Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin

(Nordic Aprotinin Patient Registry)

TRASYLOL® (Aprotinin)

EU PAS register number: **ENCEPP/SDPP/11384**

FINAL DATE: **26 March 2020**

SPONSORED BY:

Nordic Group B.V.

Siriusdreef 22

2132 WT Hoofddorp

The Netherlands

Ethics Committee Approval:

Title	**Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin** Short title: "Nordic Aprotinin Patient Registry"
Protocol version identifier	NG-APRO-PASS-2.1
Date of last version of protocol	26 march 2020
EU PAS register number	Study not registered yet
Active substance	ATC code: B02AB01 Aprotinin
Medicinal product	TRASYLOL 10,000 KIU/ml, injectable solution Aprotinin 10,000 KIU/ml Injection BP
Product reference	AT: 15663 BE: BE108631; BE197294 DE: 34579.00.00 DK: 13857 FI: 12264 FR: NL 17428; NL 20868; NL 21354 IE: PA 2252/001/001 NL: RVG 05312 PL: 10965; 10966; 10967 SE: 8177 UK: PL 05827/0015
Procedure number	EMEA/H/PSP/j/0004
Marketing authorisation holder(s)	Nordic Group B.V. Nordic Pharma Limited
Joint PASS	Yes
Research question and objectives	In order to monitor the pattern of use of Nordic Aprotinin, this Registry has been set up. Its purpose is to record utilisation information on patients at cardiac surgery centres exposed to Nordic Aprotinin when it becomes available to the market. This Registry is a risk minimisation measure as described in the current Risk Management Plan.
Countries of study	AT, BE, DE, DK, FI, FR, IE, NL, PL, SE, UK. *This list is likely to be modified in the coming years*
Author	Hélène Herman-Demars, MD International Medical Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France

Marketing authorisation holders

Marketing authorisation holder	Nordic Group B.V. Siriusdreef 22 2132 WT Hoofddorp The Netherlands
MAH contact person	Hélène Herman-Demars, MD International Medical Director 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 28 19 Fax: +33(0)1 70 37 28 20 *helene.herman-demars@nordicpharma.com*
MAH EU QPPV	Sylvie BOUDEAU, MD EU QPPV, Pharmacovigilance & Medical Information Director, Nordic Group 254 Boulevard Saint Germain 75007 Paris – France Switch: +33 (0) 1 70 37 28 00 Direct line: +33 (0)1 70 37 28 05 Mobile: + 33 (0)6 85 69 40 09 Fax: + 33 (0)1 70 37 28 29 *pv@nordicpharma.com*

Name of the EU QPPV: Sylvie BOUDEAU, MD

Date: 26/3/2020

Signature:

1. Table of content

2. List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BfArM	German Federal Institute for Drugs and Medical Devices
CABG	Coronary artery bypass graft
CHMP	Committee for Medicinal Products for Human Use of the EMA
CRA	Clinical Research Associate
CRO	Contract Research Organisation
DHPC	Direct Healthcare Professional Communication
DLP	Data lock point
EACA	Epsilon aminocaproic acid
EACTS	European Association of Cardio-Thoracic Surgery
EC	European Commission
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	U.S. Food and Drug Administration
GVP	Guideline on good pharmacovigilance practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSMC	Independent Data Safety Monitoring Committee
IgG	Immunoglobulin G
MAH	Marketing authorisation holder
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
Nordic Aprotinin	Refers either to Aprotinin 10,000 KIU/ml Injection BP or to TRASYLOL®
PASS	Post Authorisation Safety Study
PIS	Patient Inform Sheet
PRAC	Pharmacovigilance Risk Assessment Committee of the EMA
PSUR	Periodic safety update report
QA	Quality Assurance
QPPV	Qualified Person for Pharmacovigilance
SAG	CHMP scientific advisory group; meeting held on 11 October 2011
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TXA	Tranexamic acid
VKA	Vitamin K antagonist

3. Responsible parties

3.1. Contact persons within MAH

Hélène Herman-Demars, MD
International Medical Director
254 Boulevard Saint Germain
75007 Paris – France
Switch: +33 (0) 1 70 37 28 00
Direct line: +33 (0)1 70 37 28 19
Fax: +33(0)1 70 37 28 20
helene.herman-demars@nordicpharma.com

Sylvie BOUDEAU, MD
EU QPPV, Pharmacovigilance & Medical Information Director, Nordic Group
254 Boulevard Saint Germain
75007 Paris – France
Switch: +33 (0) 1 70 37 28 00
Direct line: +33 (0)1 70 37 28 05
Mobile: + 33 (0)6 85 69 40 09
Fax: + 33 (0)1 70 37 28 29
pv@nordicpharma.com

3.2. External expert consultant (from 2015 to June 2019)

Christopher SPEIRS, MSc MRCP FFPM
Director of Harefield Pharmacovigilance Limited
Fetcham Park House
Lower Road
Fetcham KT22 9HD - United Kingdom
cspeirs@harefieldpv.com

3.3. Data Management

Dendrite Clinical Systems Ltd
The Hub, Station Road
Henley-on-Thames
Oxfordshire
RG9 1AY
United Kingdom
Phone: +44 1491 411 288
Fax: +44 1491 411 377
E-Mail: info@e-dendrite.com
http://www.e-dendrite.com/

3.4. Principal Investigator

The Principal Investigator is Professor Stefan De Hert (Department of Anesthesiology, Ghent University Hospital, Belgium).

3.5. Coordinating Investigators for each participating country

The list of Coordinating Investigators is below.

As national coordinator is defined before launch in each concerned country, this list will be updated in each study report /PSUR.

Country	Local coordinating Investigators
Austria	Prof Michael Híesmayr *Med. Uni Wien, AKH Wien*
Belgium	Professor Steffen Rex *UZ Leuven*
Denmark	Dr Dorthe Viemose Nielsen *Aarhus Universitets Hospital, Skejby*
Finland	Professor Seppo Hiippala *Helsinki University Hosptail*
France	Professor Jean-Luc Fellahi *Hôpital Louis Pradel - Hospices civils de Lyon*
Germany	Professor Kai Zacharowski *Universitätsklinikum Frankfurt*
Ireland	No local coordinator
Netherland	No patient
Sweden	Professor Jan van der Linden *Karolinska University Hospital*
UK	Doctor David Royston *RBH Foundation Trust, Harefiled Hospital*
Poland	No patient

3.6. Monitoring

In accordance with local needs, CRO can be involved in training of the healthcare professionals that will use the Registry (“end-users”) and monitoring. In other countries, this will be performed by Nordic.

4. Abstract

Name of MAHs	NORDIC GROUP BV NORDIC PHARMA LIMITED
Name of finished product	TRASYLOL® 10,000 KIU/ml, injectable solution Aprotinin 10,000 KIU/ml Injection BP
Name of active ingredient	Aprotinin
Short title of the Study	Nordic Aprotinin Patient Registry
Full title of the Study	Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin
Protocol No.	NG-APR-PASS-2.1
Date of last version of protocol	26 March 2020
Author	Hélène Herman-Demars, MD Nordic Group B.V. International Medical Director
Rationale and background	This study is being conducted as part of an agreed European Risk Management Plan (EU RMP), condition of the Nordic Aprotinin marketing authorisation
Research question and objectives	This Nordic Aprotinin Patient Registry is a non-interventional Post Authorisation Safety Study as defined in the Guideline on GVP Module VIII – Post-authorisation safety study (EMA/813938/2011 Rev 1). The study is part of the European Risk Management Plan for Nordic Aprotinin as required by CHMP. The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to Nordic Aprotinin in participating countries in Europe beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter. To have access to Nordic Aprotinin, cardiac surgery centres have to commit to enrol in the Registry. The primary objectives of the Registry are to: 1. Monitor the pattern of use and record utilisation information: o the proportion of patients exposed to aprotinin in accordance with the authorized indication 2. Measure the incidence of the following adverse events: o death and the distribution of the primary cause of death

- thromboembolic events; the total and individual incidence of myocardial infarction, stroke and other thromboembolic events recorded
- incidence of renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L, and the incidence of renal dialysis
- the numbers having an anaphylactic response to aprotinin

3. Measure the effectiveness of risk minimisation measures as described in the RMP and close monitoring of adherence to the SmPC recommendations:
   - the proportion of patients receiving heparinisation monitoring as recommended in the SmPC
   - the proportion of patients with a post-operative renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L or requiring dialysis known to have received aminoglycoside antibiotics
   - the proportion of patients exposed to aprotinin without the use of test dose (or antibody test)
   - the proportion of patients administered with the recommended posology

The secondary objectives of the Registry are to:

1. Estimate the contribution of suspected risk factors to adverse events:
   - the proportion of patients with total and individual thrombotic events who did not receive heparinisation monitoring as recommended in the SmPC (regarding the risks related to heparinisation monitoring)
   - the proportion of patients with anaphylactic reactions who had previously been exposed to aprotinin (solution or fibrin sealant containing aprotinin) in the last 12 months

2. Estimate information concerning:
   - the proportion of pregnant and lactating women
   - the proportion of patients undergoing repeat isolated CABG
   - the proportion of patients having a concomitant use of drugs that affect haemostasis (including antiplatelet therapy) and/or non-VKA oral anticoagulant considered as active at time of surgery and relating safety outcomes when aprotinin is used in those patients
   - the proportion of patients over 75 years of age and outcomes: the proportion of these patients requiring re-operation for bleeding; the mortality rate

	3. Estimate optional information according to the national legislation of the countries involved: ○ the proportion of patients exposed to aprotinin for cardiothoracic surgery which indications are outside isolated cardiopulmonary bypass graft surgery ○ the proportion of patients exposed to aprotinin in the paediatric population ○ the proportion of patients exposed to aprotinin for indications other than cardiothoracic surgery
Study design	The Nordic Aprotinin Patient Registry is a multicentre, non-interventional Post Authorisation Safety Study with active surveillance via patient exposure registry. Nordic will supply Nordic Aprotinin only to centres that perform cardiac surgery on cardio-pulmonary bypass and which commit to enrol in the Nordic Aprotinin Patient Registry (participating centres). The Nordic Aprotinin Patient Registry is designed to be easy-to-use and to fit with standard clinical practice. The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to the product beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter. Nordic will provide appropriate training and support to facilitate implementation of the Registry at all participating centres. Nordic will encourage all participating centres to treat only patients conforming to the authorised indications for Nordic Aprotinin. According to the national legislation of the countries involved, Nordic will carefully monitor the number of cases in which Nordic Aprotinin is given to patients having surgery outside the authorised use and will collect data on these patients via the Registry (use outside cardiac surgery is expected to be negligible due to the limitation of supply to cardiothoracic centres) however if there is any such use, it will be monitored carefully and discussed in the PSUR. The proposed Registry will provide information on the number of patients who receive Nordic Aprotinin by centre, indication (cardiac surgical procedure, indication features) for which Nordic Aprotinin was administered, and the conditions of use, including dose and adherence to instructions for administration in the approved SmPC. Interim and progress reports will be provided to the PRAC (and the National Competent Authorities if required) and will include summary tables of analyses of patterns of use.
Study population	All patients exposed to Nordic Aprotinin at all participating cardiac surgical centre fulfilling criteria of the restricted distribution in participating countries in Europe.
Variables	The content of the Registry follows the template of the reports of the European Association for Cardio-Thoracic Surgery (EACTS) with additional data assessment relevant to the specific needs for recording the use and safety monitoring, including haemostatic monitoring, of the use of aprotinin.

	The collection of data is therefore divided into Key Pages and non-key pages. The Key Pages include the Key Data: patient demography and all of the major outcomes of identified or potential hazards in the use of aprotinin, that includes adverse drug reactions such as allergic reactions, renal dysfunction and its relationship to aminoglycoside antibiotics, coagulation control and the use of heparin and the major outcomes of renal failure, myocardial infarction, stroke and other thrombotic effects. Those Key Data allow answering the research question and objectives of this study. The Key Pages are the following: - Initial Registry data (patient demography) - Operation - Antiplatelet and anticoagulant therapy considered to be active at operation - Aprotinin use - Intra-operative coagulation and blood loss monitoring in the operating room - Transfusion (intra-operative and post-operative) - Post-operative Only adverse drug reactions, which are suspected to be associated to Nordic Aprotinin should be reported by the Investigator to Nordic Pharmacovigilance via the Routine pharmacovigilance reporting ways (such as phone, email, fax) or via the Registry and its link with Nordic Pharmacovigilance department. The information regarding these adverse drugs reactions is processed, entered into the Nordic Safety Database, assessed and reported to the Competent Authorities, if applicable, according to the regulation in force. Those adverse drugs reactions will also be discussed in PSUR according to the regulation in force. A close monitoring will be performed for risks mentioned in the RMP. All other safety information (not suspected to be associated to Nordic Aprotinin) will be included by the Investigator in the electronic case report form (eCRF). This information will be recorded in the Registry and reviewed on a continuing basis allowing recognition of any pattern that may be of cause for concern of a particular hazard in the overall use of Nordic Aprotinin or at the level of an individual country or centre. All safety information will be included in the interim and final study reports of the Registry which will be submitted to the PRAC (and other Competent Authority if required) via PSUR.
Data sources	The data source is an electronic registry that can be accessed worldwide through a web portal, working with all web browsers and designed to collect uniform data on patients exposed to Nordic Aprotinin. Data which is collected during routine clinical practice will be entered into the eCRF.
Study size	Across Europe, at least 300,000 patients are undergoing cardiac surgery. We estimate the sample size based on the occurrence of events of specific interest (such as type of procedure, death, thromboembolic, stroke …) with a reasonable precision. To obtain 95% confidence interval with a maximum margin error of 1.56%, 3,951 patients should be included. This margin error is the maximum one that can be obtained: it is the one based on the assumption that an event of interest is observed in 50% of patients (meaning a 95% CI of [48.44% ; 51.56%]). In all other cases (i.e.

	event of interest observed in less or more than 50%), precision will only be better (less than 1.56%). Taking into account around 25% excluded rate (patiente refusing data collection and un-exposed to aprotinin in the course of cardiac surgery with CPB), the maximum number of patients to include should be 5,268.
Data analysis	All data analyses will be performed by Dendrite Clinical Systems together with Nordic after the Key Data are completed. Analysed data will be reviewed by an Independent Data Safety Monitoring Committee, involving at least four (4) national coordinating investigators. The analysis of data from the Registry will be descriptive, and all information will be reported in summary tables. Summary data will be provided for all variables collected and the data will be reported overall, by country, and if required by centre. The intention is to focus on those variables most pertinent to assessing compliance with approved labelling and instructions for appropriate use, including use of heparin and monitoring of anticoagulation. The data will also be reviewed for any safety signals. The outcomes to be included in each report will include at least: death, myocardial infarction, renal failure with and without aminoglycoside use, stroke and other embolic or thrombotic event, blood loss (requiring transfusion, requiring re-operation), blood product transfusion and anaphylaxis. Analysis of each outcome will be presented by: country, age categories, sex, presence of anti-platelet agents active at time of operation, cardiac by-pass and operative type. Other variables may be included as considered appropriate by an Independent Data Safety Monitoring Committee or as requested by the PRAC. Overall reports will be synchronised with PSUR scheme and timelines.
Planned milestones	Study start: planned for Q2 2015 Recruitment completed: when a maximum of 5,268 patients will be included (estimated in January 2020). This number of patients should be enough to obtain 3,951 analysable patients. Interim statistical reports: every 6 months after launch. Interim medical report: every 2 years with PSUR. Last data collection: when a maximum of 5,268 patients will be included (estimated in January 2020). This number of patients should be enough to obtain 3,951 analysable patients. Final study report: 12 months after the end of Data collection (prospective collection). The Registry will operate for at least three years beginning with Nordic Aprotinin's return to the market in Europe, and the decision to terminate the Registry will be taken based on agreement with the PRAC.

5. Amendments and updates

Number	Date	Section of the study protocol	Amendment or update	Reason
Version 1.0			submitted 17 September 2014	
Version 1.1		Revised PASS Protocol	submitted 19 December 2014	
Version 1.2			submitted 25 February 2015	
Version 1.3	11 March 2015		submitted 11 March 2015	
Version 1.3.1 Current version in all countries except germany	11 March 2015		submitted December 2015	version similar to version 1.3 without patient initials and birth date (only year)
Version 1.4			Submitted on 12 November 2015	
Version 1.4.1			National amendment for Germany – submitted in February 2016	
Version 1.4.2 Current version in germany	27 May 2016		National amendment for Germany – submitted in May 2016	
Version 2.0	10 October, 2019	3. Responsible parties 5. Amendments and updates 6. Milestones 9.3 Variables 9.5 Study size 9.8 Quality control 9.9 Limitation of the research methods 10. Protection of human subjects 13. References	Amendment 1	Update asked by EMA following the registry rescheduling

		Annex 1.List of stand-alone documents		
Version 2.1	17 March 2020	5. Amendments and updates 6. Milestones 9.5 Study size 9.8 Quality control 9.9 Limitation of the research methods	Amendment 1	See detailed table below

Detailed summary of changes between protocol version 1.3 and protocol version 2.1 and rational for these changes:

Section of the study protocol	Protocol version 1.3 11 March 2015	Protocol version 2.1 26 March 2020	Reason
6.Milestones Final report of study results	Q4 2018 at the latest (assuming start in Q2 2015) The final report of study results (data collected prospectively only) will be made available six months after the last patient included	Estimated December 2020 The final report of study results (data collected prospectively only) will be made available twelve months after the last patient included	Protocol version 1.3, (dated March 11, 2015) mentioned a 6 months delay between the last patient included and the final report. This duration (6 months) is too short, as it should allow: analysis, presentation and discussion with DSMC members, comparison with literature and medical writing. Therefore the MAH proposes using the duration described in the EMA guideline "Guideline on good pharmacovigilance practices (GVP)" dated 9 October 2017 - page 13 section VIII.B.4.3.2 Final study report: "For non-interventional PASS conducted pursuant to an obligation imposed by an EU competent authority, the final study report shall follow the format described in this section [IR Annex III) and shall be submitted within 12 months of the end of data collection". Considering all of the above, EMA/PRAC should consider that the MAH will submit the final

			report within 12 months after the "End of data collection".
9.5 Study size	The study size cannot be planned. Indeed, all patients exposed to Nordic Aprotinin, at all participating cardiac surgical centres in European countries with marketing authorisation, are intended to be included during the study. Based on likely prescription rates and epidemiology (see table below) Nordic estimates that 12,000 patients up to 50,000 patients would be included in the Registry over a 3-year period (corresponding to 2.5% to 10% patients undergoing isolated CABG in the concerned countries, i.e. those patients at high risk of major blood loss). According to the OECD.Stat, the number of CABG procedures performed in participating countries in 2012 (except BE (2011) and NL (2010)) are: **Country** — **Number of CABG per year** Germany 55,033 Poland 20,796 France 19,388 UK 18,313 Netherlands 9,042	All patients exposed to Nordic Aprotinin, at all participating cardiac surgical centres in European countries with marketing authorisation, are intended to be included during the study. The study is designed primarily to monitor the pattern of use and record utilisation information such as the proportion of patients exposed to aprotinin in accordance with the authorized indication. Considering that the registry of Great Britain & Ireland recorded just over 400,000 operations in 5 years and that the US one collected around 280,000 operations/year[15,16], we could postulate that, across Europe, at least 300,000 patients are undergoing cardiac surgery. Thus, we estimate the sample size based on the occurrence of events of specific interest (such as type of procedure, death, thromboembolic, stroke …) with a reasonable precision. To obtain 95% confidence interval with a maximum margin error of 1.56%, **3,951 patients should be included**. This margin error is the maximum one that can be obtained: it is the one based on the assumption that an event of interest is observed in 50% of patients (meaning a 95% CI of [48.44% ; 51.56%]). In all	In Protocol version 1.3 dated March 11th, 2015, the objective of the NAPaR was: "The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to Nordic Aprotinin in participating countries in Europe, beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter." The sample size of this registry was based on "likely prescription rates and epidemiology" (https://stats.oecd.org/). In Protocol version 2.0, MAH has proposed to stop the patients inclusions in the NAPaR once 3,528 analysable patients would have been included (estimated on January 2020). Finally, the January 7, 2020 database extraction point include 3,951 analysable patients. Then in protocol version 2.1, the protocol "sample size" section was updated with this new number of patients, estimated as large enough to answer to the protocol objectives.

	Hungary 9,024 Spain 8,268 Belgium 7,497 Denmark 3,800 Austria 3,670 Sweden 3,296 Finland 2,574 Slovenia 835 Luxembourg 232 *<u>Note:</u> data are not available for Greece and Portugal.* Nordic will update this figure and the list of countries in each intermediary report.	other cases (i.e. event of interest observed in less or more than 50%), precision will only be better (less than 1.56%). There is no a priori calculation of power for this study because the main primary objective is descriptive rather than inferential and because the adverse event included in the other primary objectives such as in-hospital mortality, thromboembolic events or renal dysfunction are dependant of aprotinin's pattern of use. Taking into account an exclusion rate of 25% (patient refusing data collection, un-exposed to aprotinin in the course of cardiac surgery with CPB, or undergoing off pump surgery), **the maximum number of patients to include is 5,268**.	

9.8 Quality control	**9.8.2. Data monitoring** To ensure the quality of data collected during the study each site will be monitored centrally by review of data collected in the eCRF. In addition, if needed, and according to laws of the countries involved, some sites would be attended by a CRA or a Nordic employee. During the onsite visit by the CRA the focus of activities will be to review informed consent documents and selected source data seen as key to the recording of safety endpoints. **9.8.3. Quality Assurance (QA)** Nordic can undertake any Quality Assurance related activity upon decision of Nordic Quality Assurance department. The decision will be based on the level of risk to the study subject and on any reported/ identified problem. QA activities may be outsourced to CROs or independent consultants. A Competent Authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by such Authority, the Investigator must inform Nordic immediately that this request has been made.	**9.8.2. Data monitoring** To ensure the quality of data collected during the study each site will be monitored centrally by review of data collected in the eCRF. ~~In addition, if needed, and according to laws of the countries involved, some sites would be attended by a CRA or a Nordic employee. During the onsite visit by the CRA the focus of activities will be to review informed consent documents and selected source data seen as key to the recording of safety endpoints.~~ **9.8.3. Quality Assurance (QA)** According to local regulation in participating countries, Nordic can undertake any Quality Assurance related activity upon decision of Nordic Quality Assurance department. The decision will be based on the level of risk to the study subject and on any reported/ identified problem. QA activities may be outsourced to CROs or independent consultants. A Competent Authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by such Authority, the Investigator must inform Nordic immediately that this request has been made. According to local regulation in participating countries, the Investigator will make all the study-related source data and records available to a quality assurance auditor mandated by the	These two sections were reviewed in order to take into consideration the local regulation of countries participating to the NAPaR. In many countries, the monitoring by a CRA or by a Nordic employee is not allowed by local regulation. However, in protocol version 2.1 we saved the first sentence of section 9.8.2. Indeed, onsite monitoring is not possible, but the database is centrally reviewed at each database extraction point (every 6 months). This ensures the quality of the NAPaR database completion.

	The Investigator will make all the study-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors. The Investigator is required to support audit / inspection activities, to be available to the auditors/inspectors upon request and to permit the auditor/inspector direct access to source data/documents.	sponsor, or to domestic or foreign regulatory inspectors. The Investigator is required to support audit / inspection activities, to be available to the auditors/inspectors upon request and to permit the auditor/inspector direct access to source data/documents.	
9.9 Limitation of the research methods	**9.9. Limitations of the research methods** ….. When incomplete data will not be recovered the data manager will try to get the cause (fortuitous omission, not pertinent data due to death or other reason, lack of time...) and a field in the database will be filled by the data manager concerning the cause.	**9.9. Limitations of the research methods** ….. ~~When incomplete data will not be recovered the data manager will try to get the cause (fortuitous omission, not pertinent data due to death or other reason, lack of time...) and a field in the database will be filled by the data manager concerning the cause.~~	This sentence was deleted because the NAPaR database do not allow the justification of missing or incomplete data. There is no direct communication between the study datamanager and the participating sites. However, the NAPaR data entry completeness is centrally followed, per country and per site, in order to limit the missing data. For now, the targeted rate of complete key data above 80% has been achieved with the concourse of Medical Science Liaison (MSL) and/or local coordinator.

<table>
<tr>
<td>9.9 Limitation of the research methods</td>
<td>9.9. Limitations of the research methods
…..</td>
<td>9.9. Limitations of the research methods
…..
One limitation of the NAPaR is the detection of rare events (≥ 1/10,000 to <1/1,000).
In order to detect such outcomes with 95% precision, the sample size included in the NAPaR should be of 29,956 patients.
<table>
<tr><th>Frequency</th><th>Precision</th><th>Sample size</th></tr>
<tr><td>10/100</td><td>95,00%</td><td>28</td></tr>
<tr><td>1/100</td><td>95,00%</td><td>298</td></tr>
<tr><td>1/1,000</td><td>95,00%</td><td>2,994</td></tr>
<tr><td>1/10,000</td><td>95,00%</td><td>29,956</td></tr>
</table>
Therefore, even the initial design of the NAPaR (12,000 patients) could not allow the collection of data regarding such rare events.
An alternative channel of collection, associated with monitoring, should be favored. The MAH suggests using EudraVigilance Data Analysis System (EVDAS) for better signal detection of side effect of aprotinin.</td>
<td>Upon the rapporteur request, a paragraph about the limitation of the research methods was added in protocol version 2.1. It reviews the NAPaR ability to identify and estimate rate with reasonable precision for rare events.</td>
</tr>
<tr>
<td>12. 1 Reporting of Registry Data</td>
<td>12. 1 Reporting of Registry Data during the study period</td>
<td>12. 1 Reporting of Registry Data during the study period</td>
<td>See explanation for section 6 “Milestones”</td>
</tr>
</table>

during the study period	… The final study report (data collected prospectively only) will be submitted within 6 months following the completion of the study. If this is delayed for any reason the reasons for the delay will be communicated. The planned publication will conform to STROBE guidelines (cf. References).	… The final study report (data collected prospectively only) will be submitted within 12 months following the completion of the study. If this is delayed for any reason the reasons for the delay will be communicated. The planned publication will conform to STROBE guidelines (cf. References).	

6. Milestones

Table with planned dates for the following milestones:

Milestone	Planned date	Rationale
Start of data collection	February 2016	At the launch of Nordic Aprotinin in the first participating country (i.e. Aprotinin 10,000 KIU/ml Injection BP in the UK)
End of data collection	when a maximum of 5,268 patients will be included (estimated in January 2020).	This number of patients should be enough to obtain 3,951 analysable patients.
Study progress reports and Interim reports of study results 1	17 May 2018 (with PSUR report)	Clinical study report are done following the same timelines and scheme as PSUR. Bi-annual statistical reports are done for DSMC review
Study progress reports and Interim reports of study results 2	28 May 2020 (with PSUR report)	
Registration in the EU PAS register	8 February 2019	Last update
Final report of study results	Estimated December 2020	The final report of study results (data collected prospectively only) will be made available twelve months after the last patient included

7. Rationale and background

Note: Nordic Group B.V. is MAH for TRASYLOL® in all concerned countries except Spain and Greece at this time. Nordic acquired TRASYLOL® from Bayer in July 2012, and marketing authorisations in Spain and Greece will be transferred to Nordic prior to launch in these countries (Bayer will not be involved in the PASS). Nordic Pharma Limited is MAH for Aprotinin 10,000 KIU/ml Injection BP in the UK. Nordic Group will commercialize TRASYLOL® in the other participating countries. Nordic Pharma Limited and Nordic Group B.V. are separate entities from a legal point of view but Nordic Group B.V. owns Nordic Pharma Limited which is its affiliate in the UK. For the best scientific and clinical reasons, only one registry will be set up and this PASS is therefore a joint PASS.

In this protocol, ***"Nordic Aprotinin" will either refer to Aprotinin 10,000 KIU/ml Injection BP or to TRASYLOL®****.*

In October 2007, Bayer and regulatory authorities were notified that the BART study – a Canadian, non-Bayer sponsored, randomised, controlled trial comparing the efficacy of aprotinin with other haemostatic agents conducted in high-risk cardiac surgery patients (not in accordance with the approved label) – had been halted after an interim data analysis "indicated reduced bleeding but also an increase in all-cause mortality (that almost reached conventional statistical significance for 30-day mortality) for patients in the aprotinin treatment arm compared to patients who received either aminocaproic acid (EACA) or tranexamic acid (TXA)."

On 5 November 2007, and following consultation with the German Federal Institute for Drugs and Medical Devices (BfArM), the U.S. Food and Drug Administration (FDA), Health Canada, and other health authorities, Bayer announced that it had elected to temporarily suspend worldwide marketing of Trasylol® (aprotinin injection) until final results from the Canadian BART trial have been compiled, received and evaluated.

The German health authority, BfArM, suspended the marketing authorisation for Trasylol® on 5 November 2007, after concluding that the benefit-risk balance was unfavourable. As a consequence of BfArM's decision, the CHMP initiated a procedure under Article 107 (Directive 2001/83/EC) and recommended the suspension of all marketing authorisations in the EU of aprotinin-containing medicines for systemic use. The view of the CHMP, endorsed by the UK Committee on Human Medicines, resulted in the suspension of the UK licence on 7 December 2007. The CHMP further recommended "an Article 31 referral in order to perform a full evaluation at Community level of the additional information on the BART study and thus re-evaluate the benefit-risk balance of the product". This referral was triggered in March 2010.

Following further representations by the concerned companies the CHMP issued its revised final referral assessment report on 30 May 2013.

The Committee concluded that evidence from randomised clinical trials and observational studies support the use of aprotinin in reducing the incidence of massive bleeding, the need for transfusion of blood products and the need for re-surgery for bleeding.

The CHMP concluded that the BART data and the signal on increased mortality associated with aprotinin compared to EACA and TXA were not considered reliable, based on the totality of evidence now available since the review of aprotinin undertaken in 2007, including more recent observational studies, the new analysis of the BART study data and the identified major study flaws, and taking the advice of the SAG into account. The CHMP noted that since the initial review in 2007, more data have become available, such as new observational studies, the final study results of the BART study, and more importantly new analysis of the BART study. These new data have now made it possible to identify the major flaws of the BART study, not identifiable before.

The Committee considered that the available randomised clinical trial and meta-analysis of clinical trials (when the BART study is excluded) do not give evidence of an association between aprotinin and perioperative mortality. No firm conclusion on cardiovascular risks can be made on the BART study due to several serious methodological issues identified. In addition, results from observational studies are conflicting. Taking the totality of data into account it is judged that the previous signal for an increased mortality associated with the use of aprotinin should be refuted provided that the drug is given in the identified target population of adult patients at high risk of major blood loss undergoing isolated coronary artery bypass graft (CABG) surgery and the recommendations for its use are followed.

The Committee considered that the product information should be updated to ensure that the information to healthcare professionals and patients is up-to-date. Recommendations on adequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure should be reflected in the product information. Special attention is also to be given to patients with renal impairment and to the possible occurrence anaphylactic reactions. All risks should be captured in the risk management plan. In addition, a registry must be conducted by MAHs of aprotinin containing medicinal products in order to gather more information on the profile of aprotinin use. A restricted distribution of aprotinin is required with aprotinin available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the Registry.

The patient registry is one of conditions of the marketing authorisation: *"Marketing authorisation holders shall conduct a registry, in order to monitor the pattern of use of aprotinin. The registry shall record utilisation information on patients at cardiac surgery centres exposed to aprotinin in participating countries. It shall thus be set up in advance of placing the product on the market. The MAH shall take due account of the draft protocol and comments received during assessment. The registry's protocol shall be submitted to the national competent authorities within 2 months of Commission Decision. Updates on the Registry will be submitted to national competent authorities with periodic safety update reports (PSURs)*" (EC decision of 18 September 2013).

8. Research question and objectives

8.1. Aim of the Study

The aim of the Registry is to collect information over time on the pattern of use of Nordic Aprotinin and to record the proportion of patients exposed to aprotinin in accordance with the authorized indication in participating European countries during the three year period beginning from the day that Nordic Aprotinin becomes available to the market. To have access to Nordic Aprotinin and to become a participating centre, centres have to perform cardiac surgery on cardio-pulmonary bypass and to commit to enrol in the Registry (as described in Annex 4). Thus, it is expected that virtually all patients who receive Nordic Aprotinin at all participating cardiac surgery centre in participating countries in Europe will be included in the Registry. The Registry will provide information on the number of patients who receive Nordic Aprotinin by centre, the recorded indication (surgical procedure, features of the indication), the characteristics, including risk factors and the conditions of use, including adherence to instructions for administration in the approved SmPC. The Registry will also collect additional information from healthcare professionals relevant to patient characteristics that may be related to the decision to use Nordic Aprotinin. Information from the proposed Registry will provide a profile over time of Nordic Aprotinin utilization in participating countries following return to the market.

It is proposed to collect similar information on any patients who are given Nordic Aprotinin within or outside its licensed indications, to allow the assessment of off-label use as part of the missing information, as required in the CHMP assessment report (EMA/590581/2013). **Data collection**

regarding off-label use will be done in accordance with national legal frameworks and will be discussed with the national competent authority prior to launch if necessary and adapted accordingly.

The proposed Registry is expected to be a valuable and informative risk-management tool within the comprehensive EU Risk Management Plan. It is not intended to provide a quantitative assessment of the benefit-risk of treatment with Nordic Aprotinin. The Registry will address specific issues found in the BART study. In that study it was found that some centres were not applying the appropriate safety measures concerning monitoring of blood coagulation. It was also found that some surgical centres had high morbidity and mortality rates. However there were insufficient data available from the BART study to allow analysis of the contribution of these factors (that is the lack of appropriate risk minimisation measures) to an increased risk of morbidity and mortality. This is why this Registry collects information on the monitoring of blood coagulation.

8.2. Primary objectives

The primary objectives of the Registry are to:

1. Monitor the pattern of use and record utilisation information:
    - the proportion of patients exposed to aprotinin in accordance with the authorized indication

2. Measure the incidence of the following adverse events:
    - death and the distribution of the primary cause of death
    - thromboembolic events; the total and individual incidence of myocardial infarction, stroke and other thromboembolic events recorded
    - incidence of renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L, and the incidence of renal dialysis
    - the numbers having an anaphylactic response to aprotinin

3. Measure the effectiveness of risk minimisation measures as described in the RMP and close monitoring of adherence to the SmPC recommendations:
    - the proportion of patients receiving heparinisation monitoring as recommended in the SmPC
        - Proportion of patients with a minimal ACT-celite below 750 seconds
        - Proportion of patients with a minimal ACT-kaolin below 480 seconds
    - the proportion of patients with a post-operative renal dysfunction defined as a rise in creatinine from pre-operative to post-operative levels of > 0.5 mg/L or requiring dialysis known to have received aminoglycoside antibiotics
    - the proportion of patients exposed to aprotinin without the use of test dose (or antibody test)
    - the proportion of patients administered with the recommended posology
        - the proportion of patients administered with less than 2.5 million KIU
        - the proportion of patients administered with more than 7 million KIU

8.3. Secondary objectives

The secondary objectives of the Registry are to:

1. Estimate the contribution of suspected risk factors to adverse events:
    - the proportion of patients with total and individual thrombotic events who did not receive heparinisation monitoring as recommended in the SmPC (regarding the risks related to heparinisation monitoring)
    - the proportion of patients with anaphylactic reactions who had previously been exposed to aprotinin (solution or fibrin sealant containing aprotinin) in the last 12 months

2. Estimate information concerning:
    - the proportion of pregnant and lactating women
    - the proportion of patients undergoing repeat isolated CABG
    - the proportion of patients having a concomitant use of drugs that affect haemostasis (including antiplatelet therapy) and/or non-VKA oral anticoagulant considered as active at time of surgery and relating safety outcomes when aprotinin is used in those patients
    - the proportion of patients over 75 years of age and outcomes: the proportion of these patients requiring re-operation for bleeding; the mortality rate

3. Estimate optional information according to the national legislation of the countries involved:
    - the proportion of patients exposed to aprotinin for cardiothoracic surgery which indications are outside isolated cardiopulmonary bypass graft surgery
    - the proportion of patients exposed to aprotinin in the paediatric population
    - the proportion of patients exposed to aprotinin for indications other than cardiothoracic surgery

Table 1: Summary of safety concerns from current RMP

Important identified risks	Anaphylaxis Influence of previous exposure to fibrin and aprotinin Renal impairment Embolic and thrombotic events Anticoagulant monitoring
Important potential risks	/
Important identified drug interactions	Aminoglycoside antibiotics related to renal dysfunction
Important identified interactions with other products	Test for Activated Clotting Time related to risk of thrombosis and embolic events.
Missing information	Off-label use Experience in pregnancy and lactation Safety in patients over 75 years of age Use in paediatric population Concomitant use of: - drugs that improve haemostasis - non-VKA oral anticoagulants

9. Research methods

9.1. Study design

The Nordic Aprotinin Patient Registry is a multicentre, non-interventional Post Authorisation Safety Study with active surveillance via patient exposure registry. The main objective is to record the proportion of patients exposed to aprotinin in accordance with the authorised indication.

The Nordic Aprotinin Patient Registry in participating countries in Europe is designed to be easy-to-use and to fit with standard clinical practice.

The Registry is intended to record utilisation information on virtually all patients at cardiac surgery centres exposed to the product beginning from the day that Nordic Aprotinin becomes available to the market, and continuing for at least three years thereafter.

To have access to Nordic Aprotinin and to become a participating centre, cardiac surgery centres have to commit to enrol in the Registry (cf. restricted distribution described in Annex 5). Thus, it is expected that virtually all patients who receive Nordic Aprotinin at all participating cardiac surgery centre in participating countries in Europe will be included in the Registry. Any use in patients outside cardiothoracic surgery is anticipated to be negligible due to the limitation of supply to cardiothoracic centres and the lack of demand in other surgical procedures; however if there is any such use it will be monitored carefully and discussed in the PSUR.

The Registry will collect **prospectively** information on the number of patients who receive Nordic Aprotinin by centre, the recorded indication (cardiac surgical procedure and pre-operative assessment of risk of major blood loss for which Nordic Aprotinin was administered), the characteristics, including risk factors, of the patients who receive Nordic Aprotinin, and the conditions of use, including adherence to instructions for administration in the approved SmPC.

However, if this proposed prospective data collection for all patients exposed to aprotinin is not possible from a national legal point of view, this topic will be discussed with the national concerned authority prior to launch.

The Registry will also collect additional information from healthcare professionals relevant to patient characteristics that may be related to the decision to use Nordic Aprotinin.

9.2. Setting and study population

The Registry is intended to collect data for all patients exposed to Nordic Aprotinin at all cardiac surgical centres fulfilling criteria of the restricted distribution (cf. Annex 5) in participating countries in Europe for at least three years following Nordic Aprotinin's return to the market.

Nordic will have no influence on the selection of any cardiac surgery centres that wish to participate.

The decision to treat with Nordic Aprotinin will be made by the treating physician(s) according to clinical judgment.

During training to healthcare professionals, Nordic will insist on the fact that all patients exposed to aprotinin have to be enrolled in the Registry. Furthermore, the use of the Registry by concerned cardiac surgery centres will be continuously monitored, and Nordic will remind potential non-responders to use the Registry. It is fundamental to the study that patients are entered consecutively and none are excluded from the study.

Inclusion Criteria:

- All patients exposed to Nordic Aprotinin at all participating cardiac surgical centre fulfilling criteria of the restricted distribution in participating countries in Europe.

Exclusion Criteria:

- None

Patients may refuse to have their personal data entered in a database (even if those are anonymised), so those concerned patients will be entered in the Registry with an anonymous sequential number (relating data will not be entered) with the indication "refused to participate to the Registry". This will allow assessing the number of refusals.

The decision to terminate the Registry will be taken in agreement with the PRAC. A centre's commitment to enrol in the Registry will be a prerequisite to that centre's access to Nordic Aprotinin.

9.3. Variables

The design of the Registry follows the template of the reports of the European Association for Cardio-Thoracic Surgery (EACTS) with additional data assessment relevant to the specific needs for recording the use and safety monitoring, including haemostatic monitoring, of the use of aprotinin.

It is recognised that the success of the Registry requires adequate entry of the data. Data entry in previous European Association of Cardio-Thoracic Surgery (EACTS) registries has been very variable by region and by hospital (cf. Fourth EACTS Adult Cardiac Surgical Database Report 2010). This is primarily linked to the time needed to capture data that should take no more than 10-15 minutes according to experts in this field. The collection of data is therefore divided into Key Pages and non-key pages. The **Key Pages** include the Key Data: patient demography and all of the major outcomes of identified or potential hazards in the use of aprotinin, that includes adverse drug reactions such as allergic reactions, renal dysfunction and its relationship to aminoglycoside antibiotics, coagulation control and the use of heparin and the major outcomes of renal failure, myocardial infarction, stroke and other thrombotic effects. Those Key Data allow answering the research question and objectives of this study. These are marked with an asterisk below and by different colours in the web-based Registry.

The Key Data will be the minimum information required for each patient included in the Registry.

Considering the previous experiences with entry of data into registries it is likely that not all users would return complete or nearly complete data entry even for the Key Pages. In order to maximise the level of data entry to the Key Pages Nordic will continually monitor the data entry of each centre. When the Key Data, defined above, are not correctly completed, the site will be encouraged to improve compliance. Similarly post-discharge follow-up data may be difficult to obtain and the availability of data will vary in different Member States and at different centres. However the principal outcomes after follow-up are important and in order to maximise the return Nordic will make arrangements to obtain follow-up data according to the local arrangements and availability of data at each centre.

Other clinical information, further to the Key Data, may be of interest to evaluate some criteria in details. However, collecting these detailed information are time-consuming and cannot be done for all patients. Therefore, Nordic plans to involve academics and medical societies to collect these “non-key data”.

9.3.1. Initial Registry data *

Age;
Gender;
Centre;
Anaesthetist;
Country;
Date of surgery;
Date of admission;
Procedure group;
Use of cardiopulmonary bypass;
Renal impairment;
Last pre-operative creatinine;
Pregnancy;
Lactation;

9.3.2. Operation *

Type of operation elective, urgent, emergency or salvage;
If urgent the reason for urgency;
The number of previous heart operations;
Type of procedure (including valve surgery).
Other surgical procedures will be detailed if relevant. *Note: If the indication for using aprotinin is entirely within the authorised indication up to and at the time of aprotinin administration but complications or unforeseen circumstances arise during surgery and the concerned patient requires further surgery the patient will be considered as an “unintended off-label” case*.

9.3.3. Antiplatelet and anticoagulant therapy considered to be active at operation *

Aspirin, clopidogrel, prasugrel, ticagrelor, dipyridamole, 2b/3a inhibitors, warfarin or phenprocoumon, heparins, direct thrombin inhibitors, direct Factor Xa inhibitors and fibrinolytics.
Any other medicine interfering with the primary or secondary haemostasis.

9.3.4. Aprotinin use *

The reason for using aprotinin;
Prior exposure to aprotinin or to fibrin sealants (some contain aprotinin), if available;
Aprotinin IgG test and result if available;
Administration of the test dose to aprotinin and the reaction to the test dose (including anaphylactic reaction);
The loading dose of aprotinin, the pump priming dose and the continuous infusion dose;

The use of another haemostatic.

9.3.5. Intra-operative coagulation and blood loss monitoring in the operating room*

Coagulation prevention details, dose of heparin, either fixed or by titration, before and during surgery;
Monitoring of anti-coagulation, ACT, kaolin or celite;
The minimum operative ACT when available;
The estimated intra-operative blood loss, if available;

9.3.6. Transfusion (intra-operative and post-operative)*

Number of units of blood products transfused (red blood cells, platelets, fresh frozen plasma, cryoprecipitate, prothrombin complex concentrate, fibrinogen), if any.

9.3.7. Post-operative*

Reoperation if required with reason for re-operation;
The occurrence of post-operative stroke, post-operative myocardial infarction, other post-operative embolic or thrombotic event, and new post-operative dialysis and relative date;
Post-operative serum creatinine level;
Time to recover renal function baseline value, if available;
Any post-operative use of an aminoglycoside antibiotic;
The occurrence of multisystem failure;
Post-operative blood loss;
Status at discharge and if dead the primary cause of death before discharge;
Date of discharge (and post-operative stay).
Note: the average time-to-events for the abovementioned post-operative events are considered the following: less than one day for reoperation for bleeding (Karthik 2004), one day for renal failure (Rosner 2006), 3 days for stroke (Schwann 2007, Hogue 1999, Dafer 2006), 3 days for myocardial infarction (Thygesen 2007), and 6 days for deep vein thrombosis (Hogue 2006). All abovementioned post-operative events have to be collected at any time, even if those occur after the average time-to-events as published in the literature.

The non-key pages are the following:

9.3.8. Post-discharge follow-up if available

Patient status follow-up (after discharge), whether alive or dead and if dead the primary cause of death;
Myocardial infarction, stroke and other embolic or thrombotic event;
Renal failure.

9.3.9. Cardiac history

Angina (Canadian Cardiovascular Society Angina Grading Scale Class I- IV)[1];
Dyspnoea (New York Heart Association)[2];

[1] Angina (Canadian Cardiovascular Society Angina Grading Scale) Class I- IV.
- Class I: Angina only during strenuous or prolonged physical activity
- Class II: Slight limitation, with angina only during vigorous physical activity
- Class III: Symptoms with everyday living activities, i.e., moderate limitation
- Class IV: Inability to perform any activity without angina or angina at rest, i.e., severe limitation

[2] Dyspnoea. New York Heart Association Class I- IV
- Class I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Previous myocardial infarctions within past 90 days;
Most recent myocardial infarction;
Congestive cardiac failure;

9.3.10. Previous interventions

Previous percutaneous coronary intervention and date of most recent intervention;
Previous operation requiring sternotomy;

9.3.11. Pre-operative risk factors

Height;
Weight;
Smoking history;
Diabetes treatment (diet, oral therapy and insulin);
Hypertension;
Hypercholesterolaemia;
Antiplatelet therapy;
Chronic lung disease;
Extracardiac arteriopathy;
Neurological dysfunction;
Poor mobility due to any non-cardiac reason;
Carotid bruits;
Pre-operative cardiac rhythm;
Active endocarditis;
Critical preoperative state;
Baseline figures of coagulation tests: activated partial thromboplastin time (aPTT), thrombin time (TT) and prothrombin time (PT)
Other relevant factors are derived from the Registry: the patient's age, body mass index, body surface area, and the duration of pre-operative and post-operative stay.

9.3.12. Pre-operative haemodynamic and circulation

Ejection fraction and value;
Pulmonary artery systolic pressure;
Catheterisation details;
Number of diseased coronary vessels;
Left main stem disease;

9.3.13. Pre-operative status and support

Use of intravenous nitrates;
Use of heparin or heparinoid of any kind;
Use of intravenous inotropes;
Patient ventilation;
The presence of cardiogenic shock;

9.3.14. Myocardial protection

Cardiopulmonary bypass;
The use of an intra-aortic balloon pump;
The use of a ventricular assisted device;
Time on bypass;
Extracorporeal membrane oxygenation.

- Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
- Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

9.4. Data sources

The data source is an electronic registry that can be accessed worldwide through a web portal, working with all web browsers and designed to collect uniform data on patients exposed to Nordic Aprotinin. Data which is collected during routine clinical practice will be entered into the electronic case report form (eCRF). The Registry has been set up and implemented by Dendrite Clinical Systems on behalf of Nordic. The Registry has been tested by European experts in cardiac surgery and anaesthesiology.

9.5. Study size

All patients exposed to Nordic Aprotinin, at all participating cardiac surgical centres in European countries with marketing authorisation, are intended to be included during the study.

The study is designed primarily to monitor the pattern of use and record utilisation information such as the proportion of patients exposed to aprotinin in accordance with the authorized indication.

Considering that the registry of Great Britain & Ireland recorded just over 400,000 operations in 5 years and that the US one collected around 280,000 operations/year[15,16], we could postulate that, across Europe, at least 300,000 patients are undergoing cardiac surgery.

Thus, we estimate the sample size based on the occurrence of events of specific interest (such as type of procedure, death, thromboembolic, stroke …) with a reasonable precision.

To obtain 95% confidence interval with a maximum margin error of 1.56%, 3,951 patients should be included. This margin error is the maximum one that can be obtained: it is the one based on the assumption that an event of interest is observed in 50% of patients (meaning a 95% CI of [48.44% ; 51.56%]). In all other cases (i.e. event of interest observed in less or more than 50%), precision will only be better (less than 1.56%).

There is no a priori calculation of power for this study because the main primary objective is descriptive rather than inferential and because the adverse event included in the other primary objectives such as in-hospital mortality, thromboembolic events or renal dysfunction are dependant of aprotinin's pattern of use.

Taking into account an exclusion rate of 25% (patient refusing data collection, un-exposed to aprotinin in the course of cardiac surgery with CPB, or undergoing off pump surgery), the number of patients to include is 5,268.

9.6. Data management

Data management and statistical analyses will be the responsibility of the Data Management and Statistics department at Nordic, Dendrite and CRO's site. The Investigators will register the patient data via an electronic web-based data collection system. Data collected during routine clinical practice will be entered into the electronic case report form (eCRF), by the Investigator, or associated site staff or a CRO. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the database. The data capture software has been designed to allow for multi-layer data validation. Validation rules have been constructed so that invalid combinations of data are simply not permitted at the point of data entry. So, for example, if the end-user selected an answer of "No" to "Previous Cardiac Intervention" then all the other answers for type of procedure are greyed out including the date of previous procedure. Several logic checks have also been included. Window pops up in case Key Data are not entered.

Data collection will be by eCRF. Data will be available electronically to Nordic/CRO and an electronic copy supplied to the site.

A DHPC will be sent to cardiac surgery centres prior to launch in each participating countries in order to ensure that the information to healthcare professionals is up to date regarding aprotinin, notably the implementation of the Nordic Aprotinin Patient Registry, and the requirement to commit to enrol in the Registry to have access to Nordic Aprotinin. All participating sites will receive training in the study protocol requirements and data collection. When the end-user (Investigator or associated site staff) connects to the Registry, the end-user sees a table containing all concerned patients; when Key Data of a patient are complete, then the corresponding row is in green and when those data are incomplete the corresponding row is in yellow and reminds that "record is incomplete". All participating sites will be monitored continually for completeness of data entry. When the Key Data, defined above, are not correctly completed, the site will be encouraged to improve compliance.

9.7. Data analysis

All data analyses will be performed by Dendrite Clinical Systems together with Nordic after the Key Data are completed. Statistical programming and analyses will be performed using SAS and/or other statistical software as required.

Analysed data will be reviewed by an Independent Data Safety Monitoring Committee, involving at least four (4) national coordinating investigators.

The Registry will collect information for all patients who receive Nordic Aprotinin for any purpose in participating countries in Europe. The Registry will not allow a direct comparison of mortality and morbidity among patients treated with aprotinin to patients not with aprotinin. Mortality and morbidity outcomes vary according to patient selection criteria by centre and by country of treatment. Historical controls are not wholly reliable as patient selection and operative techniques vary over time. It is proposed to examine external data bases for comparative purposes as these may be used as a yardstick to measure patient outcomes, e.g. reports from existing national or European cardiac surgical databases. These external data will be mentioned in the Statistical Analysis Plan (SAP) prior to the first analysis.

The analysis of data from the Registry will be descriptive, and all information will be reported in summary tables.

The intention is to focus on those variables most pertinent to assessing compliance with approved labelling, including compliance with the approved indication, and compliance with instructions for appropriate use, including use of heparin and monitoring of anticoagulation. Summary data will be provided for all variables collected and the data will be reported overall, by country, and if required by centre.

The first data analyses will be conducted six months after the completion of data entry of the first subject in the study depending on PSUR scheme and timelines and will be repeated six months later. Thereafter the analyses will be conducted annually until the close of the Registry (i.e. for at least three years). Overall reports will be synchronised between each country so that **the analyses are all conducted at the same time**.

Analysis will be made of the data for Nordic Aprotinin overall, by individual country and if required by individual site. The analysis will include the following key outcomes and variables will be presented:

<u>The outcomes to be included in each report will include at least:</u>

- Death
- Myocardial infarction (fatal and non-fatal)
- Renal failure (fatal and non-fatal)
- Renal failure with and without aminoglycoside use

- Stroke (fatal and non-fatal)
- Other embolic or thrombotic event (fatal and non-fatal)
- Blood loss: requiring blood product transfusion, requiring re-operation
- Blood product transfusion
- Anaphylaxis

Note: allergic reactions and anaphylactic/anaphylactoid reactions are rare (between 1/10,000 and 1/1,000) and anaphylactic shocks are very rare (below 1/10,000) when appropriate preventative measures are taken so none may be reported. If any occur the details will be reported separately.

Variables included in the analysis:

Analysis of each outcome will be presented by: country, age categories, sex, presence of anti-platelet agents active at time of operation, cardiac by-pass and operative type (on label and off-label). Other variables may be included as considered appropriate by an Independent Data Safety Monitoring Committee or as requested by the PRAC.

The final analysis will be based on the population entered at three years following completion of the first patient. The analysis will include at least the information above and will include further analyses as suggested by the results and as requested by the Competent Authorities concerned and the Independent Data Safety Monitoring Committee (IDSMC).

A review will be conducted by the IDSMC every six months throughout the study. The results of the six months initial interim report and of each annual report will be available in full to the PRAC to allow full review for safety signals. Previous mortality and morbidity data from existing cardiac surgery databases will be available as a yardstick. This may occur when a potential safety signal arises. Outcome data between different participating centres within the Registry may also be analysed when appropriate.

Additional analyses can be made available on a flexible basis depending on the outcomes in the study. In addition to the above further analyses may be undertaken when appropriate according to the ongoing findings from the Registry and as requested by the PRAC (and other Competent Authorities if required).

Rates and confidence intervals:

Rates and exact 95% confidence intervals will be computed for all identified adverse events and potential risks and all relevant criteria.

Missing data:

As a matter of fact imputation of data is more or less invention of data that can strongly bias results in an observational study. The less speculative approach is therefore to remove from the data patients without the needed information from the analysis.

In data modelling or if a breakdown of the sample is done according a given variable, a missing data in any qualitative covariate (or factor of segmentation of the sample) can have a category called "unknown". A first model will fitted with such a categorization and a second one will be fitted after removing all patients with missing data on the covariate. If it concerns a breakdown of the sample then descriptive statistics along with 95% confidence interval will be provided for all categories including the unknown class. Regarding quantitative covariate, categorization of the covariate may be done and a first model will be fitted with only categorical variables including the "unknown" category and a

second model is fitted with quantitative covariate (patients with a missing data are excluded). Concerning the breakdown the same categorization approach will be applied and estimation will be provided for each category. If a breakdown of the sample is applied the estimation for the "unknown" category will be compared to all the other categories combined to assess whether missing data represent approximately the average of the collected data.

9.8. Quality control

9.8.1. Record maintenance and retention

Neither a subject's name nor initials are to appear on documents transmitted to Nordic in order to maintain confidentiality. Additional anonymisation / pseudo-anonymisation laws as applicable by country will also be adhered to.

In order to provide Nordic/ the CRO with accurate, complete, and legible data, the following criteria are to be maintained:

1. Source documents will be completed to support the data that is entered into the eCRF system.
2. eCRF entries should be made as close to the treatment of the subject as possible.

9.8.2. Data monitoring

To ensure the quality of data collected during the study each site will be monitored centrally by review of data collected in the eCRF.

9.8.3. Quality Assurance (QA)

According to local regulation in participating countries, Nordic can undertake any Quality Assurance related activity upon decision of Nordic Quality Assurance department. The decision will be based on the level of risk to the study subject and on any reported/ identified problem.

QA activities may be outsourced to CROs or independent consultants.

A Competent Authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by such Authority, the Investigator must inform Nordic immediately that this request has been made.

According to local regulation in participating countries, the Investigator will make all the study-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors.

The Investigator is required to support audit / inspection activities, to be available to the auditors/inspectors upon request and to permit the auditor/inspector direct access to source data/documents.

9.9. Limitations of the research methods

This study is designed to recruit all patients who are exposed to Nordic Aprotinin during routine clinical practice in participating countries in Europe. Recruitment rate of subjects has been estimated based on likely prescription rates.

Owing to differing clinical practice between countries and centres who will recruit subjects into the study protocol, the eCRF template has to be simple and flexible to allow for different assessments conducted.

This is a non-interventional study with its limitations. No control arm is planned to compare the study treatment with other alternatives. The Registry will not allow a direct comparison of mortality and morbidity among patients treated with Nordic Aprotinin to patients not treated with Aprotinin. Mortality and morbidity outcomes vary according to patient selection criteria by centre and by country

of treatment. Historical controls are not wholly reliable as patient selection and operative techniques vary over time. It is proposed to examine external data bases for comparative purposes as these may be used as a yardstick to measure patient outcomes, e.g. reports from existing national or European cardiac surgical databases.

The limitations of this study are common to all registry data collections.

Patients may refuse the use of their personal data for research purposes. The number of refusals will be kept track of. The impact of these patients on the overall results is expected to be negligible due to their low numbers and the a priori small relationship with the variables of interest.

Entry of patients may be incomplete. It will be mandatory for centres to confirm their willingness to participate in the registry in order to receive supplies of the product. The completion of the Registry for all points of information is not mandatory. In order to ensure the maximum return of individual data key pages have been included which are mandatory.

Nordic will actively follow-up all centres to ensure that Key Data are being entered. This will be performed by comparing sales figures and Registry data (number of patients included and doses used). If it is found that some patients have not been entered into the registry the company will contact the centre concerned to ensure that minimal Key Data are collected and that future patients enter the Registry.

The potential limitation induced by missing data due to incompleteness or absence of any data will be assessed through the number of missing data for each variable of key interest and the breakdown by cause of missing information provided by the data manager (see imputation of missing data).

Data are entered in some hospitals by the same person treating the patients, which may increase the risk of social desirability bias (e.g. respondents report what they think is expected to happen, rather than what they actually do). However, in most hospitals, data will be entered by a CRA or a healthcare professional responsible for data entry (under supervision of a physician) or another physician. During visits to cardiac surgery centres and trainings, Nordic (or its representatives) will advise to have different persons treating the patients and entering data. Furthermore, the requested information that needs to be entered into the Registry are factual data, therefore limiting interpretation bias.

The prospective design of the study does not allow evaluating the changes in physicians' behaviour before and after the implementation of the new recommendations. Furthermore, the participation of prescribers as investigators of the study may change their own clinical practice, taking into account that this study will be prospective. This "Hawthorne effect" could bias the results but is common to any clinical trial or registry. As the Hawthorne Effect relates to individual behaviour in response to change, it can be assumed that the healthcare professionals concerned in the Registry are indeed likely to change their behaviour. In fact this is an advantage of the Registry and one reason for it being prospective. **It is important for clinicians to adopt the risk minimisation measures, and the Registry will ensure the risk minimisation measures (and relating results) to be read and implemented multiple times** (i.e. every time a patient is entered in the Registry). Once these measures are adopted they should certainly be a part of the team protocols and so will not disappear when the Registry closes.

Primary objectives are updated to fulfil the current definition of a non-interventional study as per Directive 2001/20/EC Art 2(c). Nordic will promote the prescription of the product in accordance with the terms of the marketing authorisation. Nordic does not plan to evaluate efficacy of off-label use.

However, as required by the CHMP, Nordic Aprotinin Patient Registry has to collect information on "*the number of patients who receive aprotinin and indication for administration*", especially regarding off label use that "*should be assessed as part of the missing information*".[1]

Nordic considers that the best way to ensure that all patients are entered in the Registry and to comply with the CHMP requirement is to conduct data collection prospectively. This was confirmed by experts in the field.

If this prospective data collection regarding off-label use is not possible because e.g. from a national legal point of view, this will be discussed with the national concerned authority prior to launch and data collection in a completely retrospective way based on chart reviews or alternative retrospective approaches would be considered (such approach is likely to lead to loss of data, cf. limitations).

As mentioned above, a prospective design may lead to limitations. However a retrospective design will lead to loss of data: not all cardiac surgery centres have a detailed database that would allow retrospective data collection. Furthermore those databases do not follow all Key Data of the Nordic Aprotinin Patient Registry that have been defined in accordance with the requirements of the CHMP and in line with the approved RMP (e.g. heparinisation monitoring data, use of a test dose, prior exposure to aprotinin…). A mixed prospective/retrospective approach may also lead to confusion of healthcare professionals, and this is likely to lead to reluctance to enrol in the Registry.

One limitation of the NAPaR is the detection of rare events (≥ 1/10,000 to <1/1,000). In order to detect such outcomes with 95% precision, the sample size included in the NAPaR should be of 29,956 patients.

Frequency	Precision	Sample size
10/100	95,00%	28
1/100	95,00%	298
1/1,000	95,00%	2,994
1/10,000	95,00%	29,956

Therefore, even the initial design of the NAPaR (12,000 patients) could not allow the collection of data regarding such rare events.

An alternative channel of collection, associated with monitoring, should be favored. The MAH suggests using EudraVigilance Data Analysis System (EVDAS) for better evaluation of side effects of aprotinin.

9.10. Other aspects

None.

10. Protection of human subjects

10.1. Declaration of ethical conduct

This study will be conducted in accordance with the standard operating procedures (SOP) of Nordic and the CRO. The study will be conducted according to the following guidelines:

1. Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients"), and all its accepted amendments to date concerning medical research in humans.
2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use
3. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and repealing Directive 95/46/EC (General Data Protection Regulation)
4. Guideline on good pharmacovigilance practices (GVP) Module VIII- Post-authorisation safety studies (version in force)

This study will be conducted in accordance with national and local laws of the countries where study sites are located.

The participating physician agrees, when signing the Commitment to participate page, to adhere to the instructions and procedures described in the protocol.

10.2. Ethical, regulatory and other local review

According to local country specific requirements the protocol and associated documentation will be submitted to all relevant local approving bodies. This may include Ethics committees, data protection bodies etc.

Signed letters of positive opinion regarding the study from the relevant local approving bodies must be sent to the Investigator who will provide Nordic/ the CRO with a copy prior to the start of data collection for any subject in the eCRF.

The Registry will comply with local data protection laws.

10.3. The Investigator and associated site staff will collect information according to the protocol

The Investigator and associated site staff must comply with local regulatory laws and regulations concerning post approval safety studies.

10.4. Subject information and consent

According to local country specific requirements, informed consent will be obtained if applicable by means of a patient information sheet (PIS) and Informed Consent Form (ICF), prepared in accordance with ICH E6 Section 4.8.10 and applicable local regulations, written in non-technical language.

10.5. Data protection

Data protection will be carried out in accordance with the regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016. This will apply to all study data in whatever format it is collected and recorded.

11. Management and reporting of adverse events / adverse drug reactions

11.1. Definitions

Definition of Adverse Drug Reaction (ADR)
"ADR" means a response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Adverse drug reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Conditions of use outside the marketing authorisation include overdose, misuse, abuse and medication errors.

Definition of Causality
In accordance with the ICH-E2A guideline, the definition of an adverse drug reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse drug reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected (*cf. Guideline on good pharmacovigilance practices (GVP) – Module VI EMA/873138/2011).*

The question of the relationship of an Adverse Event to Aprotinin should be determined by the Investigator after thorough consideration of all facts that are available.

Assessment of causality is based on considering associative semiological, temporal and pharmacological relationship, previous drug knowledge, presence of specific clinical or pathological symptoms, underlying conditions, exclusion of other causes, and/or absence of alternative explanations.

Definition of a Serious Adverse Drug Reaction (SADR)
As described in the ICH-E2A guideline, a serious adverse drug reaction corresponds to any untoward medical occurrence that at any dose

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect.

The characteristics/consequences should be considered at the time of the reaction to determine the seriousness of a case. For example, life-threatening refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical judgement should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered as serious by the physicians or Nordic Pharmacovigilance department (cf. *Guideline on good pharmacovigilance practices (GVP) – Module VI EMA/873138/2011).*

"Hospitalisation" means an overnight admission.

Hospitalisation without an underlying adverse drug reaction (ADR) is not an SADR. Examples are:

- Hospitalisations for protocol procedures e.g., routine supportive treatment, a biopsy or study monitoring
- Elective hospitalisation for a pre-existing condition that has not worsened
- Admission to a rehabilitation centre or hospice
- Hospitalisation for social reasons (e.g., due to anxiety but otherwise treatable on an outpatient basis).

Note: To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.2. Reporting of Adverse Events and Adverse Drug Reactions

Only adverse drug reactions which are suspected to be associated to Nordic Aprotinin should be reported by the Investigator to Nordic Pharmacovigilance.

11.2.1. Reporting of Adverse Events

All other safety information (not suspected to be associated to Nordic Aprotinin) will be included by the Investigator in the eCRF.

This information will be recorded in the Registry and reviewed on a continuing basis allowing recognition of any pattern that may be of cause for concern of a particular hazard in the overall use of Nordic Aprotinin or at the level of an individual country or centre.

All safety information will be included in the interim and final study reports of the Registry which will be submitted to the PRAC (and other Competent Authority if required) via PSUR.

11.2.2. Reporting of Adverse Drug Reactions

Any adverse drug reaction for which a causal relationship with Aprotinin is reasonably possible must be reported immediately (or at least within 24 hours) by the Investigator to the national or regional Pharmacovigilance centre of a Competent Authority or directly to the Nordic Pharmacovigilance department.

Via routine pharmacovigilance reporting ways:

The Investigator can use the Routine pharmacovigilance reporting ways (such as phone, email and fax).

The Investigator could complete the Adverse Event Report Form (please refer to Annex 3) to report all adverse events suspected to be associated to Nordic Aprotinin and send it to the Nordic Pharmacovigilance department by email and/or fax.

Nordic Group Pharmacovigilance department:
Phone: +33 (0)1 70 37 28 01
Fax: +33 (0) 1 70 37 28 29
Email: pv@nordicpharma.com

Or

Via the Registry:

In addition to the routine Pharmacovigilance activities, Nordic plans to use the Registry to help physicians report adverse drug reaction.

To do this, Nordic added a "link with Nordic Pharmacovigilance department" in the Registry. Indeed, the Registry is a web-based registry, so it allows a direct link between the end-users (healthcare professionals) and Nordic. In case the patient experiences an adverse event and the physician considers it is associated with Nordic Aprotinin, the physician can directly report the adverse drug reaction via the Registry. This can be done at 3 pages of the Registry: "Aprotinin use", "Post-operative"

and "Post-discharge follow-up". The physician can describe the adverse drug reaction, inform its seriousness, the start and end dates and the outcomes.

Then, a form is generated and immediately transferred to the Pharmacovigilance and medical departments of Nordic Group, as well as local safety officer of the concerned country by email.

This information regarding these adverse drug reactions is processed, entered into the Nordic Safety Database, assessed and reported to the Competent Authorities, if applicable, according to the regulation in force. Those adverse drug reactions will be discussed in PSUR according to the regulation in force. A close monitoring will be performed for risks mentioned in the RMP.

11.3. Follow-up

When first received, the information in suspected adverse drug reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases.

The Investigators are encouraged to submit new information relevant for the scientific evaluation of a particular safety concern via the same ways described above (Routine pharmacovigilance reporting ways or Patient registry).

Additional information e.g. hospital reports or death certificates, may be requested by Nordic or CRO.

11.4. Specific case of pregnant and lactating women

Nordic will use the Registry to identify pregnant and lactating women treated with Nordic Aprotinin. Once reported by the physician via the Registry, follow-up and information collection is performed through routine Pharmacovigilance activities: Nordic contacts the reporter immediately, at the time of the delivery and one year after to collect information regarding the foetus/children and pregnancy/lactation outcome. In case of safety issue, the patient is closely monitored and could lead to expedited and/or periodic reporting (PSUR, RMP, etc.). Nordic agrees that information regarding the foetus/children and pregnancy/lactation outcome should be actively collected and is already performed in routine Pharmacovigilance activities.

11.5. Independent Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (IDSMC) will be set up for the study, involving at least four (4) national coordinating investigators.

The IDSMC will:

- meet at 6 monthly intervals (ad hoc meeting could be scheduled in case of safety signal),
- review accumulated data from the study at the meetings,
- advise Nordic whether or not it is recommended to continue the Registry. In that case, Nordic will discuss this with the PRAC.

The data, the IDSMC will be provided with, will comprise AEs, and possibly further data relevant for the evaluation of safety and/or the benefit/risk ratio of Nordic Aprotinin, if needed.

12. Plans for disseminating and communicating study results

12.1. Reporting of Registry Data during the study period

Summary statistical data will be submitted to the PRAC (and National Competent Authorities if required). It is planned to submit this 6 monthly for the first year of marketing and annually thereafter following PSUR scheme. Data will be made available according to any requests from any National Competent Authority.

The final study report (data collected prospectively only) will be submitted within 12 months following the completion of the study. If this is delayed for any reason the reasons for the delay will be communicated. The planned publication will conform to STROBE guidelines (cf. References).

An additional report including the results of the analysis of data collected retrospectively (including a comparison with the data collected prospectively) will be submitted within 2 years following the submission of the final study report described above.

12.2. Discontinuation of study

The Registry will be conducted for at least three years. As it is an imposed non-interventional PASS, the decision to terminate the Registry will be taken in agreement with the PRAC.

12.3. Registration and publication of study summary and results

The study design will be published on the EU PAS Register website after the PRAC advice and before launch.

This study is a non-interventional Post Authorisation Safety Study, and Nordic intends to follow the principles outlined in of the Rules Governing Medicinal Products in the European Union. Nordic agrees to report results in strict accordance with the pre-specified study protocol and statistical analysis plan, and in accordance with the STROBE guidelines as applicable. Nordic also intends to make the study design available in a publicly administered database.

The following concerns the potential scientific publications (different from the reports submitted to the Competent Authorities):

If results are intended for publication in a peer review scientific journal, no detailed results will be published on a public database beforehand. The site may publish or present the results of this protocol subject to the protection of any patentable rights of Nordic or its nominee(s) and subject to the protection of Nordic's confidential information. Nordic will be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review of confidential or patentable information. Upon notice by Nordic, however, that Nordic reasonably believes that a patent application claiming an invention relating to aprotinin made during the performance of the study will be filed prior to such publication, such publication may be delayed for an additional 30 days or until any patent application or applications have been filed, whichever will first occur.

For multi-site studies, it is mandatory that the first publication be based on data obtained from all analysed subjects; therefore Investigators participating in multi-site studies must agree not to present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by the Independent Data Safety Monitoring Committee and Nordic. Publication of clinical study results may include the presentation of such work at national and international congresses, symposia, professional meetings, peer-reviewed journals, and via other appropriate channels.

Named authors and contributors to such publications shall be determined by Nordic in accordance with both the Company Publication Policy and the criteria as outlined by standard authorship guidelines. Selected Investigators, Consultants and Scientific Advisors may be invited to be named authors on such publications by Nordic.

If the Investigator/Consultant/Scientific Advisor agrees to participate in the publication as an author, they will be asked to participate in the creation of all versions of the document(s) in question prior to submission or public dissemination. Nordic will ensure that any reasonable comments made by the invited author will be incorporated into the publication and that the named author will consent to the publication of the final version of the document. The copyright associated with any publication will be and shall remain the sole property of Nordic, unless or until the copyright of the document is transferred to the scientific peer-reviewed journal prior to and as part of the publication process.

13. References

1. BART Study: Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008 May 29;358(22):2319-31.
2. CHMP assessment report (EMA/590581/2013): Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Antifibrinolytic_medicines/WC500153601.pdf
3. Dafer 2006: Rima M. Dafer Risk Estimates of Stroke After Coronary Artery Bypass Graft and Carotid Endarterectomy. Neurol Clin 24 (2006) 795–806
4. EC decision of 18 September 2013: Commission decision of 18 September 2013 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for medicinal products for human use which contain the active substance "aprotinin"
5. Fourth EACTS Adult Cardiac Surgical Database Report 2010. Available at: https://www.surgery.cuhk.edu.hk/cardiothoracic/EACTS_2010.pdf
6. Guideline on good pharmacovigilance practices: Module VIII – Post-authorisation safety studies: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf
7. Hogue 1999: Risk Factors for Early or Delayed Stroke After Cardiac Surgery. Charles W. Hogue, Jr, Suzan F. Murphy, Kenneth B. Schechtman and Victor G. Dávila-Román/ Circulation 1999;100:642-647
8. Karthik 2004: Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. Ann Thorac Surg. 2004 Aug;78(2):527-34.
9. OECD.Stat: OECD.Stat Dataset: Health Care Utilisation. Available at: http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_PROC (data presented in the protocol were retrieved on 7 July 2014)
10. Rosner 2006: Acute kidney injury associated with cardiac surgery., Rosner MH, Okusa MD.; Clin J Am Soc Nephrol. 2006 Jan;1(1):19-32
11. STROBE: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies BMJ 2007;335:806
12. Schwann 2007: Schwann TA, Kistler L, Engoren MC, Habib RH. Epidemiology of stroke after cardiac surgery in the current era. J Thorac Cardiovasc Surg 2007;134:1121-7
13. Schwann 2010: Schwann TA, Kistler L, Engoren MC, Habib RH. Incidence and predictors of postoperative deep vein thrombosis in cardiac surgery in the era of aggressive thromboprophylaxis. Ann Thorac Surg. 2010 Sep;90(3):760-6;
14. Thygesen 2007: Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction European Heart Journal (2007) 28, 2525–2538

15. Bridgewater, B. & Society for Cardiothoracic Surgery in Great Britain & Ireland. *Demonstrating quality*. (Dendrite Clinical Systems, 2009)

16. D'Agostino, R. S. *et al.* The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2017 Update on Outcomes and Quality. *The Annals of Thoracic Surgery* 103, 18–24 (2017).

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	DHPC	15 September 2015	DHPC
2	ENCePP checklist for study protocols	11 March 2015	ENCePP checklist for study protocols
3	ENCePP checklist for study protocols	10 October 201	ENCePP checklist updated
4	Adverse Event Report Form	24 December 2018	Adverse Event Report Form
5	Details of Nordic Aprotinin Restricted distribution	NA	Details of Nordic Aprotinin Restricted distribution
6	Statistical Analysis Plan (SAP)	23 September 2019	Statistical Analysis Plan

Annex 1. DHPC

NORDIC PHARMA

APPROVED

15 September 2015

New indication and safety information for aprotinin (Trasylol®), following its re-introduction to the market

Dear Health Care Professional,

Summary

Aprotinin (Trasylol®) will be re-introduced in your country from **[date to be confirmed]** with a restricted indication and new safety information as follows:

New restricted indication for aprotinin (Trasylol®):

Aprotinin is indicated for prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).

Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available.

New safety information:

The reduced level of heparinisation in the patients treated with aprotinin increases the risk of thrombogenic events in this population. The level of heparinisation of patients is incorrectly interpreted with the use of non-appropriate activated clotting tests.

The data illustrates the risks associated with inadequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure.

Aprotinin is not a heparin-sparing agent and it is important that adequate anticoagulation with heparin be maintained during aprotinin-therapy. Elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (Celite ACT) are expected in aprotinin-treated patients during surgery, and in the hours after surgery. It is important that adequate anticoagulation with heparin be maintained and monitored during aprotinin treatment. In patients undergoing cardiopulmonary bypass who are being treated with aprotinin, one of the following three methods is recommended to maintain adequate anticoagulation:

- Activated Clotting Time (ACT)
- Fixed Heparin Dose
- Heparin Titration

Partial Thromboplastin Time (PTT) should not be used to maintain adequate anticoagulation with heparin.

An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth-based (celite) ACTs.

While protocols vary, a minimal celite ACT of 750 seconds or kaolin ACT of 480 seconds, independent of the effects of haemodilution and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of aprotinin.

Registry

In order to monitor the pattern of use of aprotinin a registry (Post Authorisation Safety Study) has been set up in Europe. The purpose of this registry is to record utilisation information on all patients at cardiac surgery centres exposed to aprotinin in participating countries in Europe beginning from the day that aprotinin becomes available to the market, and continuing for at least three years thereafter.

Restricted distribution:

A restricted distribution of aprotinin has been implemented with the product available only to centres that perform cardiac surgery on cardio-pulmonary bypass which committed to enrol in the ongoing registry.

Further information:

In February 2008, the European Commission, in agreement with the opinion of the CHMP, suspended the marketing authorisations for all aprotinin containing medicines throughout the EU largely on the basis of preliminary findings of the BART study (Blood conservation using antifibrinolytics: A randomised trial in a high-risk cardiac surgery population, Fergusson *et al*, 2008).
In March 2010 the CHMP started an evaluation of all information available from the BART study and other clinical studies and re-assessed the benefit and risks of aprotinin.

The BART study reported a higher mortality rate in aprotinin-treated patients compared to those treated with Tranexamic acid or aminocaproic acid. However due to several methodological deficiencies, no firm conclusion on cardiovascular risks can be made on the BART study results.
The re-evaluation also included evaluation of observational studies where an association between aprotinin use and increased mortality has been reported in some non-randomized observational studies (e.g., Mangano 2007, Schneeweiss 2008, Olenchok 2008, Shaw 2008) while other non-randomized studies have not reported such an association (e.g., Karkouti, 2006, Mangano 2006, Coleman 2007, Pagano 2008, Ngaage 2008, Karkouti 2009). In these studies, aprotinin was usually administered to patients who had more risk factors for increased mortality before surgery than patients in the other treatment groups.

Most of the studies did not adequately account for these baseline differences in risk factors and the influence of these risk factors on the results is not known. Therefore the interpretation of these observational studies is limited and an association between aprotinin use and increased mortality can neither be established nor refuted.

On the basis of the assessment, the CHMP recommended several new important changes to the product information and a lifting of the market suspension for aprotinin. The changes to the product information include clarification of the indication and highlighting the needs for appropriate maintenance and monitoring of anticoagulation in patients treated with aprotinin.
On 18 September 2013 the European Commission lifted the market suspension for Trasylol®.

The updated product information for Trasylol® is attached as Annex.

Registry

In order to monitor the pattern of use of aprotinin, a registry has been set up in Europe. The purpose of this registry is to record utilisation information on all patients at cardiac surgery centres exposed to aprotinin in participating countries in Europe, beginning from the day that aprotinin becomes available to the market, and continuing for at least three years thereafter. The registry will provide information on the:

- Number of patients who receive aprotinin.
- recorded indication for which aprotinin was administered
- Characteristics, including risk factors, of the patients who receive aprotinin.
- Conditions of use of aprotinin including data on of heparinisation of patients treated with aprotinin.

Information from the proposed registry will provide a profile over time of aprotinin utilization in participating countries following return to the market.

Call for reporting of adverse reactions with the use of aprotinin

[Insert nationally appropriate NCA ADR reporting information at this point]

Should you have any further questions or require any additional information regarding the use of aprotinin (Trasylol®), please contact:

NORDIC GROUP	
Global Surveillance Patient Safety, GSPS Director EU QPPV	*International Medical Director*
Name: Sylvie Boudeau, M.D.	Name: Fabienne Biville, M.D.
Tel: +33 (0)1 70 37 28 01	Tel: +33 (0)1 70 37 63 92
Mobile: +33 (0)6 85 69 40 09	Mobile: +33 (0)6 89 26 99 04
Fax: +33(0)1 70 37 28 29	Fax: +33(0)1 70 37 16 49
Email: pv@nordicpharma.com	Email: fabienne.biville@nordicpharma.com
Date:	Date:
Signature:	Signature:

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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

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

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

Study title:
Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin

Study reference number:
NG-APRO-PASS-01

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[1]	☒	☐	☐	11
1.1.2 End of data collection[2]	☒	☐	☐	11
1.1.3 Study progress report(s)	☒	☐	☐	11
1.1.4 Interim progress report(s)	☒	☐	☐	11
1.1.5 Registration in the EU PAS register	☒	☐	☐	11
1.1.6 Final report of study results.	☒	☐	☐	11

Comments:

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

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)	☒	☐	☐	12
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	17
4.2.5 Co-morbidity?	☒	☐	☐	17
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)	☒	☐	☐	17

Comments:

The Registry is intended to record all patients exposed to Nordic Aprotinin at cardiac surgery centres (i.e. no limitations in terms of age, sex, indication)

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)	☒	☐	☐	13-14
5.2 Does the protocol discuss the validity of exposure				

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
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:

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?	☒	☐	☐	18-21
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)	☒	☐	☐	18-21

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	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)	☒	☐	☐	18-21
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	18-21

Comments:

E.g. concomitant use of aminoglycoside and renal impairment

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.)	☒	☐	☐	17-21
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.)	☒	☐	☐	17-21
8.1.3 Covariates?	☒	☐	☐	17-21
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)	☒	☐	☐	17-21
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17-21
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17-21

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources **described?** (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21

Comments:
All patients exposed to Nordic Aprotinin are intended to be included

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	22-23
10.2 Is the choice of statistical techniques described?	☒	☐	☐	22
10.3 Are descriptive analyses included?	☒	☐	☐	22
10.4 Are stratified analyses included?	☒	☐	☐	22
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	22-23
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

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?	☒	☐	☐	24
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22
11.3 Are methods of quality assurance described?	☒	☐	☐	24
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	23-24
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	30

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	25-26
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	25-26

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	26-27
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	26-27
13.3 Have data protection requirements been described?	☒	☐	☐	26-27

Comments:

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?	☒	☐	☐	10-11

Comments:

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)?	☒	☐	☐	31
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	31

Comments:

Name of the main author of the protocol: Biville Fabienne

Date: 11/03/2015

Signature: 

Annex 3. ENCePP checklist updated

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:
Non-interventional post-authorisation safety study of pattern of use of Nordic Aprotinin

EU PAS Register® number: ENCEPP/SDPP/11384
Study reference number (if applicable): NG-APRO-PASS-01

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

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

30 Churchill Place ◆ Canary Wharf ◆ London E14 5EU ◆ United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
E-mail: encepp_secretariat@ema.europa.eu Website www.encepp.eu

An agency of the European Union

Comments:

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.3
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Analysis are detailed in a Statistical Analysis Plan (SAP) – See Annex 6

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				9
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

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

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☒	☐	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☒	☐	
	9.1.3 Covariates and other characteristics?	☐	☒	☐	
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11.5

Comments:

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

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.5

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.3

Comments:

Name of the main author of the protocol: Hélène Herman-Demars – Medical Director

Date: 10/OCT/2019

Signature:

Annex 4. Additional information

Adverse Event Report Form

NGR-PV-FRM-000172
Version 3.0 Effective date 24 December 2018

Adverse Event Report - All Products Form

Reserved for Nordic : *Nordic reference :* _____	**Please send this form to :** Global Surveillance Patient Safety, 254 Bd St Germain 75007 Paris, France, E-mail: pv@nordicpharma.com Tel : + 33 (0) 1 70 37 28 01 Fax :+ 33 (0) 1 70 37 28 29

1. Patient Details

Patient Initials	Gender	In case of female patient: is she pregnant?	Height	Weight	Age or date of birth *DD/MM/YYYY*
__/ __	☒Male ☐Female	☐No ☐Unknown ☐Yes, date of last menstrual period: __ /__/ ____	___ cm	___ kg	____years-old __/__/ ____

2. Suspected Nordic Drug:_____ **Batch N°** :_____ **Expiration date** : ___ / ___ / _____

Dose *ex : 2 mg / Kg*	Frequency *ex : twice per day*	Route of administration *ex : oral*	Date of first dose *DD/MM/YYYY*	Date of last treatment given prior to event *DD/MM/YYYY*
			__/__/ ____	__/__/_____
Indication: _____	Does the patient have already been exposed to suspected Nordic drug? ☐**Unknown** ☐ **No** ☐**Yes**			

3. Description of adverse event(s) (AE)

AE and severity grade	Seriousness	Date	Outcome	Action taken with drug	Evolution of AE
AE 1: _____ ☐ Mild ☐ Moderate ☐ Severe	☐ Not serious ☐ Persistent or significant disability / Incapacity ☐ Congenital anomaly / Birth defect ☐ Life threatening ☐ Hospitalisation / prolongation of Hospitalisation[1] ☐ Death[2] ☐ Other medically important condition	Start: __/__/ End: __/__/ ____	☐ Recovered ☐ Recovered with sequelae, specify: _____ ☐ Recovering ☐ Not recovered ☐ Death ☐ Unknown	☐ Withdrawn ☐ Dose reduced ☐ None ☐ Unknown ☐ NA	Recovered after drug withdrawn? ☐ Yes ☐ No ☐ NA Did reaction recur on readministration? ☐ Yes ☐ No ☐ NA
Do you suspect a reasonable possibility of causal relationship between Nordic drug and the occurrence of AE 1? ☐ **Yes**☐ **No** If the patient has already been exposed to the suspected Nordic drug, did the AE 1 already occur? ☐ **Yes**☐ **No**					
AE 2: _____ ☐ Mild ☐ Moderate ☐ Severe	☐ Not serious ☐ Persistent or significant disability / Incapacity ☐ Congenital anomaly / Birth defect ☐ Life threatening ☐ Hospitalisation / prolongation of Hospitalisation[1] ☐ Death[2] ☐ Other medically important condition	Start: __/__/ ____ End: __/__/ ____	☐ Recovered ☐ Recovered with sequelae, specify: _____ ☐ Recovering ☐ Not recovered ☐ Death ☐ Unknown	☐ Withdrawn ☐ Dose reduced ☐ None ☐ Unknown ☐ NA	Recovered after drug withdrawn? ☐ Yes ☐ No ☐ NA Did reaction recur on readministration? ☐ Yes ☐ No ☐ NA
Do you suspect a reasonable possibility of causal relationship between Nordic drug and the occurrence of AE 2? ☐ **Yes**☐ **No** If the patient has already been exposed to the suspected Nordic drug, did the AE 2 already occur? ☐ **Yes**☐ **No**					

1. In case of hospitalisation, please specify admission date __/__/ ____and discharge date __/__/ ____
2. In case of death, please specify the date __/__/ ____ and the cause _____

NB: If more than 2 adverse events occurred, please complete another form.

NGR-PV-FRM-000172
Version 3.0 Effective date 24 December 2018

Adverse Event Report - All Products Form

4. Adverse event(s) description and other relevant information

Give a concise medical chronological description of the event(s) including all relevant symptoms and any other relevant information not captured elsewhere on the form. Attaching the hospitalisation report is generally preferred.

5. Medical history

Description *ex. Any relevant medical history / concurrent conditions tests*	Date of start *DD/MM/YYYY*	Ongoing	Date of end *DD/MM/YYYY*	Comments
	__/__/____	☐Yes ☐No ☐ Unknown	__/__/____	
	__/__/____	☐Yes ☐No ☐ Unknown	__/__/____	
	__/__/____	☐Yes ☐No ☐ Unknown	__/__/____	

6. Laboratory data and clinical test

Test	Date of test *DD/MM/YYYY*	Results	Units	Normal Range
	__/__/____			
	__/__/____			
	__/__/____			

7. Concomitant treatments

Medicinal product name *Name or active substance*	Dose and Frequency	Did you suspect a causal relationship with AE ?	Route of administration *ex : oral*	Date of first dose *DD/MM/YYYY*	Date of last treatment given prior to event *DD/MM/YYYY*	Indication
		☐Yes ☐No ☐ Unknown		__/__/____	__/__/____	
		☐Yes ☐No ☐ Unknown		__/__/____	__/__/____	
		☐Yes ☐No ☐ Unknown		__/__/____	__/__/____	

8. Reporter details

Name and signature	Healthcare professional	Address:	Contact Details
	☐No ☐Yes, specify: _____	Country: _____	Tel: Fax: E-mail:
		Date *DD/MM/YYYY*: __/__/____	Number of pages :

Please attach additional pages if necessary.

Nordic Group uses health data file collected for pharmacovigilance, medical information and post-marketing medicinal products quality purposes. Those data are kept for a compliant period required by law. You have the right to access and correct by contacting us at pv@nordicpharma.com. You can also make a complaint to our Data Protection Officer by email at dataprivacy@nordicpharma.com and to the CNIL (https://www.cnil.fr) in the event of infringement of your rights. For more information visit our Nordic website (http://www.nordicpharma.fr).

Annex 5 - Details of Nordic Aprotinin Restricted distribution

Nordic Aprotinin will be available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry.

In this aim, Nordic (or distributors appointed by Nordic) will establish for each European country where Nordic Aprotinin has a valid Marketing Authorisation, a list of qualified hospitals which can order and receive Nordic Aprotinin.

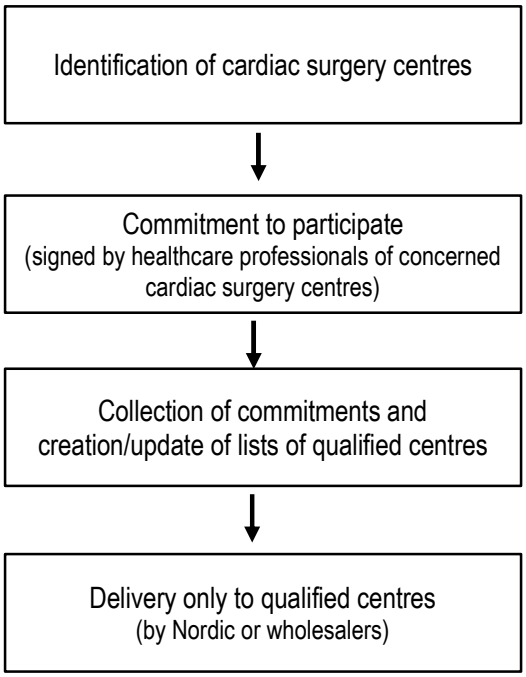
A hospital will be qualified when the following items are fulfilled:

1. The hospital has a cardiac surgery ward, which performs surgery on cardio-pulmonary bypass
2. One or several healthcare professionals of the cardiac surgery ward signed a commitment to fulfil the Aprotinin Patient Registry.

Nordic will make sure that Nordic Aprotinin is delivered only to qualified hospitals.

Controls of deliveries shall be organised regularly and potential corrective actions organised accordingly.

The process is summarized in the flowchart:



Centres identification: Nordic or distributor employees will confirm with healthcare providers that cardio-pulmonary bypass is used in the concerned cardiac surgery centres.

Commitment to participate: Nordic will train end-users of the Aprotinin Patient Registry (healthcare professionals working in cardiac surgery centres) and will ask them to sign a commitment to

participate to the Registry (at least one per cardiac surgery centre). Commitments will be collected at national level to create and to update national lists of participating centres.

Qualified centres: A centre will be qualified when (i) identified by Nordic affiliates / Distributors and (ii) has at least one signed commitment.

Delivery: Nordic will supply Nordic Aprotinin only to hospitals qualified in the list. In case Nordic delivers to wholesalers, Nordic will make sure that the wholesalers will deliver the qualified hospitals.

This process is part of the RMP (approved following worksharing procedure NL/H/9007/WS/088) and described in the “Annex 10 - Details of proposed additional risk minimisation measures” of the RMP

Annex 6 – Statistical Analysis Plan