Post Authorization Safety Study (PASS) Information

Acronym/Title	Risk association of orofacial cleft and **G**lu**c**oco**r**ti**c**oids exposure during pregnancy: a meta-analysis
Protocol version and date	1.2, 16 November 2018
IMPACT study number	20638
Study type / Study phase	Observational, Meta-analysis of published literature
EU PAS register number	TBD, Study not yet registered
Active substance	Diflucortolone valerate (BAY 866146); Glucocorticoids (drug class: corticosteroids)
Medicinal product	Nerisona
Product reference	BAY 866146
Procedure number	NA
Comparator / Reference therapy	Unexposed control
Study Initiator and Funder	Bayer AG
Research question and objectives	A systematic literature review was conducted to identify evidence on the risk of development of cleft palate in neonates after glucocorticoids exposure during pregnancy. The published meta-analyses are outdated and have some shortcomings. Evidence gathered from systematic literature review is heterogeneous and does not answer the question. Thus, a meta-analysis of the evidence identified in the systematic literature review is warranted. The primary objective of this meta-analysis is to investigate the relationship between the exposure of glucocorticoids during pregnancy and orofacial cleft development. Secondary objectives are to perform subgroup analyses for: • Potency of glucocorticoid • Route of administration • Types of orofacial cleft
Country(-ies) of study	NA

Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	[redacted]

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
CI	Credibility Intervals
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Publication Practice
HEOR	Health Economics and Outcomes Research
INN	International Nonproprietary Name
MAH	Marketing Authorization Holder
N/A	Not Applicable
OR	Odds Ratio
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
RR	Relative Risk
QPPV	Qualified Person Responsible For Pharmacovigilance
SAP	Statistical Analysis Plan
SLR	Systematic Literature Review

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible
Name:
E-mail: [redacted]

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: [redacted]

Role: MAH contact person (Regulatory Affairs)
Name: [redacted]

Role: OS Safety Lead
Name: [redacted]

Role: OS Medical Expert
Name: [redacted]

Role: OS Statistician
Name: [redacted]

Role: OS Epidemiologist
Name: [redacted]

Role: OS Health Economics and Outcomes Research (HEOR) responsible
Name: [redacted]

4. Abstract

Acronym/Title	Risk association of orofacial cleft and glucocorticoids exposure during pregnancy: a meta-analysis
Protocol version and date	1.2, 16 November 2018
IMPACT study number	20638, EU PAS TBD
Study type / Study phase	Observational, Meta-analysis of published literature
Author	[redacted]
Rationale and background	Glucocorticoids use is very common in early pregnancy or first trimester. The studies identified in a systematic literature review present an unclear picture of potential effects of glucocorticoids use during pregnancy on the orofacial developmental process in infants. Bayer's glucocorticoid product, Nerisona (INN) Diflucortolone valerate (for topical use) is contraindicated for use during pregnancy. In the scope of a regulatory procedure, the French Health Authority has requested Bayer to conduct a meta-analysis encompassing all studies investigating a possible increase in the risk of cleft palates in neonates of women treated with glucocorticoids during the first trimester of pregnancy. A meta-analysis with most recent published data will support drawing evidence-based conclusions and answer questions about the impact of glucocorticosteroid use during pregnancy on congenital malformations especially orofacial clefts.
Research question and objectives	The analysis' primary objective is to conduct a meta-analysis to investigate the relationship between the exposure of glucocorticoids during early pregnancy or first trimester and congenital orofacial cleft development. Secondary objectives are to perform subgroup analyses for: • Potency of glucocorticoid • Route of administration • Types of orofacial cleft
Study design	A meta-analysis of published literature will be conducted with 18 shortlisted observational studies identified through a Systematic Literature Review (SLR) which was conducted using keyword and MeSH terms on Embase and Medline via Ovid®. Articles published up to 25 June 2018 have been reviewed.

Population	Pregnant women exposed to any glucocorticoid or corticosteroid or steroids in early pregnancy or first trimester of pregnancy irrespective of mode of administration identified from articles published up to 25 June 2018 by pre-specified inclusion and exclusion criteria
Variables	Exposure definition • First trimester exposure • Early pregnancy Outcomes definition • Oral clefts • Cleft lip with or without palate • Cleft palate Covariate definition • Potency of glucocorticosteroids • Route of administration of glucocorticosteroids
Data sources	• Embase and Medline via Ovid®, Cochrane database, Google Scholar has been used for data collection • All records retrieved from the literature searches have been screened for relevancy based on eligibility criteria (inclusion/exclusion). Relevant back references from the shortlisted studies have also been reviewed.
Study size	18 observational studies have been selected for meta-analysis by predefined eligibility criteria in a previously conducted SLR.
Data analysis	• Direct treatment comparison: Any glucocorticoid or corticosteroid or steroids use irrespective of mode of administration vs. no use of glucocorticosteroids • Model: Fixed effect model • Measure of relative effect: For the dichotomous outcomes will be assessed by Odds ratio (OR) • Inverse variance method • Effect size are assessed by Odds ratio (OR) as it is a rare outcome • Publication bias: Using funnel plot, Egger's test, Galbraith plot • Sensitivity analysis • Sub-group analyses o Route of administration: o Types of orofacial cleft o Potency of glucocorticoid

	• Data will be analysed by using the metafor package in R software version 3.5.1 • The results of the outcomes will be described as eman with 95% credibility intervals (CI) and presented as Forrest plots
Milestones	Start of data collection (SLR): 12 June 2018 End of data collection (SLR): 25 June 2018 Final report (SLR): 9 July 2018 Meta-analysis protocol: 09 November 2018 Statistical analysis plan: 10 September 2018 Meta-analysis report: November 2018

5. Amendments

Not applicable.

6. Milestones

Table 1 presents the planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation, data release and analysis do not require amendments to the protocol.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection (SLR)	12 June 2018
End of data collection (SLR)	25 June 2018
Final report of study results (SLR)	9 July 2018
Meta-analysis protocol	16 November 2018 (version 1.2)
Registration in the EU PAS register	TBC
Statistical analysis plan	10 September 2018
Meta-analysis report	November 2018

7. Rationale and background

Cleft lip and palate are the most common congenital anomalies of the craniofacial regions occurring at a rate of 1 in 700 births (1-3). Unilateral cleft lip and palate is the most common diagnosis followed by isolated cleft lip. It is more common in males. (4). The most common manifestation of these anomalies is difficulty in feeding. Individuals also experience speech, hearing and dental problems (5).

The development of cleft lip and palate is well documented. Between 4-8 weeks of gestation, normal lip development occurs along with frontonasal prominence. Nasal placodes develop and divide the paired medial and lateral nasal processes (5, 6). By the end of week 6 of gestation, the primary palate is formed by the fusion of paired medial processes and developing premaxilla (central upper lip, maxillary alveolar arch and four incisor teeth, and hard palate). During week 6-12, the secondary palate develops along with medial projections of maxillary processes. Cleft of lip and/or palate is a result of the disruption of normal development which could be due to chemical and environmental factors(7, 8)

Corticosteroids have a wide range of clinical uses. However, its use in pregnancy is limited (9).

Corticosteroids fluctuate in their ability to cross the placenta (10). Fetal concentrations (although lower than maternal concentrations) are linearly related to maternal (cortisol) concentrations (11). Pregnancy enhances systemic absorption of inhaled corticosteroids as it increases maternal tissue perfusion. This leads to the assumption that exposure of corticosteroid in pregnancy might cause congenital anomalies (11-13).

Some epidemiological studies have reported 3-6 fold increased risk of orofacial cleft due to corticosteroid use in early pregnancy or in first trimester in humans (14-16), while, some studies have not found this association (16, 17). Thus, there remains a controversy on the implication of glucocorticoid use in pregnancy. Therefore, it is important to gather more evidence related to the risk of cleft palate in neonates following exposure to glucocorticoids during pregnancy.

Bayer's glucocorticoid product, Nerisona (INN) Diflucortolone valerate (for topical use) is contraindicated for use during pregnancy. In the scope of a regulatory procedure, the French Health Authority has requested Bayer to conduct a meta-analysis encompassing all studies investigating a possible increase in the risk of cleft palates in neonates of women treated with glucocorticoids during the first trimester of pregnancy.

In response to this request, a systematic literature review (SLR) was conducted to identify relevant studies evaluating the potential association between the exposure to glucocorticoids and the occurrence of orofacial cleft. Due to the heterogeneity findings in the 18 selected publications, a meta-analysis of their results was deemed as warranted and will be conducted as originally requested. Since this analysis will evaluate the risks of a medicinal product class used in a patient population for which safety information is limited or missing (e.g. pregnant women), it is considered as a Post Authorization Safety Study (PASS), in accordance with the European Medicine Agency Guideline on good pharmacovigilance practices (GVP) Module VIII – Post -authorisation safety studies (Rev 3) (18).

Of note, a meta-analysis for topical administration of corticosteroids during early pregnancy is not published. Nevertheless, a meta-analysis (16) was identified in the SLR that discusses effect of use of corticosteroids during early pregnancy without specifying the route of administration. This meta-analysis also has some shortcomings such as:

- Relationship between dosage and duration of medication were not examined in the included studies that could affect their results
- Confounding factors, such as race, maternal age, level of education, economic and social status, smoking, chances of repetitive enrollment of some patients in different studies were not addressed
- Dosage of glucocorticoid was not discussed
- Recall and publication bias due to retrospective design

Thus, further analyses are warranted to investigate a concrete association between the exposure to glucocorticoids and the developmental orofacial cleft. The current meta-analysis aims to also address some of the shortcoming of the existing meta-analysis such as the confounder effect by sub-group analyses. However, not all shortcomings will be addressed due to lack of data availability in the published literature.

8. Research questions and objectives

The studies identified and reported in a previously conducted SLR do not represent a clear scenario regarding the risk association of glucocorticoids exposure during pregnancy (see Appendix 1). The individual studies reported high to non-significant risk of cleft development in pregnant women exposed to glucocorticoids in comparison to non-exposed pregnant women. Consequently, it is difficult to draw a clear conclusion from these studies without pooled analysis of their findings.

8.1 Primary objective

The primary objective in this study is:

- To conduct a meta-analysis of published literature to investigate the association between the exposure of glucocorticoids during pregnancy and orofacial cleft development

8.2 Secondary objective

The secondary objective of this study is:

- To perform sub group analyses for mild, moderate and strong glucocorticoid types as well as for route of administration and types of orofacial cleft.

9. Research methods

9.1 Study design

Meta-analysis will be conducted with 18 observational studies previously identified through a systematic literature review which was conducted using keyword and MeSH terms on Embase and Medline via Ovid® (see Appendix 1).Articles published up to 25 June 2018 have been reviewed. Additionally, a supplementary search was conducted on the Cochrane database and general sources such as Google Scholar to identify additional studies that might be relevant to the scope of the search.

All records retrieved from the literature searches were screened for relevancy based on eligibility criteria (inclusion/exclusion). The results were initially screened by title and abstract, and the shortlisted results were further screened on full text. Relevant back references from the shortlisted studies have also been reviewed. The key outcomes reported were OR followed by RR for developing orofacial cleft(s) in neonates due to exposure of women to glucocorticoids in pregnant women

Meta-analysis is a powerful tool to analyse rare outcomes as individual studies provide inadequate power to test rare outcome. Meta-analysis increase precision in estimating effects.

9.2 Setting

Pregnant women exposed to any glucocorticoid or corticosteroid or steroids in early pregnancy or first trimester of pregnancy irrespective of mode of administration identified through a systematic review of articles published up to 25 June 2018 by pre-specified inclusion and exclusion criteria (see section 4 of SLR in see Appendix 1). In total 18 observational studies have been selected for this meta-analysis with sample size for individual studies ranging from 106 to 832,636 patients.

- *Source:* Embase and Medline via Ovid®, Cochrane database, Google Scholar
- *Population sampling strategy:* All records retrieved from the literature searches were screened for relevancy based on eligibility criteria (inclusion/exclusion). The results were initially screened by title and abstract, and the shortlisted results were further screened on full text. Relevant back references from the shortlisted studies have also been reviewed.

9.2.1 Selection criteria used for the Systematic Literature Review (SLR)

The inclusion and exclusion criteria used for the selection of studies as well as detailed methodology of the systematic literature review are provided in the Appendix 1.

No time period restriction was used. The systematic literature review was conducted to identify all studies (including observational studies and clinical trials) published till 25 June 2018 (search date). In addition, there were no restrictions to the route of administration.

Only 18 studies were shortlisted based on the inclusion criteria. All of the 18 studies were observational studies while no clinical trials were identified that met the inclusion criteria.

The selection criteria utilized in the SLR were the following:

Inclusion criteria

- Population: Pregnant women
- Intervention: Any glucocorticoid or corticosteroid or steroids use irrespective of mode of administration
- Comparator: Any/none
- Outcomes: Incidence/ risk of cleft lip/palate in infants
- Study Design:
    - Meta-analysis and systematic literature reviews
    - Observational studies (such as cohort study, case-control study, registries data)
    - Clinical trials – Phase IIb, III, and IV
    - Conference abstracts/posters
- Time period: No time period restriction
- Geography: No geography restriction

Exclusion criteria

- Population: Nonpregnant women
- Intervention: Drugs other than glucocorticoid or corticosteroid or steroid
- Outcomes: Incidence/ risk of cleft lip/palate in infants
- Study Design:
    - Animal Study

- In vitro studies
- Editorial, letters, comment
- Clinical trials – Phase I or preclinical
- Case reports, case series
- Reviews

- Studies focusing on:
  - Diagnosis and surgical procedure for cleft repair
  - Impact of Increased internal corticosteroids due to stress
  - The relationship between genetic mutations and cleft patients
  - Adverse events for other drugs
  - Safety profiles of glucocorticoid or corticosteroid

9.2.2 Representativeness

The recall of the performed SLR is considered as representative for the population of pregnant women using corticosteroids in early pregnancy or first trimester. The conclusions out of this research are expected to be as close as possible to a representative sample of these women.

Cleft palate, even being one of the most common congenital malformations, is too rare to conduct studies with an optimal representative sample. Furthermore, the ethical aspects of conducting interventional clinical trials in pregnant women to investigate the occurrence of congenital malformations in the offspring following drug exposure limit the availability of research in the area. Therefore it is justified to conduct this study in order to answer the research question.

9.3 Variables

9.3.1 Exposure definition

The primary exposure of interest is glucocorticoid use.

- First trimester exposure: At least one prescription for glucocorticosteroids redeemed from the first day of the last menstrual period to the end of gestational week 12

OR

- Early pregnancy: At least one prescription for glucocorticosteroids redeemed from 30 days before estimated conception to the end of the first trimester

Our primary comparison group includes women not using glucocorticoid during pregnancy.

9.3.2 Outcomes definition

The primary outcome variable is the incidence of any type of orofacial cleft. Oral clefts are defined as diagnosis of cleft lip with or without cleft palate or isolated cleft palate.
Please refer to section 4 of systematic literature review report provided in Appendix 1for the detailed scope of the research.

9.3.3 Covariate definition

Covariates of interest for this meta-analysis are:

- Potency of glucocorticoids
- Route of administration

9.4 Data sources

Embase and Medline via Ovid®, Cochrane database, Google Scholar have been used for data collection as described in Appendix 1.All records retrieved from the literature searches have been screened for relevancy based on eligibility criteria (inclusion/exclusion). Relevant back references from the shortlisted studies have also been reviewed.

Screening steps:

First level: screening based on title/abstracts

All the records retrieved from the literature search (using multi-string search strategy) were screened based on the title and abstract supplied with each citation. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that do not match the eligibility criteria were excluded at this stage; whereas unclear citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were excluded.

Second level: screening of full text

The eligibility criteria were applied to the full-text citations. Each full-text were screened by two independent reviewers, and any discrepancies between reviewers were reconciled through a third independent reviewer. Studies included after this stage were included for the next step i.e. data extraction.

Extraction of relevant data

Data from included studies was extracted by one reviewer and the quality of the data was checked by the second reviewer, with reconciliation of any differences by a third independent reviewer.

9.5 Study size / Recall

18 observational studies were selected for meta-analysis by predefined eligibility criteria. For details, please refer to section 4 of systematic literature review report provided in Appendix 1.

9.6 Data management

The evidence for the present meta-analysis was gathered through secondary research on the published studies and meta-analyses. We considered quantitative data from the research. Based on the evidence identified from SLR, risk association of orofacial cleft and glucocorticoids exposure during pregnancy was assessed by the odds ratios (ORs) with corresponding 95% credibility intervals (CIs). As this is a rare outcome, the odds ratio will be used as an approximation of the relative risk. A detailed and comprehensive data extraction table in MS Excel will be created to capture the relevant information from the studies identified from systematic literature review. This will then be imported into the R software for meta-analyses.

9.7 Data analysis

- Direct treatment comparison: Any glucocorticoid or corticosteroid or steroids use irrespective of mode of administration vs. no use of glucocorticosteroids
- Model: Fixed effect model will be used. We assume that the underlying effect size is the same across the studies. The differences in observed effects are only due to random error or sampling error within the studies. The observed effects mainly depend on the sample size and weighted average mean might give a precise estimation of the overall effect. However, any deviation from this assumption will be discussed.
- Measure of relative effect: For the dichotomous outcomes will be assessed by Odds ratio (OR). Given that the event of our interest is a rare outcome, we assume relative risk (RR) equivalent to OR.
- Inverse variance method: Studies with less variance or standard deviation are given more weight. The variance of weighted average can be minimized through this method and hence inverse variance method will be used to assess the direct treatment effect
- Effect size is assessed by Odds ratio (OR) as it is a rare outcome
- Publication bias: Reporting or publication bias will be assessed by using the funnel plot (symmetry or asymmetry) and it again confirmed by using the Egger's test (in case of asymmetry funnel plot). Further, any outliers in the effect size will be determined by Galbraith plot
- Sensitivity analysis: In order to know the robustness of the findings, sensitivity analysis will be performed with and without outlier studies so that any uncertainty can be determined. This will be done only in case of high level of heterogeneity observed. However, plausible reasons for high heterogeneity (unexplained variation) will be discussed in the MAR
- Sub-group analyses will be performed for
    - Route of administration:
        - Topical
        - Systemic
        - Any other form of use
    - Types of orofacial cleft
        - Cleft lip (CP)
        - Cleft lip with or without palate (CLP)
        - Cleft palate (CP)
        - Orofacial cleft (OC)
    - Potency of glucocorticoid
        - Mild
        - Moderate
        - Potent
        - Very potent
- 95% credibility intervals will be used as a measure for the expression of the difference (overlap / no overlap with 1 for OR)
- Data will be analysed by using the metafor package in R software version 3.5.1

9.8 Quality control

Two reviewers independently extract data and study characteristics from each citation, and any discrepancies between reviewers will be reconciled by a third independent reviewer. Citations that do not match the eligibility criteria will be excluded at this stage; whereas unclear citations will be included.

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) will be employed for reporting of included studies

Newcastle-Ottawa scale (NOS) will be used to assess and appraise the methodological quality of included studies

9.9 Limitations of the research methods

- There may have potential biases (recall and publication bias) inherent in retrospective case-control design. These types of study may also have higher sensitivity to detect low-frequency defects
- Included studies lacked data evaluating the relationship between dosage and duration of medication and teratogenic effects, which could affect the results of the study.
- Confounding factors assessed and described in the published sources could be an explaining factor for clinical heterogeneity, which includes the decision for a specific treatment / administration of glucocorticosteroids, but also other factors could be a reason for heterogeneityRange of dosages used is relatively wide in included studies which may have an influence on the results
- Conditions of skin, size of the skin surface treated and the part of the body where it is applied were not reported in all studies which may have an influence on the absorption of corticosteroids which may alter effect outcomes

9.10 Other aspects

Not applicable.

10. Protection of human subjects

This study is based on published data only. No data with personal identifiable/sensitive information will be used. All data are aggregated and anonymised. GDPR is not applicable and the analyses of data in this way is not covered and justified in the most recent release of the Declaration of Helsinki.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products [Revision 1]), individual reporting of adverse reactions is not required for non-interventional study designs that are based on secondary use of data (19). Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2014).

12. Plans for disseminating and communicating study results

As this meta-analysis is conducted in response to a query from French Health Authority Format, the content of the study protocol for post-authorization safety studies (PASS), as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012 was used. European Medicines Agency guidance for the format and content of the final study report of non-interventional post-authorization safety studies was also used to develop the protocol for current meta-analysis.

The results of this meta-analysis are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines (20)).

13. References

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18. EMA. EMA, "GPV Module VIII - Post-authorisation safety studies (Rev 1)," Guideline on good pharmacovigilance practices (EMA/813938/2011_Rev3), 09 Oct 2017. 2017. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf.

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Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	Final version and date (if available)*
Systematic Literature Review Report*	09 JUL 2018
SAP	10 SEP 2018

*Please refer to Appendix 3.

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Please check for the current version of the ENCePP checklist for study protocols at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Risk association of orofacial cleft and Glucocorticoids exposure during pregnancy: a meta-analysis

EU PAS Register® number:
Study reference number (if applicable): Impact#20638

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

EU PAS registration is ongoing.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7 and 8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

The study is not testing any hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

The study is a meta-analysis of published literature, thus uses secondary data. Reporting of findings will be done in the in the study report in aggregated form.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex	☐	☒	☐	9.1, 9.2
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☐	☒	☐	
4.2.5 Duration of follow-up	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1, 9.2

Comments:

The study is a meta-analysis of published literature. The search criteria for inclusion are described in the protocol.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	

Comments:

The study does not investigate the validity of exposure assessment, assumes that the selected literature publications fulfill quality standards to address the study objectives. Non-exposure to treatment is deemed the most appropriate comparator.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

The study is a meta-analysis of literature. The outcome investigated is orofacial cleft in the offspring of mother exposed to corticosteroids during the first trimester of pregnancy.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Reporting or publication bias will be assessed by using the funnel plot (symmetry or asymmetry) and it again confirmed by using the Egger's test (in case of asymmetry funnel plot). Further, any outliers in the effect size will be determined by Galbraith plot

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☒	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☒	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The data sources for the study are the selected literature publications.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

The meta-analysis assumes that the selected literature publications fulfill scientific quality standards to address the study objectives.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

This is a meta-analysis of published literature. Study data will be stored in accordance with quality procedures.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☐	☒	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

The feasibility of this meta-analysis has been addressed by a previous systematic literature review. Publication bias is discussed in section 9.9

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Study is based on published information.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☒	☐	

Comments:

No amendments or deviations occurred.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

Name of the main author of the protocol: [redacted]

Date: 20/11/2018

Signature: 

Annex 3: Additional information

Systematic Literature Review Report (see Appendix 1)

Appendix 1 Systematic Literature Review Report

Annex 4: Signature pages