STUDY PROTOCOL

PASS Information

Title	Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg)
Protocol version identifier	V04-00
Date of last version of protocol	05 February 2014
EU PAS register number	EUPAS2196
Active substance	Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and estrogens, fixed combinations, ATC code: G03AA14 Active substances: nomegestrol acetate and estradiol (as hemihydrate)
Medicinal product	Zoely 2.5 mg/1.5 mg film-coated tablets
Product reference	Zoely: EMEA/H/C/001213
Procedure number	Not available
Marketing authorisation holder(s)	Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01 YE64 Ireland
Joint PASS	No
Research question and objectives	Primary objective: characterization and comparison of the risks of the use of NOMAC-E2 with COC_{LNG}. Main clinical outcomes of interest: venous thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.
Country(-ies) of study	Australia, Austria, Colombia, France, Germany, Hungary, Italy, Mexico, Poland, Russia, and Spain, Sweden

PASS Information (continued)

Author	Jürgen Dinger, MD, PhD Principal Investigator Invalidenstrasse 115 10115 Berlin Germany Phone: PPD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01 YE64 Ireland
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1 Table of Contents

2 List of Abbreviations

Abbreviation	Definition
ADB	Administrative Database
AE	Adverse Event
AMI	Acute Myocardial Infarction
AT	As Treated
ATC	Anatomical Therapeutic Chemical Classification System
ATE	Arterial Thromboembolism
BMI	Body Mass Index
CHMP	Committee for Medical Products for Human Use
COC	Combined Oral Contraceptive
COC_{LNG}	Levonorgestrel-containing COC
CT	Computer Tomography
CVA	Cerebrovascular Accidents
DIMDI	German Institute for Medical Documentation and Information
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EURAS	European Active Surveillance (study)
GEP	Good Epidemiological Practices
GPP	Good Pharmacoepidemiology Practices
GXP	Good Practice Guidelines
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD-10	International Classification of Diseases, 10th revision

ICMJE	International Committee on Medical Journal Editors
INAS	International Active Surveillance Study
ITT	Intention To Treat
LNG	Levonorgestrel
MRT	Magnetic Resonance Tomography
NOMAC-E2	Nomegestrol Acetate and Estradiol
OC	Oral Contraceptive
OPS	Operations and Procedures Classification System (acronym for the German term ‘Operationen- und Prozedurenschlüssel’)
PE	Pulmonary Embolism
PIP	Pediatric Investigation Plan
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
PQC	Product Quality Complaint
SAE	Serious Adverse Event
SDB	Study Database
SMAC	Safety Monitoring and Advisory Council
TASC	Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing
VTE	Venous Thromboembolism
WHO	World Health Organization
WY	Woman-years
ZEG	Berlin Center for Epidemiology & Health Research (acronym for the German term ‘Zentrum für Epidemiologie & Gesundheitsforschung Berlin’)

3 Responsible Parties

PRINCIPAL INVESTIGATOR:
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SAFETY MONITORING AND ADVISORY COUNCIL:

Members:

PPD

Experts to the Advisory Council:

PPD

4 Abstract

Title

Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg)

Study protocol version of 05 February 2014

Author: Juergen Dinger, MD, PhD
Principal Investigator
Invalidenstrasse 115
10115 Berlin
Germany

Rationale and background

NOMAC-E2 is a novel monophasic oral contraceptive containing a fixed dose of nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg) being taken for 24 days followed by 4 days of placebo. The estrogen component is identical to the endogenous human 17β-estradiol. It is unknown whether this regimen has an impact on the cardio-vascular risk associated with the use of hormonal contraceptives. It is also unclear whether the regimen has an impact on depressive disorders, hepatobiliary disorders, inflammatory bowel disease, body weight and acne.

Research question and objectives

The primary objective of the study is to characterize and compare the risks of the use of NOMAC-E2 with levonorgestrel-containing combined oral contraceptives (COC_{LNG})[1], in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcomes of interest for follow-up are venous

[1] cf. Section 9.2.1

thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.

Study design

Multinational, controlled, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[2] and restarters[3]) of two different groups of hormonal contraceptives: NOMAC-E2 and COC_{LNG}. The study will use a non-interference[4] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting. A 'non-interference' approach is used to provide standardized, comprehensive, reliable information under routine medical conditions. Study participants will be enrolled via an international network of 2,000 – 3,000 COC prescribing health care professionals. Study participants will be followed up for one to two years. All outcomes of interest will be captured by direct contacts between the investigator team and the study participants. Reported outcomes of interest will be validated via attending physicians and relevant source documents. The classification of outcomes of interest into 'confirmed' and 'not confirmed' will be verified by blinded independent adjudication.

Population

Approximately 101,000 study participants (50,500 NOMAC-E2 and 50,500 COC_{LNG} users) will be recruited via a network of 2000 – 3000 COC-prescribing health care professionals (e.g. gynecologists and general practitioners) in Australia, 9 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, Spain and Sweden) and 2 Latin American countries (Colombia and Mexico). All starters and restarters (see above) of NOMAC-E2 or COC_{LNG} who are willing to participate in the study are eligible for enrollment into the study[5].

Variables

Primary statistical variable: VTE hazard ratio for NOMAC-E2 vs. COC_{LNG} adjusted for age, BMI, duration of current use and family history of VTE. Results are based on patient-reported VTE that will be validated via the attending physicians and medical records. Other variables include arterial thromboembolism, depressive disorders, hepatobiliary disorders, inflammatory bowel disease, body weight and acne.

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[2] First ever user of a COC

[3] User who restarts hormonal contraceptive use with a COC (same COC as before or new COC) after an intake break of at least two months.

[4] I.e., 1) all new users of NOMAC-E2 or COC_{LNG} are eligible for enrollment if they give their informed consent; and 2) recruitment of study participants should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

[5] cf. Section 9.2.2

Data sources

This is a field study. Exposure to hormonal contraceptives, concomitant medication, primary and secondary outcomes, potential confounding factors and potential effect modifiers will be documented by the study participants as well as the recruiting and attending physicians in the questionnaires, and additional documentation sheets, if needed.

*S*tudy size

The study is sufficiently powered to show non-inferiority of NOMAC-E2 compared to COC_{LNG} assuming that the true VTE risk among NOMAC-E2 users is not higher than among COC_{LNG} users. For this purpose, a total of 101,000 women (50,500 NOMAC-E2 and 50,500 COC_{LNG} users) will be followed up for approximately 150,000 woman-years (WY). The power calculations are based on the following parameters: 1) α of 0.05; 2) power (1-β) of 0.80 and 3) non-inferiority limit on hazard ratio of 1.5.

Data analysis

The final analyses will include both an "as treated" (AT) and an intention-to-treat (ITT) analysis using Cox regression models. The safety conclusions of the study, however, will be based on the AT analyses because the ITT approach potentially dilutes differences between treatments. The appropriate confounding variables will be built into the statistical models. Crude as well as adjusted hazard ratios (HRs) will be calculated. The null hypothesis to be tested is: $HR_{VTE} \geq 1.5$ (i.e., the VTE hazard ratio for NOMAC-E2 vs. COC_{LNG} is higher than or equal to 1.5). The alternative hypothesis is: $HR_{VTE} < 1.5$.

Milestones

Milestone	Planned date[6]
Start of data collection	March 2014
End of recruitment	September 2019
Last regular follow-up	September 2020
End of data collection[7]	December 2020
Interim report 1	October 31, 2015
Interim report 2	October 31, 2016 Actual Date (May 23, 2016)
Interim report 3	December 2018
Interim report 4	February 2020

[6] cf. Section 9.9 ("Limitations of the research methods"), last paragraph

[7] includes 3 months of loss to follow-up activities after the last regular follow-up

Registration in the EU PAS register	March 2014
Final report of study results	April 2021

5 Amendments and updates

Number	Date	Section of Study Protocol	Amendments and updates	Reason
1 (v3.0)	20-FEB-2019	PASS Information	EU PAS Register number added	Number assigned following registration
			Medicinal product is only Zoely not IOA	Marketing authorisation was withdrawn for IOA in 2014
			Product reference updated to exclude IOA	Marketing authorization was withdrawn for IOA in 2014
			Marketing authorization holder for Zoely changed from Theramex to TEVA to a different Theramex	Change of MAH and reflection of shared funding between MSD and Theramex
			Delete MSD as MAH	Theramex is MAH for Zoely product
			Country(ies) of study: Sweden, Colombia and Mexico added	Expansion of recruitment to additional countries
			MAH contact person updated	Personnel change at MAH
		Section 2: List of Abbreviations	Addition of PQC	Acronym added to list due to expansion
		Section 3: Responsible parties	Funder contact information updated	Personnel change at MAH
			Safety Monitoring and Advisory Council members and experts updated	Departure and addition of members/experts

		Section 4: Abstract	Addition of Sweden, Colombia and Mexico	Expansion of recruitment to additional countries
			Modification of milestones	Timelines modified to reflect study prolongation as agreed with EMA
		Section 6: Milestones	Modification of milestones	Timelines modified to reflect study prolongation as agreed with EMA
		Section 9.1: Study Design	Addition of Sweden, Colombia and Mexico	Expansion of recruitment to additional countries
		Section 9.2.2: Selection of study population	Text added to clarify expansion to Latin America.	Expansion of recruitment to additional countries
		Section 9.10: Other aspects	Correction of typos	Typos identified
		Section 11: Management and reporting of adverse events/adverse reactions	Text modified to omit Theramex	Funding of study shared between MSD and Theramex
		Section 11.1.2: Product Quality Complaint Reporting	Addition of section	To include reporting of product quality complaints for compliance with standards
		Section 11.1.3: Special Situations Reporting	Addition of section	To include special situations reporting for compliance with safety standards
1 (v.4.0)	20-JUN-2019	PASS Information	MAH contact person updated	Personnel change

		Section 3: Responsible parties	Principal Investigator information updated	Change of Principal Investigator
			Funder contact information updated	Personnel change
		Section 4: Abstract	Deletion of text referring to 'short- and long-term' use	[redacted]
			Modification of milestones	Based upon feedback from the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 6: Milestones	Modification of milestones	Based upon feedback from the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 7: Rationale and background	Deletion of text referring to 'short- and long-term' use	[redacted]
				Requested by the PRAC in their

			Addition of a rationale for the choice of secondary outcomes	Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 8: Research question and objectives		Requested by the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
			ICD-10 code I80.3 removed from the list of ICD-10 codes describing the endpoint DVT of the lower extremities.	Requested by the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
			Deletion of text referring to 'short- and long-term' use	Requested by the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
			Clarification that physicians are not required to adhere to a 1:1 (NOMAC-E2/COC-LNG) recruitment ratio	Requested by the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 9.2.2: Selection of study population	Addition of a rationale for secondary outcomes	Requested by the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 9.3.2: Secondary endpoints		[redacted]

			Deletion of text referring to 'short- and long-term' use	[redacted]
			Addition of text in relation to statistical modelling approaches	Based on feedback from the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 9.7: Data analysis	Addition of text regarding the use of multiple imputation	Based on feedback from the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
			Timeline-related text updated or deleted as appropriate.	Based upon feedback from the PRAC in their Assessment of the MAH Responses to the 1st Request for a Revised PASS Protocol [v3.0].
		Section 9.9: Limitations of research methods		

1. Preface

The Protocol was amended on March 20, 2019 primarily to reflect the shared funding by MSD and Theramex and the additional reporting of product quality complaints and special situations. Additionally, the timeline was changed to extend recruitment until the end of June 2019 and follow-up until June 2020 with a final study report in December 2020. Updates were also made to participating countries, responsible parties and the Safety Monitoring and Advisory Council.

The March 20, 2019 amendment (Study Protocol Version 3.0) affected the following sections:

- PASS Information
- Abstract: Milestones
- Section 2: List of abbreviations
- Section 3: Responsible parties
- Section 4: Abstract
- Section 6: Milestones
- Section 9.1: Study Design
- Section 9.2.2: Selection of study population
- Section 9.10: Other aspects
- Section 11: Management and reporting of adverse events/adverse reactions
- Section 11.1.2: Product Quality Complaint Reporting
- Section 11.1.3: Special Situations Reporting

All changes are indicated with “current text” and “proposed text”. “Current text” refers to the study protocol dated February 5, 2014. “Proposed text” refers to the protocol amendment of March 20, 2019. Deletions are crossed out and additions/replacements are marked in the text as underlined.

PASS Information

Current text

EU PAS Register number: Study not yet been registered

Proposed text

EU PAS Register number: ~~Study not yet been registered~~ EUPAS2196

Current text

Medicinal product: IOA 2.5 mg/1.5 mg film-coated tablets
Zoely 2.5 mg/1.5 mg film-coated tablets

Proposed text

Medicinal product: ~~IOA 2.5 mg/1.5 mg film-coated tablets~~
Zoely 2.5 mg/1.5 mg film-coated tablets

Current text

Product reference: IOA: EMEA/H/C/002068
Zoely: EMEA/H/C/001213

Proposed text

Product reference: ~~IOA: EMEA/H/C/002068~~
Zoely: EMEA/H/C/001213

Current text

Marketing authorization holder(s):

Merck Sharp & Dohme Limited
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United Kingdom +

Theramex S.R.l
Via Messina 38
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Italy

Proposed text

Marketing authorization holder(s):

~~Merck Sharp & Dohme Limited~~
~~Hertford Road, Hoddesdon~~

~~Hertfordshire EN11 9BU~~

~~United Kingdom +~~

Theramex Ireland Limited

3rd Floor, Kilmore House,

Park Lane, Spencer Dock,

Dublin 1

D01 YE64

Ireland

~~1) S.R.l~~

~~Via Messina 38~~

~~20154 Milano~~

~~Italy~~

Current text

Country(ies) of study: Australia, Austria, France, Germany, Hungary, Italy, Poland, Russia, and Spain

Proposed text

Country(ies) of study: Australia, Austria, Colombia, France, Germany, Hungary, Italy, Mexico, Poland, Russia, Spain and Sweden

Current text

MAH contact person:

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Proposed text

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Section 2: List of Abbreviations

Proposed text

PQC	Product Quality Complaint

Section 3: Responsible parties

Current text

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Current text

Safety Monitoring and Advisory Council:

Members:

PPD

Experts to the Advisory Council:

PPD

Proposed text

Safety Monitoring and Advisory Council:

Members:

PPD

Experts to the Advisory Council:

PPD

Section 4: Abstract

Current text

Population: Approximately 101,000 study participants (50,500 NOMAC-E2 and 50,500 COC_{LNG} users) will be recruited via a network of 2000 – 3000 COC-prescribing health care professionals (e.g. gynecologists and general practitioners) in Australia and 8 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, and Spain). All starters and restarters (see above) of NOMAC-E2 or COC_{LNG} who are willing to participate in the study are eligible for enrollment into the study.

Proposed text

Population: Approximately 101,000 study participants (50,500 NOMAC-E2 and 50,500 COC_{LNG} users) will be recruited via a network of 2000 – 3000 COC-prescribing health care professionals (e.g. gynecologists and general practitioners) in Australia, ~~and~~ 8 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, ~~and~~ Spain and Sweden) and 2 Latin American countries (Colombia and Mexico). All starters and restarters (see above) of NOMAC-E2 or COC_{LNG} who are willing to participate in the study are eligible for enrollment into the study.

Current text

Milestones:

Start of data collection March 2014

End of recruitment April 2016

Last regular follow-up April 2017

End of data collection June 2017

Interim report 1 October 31, 2015

Interim report 2 October 31, 2016

Registration in the EU PAS register March 2014

Final report of study results October 31, 2017

Proposed text

Milestones:

Start of data collection March 2014

End of recruitment ~~April 2016~~ June 2019

Last regular follow-up ~~April 2017~~ June 2020

End of data collection ~~June 2017~~ September 2020

Interim report 1 October 31, 2015

Interim report 2 October 31, 2016

Actual Date (May 23, 2016)

Interim report 3 December 2018

Interim report 4 December 2019

Registration in the EU PAS register March 2014

Final report of study results ~~October 31, 2017~~ December 2020

Section 6: Milestones

Current text

Milestones:

Start of data collection March 2014

End of recruitment April 2016

Last regular follow-up April 2017

End of data collection June 2017

Interim report 1 October 31, 2015

Interim report 2 October 31, 2016

Registration in the EU PAS register March 2014

Final report of study results October 31, 2017

Proposed text

Milestones:

Start of data collection March 2014

End of recruitment~~April 2016~~ June 2019

Last regular follow-up~~April 2017~~ June 2020

End of data collection~~June 2017~~ September 2020

Interim report 1 October 31, 2015

Interim report 2 October 31, 2016

Actual Date (May 23, 2016)

Interim report 3 December 2018

Interim report 4 December 2019

Registration in the EU PAS register March 2014

Final report of study results ~~October 31, 2017~~ December 2020

Section 9.1: Study Design

Current text

The study will be conducted in 8 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, and Spain) and Australia.

Proposed text

The study will be conducted in ~~8~~9 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, ~~and~~ Spain and Sweden), ~~and~~ Australia and 2 Latin American countries (Colombia and Mexico).

Section 9.2.2: Selection of study population

Current text

Overall, 101,000 study participants are needed in order to provide approximately 150,000 woman-years (WY) (cf. Section 9.5), assuming a drop-out rate of approximately 0.7% per month for both continents. Approximately 90% of subjects will be recruited in Europe and the other 10% in Australia.

Proposed text

Overall, 101,000 study participants are needed in order to provide approximately 150,000 woman-years (WY) (cf. Section 9.5), assuming a drop-out rate of approximately 0.7% per month for both continents. Approximately 90% of subjects will be recruited in Europe and the other 10% in Australia. Subsequent to these original assumptions, the study was expanded to Latin American countries (Colombia and Mexico).

Section 9.10: Other aspects

Current text

…diastolic blood pressure of more than 120 mmHG for hypertensive crisis…

Proposed text

…diastolic blood pressure of more than 120 mmH~~G~~g for hypertensive crisis…

Current text

… glycogen phosporylase isoenzyme BB…

Proposed text

… glycogen phosphorylase isoenzyme BB…

Section 11: Management and reporting of adverse events/ adverse

Current text

. . . ZEG will report all confirmed serious adverse events related to the use of a MSD and Theramex S.r.l products within 2 business days to the Funder.

A physician on the ZEG study team will assess the likelihood of a causal relationship. . .

Although non-serious adverse events are not actively solicited in this study, all validated drug-related non-serious adverse events (see procedure in Section 9.2.5) will be collected for tabulation in interim and/or final reports, and submitted to the Funder within 10 calendar days using the same method as described for SAEs.

Proposed text

11.1 Adverse event / Adverse reactions reporting

. . . ZEG will report all confirmed serious adverse events related to the use of ~~a~~ NOMAC-E2 or other MSD ~~and Theramex S.r.l~~ product within 2 business days to the Funder.

ZEG will report to MSD all death cases which occurred while using an MSD product within 2 business days of their validation. The causality assessment will remain as it was determined by ZEG's medical advisers and the SMAC.

A physician on the ZEG study team will assess the likelihood of a causal relationship. . .

Although non-serious adverse events are not actively solicited in this study, all ~~validated~~ drug-related non-serious adverse events (see procedure in Section 9.2.5) will be collected for tabulation in interim and/or final reports, and submitted to the Funder within 10 ~~10 calendar~~ calendar

days using the same method as described for SAEs.

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

Current text

Not applicable.

Proposed text

11.2 Product Quality Complaint Reporting

11.2.1 Investigator Responsibility:

Any occurrence of a product quality complaint for a MSD product identified during the conduct of the study, must be reported by the study investigator or qualified designee using the Product Quality Complaint (PQC) Reporting Form following the directions in Table 2. The PQC Reporting Form must be fully completed in English. Once the PQC Reporting Form is submitted, the investigator or designee may be contacted for further information.

If both an AE and a PQC occur, the AE should be reported according to the AE reporting requirements in the protocol and the PQC should be reported per Table 2.

Table 2: PQC Reporting Timeframes and Process for Investigators

EVENT TYPE	INVESTIGATOR TIMEFRAME
	Investigator to Merck
PQC	24 hours from receipt

PQC reports must be submitted via e-mail by the investigator to the local designated point of contact (DPOC) using a PQC form.

Submitting PQC reports to Merck: All PQCs must be submitted to the local DPOC in English using a PQC form. The following e-mail addresses should be used by country:

COUNTRY	EMAIL
Australia	PPD
Austria	
Colombia	
France	
Germany	
Hungary	
Italy	
Mexico	
Poland	
Russia	
Spain	
Sweden	

11.2.2 Definitions

11.2.2.1 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

11.2.2.2 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device

11.3 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose

- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect
- Exposure to product during pregnancy/lactation

Serious Special Situations should follow the same reporting timelines as SAEs. Non-serious Special Situations should follow the same reporting timelines as NSARs.

The Protocol was again amended in June 2019 (Study Protocol Version 4.0) to address comments made by the PRAC in their assessment of Amendment 1 (Study Protocol Version 3.0) as well as an update in the principal investigator and the funder contact information as described below.

The June 20, 2019 amendment (Study Protocol Version 4.0) affects the following sections:

- PASS Information
- Section 3: Responsible parties
- Section 4: Abstract
- Section 6: Milestones
- Section 7: Rationale and background
- Section 8: Research question and objectives
- Section 9.2.2: Selection of study population
- Section 9.3.2: Secondary endpoints
- Section 9.7: Data analysis
- Section 9.9: Limitations of research methods

All changes are indicated with “current text” and “proposed text”. “Current text” refers to the study protocol dated March 20, 2019. “Proposed text” refers to this protocol amendment of June 20, 2019. Deletions are crossed out and additions/replacements are marked in the text as underlined.

2. Amendments and updates

PASS Information

Current text

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Section 3: Responsible parties

Current text

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Proposed text

Principal Investigator:
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Section 4: Abstract

Current text

The primary objective of the study is to characterize and compare the risks of short- and long-term use of NOMAC-E2 with levonorgestrel-containing combined oral contraceptives (COC_{LNG}), in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcomes of interest for the short and long-term follow-up are venous thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.

Proposed text

The primary objective of the study is to characterize and compare the risks of the ~~short- and long-term~~ use of NOMAC-E2 with levonorgestrel-containing combined oral contraceptives (COC_{LNG}), in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcomes of interest for ~~the short and long term~~ follow-up are venous thromboembolism, specifically deep venous thrombosis of the lower extremities and pulmonary embolism.

Current text

Milestone	Planned date
Start of data collection	March 2014
End of recruitment	June 2019
Last regular follow-up	June 2020
End of data collection	September 2020
Interim report 1	October 31, 2015
Interim report 2	October 31, 2016 Actual Date (May 23, 2016)
Interim report 3	December 2018
Interim report 4	December 2019
Registration in the EU PAS register	March 2014
Final report of study results	December 2020

Proposed text

Milestone	Planned date
Start of data collection	March 2014
End of recruitment	~~June 2019~~ September 2019
Last regular follow-up	~~June 2020~~ September 2020
End of data collection	~~September 2020~~ December 2020
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Interim report 2	October 31, 2016 Actual Date (May 23, 2016)
Interim report 3	December 2018

Interim report 4	~~December 2019~~ February 2020
Registration in the EU PAS register	March 2014
Final report of study results	~~December 2020~~ April 2021

Section 6: Milestones

Current text

Milestone	Planned date
Start of data collection	March 2014
End of recruitment	June 2019
Last regular follow-up	June 2020
End of data collection	September 2020
Interim report 1	October 31, 2015
Interim report 2	October 31, 2016 Actual Date (May 23, 2016)
Interim report 3	December 2018
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Final report of study results	December 2020

Proposed text

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Interim report 3	December 2018

Interim report 4	~~December 2019~~ February 2020
Registration in the EU PAS register	March 2014
Final report of study results	~~December 2020~~ April 2021

Section 7: Rationale and background

Current text

Based on general public concerns about the safety of COCs the study will not only focus on VTE but also on arterial thromboembolism, depressive disorders, cholelithiasis, inflammatory bowel disease, effects on short- and long-term fertility, and pregnancy outcomes.

Proposed text

Based on general public concerns about the safety of COCs the study will not only focus on VTE but also on arterial thromboembolism, depressive disorders, cholelithiasis, inflammatory bowel disease, effects on ~~short- and long-term~~ fertility, and pregnancy outcomes.

Current text

The objective of the study is to assess the cardiovascular and other health risks associated with short and long-term use of NOMAC-E2 compared with COC_{LNG} during standard clinical practice.

Proposed text

The objective of the study is to assess the cardiovascular and other health risks associated with ~~short and long-term~~ the use of NOMAC-E2 compared with COC_{LNG} during standard clinical practice.

Section 8: Research question and objectives

Current text

Not applicable.

Proposed text

The secondary outcome of depressive disorders is included as an important identified risk, cholelithiasis, and inflammatory bowel disease as important potential risks, and safety in women during pregnancy as missing information in the NOMAC-E2 EU Risk Management Plan. The MAH included these outcomes in the study to further characterize the risk profile for NOMAC-E2.

Current text

The main clinical outcomes of interest for the short and long-term follow-up are venous thromboembolism (VTE), specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1, I80.2, I80.3)
- Pulmonary Embolism (PE); this includes the ICD-10 codes I26.0 and I26.9

Proposed text

The main clinical outcome~~s~~ of interest for ~~the short and long-term~~ follow-up ~~are~~ is venous thromboembolism (VTE), specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1, I80.2~~, I80.3~~)
- Pulmonary Embolism (PE); this includes the ICD-10 codes I26.0 and I26.9

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The primary objective of the study is to characterize and compare the risks of short- and long-term use of NOMAC-E2 with COC_{LNG}, in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

Proposed text

The primary objective of the study is to characterize and compare the risks of the ~~short- and long-term~~ use of NOMAC-E2 with COC_{LNG}, in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

Current text

Arterial thromboembolism (ATE) incidence rate in short- and long-term users. ATE includes acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)

Proposed text

Arterial thromboembolism (ATE) incidence rate ~~in short- and long-term users~~. ATE includes acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)

Current text

Effect on short-term and long-term fertility

Proposed text

Effect on ~~short-term and long-term~~ fertility

Section 9.2.2: Selection of study population

Current text

Physicians will recruit NOMAC-E2 and COC_{LNG} users in a 1 to 1 ratio. It is expected that this ratio reflects approximately the ratio of starter and restarter prescriptions of NOMAC-E2 and COC_{LNG} under routine clinical conditions. For every NOMAC-E2 user recruited, the physician has to recruit the next new COC_{LNG} user (starter or restarter) who is willing to participate in the study.

Proposed text

Physicians ~~will~~ should recruit NOMAC-E2 and COC_{LNG} users in an approximate 1 to 1 ratio. It is expected that this ratio reflects approximately the ratio of starter and restarter prescriptions of NOMAC-E2 and COC_{LNG} under routine clinical conditions. For every NOMAC-E2 user recruited, the physician ~~has to~~ should recruit the next new COC_{LNG} user (starter or restarter) who is willing to participate in the study.

Section 9.3.2: Secondary endpoints

Current text

Not applicable.

Proposed text

The secondary outcome of depressive disorders is included as an important identified risk, cholelithiasis, and inflammatory bowel disease as important potential risks, and safety in women during pregnancy as missing information in the NOMAC-E2 EU Risk Management Plan. The MAH included these outcomes in the study to further characterize the risk profile for NOMAC-E2.

Current text

The selection of following secondary endpoints will be investigated in this study…

- Short-Term and Long-Term Fertility

Proposed text

The selection of following secondary endpoints will be investigated in this study…

- ~~Short-Term and Long-Term~~ Fertility

Section 9.7: Data analysis

Current text

Not applicable.

Proposed text

Different modeling approaches will be used for the final multivariable model. The primary analysis model will be an *a-priori* expert model that is content driven and includes well-established prognostic factors. Additional sensitivity analysis models will be constructed to capture the influence of selected confounding factors and possible bias due to missing data.

Current text

Not applicable.

Proposed text

To assess a possible effect of missing data on the primary outcome value, the *a-priori* expert model will be accompanied by multiple imputation of missing data regarding predefined prognostic factors.

Section 9.9: Limitations of research methods

Current text

The study timelines given by the European regulatory authorities are very challenging. [redacted]

This means that the last regular follow-up and the end of recruitment have to be scheduled for April 2017 (October 2017 minus 6 months) and April 2016 (October 2017 minus 18 months), respectively. Consequently the recruitment phase will be limited to 25 months (March 2014 – April 2016). [redacted] However, it has to be acknowledged that such a large, prospective, non-interventional field study that investigates products of limited market share was never done in the area of contraception. Experience from similar but smaller studies suggests that at least 36 months will be needed for the recruitment of 101,000 women. This estimate is already based on a substantial extension of ZEG's existing large network of recruiting physicians. Therefore the study team cannot guarantee the requested timelines. From the study team's point of view a recruitment phase of 3 years and a total study period of 4.5 years (4 years for recruitment and follow-up, 6 months for loss to follow-up activities, data analyses and results reporting) would be feasible.

Proposed text

The study timelines given by the European regulatory authorities are very challenging. [redacted]

This means that the last regular follow-up and the end of recruitment have to be scheduled for September 2020 ~~April 2017 (October 2017 minus 6 months)~~ and September 2019 ~~April 2016 (October 2017 minus 18 months),~~ respectively. ~~Consequently the recruitment phase will be limited to 25 months (March 2014 – April 2016).~~ [redacted] ~~However, it has to be acknowledged that such a large, prospective, non-interventional field study that investigates products of limited market share was never done in the area of contraception. Experience from similar but smaller studies suggests that at least 36~~

~~months will be needed for the recruitment of 101,000 women. This estimate is already based on a substantial extension of ZEG's existing large network of recruiting physicians. Therefore the study team cannot guarantee the requested timelines. From the study team's point of view a recruitment phase of 3 years and a total study period of 4.5 years (4 years for recruitment and follow-up, 6 months for loss to follow-up activities, data analyses and results reporting) would be feasible.~~

6 Milestones

Milestone	Planned date[8]
Start of data collection	March 2014
End of recruitment	September 2019
Last regular follow-up	September 2020
End of data collection[9]	December 2020
Interim report 1	October 31, 2015
Interim report 2	October 31, 2016 Actual Date (May 23, 2016)
Interim report 3	December 2018
Interim report 4	February 2020
Registration in the EU PAS register	March 2014
Final report of study results	April 2021

7 Rationale and background

NOMAC-E2 is a novel monophasic oral contraceptive containing a fixed dose of nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg) being taken for 24 days followed by 4 days of placebo. Nomegestrol acetate has a strong affinity for the progesterone receptor and has strong anti-gonadotropic and progesterone receptor-mediated anti-estrogenic activity, moderate anti-androgenic activity, and is devoid of estrogenic, androgenic, glucocorticoid or mineralocorticoid activity. The estrogen

[8] cf. Section 9.9 ("Limitations of the research methods"), last paragraph

[9] includes 3 months of loss to follow-up activities after the last regular follow-up

contained in NOMAC-E2 is 17β-estradiol, an estrogen identical to the endogenous human 17β-estradiol.

Clinical experience with NOMAC-E2 and established combined oral contraceptives (COCs) suggests that serious clinical outcomes are rare when using NOMAC-E2 and COCs (including COCs containing levonorgestrel), respectively. From a public health perspective the most relevant adverse clinical outcome that has been linked to the use of COCs is venous thromboembolism (VTE). Since the year 2000 the EURAS [1] study comprehensively investigated the risk of VTE and other serious cardiovascular outcomes which might be associated with OC use. Similar comprehensive data from large, controlled, prospective studies with defined follow-up procedures of rare serious adverse events and low loss to follow-up rates are not available for NOMAC-E2. Data from randomized clinical trials did not show any serious health concerns for NOMAC-E2. However, the statistical power to detect rare adverse events is limited in these studies. Based on general public concerns about the safety of COCs the study will not only focus on VTE but also on arterial thromboembolism, depressive disorders, cholelithiasis, inflammatory bowel disease, effects on fertility, and pregnancy outcomes. The funder has asked ZEG to conduct a large epidemiological study with a robust and efficient study design.

The EURAS study and similar studies (such as INAS-OC[10] and TASC[11]) have demonstrated that a large, prospective, controlled, long-term cohort study is suitable for (1) safety monitoring of contraceptives, (2) reliable identification of relevant clinical outcomes and (3) providing robust estimates of their incidence. The study described in this protocol has a similar design with a few modifications due to country and product-specific characteristics.

This observational study is being conducted as an imposed obligation for a post-authorization safety study in accordance with an Article 10a of the EU Regulation 726/2004. This study will include European, Latin American, and Australian women using specific combined oral contraceptives (COCs): NOMAC-E2 and levonorgestrel-containing oral contraceptives (COC_{LNG})[12]. The objective of the study is to assess the cardiovascular and other health risks associated with the use of NOMAC-E2 compared with COC_{LNG} during standard clinical practice.

[10] Clinicaltrials.gov identifier: NCT00335257

[11] Clinicaltrials.gov identifier: NCT00524771

[12] cf. Section 9.2.1

8 Research question and objectives

The primary objective of the study is to characterize and compare the risks of the use of NOMAC-E2 with COC_{LNG}, in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

The main clinical outcome of interest for follow-up is venous thromboembolism (VTE), specifically:

- Deep Venous Thrombosis (DVT) of the lower extremities (ICD-10 codes: I80.1 and I80.2)
- Pulmonary Embolism (PE); this includes the ICD-10 codes I26.0 and I26.9

Secondary objectives of the study are to measure/describe for NOMAC-E2 users and compare to users of COC_{LNG} during standard clinical practice;

- All VTE, including thromboses of renal, mesenteric, portal and retinal veins[13]
- Arterial thromboembolism (ATE) incidence rate. ATE includes acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)
- Depressive disorders incidence rate (based on the assessment of attending physicians who are specialized in psychiatry and the Three Item Mental Health Inventory)
- Cholelithiasis incidence rate
- Inflammatory bowel disease incidence rate
- Effect on fertility
- Drug utilization pattern[14] and baseline risk for primary and secondary clinical outcomes – in particular cardiovascular outcomes
- Pregnancy outcomes

[13] ICD-10 codes: I26.0, I26.9, I63.6, I67.6, I80.1, I80.2, I80.3, I81, I82.2, I82.3, I82.8, I82.9, H34.8, K55.0 and N28.0

[14] Drug utilization in this study includes information on prescription and use of COCs as well as the reasons for COC use (contraception only, contraceptive and non-contraceptive reasons - such as acne, PMS/PMDD, bleeding problems, endometriosis, etc.)

The secondary outcome of depressive disorders is included as an important identified risk, cholelithiasis, and inflammatory bowel disease as important potential risks, and safety in women during pregnancy as missing information in the NOMAC-E2 EU Risk Management Plan. The MAH included these outcomes in the study to further characterize the risk profile for NOMAC-E2.

Additional secondary objectives [redacted] are to measure/describe for NOMAC-E2 users and compare to users of COC_{LNG} during standard clinical practice:

- Weight change
- General hepatobiliary disorders
- Effect on acne

9 Research methods

9.1 Study design

This is a large, multinational, controlled, prospective, active surveillance study that follows two cohorts. The cohorts consist of new users (starters[15] and restarters[16]) of two different groups of hormonal contraceptives: NOMAC-E2 and COC_{LNG}. The study will use a non-interference[17] approach to provide standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

Study participants will be recruited via an international network of 2,000 – 3,000 COC-prescribing health care professionals (e.g. gynecologists and general practitioners). After study entry, study participants will be followed for a period of 12 to 24 months for rare serious safety outcomes. Regular, active contacts with the study participants by the ZEG study team (= active surveillance) will provide the necessary information on health-related events or changes in health status. Additional follow-up procedures (cf. Section 9.2.4) will be used to validate self-reported events.

[15] First ever user of a COC

[16] User who restarts hormonal contraceptive use with a COC (same COC as before or new COC) after an intake break of at least two months.

[17] I.e., 1) all new users of NOMAC-E2 or COC_{LNG} are eligible for enrollment if they give their informed consent; and 2) recruitment of study participants should not influence the physician's prescribing, diagnostic, or therapeutic decisions.

All study participants will be contacted at 6, 12 and 24[18] months after study entry. By means of these contacts, almost all relevant clinical outcomes will be captured. However, laypersons often misclassify adverse events (e.g., pneumonia as "pulmonary embolism" or migraine attacks as "stroke" even if modern imaging procedures do not provide any indication of the perceived event). This type of inaccuracy in patient reports will require careful validation of the reported events. This will be accomplished by contacting the relevant physicians and by reviewing relevant source documents. Under routine medical conditions, clinical outcomes are not always confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes have to be classified as "confirmed" or "not confirmed" by ZEG physician(s) according to a predefined algorithm (cf. Section 9.10.1). At the end of the study this classification will be verified by blinded independent adjudication (cf. Section 9.10.2).

The study will be conducted in 9 European countries (Austria, France, Germany, Hungary, Italy, Poland, Russia, Spain and Sweden), Australia and 2 Latin American countries (Colombia and Mexico).

9.2 Setting

The study will be conducted by the Berlin Center for Epidemiology and Health Research (ZEG).

The study will be divided into 2 phases: a baseline survey, which includes an initial consultation at baseline with a participating physician, and a follow-up phase, which includes two follow-up contacts within the first year, and then a follow-up at 24 months after study entry. The follow-up phase will end approximately one year after enrollment of the last study participant. Participants who are enrolled within the last year of the recruitment phase will have their last follow-up at the end of the follow-up phase (instead of 24 months after study entry). Visits and follow-up contacts are calculated in calendar months and years following the baseline visit.

The study will be overseen by an independent committee of experts, the Safety Monitoring and Advisory Council (SMAC), who will review the study data every 6 months and on request of the Principal Investigator.

[18] Or at the end of the study if the study ends prior to the 24 month follow-up of an individual patient.

9.2.1 Treatments

Cohort 1: NOMAC-E2, a COC containing 2.5mg of nomegestrol acetate and 1.5mg of 17β-estradiol

Cohort 2: Levonorgestrel-containing COCs: 1) monophasic preparations containing 20 – 30mcg of ethinylestradiol; 2) multiphasic preparations containing up to 40mcg of ethinylestradiol

9.2.2 Selection of Study Population

Approximately 50,500 NOMAC-E2 users and 50,500 users of COC_{LNG} will be recruited by participating physicians, including adolescents. The proportion of adolescents is expected to be in the range between 10% and 15%. Overall, 101,000 study participants are needed in order to provide approximately 150,000 woman-years (WY) (cf. Section 9.5), assuming a drop-out rate of approximately 0.7% per month for both continents. Approximately 90% of subjects will be recruited in Europe and the other 10% in Australia. Subsequent to these original assumptions, the study was expanded to Latin American countries (Colombia and Mexico).

Recruitment of study participants will be conducted via existing networks of COC-prescribing health care professionals (e.g. gynecologists and general practitioners) who have participated in similar cohort studies in the past. Physicians should recruit NOMAC-E2 and COC_{LNG} users in an approximate 1 to 1 ratio. It is expected that this ratio reflects approximately the ratio of starter and restarter prescriptions of NOMAC-E2 and COC_{LNG} under routine clinical conditions. For every NOMAC-E2 user recruited, the physician should recruit the next new COC_{LNG} user (starter or restarter) who is willing to participate in the study.

Subjects will be considered for enrollment in this study after the participating physician has determined that NOMAC-E2 or COC_{LNG} use is appropriate. There will be no specific medical inclusion/exclusion criteria and no age restrictions (to fulfill the pediatric investigation plan (PIP) requirement in the EU). However, women who 1) have been pregnant within 3 months before treatment initiation or 2) have a history of cancer/chemotherapy or an increased genetic risk for VTE at baseline will be excluded from the analysis of VTE. All women who are eligible are to be asked by their physician if they are willing to participate. As this is a non-interventional study, the possibility to participate in the study should not be discussed with the study participant before both

- physician and study participant - agree upon the prescription. The physician is to explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each woman prior to her entry into the study. Each woman is to have ample opportunity to ask questions and must be informed about her right to withdraw from the study at any time without disadvantage and without having to provide reasons for her decision. This information will be provided on an informed consent and data privacy form which must be signed by all study participants. For adolescents, local law might require a parent's or guardian's signature, which will then additionally be provided on the informed consent form. All documents are to be approved by the relevant local Ethics Committees and the relevant Data Privacy Office, if applicable.

Once enrolled, a study participant may discontinue (and restart) use of hormonal contraception or may switch to another hormonal contraceptive at any time. However, subjects will continue to be followed whether or not they remain on the prescribed contraceptive, provided that they do not withdraw their consent. For the primary analysis outcomes of interest/adverse events will be assigned to the treatment at the time the outcome/event occurred. During the follow-up phase, subjects will be asked whether they have discontinued COC use. Information on the date and reason for discontinuation during the follow-up phase will also be collected.

9.2.3 Baseline Survey

Each physician's office will be provided with simple questionnaires for collecting data at baseline. The baseline visit will take place at the participating physician's office. Only after NOMAC-E2 or a COC_{LNG} has been prescribed will the physician discuss the study with the subject. This ensures that participation in the study is not considered a requirement for treatment. All women who received a new COC prescription are to be asked to participate. After discussing the study details (including follow-up procedures and intervals, content and duration of follow-up contacts, use of data collected, etc.), each subject will be asked to provide written informed consent to participate in the study. If the subject needs time to consider participation, she will be free to leave the physician's office with her prescription and take an appropriate period to decide whether to participate. She can complete the baseline questionnaire and informed consent at home, and return the documents to the physician's office.

The informed consent will include permission for study data to be collected and analyzed and for contacts to be made by the ZEG study team at intervals during the follow-up phase for collection of study information. Each subject will also be asked to provide information regarding alternative contacts (a close relative or friend, or primary

care physician) if ZEG cannot reach the subject after several attempts. Permission for ZEG to contact a subject's primary care physician/attending physician(s) and to review applicable national health databases (where possible and permissible) for relevant subject information will also be sought. Follow-up frequency by ZEG will be explained, and the content of follow-up contacts will be described.

Confidentiality will be maintained throughout the study and no personal information will be shared with alternative contacts. The funder will not have access to names, addresses, or alternative contact information for the subjects and all individual subject data will remain anonymous. Personal and medical information will be recorded on separate documents. ZEG will ensure that access to personal information is restricted in accordance with data privacy rules.

The following information will be recorded at the baseline visit after the study participant has provided written informed consent: prescribed COC, user status (starter/restarter), demographic and medical history, including medication history, acne, history and duration of use of hormonal contraceptives, as well as the addresses, e-mail addresses and phone numbers of the study participant, relatives or friends, and the primary care physician. Names, addresses and phone numbers are to be documented on a separate sheet, in compliance with data protection regulations.

9.2.4 Follow-Up Phase

ZEG will perform all follow-up activities during this phase of the study. All subjects who provide written informed consent will be contacted for follow-up regardless of the duration of treatment or whether they discontinue treatment. Subjects who withdraw their consent for follow-up will not be contacted. The funder will not have access to names, addresses, or alternative contact information for the subjects.

Follow-up questionnaires will be mailed to the study participants at 6, 12 and 24[19] months after study entry to collect information regarding major safety outcomes.

The specific safety data to be collected during follow-up will focus on VTE (in particular deep venous thrombosis of the lower extremities and pulmonary embolism), arterial thromboembolism (in particular AMI and stroke), the outcomes reflecting the other

[19] Or at the end of the study if the study ends prior to the 24 month follow-up of an individual patient.

secondary objectives as well as all other serious adverse events,[20] including cancer and specifically gynecological cancers. Subjects who report any of these outcomes will be asked to provide their primary care physician's/treating physician's name and address information. ZEG will contact the relevant physician (the attending physician is in most cases not the recruiting physician) and inform him/her about the study objectives and will share the subject's informed consent to access her medical information. Follow up by ZEG will include obtaining hospital records and/or discharge summaries, medical history, treatment dates, and concomitant medication use. A qualified medical expert (i.e., pharmacovigilance physician) on the ZEG study team will assess the likelihood of a causal relationship to study treatment for each serious or unexpected adverse drug reaction in accordance with a predefined algorithm (cf. Section 9.10.3).

At each follow-up contact, subjects will be asked about the exact details and timing of their oral contraceptive use, and whether they continue to use the prescribed study medication.

9.2.5 Validation of Self-Reported Events

A self-administered questionnaire used by study participants at short intervals is a sensitive tool which captures almost all serious clinical outcomes [1]. From a methodological point of view, it captures a much higher proportion of these outcomes than methods relying only on the prescribing health care professional who often is not involved in the diagnosis and treatment of these outcomes. However, it must be considered that there is a significant difference between the rates of reported and validated events, because laypersons often misclassify adverse events. Therefore, validation of the self-reported events is of utmost importance.

Validation of self-reported events will start at the level of the local field organizations with a review of all subject-reported "events." This will be followed by a further review at the international coordinating center (ZEG).

If an adverse event is reported by a study participant, the subjectively perceived symptoms, the signs of disease and if possible, the diagnosis as understood by the study participant are to be recorded on the follow-up questionnaire. The name and

[20] Serious adverse event means any AE that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability/incapacity, or requires medical/ surgical intervention to prevent one of said outcomes.

address of the relevant physician (attending physician, physician responsible for the follow-up treatment after discharge from hospital, or primary care physician) are also documented.

Follow-up questionnaires containing information on such an event are to be immediately passed on to the medical reviewer group at ZEG. If information is unclear or missing the woman will be contacted by phone, e-mail or other means. For many serious events it will be necessary to contact the diagnosing and/or treating physician for clarification and validation of the information received from the patient.

Under routine medical conditions, diagnosis of an SAE term is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs are classified by the investigators as “confirmed” or “not confirmed” according to a predefined algorithm (cf. Section 9.10.1).

In order to minimize classification bias - particularly if selectively affecting an individual exposure cohort - classification of self-reported serious cardiovascular outcomes, into confirmed and not confirmed cases will be adjudicated by three independent medical experts specializing in radiology/nuclear medicine, cardiology, and internal medicine/phlebology. They will review all available information on the reported outcomes. For this process, the adjudicator will be blinded to the brand names and composition of the treatments used by the reporting woman. The adjudicators will perform the reviews independently of each other and without knowing the judgement of the other adjudicators or the investigators. Details of the procedure are given in Section 9.10.2.

In addition, the ZEG physician who is responsible for the assessment of individual case reports prior to interim analyses will be blinded to the study drug (i.e. he/she will do his/her assessment based on redacted copies of the available documents). Also, individual case reports that are presented to the Safety Monitoring and Advisory Council will be blinded to the study drug.

9.2.6 Loss to follow-up

A low “loss to follow-up rate” will be essential for the validity of the study. In order to minimize loss to follow-up a multi-faceted, four-level follow-up process will be established. Level 1 activities include mailing of the follow-up questionnaire and – in case of no response – up to two reminder letters. If level 1 activities do not lead to a response, multiple attempts are to be made to contact the woman, friends, relatives

and the gynecologist/primary care physician per phone. In parallel to these level 2 activities searches in national and international telephone and address directories as well as electronic social networks are started (level 3 activities). If this is not successful, an official address search via the respective governmental administration and commercial databases will be conducted. This level 4 activity can provide information on new addresses (or emigration or death). The aim is to keep the total loss to follow-up at the end of the study at less than 10% of the Australian study population, and less than 5% of the European study population (due to compulsory registration in European countries). The EURAS study [1] has demonstrated that the chosen study design is suitable to reach this goal.

9.3 Variables

9.3.1 Primary Endpoint

Venous Thromboembolism (VTE)

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are the most relevant adverse drug reactions associated with COC use. Based on a request of the European regulatory authorities specific VTEs - DVT of the lower extremities and pulmonary embolism - was chosen as the primary outcome of interest (cf. Section 8). Inferential statistics will be based on the VTE hazard ratio for NOMAC-E2 vs. COC_{LNG} (cf. Section 9.2.1).

Information about the use of the new progestogen nomegestrol acetate in NOMAC-E2 is only available from clinical trials including a limited number of study participants. These studies demonstrated that NOMAC-E2 - a 17β-estradiol containing preparation - has less influence on hemostasis compared to ethinylestradiol (EE) containing OCs. Therefore, it is conceivable that NOMAC-E2 might be associated with a lower risk of VTE (and ATE) compared to an EE-containing regimen. However, robust estimates of the risk of VTE associated with nomegestrol acetate are not available and a reliable prediction of the combined effect of 2.5mg nomegestrol acetate and 1.5mg 17ß-estradiol on VTE risk is difficult. Therefore, a sufficiently powered study to assess the risk of VTE was deemed necessary. The study proposed in this protocol should provide data that are sufficiently robust to eliminate a 1.5-fold risk in VTE for NOMAC-E2 compared to COC_{LNG}. [redacted].

9.3.2 Secondary Endpoints

For several other clinical outcomes an association to COC use has been discussed. For some outcomes a causal relationship has to be assumed (e.g., COC use and myocardial infarction in women with a combination of risk factors - in particular smoking, advanced age and high blood pressure) for other outcomes the existing evidence is weak (e.g. prolonged time to conception after stop of COC use). The selection of following secondary endpoints will be investigated in this study (cf. Section 8):

- All VTE
- Arterial Thromboembolism (ATE)
- 'Idiopathic' VTE (VTE cases with acute risk factors – such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery, chemotherapy – excluded)
- Depressive Disorders
- Cholelithiasis
- Inflammatory Bowel Disease (IBD)
- Fertility
- Drug Utilization Pattern and Baseline Risk for primary and secondary clinical outcomes – in particular cardiovascular outcomes
- Pregnancy outcomes
- Weight change
- General hepatobiliary disorders
- Acne

Most of these secondary endpoints were successfully investigated in the EURAS study [1;2;3] and/or similar studies.

The secondary outcome of depressive disorders is included as an important identified risk, cholelithiasis, and inflammatory bowel disease as important potential risks, and safety in women during pregnancy as missing information in the NOMAC-E2 EU Risk Management Plan. The MAH included these outcomes in the study to further characterize the risk profile for NOMAC-E2.

[redacted]

Weight change:

The validity of weight measurement in an observational study is limited. The TASC[21] and the EURAS study have demonstrated that the correlation between the weight measurement at baseline (primarily based on objective measurements at the site of the recruiting physician) and the first follow-up after six months (self-reported weight) is high and similar to the correlation between the six and twelve month follow-up. An additional 'objective' measurement at the six month follow-up would put the non-interventional, real-life character of the study in question. An additional 'interventional' measurement would also require a separate informed consent of the study participant (cf. Section 10.2). The information procedure as well as the knowledge about an 'objective' measurement would probably influence the weight control and eating behavior of study participants. Therefore, it was decided to base the comparison of weight changes between the NOMAC-E2 and COC_{LNG} cohorts on the difference between the patient-reported weight documented in the 6 and 12- month follow-up, respectively and the weight at study entry.

General hepatobiliary disorders

All serious adverse events – including general hepatobiliary disorders – will be captured and validated via the attending physician (which is in most cases not the recruiting physician). As a distinct group of clinical entities hepatobiliary disorders (corresponding to the ICD-10 (cf. section 9.6) categories K70 – K87) will receive particular attention. Apart from the general questions on serious adverse events, hepatobiliary disorders will be addressed separately in the questionnaire.

Acne

The impact of NOMAC-E2 and COC_{LNG} on acne is investigated in this study. The subjective perception of acne and the potential impact of acne on the emotional status of the users are of particular interest. The evaluation of acne will be based on the change of subjective assessment of the study participant at study entry and the 6 and 12-month follow-up.

[21] http://clinicaltrials.gov/ct2/show/NCT00524771

9.4 Data sources

This is a field study. Exposure to hormonal contraceptives, concomitant medication, primary and secondary outcomes, potential confounding factors and potential effect modifiers will be documented by the study participants, the recruiting and attending physicians in the questionnaires and additional documentation sheets, if needed. Baseline data (cf. Section 9.2.3) will be recorded on a self-administered questionnaire containing questions relating to participants' state of health and potential risk factors. Participants will provide their medical history, including medication history and history of OC use. The information given by the study participants will be checked by their physicians.

In addition to the baseline variables described in Section 9.2.3 study participants will provide their addresses and phone numbers, as well as those of relatives or friends – who could serve as reserve contacts – and their primary care physician/gynecologist.

In line with data privacy regulations, these data will be documented on a separate sheet. During study conduct and study evaluation these sheets and the electronic representations of their content will be stored separately from the baseline questionnaires and their respective electronic representation. This also applies to the archiving of documents and databases at the end of the study.

Follow-up assessments for each woman in this study are scheduled 6, 12 and 24 months after study entry. Questionnaires will be mailed to the participating women, who often know more about their own personal health-related events than the physician who prescribes their OC. This is especially true for information on SAEs that were treated by other physicians. In some cases, events will be reported by the participant or by relatives, friends or attending physicians between the regular follow-ups. All reports – independent of the source of information – will validated according to the process given below (cf. Section 9.10.1)

The follow-up questionnaires address the occurrence of adverse events – in particular serious adverse events. Reasons for OC discontinuation or for a switch to another hormonal contraceptive (HC) will be requested if applicable. The variables that are recorded at each follow-up are described in Section 9.2.4.

The questionnaires will be collected in the participating countries by the local collaborators of ZEG and will be reviewed for completeness and plausibility/consistency of the responses. Missing and inconsistent information will be clarified directly with the women via telephone. The completed questionnaires will be forwarded to ZEG. At ZEG all incoming data will be subjected to comprehensive quality control including electronic and manual plausibility checks. Unclear or inconsistent information will be described in detailed queries which will be forwarded to the local collaborators for clarification with the women. ZEG will monitor and endorse the timely processing of the queries.

The overall results and particularly the results on outcomes of interest will be reviewed by the Safety Monitoring and Advisory Board (cf. Section 10.3). The results of the validation process of reported outcomes of interest will be quality controlled by blinded adjudication (cf. Section 9.10.2).

9.5 Study size

The sample size considerations are based on the expected VTE incidence for COC_{LNG}. [redacted]. It is expected that NOMAC-E2 is associated with a VTE risk that is not higher than the risk associated with COC_{LNG}.

The study should be powered to test non-inferiority of NOMAC-E2 treatment regarding VTE risk in comparison to COC_{LNG} use. Sample size calculations for a non-inferiority test of two exponential survival curves [4;5] showed that an expected number of 150 VTE cases should be sufficient to reach this goal. These calculations are based on the following assumptions: 1) one-sided α of 0.05; 2) power (1-β) of 0.80 and 3) non-inferiority limit on hazard ratio of 1.5.

At an incidence rate of 10.0/10,000 WY a total of 150 VTE cases could be expected within 150,000 WY. The drop-out rate in similar studies has been approximately 0.7% per month. Assuming 1) a recruitment phase of 36 months, 2) a follow-up phase of 12 - 24 months, and 3) a loss to follow-up rate of about 5%, follow-up of 101,000 study participants (50,500 NOMAC-E2 users and 50,500 COC_{LNG} users) for up to 24 months would result in approximately 150,000 WY (see table 1).

Based on these scenarios, the study is sufficiently powered to exclude a 1.5-fold VTE risk for NOMAC-E2 users compared to COC_{LNG} users in the event that the true VTE risk among NOMAC-E2 users is not higher than among COC_{LNG} users.

However, precise power calculations based on actual incidences and drop-out rates should be done on the basis of follow-up data 1) before the end of the recruitment phase and 2) after availability of 30,000 WY of observation. If these calculations do not confirm the assumed incidence and drop-out rates the Safety Monitoring and Advisory Council will discuss the need to decrease or increase the number of study participants and/or follow-up times.

[22] 'idiopathic' pulmonary embolism and deep venous thrombosis of the lower extremities

The sample size needed for the investigation of the VTE risk is also sufficient for the evaluation of secondary outcomes – except ATE. Acute myocardial infarction and stroke are very rare in a female population of reproductive age. This study is powered to exclude a 2.5-fold risk of ATE. This is sufficient to screen for safety signals and substantial effects.

Table 1: Expected observation time

Assumptions: approx. 101,000 study participants recruited over 36 months (~ 2,806 per month); follow-up of study participants for 12 - 24 months; drop-out rate of 0.7% per month (e.g., 20 out of 2,806 recruited women will drop-out during the first month after recruitment; therefore the average number of women during the first month is 2,796 women [(2,806+2,786) x 0.5]); loss to follow-up and loss to 'within study switchers': 11%

	Sub-cohorts recruited during month						
Time after study start [month]	**1**	**2**	**…**	**24**	**25**	**…**	**36**
	Average number of women in follow-up						
1	2,796						
2	2,776	2,796					
…	…	….	...				
24	2,379	2,395	…	2,796			
25		2,379	…	2,776	2,796		
26			…	2,757	2,776	…	
…			…	…	…	…	
36			…	2,588	2,606	…	2,796
…			…	…	…	…	…
47			…	2,395	2,412	…	2,606
48				2,379	2,395	…	2,588
WY	*5,164*	*5,164*	*…*	*5,164*	*4,965*	*…*	*2,691*
Total WY (crude)	***170,023***						
Total WY *(corrected for loss to follow-up and 'within study switchers' who do not contribute to exposure of starter and restarter)*	***~151,000***						

9.6 Data management

9.6.1 Databases

Two different databases are used for data collection; the administrative database (ADB) and the study database (SDB).

The ADB is provided by ZEG to the national field organizations. Physician details, as well as data from the study participant, can be entered and maintained in this database.

The SDB is validated according to GXP rules. It contains all questionnaire data including baseline data and all subsequent follow-ups. ZEG regularly performs cross-check and verification checks on the data and any inconsistencies or unanticipated answers are mailed to the field organizations for further clarification.

From the questionnaire data, event data is derived from the SDB. All disease diagnoses are coded using the ICD-10 (International Classification of Diseases). ZEG also uses additional codes for the coding of events that are of specific interest (e.g. VTE during pregnancy or delivery, outcome of an unintended pregnancy: induced or spontaneous abortion, delivery of a healthy child, birth defects).

Concomitant medication is coded using WHO ATC-Codes. Surgical procedures are coded using the modified operation and procedure coding list (OPS) provided by DIMDI (German Institute for Medical Documentation and Information). All other relevant information will be coded by a ZEG specific, highly standardized coding system (ZEG Coding Dictionary). All outcomes of interest are additionally described in a case narrative, the “case summary”.

9.6.2 Dataflow

When questionnaires are received from study participants, all pages are counted and the questionnaire is date-stamped. Questionnaires are to be checked for correct subject identification number, missing pages, legibility, and incomplete information on the questionnaires. Missing pages, illegible or missing information are requested from the study participants prior to data entry of the respective questionnaire.

Data is entered by double data entry via formatted entry screens designed to reflect the appearance of the questionnaire. Discrepancies between first and second data entry are identified by comparison of the two entry files within the statistical software

SAS. The decision on the true entry is done by the responsible data manager at ZEG. This may require direct contact with the study participant who filled in the questionnaire. Corrections will be made to the questionnaire only after contact with the study participant or her treating physician. All corrections are dated and initialed by the data manager who received the relevant new information (e.g., via direct contact or by a copy of medical reports/documents). The incorrect entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to it. The reason for any correction of medical data on the questionnaire must be documented.

Quality control of entered data will be supported by SAS plausibility programs which include range, coding, missing and date checks as well as cross-reference (consistency) checks between variables.

9.6.3 Database Freeze/Lock

For each interim analysis and for the final analysis the database is frozen at a predefined time point. The database will be 'cleaned' within 4 weeks of the database freeze. After the final freeze (approximately 4 months after the last follow-up questionnaires have been sent to the study participants), no additional incoming data is entered in the database – this database will represent the final data source for all analyses. Safety copies are made of each database, so that all calculations can be repeated if necessary.

9.7 Data analysis

Based on available data and pharmacological considerations the *a priori* assumption is that use of NOMAC-E2 is not associated with an increased risk of VTE compared to COC_{LNG}. That is, a statistical comparison of NOMAC-E2 and COC_{LNG} is not expected to show a difference. Therefore, the Principal Investigator and the Safety Monitoring and Advisory Council (cf. section 10.3) have chosen a non-inferiority design to investigate the VTE risk of NOMAC-E2. The primary analysis will be based on the comparison of the upper confidence limit for the point estimate of the VTE[23] hazard ratio with the predefined non-inferiority limit (see below).

[23] DVT of the lower extremities and pulmonary embolism, cf. Section 8

The final analyses will include both an “as treated” (AT) and an intention-to-treat (ITT) analysis using Cox regression models. The safety conclusions of the study, however, will be based on the AT analyses (outcomes of interest will be assigned to the treatment she used at the time of the event) because the ITT approach (outcomes of interest are assigned to the treatment which was prescribed at study entry) potentially dilutes differences between treatments.

Incidence rates, incidence rate ratios (HRs), excess risks, as well as crude and adjusted hazard ratios will be calculated. The appropriate confounding variables will be built into the model. Based on the expectation of a small absolute number of serious outcomes of interest the number of confounding variables will be limited to well-established risk factors for these outcomes (e.g., age, BMI, duration of current use, and VTE history). Different modeling approaches will be used for the final multivariable model. The primary analysis model will be an *a-priori* expert model that is content driven and includes well-established prognostic factors. Additional sensitivity analysis models will be constructed to capture the influence of selected confounding factors and possible bias due to missing data. The final decision on the confounding variables will be made by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data. In addition, alternative analysis will be performed with other potential baseline risks to check the appropriateness of this decision. Similar analyses will be performed for all VTE (cf. Section 8) and arterial thromboembolism (e.g., acute myocardial infarction and stroke), the other secondary variables and other serious adverse events.

The null hypothesis to be tested is: $\mathbf{HR}_{VTE} \geq \mathbf{1.5}$ (i.e., the VTE hazard ratio for NOMAC-E2 vs. COC_{LNG} is higher than or equal to 1.5). The alternative hypothesis is: $\mathbf{HR}_{VTE} < \mathbf{1.5}$.

In the case of VTE it is conceivable that the proportional hazard assumption that effect parameters multiply hazard does not hold. Therefore, time-dependent factors will be included in the Cox model. The appropriateness of the model will be checked by comparing results of this analysis with results of an alternative analysis which stratifies by time of exposure. This stratification addresses also the potential problem of effect modification by current duration of use.

Real-life field studies frequently face the situation of missing data. The multiple reasons include superficial reading of the questions, misunderstanding of the questionnaire or simply unwillingness to give certain information. The questionnaires of this study have a clear layout and most questions have been tested in several former studies in large populations. The amount of missing information will be minimized by contacting participating women several times. If the missing information

can also be collected by the enrolling physician (e.g. any information on prescription, details regarding pregnancies, etc.), he/she will be contacted. If these strategies are unsuccessful, missing variables will be either accepted or, for certain variables, e.g. BMI, the last value will be carried forward. In general, missing data will comprise less than 5% of all data collected. To assess a possible effect of missing data on the primary outcome value, the *a-priori* expert model will be accompanied by multiple imputation of missing data regarding predefined prognostic factors.

A detailed statistical analysis plan addressing descriptive and inferential statistics will be developed by the study team during the first year after study start. This plan will include methodological details (e.g., censorship at time of cancer diagnosis, surgery or occurrence of other acute VTE risk factors for the analysis of VTE), a specification of sub-analyses (such as stratification by dose of ethinylestradiol (e.g., HR_{VTE} for NOMAC-E2 vs. COC_{LNG} with 20mcg of ethinylestradiol) and current duration of use (e.g., HR_{VTE} during the first year of use)) as well as a comprehensive set of mock tables for the presentation of the study results. The final analysis plan will be approved by the Safety Monitoring and Advisory Council before the first interim analysis of follow-up data. Changes of this document are to be approved by the Safety Monitoring and Advisory Council.

9.8 Quality control

The organization that is responsible for the conduct of the study (ZEG) has implemented different quality assurance procedures for day-to-day work. Internal audits confirm that ZEG fully complies with GPP (‘Guidelines for Good Pharmacoepidemiology Practices’ issued by the International Society for Pharmacoepidemiology in 2007), GEP (Good Epidemiological Practice issued by the European Epidemiology Federation in 2007), GVP (Good pharmacovigilance practices issued by the EMA in 2012/2013), the ENCePP Code of Conduct, the Nuremberg Code and the Declaration of Helsinki. Additionally, ZEG has been audited three times by large pharmaceutical companies, without major issues being identified. For this study, as for all other studies conducted by ZEG, site audits in the participating local field organizations will be conducted by ZEG on a regular basis. This included organizational aspects as well as source data verification.

ZEG’s internal standard operating procedures (SOPs) manual describes standardized working procedures to ensure high quality and compliance with all applicable guidelines. The SOPs are reviewed on an annual basis and updated where necessary to ensure that all processes are in line with legal compliance and integrity of data. ZEG also uses standardized

working procedures for the Safety Monitoring and Advisory Council (SMAC), the Blinded Adjudication Board and study-specific working procedures for the local organizations.

All processes that are relevant for legal compliance of the study or the integrity of the data are subject to quality control measures. This includes 1) development of study protocol, questionnaires, databases and data entry screens, 2) data entry, 3) plausibility checks, 4) validation of clinical outcomes, 5) adverse outcome reporting, 6) data analysis, 7) report writing, 8) publication of results, 9) archiving of study materials (i.e. all baseline/follow-up questionnaires, other study documents and electronic files). All quality control measures are based on the four-eye principle (i.e., it is not sufficient that someone controls his/her own work). During study conduct the consistency between ZEG's electronic database and the original questionnaire will be audited several times by an external auditor.

The external auditor is also responsible for a systematic review of quality standards implemented at ZEG and the local organizations, as well as proposing suitable measures to ZEG management to improve quality standards.

ZEG's study work will be overseen for the whole study period by the Safety Monitoring and Advisory Council of internationally acknowledged experts in the field (cf. Section 10.3). This committee will take final decisions in all scientific matters.

9.9 Limitations of the research methods

In non-experimental studies like this prospective cohort study, the possibility of bias and residual confounding can never be entirely eliminated, and the ability to infer causation is correspondingly limited [6]. Valid information on potential sources of confounding and sophisticated statistical and epidemiologic methodology help to reduce the impact of bias and residual confounding [7]. However, the difficulty remains unresolved when all that exists is a weak association [8;9]. Relative risk estimates that are close to unity may not allow differentiation between causation, bias and confounding [10;11]. In general, it is difficult to interpret a relative risk of two or less in observational research [12;13].

Within these limitations of non-experimental studies the chosen study design is capable of minimizing bias and residual confounding. In our judgment, selection bias will not be a major issue in this study because the adverse events will be captured for in- and out-patients, and the demographic characteristics of the participants will be representative for adult OC users [1]. Also, misclassification bias will probably have no substantial impact on the results as precise information on the exposure and the

outcomes of interest will be available. In addition, reliable information on duration of current COC use will be available. Accordingly, the study will capture the well-known increased VTE risk during the first months of combined OC use [14;15;16]. Furthermore, the comprehensive follow-up procedures will ensure a low loss to follow-up rate. In theory, a disproportionately high percentage of SAEs (including VTE and ATE) could occur in those patients who are lost to follow-up, because SAEs could be the reason for the break in contact with the health care professional who prescribed their COC. An advantage of the study design, however, is that the investigator team will have direct contact with the participants; contact will not be lost if the women change health care professionals, for example (e.g., due to change of residence or dissatisfaction with treatment).

In contrast, it will be impossible to exclude diagnostic bias. Clinical symptoms of VTE cover the spectrum from a complete absence or unspecific, slight symptoms to dramatic, acute, life-threatening symptoms [17;18;19]. A high awareness of potential cardiovascular risks of combined oral contraceptive use may lead to more diagnostic procedures and, therefore, to more detected VTE. It is conceivable that this potential bias lead to an overestimate of the relative risk of a new product (such as NOMAC-E2) cohorts compared to the LNG-cohort. Therefore, diagnostic bias should not result in an underestimate of the VTE risk carried by NOMAC-E2.

Unlike in many other observational studies on hormonal contraceptives, a strength of the study will be the availability of information on many important prognostic factors for the outcomes of interest. Nevertheless, we acknowledge that due to the non-interventional character of the study, information on specific gene mutations will only be available for VTE cases but not for the vast majority of study participants who will not experience a VTE. This limitation will be mitigated through information on family history of VTE which has a higher predictive value for VTE compared to gene mutations [20].

This study combines several methodological strengths that are substantial for the validity of the results: i) prospective, comparative cohort design; ii) availability of important confounder information (e.g., BMI and family history of VTE); iii) validation of outcomes of interest and the exposure of the relevant cases; iv) comprehensive follow-up procedure and very low loss to follow-up to minimize underreporting; v) independent, blinded adjudication of VTE cases; vi) relevant statistical analyses (e.g., stratified analyses by user status and exposure period; comparison of isochronous, new user cohorts; sensitivity analyses on the impact of the adjudication process, outcome definition, and prognostic factor/covariate selection); vii) study population representative for oral contraceptive users under routine clinical conditions; viii) generalisability of results as COC use in this study reflects routine clinical use and

study participation is not limited by medical inclusion and exclusion criteria; ix) supervision by an independent Safety Monitoring and Advisory Council, and scientific independence from the study funder.

The study timelines given by the European regulatory authorities are very challenging. This means that the last regular follow-up and the end of recruitment have to be scheduled for September 2020 and September 2019, respectively.

9.10 Other aspects

9.10.1 Validation of self-reported events

Under routine medical conditions, diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs will be classified by the investigator team as “confirmed” or “not confirmed” according to the following predefined algorithm:

- Definite Event:

Confirmed by diagnostic measures with high specificity (e.g., phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRT for cerebrovascular accidents, ECG with typical ST segment elevation for acute myocardial infarction, histology for gynecological cancer, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mmHg for hypertensive crisis)

- Probable Event:

Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (such as D-dimer for VTE or typical ECG/blood gas tests for PE). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event will be classified as a probable event even if specific treatment was not given.

- Event not confirmed:
  - Diagnosis reported by the patient is excluded by diagnostic procedures
  - A different medical condition is diagnosed by the attending physician
  - The woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

The exposure data reported by the patients will be validated via the prescribing physicians. Definite and probable events will be classified as ‘confirmed events’.

For VTE, the definition of “definite”, “probable” and “not confirmed” is further specified:

- **Definite VTE:** Confirmed by imaging procedure
  - DVT: phlebography, duplex sonography, magnetic resonance imaging
  - PE: pulmonary angiography, ventilation-perfusion scan, spiral computed tomography, magnetic resonance imaging, transesophageal echocardiography

- **Probable VTE:**

Absence of confirmation by an imaging test, but a clinical diagnosis was confirmed by a health professional or is supported by a non-imaging test (such as ultrasound doppler, plethysmography, D-dimer for VTE or typical ECG/blood gas tests for PE). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirmed that the diagnosis is correct, the event was classified as a VTE, even if a specific treatment was not given.

- **VTE not confirmed:**
  - VTE excluded by a physician
  - A different medical condition was diagnosed by the attending physician
  - Woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

For the final analysis this classification will be verified by means of an independent blinded adjudication process (cf. Appendix 3).

For ATE, the definition of “definite”, “probable” and “not confirmed” Is further specified as follows:

- **Definite ATE**: Confirmed by a diagnostic method with high specificity (incl. intraoperative or post-mortem)
  - AMI: typical change of cardiac enzymes with high specificity (CK-MB, cardiac troponin, glycogen phosphorylase isoenzyme BB), typical ECG changes (e.g., ST-segment elevation), coronary angiography
  - Stroke: typical clinical signs persisting for days, confirmation by imaging with high specificity (e.g., CT, MRI, cerebral angiography, PET)

- TIA: typical clinical signs (followed by resolution within 24 hours) and imaging with high specificity and sensitivity (e.g., MRI) does not indicate tissue necrosis
- Other organs and peripheral arteries (e.g. kidney, gut, adrenals, femoral artery): confirmed by imaging with high specificity (e.g., arteriography, CT, MRI)

- **Probable ATE**: No confirmation by a diagnostic method with high specificity, but other evidence pointing in the direction and the clinical diagnosis is confirmed by attending physician
  - AMI: typical clinical symptoms, change of cardiac enzymes with low specificity (e.g., CK, AST, LDH) or indirect ECG signs (e.g., ST-segment depression in case of posterior myocardial infarction), and clinical diagnosis confirmed by attending physician
  - Stroke: clinical signs persisting for days, confirmatory imaging not done or inconclusive, but clinical diagnosis confirmed by attending physician
  - TIA: typical clinical signs, followed by resolution within 24 hours, but no imaging with high specificity; and the clinical diagnosis is confirmed by attending physician
  - Other organs and peripheral arteries (e.g. kidney, gut, adrenals, femoral artery): confirmatory imaging not done or inconclusive, but clinical diagnosis confirmed by attending physician

- **ATE not confirmed:**
  - ATE excluded by a physician
  - A different medical condition was diagnosed by the attending physician
  - Woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis

9.10.2 Blinded adjudication

The following adjudication procedure will be established:

1) Independent adjudication by the individual specialists
2) Documentation of the individual assessments
3) Comparison of the individual assessments
4) Discussion of “split decisions” among the adjudicators without enforcement of a unanimous decision

5) Independent re-adjudication of the discussed cases by the individual adjudicators
6) Documentation of the individual post-discussion assessments

Based on this procedure six different classification strategies will be possible

I. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed before the discussion of "split decisions" took place (i.e., the decision is based on step 2 of the six-step procedure described above)
II. Classification of the reported event as confirmed if all adjudicators classify the event as confirmed after discussion of "split decision" takes place (i.e., the decision is based on step 6 of the six-step procedure described above)
III. Classification of the reported event according to the assessment of the majority of adjudicators before the discussion of "split decision" takes place (i.e., "majority vote" based on step 2 of the six-step procedure described above)
IV. Classification of the reported event according to the assessment of the majority of adjudicators after discussion of "split decision" takes place (i.e., majority classification based on step 6 of the six step procedure described above)
V. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place (i.e., "worst case decision" based on step 2 of the six-step procedure described above)
VI. Classification of the reported event as confirmed if at least one adjudicator had classified the event as confirmed after the discussion of split decisions took place (i.e., "worst case decision" based on step 6 of the six-step procedure described above)

The final analysis will be based on strategy V (worst case decision without discussion of split decisions) because it represents the most conservative approach. Alternative analyses will be possible on request of the Safety Monitoring and Advisory Council or regulatory authorities.

9.10.3 Drug relationship

Categories (Code)	Definition
no (1)	The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/worsening of the adverse event exists.
unlikely (2)	The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known and/or regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the study drug or the substance class, but another cause is much more probable and/or another cause is confirmed and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.
possible (3)	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the study drug or the substance class, but another cause just as likely to be involved is also known or although the pharmacological properties of the study drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation
probable (4)	The pharmacological properties of the study drug or of the substance class and/or the course of the adverse event after dechallenge and, if applicable, after rechallenge and/or specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.
definite (5)	The pharmacological properties of the study drug or of the substance class and the course of the adverse event after dechallenge and, if applicable, after rechallenge and specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the adverse event and no indication of other causes exists.

10 Protection of human subjects

The study will be conducted in a manner that is consistent with all relevant European and national guidelines and regulations for conducting studies with human subjects. Specifically, the latest version (2008) of the Helsinki Declaration[24] and the guidelines for Good Epidemiological Practice (GEP)[25], Good Pharmacoepidemiology Practices[26] Good Pharmacovigilance Practices (GVP)[27] as well as the ENCePP code of conduct[28], will be observed. All steps will be taken to protect subject's privacy and all relevant rules on data privacy will be followed. It will be ensured that subjects' names and addresses cannot be accessed by the funder.

10.1 Institutional Review

Review of the study protocol will be obtained at ethics committees in the appropriate geographies as required by local law. Non-interventional studies are not within the scope of the European Clinical Trial Directive (2001/20/EC). Accordingly, clinical trial applications to individual European national authorities will not be filed. However, regional regulatory approval within certain European member states will be obtained as required by national regulations. Ethical approval in Australia will be obtained according to the 'National Statement on Ethical Conduct in Human Research' of 2007. All relevant data protection laws in the participating continents and countries will be followed.

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[24] Internationally recognized document defining the ethical principles of clinical research; it resulted from a series of meetings of the World Medical Association – a global organization representing physicians – between 1964 and 2008.

[25] 'Good Epidemiologic Practice (GEP) – Proper Conduct in Epidemiologic Research' issued by the European Epidemiology Federation in 2007; http://www.ieaweb.org/index.php?option=com_content&view=article&id=15&Itemid=43

[26] 'Guidelines for Good Pharmacoepidemiology Practices (GPP)' issued by the International Society for Pharmacoepidemiology in 2007; http://www.pharmacoepi.org/resources/guidelines_08027.cfm

[27] issued by the EMA in 2012/2013

[28] http://www.encepp.eu/documents/encepp_studies/ENCePP%20Code%20of%20Conduct_20100507.pdf

10.2 Informed Consent

Subjects will sign informed consent forms at baseline after reading a subject information sheet and discussing the study with the participating physician. The physician will describe the purpose of the study, the non-interventional character of the study, timing and content of follow-up phase contacts, and collection of alternative contact information. Consent will include permission to contact any treating physician to follow up on specific safety outcomes. Subjects will be informed that ZEG will contact them during the follow-up phase (24 to 72 months) to ask a predefined set of safety related questions or to update alternative contact information. Answers to these questions collected by ZEG will remain anonymous when forwarded to the funder or the Safety Monitoring and Advisory Council.

Subjects will be asked to provide personal contact information (e.g., telephone number, home and e-mail address) and information regarding alternative contacts (e.g., relative, friend, physician other than the COC-prescribing physician). In the event that a subject cannot be reached during the follow-up phase, ZEG will attempt to reach an alternative contact to re-establish contact with the subject, or, in the event of a subject's death, to confirm the cause of death. Subjects may be contacted between two follow-up points to confirm that their personal contact information is correct.

Subjects retain the right to withdraw their consent at any time during the study.

10.3 Safety Monitoring and Advisory Council

This study will maintain scientific independence from the Sponsor and will be governed by an independent Safety Monitoring and Advisory Council (SMAC). The council will be responsible for regular review and evaluation of safety data during study conduct as well as for review and approval of the study protocol, statistical analysis plan, interim results, study report, and publications. The funder will assure financing of the study. ZEG and its research team will be accountable to the council in all scientific matters. ZEG will present all relevant safety data to the council in a timely fashion. The members of the council will be international experts in relevant scientific fields (e.g., epidemiology, drug safety, gynecology, cardiology, statistics, endocrinology). The members will receive remuneration of expenses and an honorarium to compensate for loss of potential earnings during their work for the SMAC. The members will not be involved in or paid for the operational conduct of the study.

Additionally, experts will be invited as and whenever necessary to provide advice to the SMAC in selected fields (e.g. gastroenterology, psychiatry)

11 Management and reporting of adverse events/ adverse reactions

11.1 Adverse Event/ Adverse Reactions Reporting

This is a non-interventional study and no medical procedures are required as part of this protocol. All reported Adverse Events – non-serious as well as serious events – will be recorded in the study database and will be reported in the final study report. ZEG's medical event validation team will perform a causality assessment for all serious adverse events. ZEG will report all confirmed serious adverse events related to the use of NOMAC-E2 or other MSD products within 2 business days to the Funder.

ZEG will report to MSD all death cases which occurred while using an MSD product within 2 business days of their validation. The causality assessment will remain as it was determined by ZEG's medical advisers and the SMAC.

A physician on the ZEG study team will assess the likelihood of a causal relationship to NOMAC-E2 use for each serious adverse event in accordance with a predefined algorithm (cf. 9.10.3). In addition, ZEG will report all confirmed pregnancies within 2 business days to the Funder. All confirmed pregnancies where fetal COC exposure may have taken place during a certain period of the pregnancy will be followed up for final outcome and reported.

Although non-serious adverse events are not actively solicited in this study, all drug-related non-serious adverse events (see procedure in Section 9.2.5) will be collected for tabulation in interim and/or final reports, and submitted to the Funder within 10 days using the same method as described for SAEs.

ZEG will not monitor whether the relevant pharmaceutical companies meet their obligation to report these events to the Health Authorities according to (inter)national rules.

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

11.2 Product Quality Complaint Reporting

11.2.1 Investigator Responsibility:

Any occurrence of a product quality complaint for a Merck product identified during the conduct of the study, must be reported by the study investigator or qualified designee using the Product Quality Complaint (PQC) Reporting Form following the directions in Table 2. The PQC Reporting Form must be fully completed in English. Once the PQC Reporting Form is submitted, the investigator or designee may be contacted for further information.

If both an AE and a PQC occur, the AE should be reported according to the AE reporting requirements in the protocol and the PQC should be reported per Table 2.

Table 2: PQC Reporting Timeframes and Process for Investigators

EVENT TYPE	**INVESTIGATOR TIMEFRAME**
	Investigator to Merck
PQC	24 hours from receipt
PQC reports must be submitted via e-mail by the investigator to the local designated point of contact (DPOC) using a PQC form.	
Submitting PQC reports to Merck: All PQCs must be submitted to the local DPOC in English using a PQC form. The following e-mail addresses should be used by country:	

COUNTRY	**EMAIL**
Australia	PPD
Austria	
Colombia	
France	
Germany	
Hungary	
Italy	
Mexico	
Poland	
Russia	
Spain	
Sweden	

11.2.2 Definitions

11.2.2.1 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

11.2.2.2 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

11.3 Special Situations Reporting

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect
- Exposure to product during pregnancy or lactation

Serious Special Situations should follow the same reporting timelines as SAEs. Non-serious Special Situations should follow the same reporting timelines as NSARs.

12 Plans for disseminating and communicating study results

The final study protocol and the results of this study will be published. In accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical studies in a public registry as a condition for publication, the study will be registered in ENCePP's electronic register of studies (http://www.encepp.eu/encepp/studiesDatabase.jsp). Annual interim results of the study will be submitted to all relevant regulatory authorities. The final results will be published in a peer-reviewed journal.

13 References

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3 Cronin M, Schellschmidt I, Dinger J. Rate of pregnancy following use of drospirenone- and other progestin-containing oral contraceptives. Obstet Gynecol 2009;114(3):616-22

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

(Revison 2; adopted by the ENCePP Steering Group on 14/01/2013)

Study title:

Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg)

Study reference number:

ZEG2013_08

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[29]	☒	☐	☐	10
1.1.2 End of data collection[30]	☒	☐	☐	10
1.1.3 Study progress report(s)	☐	☐	☒	- - -
1.1.4 Interim progress report(s)	☒	☐	☐	10
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

Comments:

None

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	27
	☐	☐	☒	- - -

[29] 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.

[30] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.5 If applicable, that there is no *a priori* hypothesis?				

Comments:

None

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	13 - 14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12 - 13
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	26 - 27

Comments:

None

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10
4.2.2 Age and sex?	☒	☐	☐	15
4.2.3 Country of origin?	☒	☐	☐	14
4.2.4 Disease/indication?	☒	☐	☐	15
4.2.5 Co-morbidity?	☐	☐	☒	- - -
4.2.6 Seasonality?	☐	☐	☒	- - -
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	15

Comments:

None

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14;16;17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	31
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	13;15
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	- - -
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	- - -

Comments:

None

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	19 - 21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	14; 17 - 18; 29 - 32

Comments:

None

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	26 - 27
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	27

Comments:

None

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	16 - 17; 31
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	30 - 32
8.1.3 Covariates?	☒	☐	☐	16 - 17
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16; 17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	25
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	12; 25
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	14
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	- - -

Comments:

None

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	22 - 24

Comments:

None

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	26
10.2 Is the choice of statistical techniques described?	☒	☐	☐	26 - 27
10.3 Are descriptive analyses included?	☒	☐	☐	27
10.4 Are stratified analyses included?	☒	☐	☐	26 - 27
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	26 - 27
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	27

Comments:

None

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24 - 26
11.3 Are methods of quality assurance described?	☒	☐	☐	27 - 28
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	17; 30 - 32
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	27 - 28

Comments:

None

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	28 - 29
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	28 - 29

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	29 - 30
12.3 Does the protocol address other limitations?	☒	☐	☐	28 - 30

Comments:

None

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	35 - 36
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	- - -
13.3 Have data protection requirements been described?	☒	☐	☐	16; 35

Comments:

Ethical review will be applied for after regulatory approval of the protocol.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	9

Comments:

None

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	7; 37
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	37

Comments:

None

Name of the main author of the protocol: Jürgen Dinger

Date: 02/05/2014

Signature PPD 

Annex 3. Additional information

None