NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
VERSION NUMBER:	4.0
EU PAS REGISTER NUMBER	EUPAS23177
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
AUTHOR:	[redacted] *Principal Data Scientist, PDD Real World Data Science* *F. Hoffmann - La Roche Ltd, Basel, Switzerland* [redacted]
DATE FINAL:	See electronic stamp below
ACTIVE SUBSTANCE:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
PRODUCT REFERENCE NUMBER:	EMEA/H/C/004406
PROCEDURE NUMBER:	Not applicable
JOINT PASS	No

Date and Time (UTC)	Title	Approver's Name
20-Dec-2023 10:48:04	Deputy EU QPPV	[redacted]
20-Dec-2023 16:31:11	Company Signatory	PROTOCOL AMENDMENT APPR [redacted]

RESEARCH QUESTION AND OBJECTIVES:	The main goal of this study is to assess the incidence of thromboembolism (TE), thrombotic microangiopathy (TMA), and anaphylaxis in real-world conditions, in patients exposed to emicizumab and treated at centers participating to the European Haemophilia Safety Surveillance System (EUHASS) registry. The primary objective for this study is as follows: • To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without replacement factor products The secondary objectives for this study are as follows: • To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: activated prothrombin complex concentrate (aPCC), recombinant activated factor VII (rFVIIa), and factor VIII (FVIII) products • To describe individual cases of TE and TMA • To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab • To describe individual cases of "unexpected poor efficacy" reported to EUHASS based on the available information
COUNTRIES OF STUDY POPULATION:	Countries with hemophilia centers participating in the EUHASS registry: Austria, Belgium, Bulgaria, *Croatia*, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, *Hungary*, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, *Norway*, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and United Kingdom
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barrell-Strasse 1 79639 Grenzach-Wyhlen Germany

MAH CONTACT PERSON:	[redacted] *c/o Roche Registration GmbH* *Emil-Barell-Strasse 1* *79639 Grenzach-Wyhlen* *Germany*

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol GO40162 has been amended to extend the study to include data collected up to 31 December 2024.

In addition, the list of countries with hemophilia centers participating in the EUHASS has been updated as of November 2023.

Finally, further clarification on the study population has been added. Depending on the local approval/reimbursement decisions in the participating countries, the study population may include patients with any level of disease severity without FVIII inhibitors (including mild and moderate HA without FVIII inhibitors).

Additional minor changes have been made to improve clarity and consistency.

Substantive new information appears in italics.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
aPCC	activated prothrombin complex concentrate
EAHAD	European Association for Haemophilia and Allied Disorders
EMA	European Medicines Agency
EUHASS	European Haemophilia Safety Surveillance System
FVIII	factor VIII
FFP	fresh frozen plasma
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation
IgG4	immunoglobulin G4
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
MA	market authorization
MAH	Marketing Authorization Holder
NI-PASS	non-interventional post-authorization safety study
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report
PSUR	periodic safety update report
PT	Preferred Term
rFVIIa	recombinant activated factor VII
TE	thrombotic event
TMA	thrombotic microangiopathy

2. RESPONSIBLE PARTIES

Protocol Development Responsible

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Principal Data Scientist, PDD Real World Data Science

F. Hoffmann - La Roche Ltd, Basel, Switzerland

[redacted]

Scientific Responsible

[redacted], Principal Data Scientist, PDD Real World Data Science

F. Hoffmann - La Roche Ltd, Basel, Switzerland

Complementary information is given in the appendices.

3. ABSTRACT/SYNOPSIS

TITLE:	**SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
DATE OF SYNOPSIS:	13 December 2023
EU PAS REGISTER NUMBER:	EUPAS23177
STUDIED MEDICINAL PRODUCT:	Emicizumab
SCIENTIFIC RESPONSIBLE	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Hemophilia A
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barrell-Strasse 1 79639 Grenzach-Wyhlen Germany

RATIONALE AND BACKGROUND

Emicizumab (also known as Hemlibra®, ACE910, and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody being developed for the treatment of patients with hemophilia A.

Emicizumab was first granted marketing approval in the United States (US) on 16 November 2017. Subsequently, it was first approved in the European Union (EU) on 23 February 2018 and in Japan on 23 March 2018 for patients with congenital hemophilia A with FVIII inhibitors. Over 25,000 patients have received emicizumab through clinical trials and post-authorisation to date.

As of October 2023, emicizumab is approved in approximately 119 countries worldwide in patients with hemophilia A with FVIII inhibitors and is approved in approximately 107 countries worldwide for the expanded indication to include patients with hemophilia A without FVIII inhibitors, including approval in the US, Japan, and the EU.

Two important risks have been identified with the concomitant use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: thromboembolic events (TE) and thrombotic microangiopathy (TMA). In addition, anaphylaxis, anaphylactoid, or systemic hypersensitivity reactions were considered as potential safety risks based on the class of biological drugs.

In order to better assess the incidence of TE, TMA, and anaphylaxis, the Sponsor will use information collected by the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program. EUHASS will provide the Sponsor with an emicizumab-specific annual report, the findings of which will be used to calculate the incidence of the TE, TMA, and anaphylaxis in the real-world setting.

RESEARCH QUESTION AND OBJECTIVES

The main goal of this study is to assess the incidence of TE, TMA, and anaphylaxis under real-world conditions in patients exposed to emicizumab.

OBJECTIVES

The primary objective for this study is as follows:

- To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products

The secondary objectives for this study are as follows:

- To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: aPCC, recombinant factor VII activate (rFVIIa), and FVIII product
- To describe individual cases of TE and TMA identified in EUHASS
- To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab
- To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information

STUDY DESIGN

This is a cohort surveillance study based on data provided in the EUHASS emicizumab-specific annual report.

The EUHASS is an adverse event (AE) reporting system for Europe dedicated to monitoring the safety of treatments for people with inherited bleeding disorders led by European Association for Haemophilia and Allied Disorders (EAHAD) and coordinated by Prof. Dr. [redacted].

There are four associate partners:

- European Hemophilia Consortium
- EAHAD
- University Medical College Utrecht
- Medical Data Solutions and Services Ltd.

Hemophilia centers participating in the registry provide information on patients who experience certain adverse events, including but not limited to thrombosis events and allergic and other acute reactions. Other adverse events collected are: transfusion transmitted infections, new inhibitors, new malignancy, death, unexpected poor efficacy, and other adverse events possibly related to concentrate. For each type of adverse

event, the subtype is specified (e.g., TMA will be collected under the 'thrombosis' category, while anaphylaxis is collected under 'allergic and other acute reactions' category). Following an event report, the center will complete additional information about the patient. Participating centers provide information on adverse events quarterly by completing a Web-based adverse event reporting form and also have the option of reporting the event at the time of the occurrence.

Annually, centers participating in the EUHASS program also provide information on the number of patients with bleeding disorders treated with each type of product, allowing for calculation of incidence of each adverse event collected across the entire registry by product. In addition, EUHASS will also collect aggregate information on the number of patients who use, in the same year, emicizumab and aPCC, emicizumab and rFVIIa, and emicizumab and FVIII, thus allowing for calculation of annual incidence of TE and TMA among patients exposed to emicizumab concomitantly with each of these drugs.

DESCRIPTION OF STUDY

Based on information collected from the participating centers, **EUHASS will generate emicizumab-specific annual reports** starting with the year of the market authorization (MA) for emicizumab by the EC, indicating the number of patients who receive emicizumab, listings of patients exposed to emicizumab who develop each type of adverse event, as well as limited additional information related to the occurrence of each adverse event, as described above for thrombotic events and allergic or other acute reactions. Based on these, the **Sponsor will generate annual post-authorization safety study (PASS) reports**, presenting the following:

- Number of patients exposed to emicizumab (directly from EUHASS report)
- Number of patients exposed to emicizumab who experienced TE, TMA, and anaphylaxis (directly from EUHASS report)
- Proportion of patients who experienced TE, TMA, anaphylaxis among patients receiving emicizumab (calculated based on information from EUHASS report if relevant)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, and FVIII (directly from EUHASS report)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, and FVIII who experienced TE and TMA (directly from EUHASS report)
- Proportion of TE and of TMA among patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, FVIII (calculated based on information from EUHASS report if relevant).

Descriptions of the individual cases of TE, TMA, and anaphylaxis in patients treated with emicizumab will also be generated based on the information provided by EUHASS. The frequency of other adverse events and other reported events collected by EUHASS will be reported in patients exposed to emicizumab. Descriptions of the individual cases of unexpected poor efficacy will also be presented based on the information reported by

the centers to the registry and to the extent that EUHASS can share this individual-level information with the Marketing Authorization Holder (MAH).

POPULATION

The study population will consist of patients with Hemophilia A treated with emicizumab at centers participating in the EUHASS registry. *Depending on the local approval/reimbursement decisions in the participating countries, the study population may include patients with any level of disease severity without FVIII inhibitors.*

VARIABLES

The following variables will be obtained from the EUHASS emicizumab-specific annual reports. All variables are captured using information from standard patient management. No additional evaluations are done as a consequence of participation to the EUHASS registry or as a consequence of this study.

PRIMARY SAFETY VARIABLES

The primary variables for this study are as follows:

- TEs
- TMA events
- Anaphylaxis events
- Exposure to emicizumab

SECONDARY VARIABLES

The secondary variables for this study are as follows:

- Transfusion transmitted infections
- New inhibitors (antibodies against the coagulation factor)
- Allergic and other acute reactions, with the exception of anaphylaxis
- New malignancy diagnosis
- Death
- Unexpected poor efficacy
- Other adverse events possibly related to concentrate
- Exposure to emicizumab, without replacement factor products in the same calendar year
- Exposure to both aPCC and emicizumab in the same calendar year
- Exposure to both rFVIIa and emicizumab in the same calendar year
- Exposure to both FVIII and emicizumab in the same calendar year

DATA SOURCES

Emicizumab-specific annual reports produced by EUHASS.

STUDY SIZE

The sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the EUHASS registry. As per last data available at the time of this protocol amendment (1 January 2021- 31 December 2021), 1,319 patients were treated with emicizumab alone, 71 patients were treated with emicizumab and NovoSeven, 490 patients were treated with emicizumab and other FVIII (other than Obizur), and 3 patients were treated with emicizumab and factor eight inhibitor bypassing activity (FEIBA).

DATA ANALYSIS

Data generated within the first 7 calendar years post-marketing authorization (2018–2024) are analyzed annually. Proportions of each adverse event, along with corresponding 95% confidence intervals, may be calculated annually for all patients exposed to emicizumab if relevant. In addition, the proportion of TE and TMA may be calculated annually for patients exposed to emicizumab and each of the following agents: aPCC, rFVII, and FVIII if relevant.

MILESTONES

Start Date of Study

The study start date will be the date of the first data extraction by EUHASS (January 2019).

End of Study

The end of the study is the date when the final (seventh) analytic dataset is available to Roche, which corresponds to the seventh emicizumab-specific annual report provided by EUHASS (expected February 2026; see Table 2).

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: See table below.

Amendment/ *Version* Number	Date	Section of Study Protocol	Amendment or Update	Reason
3	*8 February 2019*	7 and 8	Added one secondary objective on "unexpected poor efficacy"	To reflect what is captured by EUHASS
2	*7* September 2018	3 and 6	Updated information regarding marketing authorization in the European Union	to reflect latest status
2	*7* September 2018	8.3.1 and 10	Listing of AEs reported by EUHASS with the corresponding MedDRA attribution will be provided	for clarification

2	7 September 2018	8.8	Data quality assurance procedures	for clarification

AE = adverse event; EUHASS = European Haemophilia Safety Surveillance System.

5. MILESTONES

Table 1 Milestones

Milestone	Planned Date
Registration of protocol in the EU PAS register	23 March 2018
Start of study dataset creation	January 2019 (first data extraction by EUHASS)
End of study	Anticipated February 2026 (last analytic dataset available)
Study progress report	NA
PASS Interim report	June, annually between 2020 and *2025*[a]
Final report of study results (CSR)	June *2026* [a]
Registration of the results in the EU PAS register	After study completion

CSR = clinical study report; EC = European Commission; EMA = European Medicines Agency; EU PAS = European Union Post-Authorization Studies; MA = market authorization; NA = not applicable; PASS = post-authorization safety study; PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report.

[a] The Sponsor will receive emicizumab-annual reports generated by EUHASS 12–14 months following the end of each calendar year (e.g., 2018 annual report will be received in December 2019–February 2020). Based on this, each PASS interim report will be produced within 4 months and incorporated in the next PBRER/PSUR submission to EMA. The final report (CSR) is anticipated to be available 16–20 months following end of study.

Table 2 Detailed Milestones for Each Study Year

	Data Collection	Start Data Extraction by EUHASS	EUHASS Report to Roche	PASS Report Available
Year 1	April 2018–December 2018	January 2019 (study start)	February 2020	June 2020
Year 2	January–December 2019	January 2020	February 2021	June 2021
Year 3	January–December 2020	January 2021	February 2022	June 2022
Year 4	January–December 2021	January 2022	February 2023	June 2023
Year 5	January–December 2022	January 2023	February 2024	June 2024
Year 6	*January–December 2023*	*January 2024*	*February 2025*	*June 2025*
Year 7	*January–December 2024*	*January 2025*	*February 2026 (analytic dataset final, available to Roche = end of study)*	*June 2026 (final CSR)*

CSR = clinical study report; EUHASS = European Haemophilia Safety Surveillance System; PASS = post-authorization safety study.

6. RATIONALE AND BACKGROUND

Emicizumab (also known as Hemlibra®, ACE910, and RO5534262) is a humanized monoclonal modified IgG4 antibody that bridges activated factor IX and factor X to restore the function of missing activated FVIII needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors. Emicizumab is being developed for the treatment of patients with hemophilia A.

Emicizumab was first granted marketing approval in the United States (US) on 16 November 2017. Subsequently, it was first approved in the European Union (EU) on 23 February 2018 and in Japan on 23 March 2018 for patients with congenital hemophilia A with FVIII inhibitors. Over 25,000 patients have received emicizumab through clinical trials and post-authorisation to date.

As of October 2023, emicizumab is approved in approximately 119 countries worldwide in patients with hemophilia A with FVIII inhibitors and is approved in approximately 107 countries worldwide for the expanded indication to include patients with hemophilia A without FVIII inhibitors, including approval in the US, Japan, and the EU. In the EU, this last indication was restricted to patients with severe disease.

On 23 January 2023, the European Commission decided for expansion of the indication for Hemlibra to include routine prophylaxis of bleeding episodes in patients with congenital HA without FVIII inhibitors who have moderate disease (1% ≤ FVIII ≤ 5%) with severe bleeding phenotype.

Two important risks have been identified with the use of aPCC in patients treated with emicizumab prophylaxis: TE and TMA. One patient developed an anti-drug antibody (ADA) to emicizumab with neutralizing potential that led to loss of clinical efficacy and subsequent resumption on prior therapy without any untoward events. In addition, anaphylaxis, anaphylactoid, or systemic hypersensitivity reactions were considered as potential safety risks based on the class of biological drugs.

In order to better assess the incidence of TE, TMA, and anaphylaxis, the Sponsor will use information collected by the EUHASS pharmacovigilance program. EUHASS will provide the Sponsor with an emicizumab-specific annual report whose findings will be used to calculate the incidence of the TE, TMA, and anaphylaxis.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The main goal of this study is to assess the incidence of TE, TMA, and anaphylaxis under real-world conditions in patients exposed to emicizumab.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products

The secondary objectives for this study are as follows:

- To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and concomitantly with each of the following drugs: aPCC, rFVIIa, and FVIII product
- To describe individual cases of TE and TMA based on available information
- To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab
- To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information

8. RESEARCH METHODS

8.1 STUDY DESIGN

This is a cohort surveillance study based on data provided in the EUHASS emicizumab-specific annual report.

EUHASS is a pharmacovigilance program dedicated to monitoring the safety of treatments in people with inherited bleeding disorders across Europe. Participating centers provide information on patients who experience certain adverse events, including but not limited to thrombosis and allergic and other acute reactions. Other adverse events collected are: transfusion transmitted infections, new inhibitors, new malignancy, death, unexpected poor efficacy, and other adverse events possibly related to concentrate. For each type of adverse event, the subtype is specified according to a pre-specified list (e.g., TMA will be collected under the 'thrombosis' category, while anaphylaxis is collected under 'allergic and other acute reactions' category). For all patients who experience reported adverse events, centers are asked to collect selected demographic and disease-related information (i.e., age, gender, diagnosis, factor level, event date). Additionally, specific information is requested for each type of adverse event. This information includes:

- In the case of a thrombotic event: nature of thrombotic event, concentrate administered in the 30 days prior to the event (Y/N), prophylactic treatment (Y/N), time from last dose and event onset, all the concentrate products infused in the last 3 months prior to event, additional blood products used (blood, fresh frozen plasma [FFP], cryoprecipitate) thrombosis associated with central venous catheter (Y/N) and catheter type, surgery in the last 3 months (Y/N), type of surgery, thromboprophylaxis treatment associated with surgery (Y/N), risk factors for thrombosis.
- In the case of allergic or other acute reactions: type of acute event (including anaphylaxis), product infused, other blood products, time from infusion to event onset, lifetime exposure days, history of the same event, outcome, relationship between concentrate and event (in physician's opinion).

Participating centers are asked to provide information on the adverse events quarterly by completing a Web-based adverse event reporting form and have the option of reporting an event at the time of its occurrence. Annually, centers also provide information on the number of patients treated with each type of coagulation product, allowing for calculation of annual incidence rates of each adverse event collected across the entire registry by product. In addition, EUHASS will also collect aggregate information on the number of patients who use emicizumab and aPCC, emicizumab and rFVIIa, and emicizumab and FVIII, thus allowing for calculation of incidence rates of TE and TMA among patients exposed to emicizumab concomitantly with each of these drugs.

Based on information collected from the participating centers, **EUHASS generates emicizumab-specific annual reports** indicating the number of patients who receive

emicizumab, listings of patients exposed to emicizumab who develop each type of adverse event, as well as limited additional information related to the occurrence of each adverse event, as described above for thrombotic events and allergic or other acute reactions. Based on these, the **Marketing Authorization Holder generates annual PASS reports**, presenting the following:

- Number of patients exposed to emicizumab (directly from EUHASS report)
- Number of patients exposed to emicizumab who experienced TE, TMA, and anaphylaxis (directly from EUHASS report)
- Proportion of each adverse event among patients receiving emicizumab (calculated based on information from EUHASS report if relevant)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, FVIII (directly from EUHASS report)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, FVIII, who experienced TE and TMA (directly from EUHASS report)
- Proportion of TE and of TMA among patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, and FVIII (calculated based on information from EUHASS report if relevant)

Descriptions of the TE, TMA, and anaphylaxis cases in patients treated with emicizumab are also generated based on the information provided by EUHASS. The frequency of other adverse events and other reported events collected by EUHASS (transfusion transmitted infections, new inhibitors [defined as antibodies against coagulation factors], new malignancy, death, allergic and other acute reactions except anaphylaxis, unexpected poor efficacy, other adverse events possibly related to concentrate) are reported in patients exposed to emicizumab. Descriptions of the individual cases of unexpected poor efficacy will also be presented based on the information reported by the centers to the registry and to the extent that EUHASS can share this individual-level information with the Marketing Authorization Holder (MAH).

Population

The study population consists of patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS registry. *Depending on the local approval/reimbursement decisions in the participating countries, the study population may include patients with any level of disease severity and without FVIII inhibitors.*

Start Date of Study:

The study start date was the date of the first data extraction by EUHASS (January 2019).

Data collection in the EUHASS registry has been ongoing since 2008; however, only information collected starting at the time of emicizumab MA by the EC is included in the study.

End of Study:
The end of the study is the date when the final (seventh) analytic dataset is made available to Roche, which corresponds to the seventh emicizumab-specific annual report provided by EUHASS (expected February 2026).

8.2 SETTING

EUHASS is a pharmacovigilance program dedicated to monitoring the safety of treatments for people with inherited bleeding disorders in Europe. It is investigator-led, coordinated by the University of Sheffield, and its activities are overseen by an independent Steering Committee. The 96 participating centers in 30 countries report information on all the patients they treat, thus preventing selection bias. Since its initiation in 2008, EUHASS has been used by pharmaceutical companies to conduct post-approval authorization studies.

8.3 VARIABLES

Variables are captured using information from standard patient management. No additional evaluations are done as a consequence of participation in the EUHASS registry or as a consequence of this study.

8.3.1 Primary Safety Variables

The primary variables for this study are as follows:

- TEs
- TMA events
- Anaphylaxis events
- Exposure to emicizumab

Adverse events collected in EUHASS are not collected according to MedDRA Classification. Most events are collected according to pre-specified lists; however, free-text fields are also available for each event. For the purpose of this protocol, whenever possible the adverse events are coded by Roche according to MedDRA Preferred Term (PT) level using the most current MedDRA version. A listing of the events reported by EUHASS with the corresponding MedDRA attribution assigned will be provided.

8.3.2 Secondary Variables

The secondary variables for this study are as follows:

- Transfusion transmitted infections
- New inhibitors (antibodies against the coagulation factor)
- Allergic and other acute reactions, with the exception of anaphylaxis
- New malignancy diagnosis
- Death

- Unexpected poor efficacy
- Other adverse events possibly related to concentrate
- Exposure to emicizumab, without replacement factor products in the same calendar year
- Exposure to both aPCC and emicizumab in the same calendar year
- Exposure to both rFVIIa and emicizumab in the same calendar year
- Exposure to both FVIII and emicizumab in the same calendar year

8.4 DATA SOURCE(S)

Data collection through the EUHASS system is described in detail in the EUHASS Working Protocol (see Appendix 1) and Data Entry Site User Manual (see Appendix 2). Briefly, the reporting is done electronically through a Web-based system. Participating centers are asked to provide information on selected adverse events quarterly by completing a Web-based adverse event reporting form and also have the option of reporting an event at the time of its occurrence. If they report occurrence of an event, additional questions are asked as described in Section 7.1.

In addition, centers also provide annual information on the number of patients treated with each type of coagulation product allowing for calculation of incidence proportion of each adverse event collected across the entire registry by product. Additionally, EUHASS will also collect aggregate information on the number of patients who use emicizumab and aPCC, emicizumab and rFVIIa, and emicizumab and FVIII, thus allowing for calculation of incidence rates of TE and TMA among patients exposed to emicizumab concomitantly with each of these drugs.

8.5 STUDY SIZE

The sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the EUHASS registry. As per last data available at the time of this protocol amendment (1 January 2021- 31 December 2021), 1,319 patients were treated with emicizumab alone, 71 patients were treated with emicizumab and NovoSeven, 490 patients were treated with emicizumab and other FVIII (other than Obizur), and 3 patients were treated with emicizumab and Factor Eight inhibitor bypassing activity (FEIBA).

Table 3 provides exact incidence proportions and 95% confidence intervals that apply to each of the primary safety variables (TMA, TE, anaphylaxis), for a range of numbers of events observed.

Table 3 Incidence Proportions and Corresponding 95% CIs for Each Primary Safety Variable Based on 680 Patients Receiving Emicizumab, Assuming Different Numbers of Events

Number of Patients with at least One Adverse Event Observed	Corresponding Proportion (95% Two-Sided CI Exact Binomial)
0	0% (0% – 0.05%)
1	0.15% (0%; 0.82%)
5	0.74% (0.24%; 1.71%)
10	1.5% (0.71%; 2.69%)
20	2.9% (1.81%; 4.51%)
50	7.3% (5.51%; 9.58%)

8.6 DATA MANAGEMENT

Treating centers transmit information regarding observed adverse events via the EUHASS website. Data is anonymized using a Soundex coding system derived by the reporting center; it is not possible to identify the patient from the information transmitted to EUHASS. No data audit is performed at the centers.

Individual level data related to adverse events are processed, analyzed, and summarized by EUHASS. Roche, as the MAH, receives the aggregate information in the form of annual emicizumab-specific annual reports. These annual reports may include selected information on individual adverse events. No other patient-level data are received by the MAH.

8.7 DATA ANALYSIS

Descriptive statistics on endpoints, including number and percentage of patients, will be provided. Continuous variables will be summarized by mean, median, minimum, maximum, and IQR. Categorical variables will be summarized by counts, percentages, and corresponding 95% CIs. Data generated within the first 7 calendar years post-marketing authorization (2018–2024) are analyzed annually. Proportions of each adverse event, along with corresponding 95% CIs, may be calculated annually for all patients exposed to emicizumab if relevant. In addition, proportion of TE and TMA may be calculated annually for patients exposed to emicizumab and each of the following agents: aPCC, rFVII, and FVIII if relevant.

8.7.1 Analyses Timelines

Emicizumab-specific annual reports are expected to be received from EUHASS 12–14 months following the end of each calendar year (e.g., 2018 report is expected between December 2019 and February 2020). Based on this, the Sponsor will analyze the data according to this protocol within 4 months. The results of the analyses will be

provided to European Medicines Agency (EMA) via the next periodic safety update report (PSUR)/periodic benefit-risk evaluation report (PBRER).

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol and protocol amendments. EUHASS standard operating procedures, internal policies and process guidance, and/or routine guidance will be used for data collection, which is performed independent of the MAH and this PASS. These procedures may include, among others, rules for data storage, methods to maintain and archive study documents, and quality-control procedures. Although EUHASS follows up and confirms the accuracy of each adverse event reported, no systematic site audits are performed. EUHASS is responsible (outside of this study) to obtain and maintain Informed Consent Forms (if applicable) and documentation of Institutional Review Board (IRB)/Ethics Committee from the participating centers.

Retention of Records

Records and documents pertaining to the conduct of this study at the MAH must be retained for at least 15 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

8.9 LIMITATIONS OF RESEARCH METHODS

Participating centers report to EUHASS information on adverse events and aggregate data on the number of patients receiving each hemostatic drug. Although EUHASS follows up and confirms the accuracy of each adverse event reported, no systematic site audit is performed to confirm the accuracy and completeness of the information recorded.

Centers provide information on the number of patients who receive, during the same calendar year, emicizumab alone and with each of the following drugs: aPCC, rFVIIa, and FVIII. This information is used to calculate, as part of the secondary objective, the annual incidence of TE and TMA among patients who receive emicizumab and one of these drugs. However, it is not possible to know with certainty if the co-administration of the drugs was sequential (patients switched from a different drug to emicizumab) or concomitant (e.g., patients treated with emicizumab prophylaxis received another drug to treat a breakthrough bleed or peri-operatively). The proposed analysis assumes that the administration is concomitant, and therefore it is the most conservative approach as it may overestimate the annual incidence of TE and TMA in patients receiving emicizumab with a coagulation factor product and may underestimate the annual incidence of TE and TME in patients receiving emicizumab alone.

EUHASS is set up as a pharmacovigilance reporting system, rather than a research study, and patient informed consent is only obtained in selected centers where this is

required by the local Ethics Committee. Therefore, in the case of adverse event reporting, EUHASS does not have the ability to systematically collect additional and follow-up information that may be valuable to understand the context in which the adverse event occurred and the outcomes of these events.

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

Each individual center participating in the EUHASS Registry determines if patient informed consent is required, according to the local Ethics Committee opinion. A generic patient information sheet and consent form provided by EUHASS are in Appendix 1 (see Appendix 4 of the EUHASS Working Protocol).

Centers may not submit event data to EUHASS until the opinion of their local ethics or institutional review board is known and its approval obtained, if required.

Information on patients who experience adverse events is reported anonymously on the EUHASS website, using a coding system derived by the reporting center. It is not possible to identify the patient from the details transmitted to the EUHASS project.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety study (NI-PASS).

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Participating centers must find out if a formal application for approval to submit data to EUHASS is required. Each center must notify the Steering Committee of the outcome of their enquiry and progress with obtaining approval is recorded via SharePoint on the EUHASS website. The decision on whether patient consent is sought is the responsibility of individual centers and depends on their ethics committee's opinion.

Centers may not submit events data to EUHASS until the opinion of their local ethics committee or institutional review board is known and its approval obtained, if required.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a NI-PASS involving the use of secondary data. As per the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI–Management and reporting of

adverse reactions to medicinal products, the reporting of adverse reactions in the form of individual case safety reports (ICSRs) is not required (GVP VI.C.1.2.1.b). Information received from EUHASS on all the pre-specified adverse events will be included in the study interim and final reports.

It is assumed that safety reporting of data that are going to be extracted/analyzed as part of this study have been appropriately performed and documented at the time these data are collected through primary data collection mechanism.

Adverse events collected in EUHASS are not collected according to MedDRA classification. Most events are collected according to pre-specified lists; however, free-text fields are also available for each event. To the possible extent, adverse events will be coded by Roche according to MedDRA PT level using the most current MedDRA version.

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses and in the final study report and final publication. A listing of the events reported by EUHASS with the corresponding MedDRA attribution assigned will be provided.

As per protocol, these aggregate summaries may include the following adverse event types:

- Serious adverse events, including all deaths
- Non-serious adverse events
- Reports of lack of efficacy
- Drug interactions

10.1 ADVERSE EVENTS

According to the International Conference of Harmonisation (ICH), an adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.2 SERIOUS ADVERSE EVENTS

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are <u>not</u> synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

11. <u>PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS</u>

Regardless of the outcome of NI-PASS, the MAH is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

The results of the study will be provided to the EMA on an annual basis, as part of the PSUR/PBRER reporting.

Appendix 1
EUHASS Working Protocol

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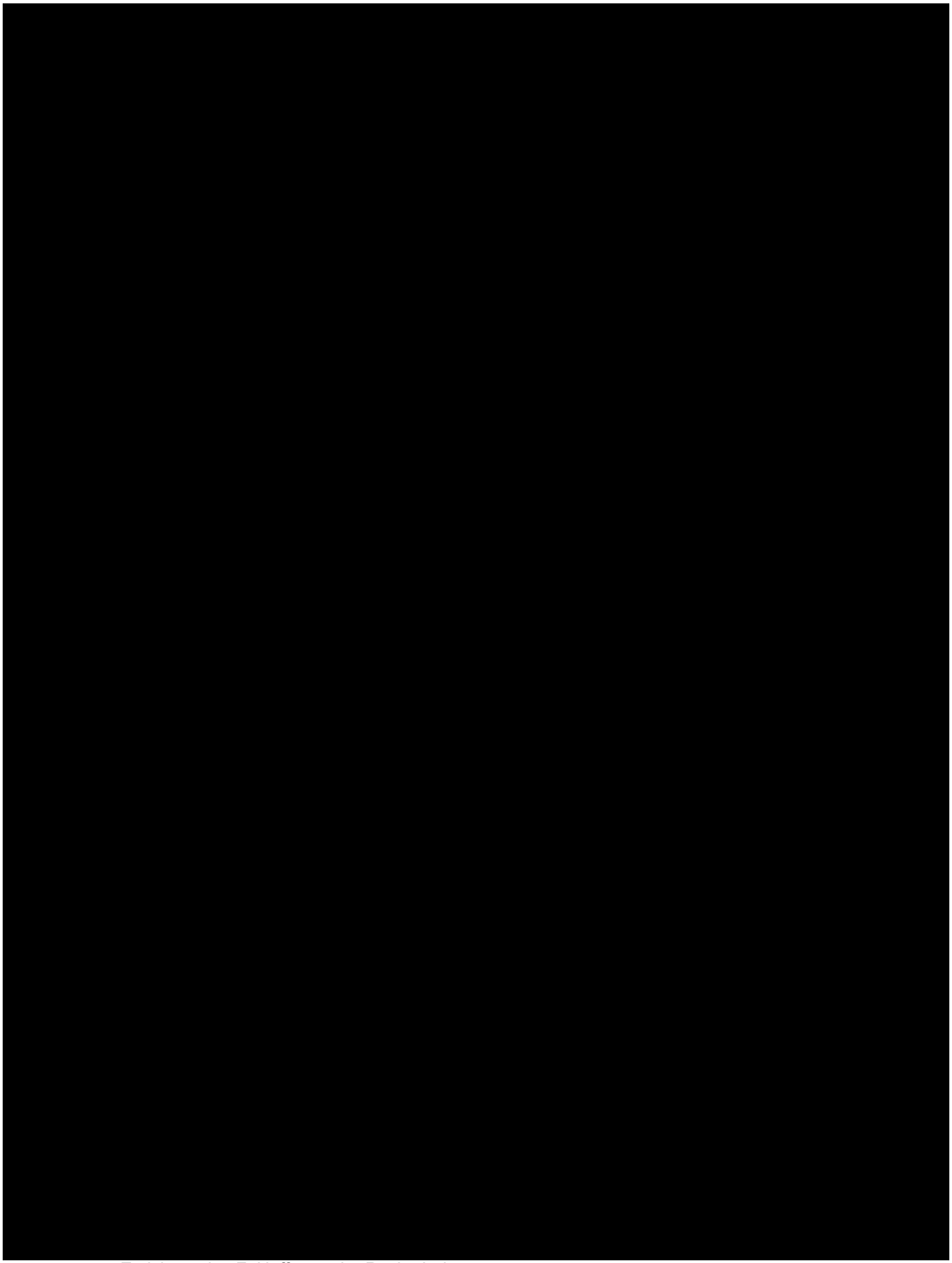

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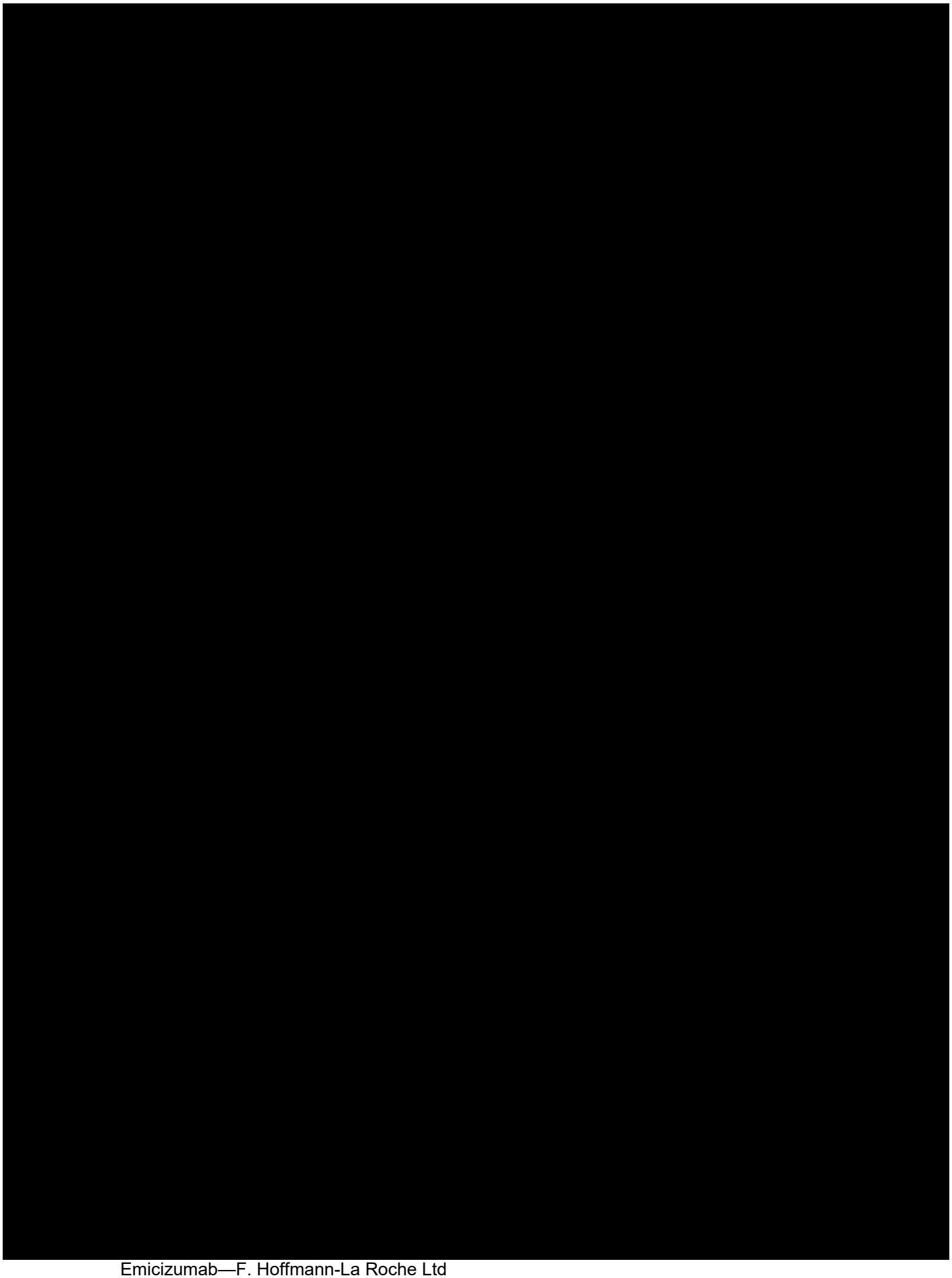

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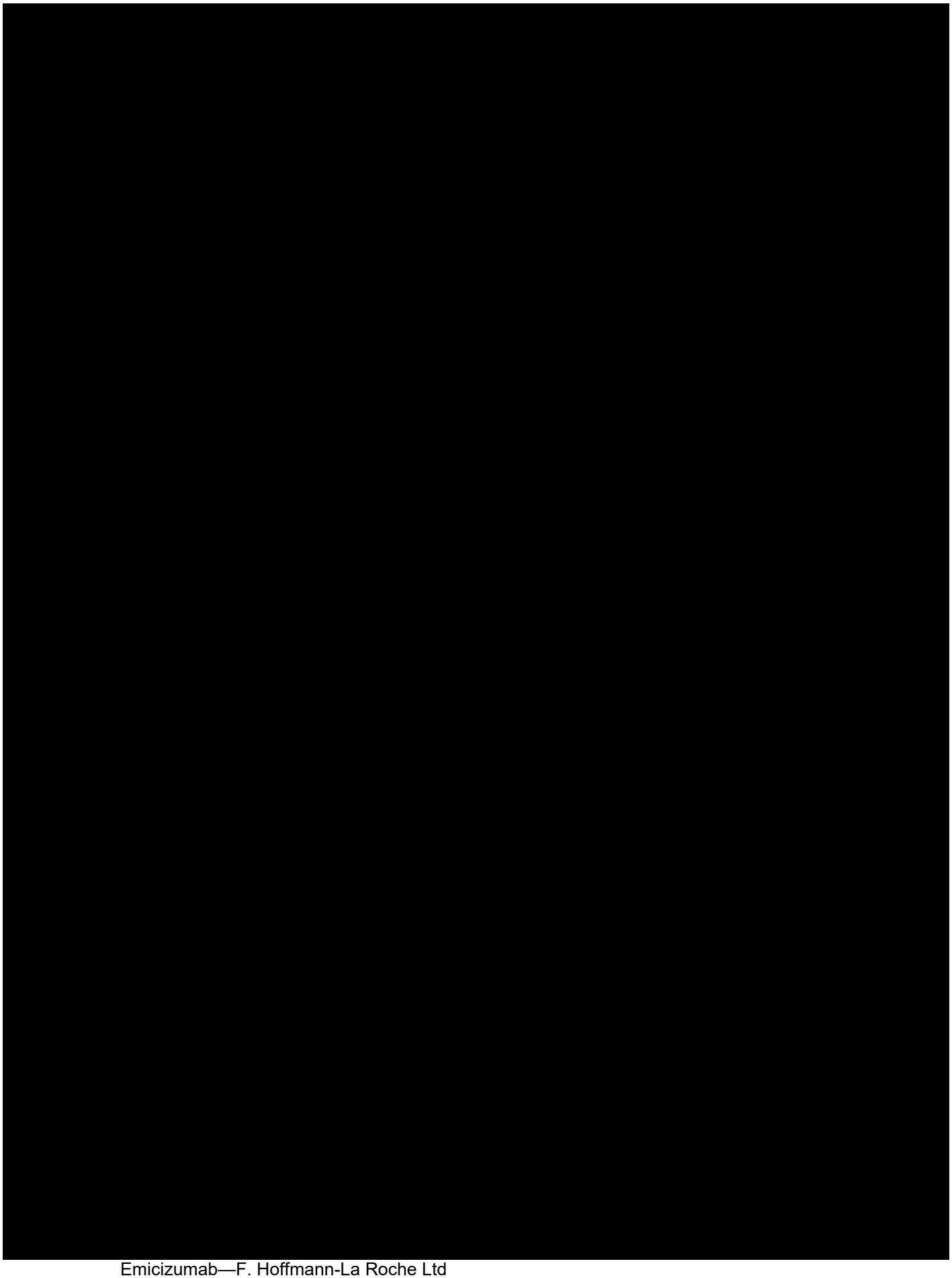

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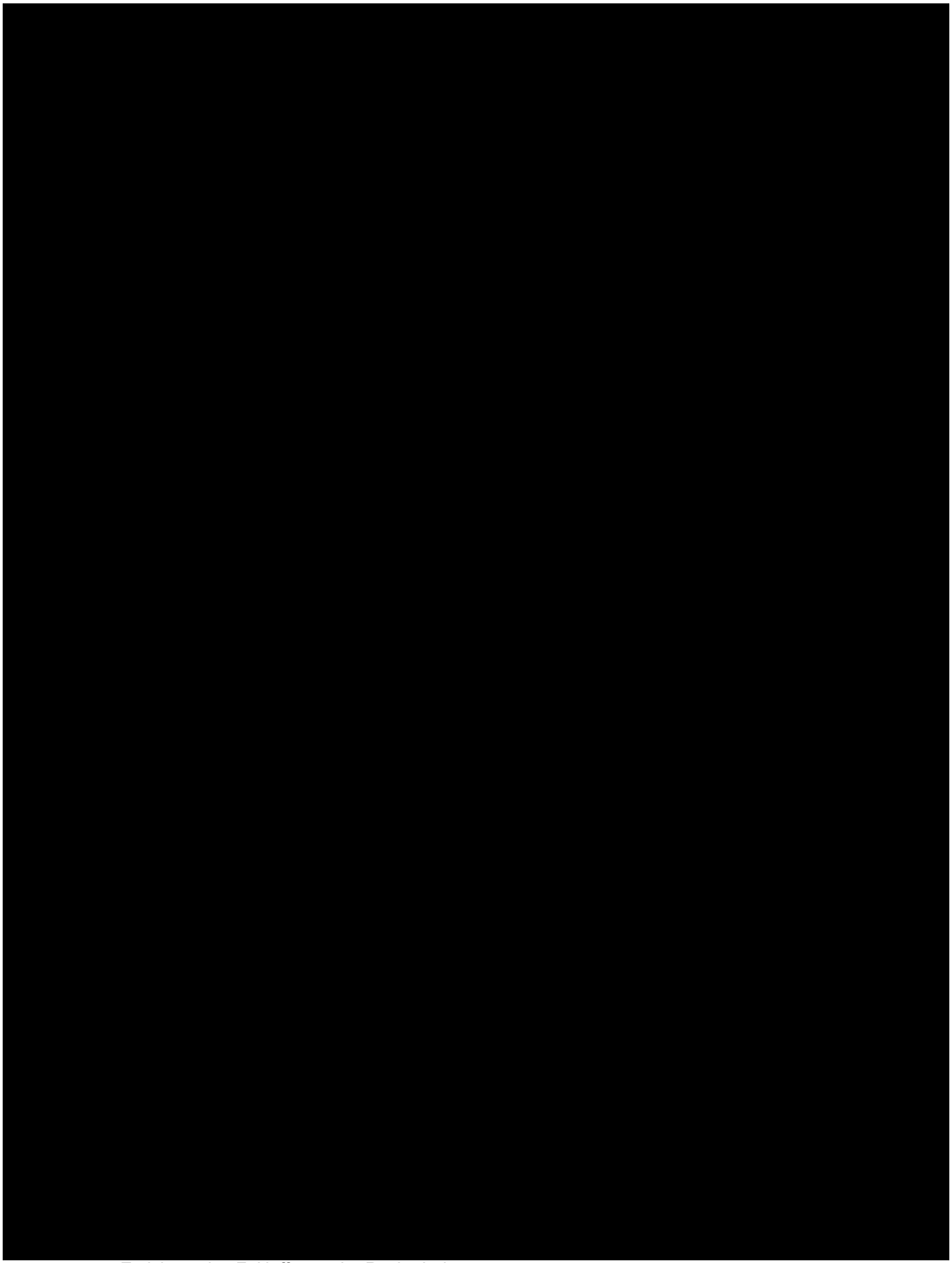

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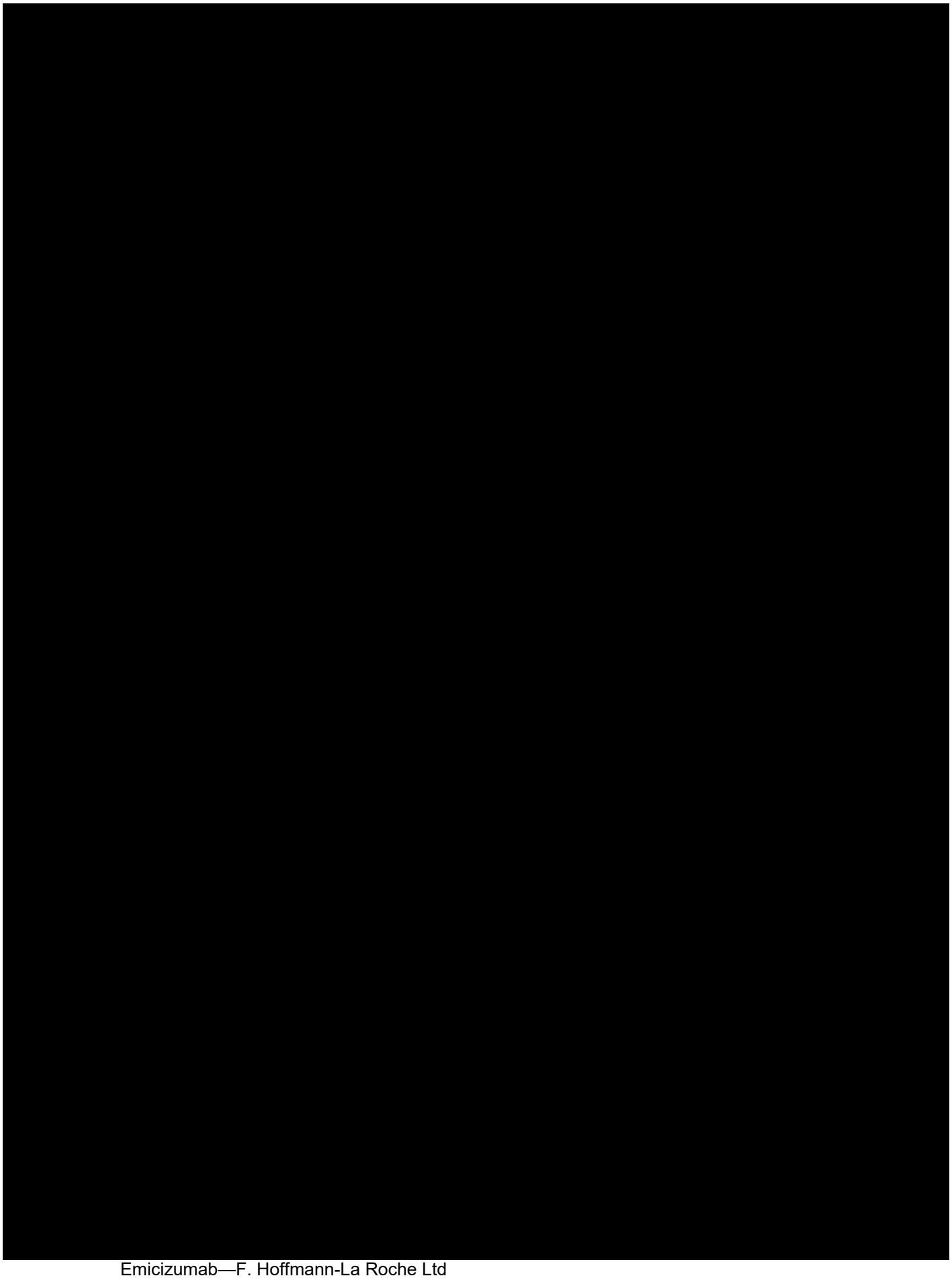

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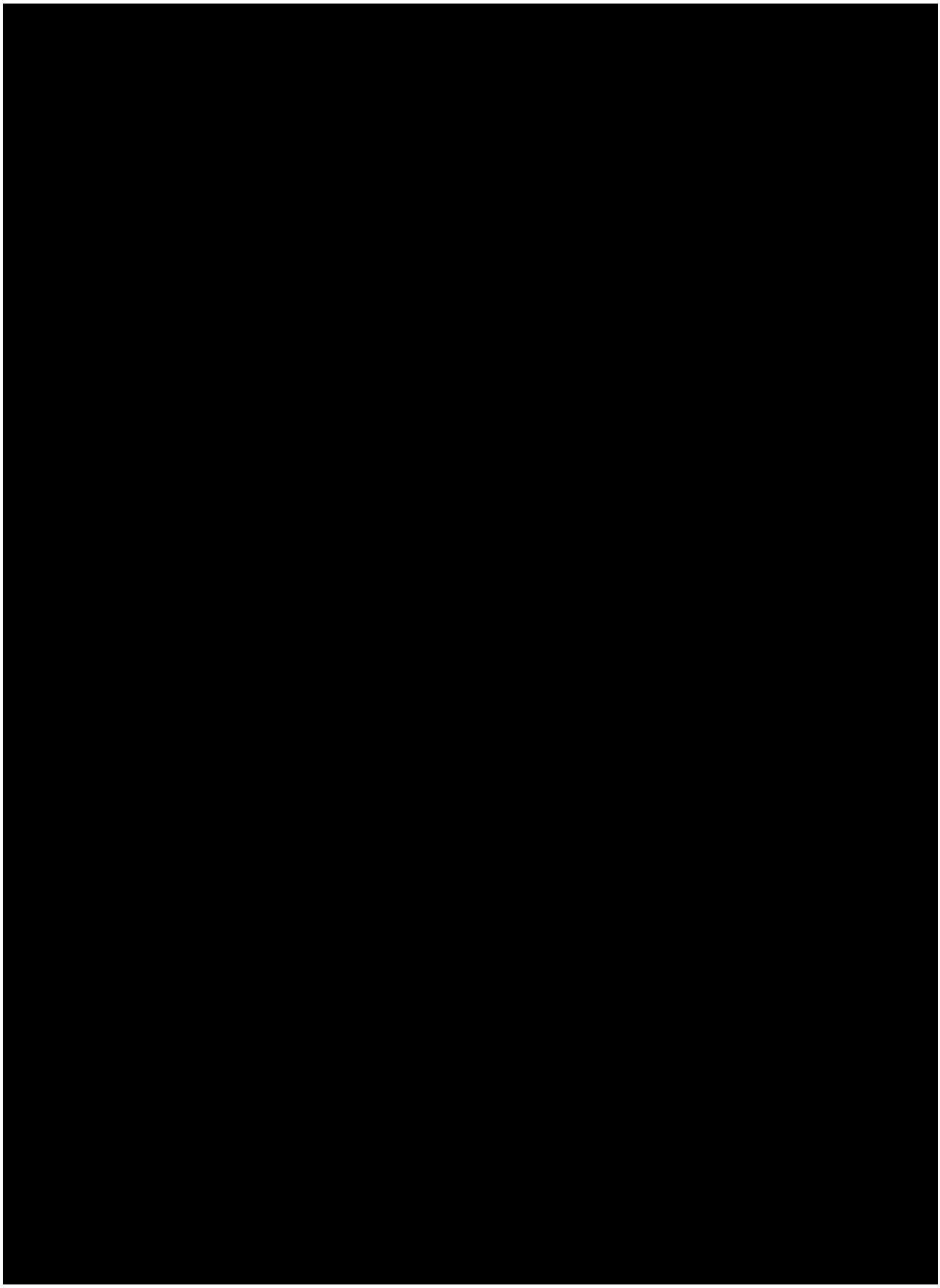

Appendix 2
Data Entry Site User Manual

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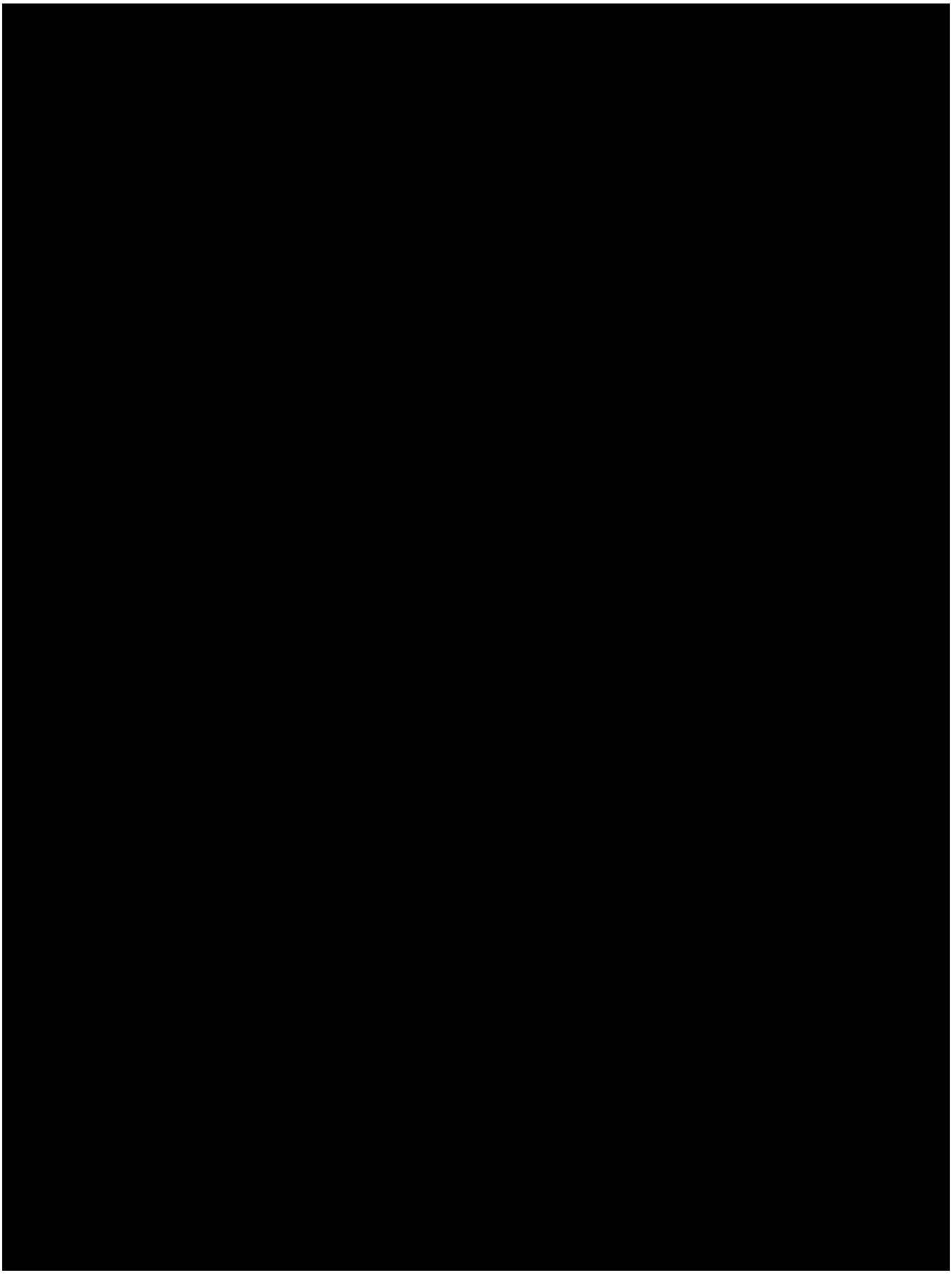

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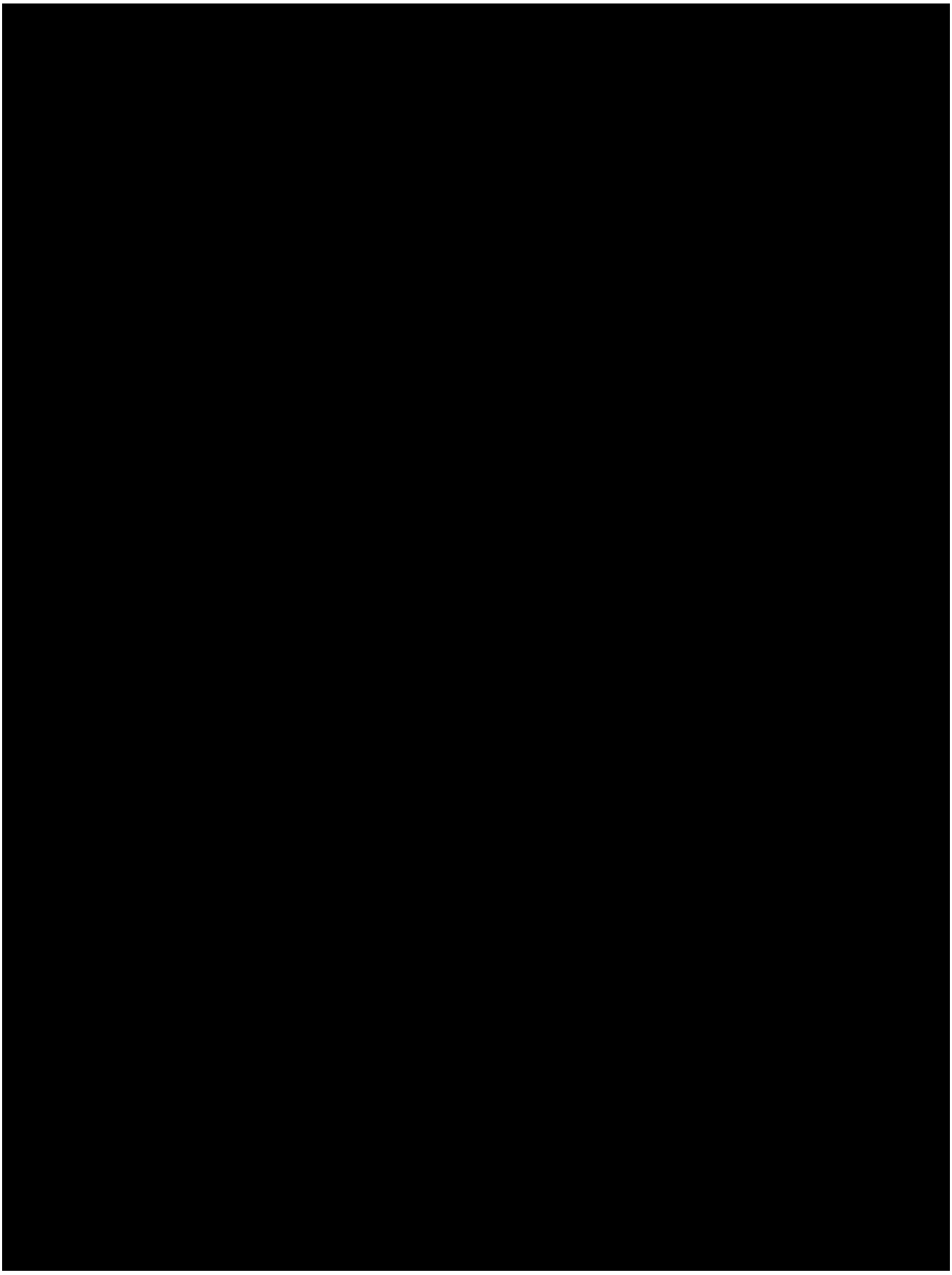

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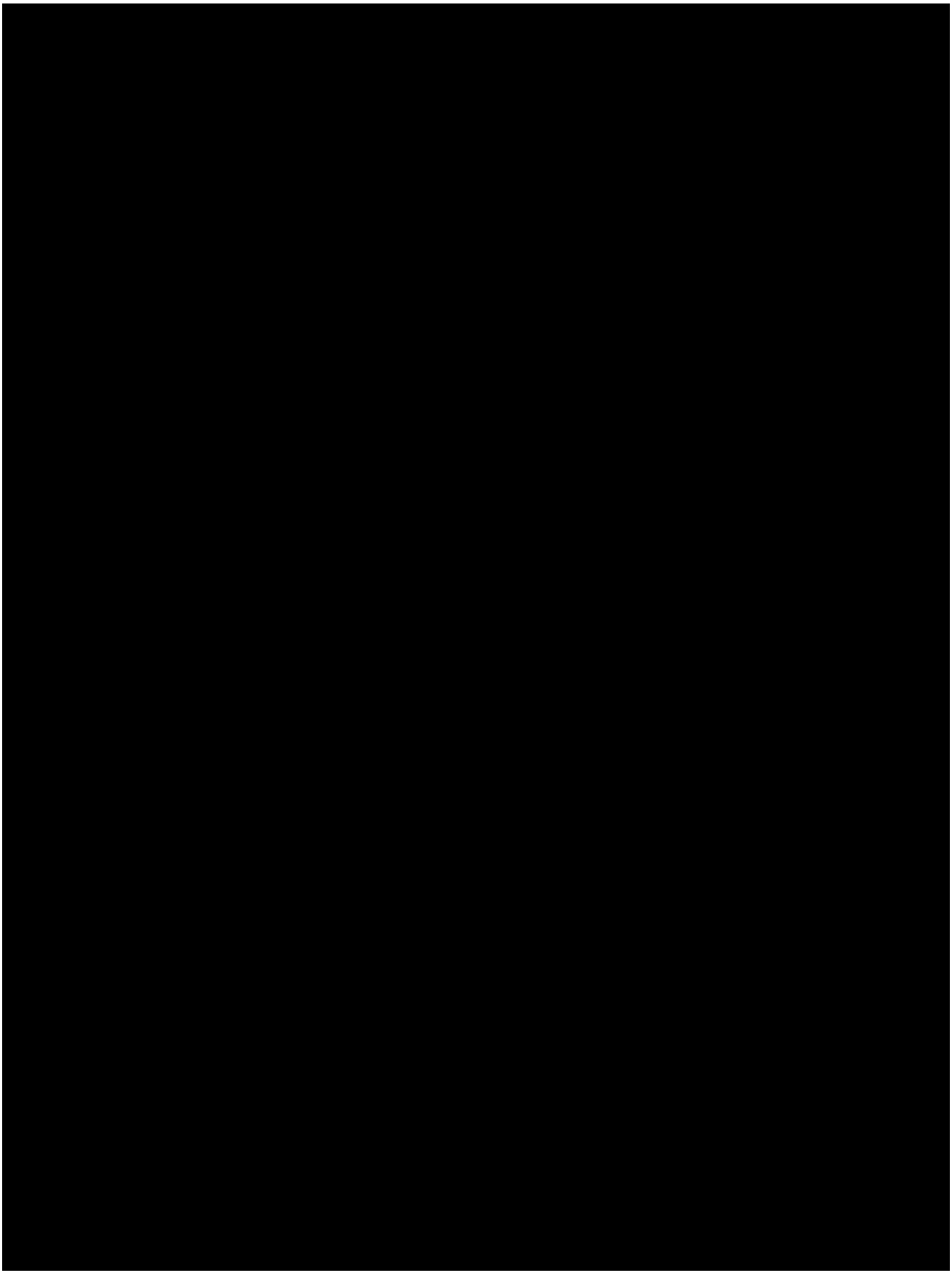

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