potential risk of neurodevelopmental disorders following paternal exposure in the product information and additional risk minimisation measures on the totality of available evidence, in particular to briefly reflect on the up-to-date evidence from epidemiological studies.

A 60/60 timetable is proposed.

3.6. Adopted PRAC recommendation

Having considered the available evidence from the epidemiological studies, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of the innovator products containing valproate and related substances (Sanofi) should submit by 11/03/2026 responses to the below List of Questions (LoQ).

List of Questions to MAH:

1. A detailed discussion of the study results of the French EPI-MÈRES study (Botton et al, 2025), including strengths and limitations of the study, a review of study methodology (e.g. inclusion/exclusion criteria, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, etc) and study results, including discussion on the complementary analyses compared to fathers who had stopped valproate before spermatogenesis or who had epilepsy not treated with valproate, lamotrigine or levetiracetam, as well as a comparison with the paternal PASS and other available studies reviewed in current procedure. This should include a discussion on the potential impact of considering paternal epilepsy as covariate in the statistical models. Any other potential reasons for the observed differences between study results should be provided and explained.

2. A discussion of the recently published article by Olstad et al (2025), as well as any other new relevant literature or non-clinical data, if available.

3. An overall conclusion regarding the risk of NDD following paternal exposure in view of totality of all available evidence from all sources.

4. A proposal for an update of the currently included information regarding the potential risk of neurodevelopmental disorders following paternal exposure in the product information and additional risk minimisation measures on the totality of available evidence, in particular to briefly reflect on the up-to-date evidence from epidemiological studies.

Additionally, as there are recent results of another new study evaluating the risk of neurodevelopmental disorders in offspring paternally exposed to valproate in the spermatogenic risk window which have been published on the ANSM website (Botton et al, 2025), PRAC is requesting the study authors for some clarifications as well. These responses to the below LOQs are awaited by the 11/03/2026.

List of Questions to the study authors from Botton et al, 2025:

1. The authors are kindly requested to provide a re-run of the main analysis for NDD composite and NDD subtypes, the complementary analyses in former users or fathers with untreated epilepsy, as well as relevant sensitivity analyses with valproate monotherapy (e.g. analyses restricted to fathers with epilepsy indication). In the analysis of monotherapy, it is important to adjust also for paternal epilepsy.

2. It would be preferred to only include covariates prior to exposure in the propensity score model. In case infant neonatal characteristics such as prematurity, weight for gestational age, hypoxia at birth were included in the propensity score; the authors are requested to rerun the model without these factors.

3. Regarding intellectual disability, the authors are kindly requested to comment on the low precision of the risk estimates for NDD, particularly the low number of events the analyses regarding NDD are based on, the main analyses being for valproate combination therapy, and not adjusting for paternal epilepsy in analyses for valproate monotherapy.

4. The study mostly used robust standard errors to calculate confidence intervals following propensity score weighting. One sensitivity analysis (matching on birth year) involved bootstrapping. Other analyses, including the sensitivity analysis of association of combination therapy with IDD with adjustment for paternal epilepsy (where lower bound of 95% CI is 1.01), used robust standard errors. Considering the margins by which some findings such as this reach significance, literature suggesting that robust standard errors may not be valid and that other methods may be preferable in this setting is noted (Reifeis & Hudgens 2022)[1]. We kindly request the authors to consider a sensitivity analyses of the primary analysis (valproate monotherapy versus lamotrigine/levetiracetam) using bootstrap methods.

5. It is not fully clear whether the rate differences and their 95% confidence intervals were calculated by applying the weighted hazard ratios to the incidence rates of NDD in the comparator cohorts before or after weighting these cohorts. The authors are requested to explain how the rate differences and 95% confidence intervals were calculated.

The PRAC will assess the further data within a 90-day timetable.

3.7. Comments from MAH

On 16 December 2025, the MAH Sanofi sent a letter to EMA to request for clarifications on the EPI-PHARE study (Botton et al, 2025).

The MAH had noted that PRAC raised a list of questions of the study authors to be answered by 11 March 2026. Results from these new requested analyses will constitute additional data.

To address PRAC's request to provide by 11 March 2026 "*an overall conclusion regarding the risk of NDD following paternal exposure in view of the totality of all available evidence from all sources",* the MAH would appreciate access to the below-mentioned data in order to deliver a comprehensive assessment based on the full body of scientific evidence to date. The MAH therefore asks PRAC to share, at the earliest convenience:

- The manuscript of the Norway and Taiwan study (Meng et al)
- The response that will be provided by Botton et al (2025) to the PRAC (together with the updated report when available).

The MAH commits to treat these data as confidential information (as previously done for the Christensen et al (2024) manuscript in the frame of the PASS Paternal procotol – *[number redacted]*.

Based on results of the French EPI-PHARE study (Botton et al, 2025), several methodological choices and sensitivity results raise questions. Sanofi identified areas where clarifications and additional analyses could materially strengthen interpretation and alignment with the broader evidence base, as listed below:

1. Re-run primary analyses restricted to valproate monotherapy Could HRs for composite NDD and each subtype (including IDD) be re-estimated restricting exposure to valproate monotherapy only and comparators to lamotrigine/levetiracetam monotherapy, with explicit adjustment for paternal epilepsy?

2. Clarification about Group size changes in Lamotrigine/Levetiracetam during "valpromide/divalproate" sensitivity Could it be clarified why comparator counts change (e.g., 310/3115 to 320/3165) when valpromide/divalproate are added to exposure definition. Could it also be confirmed that comparator definition remained constant and rule out reclassification leakage. (Table S3 rows "Inclusion of valpromide and divalproic acid.")

3. Re-run primary analyses restricted to valproate monotherapy Could HRs for composite NDD and each subtype (including IDD) be re-estimated restricting exposure to valproate monotherapy only and comparators to lamotrigine/levetiracetam monotherapy, with explicit adjustment for paternal epilepsy?

4. Separate and report polytherapy only analyses Could full results for polytherapy only exposure (valproate + other ASMs) vs polytherapy comparators (lamotrigine/levetiracetam + other ASMs except valproate) be provided, and contribution of polytherapy to overall signals be quantified, as polytherapy can be a proxy of disease severity?

5. Dose response and treatment intensity Could cumulative valproate dose, average daily dose, and number of dispensations in the 90–120 days preconception; categorize doses (e.g., <500 mg/day,

500–1000, >1000) be examined (and considered) in the NDD composite and per subtypes analyses, especially when comparing VPA preconception exposure in monotherapy vs exposure to Lamo/leve monotherapy?

6. Comparator refinement: split "epilepsy not treated with VPA/LTG/LEV" Could the analyses (provide separate HRs) be re-run splitting the comparator into: (a) Untreated epilepsy (no ASM in spermatogenesis), and (b) Epilepsy treated with other ASMs (carbamazepine, oxcarbazepine, topiramate, phenobarbital, etc.)?

7. Alternative confounding control: PS matching with calipers Could SMR weighting be complemented with propensity score matching (e.g. nearest neighbor; caliper = 0.2 SD of logitPS), for composite NDD and IDD?

8. Sibling analysis—composite NDD (and descriptive for IDD) Could sibling fixed effects analyses be conducted for composite NDD; for IDD, it is stated in the report that power was insufficient, but descriptive distribution is of interest and could be provided even if underpowered.

9. Considering parental neuropsychiatric history & family-history (ICD-10 code Z81) Could IDD and composite NDD models be re-run adjusting for parental NDD diagnoses (ASD, ADHD, IDD) and family-history codes Z81 (mental/behavioural disorders), separately and jointly; provide sensitivity analyses excluding families with such history.

10. Considering Paternal lifestyle/substance characteristics Could paternal factors potentially affecting sperm quality, e.g. paternal alcohol/drugs, and smoking, be considered as done for the mother's same characteristics.

11. Perinatal hypoxia/asphyxia as covariate As asphyxia/hypoxia/ischemia/encephalopathy are known major risk factors for IDD and their incidence in the study population seems higher than the one expected from the literature, could more detailed results on these variables (e.g. 2x2 tables with the events) be provided along with analyses adjusted for these covariates?

12. Birth cohort stratification to address diagnostic trends Could the analyses be stratified by year of birth cohorts (2010–11; 2012–13; 2014–15) and HRs per cohort be presented?

13. "Pure" IDD analysis (no co-occurring NDDs) Could an analysis restricted to IDD without ASD/ADHD/communication/learning disorders be performed to test specificity?

Rare event modeling for IDD Could IDD risk be re-estimated using Firth's penalized likelihood and Poisson models?

15. Re-calculate Evalues under more appropriate contrasts Could Evalues be provided for monotherapy only and epilepsy restricted contrasts?

PRAC Rapporteur assessment

After circulation of the updated assessment report in December 2025, the MAH Sanofi contacted EMA with 1) a request to gain confidential access to the manuscript of the Norway and Taiwan study (Meng et al), 2) to receive the response that will be provided by Botton et al (2025) to the PRAC LoQ as detailed in the UAR (see section 3.6 above) together with the updated report when available, 3) a proposal for further clarifications and additional analyses to be forwarded to study authors that could strengthen interpretation and alignment with broader evidence available.

Access to the Meng et al manuscript and responses by Botton et al would be welcomed by the MAH to be used in their overall discussion regarding risk of NDD following paternal exposure in view of totality

of available evidence from all sources (as included in updated PRAC Rapporteur recommendation to MAH, section 3.6).

Ad 1)

The manuscript by Meng et al is expected to be published soon and will then be available in the public domain. If the study is not published soon, EMA can inquire about the possibility of establishing a confidentiality agreement with the MAH.

Ad 2)

The responses by Botton et al to the PRAC LoQ are expected to be submitted by 11 March 2026, which is the same date the responses of the MAH are currently expected. In case responses or an updated manuscript by Botton et al will be made available to PRAC sooner, the possibility of providing the MAH access to these data may be considered, provided a confidentiality agreement will be signed.

Ad 3)

The proposed clarifications and requests for additional analyses have been considered by the PRAC Rapporteur, and it is acknowledged that several questions may provide relevant additional clarification and interpretation of study results. The PRAC Rapporteur considered the following:

Regarding Q1 and Q3, analyses restricted to monotherapy, and with adjustment for paternal epilepsy have already been covered by the PRAC LoQ to the study authors. Regarding Q2 and Q4, the clarifications regarding group size changes in the lamotrigine/levetiracetam arm and polytherapy results are understood; however, as the PRAC considers the analyses in VPA monotherapy (requested to be provided by PRAC) most relevant for the interpretation of study results, as it is expected that there may still be differences in severity of disease in patients taking polytherapy with or without valproate, it is proposed to not further pursue this question. Regarding Q9, paternal mental health disorders and NDD were adjusted for in the analyses in the EPI-MERES study and a separate analysis excluding offspring with paternal mental/behavioural disorders has been provided. In paternal PASS, paternal NDD was an exclusion criterion; however, for TANGO, paternal NDD will not be an exclusion criterion but will be adjusted for in the analyses to enhance power. Therefore, this question is not further pursued. Regarding Q12, it is noted that due to the restricted inclusion in the period 2019-2015, follow-up time in the EPI-MERES study is comparable in the valproate and lamotrigine/levetiracetam group (median follow-up time [IQR] 11.9 years [10.3-13.3] and 11.2 years [9.9-12.8], respectively). This in contrast to paternal PASS, in which follow-up time was different between valproate and comparator arm. Considering the restricted inclusion period (2005-2010) applied in the EPI-MERES study and balanced follow-up time observed, we currently do not consider it necessary to pursue this issue. Regarding Q11, it is noted that analyses in the EPI-MERES registry were adjusted for infant characteristics including perinatal hypoxia/asphyxia. A request for a 2x2 table can be forwarded to the study authors. Regarding Q13, 'pure IDD analysis', it is acknowledged that co-occurring NDDs were common in the IDD subtype group. However, as the number of events in the IDD analyses is already limited, resulting in imprecision in risk estimates, and co-occurrence of NDD was reported in 60% of IDD cases, a restricted analysis to IDD is unlikely to be sufficiently powered to draw conclusions. In addition, as NDD co-morbidity is high in ID, the clinical relevance of analyzing IDD only is considered limited. Therefore, this issue is not further pursued.

The remaining questions will be forwarded to the study authors for consideration.

3.8. Updated Rapporteur's proposed recommendation

Having considered the available evidence from the epidemiological studies, the PRAC has agreed that the Marketing Authorisation Holder (MAH) of the innovator products containing valproate and related substances (Sanofi) should submit by 11/03/2026 responses to the below List of Questions (LoQ).

List of Questions to MAH:

1. A detailed discussion of the study results of the French EPI-MÈRES study (Botton et al, 2025), including strengths and limitations of the study, a review of study methodology (e.g. inclusion/exclusion criteria, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, etc) and study results, including discussion on the complementary analyses compared to fathers who had stopped valproate before spermatogenesis or who had epilepsy not treated with valproate, lamotrigine or levetiracetam, as well as a comparison with the paternal PASS and other available studies reviewed in current procedure. This should include a discussion on the potential impact of considering paternal epilepsy as covariate in the statistical models. Any other potential reasons for the observed differences between study results should be provided and explained.

2. A discussion of the recently published article by Olstad et al (2025), as well as any other new relevant literature or non-clinical data, if available.

3. An overall conclusion regarding the risk of NDD following paternal exposure in view of totality of all available evidence from all sources.

4. A proposal for an update of the currently included information regarding the potential risk of neurodevelopmental disorders following paternal exposure in the product information and additional risk minimisation measures on the totality of available evidence, in particular to briefly reflect on the up-to-date evidence from epidemiological studies.

Additionally, as there are recent results of another new study evaluating the risk of neurodevelopmental disorders in offspring paternally exposed to valproate in the spermatogenic risk window which have been published on the ANSM website (Botton et al, 2025), PRAC is requesting the study authors for some clarifications as well. On 16 December 2025, the MAH Sanofi sent a letter to EMA to request for clarifications on the EPI-PHARE study. The clarifications and requests for additional analyses proposed by the MAH have been considered by the PRAC Rapporteur, and it is acknowledged that several questions may provide relevant additional clarification and interpretation of study results. The LOQ to the study authors has been updated accordingly.

These responses to the below LOQs are awaited by the 11/03/2026.

List of Questions to the study authors from Botton et al, 2025:

1. The authors are kindly requested to provide a re-run of the main analysis for NDD composite and NDD subtypes, the complementary analyses in former users or fathers with untreated epilepsy, as well as relevant sensitivity analyses with valproate monotherapy (e.g. analyses restricted to fathers with epilepsy indication). In the analysis of monotherapy, it is important to adjust also for paternal epilepsy.

2. It would be preferred to only include covariates prior to exposure in the propensity score model. In case infant neonatal characteristics such as prematurity, weight for gestational age, hypoxia at birth were included in the propensity score; the authors are requested to rerun the model without these factors.

3. Regarding intellectual disability, the authors are kindly requested to comment on the low precision of the risk estimates for NDD, particularly the low number of events the analyses regarding NDD are based

on, the main analyses being for valproate combination therapy, and not adjusting for paternal epilepsy in analyses for valproate monotherapy.

4. The study mostly used robust standard errors to calculate confidence intervals following propensity score weighting. One sensitivity analysis (matching on birth year) involved bootstrapping. Other analyses, including the sensitivity analysis of association of combination therapy with IDD with adjustment for paternal epilepsy (where lower bound of 95% CI is 1.01), used robust standard errors. Considering the margins by which some findings such as this reach significance, literature suggesting that robust standard errors may not be valid and that other methods may be preferable in this setting is noted (Reifeis & Hudgens 2022)[1]. We kindly request the authors to consider a sensitivity analyses of the primary analysis (valproate monotherapy versus lamotrigine/levetiracetam) using bootstrap methods.

5. It is not fully clear whether the rate differences and their 95% confidence intervals were calculated by applying the weighted hazard ratios to the incidence rates of NDD in the comparator cohorts before or after weighting these cohorts. The authors are requested to explain how the rate differences and 95% confidence intervals were calculated.

6. Could cumulative valproate dose, average daily dose, and number of dispensations in the 90–120 days preconception; categorize doses (e.g., <500 mg/day, 500–1000, >1000) be examined (and considered) in the NDD composite and per subtypes analyses, especially when comparing VPA preconception exposure in monotherapy vs exposure to lamotrigine/levetiracetam monotherapy?

7. In the comparison with 'epilepsy not treated with VPA/LTG/LEV' patients with untreated epilepsy (no ASM in spermatogenesis) are grouped with epilepsy treated with other ASMs (e.g. carbamazepine, oxcarbazepine, topiramate, etc), which may be populations with different disease severity. Could the authors provide separate HRs for comparison with 1) untreated epilepsy, and 2) epilepsy treated with other ASMs?

8. Could SMR weighting be complemented with propensity score matching (e.g. nearest neighbor; caliper =0.2 SD of logitPS) for composite and IDD? We also kindly request the authors to describe how influential subjects/extreme scores were handled in the PS model.

9. The authors are requested to consider whether paternal factors affecting sperm quality (e.g. paternal alcohol/drugs, smoking) can be considered in the analyses as done for these characteristics in mothers.

10. The incidences of asphyxia/hypoxia seem higher than expected from literature. Could the authors provide more detailed results on these variables (2x2 table with events).

11. The authors are requested to consider rare event modeling for IDD (re-estimation of IDD risk using Firth's penalized likelihood and Poisson models), considering the low number of events observed.

12. Considering the request for a re-run of the main analyses with monotherapy only, the authors are kindly requested whether the E-values will also be provided for monotherapy only and epilepsy restricted contrast?

The PRAC will assess the further data within a 90-day timetable.

4. Second round of Additional evidence

4.1. Assessment of additional data

4.1.1. Response of study authors from Botton et al 2025

The authors of the Botton et al (2025) study provided the following response, as well as a response to each question proposed by PRAC, see below.

Jérémie Botton, Paula Rios, Jérôme Drouin, Sara Miranda, Mahmoud Zureik, Alain Weill, Rosemary Dray-Spira. Paternal exposure to valproate during spermatogenesis and risk of neurodevelopmental disorders in children - National study based on the French EPI-MÈRES Register.

4.1.2. MAH response to second request for supplementary information

Question 1

A detailed discussion of the study results of the French EPI-MÈRES study (Botton et al, 2025), including strengths and limitations of the study, a review of study methodology (e.g. inclusion/exclusion criteria, outcome definitions used, type of analyses applied and considerations of confounders and risk factors, etc.) and study results, including discussion on the complementary analyses compared to fathers who had stopped valproate before spermatogenesis or who had epilepsy not treated with valproate, lamotrigine or levetiracetam, as well as a comparison with the paternal PASS and other available studies reviewed in current procedure. This should include a discussion on the potential impact of considering paternal epilepsy as covariate in the statistical models. Any other potential reasons for the observed differences between study results should be provided and explained.

MAH response

Please find below a discussion of the EPI-PHARE study in view of all other available evidence with regards to NDD and paternal valproate exposure.

Several studies were performed to assess the association between paternal exposure to valproate during spermatogenesis and risk of neurodevelopmental-disorder (NDD) in children: Christensen 2024 and 2025, PASS Paternal (EUPAS34201 - conducted by Consortium of MAHs – referred in this response document as "PASS Paternal" published in 2025 by Colas et al), EPI-PHARE study conducted by Botton et al, a study conducted in Norway and Taiwan by Meng et al. (2026; EUPAS1000000417) and a study conducted in Sweden and Norway by Razaz et al (2026).

All these studies were not conducted with the same methodology and therefore the comparison of the findings is limited.

The PASS Paternal study reported a potential increased risk of NDD in offspring of father exposed to valproate monotherapy during the spermatogenic window compared with offspring of fathers exposed to lamotrigine or levetiracetam monotherapy in the same window, and the EPI-PHARE study available on EPI-PHARE website, reported an increased risk of NDD in offspring of father exposed to valproate when including polytherapy and monotherapy, but the result became non-significant in monotherapy.

Other studies, which were peer reviewed, assessed the question of valproate monotherapy (Christensen et al. 2024 and 2025, Meng et al. 2026, Razaz et al. 2026) and found no higher risk of

NDD in the offspring associated with paternal exposure to valproate during the spermatogenesis (these studies are further discussed in answers to question 2 (Razaz et al. and Meng et al.) and question 3 (Christensen et al. 2025, Razaz et al. and Meng et al.)

In addition, Sanofi would like to note that EPI-PHARE's response shared on 13 March 2026 cannot be incorporated into the general discussion. Consequently, only the results presented in EPI-PHARE's report dated 07 November 2025 are considered here.

Indeed, the information provided in response to the PRAC questions is incomplete and cannot be interpreted without the full contextual framework. This new information provided by EPI-PHARE notably lacks essential methodological details, including the exposure derivation approach, crude incidence rates, hazard ratios, and sample sizes for individual NDD subtypes.

Given the gaps and inconsistencies in the information provided, these elements cannot be regarded as relevant or conclusive evidence. An analysis of these elements is presented at the end of answer to Question 1.

PASS Paternal

The PASS Paternal (using Nordic registries: Denmark, Norway, Sweden) primary objective was to investigate the risk of NDD (composite, any subtype), including ASD, in offspring of father exposed to valproate (monotherapy), compared to lamotrigine/ levetiracetam (composite monotherapy) treatment at the time of conception. It reports a pooled PS-weighted HR for composite NDD of 1.50 (95%CI 1.09-2.07). Sensitivity analyses confirmed this main finding. In terms of NDD subtypes analyses, only ASD subtype was analyzed, but results were inconclusive, due to major limitations.

EPI-PHARE study

EPI-PHARE (France, SNDS/EPI-MERES) main objective was to measure the association between fathers' exposure to valproate in monotherapy or polytherapy during the spermatogenic window and the risks of NDDs (overall and by subtype) in the children, compared to lamotrigine/levetiracetam in monotherapy or polytherapy during the same window.

<u>Main analyses</u>

- It reports an SMR-weighted Cox HR of 1.24 (95%CI 1.07-1.44) for NDD overall and of 2.12 (95%CI 1.05-4.30) larger effect for intellectual development disorders (IDD);
- For all other studied NDD subtypes no higher risk was found:
    - SMR weighted HR (wHR) for attention deficit disorders with or without hyperactivity weighted of 1.24 [0.92-1.65];
    - wHR for autism spectrum disorders of 1.24 [0.82-1.87];
    - wHR for communication disorders of 1.23 [1.00-1.52];
    - wHR for learning disorders of 1.08 [0.83-1.41]. (EPI-PHARE report Table 3).

<u>Sub analyses</u>

These main results remain stable across most sensitivity analyses, except:

- those considering paternal epilepsy, suggesting residual confounding by epilepsy wHR 1.32 (95%CI 1.13-1.55) and
- when limiting to monotherapy exposure, where all HRs become non-significant:
    - wHR 1.17 (95%CI 0.98-1.40) for main analysis
    - and wHR 2.07 (95%CI 0.78-5.53) for IDD (EPI-PHARE report Table S3).

Complementary analyses were also performed with comparators different from lamotrigine/levetiracetam: children of valproate exposed fathers were compared 1) *to children of fathers who had stopped valproate before spermatogenesis*, and 2) to children of *fathers with epilepsy not treated by valproate/lamotrigine/levetiracetam*.

- The complementary analyses of children of fathers "exposed during spermatogenesis" vs "having stopped valproate before spermatogenesis" probe whether timing during spermatogenesis per se matters versus background characteristics of valproate users.
    - The overall NDD wHR of 1.11 (0.91-1.34) is null and did not confirm the spermatogenesis-timing effect.
    - For IDD, the two-fold point estimate remains elevated but non-significant in both main analysis (HR 2.32, 95%CI 0.94- 5.76) (mono+polytherapy exposure) and the monotherapy-restricted sensitivity analysis (HR 2.46, 95%CI 0.86-7.05) (EPI-PHARE report Table S7).

Thus, fathers' exposure timing (during spermatogenesis vs before spermatogenesis) alone is not established for composite NDD, and evidence for IDD exposure timing remains uncertain.

- The "father with epilepsy not treated by valproate/lamotrigine/levetiracetam" comparator assesses valproate specificity.
- Overall NDD HR is near to the null (HR 1.06, 95%CI 0.94-1.20);
- IDD remains around 2-fold and statistically significant in the main analysis (HR 2.10, 95%CI 1.17-3.76), but non-significant in monotherapy-restricted analysis (HR 1.81, 95%CI 0.96-3.43) (EPI-PHARE report Table S8).

This pattern is compatible with some valproate-specific signal for IDD, yet sensitive to exposure refinement and limited by very low counts (42 events, among the 4773 children in the valproate exposed group).

These complementary analyses showed that HRs were close to the null for overall NDD, whereas for IDD the two-fold increased risk remained, albeit with imprecision in some subgroups.

Taken together, the increased risk for overall NDD and all subtypes (except IDD) is small (HR <1.3) and appears to be model-sensitive whereas for IDD the risk is high (HR >2) and more consistent across analyses, albeit with imprecision in some subgroups. IDD remains very infrequent (42 exposed cases in the main analyses), a very low incidence rate, the lowest incidence rate of all the studied NDD subtypes (0.7 [0.5; 1.0] and 0.3 [0.1; 0.5] per 1,000 births in the valproate exposed group and lamotrigine or levetiracetam groups respectively), and the absolute effect is very small: estimated 3.5 extra IDD cases per 1,000 births) despite the 2-fold relative increase (EPI-PHARE Report, Table 3).

Nevertheless, the methods used differ between EPI-PHARE and PASS Paternal studies (cf. Table 1, in appendix of this response document), making the structure and the magnitude of the association not directly comparable.

The most salient methodological difference is the exposure considered in the main analyses in each study: the PASS Paternal restricts to monotherapy, whereas EPI-PHARE's primary analyses include monotherapy or polytherapy. In EPI-PHARE, restricting to monotherapy attenuated HRs across all outcomes (non-significant), including for IDD.

Still, this pattern is consistent with residual confounding by indication/severity: polytherapy is a proxy for more severe or refractory epilepsy (and possibly for genetic epilepsies), patient complexity, and co-treatment-factors associated with neurodevelopmental risk independent of any sperm-mediated effect of valproate.

Although EPI-PHARE used Propensity Score (PS) weighting and numerous sensitivity analyses, unmeasured dimensions of epilepsy type (e.g., idiopathic generalized), seizure burden, or genetic architecture are not captured in administrative data, and could inflate risk estimates in mixed-exposure cohorts. Thus, monotherapy analyses, better controlling for the above listed factors, are more appropriate to assess the potential drug effect; attenuation of all incidences and HRs in the monotherapy restricted analyses requires caution in attributing the primary mixed-exposure HRs solely to valproate's paternal effect.

Strengths and limitations

In both PASS Paternal and EPI-PHARE studies, strengths include population-based coverage, active comparators, long follow-up, and extensive sensitivity analyses.

Main limitations shared across studies are dependence on administrative coding for NDDs ascertainment, inability to capture epilepsy type/severity, dose and adherence, and familial/genetic and socioeconomic factors not fully measurable in claims data or prescriptions registries.

The PASS Paternal additionally confronts between-country heterogeneity and differential follow-up; EPI-PHARE's mixed-exposure primary analysis likely over-represents more severe epilepsy via polytherapy, with large attenuation in monotherapy pointing to residual confounding.

Overall discussion

The first part of this discussion is applicable to all results; second part is further addressing the two main outcomes: 1) All NDD and 2) Intellectual Development Disorders.

The most important analysis to consider is the one restricted to monotherapy, which shows consistent non-significant adjusted HRs for all outcomes and across all comparator groups, without exception. This loss of signal in monotherapy exposure does not support a direct effect of the medication. Additionally, results in polytherapy only are not provided unfortunately, this would have added insight to measure its relationship with the risk. Further to that, when looking at the second noticeable sensitivity analysis, restricting to fathers with epilepsy, it can be observed that the HRs increase across

all outcomes and all comparator groups, again supporting the possible role of underlying disease in the observed association.

Overall, it might imply that either the polytherapy, the severity of the underlying condition or both are driving at least part of the estimated risk.

All NDD

As a first point regarding additional comparisons, a pattern emerges when examining the results for children of epileptic fathers not treated with valproate/lamotrigine/levetiracetam. This group consistently demonstrates higher NDD incidence rates compared to children whose fathers were exposed to lamotrigine/levetiracetam, a pattern that remains consistent across both main and sensitivity analyses. This observation suggests that epilepsy itself (when not treated with valproate, lamotrigine or levetiracetam) may predispose fathers to having children with NDD. While no direct statistical comparison (aHR) is available between these two groups, the consistently higher incidence rates are noteworthy. More importantly, the direct comparison between children of valproate-exposed fathers and children of fathers with epilepsy not treated with valproate/lamotrigine/levetiracetam reveals an aHR for all NDD near the null threshold with narrow confidence interval (1.06, 95% CI 0.94-1.20), suggesting equivalent risk between these groups. Collectively, these findings indicate that both children of valproate-exposed fathers and children of fathers with epilepsy not treated with valproate/lamotrigine/levetiracetam carry higher NDD risk compared to children of fathers exposed to lamotrigine/levetiracetam alone. These findings suggest that the NDD risk observed in children of valproate-exposed fathers might not be associated with valproate, as a similar higher risk is also present in children of fathers with epilepsy not treated with valproate, lamotrigine, or levetiracetam. This suggests that NDD risk may be associated with a shared factor between these two groups (such as the underlying epilepsy type or severity), rather than being attributable to valproate exposure during spermatogenesis, as concluded in the EPI-PHARE report.

Secondly, another point to consider when investigating a possible effect of valproate, one should put it into perspective with biological plausibility. The foundation for paternal transmission of drug-related risks relies on the potential impact of the medication on spermatozoa, notably through genetic or epigenetic modifications occurring during spermatogenesis. Consequently, the biologically relevant exposure window for investigating paternal drug effects is the period of spermatogenesis (≈ 3 months before child conception date). In that regard, the comparator group "*fathers who discontinued valproate before spermatogenesis*" provides insightful data. Especially, given that 93% of these fathers received no antiepileptic medication, making them unexposed to any ASM during spermatogenesis. The incidence rates in children of fathers who discontinued valproate before spermatogenesis are consistently higher than in children of fathers exposed to lamotrigine/levetiracetam. As for children of fathers with epilepsy not treated with valproate/lamotrigine/levetiracetam, this pattern holds true in both the main and all sensitivity analyses. This observation shows that elevated incidence rates are not limited to the children of valproate-exposed fathers, but also to children of fathers who discontinued the medication before the biologically relevant exposure window, suggesting that factors other than valproate exposure during spermatogenesis may contribute to the observed associations. Further into that, the direct comparison between children of fathers exposed to valproate during spermatogenesis *versus* children of fathers who discontinued valproate before spermatogenesis shows a non-significant all NDD HR with narrow 95% CI of 1.11 (0.91-1.34), based on a large number of events (583/4773 in exposed vs 164/1372 in the discontinuers comparator group), consistent with an absence of risk difference. Taking into account the biological basis of paternal transmission through spermatogenesis,

this observation suggests that the underlying condition requiring valproate treatment drives all or part of the NDD risk. Therefore, these findings most likely imply that the observed association in the main analysis (versus Lamotrigine/levetiracetam) primarily reflect confounding by the underlying condition rather than a causal effect of valproate exposure during spermatogenesis.

In summary, while the main analysis comparing children of fathers exposed to valproate with children of fathers exposed to lamotrigine/levetiracetam suggests a higher risk of "all NDDs" in the children of valproate-exposed fathers, the aforementioned observations reveal that this increased risk becomes non-significant in monotherapy, is independent of valproate exposure during spermatogenesis and is also present in children of fathers with epilepsy not treated with valproate, lamotrigine, or levetiracetam. Collectively, these above findings raise questions about unmeasured confounding factors, particularly the underlying pathology or disease severity, that may account for a substantial portion of the observed risk.

IDD

"Intellectual developmental disorders" is the second main outcome discussed by the authors in the report and for which they conclude that "*Several arguments support the plausibility of this association between paternal exposure to valproate during spermatogenesis and the risk of TDI in children".*

Although the results point out to a possible association, several observations also suggest residual confounding despite the apparent persistence of significance in certain comparator groups.

Firstly, unlike the analysis made on "all NDD", this significance seems to rely on a very small number of cases (42 cases vs 11 cases vs 11 vs 7, among respectively the children of fathers exposed to i) valproate during spermatogenesis, ii) lamotrigine/levetiracetam during spermatogenesis, iii) to valproate pre-spermatogenesis and lastly children of fathers with epilepsy not treated with valproate/lamotrigine/levetiracetam), with consistently wide confidence intervals often bordering the significance threshold, making the results very sensitive to a few additional or missing cases.

Secondly, as highlighted by the authors, a "*decline in IDD diagnoses over time*" was observed in France. This point is important to consider given that "*exposed children were more often born between 2010 and 2012 (51.7% versus 40.6%)*". This temporal distribution implies that by virtue of their birth period, children of father exposed to valproate, inherently had a higher probability of being detected with having an IDD compared to children of fathers exposed to lamotrigine/levetiracetam. This consideration becomes particularly important given the overall low number of events observed, with each event carrying considerable statistical weight that is difficult to account for in the analysis. This finding must be taken into account when interpreting IDD data, as acknowledged by the authors: "*such temporal changes are likely to cause biases that cannot be taken into account by statistical modelling*".

Thirdly, as for all NDDs, the analysis restricted to monotherapy shows consistent decrease of the risk, with a marked widening of the confidence interval and adjusted HRs becoming non-significant for all comparator groups (e.g. against lamotrigine/levetiracetam, aHR changing from 2.12 [1.05-4.30] to 2.07 [0.78-5.53]). This instability seems difficult to reconcile with a direct effect of valproate, which should theoretically be more pronounced in monotherapy group.

Importantly, the pattern observed for IDDs is inconsistent with the findings for all NDDs: while all NDD types lose significance in monotherapy and show no association with exposure timing during spermatogenesis, IDDs appear to maintain borderline significance in some comparisons. When restricting to fathers with identified epilepsy, the IDD results show widening confidence intervals and reduced precision, yet maintain nominal significance in some comparators, contrasting with the non-significant results for all NDDs under the same restriction. This divergence is paradoxical: if the underlying epilepsy contributes substantially to NDD risk (as suggested by the "all NDD" analyses), it can be expected that this confounding affects all neurodevelopmental outcomes, similarly, rather than selectively preserve an association for IDDs alone. When looking at it from a biological perspective, it is difficult to explain how an epigenetic mechanism would specifically affect intellectual development but not significantly impact other aspects of neurodevelopment, especially ASD which is often associated with IDD. Particularly, the analysis comparing children of fathers exposed to valproate to children of fathers who discontinued valproate before spermatogenesis shows no difference in "all NDD" risk (HR 1.11 [0.91-1.34]). This specificity is more consistent with detection bias or confounding by indication than an association as concluded in the EPI-PHARE report.

Overall, a key observation for the interpretation of the data, is also the lack of consistency in the risk estimates for all NDDs and for IDDs, especially in the children of fathers unexposed during spermatogenesis. This apparent difference between the results for IDD and other NDDs could be explained by a combination of statistical chance related to the small number of cases, differential detection bias, and potentially confounding factors more strongly associated with IDDs than with other types of neurodevelopmental disorders. In that regard, a recent Norwegian study by Willoch Olstad et al. (2025) corroborates the possible presence of residual confounding, putting into perspective the interpretation of pharmaco-epidemiological data (see answer to Question 2).

Conclusion

Overall, the conclusion in the EPI-PHARE study report available on their website is not supported by the estimates produced in the different analyses. Indeed, several results from the EPI-PHARE study report might indicate the presence of substantial residual confounding, which limits the ability to conclude on an isolated effect of valproate on the risk of NDD or IDD. Furthermore, beyond these methodological concerns, the pattern of findings — including the instability of results, the loss of statistical significance in monotherapy analyses, and the absence of risk difference of NDD between children of fathers exposed to valproate during spermatogenesis versus i) those of fathers exposed to valproate before spermatogenesis, and ii) those of fathers with epilepsy not treated with valproate or lamotrigine/levetiracetam — collectively suggest that reported risks may be attributable to other factors, such as underlying disease characteristics.

	EPI-PHARE	PASS Paternal	Comments / Implications
1. Design	Nationwide French cohort using SNDS	Multinational registry-based cohort (Denmark-DK, Norway-NO, Sweden-SE)	Multi-country vs France (FR) only, but higher statistical power in FR because larger population
2. Population **Inclusion criteria (I)** **Exclusion criteria (E)**	I: Live-born **singletons** (2010–2015) with identified parents E: Assisted reproduction, maternal teratogenic exposure, major brain malformations, uncertain paternal exposure Study population (main analyses) Valproate 4773 ; lamotrigine/levetiracetam 3115	I: Live-born **singletons** (DK: 1997-2018, NO: 2010-2019, SE: 2007-2019), linked to both parents E; Adopted children, Pregnancy associated with in vitro fertilization, Maternal ASM exposure, offspring epilepsy or post-natal exposure to ASM, prior teratogenic drugs Study population (main analyses) Valproate lamotrigine/levetiracetam Denmark: 793 1157 Norway: 617 1326 Sweden: 930 1425	Methods quite aligned, mostly with Norway (especially regarding the study dates)
3. Exposure **Exposure Window** **Exposure of interest** **Comparator**	4 months pre-conception (covers spermatogenesis) Valproate **mono or polytherapy** Lamotrigine or levetiracetam **monotherapy or polytherapy**	3 months pre-LMP2 (spermatogenesis) Valproate **monotherapy only** Lamotrigine or levetiracetam **monotherapy only**	**Major difference:** **- EPI-PHARE main analyses (and complementary with comparators groups different from lamotrigine/levetiracetam) monotherapy or polytherapy,** which reflects real-world practice but may introduce **confounding by severity**. Sensitivity analyses, with monotherapy only address this. - PASS Paternal: **monotherapy only**, reduces confounding by other therapies, but may limit generalizability
4. Exposure Ascertainment	Defines exposure as ≥1 dispensation in 4 months pre-conception. Sensitivity analyses: ≥3 dispensations, 2-month window, monotherapy only, +valpromide/divalproate.	Defines exposure as ≥1 Dispensation within 4 months pre-LMP2; Sensitivity: within 6 months within LMP2	**Methods mostly similar** EPI-PHARE's flexible definitions reduce misclassification risk
5. Follow-up	Median F-up (until Sept 2024): valproate~12y / Lamotrigine-Levetiracetam ~11y	Up to 12 years (10 in Norway). Actual median F-up valproate group : DK 11.5y; NO 5.0y; SE: 6.6y Comparator: DK 6.4y; NO 4.8y; SE 4.5y	Less difference follow-up between the two groups in EPI-PHARE
6. Outcome Definition and Ascertainment	NDD Composite + 5 specific subtypes: ADHD, intellectual disability, ASD, communication, learning disorders (ICD-codes from claims + hospital discharge + Long-Term Disease Records + therapy acts (e.g. orthophony)	Composite NDD (ICD-10 codes from hospital discharge): ASD, intellectual disability, communication/scholastic disorders, movement disorders, tic disorders) + 1 specific subtype ASD No subtypes	PASS may under capture milder cases vs severe phenotypes (hospital discharge). Better sensitivity in EPI-PHARE and analyses by sub-type.
7. Confounding Control	PS weighting with covariates: socio-economic status ("FDep" Social disadvantage index, income proxy), maternal/paternal clinical covariates, pregnancy characteristics, parental mental health, epilepsy status. Sensitivity analyses adjusting for paternal epilepsy and excluding families with mental health disorders.	Propensity score weighting (PSW) using maternal/paternal clinical covariates (psychiatric history, comorbidities, pregnancy characteristics, year of conception). No socioeconomic or lifestyle factors. Residual imbalance addressed by double adjustment in Denmark only.	**Critical Gap in both studies: Epilepsy subtype and severity absent**, leaving major residual confounding. Fathers on valproate likely represent more severe epilepsy phenotypes, which correlate with genetic risk for NDD.

	EPI-PHARE	PASS Paternal	Comments / Implications
8. Statistical Modeling	- Main Model: Cox regression with SMR weighting (propensity-based - Pooling: None: single country analyses - Sensitivity analyses: Multiple scenarios (stricter exposure, monotherapy only, extended period, epilepsy restriction, exclusion of parental mental health) - Complementary analyses Comparator changes (stopped valproate before spermatogenesis, epilepsy untreated or not treated with valproate, lamotrigine or levetiracetam)	- Main Model: Cox regression with PSW; pooled via meta-analysis - Pooling: Random-effects meta-analysis across countries - Sensitivity analyses: 11 scenarios (ASD-only, NDD more stringent definition, extended exposure, variations in the exclusion criteria, cumulative dose)	EPI-PHARE tested alternative exposure definitions, extended study period, exclusion/restriction by parental epilepsy or mental health, comparator changes to test (i) effect of current exposition and (ii) if the observed association is attributable to valproate exposure itself.

PRAC Rapporteur assessment

As requested, the consortium provided a discussion of the French EPI-PHARE study, based on the final study report as published on the ANSM website, as well as the additional responses provided by the study authors in response to the PRAC request (see section 4.1.1 above). However, the consortium notes that the additional responses provided cannot be incorporated in the general discussion on study results as essential methodological details (e.g. how exposure is classified, samples sizes from individual NDD subtypes, etc) for these additional analyses were not provided by the authors. This is acknowledged.

This study provides additional information regarding the risk of paternal valproate use and offspring NDD risk from a data source not used in either the paternal PASS or other published studies. The authors report an increased risk NDD (composite) in children from fathers who used valproate compared to fathers who used lamotrigine/levetiracetam (aHR 1.24 [95%CI 1.07-1.44]). In the paternal PASS these were aHR 1.34 (0.79-2.25) for DK, aHR 1.54 (0.95-2.51) for SE and aHR 1.76 (0.83-3.71) for NO, and meta-analysis pooled aHR 1.50 (1.09-2.07).

Similar to the paternal PASS and other published studies, the **objective** of the EPI-PHARE study was to evaluate the association between valproate exposure during spermatogenesis and offspring risk of NDD, compared to lamotrigine/levetiracetam. A key difference is that the paternal PASS considered valproate monotherapy only, whereas the EPI-PHARE study considered valproate mono+polytherapy, and monotherapy only was only considered in a sensitivity analysis.

Regarding **inclusion and exclusion criteria**, the EPI-PHARE study included all live-born children between 2010-2015 with an identified mother and father. Children with a brain malformation, from pregnancy with medically assisted procreation or exposure to a medicine associated with increased NDD risk after in utero exposure (valproic acid, valpromide, carbamazepine) were excluded. The paternal PASS also included offspring with parental history of CM or NDD, adopted children, offspring exposed to AEDs in utero or in the 3 months prior to LMP and offspring of mothers with epilepsy. The EPI-PHARE study included some sensitivity analyses applying additional exclusion criteria (e.g. children with epilepsy or children with parental history of mental health disorder or NDD). Overall, inclusion and exclusion criteria slightly differ between paternal PASS, EPI-PHARE study and other published studies (Christensen et al, 2025; Meng et al, 2026; Razaz et al, 2026) resulting in differences in study population.

Exposure was classified as at least 1 reimbursed dispensation of a drug containing valproate indicated in epilepsy (any medication of ATC N03AG01, excluding divalproic acid). In the paternal PASS exposure was classified as brand names and generics of all forms of valproate salts will be considered (sodium valproate, valproic acid, valproate semisodium, valpromide) using ATC code N03AG01. The period of exposure was four months instead of 90 days in the paternal PASS which more closely aligns to the biological spermatogenesis window. A sensitivity analysis in the paternal PASS extending the window to 6 months prior to conception (also including offspring of fathers exposed 3 months prior to conception) still suggested a borderline increased risk (aHR 1.37 [1.00 – 1.89]).

Similar to the paternal PASS and other published studies (Christensen et al, 2025; Meng et al, 2026; Razaz et al, 2026), the EPI-PHARE study used **NDD as composite outcome** as the primary study outcome. The authors adapted the validated outcome algorithm of Straub et al (2021), that was also using in the Meng et al (2026) study, requiring a minimum age for diagnosis and at least 2 diagnoses

of different dates. Compared to Straub et al (2021) and Meng et al (2026), the study did not include Developmental Coordination Disorder (ICD10 F82.x) and Behavioural Disorder (ICD10 F63.x, F91.x, F93.8, F93.9x, F94.x, F98.8x, F98.9x). The paternal PASS is the only study including movement and tic disorders in the composite NDD outcome. As noted previously (also see sections 3.1.1 and 3.1.2 above), there are differences regarding the specific NDD included in the composite outcome as well as the ICD codes used to identify the NDD across the different (published) studies.

Regarding **sample** size, the EPI-PHARE study included 4773 children in the valproate group (583 cases NDD) and 3115 children in the lamotrigine/levetiracetam group (310 cases NDD). For the paternal PASS, minimum sample size to observe a HR of 2.00 with 5% significance and 80% power was calculated to be 1178, with 598 per exposure group. This sample size was reached in the EPI-PHARE study. From all available studies investigating the risk of neurodevelopmental disorders after paternal exposure, the EPI-PHARE study concerns the largest study to date.

In the EPI-PHARE study, the median **follow-up time** was comparable in the valproate and lamotrigine/levetiracetam exposure groups, with 11.9 and 11.2 years follow-up time, respectively. The unbalanced follow-up time in the valproate compared to the lamotrigine/levetiracetam group was considered a major limitation of the paternal PASS, as well as some published studies (e.g. Christensen et al, 2025). In addition, the long follow-up time of almost 12 years is considered sufficient for diagnoses of most NDD. Mean age of ASD diagnosis is known to be around 4-5 years of age and may be higher for other NDDs (e.g. ADHD), but can also vary between countries.

Similar to the paternal PASS and Meng et al (2026), the authors used a propensity score model to adjust for a wide range of **covariates.** Similar to other studies, the EPI-PHARE study considered various paternal and maternal characteristics, including sociodemographic (age) and health characteristics including mental health disorders (mood disorders, personality disorders, schizophrenia and other disorders), NDD, epilepsy, although paternal epilepsy was not adjusted for in all analyses (see below). For fathers, the study considered antiepileptic treatment as monotherapy or as combination therapy. The study included additional maternal characteristics, including social disadvantage index, level of resources, use of psychotropic drugs during pregnancy (including antidepressants, antipsychotics, anxiolytics, hypnotics), as well as obesity, smoking and alcohol consumption. In contrast to the paternal PASS as well as other published studies, the study also considered neonatal characteristics including prematurity, weight for gestational age at birth, and hypoxia at birth, as well as pregnancy characteristics including gravidity, multiple pregnancy and folic acid dispensation (also see section 4.1.1. above). Various sensitivity analyses were conducted to test the robustness of the study results across variations in statistical methodology, exposure definition and population considered.

In the final study report, the **main results** of the EPI-PHARE study (considering mono+polytherapy) showed a significantly increased risk for NDD overall (1.24 [1.07-1.44]). Updated analyses (considering mono+polytherapy restricted to fathers with epilepsy and considering monotherapy only restricted to fathers with epilepsy) were provided in response to the PRAC's request for supplementary information (see section 4.1.1 above) and showed similar and statistically significant risk estimates for the NDD overall endpoint. For the individual NDD subtypes, the final study report described a significantly increased risk for IDD (2.12 91.05-4.30] and borderline increased risk for communication disorders (1.23 [1.00-1.52). In the updated analyses in monotherapy (see section 4.1.1 Q1), the HR for IDD is lower with lower level of confidence interval above 1. For ADHD, the HR was slightly higher with lower level of the confidence interval just above one. For the remaining NDD subtypes, estimated

HRs were comparable to the analyses also including valproate in combination therapy. None of the other studies report and increased risk for a specific NDD subtype; however, these study were not sufficiently powered. The authors of the EPI-PHARE study did not comment on the power of their study. Results of various sensitivity analyses provided in the final study report were generally consistent with the main analysis of the study.

Although the main analysis in the EPI-PHARE study was not **adjusted for epilepsy**, in the final study report (based on mono+polytherapy), higher risk estimates for all NDD were observed in the sensitivity analyses adjusted for epilepsy (1.32 [1.13-1.55] vs 1.24 [1.07-1.44] in main analysis) or restricted to fathers with epilepsy (1.38 [1.15-1.65]), this was also observed Christensen et al (2025) (although in the latter these risk estimates were attenuated when matching on offspring year of birth, see section 3.1.1 above). In current round, the authors provided updated results of the main and complementary analyses in monotherapy only and restricted to fathers with epilepsy for which the risk estimate is comparable to the main analysis in the Nov 2025 report (1.25 [1.07-1.47] vs 1.24 [1.07-1.44]. As noted above (see section 4.1.1 Q1) and by the consortium, the algorithm to identify epilepsy was amended which led to changes in study population and cohort sizes. As the algorithm and cohort sizes were not provided, it is difficult to interpret these updated results.

A strength of the EPI-PHARE study are the **complementary analyses** in which children from fathers exposed to valproate were compared to 1) children from **former users** (previous use of valproate in the 2 years to 5 months before spermatogenesis), but no exposure during the spermatogenic risk window) and 2) children of fathers with **epilepsy not treated** with valproate, lamotrigine or levetiracetam. For the former user analyses, in both the final study report (considering valproate mono+polytherapy), the updated analyses in fathers restricted to epilepsy (considering valproate mono+polytherapy), and updated analyses in fathers restricted to epilepsy (considering monotherapy only), the risk estimates for NDD overall as well as individual NDD subtypes are attenuated and no longer significant (Tables 3 and 4 in final study report; and section 4.1.1 above), except for IDD in the main analysis and ASD in the updated analysis restricted fathers with epilepsy (higher HR, but non-signification). Similarly, in the analysis in fathers with epilepsy not using valproate, lamotrigine or levetiracetam, risk estimates were attenuated and no longer significant compared to results in the main analyses, with the exception of IDD in the updated analyses in fathers restricted to epilepsy (lower HR, but lower level of CI above 1).

The **strengths** of the study as highlighted by the consortium (population-based coverage, active comparators, long follow-up, and extensive sensitivity analyses) are acknowledged. The comparable and long follow-up time between exposure cohorts, large sample size, and use of an outcome algorithm including minimum age at diagnoses and at least 2 diagnoses codes are considered particular strengths by the PRAC Rapporteur.

The main **limitation** of the EPI-PHARE study is the use of mono+polytherapy in the majority of analyses. Although it is acknowledged that this may represent real-world use, this limits the attribution of an observed risk to valproate exposure in specific. In addition, as with the paternal PASS and other published studies, other limitations include the potential for residual confounding due to unmeasured or inadequately/incomplete measures variables (e.g. misclassification of outcome and exposure, environmental exposure, parental lifestyle, genetic susceptibility, socioeconomic factors, inability to capture dose and adherence). The results of EPI-PHARE are based on one country only but with large sample size and long and balanced follow-up time. An additional limitation is the lack of information on methodological details in the responses provided by the study authors, which hampers interpretation of

the results in monotherapy and comparison of the updated analyses to the results of the original study report.

In their discussion of the EPI-PHARE study, the consortium notes that the analysis restricted to monotherapy is considered the most important analysis to consider which is agreed. In the final study report, the risk estimate was attenuated and no longer significant in the sensitivity analysis restricted to monotherapy (unadjusted for paternal epilepsy). In the updated analyses provided by the study authors restricted to monotherapy only and restricted to fathers with epilepsy, the risk estimate for NDD was significant (see Q1 in section 4.1.1 above); however, uncertainty regarding changes in methodological aspects hampers interpretation of these updated analyses.

The consortium further highlights the results of the complementary analyses in which children of fathers exposed to valproate were compared to children of former users of valproate or children of fathers with epilepsy not treated with valproate. In both of these complementary comparator groups, incidence rates for NDD overall and for NDD subtypes are higher than in the lamotrigine/levetiracetam comparator group used in the main analyses. In addition, in both complementary analyses, the risk estimates are attenuated and not significant. Although these complementary analyses in the final study report were not restricted to monotherapy, the updated analyses in monotherapy provided by the study authors show similar results (although hampered by limited details regarding changes made to study methodology). It is agreed with the consortium that the results of these complementary analyses suggest the observed increased risk of NDD in the main analyses may be (at least partially) explained by other factors, such as underlying disease or disease severity, rather than an effect of valproate exposure per se.

For IDD, a significantly increased risk was observed in the main analysis as well as across sensitivity analyses in the final study report of the EPI-PHARE study (Nov 2025). It is agreed with the consortium that the conclusions on IDD are based on a very low number of cases with low precision of the risk estimates (see also section 4.1.1 above). Additionally, the decline in IDD diagnoses over time in France, combined with the temporal distribution of exposed children, implies that children of fathers exposed to valproate had a higher probability of being detected with IDD, which is agreed. The attenuation, non-significance and reduced precision of the risk estimate in monotherapy are acknowledged, with aHR changing from 2.12 (1.05-4.30) to 1.95 (0.88-4.33). The analyses in monotherapy are likely based on an even lower number of events; however, cohort sizes and event numbers for this analysis were not provided, limiting interpretation of results. Lastly, the lack of consistency in the risk estimates for all NDDs and for IDDs, especially in the children of fathers unexposed during spermatogenesis, suggests that the results may be explained by a combination of statistical chance, differential detection bias, and potentially confounding factors. This is agreed.

To conclude, while this study has several strengths (e.g., large sample size, long and balanced follow-up), its conclusions are limited by the methodology used and the limited details provided for the updated analyses, like inclusion of polytherapy in most analyses and uncertainty regarding the epilepsy only cohort. The study suggest a significantly increased risk of NDD overall in children of fathers who use valproate compared to those who use lamotrigine/levetiracetam but this risk is attenuated when analyses are restricted to monotherapy. Additionally, complementary analyses do not show increased risk of NDD in children of fathers who used valproate compared to children of former users or children of fathers with untreated epilepsy, which suggests that the observed increased risk of NDD may be explained by other factors, such as underlying disease or disease severity, rather than a direct effect of valproate exposure. Overall, the study provides valuable information on the risk of NDD in children of

fathers who use valproate, but its results should be interpreted with caution due to methodological limitations/limited details on the methodology.

Discussion on Answers from EPI-PHARE to the questions raised by PRAC to EPI-PHARE (shared by EMA with Sanofi on 13 March 2026)

The responses provided by EPI-PHARE to the PRAC questions raise several methodological concerns that warrant careful consideration for appropriate scientific evaluation. When taken together, these aspects affect the interpretability of the findings and their alignment with established scientific standards.

1. Population Modification and Methodological Consistency

The study population was substantially modified from the design used in the report available on EPI-PHARE website, shifting from all fathers exposed to valproate, regardless of therapeutic indication, to a population restricted to epileptic fathers only. This modification was presented with limited documentation of its methodological rationale and underlying assumptions.

This population restriction raises a concern regarding methodological consistency. Indeed, the initial population definition (joint inclusion of fathers on monotherapy and polytherapy) had been explicitly justified based on the objective to examine real-world patterns of valproate use. Therefore, excluding fathers treated for bipolar disorders, the second indication for valproate in France, seems to scientifically contradict the initial objective of assessing "real-world" utilization. This exclusion of a clinically relevant population is not explicitly justified in the responses.

The restriction to epileptic fathers defines a clinically distinct population, with different characteristics regarding comorbidities, disease severity, and socio-economic profiles compared to the broader valproate-exposed population. Thus, results in this restricted population are not generalizable to all valproate-exposed fathers.

The modification of the study population has also direct implications for results interpretation. Results from the restricted epileptic population cannot be directly compared to those from the initial broader population, as they represent different study cohorts with potentially distinct characteristics and risk profiles.

The population change represents a methodological discontinuity that affects direct comparability. This aspect requires further rationale for appropriate interpretation of the findings.

2. The question of polytherapy

Another point is the maintenance of polytherapy in the exposure group of interest. From an epidemiological perspective, in order to draw conclusions about the specific effect of a drug on the risk of neurodevelopmental disorders, it would be more scientifically-sound to limit the analysis to fathers treated with monotherapy. In the presence of antiepileptic polytherapy, it becomes more difficult to attribute the observed risk to a specific medication, as multiple active agents are present simultaneously.

3. Additional information for appropriate scientific evaluation

The response to the PRAC provides only a fraction of the information necessary for rigorous scientific evaluation of the new results. To allow for a complete scientific evaluation of the new results, certain additional information is missing. Hazard ratios (assumed to be adjusted) and their 95% confidence intervals are provided, but more complete documentation would be required.

In particular, detailed tables containing the number of subjects by exposure group, the number of events by type of neurodevelopmental disorder, and crude incidence rates would allow for better interpretation of the results. The baseline characteristics of the new population restricted to those with epilepsy would also be useful in understanding the comparability of groups and the effect of propensity score adjustment. The details of the covariates included in the new propensity score model, which necessarily had to be revised following the population change, would also merit documentation.

Finally, sensitivity analyses with the new methodology would allow for evaluation of the robustness of the new results and testing of the stability of conclusions under different methodological assumptions.

4. Some variability in the results

When observing the results from the initial population and those from the new population restricted to fathers with epilepsy, some important variability is observed depending on methodological choices. The composite neurodevelopmental disorder outcome, which was not significant in monotherapy in initial analysis, becomes significant in the new population. Attention-deficit/hyperactivity disorder, also not significant initially, becomes significant. Conversely, intellectual disability, which constituted the most marked result according to the authors in the initial report, loses its statistical significance in the new population.

This variability in results depending on population and methodological choices is an aspect that merits attention. It suggests that the observed associations could be sensitive to the methodological assumptions retained. A more in-depth discussion of this variability, and an exploration of the reasons that might explain it, would be useful for better understanding the robustness of the conclusions.

To summarize, the responses from EPI-PHARE to the PRAC present several aspects that would merit clarifications or additional documentation. These include: (i) the change in study population without detailed justification; (ii) the limited comparability between previous and current results; (iii) maintaining polytherapy analysis, (iv) the insufficiency of certain information (complete tables, characteristics of the new population, details of covariates, sensitivity analyses). These factors collectively affect the ability to fully discuss the presented estimates.

The variability observed in results depending on methodological choices raises questions about the robustness and generalizability of the conclusions.

To enable comprehensive evaluation, additional documentation would be essential including: detailed rationale for methodological choices, complete results tables, sensitivity analyses examining key assumptions, and thorough discussion of study limitations and their potential impact on conclusions.

PRAC Rapporteur assessment

The consortium highlights 4 points that hamper interpretation of the updated analyses: 1) population consistency and methodological consistency, 2) polytherapy, 3) limited information for appropriate evaluation, 4) variability in study results, which is agreed.

Regarding the population consistency and methodological consistency, the authors were requested to adjust for paternal epilepsy in their analyses, but instead provided analyses restricted to fathers with epilepsy. Although restricted analyses by indication can provide insight in potential confounding by indication, it is agreed with the consortium that a population restricted to epilepsy does not fully reflect real-world use, and these results may not be generalizable to the overall valproate population. In addition, the lack of information regarding the updated algorithm applied, which has led to significant changes in the number of subjects considered to have an epilepsy diagnosis, makes it difficult to compare the results of the updated analyses to the final study report, and hampers interpretation of these new study results.

Regarding the issue of polytherapy, it is agreed that the use of polytherapy in most updated analyses precludes drawing conclusions on an effect of valproate alone; hence, the previous PRAC request for updated analyses in monotherapy only.

Regarding the limited information or appropriate evaluation, it is agreed with the consortium that the limited details on the updated analyses (including number of subjects, number of NDD events, crude incidence rates, baseline characteristics) limits interpretation of the updated analyses provided.

Regarding the variability in study results, the consortium notes that the NDD overall outcome is now significant, while the IDD outcome that was significant across various sensitivity analyses in the final study report is no longer significant. Considering the methodological changes applied that have impacted the study population, it is agreed with the consortium that further information on the methodological assumptions would be need to better understand the observed associations and robustness of study results.

Question 2

A discussion of the recently published article by Olstad et al. (2025), as well as any other new relevant literature or non-clinical data, if available.

MAH response

1) Olstad EW, Nordeng HME, Bjørk MH, Selmer K, Gervin K. Paternal valproate use and impact of shared genetic susceptibility on child neurodevelopment. Sci Rep. 2025 Nov 7;15(1):39033. Olstad et al. (2025)

This study was designed to investigate the potential for genetic confounding in the neurodevelopmental risks, comparing genetic susceptibility between fathers using valproate and those using other Anti-seizure medications (ASMs).

Design: This study is based on data from the Norwegian MoBa study conducted by the Norwegian Institute of Public Health. MoBa is an ongoing prospective, population-based Mother, Father and Child cohort study which is also linked to the Medical Birth Registry of Norway (MBRN). The participants completed the questionnaires throughout pregnancy and childhood. Sample selection was based on paternal responses to a questionnaire distributed around week 15 of pregnancy (*n* = 76,380 pregnancies). Analyses were restricted to pregnancies with live birth outcomes for which paternal genotype data was available from MoBa Genetics. Men using valproate together with lamotrigine and/or levetiracetam were excluded (*n* = 2 pregnancies).

Exposure: Exposure was defined as any use throughout the 6-month period before pregnancy.

Outcome: Child neurodevelopmental traits were assessed throughout childhood until eight years of age and measured based on the questionnaires using validated psychometric tests. The neurodevelopmental traits included hyperactivity (1.5–8 years), inattention (1.5–8 years), language difficulties (1.5–8 years), motor difficulties (0.5–5 years), repetitive behaviours (1.5–8 years), and social communication (0.5–8 years).

Statistical Analysis: Polygenic Risk Scores (PRS) were generated for 3 traits – epilepsy, ASD and ADHD. Various statistical analyses were used to test difference in standardized PRSs between treatment groups.

Results: PRSs for epilepsy were significantly higher in fathers treated with valproate compared to those treated with lamotrigine or levetiracetam (mean difference: 0.66, CI = 0.21–1.11, p ≈ 0.005), other ASMs (mean difference: 0.41, CI = 0.02 0.81, p ≈ 0.04), reflecting distinct genetic profiles. No robust associations of ASM could be found with ASM use and neurodevelopmental traits. A genetic overlap between epilepsy, ADHD, and ASD, was seen which together with the higher epilepsy PRSs highlight the possibility of genetic confounding of paternal ASM use and child neurodevelopmental outcomes associations. No robust associations between father's exposure to valproate and any of the six child neurodevelopmental outcomes was seen when adjusting for infant sex and paternal education. The only exception was a borderline significant association of father's valproate use with motor difficulties in children at three years compared to the lamotrigine/levetiracetam group, and with language difficulties at five years of age compared to the control group in a small sample.

The observed genetic overlap between the PRSs for epilepsy, ADHD, and ASD, provides evidence for shared genetic susceptibility, which may influence both paternal epilepsy and comorbidity, as well as child neurodevelopmental outcomes.

Strengths: The strengths of the study included large population-based coverage, focus on specific trait measures like ADHD, ASD. Use of PRSs allowed for analyses of genetic susceptibility and its potential impact on neurodevelopmental outcomes.

Limitations: The study was underpowered to investigate group differences in neuropsychiatric traits. Also, generalized and focal epilepsies could not be differentiated due to unavailability of information in MoBa questionnaires.

Conclusion: This study provides complementary insight into the question of residual confounding bias in studies investigating the association between NDD in children and father's exposure to valproate.

Using the MoBa cohort (Norwegian Mother, Father, and Child Cohort Study) and a different methodological approach based on polygenic risk scores (PRS), this study showed that fathers treated with valproate have significantly higher genetic predispositions for epilepsy compared to fathers treated with lamotrigine/levetiracetam, other antiepileptic drugs, or healthy controls. The study also reveals significant genetic overlap between epilepsy, ADHD, and autism spectrum disorders, with 428 shared genes enriched in common neurodevelopmental pathways. In contrast to the EPI-PHARE study findings, this Norwegian study finds no robust associations between father's exposure to valproate and neurodevelopmental traits in children, with only two borderline associations observed (motor difficulties at 3 years and language difficulties at 5 years) in very small samples. According to the authors, "*Concomitantly, the shared genetic pathways between epilepsy, ADHD and ASD, may result in children inheriting genetic risk factors independently of ASM exposure and creates a potential for genetic confounding. As a result, associations between paternal valproate use and child NDDs may be confounded by these shared genetic susceptibilities.*"

These results corroborate the possible presence of residual confounding, putting into perspective the interpretation of pharmaco-epidemiological data.

PRAC Rapporteur assessment

Olstad et al. conducted an exploratory study that aimed to assess the potential for **genetic confounding** in the reported neurodevelopmental risks for valproate after paternal exposure during spermatogenesis. This study compared genetic susceptibility for epilepsy and neurodevelopmental risks between fathers using valproate and those using other ASMs, i.e., the study assessed whether inherited genetic factors in fathers might confound the association between valproate use and child NDDs. Thus, this study has a different approach than the previous pharmaco-epidemiological studies discussed in relation to this signal.

This study used the Norwegian Mother, Father and Child Cohort Study (MoBa) as **data source**, linked to the Medical Birth Registry of Norway and with paternal genotype data available. Exposure groups comprised fathers with epilepsy using valproate (n = 41), lamotrigine/levetiracetam (n = 37), other ASMs (n = 80), and a comparison group without ASM use or epilepsy (n = 54,752). Paternal ASM use was self-reported (high agreement between self-reported ASM exposure and dispensed ASM prescriptions) for the 6 months preconception. Child neurodevelopmental traits were assessed throughout childhood until eight years of age and measured based on questionnaires. PRSs (an estimate of an individual's genetic liability to a disease) for epilepsy, ADHD, and ASD were computed based on GWAS data. Statistical analyses included group comparisons and adjusted regression models.

Fathers differed across treatment groups in age and educational level, but not in psychiatric comorbidities (whereas differences in baseline psychiatric diagnoses were observed in pharmacoepidemiologic studies). Maternal characteristics were largely similar across groups, with only a minor difference observed in sporadic smoking. PRSs for ADHD and ASD were similar across groups, whereas epilepsy PRSs were significantly higher in fathers using valproate compared to the other groups, indicating genetic liability. After adjustment, no associations were found between paternal valproate use and child NDD outcomes, but sample size is too small to draw conclusions. Overlap analyses of the top 1% of SNPs revealed modest genetic overlap across epilepsy, ADHD, and ASD, including five overlapping SNPs and a significant overlap of 428 annotated genes. These genes were enriched for biological processes related to synaptic function, cell adhesion, and neurodevelopment, suggesting shared underlying mechanisms across these conditions.

This study has as **strength** that it assessed PRSs to assess genetic susceptibility and provides a different view on the potential association between paternal valproate exposure and child NDD outcomes. It also has important **limitations** including limited statistical power, small sample size, and lack of information on epilepsy subtypes.

Overall, the higher epilepsy PRS in fathers using valproate compared to the other groups indicates a different underlying genetic liability, potentially reflecting distinct epilepsy subtypes and non-genetically comparable groups. This study also observed genetic overlap between epilepsy, ADHD, and ASD, which is consistent with known shared biological mechanisms underlying these conditions. The finding of this explorative study might highlight the potential for genetic confounding/confounding by indication, as shared genetic susceptibility/underlying disease may contribute to child neurodevelopmental outcomes independently of valproate exposure.

2) Two additional new relevant pharmaco-epidemiological studies have been published which are discussed below -

Razaz N, Soderling J, Tomson T, et al. *Risk of neurodevelopmental disorders associated with paternal use of valproate during spermatogenesis.* J Neurol Neurosurg Psychiatry, 2026. doi:10.1136/jnnp-2025-337441

This is a population-based cohort study from Sweden and Norway and included all singleton, live-births at ≥ 22 completed gestational weeks between 1 Jan 2007 and 31 Dec 2020 in Sweden and 1 Jan 2010 and 31 Dec 2018 in Norway. The Swedish cohort included 1595 live births to fathers using valproate monotherapy and 3097 exposed to lamotrigine or levetiracetam monotherapy during spermatogenesis. The Norwegian cohort included 463 exposed to valproate and 1109 to lamotrigine or levetiracetam.

Exposure & Outcome: Exposure included children of father exposed to valproate monotherapy (≥1 prescription in 120 days before LMP) compared against children of father exposed to lamotrigine/ levetiracetam monotherapy. Outcome measure included incidence of NDDs in offspring and separately by NDD sub-type [ASD, ADHD, Intellectual disability (IDD) and psychological development disorders]. Dose-event analyses were also conducted with comparison of high dose and low dose of valproate vs any dose of lamotrigine/levetiracetam. In addition, the main analysis was restricted to the cohort of fathers with epilepsy and within this group the children of father treated with valproate were compared to children of father treated with lamotrigine/levetiracetam.

Statistical analysis: Cox proportional hazards regression, was used to estimate HRs with 95% CIs for NDDs, comparing children of father exposed to valproate with those of father exposed to lamotrigine/levetiracetam. Adjustments were made for child sex, birth year, maternal cohabitation status and parental characteristics (age at birth, psychiatric history, psychotropic medication use and epilepsy diagnosis). In Sweden, additional adjustment for parental education level was done, however this was not available in Norway. Analyses were performed separately for Sweden and Norway, and combined using random-effects meta-analysis via the inverse variance method with restricted maximum likelihood.

Results: No statistically significant increased risk of NDDs was found for paternal valproate monotherapy vs. lamotrigine/levetiracetam monotherapy:

Outcome	Pooled aHR	95% CI
Any NDD	1.06	0.85–1.30
ASD	1.29	0.89–1.85
ADHD	0.98	0.76–1.25
Intellectual Disability	1.20	0.65–2.21
Psychological Dev. Disorders	1.28	0.84–1.97

Results were consistent for individual countries and across:

- Dose-response analyses (high vs. low dose valproate)
- Subgroup restricted to fathers with confirmed epilepsy

Strengths:

- Nation-wide population-based coverage with minimal loss to follow-up,
- Restriction of cohort to fathers with epilepsy,
- Minimizing the confounding by indication,
- Adjustment for cohabitation/ marital status and both parent's education (Sweden only) as proxy for socio-economic status

Limitations:

- Residual confounding - Despite extensive adjustment, unmeasured confounders remain a concern (e.g., severity of epilepsy, genetic predisposition to NDD etc.)
- The wider exposure window (120 days before LMP) could dilute risk estimates if fathers discontinued valproate well before conception
- Long-term valproate use prior to the defined spermatogenic window was not accounted for.
- Shorter median follow-up period in Norway reducing the power for NDD subtypes.

Key Differences between PASS Paternal (Colas et al., 2025) and Razaz et al. (2026):

- Exposure window: Razaz et al. used a wider 120-day window vs. 90 days in PASS Paternal. A wider window could theoretically dilute risk estimates, but since Colas et al. (2025) also extended lookback to 6 months when duration overlapped, this difference is considered unlikely to explain the divergent results.
- Outcome definition: PASS Paternal applied a broader definition including dyslexia, tic disorders, hyperkinetic disorders and dystonia. However, the sensitivity analysis using a stricter definition yielded similar results as Razaz et al (2026).
- Adjustment for paternal epilepsy: PASS Paternal did not adjust for paternal epilepsy in any of their models, leaving confounding by indication unaddressed. Razaz et al. explicitly adjusted for this and confirmed null findings in an epilepsy-restricted subgroup. Notably, the ASD estimate was markedly higher in PASS Paternal (aHR 2.70 vs. 1.29), a discrepancy most plausibly attributable to this omission.
- Adjustment strategy and covariate selection — PASS Paternal relied on propensity score weighting (which yielded higher estimates than their own regression-adjusted model), while Razaz et al. used Cox regression adjusting for parental education and cohabitation as socioeconomic proxies — variables not included in PASS Paternal.

Conclusion: Razaz et al. (2026) present the largest Nordic cohort to date (n=2,051, children of father exposed to valproate) with robust methodology including active comparator design, explicit adjustment for paternal epilepsy, dose-response analyses, and replication across two independent national cohorts. Their null finding (pooled aHR 1.06; 95% CI 0.85–1.30) is consistent with the majority of the existing literature, including two independent Danish register studies (Christensen et al., 2024; 2025), a prior Swedish cohort (Tomson et al., 2020), and a population-based study from Norway and Taiwan (Meng et al, 2026). Critically, no dose-response relationship has been demonstrated across studies, undermining a key criterion for causality.

The PASS Paternal study which formed the basis for PRAC precautionary measures reported an increased risk of NDD in children of father exposed to valproate in monotherapy in the 3 months prior to conception, compared to those of father exposed to lamotrigine or levetiracetam in monotherapy in the same window, whereas the other available epidemiological studies did not. The divergence in results could be explained by residual confounding and other limitations such as differential length of follow-up in PASS Paternal, stemming from the absence of adjustment for paternal epilepsy.

PRAC Rapporteur assessment

Razaz et al. conducted a **cohort study in Sweden and Norway** that aimed to assess the association between paternal valproate exposure during spermatogenesis and the risk of NDDs in offspring. In this study, nationwide population-based databases in Sweden and Norway were used and included all singleton live births (≥22 completed gestational weeks) between 2007 and 2020 (Sweden) and 2010 and 2018 (Norway) and followed up through 2022 (Sweden) and 2019 (Norway). Offspring exposed to paternal valproate monotherapy and offspring exposed to paternal lamotrigine/levetiracetam monotherapy were included (≥1 prescription from 120 days before the first day of the LMP to LMP+14 days). Offspring were considered to have the NDD if they had at least one recorded diagnosis (based on the listed diagnostic codes) from 1 years old onwards. HRs with 95% CIs for NDDs comparing valproate exposed offspring to lamotrigine/levetiracetam offspring were estimated using Cox proportional hazards regression. Compared with paternal lamotrigine/levetiracetam monotherapy, paternal valproate exposure was not associated with increased pooled risk of any NDD (aHR, 1.06; 95%CI 0.81 to 1.22), including ASD (aHR, 1.29; 95%CI 0.89 to 1.85), ADHD (aHR, 0.98; 95%CI 0.76 to 1.25), intellectual disability (aHR, 1.20; 95%CI 0.65 to 2.21; Sweden only) or psychological development disorders (aHR, 1.28; 95%CI 0.84 to 1.97). Findings remained consistent in dose–response analyses and when restricted to fathers with epilepsy.

The **data sources** used in this study are similar to two of the data sources used in the paternal PASS, only the nationwide birth registry of Denmark was not included in the study of Razaz et al. The included study population slightly differed between the studies: singleton live births (≥22 completed gestational weeks) between 2007 and 2020 (Sweden) and 2010 and 2018 (Norway) in the study of Razaz et al. compared to singleton live births (≥12 completed gestational weeks) between 2007 and 2019 (Sweden) and 2010 and 2019 (Norway) in the paternal PASS. Both studies looked at valproate and lamotrigine/levetiracetam monotherapy. The paternal PASS on the other hand additionally excluded adopted children, children of fathers or mother without continuous enrolment in the 12 months prior to index date, offspring with parents with history of CM or NDD, offspring exposed to AEDs in utero or in 3 months prior to LMP (Razaz et al. only excluded offspring of mother who used valproate from 30 days before last menstrual period to birth) and offspring or mother with epilepsy. Summarizing, the included study populations differed, while the same data sources from NO and SE were used in both studies.

The **exposure** window started from 120 days before the first day of the LMP for the studies of Razaz et al. and Christensen et al. whereas this was 90 days for the paternal PASS and the study of Meng et al. However, as also acknowledged by the MAH, the PASS paternal also extended the exposure window, which did not significantly alter their results.

Regarding **sample size**, the Swedish cohort included 1595 (159 with NDD) live births to fathers using valproate monotherapy and 3097 (247 with NDD) exposed to lamotrigine or levetiracetam monotherapy during spermatogenesis. The Norwegian cohort included 463 (21 with NDD) exposed to valproate and 1109 (39 with NDD) to lamotrigine or levetiracetam. Overall, the sample size is thus larger than in the paternal PASS study, which reported the following sample size per exposure group and country: Sweden (valproate: 968 [52 with NDD]; lamotrigine/levetiracetam: 1483 [52 with NDD]; Norway (valproate: 413 [17 with NDD]; lamotrigine/levetiracetam: 1058 [25 with NDD]

Regarding **outcomes**, NDD composite outcome was the primary outcome in the study of Razaz et al., in line with the other studies. The NDD composite outcome used by Razaz et al. included intellectual disability, psychological development disorders, autism spectrum disorder and ADHD, which was similar to the outcome definition used by Christensen et al and the NDD narrow outcome of the paternal PASS. The NDD composite outcome used by the paternal PASS and Meng et al was broader compared to the study of Razaz et al. Compared to the paternal PASS NDD composite outcome, this study did not include movement disorders and tic disorders. Compared to Meng et al., this study did not include behavioral and emotional disorders and disorders of social functioning with onset specific in childhood. In the study of Razaz et al., only one recorded diagnosis was needed for the NDD outcome, whereas this was based on a validated outcome algorithm for the study by Meng et al., including at least 2 diagnosis of the NDD on a different date. Follow-up also differed for each study, and in the study of Razaz et al diagnosis of NDD after the first year of life were assessed. The study outcomes are thus not fully comparable between all studies. The included covariates in the statistical analysis also differ per study.

A major limitation of the paternal PASS in general concerned differences in **follow-up time** in the valproate group compared to the lamotrigine/levetiracetam group. Due to longer follow-up time in the valproate group, offspring in the valproate group may have had a higher chance of being diagnosed with NDD due to longer follow-up. This may be particularly the case for NDD diagnosed later in childhood. For the study of Razaz et al., no follow-up time was reported stratified per exposure group, thus it cannot be determined whether there might be an impact of the follow-up time on the occurrence of NDD. Overall follow-up time was relatively short (median 6.6 years and 5.2 years for Sweden and Norway, respectively), which is an important limitation of this study.

Strengths of the study include use of population-based data sources with high linkage in both cohorts, using diagnosis of NDD only after 1 year of age, use of an active comparator, and consideration of various covariates, including indication (and analysis restricted to fathers with epilepsy), and paternal and maternal factors.

Compared to the paternal PASS, the study of Razaz et al. also included an analysis **restricted to fathers with epilepsy only**. This analysis did not show a statistically increased risk of NDD associated with paternal exposure to valproate monotherapy during spermatogenesis, compared with exposure to lamotrigine or levetiracetam monotherapy. It should however be noted that confounding by disease severity or type of epilepsy can still not be excluded. Dose-event analysis were also performed and did also not result in statistically increased risks of NDD and subtypes. It should be

noted that point estimates (adjusted HRs) were higher for the high-dose valproate in Norway. This might also be explained by residual unmeasured confounding, such as disease severity and cannot be attributed to the valproate dose based on this study. Of note, other studies with information on valproate dose available did not find any dose-related effect (Christensen et al.) or inconsistent results (paternal PASS).

In the study of Razaz et al. separate analyses were also performed for the specific **types of NDD**. The pooled point estimates (adjusted HRs) for NDD overall and ADHD were around 1 and indicate no increased risk for these events in children of fathers who used valproate monotherapy compared to lamotrigine/levetiracetam monotherapy. The pooled point estimates (adjusted HRs) for ASD, ID and disorders of psychological development were around 1.2 but with confidence intervals that cross and extend well beyond 1. Notably, the number of cases in the valproate exposed group was relatively small for these outcomes ranging from 25 to 66 events, likely underpowering the study to assess individual types of NDD.

In conclusion, the study by Razaz et al. did not demonstrate a significantly increased risk of NDDs in children of fathers who used valproate monotherapy during spermatogenesis, compared to fathers who used lamotrigine or levetiracetam monotherapy. The study has several strengths, including the use of population-based data sources, the use of an active comparator, the consideration of various covariates, analysis restricted to epilepsy fathers. However, the study also has some limitations, including the relatively short follow-up time, and the fact that confounding by disease severity or epilepsy type cannot be fully excluded. Analyses stratified by NDD subtype showed higher HR point estimates compared to the main analyses, but with low precision due to small numbers.

Meng L-C, van Gelder MMHJ, Chuang H-M, et al. Valproate use by fathers and risk of neurodevelopmental disorders in children. NEJM Evid 2026;5(3).

This is a cross-national cohort study using population-based databases in Norway and Taiwan covering the period from January 1, 2008, to December 31, 2021. The study included live singletons born between 2010 and 2015 with available paternal data and followed up until 2021. The Norwegian cohort included 339,500 offspring, among whom 319 (0.09%) had a father exposed to valproate monotherapy and 730 (0.22%) had a father exposed to lamotrigine or levetiracetam monotherapy. The Taiwanese cohort included 1,051,488 offspring, among whom 564 (0.05%) had a father exposed to valproate monotherapy and 96 (0.01%) had a father exposed to lamotrigine or levetiracetam. Median follow-up was 8.7years (Valproate) and 8.4years (Comparator) in Norwegian cohort and 7.7years (valproate) and 7.8 years (comparator) in Taiwanese cohort.

Exposure & Outcome: This study examined associations between father's exposure to valproate monotherapy during the 90 days preceding conception and incidence of NDDs among offspring after at least 6 years of follow-up. This study compared risks of NDDs among offspring whose fathers were exposed versus not exposed to valproate in the overall cohort (population control); exposed versus not exposed with valproate among fathers with an indication for antiseizure medication (indication-restricted); and exposed to valproate monotherapy versus lamotrigine or levetiracetam monotherapy (active-comparator).

The primary outcome was the incidence of an NDD among offspring, defined as having any of the following: autism spectrum disorder, attention-deficit/hyperactivity disorder, specific learning disability, developmental speech or language disorder, developmental coordination disorder, intellectual

disability, and behavioral disorder. Analyses examining the association between valproate exposure and the incidence of individual components of the NDD outcome was also conducted.

Statistical Analysis: Propensity Score Fine Stratification Weighting (PS-FSW) was used after estimating propensity scores using logistic regression models that included various covariates. Multiple covariates were considered including year of offspring birth, paternal age, paternal indications for ASM (e.g., epilepsy, psychiatric disorders), paternal chronic comorbidities (e.g., sleep disorders, substance use disorders, NDDs), and paternal use of other medications (e.g., other ASMs, antipsychotics, antidepressants). In addition, maternal age, epilepsy, psychiatric and chronic somatic health conditions, medication use (including ASMs) and lifestyle factors as proxies for potential confounders and risk factors for NDDs were also included.

Results: No increased overall risk for NDD was found in children whose fathers used valproate monotherapy compared to children whose fathers were unexposed (population-control analysis), or whose fathers were exposed to lamotrigine/levetiracetam monotherapy (active comparator analysis)

Incidence Rates by Cohort

Cohort	Group	NDD Cases	Incidence Rate
Norway	Paternal valproate-exposed	24/319 (7.5%)	8.7/1000 PY
Norway	Unexposed (population control)	15,923/337,109 (4.7%)	5.3/1000 PY
Taiwan	Paternal valproate-exposed	127/564 (22.5%)	29.7/1000 PY
Taiwan	Unexposed (population control)	185,600/1,045,300 (17.7%)	22.0/1000 PY

Indication-restricted analysis

Analysis Stage	Norway HR (95% CI)	Taiwan HR (95% CI)	Pooled
Crude (population control)	1.67 (1.10–2.54)	1.35 (1.13–1.63)	1.40 (1.18-1.65)
Indication-restricted (crude)	1.43 (0.93–2.18)	1.35 (1.12–1.62)	1.36 (1.15-1.61)
Indication-restricted + PS-FSW adjusted	1.20 (0.75–1.94)	1.12 (0.92–1.35)	1.13 (0.94-1.35)

Active-comparator analysis

Cohort	Crude HR	95% CI	Adjusted HR	95% CI
Norway	0.94	0.57–1.56	1.02	0.57–1.82
Taiwan	1.39	0.81–2.36	1.22	0.64–2.33
Pooled	—	—	1.10	0.72–1.70

Analysis of specific NDD subtypes were consistent, although the precision was limited by small event numbers. Results remained consistent after stratification by specific ASM indications and in the sensitivity analyses.

Strengths:

Nation-wide population-based coverage, use of minimum follow-up time of 6 years, use of a validated outcome algorithm, consideration of various covariates, indication-restricted and stratified analysis and use of PS-FW model for statistical analysis were main strengths of this study.

Limitations:

The limitations included - small sample size in the comparative analysis, insufficient power to study NDD subtypes, residual confounding – on missing data on lifestyle or genetic factors, type and severity of underlying conditions etc.

Key Differences between PASS Paternal and Meng et al.

- Different outcome measures - NDD composite outcome used by Meng et al. was broader. Use of this validated outcome algorithm limits outcome classification and improves validity.

- Difference in the follow-up time in valproate and lamotrigine/levetiracetam group in PASS Paternal as opposed to comparable follow-up time in both groups in Meng et al.

- Residual confounding – Meng et al. used a stepwise analysis to evaluate effect of residual confounding, including analyses compared to general population, as well as indication-restricted and active comparator analysis.

Conclusion:

This is a methodologically robust study which used systematic confounder control, longer minimum follow-up (6+ years), and validated outcomes, which likely explain the contrasting findings between both studies. While the active-comparator analysis suffers from small sample sizes and potential underpowering (especially in Taiwan cohort), the study contributes important evidence to the ongoing evaluation of paternal valproate-associated NDD risk.

PRAC Rapporteur assessment

Sanofi discussed the recent publication by Meng et al (2026), who evaluated the risk of NDD in offspring of fathers exposed to valproate during spermatogenesis using NO and TW population-based data sources. A preliminary draft of this publication was discussed in the previous round of this signal, see section 3.1.2. The final study results do not differ from the results presented in the preliminary draft. The discussion provided by Sanofi is generally consistent with the previous PRAC Rapporteur's assessment and conclusion on this study (see sections 3.1.2, 3.2 and 3.3 above), and therefore this publication is not further discussed in current round.

Question 3

An overall conclusion regarding the risk of NDD following paternal exposure in view of totality of all available evidence from all sources.

MAH response

The Consortium of MAHs sponsored post-authorization safety study (PASS Paternal; *number redacted*) evaluated the risk of neurodevelopmental disorders (NDDs) in children of father exposed to valproate in monotherapy in the 3 months prior to conception, compared to those of fathers exposed to lamotrigine or levetiracetam in monotherapy in the same window. Using pooled data from Denmark, Norway, and Sweden, the study identified a borderline but statistically significant increased risk of NDDs in children of fathers receiving valproate monotherapy in the three months prior to conception compared with those of fathers receiving lamotrigine or levetiracetam monotherapy (HR 1.50; 95% CI:

1.09–2.07). While this finding prompted regulatory precautionary measures, despite the limitations in the study design of the PASS Paternal, it is important to note that country-specific analyses within the same PASS Paternal study did not individually demonstrate statistically significant elevated risks.

After the completion of this PASS Paternal, several independent studies have been published to further investigate this signal. Christensen et al. (Denmark, 2025), Meng et al. (Norway and Taiwan, 2026), and Razaz et al. (Sweden and Norway, 2026) have each reported no statistically significant increased risk of NDDs associated with father's exposure to valproate. Notably, these null findings are broadly consistent with the individual country-level results from the original PASS Paternal study. However, two important contextual observations warrant consideration: first, the risk estimates reported in the newer studies are generally lower than those observed in the PASS Paternal, a discrepancy that is likely attributable to meaningful methodological differences between studies, including differences in confounding strategies, follow-up duration, outcome definitions, and study population characteristics; second, none of the recent studies replicates the three-country pooled analysis that formed the basis of the PASS Paternal conclusion, limiting direct comparability and reproducibility of the results.

In addition to these studies, Olstad et al. (2025), highlighted that the elevated risk of neurodevelopmental disorders in children may be partially explained by inherited genetic vulnerability which, as stated by the authors, questions the attribution of NDD risks to direct effects of valproate. In this study, fathers using valproate demonstrated greater genetic susceptibility to epilepsy than those prescribed alternative ASMs. At the same time, because epilepsy, ADHD, and ASD share common genetic mechanisms, children may inherit these risk factors through genetic transmission alone, regardless of ASM exposure—introducing the possibility of genetic confounding. Consequently, the observed associations between fathers' valproate use and NDDs in their children may actually be influenced by these overlapping genetic predispositions rather than the medication itself.

In addition to the recent epidemiological studies, Sanofi is conducting a non-clinical epigenetic program post Article 31 referral *[number redacted]* aiming to "study the impact of valproate on the epigenome of male and female germ cells".

Additional evidence derived from a recently published French epidemiological study using the EPI-MERES registry, Botton et al. (2026) initially documented increased NDD risk, including a greater than two-fold elevation in intellectual developmental disorders among children of fathers exposed to valproate mono- or polytherapy during the spermatogenic period. However, as noted in the answer to Question 1, these associations are attenuated and no longer significant when restricted to monotherapy. Besides, based on the results of the sub-analysis between (i) children of father exposed to valproate during spermatogenesis vs (ii) those of father exposed to valproate before spermatogenesis and (iii) those of father with epilepsy not treated with valproate / lamotrigine/ levetiracetam, the risk of NDD associated with valproate is the same regardless of exposure and exposure window. The findings from this study also suggest that substantial uncontrolled confounding variables may be present, which could undermine the ability to draw definitive conclusions about valproate's potential independent effects.

Subsequently, EPI-PHARE provided response to PRAC questions on this study, which incorporated methodological modifications to the study design, specifically revising the epilepsy identification algorithm and restricting the study population to children of fathers with epilepsy. These design changes resulted in major alterations to the exposure group sizes and corresponding shifts in NDD incidence rates. Indeed, when the analysis was limited to valproate monotherapy, the risk of overall NDD and ADHD which was non-significant in the initial analysis, became significant in the new population. The risk of IDD which was the most important result in the initial analysis, became non-significant after the design changes. This raises serious questions on the methodology used in the study to achieve these different results.

Thus, considering the totality of available evidence, the current available data is characterized by significant inconsistency. The original PASS Paternal finding of an increased risk of NDD in children of father exposed to valproate in monotherapy in the 3 months prior to conception, compared to those of father exposed to lamotrigine or levetiracetam in monotherapy in the same window, is in contrast to the subsequent evidence gained through several epidemiological studies, which has consistently pointed toward a null or very modest association.

In view of this ongoing uncertainty, the MAH therefore considers that results from the PASS TANGO study should be awaited for, before taking any further regulatory actions. As agreed with PRAC, the TANGO study has been specifically designed to overcome the key methodological shortcomings of prior PASS Paternal study, which will include analyses restricted to former users of valproate, and stratified analysis by indication and sub-types of epilepsy. Additionally, PASS TANGO will include additional countries, thus increasing the sample size enabling to detect smaller HR. By addressing the limitations in a single study, TANGO study will contribute to the comprehensive interpretation of data, which should help shape the conclusions drawn about this signal.

Therefore, the current MAH position regarding the risk of NDD in children of fathers treated with valproate is that it should remain as an "important potential risk" [as defined in the GVP Annex I - Definitions (Rev. 5)], with all precautionary measures in place.

PRAC Rapporteur assessment

The consortium considers that in view of the totality of evidence from all sources, the risk of NDD in children of fathers treated with valproate should remain an important potential risk in the RMP with all precautionary measures in place.

The precautionary measures were implemented following the final study results of the paternal PASS which showed a borderline but statistically significant increased risk of NDDs in children paternally exposed to valproate monotherapy compared to lamotrigine/levetiracetam using pooled data from DK, SE and NO, despite limitations in study design leading to uncertainties regarding the strength of evidence.

The more recently published pharmacoepidemiological studies by Christensen et al (2025), Meng et al (2026) (discussed in previous assessment round) and Razaz et al (2026) (new in current assessment round, see Q2 above) did not demonstrate an increased risk. The consortium notes that these null findings are consistent with the results of the individual country results in the paternal PASS, which is not fully agreed as the HR observed in the paternal PASS was higher (pooled aHR 1.50 [1.09-2.08]) than the observed HRs in the other published studies, with a trend for an increased risk observed in data for all 3 individual countries), and risk estimates were higher in a sensitivity analysis using a more narrow composite NDD outcome (excluding disorders of psychological development, hyperkinetic disorders, tic disorders and movement disorders), both in the individual countries and pooled (pooled aHR 1.69 [1.20-2.39]). As also discussed in the previous round, it is agreed that methodological differences, including differences in in- and exclusion criteria, covariates considered, could impact study results. Similarly, the method of analysis can impact the study results as illustrated in the paternal PASS by the sensitivity analysis using a multivariable regression model that considered less covariates and showed attenuated risk estimates compared to the PS-weighted analyses.

The recent results from Botton et al (2025) did show a statistically significant increased risk for the NDD composite outcome for children paternally exposed to valproate compared to children paternally exposed to lamotrigine/levetiracetam both in the final study report and in the updated analyses in monotherapy provided by the authors in response to further questions from PRAC. This study provides additional information regarding the risk of paternal valproate use and offspring NDD risk from a data

source not used in either the paternal PASS or other published studies. However, in the final study report, valproate was used in polytherapy limiting interpretation of study results, and the limited details on the updated study methodology (e.g. change in algorithm to identify epilepsy, cohort numbers or NDD event numbers, HRs not provided, etc) complicate interpretation of the updated analyses provided in the responses. The reasons for not including the updated analyses provided by the EPI-PHARE authors in the final discussion of the totality of evidence by the consortium are understood, considering the uncertainties regarding study methodology in the responses provided by the authors.

It is acknowledged that genetic predisposition may influence the risk of NDD in offspring. The Botton et al (2025) study is currently the only study providing an analysis with negative exposure control (i.e. former users who stopped valproate prior to spermatogenesis) in valproate monotherapy as well as an analysis in fathers with epilepsy not treated with valproate, lamotrigine and levetiracetam. The analysis with negative exposure control by Christensen et al (2024) (valproate-exposed children compared with children of fathers who filled prescriptions for valproate 2 years prior to the exposure period but not during the exposure therapy) also included polytherapy (aHR 0.96 [0.64-1.44]). The absence of increased risk in the complementary analyses in former users and fathers with epilepsy not treated with valproate, lamotrigine or levetiracetam as reported by the EPI-PHARE study suggests that paternal factors other than valproate exposure may influence the observed association between the risk of NDD after paternal exposure to valproate. Exploratory findings from Olstad et al. suggest that fathers treated with valproate may have a higher genetic liability for epilepsy compared with those treated with other anti-seizure medications. The results point to possible confounding (e.g. genetic factors, indication, disease severity, or epilepsy subtype) that may affect child neurodevelopment independently of valproate exposure. However, given the limited sample size, these findings should be interpreted with caution.

The PRAC Rapporteur agrees with the consortium that the totality of evidence shows inconsistency: only 1 study (paternal PASS) showed a borderline statistically increased risk of NDD when results across 3 countries were pooled, whereas other published studies using broadly similar data sources, but with differences in study methodology (Christensen et al, 2025; Meng et al, 2026; Razaz et al, 2026) did not report an increased risk. The findings by Botton et al (2025) are currently difficult to interpret due to limited information on study methodology; however, their analyses in former users and fathers with epilepsy not treated with valproate or lamotrigine/levetiracetam suggest that other factors than valproate use may be contributing to the observed increased NDD risk in the valproate exposed group.

Question 4

A proposal for an update of the currently included information regarding the potential risk of neurodevelopmental disorders following paternal exposure in the product information and additional risk minimization measures on the totality of available evidence, in particular to briefly reflect on the up-to date evidence from epidemiological studies.

MAH response

Precautionary measures including SmPC and PIL update, as well as aRMMs for male patients have been implemented in 2024 following the final results of the PASS Paternal *[number redacted]*. This study compared valproate monotherapy vs lamotrigine/levetiracetam monotherapy and suggested an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception.

Since then, as outlined in answer to Question 3, inconsistent findings from epidemiological studies have emerged (results of Christensen et al. (2025), Meng et al. (2026), Botton et al. (2025) and Razaz et al. (2026) studies) that did not show an increased risk of NDD in children of father exposed to valproate in monotherapy compared to children of father exposed to lamotrigine or levetiracetam in monotherapy, that was observed in the PASS Paternal study.

The MAH therefore considers that results from the PASS TANGO study should be awaited for, as PASS TANGO study has been designed to address the limitations identified in the previous PASS Paternal and other completed studies.

In conclusion, the MAH has carefully reviewed the totality of available evidence to date (March 2026) and is of the opinion that the current information and recommendations reflected in the Product Information and aRMMs remain adequate, as precautionary measures.

PRAC Rapporteur assessment

Based on the data discussed in current round, the MAH does not propose any changes to the currently included information regarding the potential risk of NDD following paternal exposure in the product information or the additional risk minimisation measures. This is not agreed.

In general, it is agreed to maintain the precautionary measures in the product information and additional risk minimisation measures. The final report of the PASS TANGO study will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies. However, an update on the information provided in the product information is necessary, as the current product information only describes the results of the paternal PASS whereas other available (epidemiological) studies have shown variable results. It is considered important to reflect this in the product information for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information, and to acknowledge to totality of available evidence on this potential risk. Therefore, the SmPC sections 4.4 and 4.6 and the PL section 2 should be updated. Please see proposals for updated wording in section '4.3. Updated Rapporteur's proposed recommendation' of this assessment report.

Furthermore, an update on the information provided in the aRMM is necessary, as (epidemiological) studies have shown inconsistent results and current aRMM only reports the results of the paternal PASS. It is important to reflect the totality of available evidence in the aRMM for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information on this potential risk. The following additional risk minimisation measures should be updated for medicinal products containing the active substance valproate: HCP Guide and Patient Guide for male patients. The updated English 'core version of the HCP guide' and 'core version of the patient guide for male patients' are provided in Annex III. No update of the 'core version' of the patient card, attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing, is considered necessary, as the advice provided on this card remains valid and appropriate.

4.2. Rapporteur's discussion

The risk of NDD after paternal exposure to valproate during spermatogenic risk window was considered a potential risk in previous assessments. In current assessment round, the MAH provided a detailed discussion of the French EPI-PHARE study report by Botton et al (recently published on ANSM website; also taking into account responses from the author team to PRAC queries)), the newly published pharmacoepidemiologic study by Razaz et al (2026), the recent study by Olstad et al (2025) that investigated shared genetic susceptibility between epilepsy and NDDs. Based on the totality of

evidence available, the MAH does not propose any changes to the product information or existing aRMM regarding the offspring risk of NDD after paternal exposure to valproate.

The French EPI-PHARE study by Botton et al provides additional information regarding the risk of paternal valproate use and offspring NDD risk from a French data source not used in either the paternal PASS or other published studies. An increased risk of NDDs (composite outcome) was observed in children of fathers treated with valproate compared with lamotrigine/levetiracetam (aHR 1.24 [95% CI 1.07–1.44]). For the individual NDD subtypes, the final study report described a significantly increased risk for IDD (2.12 [1.05-4.30] and borderline increased risk for communication disorders (1.23 [1.00-1.52]). The results were consistent across various sensitivity analyses. However, risk estimates for NDD overall and individual NDD subtypes were attenuated and no longer significantly increased in complementary analyses comparing children from fathers exposed to valproate with children from former users (previous use of valproate in the 2 years to 5 months before spermatogenesis, but no exposure during the spermatogenic risk window) or compared to fathers with epilepsy not treated with valproate/lamotrigine/levetiracetam.

The EPI-PHARE study is the largest study to date (4773 children in valproate group; 3115 children in the lamotrigine/levetiracetam group) and includes long and balanced follow-up across exposure groups (median: ~11 years). A propensity score model was used to adjust for various paternal (but not always for paternal epilepsy), maternal and child characteristic. As in the paternal PASS and other studies (Christensen et al, 2025; Meng et al, 2026; Razaz et al, 2026), NDDs were assessed as a composite endpoint, although differences in included outcomes and ICD coding remain across studies. The authors adapted the validated outcome algorithm of Straub et al, that was also used in the Meng et al study, requiring a minimum age for diagnosis and at least 2 NDD diagnoses at different dates. A major limitation is that the EPI-PHARE study considered valproate monotherapy and polytherapy in most analyses, which limits interpretation of study results. Results of an updated analysis in monotherapy provided by the authors as response to PRAC requests, showed comparable risk estimate for NDD overall in monotherapy (restricted to children born to fathers with epilepsy) to the analyses including valproate in polytherapy, with an estimated adjusted HR of 1.25 (95% CI: 1.07-1.47). Similar to the final study report, the complementary analyses restricted to monotherapy in former users and untreated epilepsy did not show an increased risk for NDD overall or NDD subtypes in offspring of fathers treated with valproate. However, limited details on the updated study methodology (e.g. change in algorithm to identify epilepsy, cohort numbers or NDD event numbers, HRs not provided) complicate interpretation of these updated results.

Overall, the EPI-PHARE suggests an increased risk of NDDs in offspring of fathers treated with valproate versus lamotrigine/levetiracetam. However, the complementary analyses in former users and epilepsy not treated with valproate/lamotrigine/levetiracetam further suggest that the observed association in the main analysis may not reflect a direct causal effect of valproate. While this study has several strengths (large sample size, long and balanced follow-up across exposure groups), the findings are subject to uncertainty due to methodological limitations, including polytherapy use and potential residual confounding (e.g. underlying disease severity).

The study by Razaz et al (2026) is a well-conduced study using nationwide registry data from Sweden and Norway, which were also included in the paternal PASS. Compared with lamotrigine/levetiracetam monotherapy, paternal valproate monotherapy was not associated with an increased offspring risk of overall NDDs (adjusted HR of 1.06 [95% CI: 0.81-1.22]), nor for individual NDD subtypes. The results were consistent across various sensitivity analyses.

While data sources overlap with those used in the paternal PASS, comparability is limited due to differences in study populations, follow-up time and exposure window. The exposure window was 4 months before conception, but an extension of the exposure window in the paternal PASS did not

affect the results. As in the paternal PASS and other pharmacoepidemiologic studies (Christensen et al, 2025; Meng et al, 2026), NDDs were assessed as a composite endpoint, and the NDD composite was comparable to the definition used by Christensen et al (2025) and the NDD narrow outcome of the paternal PASS. In this study, no validated outcome algorithm was used. The study included a larger sample size than the paternal PASS (968 [SE] and 413 [NO] children in valproate group; 1483 [SE] and 1058 [NO] children in the lamotrigine/levetiracetam group). However, the follow-up time was relatively short (median: 6.6 years [SE]; 5.2 years [NO]), and it is unknown whether follow-up time differed between treatment groups. Although analyses restricted to fathers with epilepsy were performed, residual confounding by disease severity or epilepsy type cannot be fully excluded.

Overall, the study by Razaz et al. (2026) does not support an increased risk of NDDs following paternal valproate exposure. While strengths include large, population-based data, adjustment for and analysis restricted to paternal epilepsy, limitations such as shorter follow-up time and potential residual confounding should be considered. Moreover, estimates for NDD subtypes were imprecise due to small numbers.

The study by Olstad et al (2025) investigated the potential genetic confounding in the association between paternal valproate use and NDD outcomes in children using Norwegian cohort and genotype data. Polygenic risk scores (PRSs) were used to evaluate genetic susceptibility. Fathers using valproate had higher epilepsy PRSs compared to those using lamotrigine/levetiracetam and other antiseizure medications, while PRSs for ADHD and ASD were similar. No association between paternal valproate use and child neurodevelopmental outcomes was observed after adjustment in this study, although the sample size was small and underpowered.

The findings of the study by Olstad et al (2025) suggest that fathers treated with valproate may have a higher genetic liability for epilepsy compared with those treated with other anti-seizure medications and support the potential for confounding by indication. Observed genetic overlap between epilepsy, ADHD, and ASD further indicates shared biological mechanisms. Overall, this study provides explorative information that underlying genetic susceptibility may contribute to offspring NDD risk independently of valproate exposure.

Considering all available evidence, inconsistent findings were reported and it is uncertain whether paternal valproate exposure causes NDD in children. Only the paternal PASS showed a borderline statistically increased risk of NDD when results across 3 countries were pooled whereas other well-conducted published studies using broadly similar data sources, but with differences in study methodology (Christensen et al, 2025; Meng et al, 2026; Razaz et al, 2026) did not report an increased risk. The findings of the EPI-PHARE study by Botton et al are currently difficult to interpret due to limited information on study methodology; although they report an increased risk of NDD in their main analysis, their analyses in former users and fathers with epilepsy not treated with valproate or lamotrigine/levetiracetam suggest that other factors than valproate use may be contributing to the observed increased NDD risk in the valproate exposed group.

With the new data that became available in current round, there is further uncertainty regarding the strength of evidence of the observed increased risk of NDD after paternal valproate exposure in the paternal PASS. On the other hand, the currently available studies do not address the most important outstanding uncertainties of the paternal PASS. The final report of the PASS TANGO study, designed to address limitations of the original PASS and including additional countries and sample size, will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results. It is therefore agreed to maintain the precautionary measures in the product information and additional risk minimisation measures for now. However, an update on the information provided on the potential risk of NDD after paternal valproate exposure in the product information and aRMMs for HCPs and male patients is necessary. It is important to reflect the latest

available data in the product information and aRMMs for transparency, to ensure that HCPs and patients have access to accurate and update information, and to acknowledge to totality of available evidence on this potential risk.

4.3. Updated Rapporteur's proposed recommendation following assessment of second round of additional data

Taking into account the evidence reviewed in current assessment round, the PRAC Rapporteur considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk.

In general, it is agreed to maintain the precautionary measures in the product information and additional risk minimisation measures. The final report of the PASS TANGO study will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies. However, an update on the information provided in the product information is necessary, as the current product information only describes the results of the paternal PASS whereas other available (epidemiological) studies have shown variable results. It is considered important to reflect this in the product information for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information, and to acknowledge to totality of available evidence on this potential risk. The aRMM should be updated in line with the proposed PI updates.

Proposed Product information updates

Please find a proposal to update SmPC wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

SmPC section 4.4

[…]

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam**. However, results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent** (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[…]

SmPC section 4.6

[…]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). ~~The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.~~ **Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.** ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

[…]

In line, please also find a proposal to update PL wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ The study has limitations and ~~therefore~~ it is not clear **whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

Other studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

Proposed updates to aore additional Risk Minimisation Measures (aRMM)

An update on the information provided in the aRMM is necessary, as (epidemiological) studies have shown variable results and current aRMM only reports the results of the paternal PASS. It is important to reflect the totality of available evidence in the aRMM for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information on this potential risk.

Updated HCP Guide

An updated English 'core version of the HCP guide' with a revised section on the use of valproate in male patients is provided in Annex II.

Updated Patient Guide for male patients

An updated English 'core version of the patient guide for male patients' is provided in Annex III.

Patient Card

No update of the 'core version' of the patient card, attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing, is considered necessary, as the information provided on this card remains valid and appropriate.

Final versions of updated HCP and patient guides should be implemented at national level in agreement with the NCA.

4.4. Comments from other PRAC members

MS 1

We generally agree with the rapporteur's assessment and conclusions but would like to provide some additional comments. The new evidence presented in this AR weakens the association between paternal use of valproate and the development of neurodevelopmental disorders (NDD) in their offspring. The absence of a negative effect is supported by studies employing various methodological approaches, which we consider a strength of the data.

Only the paternal PASS and the French EPI-PHARE studies reported a statistically significant increased risk. However, it is important to note that the paternal PASS study showed this risk only marginally—and only when pooling data from three Nordic datasets, which individually did not demonstrate a statistically significant increased risk. Furthermore, the paternal PASS study did not adjust for sociodemographic factors, which is an important limitation.

The EPI-PHARE study reported an increased risk exclusively in cases of polytherapy, making it difficult to draw definitive conclusions regarding the specific effect of valproate. Additionally, the EPI-PHARE sub-analysis revealed no increased risk of NDD in offspring of fathers who discontinued valproate use during the spermatogenic window compared to those who continued. While this was only a sensitivity analysis, we agree with the MAH that this finding strongly suggests that inherited patient factors may explain the observed increased risk and should be carefully accounted for.

Further supporting this notion is the study by Olstad et al., which highlights overlapping genetic risk scores between valproate users and the risk of certain NDDs, such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD).

A common limitation across all studies is the use of NDD as a composite measure encompassing multiple neurodevelopmental disorders (e.g., ASD, ADHD, intellectual disability, language disorders, etc.). We question whether this approach is biologically justified, as these disorders present distinct clinical manifestations and are unlikely to share the same underlying organic deficiencies. Importantly, all but the EPI-PHARE study did not demonstrate an increased risk for individual NDDs.

The EPI-PHARE study initially reported an increased risk for intellectual developmental disorders (IDD) in its main analysis; however, this finding was not replicated in the updated analysis, which instead showed an increased risk for ASD and ADHD. These fluctuations underscore the sensitivity of the results to minor changes in the data.

Given the amount of new data attenuating an effect of paternal use of valproate and the risk of (any) NDD in their offspring we agree that an update of the PI is justified reflecting this new information. We support the wording proposed by the rapporteur but have additional suggestion for revision of the PI.

As the new information have weakened the association with paternal use of valproate and the risk of NDDs in their offspring we consider it no longer risk proportionate to include specific advice to discuss the need for contraception for males using valproate. We therefore suggest deleting the following information from the PI (in red and ~~strike through~~):

SmPC section 4.4

[…]

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam**. However, results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent** (see section 4.6).

~~As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.~~

SmPC section 4.6

[…]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). ~~The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.~~ **Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.** ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.

~~As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).~~

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ The study has limitations and ~~therefore~~ it is not clear **whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

Other studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• ~~The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment~~

• ~~The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)~~

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

~~Do not donate sperm when taking valproate and for 3 months after stopping valproate.~~ ~~Talk to your doctor if you are thinking about having a baby.~~

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

We also consider that our amendments to the proposed changes to the product information should be reflected in the HCP guide and the patient guide for males

PRAC Rapporteur assessment

We appreciate the comments from the MS 1 colleagues, and acknowledge their different view on the necessity of keeping the precautionary measures for male patients as were implemented following the paternal PASS.

We agree that the new data that became available in current procedure further weakens the association between paternal valproate and offspring risk of neurodevelopmental disorders, as also reflected in the Rapporteur's overall discussion. Similarly, the limitations of the paternal PASS are acknowledged, and have been extensively discussed previously.

It is agreed that using a composite NDD endpoint is not ideal as clinical presentation and disease etiology can be heterogeneous across NDDs; however, sample size of available studies has generally not been sufficient to investigate the risk of NDD subtypes, The heterogeneity in risk observed for specific NDDs in the EPI-PHARE study (as well as other studies) is noted and this is also the reason why we consider that no specific NDD should currently be mentioned in the product information (or aRMM).

We acknowledge the MS 1 position that it is no longer risk proportionate to include specific advice for male patients, specifically to need to discuss this risk with patients, the use of contraception, and the advice not to donate sperm. However, although we agree that the newly available studies increase uncertainty regarding the strength of evidence, we still consider the risk of neurodevelopmental disorders remains an important potential risk and therefore the previously implemented precautionary measures are still proportionate also considering the ongoing TANGO PASS.

MS 2

Endorsement without further comments

PRAC Rapporteur assessment

The endorsement is appreciated.

MS 3

We fully endorse the PRAC Rapporteur's conclusion and appreciate the thorough assessment.

It is agreed that the evidence available should be reflected in the product information and additional risk minimisation measures. Further, it is agreed that the final report of the PASS TANGO study should be awaited before considering any major changes to the current risk minimisation measures in place.

Overall, the wording proposed for the product information and the aRMM is supported, however a minor change to the proposed wording in the Patient guide for males is suggested (proposed deletion in ~~strikethrough~~):

Other studies have also investigated the possible risk for physical and mental developmental disorders in children born to fathers treated with valproate in the 3 to 4 months before conception. These studies did not show an increased risk for physical and mental developmental disorders in children born to fathers treated with lamotrigine or levetiracetam or compared with fathers not treated with valproate.

Overall, the results from different studies are not consistent~~, and most studies do not suggest an increased risk~~. It is not clear whether any possible risk for physical and mental developmental disorders is caused by valproate itself or by other factors, such as the father's underlying illness. The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is also not known.

It is proposed to remove ", and most studies do not suggest an increased risk" from the patient Guide. This phrase is not reflected in the proposed PI updates and updates to HCP guide. DK considers that the main message to be stated in the aRMM is that the results from the different studies are not consistent, and it is therefore no need to include the sentence about "most studies".

PRAC Rapporteur assessment

We thank the MS 3 colleagues for their endorsement of the assessment and PI proposals. We agree with the comments regarding the patient guide and have amended our proposal for the patient guide

accordingly. Please see updated proposal for aRMM taking into account MS comments, input from independent scientific experts and MAH below.

MS 4

We would like to thank the colleagues for their concise assessment and generally endorse their evaluation.

In light of the inconsistent evidence regarding the risk of neurodevelopmental disorders after paternal exposure to valproate during the spermatogenic risk window, we support the proposed amendments to the product information, as well as to the educational materials for healthcare professionals and male patients, in order to ensure the provision of up to date information.

However, we would like to provide additional comments on the proposed wording (see comments below).

Regarding the proposed amendments in the SmPC and PL, we have the following comment:

The information regarding the uncertainty of risk associated with valproate exposure more than three months prior to the spermatogenic window is considered to be of importance for both patients and healthcare professionals.
Given that the available evidence on this aspect, including the study by Batton et al., is limited, and as this information is proposed to be retained in the HCP and male patient guide, it is considered appropriate that it should also be maintained within the product information texts.

Furthermore, it is noted that the patient-friendly terminology used to describe "NDD" is inconsistent between the PL ("movement and mental developmental disorders") and the male patient guide ("physical and mental developmental disorders"). In order to ensure consistency across materials, it is proposed that a single, harmonised term be used throughout both, the PL and the male patient guide. Consideration should be given to determining which terminology is most appropriate for patient understanding.

SmPC

We therefore propose the following amendments in SmPC section 4.6 and PL section 2 (based on the wording proposed by the Rapporteur, additions in **underlined bold and blue**; deletions in ~~strikethrough and blue~~):

SmPC section 4.4
[…]
Use in male patients
A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. ***However, available evidence is inconsistent as results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure.*** ~~*Thus, the available evidence is inconsistent*~~ *(see section 4.6).*
[…]

SmPC section 4.6
[…]
Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated

with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). ~~*The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.*~~ ***Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.*** ~~*The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed.*~~ ~~***The***~~ ***study also did not assess the risk of NDDs in children of men who discontinued valproate more than three months before conception, allowing for spermatogenesis without valproate exposure.***

Other retrospective observational studies did not show a ~~*statistically*~~ ***significant increased risk of NDDs in children born to men treated with valproate monotherapy*** ~~*in the*~~ ***3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.***

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate ~~*in the*~~ ***3 months prior to conception is possible, however, the causal role of valproate is not established.***

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

PL

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

One *study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).* ***It is not known whether there is any risk for children whose fathers stopped taking valproate at least three months before conception, giving the body time to produce new, unexposed sperm.*** *The study has limitations and* ~~*therefore*~~ *it is not clear* ***whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.*** ~~*if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.*~~ *The study was not large enough to show which* ~~*particular*~~ ***specific*** *type of movement and mental developmental disorder children may be at risk of developing.*

Other studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

HCP guide

Regarding the proposed amendments in the HCP guide, we have the following comment:

While it is acknowledged that the Paternal PASS is associated with certain limitations, it should be noted that comparable limitations are also inherent in the other studies. Therefore, we propose to add a similar statement following the paragraph describing the other studies as follows (based on the wording proposed by the Rapporteur, additions in **underlined bold and blue**; deletions in ~~strikethrough and blue~~):

The study was not large enough to investigate associations with specific NDD subtypes (composite endpoint including autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). ~~*Due to study*~~ ***The study has*** *limitations including potential confounding by indication and differences in follow-up time between exposure groups*~~*, the causal role of valproate is possible and not considered to be confirmed*~~*.*

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.

Other retrospective observational studies from Norway, Sweden, Denmark, and Taiwan did not show a ~~*statistically*~~ ***significant increased risk of NDDs in children born to men treated with valproate monotherapy*** ~~*in the*~~ ***3–4 months prior to conception compared to men treated with lamotrigine/levetiracetam monotherapy (estimated HRs ranged between 1.02 and 1.10, with confidence intervals including 1) or men not treated with valproate. These studies are also associated with inherent limitations, including potential confounding by indication.***

Differences in study design, including control for confounding and population selection, may contribute to variability in findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.

The risk to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

Male patient guide

Regarding the proposed amendments in the male patient guide, we have the following comment:

The removal of the second part of the following sentence should be reconsidered, as it is unclear what information and implications arise for the patient solely from the statement that "the study has limitations".

The study has limitations ~~*and therefore it is not entirely clear if the increased risk for physical and mental developmental disorders suggested by this study is caused by valproate*~~*.*

Furthermore, not only the Paternal PASS but also the other studies have limitations (e.g. residual confounding, wider exposure window (120 days before LMP) in Razaz et al., differences in follow-up time between exposure groups) and only mentioning this point for the Paternal PASS could lead to a bias of patients' perception of available evidence.

It is therefore proposed to relocate the statement on study limitations to follow the paragraph describing the other studies and to include a brief explanation outlining the implications of these limitations for patients as follows (based on the wording proposed by the Rapporteur, additions in **underlined bold and blue**; deletions in ~~strikethrough and blue~~):

In this study, around 5 children in every 100 had problems with neurodevelopment when born from fathers treated with valproate, and around 3 children in every 100 when born from fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). For example, problems with your child's neurodevelopment as they grow up may include:

Being late in learning to walk and talk.

Lower intelligence than other children of the same age.

Poor speech and language skills.

Memory problems.

Autism or autistic spectrum problems

Attention Deficit and/or Hyperactivity Disorder.

~~*The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.*~~

~~*The study has limitations*~~ ~~*and therefore it is not entirely clear if the increased risk for physical and mental developmental disorders suggested by this study is caused by valproate*~~*. A wide range of physical and mental developmental disorders were investigated in the study. However, the study could not show which particular type of disorder that children born to fathers taking valproate may be at risk of developing.*

Other studies have also investigated the possible risk for physical and mental developmental disorders in children born to fathers treated with valproate in the 3 to 4 months before conception. These studies did not show an increased risk for physical and mental developmental disorders in children born to fathers treated with lamotrigine or levetiracetam or compared with fathers not treated with valproate.

~~***All studies mentioned have limitations that complicate a robust assessment of a causal relationship.***~~

Overall, all studies mentioned have limitations that complicate a robust assessment of a causal relationship . T~~t~~he results from different studies are not consistent, and most studies do not suggest an increased risk. It is not clear whether any possible risk for physical and mental developmental disorders is caused by valproate itself or by other factors, such as the father's underlying illness. The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is also not known.

PRAC Rapporteur assessment

We value the suggestions provided by the MS 4 colleagues.

We acknowledge the difference in patient-friendly terminology used to describe NDD in the PIL versus the aRMM, and have amended our proposals so that this is aligned.

We appreciate all the textual suggestions provided for the proposed SmPC and PIL wordings, as well as the information to be included in the aRMM for HCPs and patients. Please see updated proposals for PI wording and aRMM after consideration of MS comments, input from independent scientific experts and MAH below.

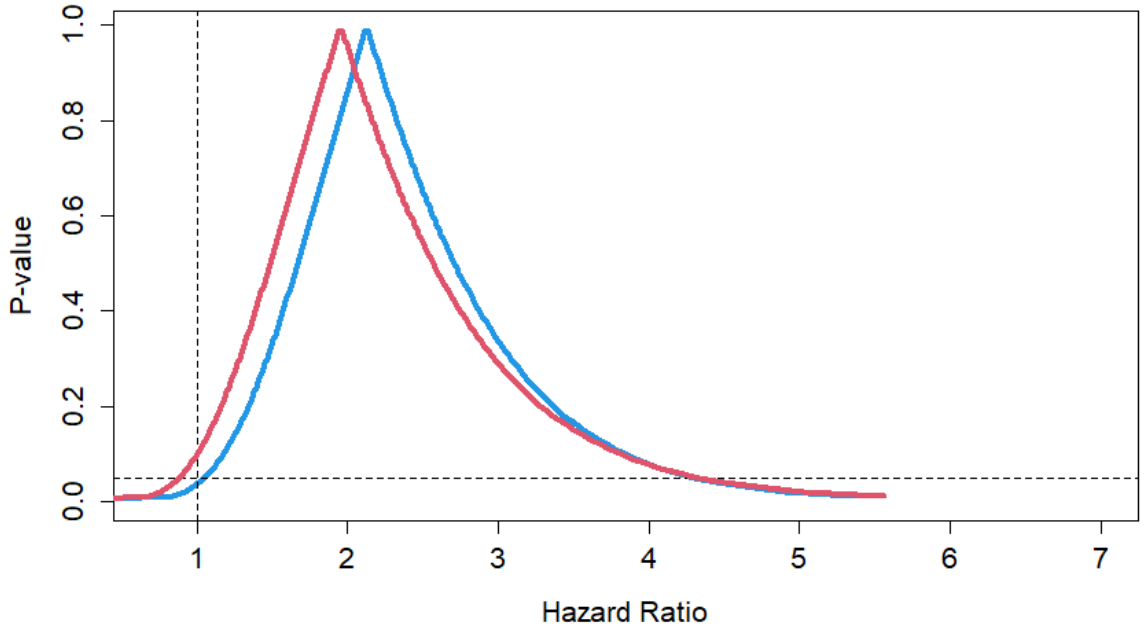
MS 5

We agree with the PRAC Rapporteur that the currently available data justifies that the precautionary statements in the product information and additional risk minimisation measures should be maintained. However, we have some comments on the methodological aspects of the Rapporteur's and the MAHs assessments of the EPI-PHARE study (and other key epidemiological study results) for reasons specified below. We agree with the Rapporteur that the SmPC text requires revision, but do not fully agree with the currently proposed text.

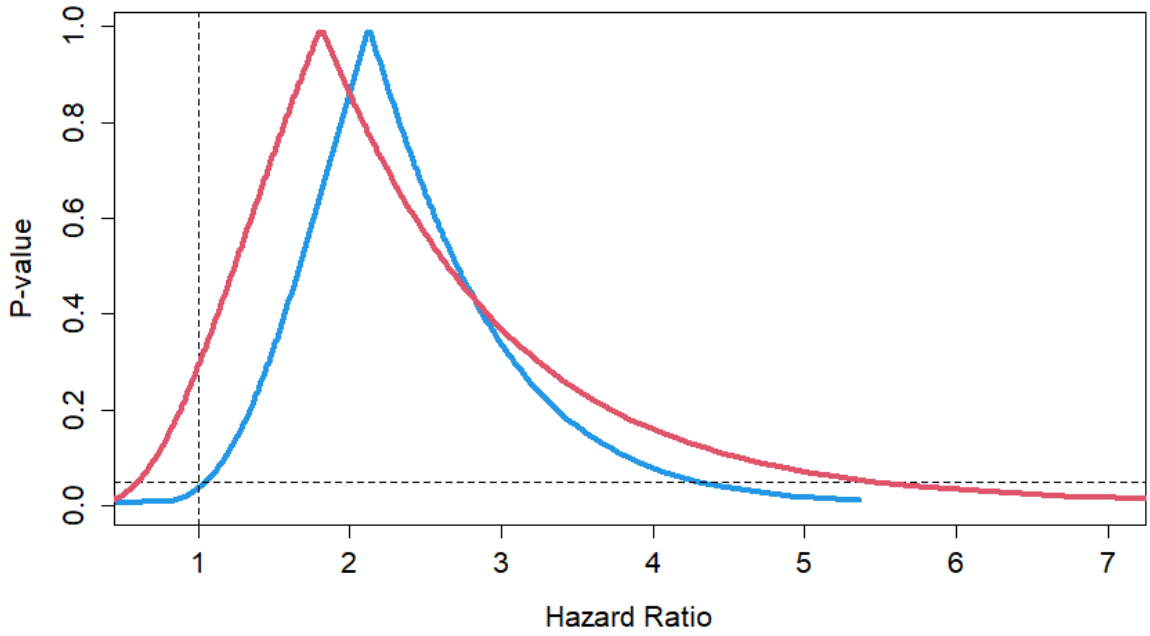
Assessments of the response from the EPI-PHARE study authors

The focus on the presence or absence of statistical significance is best avoided in the evaluation of this type of studies since it may lead to serious misinterpretations. The cut-off level for statistical significance is entirely arbitrary. Only random error is addressed by significance testing and other sources of bias are in these observational studies major concerns. Statistical significance is no safeguard against random error. On the contrary, a statistically significant result on the 5% level is often associated with a substantial risk for being the results of chance [1]. Absence of statistical significance should never be interpreted as evidence supporting absence of an association or an effect, particularly when a safety outcome is the focus of the analysis. For an authoritative discussion of this issue please see guidance from the American Statistical Association [2], and especially the accompanying background texts; and the *EMA Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes*.

The current assessment exemplifies this problem well. Please consider the complementary analysis of monotherapy as an important illustration of the problem. Requesting and focusing on this complementary analysis restricted to monotherapy is clearly warranted. The underlying concern is that other treatments could introduce a bias in the estimation of the associations. The problem is that the MAHs and the Rapporteur raise concerns when the estimate for IDD loses statistical significance when the analysis is restricted to monotherapy. This reasoning is not appropriate. When restricting the analysis to monotherapy, this reduces the number of patients and outcomes and consequently precision but importantly should reduce the potential bias from polytherapy. The latter is reflected by the movement of the point estimate. This type of analysis represents a trade-off between reduced bias and reduced precision. The P-value functions (*Lash et al. Modern epidemiology 4th Ed. Page 342-347*) below can illustrate the result, with the distribution for VPA Poly in blue and VPA mono in red. The shift of the distribution is minor, indicating a negligible bias from polytherapy. The loss of statistical significance simply reflects the expected reduction of precision, which is of no relevance to the key question of bias in the estimate.



Also the assessment of the important analysis using children of former valproate user fathers as reference group suffers from the same concern with the interpretation, as illustrated with the P-value functions below, with the distribution for VPA Poly in blue and VPA mono/former users in red:



The movement of the distribution is modest but the reduced precision notable. Again, it is recommended not to interpret this as a "null finding" due to absence of statistical significance. The attenuation of the estimated association, and consequently the influence of bias, is only modest. This is the key finding from this analysis.

Overall, these important complementary analyses indicate that the impact of bias is modest and does not remove the signal of an increased risk. Conclusions based on absence/presence of statistical significance are not informative.

The potential impact of residual confounding

A key concern expressed in the AR and also proposed to be included in the SmPC is the risk for residual confounding. The concern regarding a potential bias from a calendar time effect is noted. This could in principle potentially have been addressed by modelling with Poisson regression instead of Cox regression and including calendar time in the model, but this has been assessed as unfeasible by the authors of the EPI-PHARE study, and their judgement must in this respect be acknowledged and respected.

It is, however, recommended that the discussion on potential residual confounding acknowledges the E-value calculations and considers if there is plausible confounding from genetic factors that could be compatible with an E-value of 3.31 as estimated for the association between paternal exposure to valproate monotherapy and ID. Are such an imbalance and strength of association plausible for genetic factors in this context?

Limitations in the results presentation from the EPI-PHARE study

Both the Rapporteur and the MAHs raise concerns regarding missing pieces of results presentation from the EPI-PHARE study. While we agree that the data mentioned as missing would be desirable in a complete results presentation, we do not find that these specific parts of the results could materially influence conclusions and therefore recommend that such critical remarks towards the authors are avoided in the discussion. It would rather be appropriate to clearly gratefully acknowledge the efforts by the authors to respond to PRACs repeated requests.

Study design and estimand for the primary analyses

The purpose of a comparative study design is to approximate a counterfactual comparison, i.e. that a study subject is exposed to valproate and followed over time to detect the potential outcome. The subject is then placed in a time capsule and brought back in time to the index date, now instead being exposed to the control treatment and again observed for the outcome over the same time period. Since this is impossible, we approximate this situation with a group comparison. But the essential take-home message to be considered in the study design is that each study subject must be eligible for both treatments, valproate and the active comparators levetiracetam/lamotrigine.

This is unfortunately not the case in the studies at hand, and the design of this comparison is not compatible with reality. This problem would have been apparent if the design had been made with an emulated target trial approach [3]. Consider the design of a randomised, pragmatic, low-intervention trial (treatments according to approved SmPC). A man with bipolar disease can be treated with valproate but not with levetiracetam. This man is consequently not eligible for randomisation to both treatment armes and is therefore not eligible for participation in the trial. He should therefore not be included in a relevant comparison in an epidemiological study.

The practical consequence is that the analyses stratified by individual indication are of utmost importance. This is also highlighted by the PRAC Rapporteur and agreed but requires further emphasis. In the case of the Christensen et al 2025 study it means that it is the estimates highlighted in yellow below (extract from Table 1 in the publication) that avoids this critical design problem. The discrepancy with the main analysis is apparent.

This makes it difficult to agree with the authors conclusion that they were "unable to replicate the signal for NDDs in children with paternal valproate exposure".

Overall, the attention to the epilepsy indication is therefore important, and the Christensen et al 2025 study should not be viewed as a "null finding" contradicting the paternal PASS results. Other study results, however, fail to identify this association.

Mechanistic support

Summary conclusion regarding currently available evidence

Currently available data provide a persistent but not fully consistent support for a weak association between paternal exposure to valproate during spermatogenesis and NDD in the offspring. There is a substantial remaining uncertainty regarding the validity and clinical relevance of these findings, and the mechanistic support is weak. The data supports maintenance of already implemented risk minimisation measures. It is relevant to update the product information to reflect currently available data, but this update should avoid mentioning specific studies. Instead, a brief summary justifying the risk minimisation but also in general terms reflecting remaining uncertainty (please see detailed proposal below). A more elaborate revision should be based on the final results of the category 1 PASS expected in Q1 2028.

1. Nuzzo R. Scientific method: statistical errors. Nature 2014;506(7487):150-2. (In eng). DOI: 10.1038/506150a.
2. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. The American Statistician 2016;70(2):129-133. DOI: 10.1080/00031305.2016.1154108.
3. Hernán MA,Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183:758-64.

We have the overall comments regarding the SmPC text:

- Given the many different studies and estimates at hand, considering methodological challenges, it is proposed in this case to avoid presenting actual estimates. This also acknowledges that we await further evidence from the requested PASS.
- We propose to avoid mentioning specific methodological aspects in the SmPC-text, in particular "power" and "*statistical significance*".
- We do not agree to include statements such as "*…did not show a statistically significant increased risk of NDDs…*".
- We do not agree with the proposed statement "*…did not show increased risk of NDD in children of fathers who used valproate during spermatogenesis compared to children of fathers who were former users of valproate…*". As discussed above, this is based on loss of statistical significance, which is an inappropriate basis for the assessment.
- We propose that key elements in the text should be that estimated associations are in general weak and that there is substantial remaining uncertainty regarding causality.
- We do not agree with the proposed statement "*…the causal role of valproate is not established*" since this is essentially impossible to accomplish with scientific methods. The scientific support can only make a causal role more or less probable.

Please find our proposal for revised SmPC and PL texts below:

SmPC section 4.4 (PRAC RAPP proposal, MS 5 proposal)

[…]

Use in male patients

~~A retrospective o~~**O**bservational stud**ies**~~y~~ suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. **The estimated associations are in general weak and there is a substantial remaining uncertainty regarding the validity and clinical relevance of these findings. Precautionary measures are warranted.** ~~**However,**~~

~~**results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent**~~ (see section 4.6).

[…]

SmPC section 4.6

[…]

~~A retrospective o~~**O**bservational stud**ies**~~y in 3 Nordic countries~~ suggest~~s~~ an increased risk of neuro-developmental disorders (NDDs) in children ~~(from 0 to 11 years old)~~ born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy~~, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07).~~ **The estimated associations are in general weak and there is a substantial remaining uncertainty regarding the validity and clinical relevance of these findings. The mechanistic support for these associations is weak.** ~~The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.~~ ~~**Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.**~~ ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

~~**Other retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.**~~

~~**Additional analyses in one study did not show increased risk of NDD in children of fathers who used valproate during spermatogenesis compared to children of fathers who were former users of valproate (2 years to 5 months before spermatogenesis). One preclinical study found no rational to suggest an impact on spermatogenesis following exposure of valproate in mice. Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that f**~~**Factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association.**

~~**Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.**~~

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

[…]

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

~~One~~ ~~s~~**S**tud~~y~~**ies** suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. ~~In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore I~~**, however, i**t is not clear **whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study was not large enough to show which particular **specific** type of movement and mental developmental disorder children may be at risk of developing.~~

~~**Other studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.**~~

PRAC Rapporteur assessment

We thank the MS 5 colleagues for their endorsement of the maintenance of the risk minimization measures currently implemented.

Regarding the methodological considerations raised by the MS 5 colleagues, it is acknowledged that presence or absence of statistical significance should not be the main focus when interpreting the pharmacoepidemiological study results, and we have considered other aspects (e.g. magnitude of effect, precision of estimates, consistency across analyses) as well.

Regarding the risk estimates for IDD in the FR EPI-PHARE study, we consider these risk estimates to be uncertain due to the low precision and small number of events these risk estimates are based on. In the original study report, the former user analyses included 4773 offspring with 42 events in the valproate group and 1372 offspring with 7 events in the comparator group. In the updated analyses restricted to fathers with epilepsy, the group sizes were further reduced most notably for the former user group (from 1372 to 795 offspring), with a probable further reduction in the analyses restricted to monotherapy. This further reduction in group size has likely reduced the already small number of events in the comparator group even more. Thus, although point estimates consistently suggest an increased risk, the risk estimates are uncertain and of low precision due to the limited number of events.

For the main outcome NDD overall in the FR EPI-PHARE study, in the final study results (thus population not restricted to epilepsy and valproate use including polytherapy), all risk estimates (main analysis, former user analysis, analysis in fathers with epilepsy not using valproate/lamotrigine/levetiracetam) were above 1; however, risk estimates in the complementary analyses were lower than in the main analysis. Overall, an increased risk cannot be excluded as all point estimates were above 1; however risk estimates were not consistent across comparator groups.

However, in the updated analyses provided by the authors (population restricted to epilepsy, use including polytherapy or use restricted to monotherapy), the risk estimates in the former user analysis and analysis in fathers not using valproate/lamotrigine/levetiracetam) were attenuated towards the null (polytherapy: former users 1.04 [0.81-1.32], untreated 1.05 [0.92-1.19]); monotherapy: former users 1.02 [0.80-1.30], untreated 1.04 [0.92-1.18]). Thus, in these updated analyses, although the main analysis suggested an increased risk, this was not observed in the complementary analyses with both risk estimates moving close to 1. This weakens the evidence for a causal association with valproate treatment.

It is acknowledged that analysis stratified by indication are of importance. It is noted that several published epidemiological studies have provided analyses restricted to fathers with epilepsy. In these stratified analyses, risk estimates were higher compared to the risk estimates in the overall population in the publications by Christensen et al (2025) and Razaz et al (2026), but not in the publication by Meng et al (2026); thus results are not consistent across studies. Stratified analyses (if feasible) by indication and type of epilepsy are also planned for the TANGO PASS.

We appreciate the input provided to the SmPC wording. Of note, the original 4.6 text used by the MS 5 colleagues does not seem to be based on the proposed wording by the PRAC Rapporteur, as reference to additional analyses in former users or results of the preclinical study was not proposed by the PRAC Rapporteur. We generally agree with the MS 5 suggestions to limit inclusion of too detailed information on individual studies, and to mention specific methodological aspects. Please see our updated proposals for PI wording and aRMM after consideration of all MS comments, input from independent scientific experts and MAH in the updated recommendation.

MS 6

Thanks to the Rapporteur for the comprehensive and well-structured assessment provided.

Having carefully reviewed the totality of the evidence presented, it is acknowledged that the currently available data remain heterogeneous and inconclusive with regard to a potential causal relationship between paternal exposure to valproate and the risk of NDDs in offspring, however, more data do not point to the risk, neither any mechanism has been detected.

As the current PI wording suggests an increased risk based on results from paternal PASS, we find it important to point to the fact that several other studies did not find an increased risk. The aim of PI is to reflect the important current knowledge – when this knowledge is modified, PI should be modified as well. In case we are not able to give a clear recommendation based on data which are diverse, we should reflect the ambiguity of data so that HCPs and patient could make themselves an informed decision.

Although we support the current update of PI, the related update of EM is questionable. EM have been updated recently (Low Birth Weight). In our view, additional changes to EM at this stage may contribute to information fatigue among the target audience and could undermine the effectiveness of the existing risk minimisation framework. Therefore the need for EM update should be discussed by PRAC to reach the most appropriate conclusion.

The final results of the ongoing TANGO study, which is specifically designed to address key limitations of the previous PASS and to provide more robust and comprehensive evidence could probably better elucidate the risk and lead to adequate update of all existing information.

PRAC Rapporteur assessment

We thank the MS 6 colleagues for their comments and support for the proposed PI wordings. Regarding the need to update the aRMM, we consider that the information on the potential risk of NDD after paternal exposure in the EM should be kept in line with the information included in the product information and reflect the most up-to-date information, also see comment to MS 9 proposal below.

It is acknowledged that repeated distribution of EM may lead to information fatigue; however, the need for active (re-)distribution of updated aRMM is up to decision by national NCAs, and it may be considered nationally to not actively distribute updated aRMM when actionable recommendations do not change and the information provided in the aRMM is fully in line with information included in the product information (e.g. in NL the aRMM was not actively distributed following the recent update with information on SGA) or to consider alternative ways of active distribution, for example by actively distributing the aRMM to professional organisations rather than to individual HCPs.

Of note, a proposal to include information regarding the outcome of current procedure in the PRAC highlights is included in the updated recommendation in order to provide awareness to the new evidence that became available in current assessment, see section 4.6 below.

MS 7

We thank the Rapporteur for their thorough assessment of the multiples studies and for presenting comprehensive conclusions and recommendations on this complex safety concern.

We fully support the Rapporteur's proposal to update the PI and the aRMM available for male patients exposed to valproate, highlighting in full transparency the current uncertainty on a putative causal association between increased risk of NDDs and paternal exposure to valproate during the spermatogenesis window (3-4 months before conception). This will help HCPs and male patients considering fatherhood to make fully informed decisions, while waiting for the final report of the PASS TANGO study.

We have a few minor suggestions on the various proposals from the Rapporteur. Please find them below.

Proposal for the PI

We mostly support the Rapporteur's proposal for the PI, as the updated wording adequately outlines the current state of evidence, mentioning the inconsistency of the results available from different studies, as well as possible reasons for these discrepancies.

As a minor comment for the wording intended for SmPC section 4.6, we propose the addition highlighted in grey below. We believe that it better reflects the hypothesis conveyed by the study from Olstad et al (2025) to which the sentence refers to:

Section 4.6:

[…]

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including genetic factors underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.

[…]

However, this addition is not proposed for the Patient Leaflet, not to complexify the message for lay readers.

Proposal for the HCP Guide

We mostly agree with the updates proposed to the core version of the HCP Guide. We however have the two following proposals:

1. To align the text on our proposal formulated above for the SmPC section 4.6, specifying "genetic factors" underlying paternal disease;
2. Considering the updated data, we question the adequacy of including a pictural representation of the Paternal PASS study results suggesting an increased risk of NDD in children born to fathers exposed to valproate 3 months prior to conception. Pictures are powerful tools to draw readers' attention, but here it may also give the false impression that this study supersedes others described below the picture, refuting this association. We propose to remove it from the core version of the HCP.

Proposal for the male Patient Guide

We fully support the Rapporteur's proposal.

Proposal for the Patient Card

We agree with the Rapporteur that no update is needed for the card, as the current messages remain valid regardless of the new information discussed during this Signal.

PRAC Rapporteur assessment

We appreciate the feedback from MS 7. Regarding the suggestion to specifically mention genetic factors underlying paternal epilepsy, we consider that the proposed inclusion of 'factors other than valproate exposure, including underlying paternal disease' is currently sufficient to reflect the available information, as this already includes genetic factors. The publication by Olstad et al (2025) provides important additional information to the previously published pharmacoepidemiological studies and describes that fathers using valproate may have a different underlying genetic liability, potentially reflecting distinct epilepsy subtypes compared to fathers using lamotrigine/levetiracetam, indicating potential for genetic confounding/confounding by indication. However, to what extent these genetic factors can explain the observed risk is currently unclear, and therefore we consider a general statement to be sufficiently reflecting the current available evidence.

Regarding HCP guide, the section for male patients includes a pictural representation of the adjusted cumulative risk of NDD in the valproate and lamotrigine/levetiracetam groups as observed in the paternal PASS. This provides contextualization to the observed magnitude of risk in the paternal PASS. It is considered that HCPs should be able to interpret the difference in risk as the figure also includes the actual numbers. As this Further information on the studies can be retrieved in the publications referenced in the material.

See updated proposals for PI wording and aRMM after consideration of all MS comments, input from independent scientific experts and MAH below.

MS 8

We thank the Rapporteur for the clear presentation and comprehensive assessment of additional data provided by the authors of the FR EPI-PHARE study as well as by the MAH Consortium.

We are in general agreement with the Rapporteur in terms of the need to update PI to reflect the findings of recent large pharmacoepidemiological studies so that the totality of available evidence relating neurodevelopmental outcomes of children exposed to paternal use of valproate is reflected, and not only the findings of the MAH consortium paternal PASS.

However, we have further comments with respect to the reflection of the available data and the precautionary measures in the product information.

Context for Precautionary Measures and TANGO

At the time of the assessment of the paternal PASS, important limitations, in particular the potential for confounding by indication given the lack of adjustment for paternal epilepsy, were acknowledged. However, given the finding of an increased risk of NDD following paternal exposure to valproate and given limited other available data to confirm or exclude a risk, precautionary measures were agreed.

While these measures were introduced on a precautionary basis and highlight the importance of evaluating individual circumstances, they are nonetheless impactful, including the need to consider effective contraception, including for female partners, during treatment with valproate and for 3 months after discontinuation, and recommendations to consider alternative treatment options for male patients planning to conceive a child, as well as recommendations for regular review of male patients as to the appropriateness of valproate treatment.

Given the study limitations, the imposed PASS TANGO was also agreed at the time in order to further explore the impact of the limitations of the paternal PASS, including confounding by paternal epilepsy, on its key findings.

Emerging Evidence and Impact on the Dataset

When the EPIPHARE study data emerged, also suggesting an association of paternal valproate exposure with NDD in offspring, several key limitations were noted, firstly that the analyses concerned valproate polytherapy, leading to the potential for confounding by epilepsy of greater severity, and secondly lack of adjustment of the monotherapy analyses for paternal epilepsy. However, at that time, the impact of this latter limitation on the study results was unclear.

Since then, a number of large pharmacoepidemiological studies (Razaz et al, Meng et al and Christensen et al 2025) have been published which do not support an association of an increased risk introducing significant uncertainty into the overall dataset. In particular, a key strength of these studies as compared with the paternal PASS and the initial results of EPIPHARE which must be acknowledged is that they endeavoured to take into account in their analyses the indication for valproate, in particular paternal epilepsy.

It can also be acknowledged that the PASS combines data from three countries. However, we wish to highlight a meta-analysis by Christensen *et al* 2026 [4] of estimates of NDD from these recent pharmacoepidemiological studies: Razaz et al[5], Meng et al[6] and Christensen et al 2025[7] along with a sensitivity analysis which included the estimates from the FR EPI-PHARE study to assess their impact on pooled estimates.

This metanalysis by Christensen *et al* 2026 did not identify evidence of an association between paternal valproate (monotherapy) and NDD compared with paternal lamotrigine or levetiracetam monotherapy. As there was overlapping Norwegian data from Razaz et al (labelled Norway 1) and from Meng et al (labelled Norway 2) pooled HRs for NDD and for individual disorders of ASD, ADHD, ID and Disorders of Psychological Development were presented.

- In meta-analysis of data from Denmark, Sweden and Norway 1, the pooled HR of offspring NDDs was 1.05 (95% CI 0.87 to 1.27; I2=0.0%), and in meta-analysis of data from Denmark, Sweden and Norway 2, it was 1.03 (95% CI 0.85 to 1.24; I2=0.0%).
- In the meta-analysis including Taiwan, Denmark, Sweden and Norway 1, the pooled HR was 1.06 (95% CI 0.88 to 1.27; I2=0.0%), and when including data from Taiwan, Denmark, Sweden and Norway 2, the pooled HR was 1.04 (95% CI 0.87 to 1.25; I2=0.0%).
- When the authors included data from EPI-PHARE final report (restricted to monotherapy where the analysis did not appear to be adjusted for paternal epilepsy) the pooled HR when meta-analysed with data from Norway 1, Denmark, Sweden and Taiwan was 1.11 (95% CI 0.98 to 1.27; I2=0.0%), and 1.11 95% CI 0.97 to 1.26; I2=0.0%), with data from Norway 2, Denmark, Taiwan and Sweden.

Confounding by Indication and Study Limitations

Further relevant data has also emerged in the interim from the findings of Olstad *et al* 2025, the Rapporteur's conclusions on which are particularly pertinent:

"*Overall, the higher epilepsy PRS in fathers using valproate compared to the other groups indicates a different underlying genetic liability, potentially reflecting distinct epilepsy subtypes and non-genetically comparable groups. This study also observed genetic overlap between epilepsy, ADHD, and ASD, which is consistent with known shared biological mechanisms underlying these conditions. The finding of this explorative study might highlight the potential for genetic confounding/confounding by indication, as shared genetic susceptibility/underlying disease may contribute to child neurodevelopmental outcomes independently of valproate exposure"*

Previously confounding by indication may have been considered a more general limitation that may have been mitigated by the use of the active comparator. However, the findings of Olstad raise concerns that even with the active comparator, confounding by indication is plausible. Indeed, even where analyses are adjusted for a broad paternal epilepsy indication, in the absence of granular information on severity and subtype of epilepsy (including genetic variants of which there are many), this raises fundamental questions as to the limitations of lamotrigine/levetiracetam as a comparator group and the resulting

[4] Christensen J, Trabjerg BB, van Gelder MMHJ*, et al* Risk of neurodevelopmental disorders associated with paternal use of valproate during spermatogenesis: a living meta-analysis—version 1 *Journal of Neurology, Neurosurgery & Psychiatry* Published Online First: 12 May 2026. doi: 10.1136/jnnp-2026-338454
[5] Razaz N, Soderling J, Tomson T*, et al* Risk of neurodevelopmental disorders associated with paternal use of valproate during spermatogenesis *Journal of Neurology, Neurosurgery & Psychiatry* Published Online First: 04 March 2026. doi: 10.1136/jnnp-2025-337441
[6] Meng LC, van Gelder MMHJ, Chuang HM, Lai HY, Chen LK, Hsiao FY, Nordeng HME. Valproate Use by Fathers and Risk of Neurodevelopmental Disorders in Children. NEJM Evid. 2026 Mar;5(3):EVIDoa2500254. doi: 10.1056/EVIDoa2500254. Epub 2026 Feb 24. PMID: 41733407.
[7] Christensen J, Trabjerg BB, Dreier JW. Risk of Neurodevelopmental Disorders and Paternal Use of Valproate During Spermatogenesis. JAMA Netw Open. 2025;8(5):e2512139. doi:10.1001/jamanetworkopen.2025.12139

impact of confounding by indication, particularly on the findings of the paternal PASS which is not adjusted for paternal epilepsy, but also the recent results of EPIPHARE for monotherapy restricted to fathers with epilepsy and the Christensen result restricted to fathers with epilepsy of unknown cause.

In addition to the limitations of the analysis of ID in EPIPHARE (in particular the low numbers of events), we consider that the conclusions with respect to Olstad et al as well as the limited understanding of the pathogenesis of NDD including individual outcomes greatly hinders quantitative evaluation of the impact of confounding by indication through the E-value. Further, although prespecified analyses would have been preferable, considering that a particular outcome appears to have been selected for calculation of the E-value, it may be informative to assess other analyses for such value. In particular, it is noted that assuming NDD are rare, the E-value for the overall risk of NDD (HR=1.25) as reported in EPIPHARE could be estimated as being substantially lower, E-value = 1.81, and that to attenuate the lower bound of the 95% confidence interval (1.07) such that it would include the null value an E-value of 1.34 may be estimated (Mathur et al 2018[8]).

These fundamental questions with respect to the ability to handle confounding by indication in the available data sources will also apply to TANGO, particularly in the event that an association persists. In light of the emerging data, the extent to which the anticipated TANGO study is likely to allow a definitive conclusion on a causal relationship between parental exposure and NDD is unclear.

Overall Interpretation of the Evidence

Overall, we consider that at this point that there is substantial uncertainty around the strength of evidence supporting classification of a risk of NDD following paternal exposure to valproate during the spermatogenic risk window as an important potential risk, in particular given the potential impact of confounding by indication, and that this uncertainty should be reflected in the product information.

Proportionality of Risk Minimisation Measures

Regarding the precautionary and additional risk minimisation measures, the rationale put forward by the Rapporteur for their maintenance (pending the findings of the imposed PASS TANGO) can be acknowledged.

However, as outlined above, we consider that the landscape since TANGO was agreed has changed. In light of the data that has emerged in the interim as well as the questions raised regarding the feasibility of confirming such a risk, there is a need for PRAC to consider the proportionality of the current precautionary measures at this juncture in the context of the increased uncertainties in the evidence base.

Proposals for Product Information

We are of the view that healthcare professionals should continue to discuss the PASS findings with male patients but in the context of the overall data. In particular the uncertainty regarding the risk of NDD in children born to fathers treated with valproate should be clearly communicated, alongside a greater emphasis on taking individual circumstances and patient perspectives into account in the implementation of risk minimisation measures.

We also have a query on reference of movement disorders in the Patient Leaflet in the context of these new studies, as we understand movement disorders were not included in the NDD algorithm for these.

Based on these considerations, we have proposed refinements to the product information updates suggested by the Rapporteur in relation to the available data.

[8] Mathur, M, Ding, P, Riddell, CA, VanderWeele, TJ, 2018, 'Website and R package for computing E-values', *Epidemiology*, vol. 29, no. 5, e45-e47, doi: 10.1097/EDE.0000000000000864

We agree with the Rapporteur that the final agreed updates to the PI should also be incorporated into the educational materials for HCPs and patients.

MS 8 added text highlighted in yellow

SmPC section 4.4

[…]

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam**. However, results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent and overall the risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is uncertain** (see section 4.6).

~~As a precautionary measure,~~ P~~p~~rescribers should ~~inform~~ **discuss with** male patients **these data and the uncertainty of the risk** (see section 4.6) **Depending on individual patient circumstances and preferences this discussion may include consideration of** ~~and discuss the need to consider effective~~ contraception, ~~including for a female partner, while using valproate and for at least 3 months after treatment discontinuation~~ **and the continued appropriateness of treatment with valproate. Given the uncertainty m**ale patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

~~Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients~~. Individual ~~circumstances should be evaluated in each case~~

It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[…]

SmPC section 4.6

[…]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). ~~The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.~~ **The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.** ~~The study~~

~~was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

A number of other retrospective observational population based studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.

Differences in study design, ~~including control for confounding and population selection~~ may contribute to variability in study findings. ~~In addition, available data suggest that F~~factors other than valproate exposure, including underlying paternal disease ~~may contribute to the observed association~~ which may be important determinants of risk, could not be completely accounted for.

Overall, ~~an increased~~ a risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is ~~possible, however, the causal role of valproate is not established~~ uncertain.

~~As a precautionary measure~~, Prescribers should **discuss with** ~~inform~~ male patients ~~about this potential risk~~ **these data and the uncertainty of the risk**. **Depending on individual patient circumstances and preferences this discussion may include consideration of contraception and continued appropriateness of treatment with valproate**~~. discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4).~~ **Given the uncertainty m**~~M~~ale patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

[…]

In line, please also find a proposal to update PL wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

PL section 2

Important advice for male patients

A risk of neurodevelopmental disorders in children of fathers ~~Potential risks relating to~~ taking valproate in the 3 months before conception of a child **is uncertain.**

One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ The study has limitations and ~~therefore~~ it is not clear **whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying**

illness. ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

A number of o~~O~~ther studies did not show an increased risk ~~of movement~~ ~~and~~ mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies, the risk was similar whether a father was treated with valproate or with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Factors other than valproate exposure such as the father's underlying medical condition may affect early childhood development. The studies could not fully account for these important factors.

~~As a precautionary measure~~ Your doctor will discuss with you **the findings in these studies and the uncertainty of the risk.**

Depending on your personal circumstance and preferences your discussion with your doctor may include consideration of contraception and the continued appropriateness of treatment with valproate. As a risk is uncertain, do not donate sperm when taking valproate and for 3 months after stopping valproate.

~~•The potential risk in children born to fathers treated with valproate~~

~~• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment~~

~~• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)~~

~~• The possibility of other treatments that can be used to treat your disease, depending on your individual situation~~

~~Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby~~

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

PRAC Rapporteur assessment

We appreciate the input provided by the MS 8 colleagues.

We acknowledge that the precautionary measures that were implemented after the paternal PASS are impactful. The limitations of the paternal PASS have been considered by the Rapporteur and by PRAC during discussion of these results, and precluded drawing final conclusions regarding causality. Despite the study limitations, and after consideration of input from various stakeholders, precautionary measures were implemented. It is fully agreed that the newly available studies increase uncertainty

regarding the strength of evidence, as also reflected in the PRAC Rapporteur's discussion of the overall data.

We have also noted the meta-analyses of Christensen et al (2026) that included data from the publications by Christensen et al (2025), Meng et al (2025), and Razaz et al (2026), as well as an additional analyses also including the EPI-PHARE monotherapy results (as provided in the sensitivity analyses in the final study report from November 2025). This new publication provided pooled HRs for NDD composite outcome as well as individual NDDs. The pooled HR for the NDD composite (1.05 [0.87-1.27]) does not show evidence of an increased risk. Pooled HRs were higher for some of the individual NDD subtypes, but were less precise and cannot exclude or confirm an increase in risk. The MS 10 colleagues have also informed us of a meta-analysis performed by ANSM, see MS 10 comment below.

Confounding by indication is an important limitation, and it has previously also been discussed that using an active comparator design alone does not fully address this limitation, as type or severity of epilepsy can differ between patients treated with valproate compared to patients treated with lamotrigine/levetiracetam. The findings by Olstad et al (2025) indeed showed that fathers treated with valproate have higher genetic predisposition for epilepsy compared to fathers treated with lamotrigine/levetiracetam, and genetic overlap in epilepsy, ADHD, and ASD thus offspring may inherit elevated genetic susceptibility. However, the study was underpowered to detect group differences in neuropsychiatric traits, thus it remains uncertain to what extent this shared genetic susceptibility can explain the previously observed increased risk. Further stratified analyses by indication and by type of epilepsy (if feasible) are planned for TANGO. In addition, analyses in former users (as also performed in the EPI-PHARE study) and sibling-matched analysis (planned for TANGO) may provide more insight into the extent to which characteristics other than valproate exposure may contribute to the risk of NDD.

Overall, we agree with the MS 8 colleagues that taking into account all available evidence there is uncertainty regarding strength of evidence currently available. Regarding the proportionality of the precautionary measures, the MS 8 colleagues propose amendment to the precautionary measures that were implemented following the paternal PASS. MS 8 suggests that the risk of NDD should still be discussed with patients, but proposes to place more emphasis on taking individual circumstances and patient perspectives into account. Although agreed that the evidence that became available in current procedure further weakens the strength of evidence available, we have currently not proposed any changes in the previously agreed wording for the precautionary measures, that were already drafted in such way to leave room for individual circumstances (*considered, recommended as appropriate)* and also specifically state that individual circumstances should be evaluated in each case

The input provided to the PI wording appreciated. Please see updated proposals for the HCP guide and patient guide after MS comments, input from independent scientific expert and MAH below in this AR.

MS 9

We thank PRAC Rapporteur for their thorough assessment on this complex procedure and fully endorse their conclusion and proposal.

We agree that the new evidence available regarding the potential association of paternal exposure to valproic with NDD development in offspring is necessary to be included in subsequent sections of PI, for transparency purposes.

We have some comments regarding the additional risk minimisation measures.

We do not consider necessary to update the patient guide for males with the aim to include new information regarding these studies. According to the GVP Module XVI, "educational tools are meant to support adherence to the intended actions for risk minimisation". As the precautionary measures have not been amended in this procedure and must continue to be carefully followed, including uncertainties and discrepancies related to study results could create confusion among patients. Furthermore, we would like to suggest removing the results of the study already included in the section "What are the risks of taking valproate* when conceiving a child" (proposal to delete the strikethrough text):

A study suggests a possible risk of physical and mental developmental disorders (problems with early child development) in children born to fathers treated with valproate in the 3 months before conception.

~~In this study, around 5 children in every 100 had problems with neurodevelopment when born from fathers treated with valproate, and around 3 children in every 100 when born from fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).~~ Although the study could not show which particular type of disorder that children born to fathers taking valproate may be at risk of developing. For example, problems with your child's neurodevelopment as they grow up may include:

- *Being late in learning to walk and talk.*
- *Lower intelligence than other children of the same age.*
- *Poor speech and language skills.*
- *Memory problems.*
- *Autism or autistic spectrum problems*
- *Attention Deficit and/or Hyperactivity Disorder.*

~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~

Although it is not entirely clear if the increased risk for physical and mental developmental disorders suggested by this study is caused by valproate, the following precautionary measures should be followed…" ~~. A wide range of physical and mental developmental disorders were investigated in the study.~~

In addition, we believe that the text proposed for inclusion in the guide for healthcare professionals could be further streamlined. Educational tools should be kept as simple as possible and, since information on the studies will be included in the SmPC, we suggest shortening the proposed wording to state only that the results of other studies are inconsistent with a reference to the product information for further details.

PRAC Rapporteur assessment

We thank the MS 9 colleagues for their feedback and support for the proposed PI updates. Regarding the need to update the aRMM, the MS 9 colleagues propose to not update the aRMM with information on the new information that became available in current procedure as the precautionary measures have not been amended. We consider that the information on the potential risk of NDD after paternal exposure in the EM should be kept in line with the information included in the product information and reflect the most up-to-date information. The precautionary approach to inform male patients about this potential risk and corresponding updates of PI and aRMM were discussed with external stakeholders during finalization of the paternal PASS and it was noted that it should be ensured that balanced information would be disseminated to HCPs and patients to contextualize available data. We consider that the new information on the risk of NDD that became available in current procedure is important contextualization of the risk and therefore should also be included in the aRMM.

The input provided to the male patient guide and suggestion for the HCP guide is appreciated. Please see updated proposals for the HCP guide and patient guide after MS comments, input from independent scientific expert and MAH below in this AR.

MS 10

We thank the rapporteur for their assessment.

With regard to the available data, we agree with the rapporteur that, in light of recently published findings, maintaining the current risk minimization measures is necessary as well as an update of the information to ensure that healthcare professionals and patients have access to accurate and up-to-date data.

Indeed, we generally support the rapporteur's proposal to globally highlight the various published studies in the section 4.6. of the SmPC (to be reflected in the package leaflet in a patient-friendly text) but disagree with the proposed text which does not sufficiently counterbalance the weight of all available studies.

First, we do not agree with removing details from the initial PASS data. Indeed, removing these data which remain valid can be misinterpreted by HCPs and patients and hamper to provide a fully transparent presentation of the evidence even though the purpose of the update would be to further emphasize the study limitations. The protocol and the results of the imposed PASS have been reviewed in-depth by the PRAC which recommended a well-balanced text, explaining the results and their limitations. These study limitations from the initial PASS were already known at that time and there is no need to further emphasize the study limitations of this PASS and to remove the detailed results without applying the same precaution for the other available studies.

Furthermore, exclusively referring to the results of monotherapy studies, which did not replicate the findings of the initial PASS study, appears too restrictive. The proposed revised wording could weaken the overall message and may not adequately inform healthcare professionals about this potential risk.

In addition, we note that, at this stage, data from the French cohort are not included in the product information (SmPC/PL), as additional information from the authors would be required to fully interpret the results and the methodology. However, we emphasize the importance of including these data—similar to the PASS results—since results in polytherapy cannot be totally disregarded and in the interest of full transparency, given the potential risks identified and the rationale below.
The French study is based on the largest cohort of children paternally exposed to VPA to date and on an extended follow-up, allowing to properly assess the specific risks of individual NDD subtypes, which may be diluted when combining NDDs altogether. The risk of intellectual disability among exposed children appears significantly increased when applying the most appropriate methodology to minimize indication biases and residual confounding from unmeasured variables, i.e. when restricting the study population to children born to a father with epilepsy and using an active comparator design. Notably, the populations considered in the other available studies were heterogeneous in terms of paternal morbidity, with paternal epilepsy accounting for only 30 to 77% of the children in the exposed group and 34 to 54% of those in the reference group across the studies. This may have resulted in substantial residual confounding, as suggested by the increase in HR estimates in additional analyses restricted to children born to a father with epilepsy (when they were provided, e.g. in the Christensen, Meng (Taiwan) and Razaz (Sweden) studies).

Although in the French study the association with intellectual disability was no further statistically significant in the analysis considering only children whose father was treated in monotherapy, the HR point estimate was very close to that obtained when considering exposure either in monotherapy or in polytherapy. Similarly, results of the analyses allowing exposure in combination therapy were very close to those restricted to monotherapy in the other studies providing such analyses, with HRs for any NDDs of 1.06 [0.74; 1.50] versus 1.02 [0.67; 1.54] in Christensen study, and 0.86 [0.52; 1.40] versus 1.02 [0.57; 1.82] in Meng Norway study (active comparator analysis). This suggests that the lack of significant association observed after restriction to monotherapy in the French study is most likely due to a loss of statistical power rather than to heterogeneity in the association according to exposure in mono or in polytherapy. Given the rarity of the outcomes of interest, this supports the approach focusing primarily on exposure both in monotherapy or in combination therapy, rather than on monotherapy alone, in order to ensure sufficient statistical power to identify potential associations with NDD risks in the offspring.

Since the beginning of this signal procedure, new data have regularly emerged which highlight the public health concern and the willingness to further elucidate whether the risk of NDD following paternal exposure can still be considered as potential. All these data have been taken into account throughout this procedure, such as the French study, the NO-TW study, and more recently the study from Razaz et al. In addition, we would like to highlight the very recent study from Christensen et al. (2026) which has been published after circulation of the pAR of this round. This article is a meta-analysis initially based on data from SE, NO, and DK, derived from studies other than the PASS:

- NDD as a whole: HR 1.05, 95% CI (0.87; 1.27)
- ASD: HR 1.07, 95% CI (0.69; 1.68)
- ADHD: HR 0.90, 95% CI (0.70; 1.17)
- ID: HR 1.36, 95% CI (0.82; 2.28)
- Psychological Development Disorders: HR 1.21, 95% CI (0.82; 1.77)

The authors then incorporated results from the Taiwanese dataset published by Meng. We would like to highlight that including Meng's data in the assessment of neurodevelopmental disorders as a whole appears debatable, as the definition of this outcome in that study is very broad (its weight in Christensen's analysis is low). Finally, they evaluated the results by incorporating data from the French EPIPHARE cohort (analyses restricted to monotherapy exposure) as non-peer-reviewed literature data (Botton et al., 2025 – no publication in a scientific journal to date, report publicly available on the EPIPHARE website) to assess the risk of NDD as a whole (HR 1.11, 95% CI [0.98; 1.27] or HR 1.11, 95% CI [0,97; 1.26] depending on the selection criteria of datasets from DK/NO/SE/TW) .

We also take this opportunity to share the results of a meta-analysis performed by the ANSM with the tool MetaPreg. The full report in English is attached for your convenience.

systematic review and metaanalysis_VP/

Please note that although it is based on published data (including the French study), the results of this meta-analysis are not yet public but could be shared with the MAHs and the PRAC. The protocol is available on PROSPERO. Similarly to the meta-analysis very recently published (Christensen et al, 2026),

the ANSM conducted a meta-analysis using data from various studies based on monotherapy results, including relevant subgroups (i.e. unexposed controls, sick controls exposed to other treatments), and sensitive analyses to test the robustness of the findings. These results complement those from the Christensen's meta-analysis, as the ANSM applied the same approach to all outcomes. The MetaPreg meta-analysis included 8 publications (Meng et al., 2026; Razaz et al., 2026; Botton et al., 2025; Colas et al., 2025; Christensen et al., 2025; Christensen et al., 2024; Tomson et al., 2020; Yang et al., 2019), representing 11 retrospective cohort studies from 5 countries (Denmark, France, Norway, Sweden, and Taiwan), with overlapping populations. As described in the attached report, after dealing with overlaps, 2–5 independent datasets per outcome were retained for the analysis. A summary of the key findings from the ANSM meta-analysis is provided as follows:

- Major malformations: OR 0.84; IC95% (0.64;1.10); 2 studies; 1510 exposed;
- NDD as a whole: OR 1.11; IC95% (0.99;1.25); 4 studies; 6496 exposed;
- ADHD: OR 1.02; IC95% (0.87;1.20); 5 studies; 6792 exposed;
- ASD: OR 1.10; IC95% (0.89;1.35); 5 studies; 6883 exposed;
- Intellectual disorders: OR 1.35; IC95% (0.95;2.35); 4 studies; 6288 exposed;
- Language disorders/delay: OR 1.28; IC95% (1.05;1.57); 3 studies; 4331 exposed;
- Learning disorders/delay: OR 1.08; IC95% (0.78;1.49); 2 studies; 4027 exposed.

The report shows that subgroup analyses yield consistent results across all comparator groups, including unexposed controls and sick controls exposed to other treatments. Regarding NDD as a whole, additional analysis was performed with a different methodology to resolve overlapping issue which yielded to a higher point estimate and a significant association (OR = 1.33, IC 95% (1.07;1.66)), with a slight increase of heterogeneity (I2=17%). Similarly, Christensen et al. (2026) also conducted this analysis, identifying a slight increased risk (HR = 1.24; 95% CI [1.06; 1.44]).

Given all these results and methodological limitations—such as exposure and outcome misclassification, a definitive conclusion cannot be reached, in particular for intellectual and language disorders, where odds ratios (ORs) are highest and the upper confidence interval bound exceeds 1.5. At this stage, we consider that the level of evidence is currently insufficient to exclude a potential risk. Additional high-quality studies are needed to confirm or refute this potential risk. Regarding the TANGO PASS, although it is not acceptable to wait for the results before any revision of the SmPC, the results are still needed to further elucidate the outcomes of the initial PASS. It should also be emphasized that any additional data which would be available before the final results of the PASS (planned in 2028) should be duly assessed and highlighted in case these would be relevant enough to modify the outcome of this signal procedure.

Finally, given the uncertainties, we agree with the rapporteur that additional risk minimization measures should be maintained as a precaution, along with updated information for full transparency towards HCPs and patients.

Given the complexity and sensitivity of this safety topic from a public health perspective and different ways to interpret the results and their robustness, trust in the European assessment should remain essential and the inputs from external experts and stakeholders within the framework of this procedure could be considered (e.g. stakeholders meeting, ad hoc expert groups). The PRAC assessment is based on public data and misinterpretation and/or miscommunication of the results at EU level could be all the more deleterious as individual HCPs and patients could also perform their own analysis of the risk and reach different conclusions. In this context, it would be worthwhile to consider this option to seek for

additional advice to ensure a correct understanding of the results and the proposed measures (mainly PI updates) from HCPs and patients perspectives.

If the last round of this procedure is expected in June, PRAC highlights would be needed as an outcome of the June PRAC meeting and should be considered by the PRAC and the EMA, in line with previous public communications informing HCPs and patients about this safety topic for which the public health concern remains high. Many questions can arise from the public and any communication should be sufficiently detailed to explain why the uncertainties and corresponding precautionary measures remain regarding this potential risk.

We also suggest the following modifications for the SmPC and PL (please see below in yellow) to include the French study and to keep the initial wording surrounding the initial PASS.

Proposed Product information updates
Please find a proposal to update SmPC wording on use in male patients below (additions in **underlined bold**; deletions in strikethrough):
SmPC section 4.4
[…]
Use in male patients
Two ~~A~~ retrospective observational stud**iesy** ~~suggests~~ an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam**. However, results from other studies in monotherapy do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the risk remains uncertain** ~~**Thus, the available evidence is inconsistent**~~ (see section 4.6).
As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.
Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.
Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.
[…]
SmPC section 4.6
[…]
Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception
A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. ~~**Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.**~~ The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

A nationwide French cohort study not restricted to monotherapy showed a significantly increased risk for NDDs overall, compared with men treated with lamotrigine or levetiracetam (monotherapy or polytherapy).
Other retrospective observational studies in monotherapy did not show a statistically significant increased risk of NDDs in children born to men treated with valproate ~~monotherapy~~ in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam ~~monotherapy~~.
Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. Limitations of epidemiological studies include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate ~~is~~ cannot be established.
As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.
Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.
[…]

In line, please also find a proposal to update PL wording on use in male patients below (additions in **underlined bold**; deletions in strikethrough, proposed additional suggestions in yellow):

PL section 2
Important advice for male patients
Potential risks related to taking valproate in the 3 months before conception of a child
One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known~~. The study has limitations and ~~therefore~~ it is not clear ~~**whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.**~~ if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study was not large enough to show which particular ~~**specific**~~ type of movement and mental developmental disorder children may be at risk of developing.
Another study shows an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception compared who does not. However, some other studies did not suggest this risk which was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.
Overall, given the uncertainties, it cannot be established whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.

PRAC Rapporteur assessment

We appreciate the input provided by the MS 10 colleagues and their agreement with our proposal to maintain the current risk minimization measures and to reflect the currently available evidence in the PI (and aRMM).

The MS 10 colleagues provided an alternative text proposal for the information to be included in the SmPC, which is appreciated. The disagreement to remove details from the paternal PASS is noted. It is acknowledged that the results of the imposed PASS and the corresponding PI wordings were carefully

considered by PRAC, also taking into account input from various external stakeholders. However, we do not agree that removing some of the (very) detailed information on the paternal PASS results in a less transparent presentation of the evidence. The description of the PASS results as currently included in section 4.6 is rather elaborate compared to information commonly included in this section. We consider it important to reflect the totality of evidence, and with more studies becoming available, such detailed presentation of information from all available studies would lead to an overly long and detailed section with information that is not always immediately relevant to prescribers. Instead of presenting detailed results of individual studies, which can become outdated quickly in case new study results become available, we prefer a more high level description of studies, including the most important aspects and conclusions of the available studies with clear recommendations for prescribers. Since previous consideration of the paternal PASS results, all studies, including paternal PASS, have been published, thus further detailed information can be found in the public domain if HCPs wish to obtain more detailed information.

The MS 10 colleagues further note that only referring to monotherapy studies appears too restrictive in the reflection of the totality of evidence and propose to also include data from studies that investigated the risk of NDD after exposure to valproate polytherapy, such as the French EPI-PHARE study. The noted strengths of the French EPI-PHARE study (large cohort and long and balanced follow-up time) are fully agreed, and the use of valproate in polytherapy does reflect real-world use. However, when mono and polytherapy are combined it becomes difficult to draw conclusions regarding any risk specific to valproate. As polytherapy users may have more severe or refractory epilepsy this increases the potential for confounding by indication or disease severity. This was also the rationale for PRAC to request additional analyses in monotherapy that were kindly provided by the authors. We consider the complementary analysis in former users to be an important analysis in the FR-EPIPHARE study. While the main analysis showed an increased risk for NDD (HR 1.26 [95% CI, 1.07-1.43]), an increased risk was not observed in the former user analysis, with the risk estimate attenuated towards the null (1.04 [0.81-1.32]). This weakens the evidence for a causal association with valproate treatment. Although we can understand the argument to include information on the EPI-PHARE study for transparency reasons (the EPI-PHARE study is also available in the public domain and referred to by the recent publication by Christensen et al (2026)), we had not proposed to include the results from the updated analyses in the SmPC due to limited availability of methodological details for the updated analyses which makes it difficult to fully assess robustness of the study results.

It is acknowledged that the risk estimates for IDD consistently suggest an increased risk across analyses in polytherapy and monotherapy; however, the risk estimates are uncertain and of low precision due to the limited number of events. Thus, although point estimates consistently suggest an increased risk, the risk estimates are uncertain and of low precision due to the limited number of events. That is why we have not proposed to mention a potential increased risk in any NDD subtype.

We have noted the recently published meta-analyses by Christensen et al (2026) that included data from the publications by Christensen et al (2025), Meng et al (2025), and Razaz et al (2026), as well as an additional analyses also including the EPI-PHARE monotherapy results (as provided in the sensitivity analyses in the final study report from November 2025). This new publication provided pooled HRs for NDD composite outcome as well as individual NDDs. The pooled HR for the NDD composite (1.05 [0.87-1.27]) does not show clear evidence of an increased risk. Pooled HRs were higher for some of the individual NDD subtypes, but were less precise and cannot exclude or confirm an increase in risk.

The MS 10 colleagues also shared the results of a meta-analysis performed by ANSM that is currently unpublished. This meta-analysis included additional studies compared to the meta-analysis by Christensen et al (2026), i.e. Colas et al (2025; paternal PASS), Christensen et al (2025), Tomson et al

(2020). Similar to the approach taken by Christensen et al (2026), when multiple publications reported results for the same underlying database, overlapping populations were identified and managed to avoid double counting (selection based on sample size, follow-up duration, completeness of confounder adjustment). Additional analyses included use of all available comparator groups (e.g. unexposed) and alternative overlap handling resulting in different studies included. Overall, the study describes a borderline significant risk for NDD overall (OR 1.11 [0.99-1.25]), with pooled OR including studies including different comparator groups and exposure. Results of the additional analyses (use of different comparator groups; alternative handling overlap) did not majorly differ from the results presented above. For individual NDD, the presented analyses do not suggest an increased risk of ADHD, ASD or learning disorders/delay. For Global developmental disorder/intellectual disorder and language disorder/delay, higher risk estimates were observed; however, overall data is insufficient to exclude or conclude on an increased risk.

Input from external stakeholders was considered after assessment of the results of the paternal PASS and was taken into account in the original proposal to reflect information on the paternal PASS in the product information. There is currently no change proposed to the previously implemented precautionary measures. The need for further consultation of external stakeholder for the currently proposed updated to the PI and aRMM can be further discussed in PRAC plenary.

We fully agree with the MS 10 proposal that some form of public communication informing patients and HCPs about the current topic is needed after finalization of current procedure. The suggestion to include information in the PRAC highlights is supported. In addition, NCAs may be encouraged to inform professional organization about the outcome of current procedure.

The suggestions for the proposed PI wordings are appreciated. Please see an updated proposal for PI wording and aRMM taking after consideration of all MS comments and input from independent scientific experts in the updated recommendation.

ISE #1

Independent Scientific Expert #1 provided the following feedback:

I would like to congratulate the rapporteur on a thorough and comprehensive assessment of this difficult and delicate matter.

The new epidemiological and non-clinical evidence is thoroughly examined, and I agree that though further evidence is awaited amongst others from the PASS TANGO study, updates are warranted at this time, but not major changes to the current risk minimization matters.

I think this and previous discussions regarding the safety and benefit-risk-balance of valproate needs to be considered carefully in future procedures, that includes clinical neurological input of how this product is placed in the treatment. I find that it might be questionable to use valproate in non-life threatening situations. Valproate is one of several antiseizure medications (ASMs) available. When we know that this product can cause serious birth defects and we suspect it has the potential to harm the gametocytes and possibly the genome.

I suggest the following slight changes to the rapporteur's proposal:

Proposed Product information updates

Please find a proposal to update SmPC wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

SmPC section 4.4

[…]

Use in male patients

The available evidence is inconsistent, the results from some studies do not suggest an increased risk of NDDs after paternal valproate exposure. However, a retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam~~. However, results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent~~ (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[…]

SmPC section 4.6

[…]

~~Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception:~~

Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established, and studies show conflicting results:

Retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy. However, a retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). ~~The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group.~~ **Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.** ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

~~**Other retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.**~~

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the

observed association. ~~**Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.**~~

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

[…]

In line, please also find a proposal to update PL wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

Some studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ The study has limitations and ~~therefore~~ it is not clear **whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

~~**Other studies did not show an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.**~~

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

Proposed updates to Core aRMM

The proposed updates to core aRMM are overall agreed.

Need for Communication

Taking into account the ultimate PRAC recommendations, consideration should be given as to how this emerging data and its impact on the understanding of the risk of NDD following paternal exposure to valproate and any agreed changes to the risk minimisation measures, will be communicated to HCPs and patients following conclusion of this procedure.

PRAC Rapporteur assessment

We appreciate the feedback provided and the proposed suggestions to the SmPC and PL wordings. Please see an updated proposal for PI wording and aRMM taking after consideration of all MS comments and input from independent scientific experts in the updated recommendation.

We acknowledge that for transparency reasons, and due to previous public interest and awareness about the risk of NDD after paternal exposure, communicating about the results of current procedure is desirable. A proposal for communication in our updated recommendation.

ISE #2

Independent Scientific Expert #2

My apologies for my late comments on the assessment report. I appreciate all the work that clearly has gone into it and am impressed by the thorough evaluation of so much data.

I agree that the SmPC and PIL and risk management plan should be updated to ensure that the product information and RMM accurately reflects all (new) evidence. My main suggestions are to slightly shorten and rephrase some of the sentences in the SmPC, as follows:

****

Other ~~retrospective~~ observational studies did not show a ~~statistically~~ significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to ~~variability~~ differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. ~~Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.~~ Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconclusive, and the causal role of valproate remains uncertain.

****

I suggest omitting "retrospective" and "statistically", as its strictly not necessary when the intent is to communicate that the other observational studies did not provide evidence of an increased risk. I would also replace "variability" with "differences in study findings", as the observed differences likely reflect systematic design differences, and "variability" can be read as a biostatistical term referring to random variation in estimates (e.g., sampling variability, variability around a mean, variability in measurements). I also suggest rephrasing and using "inconclusive" and "remains uncertain" in the last sentence, to convey that uncertainties remain (while awaiting the results of the TANGO study to further clarify the risk).

Besides this, I have a comment regarding the reflections in the assessment report on the differences observed across NDD subtypes (e.g., IDDs). I would not expect the associations to be similar across all NDDs. Such differences may arise from both underlying disease mechanisms, but also study characteristics because 1) NDDs are a heterogeneous group of conditions with distinct etiologies and genetic architectures, 2) Shared genetic liability between epilepsy and NDDs may differ by NDD type. Familial or genetic factors could therefore contribute more strongly to certain NDDs than others, 3) Outcome ascertainment and diagnostic practices may vary across NDDs. For example, IDDs may be detected and recorded differently than ADHD, ASD, or other NDDs, leading to differential susceptibility to detection bias, 4) Given the small number of exposed cases and events, random variation may have a substantial impact on outcome-specific risk estimates, resulting in heterogeneous findings across NDD types.

I also think it may be worthwhile to consider a DHPC alongside the update. This demonstrates well PRAC's responsiveness to new evidence and ensure that healthcare professionals are informed of the newer studies, especially given all the interest and feedback received from professional organisations.

PRAC Rapporteur assessment

We greatly appreciate the input provided in the assessment report and proposals for the PI wording, See updated proposals for PI wording and aRMM after consideration of all MS comments, input from independent scientific experts and MAH in the updated recommendation.

The comment regarding the differences observed across NDD subtypes is noted, and it is agreed that associations are not necessarily expected to be similar across NDD subtypes due to differences in underlying mechanism or study characteristics.

The need for communicating the proposed updates of the PI and aRMM to the field is acknowledged and agreed, especially considering the interest and feedback previously received from professional organisations. However, we consider that a DHPC may not be the best communication tool to inform healthcare professionals about the new evidence that has become available in current procedure as there is currently no new emergent safety information that needs to be communicated, nor is there a any update to the existing advices or need to take immediate action or change current practice. Instead we propose that information on current procedure will be published by EMA in the PRAC highlights and recommend that NCAs may inform professional organisations about the PRAC review of the new evidence that has become available. This can be discussed further at PRAC plenary.

4.5. Comments from MAH

On 27 May 2026, the MAH sent the following comments on the Rapporteur preliminary assessment report dated 15 May 2026 on answers to questions to second RSI:

Dear Madam, Dear Sir,

We thank you for sharing with us the Rapporteur Preliminary Assessment Report (dated 15 May 2026) on our answers to second RSI for PRAC signal of Neurodevelopmental disorders with paternal exposure to Valproate and related substances (EPITT ref. No. 20191). Please find below and attached our comments, as MAH.

The company agrees with the Rapporteur *"to maintain the precautionary measures in the product information and additional risk minimisation measures and to await the final report of the PASS TANGO study before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies".*

In light of the inconsistency in the available data to date and as shared in our response to second Request for Supplementary Information in April 2026, the company remains of the opinion that the current information and recommendations reflected in the Product Information and aRMMs remain adequate, as precautionary measures.

We however acknowledge PRAC Rapporteur recommendation to introduce information on the inconsistency of study results in Product Information and aRMMs.

Having considered the Rapporteur proposed updates in SmPC, Package Leaflet, Core HCP Guide and Core male Patient Guide, we would like to make some comments, including rewording proposals, mainly for consistency/alignment across these documents.

Please find in the attached documents (Common EU PI, Core HCP Guide and Core Patient Guide in clean and track changes version, word and pdf), our proposals with justifications for proposed changes as notes/comments.

We thank you for your consideration of these remarks and would be grateful if the updated Product information and aRMMs that will be proposed for endorsement to PRAC following Member States comments could be shared with us, separately or as part of the updated Rapporteur Assessment Report.

Rapporteur assessment comment

The MAH provided input to the PAR and agrees with the PRAC Rapporteur's overall conclusion to maintain the precautionary measures in the product information as well as additional risk minimisation measures for male patients.

The MAH generally agrees with the PRAC Rapporteur's proposal to update the product information and aRMM to reflect the latest available data, but provided further proposals to the proposed wordings with justification, which is separately assessed below.

MAH proposals for Product Information

SmPC

- **Section 4.4**

The MAH suggests to add 'as monotherapy' for the sake of clarity and to reflect the considered data – the same has been done for the Package leaflet.

PRAC Rapporteur proposed updates in **underlined bold**, MAH proposed changes highlighted.

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy. **However, results from other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, the available evidence is inconsistent** (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

PRAC Rapporteur assessment

The editorial changes are noted. We consider the information on section 4.4 can remain concise as further details on the paternal PASS (including that use was limited to monotherapy) is already included in section 4.6 and does not need to be repeated here. Please see an updated proposal taking into account MS comments, input from independent scientific experts and MAH below in this AR.

- **Section 4.6**

The MAH proposes to:

- Specify the countries for PASS paternal for consistency with information on other retrospective studies
- To keep information on adjusted cumulative risk of NDDs as observed in the PASS paternal for consistency of information in the Package Leaflet and HCP guide
- Editorial changes in the PRAC Rapporteur proposed paragraph on the results of other observational studies

- To add information on HRs observed in the retrospective studies not showing a statistically increased risk, for consistency with the HCP guide. The MAH further notes that it is unclear why 1.10 was suggested by the PRAC Rapporteur as upper limit of the observed HRs in these studies. The range (1.02-1.10) mixes aHR from a country level analysis (1.02 in Denmark, from Christensen et al (2025) with a pooled aHR (1.10 from Meng et al, 2026). The MAH would rather suggest to mention the lowest and highest aHRs from the 3 referenced studies, i.e. 1.02-1.22 (1.22: in Taiwan from Meng et al, 2026).

PRAC Rapporteur proposed additions in **underlined bold**, MAH proposed additions highlighted, deletions in ~~strikethrough~~):

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception**Error! Bookmark not defined.**.

A retrospective observational study in 3 Nordic countries (Denmark, Norway, Sweden) suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (aHR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. **Limitations include potential confounding by indication, differences in follow-up duration between exposure groups, and insufficient power to assess specific NDD subtypes.** ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other retrospective observational studies did not show a statistically significant increased risk of NDDs in children born to men treated with valproate as **monotherapy in the 3-4 months prior to conception compared** to those born to ~~**with**~~ **men treated with lamotrigine or levetiracetam** as **monotherapy** (in Denmark, Sweden, Norway, and Taiwan, estimated aHRs ranged between 1.02 and 1.22, with confidence intervals including 1), or to men not treated with valproate (in Norway and Taiwan).

Differences in study design, including control for confounding and population selection, may contribute to variability in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal ~~**disease**~~medical condition**, may contribute to the** ~~**observed association**~~increased risk of NDDs in children. **Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.**

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> should be sought as appropriate.

PRAC Rapporteur assessment

Regarding the proposed additions by the MAH, we do not consider it necessary to specify the countries in which the respective studies were performed. When including too detailed information on studies

there is a risk that this information quickly becomes outdated when additional studies become available. In addition, all studies reflected in the proposed SmPC wording are available in the public domain, thus detailed information on these studies can be retrieved if this is desired. The same argument holds true for the inclusion of the observed HRs in the retrospective studies that did not show an increased risk. The PRAC Rapporteurs proposal for the HCP guide has been amended accordingly.

The editorial changes are noted. Please see an updated proposal taking into account MS comments, input from independent scientific experts and MAH below in this AR.

Patient Leaflet

- **Section 2**

PRAC Rapporteur proposed additions from preliminary recommendation in **underlined bold**, MAH proposed additions highlighted, deletions in ~~strikethrough~~):

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

One study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as monotherapy as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease) as monotherapy. ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore it is not clear~~ **~~whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.~~** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study has limitations and was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

Other studies did not ~~show~~ suggest **an increased risk of movement and mental developmental disorders in children born to fathers treated with valproate** as monotherapy in the 3-4 months **before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam** as monotherapy or to children of fathers not treated with valproate **~~before conception~~.**

The results of different studies are not consistent. It is not established whether any possible risk for movement and mental developmental disorders is caused by valproate use in the 3 months prior to conception or by other factors, such as the father's underlying condition.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

PRAC Rapporteur assessment

The proposed changes are noted. Please see an updated proposal taking into account MS comments, input from independent scientific experts and MAH below in this AR.

MAH comments to HCP guide

PRAC Rapporteur comment

It is noted that the core version of the HCP guide used by the PRAC Rapporteur in Annex II was erroneously not the final approved version. This has been corrected in the updated recommendation.

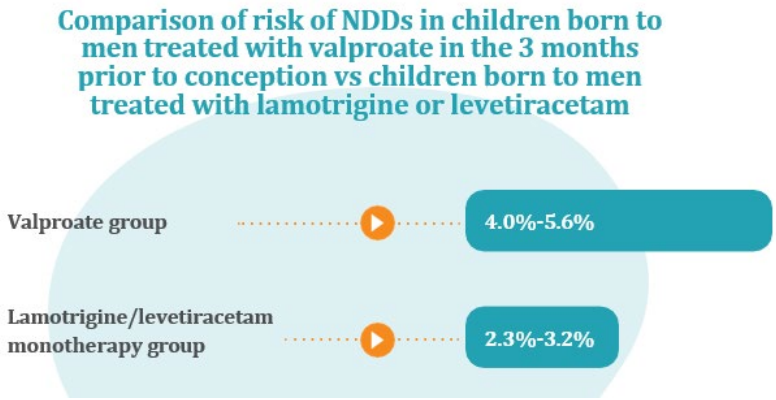
The MAH provided the following comments to the HCP guide:

- The Company is not in favor of changing the recommendation on initiation and supervision of the treatment of male patients by a specialist, since there are no new data requiring more stringent measures. No such update was proposed for SmPC. «*Must*» should be kept for female patients only.
- The company suggests to specify the countries for PASS Paternal for consistency with information on other retrospective studies. Also, the references to all 4 studies were included in the guide.
- Topic II in the box 'Specialist and general practitioner' is suggested to be deleted for consistency with the information provided in the section I on the risks and with the updated SmPC.
- It is unclear for the Company why 1.10 is suggested here; the range (1.02-1.10) mixes aHR from a country level analysis (1.02 in Denmark, from Christensen et al. 2025) with a pooled aHR (1.10 from Meng et al. 2026). We would rather suggest to mention the lowest and highest aHRs from the 3 referenced studies, i.e. 1.02-1.22 (in Taiwan from Meng et al. 2026).
- The Company proposed editorial changes to facilitate reading and to be more accurate. The proposed changes are consistent with the proposed SmPC.

PRAC Rapporteur proposed additions from PAR in **underlined bold**; deletions in ~~strikethrough~~, MAH proposed amendments highlighted:

1. What you must know about the risk to children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 European Nordic countries (Denmark, Norway, Sweden) suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.



The pooled adjusted hazard ratio (aHR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% Confidence Interval: 1.09, 2.07).

The study was not large enough to investigate associations with specific NDD subtypes (composite endpoint including autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). ~~Due to study~~ **The study has** limitations including potential confounding by indication and differences in follow-up time between exposure groups~~, the causal role of valproate is possible and not considered to be confirmed~~.

~~The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.

Other retrospective observational studies ~~from Norway, Sweden, Denmark, and Taiwan~~ did not show a statistically significant increased risk of NDDs in children born to men treated with valproate as **monotherapy in the 3–4 months prior to conception compared** those born to **men treated with lamotrigine/levetiracetam** as **monotherapy (estimated HRs ranged between 1.02 and ~~1.10~~** 1.22**, with confidence intervals including 1) or men not treated with valproate** (in Norway and Taiwan)**.**

Differences in study design, including control for confounding and population selection, may contribute to variability in study **findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal ~~disease~~** medical condition, may contribute to the increased risk of NDDs in children **~~observed association~~. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.**

~~The risk to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.~~

2. What is your role, when managing, treating or taking care of male patients with Epilepsy or Bipolar Disorder

• ~~It is recommended that~~ Valproate ~~is must~~ should **be** initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder <or migraine>.

{to be adapted depending on healthcare system}

SPECIALIST and GENERAL PRACTITIONER

Explain/remind and ensure patient's knowledge of

I. **The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception**

II. ~~The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception.~~

III. As a precautionary measure, discuss with the patient regularly **the need:**

- To consider **effective contraception**, including for a female partner, while using valproate and for 3 months after stopping the treatment
- To consult a specialist **to discuss treatment alternatives**, when they are planning to conceive a child and before discontinuation of contraception
- ~~Male patients should not~~ **Not to donate sperm** during treatment and for ~~at least~~ 3 months after ~~the~~ **stopping the** treatment

~~Male patients treated with valproate~~ A specialist should ~~be~~ regularly reviewed ~~by their prescriber to evaluate~~ whether valproate ~~remains~~ **is** the most suitable treatment for the patient.

For male patients planning to conceive a child suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.

~~It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.~~

PHARMACIST

•Ensure the patient received the Patient Guide and Patient Card

•**Discuss the need to consider effective contraception, including for a female partner**

•{Subject to national implementation} <Remind that online information can also be found by scanning the QR code (on the leaflet / on the box)>

PRAC Rapporteur assessment

Regarding the comments raised by the MAH, we fully agree that the recommendation on initiation and supervision of the treatment of male patients by a specialist should be in line with the approved SmPC text. The version of the HCP guide used in Annex II was erroneously not the final version of the approved core version of the HCP guide. This has been corrected in the updated recommendation.

Similar to the SmPC, we do not consider it necessary to specify the countries in which the studies were performed or to include observed HRs in the retrospective studies that did not show an increased risk as this information quickly becomes outdated when additional studies become available and all studies reflected are available in the public domain. We agree that the references should be updated to reflect all studies.

The editorial changes are noted. Please see updated proposal for the HCP guide below in this AR.

Core version patient guide

The MAH provided the following comments to the guide for male patients:

- For alignment with the PIL, the company does not support to use '*physical'* instead of '*movement*'. In addition, physical developmental disorders corresponds rather to congenital malformations which are not described here.
- The Company proposes to reflect that valproate was used in monotherapy, for the sake of clarity and to reflect the considered data – the same has been done for the Package Leaflet.
- The Company prefers to keep '*such disorders*' since they are already specified just above, and it is a more patient-friendly wording than '*problems with neurodevelopment'* (which were not previously defined)
- Please note that the initial list of conditions corresponds to those of composite endpoint investigated in PASS paternal. The company is not supporting this update: '*being late in learning to walk and talk'* and '*memory problems'*. If indeed these are mentioned in the guide for female patients, they are not related to the PASS paternal data.
- The MAH provided further editorial suggestions to align with the PIL.

Valproate* guide for male patients

Read this guide along with the patient information leaflet for a complete product information

VALPROATE <INVENTED NAME>

What you should know

This guide contains key information about the potential risks of valproate* when used by male patients in the 3 months before conception of a child.

Ask your doctor or pharmacist if you have any questions.

KEEP THIS GUIDE. YOU MAY NEED TO READ IT AGAIN.

{Subject to national implementation} <Information about the use of valproate in male patients can also be found online at <webpage>>

*Valproate also known as <invented name>

What are the risks of taking valproate* when conceiving a child

~~**A**~~ **One** study suggests a possible risk of movement ~~**physical**~~ and mental developmental disorders (problems with early child~~**hood**~~ development) in children born to fathers treated with valproate as montherapy in the 3 months before conception.

In this study, around 5 children in every 100 had such disorders ~~**problems with neurodevelopment**~~ when born from fathers treated with valproate, **and** ~~**as compared to**~~ around 3 children in every 100 when born from fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease) as monotherapy.

~~**However,** t~~**T**he study has limitations ~~and therefore it is not entirely clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~

~~A wide range of movement and mental developmental disorders were investigated in the study. However, the study could not~~ **and** was not large enough to show which ~~particular~~ specific type of movement and mental developmental disorder children may be at risk of developing.

For example, problems with your child's movement and mental development ~~neurodevelopment~~ as they grow up may include:

- ~~Being late in learning to walk and talk.~~
- Movement ~~Memory~~ problems

- Lower intelligence than other children of the same age.
- Poor speech and language skills.
- Memory problems.
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder.

~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~

Other studies ~~have also investigated the possible risk for physical and~~ did not suggest an increased risk of movement and **mental developmental disorders in children born to fathers treated with valproate** as monotherapy **in the 3 to 4 months before conception. ~~These studies did not show an increased risk for physical and mental developmental disorders in children born to fathers treated with lamotrigine or levetiracetam or compared with fathers not treated with valproate.~~** In these studies the risk was similar compared to children of fathers treated before conception with lamotrigine or levetiracetam as monotherapy or to children of fathers not treated with valproate.

~~Overall, t~~T**he results from different studies are not consistent~~, and most studies do not suggest an increased risk~~. It is not** established **~~clear~~ whether any possible risk for physical** movement **and mental developmental disorders is caused by valproate** use in the 3 months prior to conception **~~itself~~ or by other factors, such as the father's underlying ~~illness~~** medical condition**. ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is also not known.~~**

What does this mean for me?

As a precautionary measure, your doctor will discuss with you the potential risk in children born to fathers treated with valproate in the 3 months before conception.

Your doctor will also discuss with you:

- The need to consider **effective contraception** (birth control) for you and your female partner during valproate use and for 3 months after stopping valproate (the time needed for new sperm to be formed).

- The need to consult your doctor when you are **planning to conceive a child** and before stopping contraception (birth control).

- The possibility of **other treatments** that can be used to treat your disease, ~~depending on your individual situation~~.

Do not donate sperm when taking valproate and for 3 months after stopping valproate treatment. Talk to your doctor if you think about having a baby.

If your **female partner becomes pregnant** while you used valproate in the 3 months before conception and you have questions, **both of you may contact your doctor**.

Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

~~You should **get regular appointments** with your prescriber.~~ **Your specialist will review your treatment regularly.**
During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

*Valproate also known as <invented name>

Rapporteur assessment comment

Unfortunately, it was noted that the core version of the patient guide for male patients as reflected in Annex III was erroneously not the final agreed core version. Therefore, some of the changes proposed by the Rapporteur as reflected in the MAH's version were not intended. In the updated recommendation the correct final version of the previously agreed guide for male patients has been used.

Regarding the MAH's comments on the patient guide for male patients, these have been taken into account in the updated Rapporteurs proposal, see section 4.6 below.

4.6. Updated Recommendation

Taking into account the evidence reviewed in current assessment round, the PRAC Rapporteur considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk.

In general, the MAH's proposal to maintain the precautionary measures in the product information and additional risk minimisation measures is agreed. The final report of the PASS TANGO study will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies. However, an update on the information provided in the product information is necessary, as the current product information only describes the results of the paternal PASS whereas other available (epidemiological) studies have shown variable results. It is considered important to reflect this in the product information for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information, and to acknowledge to totality of available evidence on this potential risk. The aRMM should be updated in line with the proposed PI updates.

Considering the previous interest and feedback from the field and professional organisations, we propose information on current procedure will be published by EMA in the PRAC highlights. In addition, NCAs may consider informing professional organisations about the PRAC review of the new evidence that has become available in current procedure.

Proposed Product information updates

Please find a proposal to update SmPC wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

SmPC

SmPC section 4.4

[…]

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. **However, other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, available evidence is inconsistent and the causal role of valproate is uncertain** (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[…]

SmPC section 4.6

[…]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children

of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

[…]

In line, please also find a proposal to update PL wording on use in male patients below (additions in **underlined bold**; deletions in ~~strikethrough~~):

Package Leaflet

PL section 2

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ ~~The study has limitations and therefore it is not clear~~ **~~whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.~~** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate.~~ The study **has limitations and** was not large enough to show which ~~particular~~ **specific** type of movement and mental developmental disorder children may be at risk of developing.

Other studies did not suggest an increased risk of mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Overall, it is not known whether any possible risk of childhood developmental disorders is caused by valproate itself or by other factors, such as the father's underlying medical condition.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

Proposed updates to Core aRMM

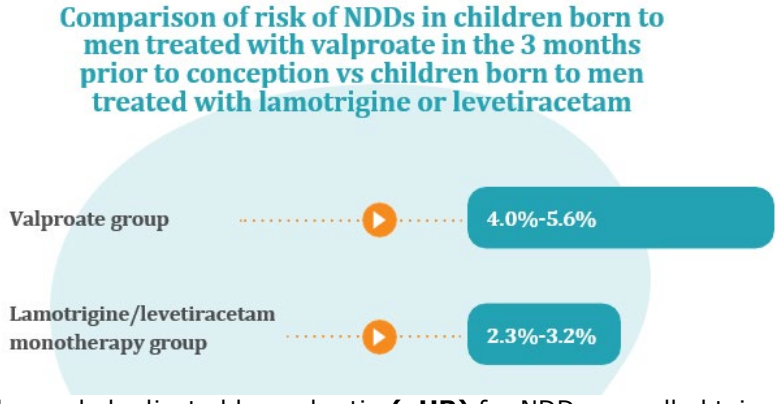
An update on the information provided in the aRMM is necessary, as (epidemiological) studies have shown variable results and current aRMM only reports the results of the paternal PASS. It is important to reflect the totality of available evidence in the aRMM for transparency.

Updated HCP Guide

Please find a proposal to update the core version of the HCP guide below, including only the section related to male patients (additions in **underlined bold**; deletions in ~~strikethrough~~):

3. What you must know about the risk to children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 European Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.



The pooled adjusted hazard ratio **(aHR)** for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% Confidence Interval: 1.09, 2.07). The study was not large enough to investigate associations with the specific NDD subtypes studied (composite endpoint included autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). ~~Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the causal role of valproate is possible but not considered to be confirmed.~~

~~The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~
The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.
Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy. Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

4. What is your role, when managing, treating or taking care of male patients with Epilepsy or Bipolar Disorder

- It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder <or migraine>. {to be adapted depending on healthcare system}

SPECIALIST and GENERAL PRACTITIONER

Explain/remind and ensure patient's knowledge of

I. The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception.

~~II. The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception.~~

~~III.~~**II.** As a precautionary measure, discuss with the patient regularly the need:

- To consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment
- To consult a specialist to discuss treatment alternatives, when they are planning to conceive a child and before discontinuation of contraception.

~~IV.~~**III.** Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient.

For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.

It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar> <migraine> should be sought as appropriate.

Provide the Patient Guide

PHARMACIST

- Ensure the patient received the Patient Guide and Patient Card
- {Subject to national implementation} <Remind that online information can also be found by scanning the QR code (on the leaflet / on the box)>

Updated Patient Guide for male patients

Please find a proposal to update the core version of the HCP guide below, including only the section related to male patients (additions in **underlined bold**; deletions in ~~strikethrough~~):

What are the risks of taking valproate* when conceiving a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception.

In this study, around 5 children in every 100 had such disorders when born to fathers treated with valproate, as compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).

However, the study has limitations and ~~therefore it is not entirely clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. A wide range of movement and mental developmental disorders were investigated in the study.~~

~~However, the study~~ was not large enough to show which particular type of disorder children may be at risk of developing.

For example, problems with your child's movement and mental development as they grow up may include:

- Movement problems
- Lower intelligence than other children of the same age
- Poor speech and language skills
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder.

~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~

Other studies did not suggest an increased risk of mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Overall, it is not known whether any possible risk of childhood developmental disorders is caused by valproate itself or by other factors, such as the father's underlying medical condition.

What does this mean for me?

As a precautionary measure, your doctor will discuss with you the potential risk in children born to fathers treated with valproate in the 3 months before conception.

Your doctor will also discuss with you:

- The need to consider **effective contraception** (birth control) for you and your female partner during valproate use and for 3 months after stopping valproate (the time needed for new sperm to be formed).
- The need to consult your doctor when you are **planning to conceive a child** and before stopping contraception (birth control).
- The possibility of **other treatments** that can be used to treat your disease, depending on your individual situation.

Do not donate sperm when taking valproate and for 3 months after stopping valproate treatment.

Talk to your doctor if you are thinking about having a baby.

If your **female partner becomes pregnant** while you used valproate in the 3 months before conception and you have questions, **contact your doctor.**

Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber.

During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Patient Card

No update of the 'core version' of the patient card, attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing, is considered necessary, as the information provided on this card remains valid and appropriate.

Final versions and distribution of updated HCP and patient guides are subject to national assessment and consideration.

4.7. Adopted PRAC Recommendation

Taking into account the available evidence in the literature, the PRAC considers there remains uncertainty regarding the risk of NDD after paternal exposure to valproate during the spermatogenic risk window and therefore this remains an important potential risk. The PRAC agreed to maintain the precautionary measures in the product information and additional risk minimisation measures. The final report of the PASS TANGO study will be awaited before considering any major changes to the current risk minimisation measures in place considering the inconsistent results in the currently available studies. However, an update on the information provided in the product information is necessary, as the current product information only describes the results of the paternal PASS whereas other available (epidemiological) studies have shown variable results. It is considered important to reflect this in the product information for transparency, to ensure that HCPs and patients have access to accurate and up-to-date information, and to acknowledge the totality of available evidence on this potential risk. The aRMM should be updated in line with the proposed PI updates.

Therefore, the PRAC has agreed that the MAHs of valproate containing products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below taking into account the already existing wording in some nationally authorised products the text needs to be adapted by MAHs to individual products (new text underlined and in **bold** and deletions in ~~strikethrough~~):

Summary of Product Characteristics

Section 4.4 Special warnings and precautions for use

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam. **However, other studies do not suggest an increased risk of NDDs after paternal valproate exposure. Thus, available evidence is inconsistent and the causal role of valproate is uncertain** (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

Section 4.6 Fertility, pregnancy and lactation

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. ~~The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy.

Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male

patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Package Leaflet

Section 2 What you need to know before you take <product name>

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). ~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~ ~~The study has limitations and therefore it is not clear~~ **~~whether any possible risk is caused by valproate itself or by other factors, such as the father's underlying illness.~~** ~~if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study has limitations and was not large enough to show which particular specific type of movement and mental developmental disorder children may be at risk of developing.~~

Other studies did not suggest an increased risk of mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Overall, it is not known whether any possible risk of childhood developmental disorders is caused by valproate itself or by other factors, such as the father's underlying medical condition.

As a precautionary measure, your doctor will discuss with you:

•The potential risk in children born to fathers treated with valproate

• The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment

• The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)

• The possibility of other treatments that can be used to treat your disease, depending on your individual situation

Do not donate sperm when taking valproate and for 3 months after stopping valproate. Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

Proposed updates to Core aRMM

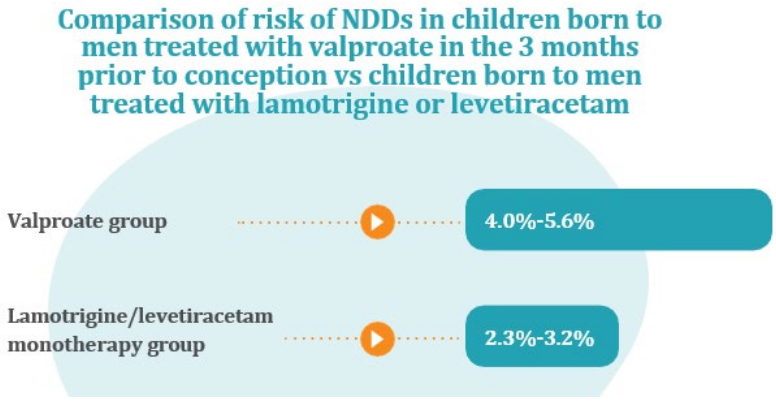
An update on the information provided in the aRMM is necessary, as (epidemiological) studies have shown variable results and current aRMM only reports the results of the paternal PASS. It is important to reflect the totality of available evidence in the aRMM for transparency.

Updated HCP Guide

Please find a proposal to update the core version of the HCP guide below, including only the section related to male patients (additions in **underlined bold**; deletions in ~~strikethrough~~):

5. What you must know about the risk to children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 European Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.



The pooled adjusted hazard ratio **(aHR)** for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% Confidence Interval: 1.09, 2.07). The study was not large enough to investigate associations with the specific NDD subtypes studied (composite endpoint included autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). ~~Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the causal role of valproate is possible but not considered to be confirmed.~~

~~The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).~~

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.

Other observational population-based studies did not show an increased risk of NDDs in children born to men treated with valproate as monotherapy in the 3–4 months prior to conception compared with men treated with lamotrigine or levetiracetam as monotherapy. Differences in study design, including control for confounding and population selection, may contribute to differences in study findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, the evidence regarding an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is inconsistent, and the causal role of valproate is uncertain.

6. What is your role, when managing, treating or taking care of male patients with Epilepsy or Bipolar Disorder

- It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder <or migraine>. {to be adapted depending on healthcare system}

SPECIALIST and GENERAL PRACTITIONER

Explain/remind and ensure patient's knowledge of

I. The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception.

~~II. The study did not evaluate the risk of NDDs in children born to men who had discontinued valproate for more than 3 months prior to conception.~~

~~III.~~**II.** As a precautionary measure, discuss with the patient regularly the need:

- To consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment
- To consult a specialist to discuss treatment alternatives, when they are planning to conceive a child and before discontinuation of contraception.

~~IV.~~**III.** Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient.

For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.

It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar> <migraine> should be sought as appropriate.

Provide the Patient Guide

PHARMACIST

- Ensure the patient received the Patient Guide and Patient Card
- {Subject to national implementation} <Remind that online information can also be found by scanning the QR code (on the leaflet / on the box)>

Updated Patient Guide for male patients

Please find a proposal to update the core version of the HCP guide below, including only the section related to male patients (additions in **underlined bold**; deletions in ~~strikethrough~~):

What are the risks of taking valproate* when conceiving a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception.

In this study, around 5 children in every 100 had such disorders when born to fathers treated with valproate, as compared to around 3 children in every 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).

However, the study ~~has limitations and therefore it is not entirely clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. A wide range of movement and mental developmental disorders were investigated in the study.~~

~~However, the study~~ was not large enough to show which particular type of disorder children may be at risk of developing.

For example, problems with your child's movement and mental development as they grow up may include:

- Movement problems
- Lower intelligence than other children of the same age
- Poor speech and language skills
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder.

~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~

Other studies did not suggest an increased risk of mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3-4 months before conception. In these studies the risk was similar compared to children of fathers treated with lamotrigine or levetiracetam before conception.

Differences in how these studies were designed may explain the different results. Overall, it is not known whether any possible risk of childhood developmental disorders is caused by valproate itself or by other factors, such as the father's underlying medical condition.

What does this mean for me?

As a precautionary measure, your doctor will discuss with you the potential risk in children born to fathers treated with valproate in the 3 months before conception.

Your doctor will also discuss with you:

- The need to consider **effective contraception** (birth control) for you and your female partner during valproate use and for 3 months after stopping valproate (the time needed for new sperm to be formed).
- The need to consult your doctor when you are **planning to conceive a child** and before stopping contraception (birth control).
- The possibility of **other treatments** that can be used to treat your disease, depending on your individual situation.

Do not donate sperm when taking valproate and for 3 months after stopping valproate treatment.

Talk to your doctor if you are thinking about having a baby.

If your **female partner becomes pregnant** while you used valproate in the 3 months before conception and you have questions, **contact your doctor.**

Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber.

During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Patient Card

No update of the 'core version' of the patient card, attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing, is considered necessary, as the information provided on this card remains valid and appropriate.

Final versions and distribution of updated HCP and patient guides are subject to national assessment and consideration.

5. References

Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011 May 46(3): 399-424. doi: 10.1080/00273171.2011.568786.

Botton J, Rios P, Drouin J, Miranda S, Zureik M, Weill A, Dray-Spira R. Paternal exposure to valproate during spermatogenesis and risk of neurodevelopmental disorders in children: national study based on the French EPI-MÈRES Register. EPI-PHARE (ANSM-Cnam). Saint-Denis, 6 November 2025, 61 pages.

Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer, T. Variable selection for propensity score models. Am Journal of Epidemiology 2006 Vol 163(12): 1149–1156. DOI: 10.1093/aje/kwj149

Christensen J, Trabjerg BB, Dreier JW. Valproate use during spermatogenesis and risk to offspring. JAMA Netw Open. 2024;7(6):e2414709. doi: 10.1001/jamanetworkopen.2024.14709

Christensen J, Trabjerg BB, Dreier JW. Risk of Neurodevelopmental Disorders and Paternal Use of Valproate During Spermatogenesis. JAMA Netw Open. 2025;8(5):e2512139. doi:10.1001/jamanetworkopen.2025.12139

Coste J, Mandereau-Bruno L, Carcaillon-Bentata L, Mikaeloff Y, Bouilleret V. Prevalence, demographic and spatial distribution of treated epilepsy in France in 2020: a study based on the French national health data system. J Neurol. 2024 Jan 1;271(1):519–25.

Meng LC, van Gelder MMHJ, Chuang HM, Lai HY, Chen LK, Hsiao FY, Nordeng HME. Valproate Use by Fathers and Risk of Neurodevelopmental Disorders in Children. NEJM Evid. 2026 Mar;5(3):EVIDoa2500254. doi: 10.1056/EVIDoa2500254. Epub 2026 Feb 24. PMID: 41733407.

Olstad EW, Nordeng HME, Bjørk MH, Selmer K, Gervin K. Paternal valproate use and impact of shared genetic susceptibility on child neurodevelopment. Sci Rep. 2025 Nov 7;15(1):39033.

Perkins SM, Tu W, Underhill MG, Zhou X-H, Murray MD. The use of propensity scores in pharmacoepidemiologic research. Pharmacoepidemiology and Drug Safety. 2000; Volume 9:93-101

Razaz N, Soderling J, Tomson T, Werenberg Dreier J, Christensen J, Bjørk MH, Igland J. Risk of neurodevelopmental disorders associated with paternal use of valproate during spermatogenesis. J Neurol Neurosurg Psychiatry. 2026 Mar 4:jnnp-2025-337441. doi: 10.1136/jnnp-2025-337441. Epub ahead of print. PMID: 41781215.

Reifeis, SA, Hudgens, MG, 2022, 'On Variance of the Treatment Effect in the Treated When Estimated by Inverse Probability Weighting', American Journal of Epidemiology, vol. 191, no. 6, pp. 1092–1097. doi: 10.1093/aje/kwac014

Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiological studies. Epidemiology 2009 July: 20(4): 488-495. doi:10.1097/EDE.0b013e3181a819a1

Shabani N, Proverbio AM. Neonatal hypoxia: impacts on the developing mind and brain. Frontiers in Cognition, Volume 4 -2025. https://doi.org/10.3389/fcogn.2025.1565759

Straub L, Bateman BT, Hernandez-Diaz S, et al. Validity of claims-based algorithms to identify neurodevelopmental disorders in children. Pharmacoepidemiol Drug Saf. 2021;30(12):1635-1642. doi:10.1002/pds.5369

Annex I Tabulated overview of (published) studies discussed in current signal report

Table 2 Comparison of Paternal 1 PASS; Christensen et al (2025); Meng et al (unpublished draft manuscript)

	Paternal 1 PASS (IQVIA)	**Christensen 2025**	**Meng et al (unpublished draft manuscript)**	**Razaz et al (2025**
Countries	DK, NO, SE	DK	NO, TW	NO, SE
Data source	DK The Danish Civil Registration System Register of Medicinal Product Statistics (RMPS) National Patient Registry Cause of Death Register Medical Birth Registry The In Vitro Fertilisation Register NO Central Person Registry Norwegian prescription database Norwegian patient registry Medical birth registry Cause of death register	The Danish Civil Registration System Danish prescription Register (equal to Register Medicinal Product Statistics (RMPS)) National Patient Registry Cause of Death Register Medical Birth Registry Danish Psychiatric Central Research Register	NO Medical Birth Registry Norway (MBRN) NO prescription database (NorPD) Norwegian patient registry (NPR) Norwegian control and payment of health reimbursements (KUHR) TW National Birth Certificate Application (BCA) National Health Insurance Database (NHI) Maternal and Child Health Database (MCHD)	NO Medical Birth Registry Norwegian Patient Registry Norwegian prescribed drug registry Statistics Norway SE Medical Birth Register National Patient Register Prescribed Drug Register Multi-Generation Register Total Population Register (sociodemographic data) Education Register (sociodemographic data)
Study inclusion period	1 Jan 2007 -31 Dec 2018	1 Jan 2007 -31 Dec 2017	Pregnancies with delivery dates between Jan 2010 and Dec 2015	Singleton live births at ≥22 completed gestational weeks SE between 1 January 2007 and 31 December 2020 NO between 1 January 2010 and 31 December 2018
Study follow-up period		Up to 31 Dec 2018	Up to Dec 2021	SE Up to 31 Dec 2022 NO Up to 31 Dec 2019
Inclusion criteria	Live born children were included if it concerned singleton pregnancies, with known pregnancy-length of at least 12 weeks within the study time period, medical record linkage to mother and father available. Father with a continuous enrolment in the database for ≥12 months prior to linked mother at the date of LMP2, father with at least one AED in the data available.	Singletons children born alive in Denmark between 1 Jan 2007 -31 Dec 2017	Pregnancies with delivery dates between Jan 2010 and Dec 2015	Singleton live births at ≥22 completed gestational weeks
Exclusion criteria	Pregnancies with missing gestational age and/or missing maternal LMP2, Adopted children, IVF pregnancies Children whose parent(s) have a history of CM or NDD (according to available records), Children of parents who used teratogenic drugs were excluded	Children with unknown/unlikely gestation age Children with no link to father IVF pregnancy	Missing identification for parent or child, missing gestational age, missing parental birthdates, multifetal gestations, non-live births, unknown offspring sex	Implausible gestational age (≤154 or ≥315 days), No registered father in Medical Birth registries Died or emigrated before age 1 year Children whose mothers used VPA from 30 days before LMP to birth Children whose fathers were exposed to more than one ASM during spermatogenesis

				Children whose fathers had no exposure to VPA, lamotrigine or levetiracetam
Comparator	Exposure to levetiracetam/lamotrigine monotherapy (composite outcome)	VPA monotherapy vs children exposed to lamotrigine or levetiracetam monotherapy,	1) unexposed group from the general population 2) unexposed group restricted to fathers with an ASM-diagnosis (indication-restricted analysis 3) indication-restricted analysis with PS-FSW 4) active comparator analysis comparing VPA to lamotrigine/levetiracetam with PS-FSW	Lamotrigine or levetiracetam
Exposure	Valpraote monotherapy Window: LMP2- 3 months	Paternal monotherapy exposure to valproate, lamotrigine, and levetiracetam was defined as filling 1 or more prescriptions for only 1 of these medications from 120 days before the first day of the last menstrual period (LMP) to 14 days after the LMP Additionally, we conducted a sensitivity analysis with a restricted exposure window from 60 days before to 14 days after the LMP.	Valproate monotherapy Window LMP2 – 3 months Valproate combination therapy	Paternal monotherapy with VPA, lamotrigine or levetiracetam was defined as filling ≥1 prescription for only one of these medications from 120 days before the first day of the LMP to LMP+14 days (i.e. covering spermatogenesis and accounting for early prescription) without filling of prescriptions for other ASMs. Mean daily dose – dividing total mg dispensed in exposure period by number of days. High dose (>750 mg) vs low dose (≤750 mg/day)
Outcome	<u>NDD incl ASD</u> Intellectual disability (ICD-10: F70-79) Communication disorders: F80 Disorders of psychological development (ICD 10: F81-84, F88, F88, R48) ADHD (ICD 10: F90.0+F98.8) Tic disorders F95 Movement disorders F82, F84, G250-G259, G242-G249, G26 <u>NDD narrow definition</u> Same as above, without tic and movement disorders <u>ASD</u>	<u>NDD</u> Main analysis: composite of ID+ASD+PD+ADHD subtype:ID, ASD, PD, ADHD ICD-10 codes: Intellectual disability (ICD-10: F70-79) Disorders of psychological development (ICD 10: F80-83) Autism spectrum disorders (ICD 10: F84 (excl F84.2-F84.4)) ADHD (ICD 10: F90.0+F98.8)	<u>Any NDD (ICD9/ICD10 codes)</u> Primary; composite of ASD (ICD10 F84.xx, except F84.2, F84.3), ADHD (ICD-10 90.xx), specific learning disorders (ICD-10 F81.0x, F81.2x, F81.8x, R48.0x), developmental speech/language disorder (ICD10 F80.xx (except F80.4; H93.25), developmental coordination disorder (ICD10 F82.xx), intellectual disability (ICD10 F70.xx-F79.xx), behavioral disorder (ICD10 F63.xx, F91.xx, F93.8x, F93.3x, F93.9x, F94.xx, F98.8x, F98.9x)	<u>NDD from 1st birthday</u> Same definition as Colas et al (=IQVIA PASS) NDD composite ID (ICD 10 F70-F79) Psychological development disorders (F80-F83) ASD (F84 except F84.2-F84.4) ADHD (F90.0-F98.8) At least 1 code aged 1 year and above

	F84.0 Childhood autism F84.1 Atypical autism F84.2 Rett's syndrome F84.3 Other childhood disintegrative disorder F84.5 Asperger syndrome F84.8 Other pervasive developmental disorders F84.9 Pervasive developmental disorder, unspecified		Secondary: individual NDDs (indication restricted analysis; active comparator analysis Validated outcome algorithm (≥2 diagnoses same NDD on different dates; age limits) (Straub et al, 2021), sensitivity analysis with 1 NDD code without age restriction (ie similar to PASS) Only outcomes with sufficient cases (≥3 reported)	
Follow-up	Up to child turned 12 years of age	Up to first diagnoiss of NDD or until death, emigration or end of follow-up 31 dec 2018 (max 11 years)	NO-Up to first NDD diagnosis or study period end (Dec 2021); TW up to first NDD diagnosis, death or study period end	
Analysis	NDD: Crude and propensity score (PS) weighted regression models were estimated	Cox regression to estimate aHR adusted for relevant confounders Multivariate model	Crude and propensity score-fine stratification weighted regression models HR estimates from 2 countries pooled with random-effects meta-analysis	Cox proportional hazard model adjusted for relevant confounders Random effects meta analysis via the inverse variance method with restricted maximum likelihood combined results from both countries
Sensitivity analysis		Sensitivity analysis to mirror IQVIA study: excluding children of parents with NDDs or congenital malformations, excluding children of mothers with epilepsy; excluding children with epilepsy, rerunning analyses without adjustment for parental epilepsy and education, and stopping follow-up at age 12 years.	Subgroup analysis stratified by indication Sensitivity analysis: - minimum follow-up 8 years (births between 2010-2013) - outcomes defined as single code without age restriction to maximixe NDD cases - fathers with at least 1 prescription during spermatogenesis window - NO – VPA exposure daily dose 0.5 DDD - Excluded pregnancies in which mother used VPA during pregnancy - Restricted analysis to fathers without documented diagnosis NDD - NO – exclusion children assisted reproductive technology	
Confounders /risk factors considered	Potential confounding factors: sex of the child, age of the father, calendar year of offspring, bipolar affective disorder and mania, neurotic	Variables for adjustment in main analysis sex of the child, year of birth,	Calendar year of offspring birth, Paternal age, paternal indications for ASM use (epilepsy, psychiatric disorders, somatic	Adjustments were made for Child sex Child birth year

	disorder, schizophrenia, Maternal: obesity, smoking, alcohol abuse, rubella, CMV, diabetes Maternal and paternal: substance abuse, medications associated with valproate-indicated psychiatric conditions, medications associated with neuropsychiatric adverse effects.	paternal and maternal characteristics (age, psychiatric diagnoses, psychotropic medication use, epilepsy diagnosis, and educational level) maternal valproate use during pregnancy.	disorders), paternal chronic comorbidities (sleep disorders, substance abuse, NDD), paternal medication (other ASMs, triptans, antipsychotics, antidepressants, anxiolytics, hypnotics and sedatives, opioids) Maternal age, chronic comorbidities (epilepsy, psychiatric disorders, somatic conditions, sleep disorders, substance abuse, NDDs), maternal medication use (ASMs, triptans, antipsychotics, antidepressants, anxiolytics, hypnotics and sedatives, opioids), maternal lifestyle factors (smoking, obesity)	Maternal cohabitation status Parental characteristics (year of birth, psychiatric history, psychotropic use, epilepsy diagnosis) Parental education level (SE only) Restricted main analysis to cohort of fathers with epilepsy and compared valproate-exposed children to lamotrigine/levetiracetam exposed children within this group (no adjustments were made for multiple comparisons, so results are considered exploratory).
Subjects included	**DK** Primary cohort (NDD) 832 valproate exposed in descriptive cohort. <u>Comparative cohort:</u> VPA exposed: 678 Lamotrigine/Levetiracetam exposed: 1118 **NO** 1,471 offspring in descriptive cohort, 413 exposed to VPA <u>Comparative cohort (NDD)</u> VPA exposed: 398 Lamotrigine/levetiracetam: 1,018	961 children exposed to VPA 1401 children (725 male [51.8%]; median [IQR] age at end of follow-up, 5.5 [2.7-9.3] years) exposed to lamotrigine or levetiracetam monotherapy	NO 367,960 offspring (319 VPA) TW 1,234,223 offspring (564 VPA) ASM indication: NO VPA 304 Unexposed 121306 TW VPA 543 Unexposed 500498 Active comparator: NO VPA 319 Lamotrigine/levetiracetam 730 TW VPA 564 Lamotrigine/levetiracetam 96	SE 4681 VPA exposed 1588 Lamotrigine/levetiracetam 3093 NO 1572 VPA 463 L/L 1109
Follow-up	The mean follow-up time (in years) per offspring DK was 9.2 for the valproate group and 6.6 for the lamotrigine/levetiracetam group SE: 6.7 years for the valproate group and 5.1 for the lamotrigine/levetiracetam group	VPA group: median [IQR] age at the end of follow-up, 10.6 [5.4-15.0] years) L/L group: median [IQR] age at end of follow-up, 5.5 [2.7-9.3] years)	Median follow-up time (IQR) NO Indication ASM VPA (304) 8.7 (7.2-10.2) Comparator unexposed (121306) 8.7 (7.1-9.9) Vs active comparator VPA (319) 8.8 (7.2-10.2) Lamotrigine/levetiracetam (730) 8.6 (7.2-10.2)	SE Median age at follow-up 6.6 years NO Median age at follow-up 5.2 years

	NO: 5 years for the valproate group and 4.8 years for the lamotrigine/levetiracetam group		TW Indication ASM VPA (543) 7.7 (6.3-9.6) Unexposed (500498) 7.8 (6.5-9.5) Vs active comparator VPA (564) 7.8 (6.3-9.7) Lamotrigine/levetiracetam (96) 8.1 (6.7-9.4)	
NDD	**DK** For all NDD: Adjusted HR 1.34 (0.79, 2.25) for VPA compared to lamo/levetiracetam 38 VPA cases vs 36 L/L cases in this analysis NDD narrow case def: Adjusted HR 1.59 95%CI [0.89, 2.86] for VPA compared to lamo/levetiracetam **NO** For all NDD: aHR 1.76 (0.83-3.71) for VPA compared to lamotrigine/levetiracetam (13 VPA vs 21 L/L cases) NDD (narrow): aHR 1.87 (0.86-4.08) for VPA compared to lamotrigine/levetiracetam	NDD composite (ID+ASD+PD+ADHD): 67 NDD cases in VPA group 50 NDD cases in L/L group aHR, 1.02; (0.67-1.54) sub-types: ID 21 VPA, 7 L/L cases aHR: 1.85 (0.72-4.76) PD 14 VPA, 11 L/L cases aHR: 0.69 (0.37-1.28) ASD 24 VPA, 31 L/L cases aHR: 0.92 (0.38-2.24) ADHD 26 VPA, 27 L/L aHR: 0.60 (0.33-1.12) Restricted to fathers with epilepsy: aHR 1.42 (0.82-2.46) Restricted to fathers with epilepsy matched on birthday: aHR 1.14 (0.59-2.21) Restricted to fathers with epilepsy of unknown underlying cause aHR 2.48 (1.13-5.44) Restricted to fathers with epilepsy of unknown underlying cause, matched on birth year: aHR 2.33 (1.00-5.44)	NO Population-controlled: crude HR 1.67 (1.10-2.54) (24/319 cases VPA; 15923/337109) Indication-restricted: crude HR 1.43 (0.93-2.18), PS HR 1.20 (0.75-1.94) (cases VPA 24/319; comparator 6377/121306) Active comparator crude HR 0.94 (0.57-1.56), PS HR 1.02 (0.57-1.82) (cases VPA 24/319; comparator 59/730) TW Population-controlled crude HR 1.35 (1.13-1.63) (cases VPA 127.564; comparator 185600/1045300) Indication-restricted crude HR 1.35 (1.12-1.62), PS HR 1.12 (0.92-1.35) (cases VPA 126/543; comparator 90914/500498) Active comparator: crude HR 1.39 (0.81-2.36) adjusted HR 1.22 (0.64-2.33) (cases VPA 127/564; 16/96) Restricted to fathers with epilepsy NO Indication-restricted PS HR 1.19 (0.65-2.19) Active comparator PS HR 1.00 (0.47-2.13) Restricted to fathers with psychiatric indications NO Indication-restricted PS HR 0.95 (0.46-1.97) Active comparator PSHR 0.78 (0.31-1.91) Restricted to fathers with somatic indications NO Indication-restricted PS HR 0.83 (0.32-2.15) Active comparator PSHR 0.92 (0.31-2.73) TW Restricted to father epilepsy	NDD aHR 1.06 (0.81-1.22) ASD 1.29 (0.89-1.85) ADHD 0.98 (0.76-1.25) ID (SE only) 1.20 (0.65-2.21) Psych development 1.28 (0.84-1.97) Consistent in dose-response analyses and when restricted to fathers with epilepsy

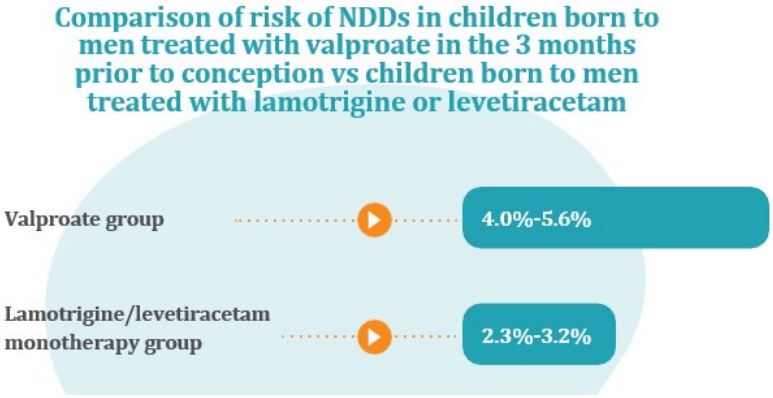
		to mirror IQVIA study: excluding children of parents with NDDs or congenital malformations, aHR: 0.99 (0.64-1.52) excluding children of mothers with epilepsy; aHR: 0.97 (0.64-1.49) excluding children with epilepsy, aHR: 0.98 (0.63-1.51) rerunning analyses without adjustment for parental epilepsy aHR 0.99 (0.65-1.49) rerunning analyses without adjustment for education, aHR 1.11 (0.73-1.67) and stopping follow-up at age 12 years. aHR: 0.85 (0.53-1.36)	Indication-restricted PSHR (0.93 (0.62-1.40) Active comparator PSHR 2.51 (0.74-8.47) Restricted father psych Indication-restricted PSHR 1.21 (0.96-1.53) Active comparator PSHR 1.15 (0.73-1.82) Restricted father som Indication-restricted PSHR 1.17 (0.94-1.46) Active comparator PSHR 1.49 (0.72-3.08)	
ASD	**DK** Adjusted HR (0.76 [0.30, 1.89]) for VPA compared to lamotrigine/levetiracetam 9 VPA cases /671 vs 17 L/L cases /1115 in adjusted analyses **NO** Not possible due to low event counts	ASD 24 VPA, 31 L/L cases aHR: 0.92 (0.38-2.24)	ASD NO Indication restricted aHR 1.48 (0.82-2.68) (VPA 7/304; comparator 1199/121306) Active comparator aHR 1.66 (0.55-4.98) (7/319; 10/730) TW Ind restr aHR 1.14 (0.67-1.73) (cases VPA 15/543; comparator 10373/500498) Act comp: insufficient events ADHD NO Indication-restricted aHR 1.85 (0.77-4.48) (VPA cases 9/452; comparator 3356/121306) Active comparator aHR 1.28 (0.64-2.56) (VPA cases 14/319; comparator 26/730). TW Ind restr aHR 1.16 (0.89-1.51) (cases VPA 61/543; comparator 26/730) Act comp aHR 0.93 (0.39-2.22) (cases VPA 62/543; comp 9/96)	

Annex II Core version HCP guide

Please find a proposal to update the core version of the HCP guide below, including only the section related to male patients (additions in **underlined bold**; deletions in ~~strikethrough~~):

7. What you must know about the risk to children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 European Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy.



The pooled adjusted hazard ratio for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% Confidence Interval: 1.09, 2.07).

The study was not large enough to investigate associations with specific NDD subtypes (composite endpoint including autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders). ~~Due to study~~ **The study has** limitations including potential confounding by indication and differences in follow-up time between exposure groups~~, the causal role of valproate is possible and not considered to be confirmed~~.

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy.

Other retrospective observational studies from Norway, Sweden, Denmark, and Taiwan did not show a statistically significant increased risk of NDDs in children born to men treated with valproate monotherapy in the 3–4 months prior to conception compared men treated with lamotrigine/levetiracetam monotherapy (estimated HRs ranged between 1.02 and 1.10, with confidence intervals including 1) or men not treated with valproate.

Differences in study design, including control for confounding and population selection, may contribute to variability in findings. In addition, available data suggest that factors other than valproate exposure, including underlying paternal disease, may contribute to the observed association. Overall, an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible, however, the causal role of valproate is not established.

The risk to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.

8. What is your role, when managing, treating or taking care of male patients with Epilepsy or Bipolar Disorder

•Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder <or migraine>.

{to be adapted depending on healthcare system}

SPECIALIST and GENERAL PRACTITIONER

Explain/remind and ensure patient's knowledge of

IV. **The potential risk of neurodevelopmental disorders for children born to men treated with valproate in the 3 months prior to conception**

V. The risk of NDDs in children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known

VI. As a precaution measure, discuss with the patient regularly **the need:**

- To consider **effective contraception**, including for a female partner, while using valproate and for 3 months after stopping the treatment
- To consult a specialist **to discuss treatment alternatives** , when they are planning to conceive a child and before discontinuation of contraception
- **Not to donate sperm** during treatment and for 3 months after stopping the treatment

A specialist should regularly review whether valproate is the most suitable treatment for the patient.

For male patients planning to conceive a child suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case.

PHARMACIST

•Ensure the patient received the Patient Guide and Patient Card

•Discuss the need to consider effective contraception, including for a female partner

•{Subject to national implementation} <Remind that online information can also be found by scanning the QR code (on the leaflet / on the box)>

Annex III Core version patient guide for males

Please find a proposal to update the core version of the patient guide for males below (additions in **underlined bold**; deletions in ~~strikethrough~~):

Valproate* guide for male patients

Read this guide along with the patient information leaflet for a complete product information

VALPROATE <INVENTED NAME>

What you should know

This guide contains key information about the potential risks of valproate* when used by male patients in the 3 months before conception of a child.

Ask your doctor or pharmacist if you have any questions.

KEEP THIS GUIDE. YOU MAY NEED TO READ IT AGAIN.

{Subject to national implementation} <Information about the use of valproate in male patients can also be found online at <webpage>>

*Valproate also known as <invented name>

What are the risks of taking valproate* when conceiving a child

A study suggests a possible risk of physical and mental developmental disorders (problems with early child development) in children born to fathers treated with valproate in the 3 months before conception.

In this study, around 5 children in every 100 had problems with neurodevelopment when born from fathers treated with valproate, and around 3 children in every 100 when born from fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). For example, problems with your child's neurodevelopment as they grow up may include:

- Being late in learning to walk and talk.
- Lower intelligence than other children of the same age.
- Poor speech and language skills.
- Memory problems.
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder.

~~The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known.~~

The study has limitations~~ and therefore it is not entirely clear if the increased risk for physical and mental developmental disorders suggested by this study is caused by valproate~~. A wide range of physical and mental developmental disorders were investigated in the study. However, the study could not show which particular type of disorder that children born to fathers taking valproate may be at risk of developing.

Other studies have also investigated the possible risk for physical and mental developmental disorders in children born to fathers treated with valproate in the 3 to 4 months before conception. These studies did not show an increased risk for physical and mental developmental disorders in children born to fathers treated with lamotrigine or levetiracetam or compared with fathers not treated with valproate.

Overall, the results from different studies are not consistent, and most studies do not suggest an increased risk. It is not clear whether any possible risk for physical and mental developmental disorders is caused by valproate itself or by other factors, such as the father's underlying illness. The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is also not known.

What does this mean for me?

As a precautionary measure, your doctor will discuss with you the potential risk in children born to fathers treated with valproate in the 3 months before conception.

Your doctor will also discuss with you:

- The need to consider **effective contraception** (birth control) for you and your female partner during valproate use and for 3 months after stopping valproate (the time needed for new sperm to be formed).

- The need to consult your doctor when you are **planning to conceive a child** and before stopping contraception (birth control).

- The possibility of **other treatments** that can be used to treat your disease.

Do not donate sperm when taking valproate and for 3 months after stopping valproate treatment.
Talk to your doctor if you think about having a baby.

If your **female partner becomes pregnant** while you used valproate in the 3 months before conception and you have questions, both of you may **contact your doctor**.

Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

Your specialist will review your treatment regularly.
During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

*Valproate also known as <invented name>